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Sincerely yours.

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CONTENTS

Original Article

CONTENTS

Original Article

Case Report

Original Article

HEALTH SCIENCES
MEDICINE

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J Health Sci Med 2021; 4(1): 1-6

Characteristics of post cesarean section pain

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ABSTRACT

Aim: The aim of this study was to analyze the characteristics of postoperative pain in patients undergoing cesarean delivery for elective or urgent reasons.

Material and Method: This study is an observational descriptive cross-sectional analysis involving 78 patients who underwent cesarean delivery. Visual pain scale (VAS) scores of 78 patients were evaluated in the first 6 hours and the patients were asked about the characteristic descriptions of the pain.

Results: Mean VAS scores in the first 6 hours postoperatively were 5.56±1.31. Body localizations where the patients feel pain were 7.7% in the incision site, 14.1% under the umbilicus, 23.1% in the whole abdominal region, 50% on the right side of the incision, 1.3% on the left side of the incision and 3.8% on both sides of the incision. There was no statistically significant difference between the location of pain and the number of cesarean sections ($p>0.05$). There was a statistically significant relationship between the postoperative mobilization hours and the patients' satisfaction scores ($p<0.05$).

Conclusion: Treatment of the post-cesarean pain is very important for the recovery process of the mother and the development of the early bond between the mother and the infant. If the post-cesarean delivery pain is identified, evaluated and its characteristics are determined, appropriate interventions can be made to reduce or eliminate the pain.

Keywords: Cesarean, delivery, pain

INTRODUCTION

Post cesarean section pain is still a problem to be solved (1). To prevent or minimize postoperative pain, the characteristics of the pain should be analyzed well (2). Thus, maternal and infant compliance can be increased and the mother can better focus on breastfeeding (3,4). Pain that is not effectively relieved postoperatively may increase the stress response of the body which begins with surgery (5). Prolonged stress response may affect the healing process, leading to complications (6,7).

Being a mother is a very important experience in women's life. Feeling less pain during this period is important both for the health of the mother and the happiness of the mother and her baby (8). The satisfaction of the mother with childbirth experience ensures the harmony between the mother and the baby quickly and has a positive long-term effect (9).

Over the past 20 years, there has been a serious increase in the cesarean delivery rate in the world (10). In our country, cesarean delivery frequency was reported as 51.2% (11). After the cesarean delivery, the pain in the incision area prevents the mother from performing several activities from activities of daily living to breastfeeding (12). The pain suffered by the mother should be controlled to take care of her baby immediately after cesarean delivery (13). Pain is a subjective symptom and the objective measurement is very difficult. Pain scores were developed to determine the pain severity more objectively. The most commonly used scoring system is the visual analogue scale (VAS). Pain intensity and pain relief can be evaluated with VAS (14). In the VAS score, patients evaluate the severity of pain between no pain and the worst pain on the 100 mm line (15). VAS has been evaluated by several researchers and is generally found valid and reliable (16,17). It has been reported that patients with visual impairment may have difficulty seeing the scale or elderly patients may have difficulty marking scale (18). Dissatisfaction and painful experiences after birth can cause pathologies such as depression, post-traumatic stress disorder, sexual dysfunction, negative feelings fed to the baby, the mother's inability to adapt to her role and breastfeeding problems (19). This study aimed to investigate the characteristics of post-cesarean section pain.

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MATERIAL AND METHOD

The study included 78 volunteer patients who fulfilled the research criteria. This study was approved by the university/local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was carried out with the permission of Research Ethics Committee of Beykoz University (Permission granted/CAAE number: 2019/30.4, Decision no: 1). Inclusion criteria included cesarean delivery in the hospital where the research was carried out, literacy, not having communication problems, being in 24 hours after surgery, postoperative mobilization, infant not being in the neonatal intensive care unit and postpartum unit and accompanying the baby during the interview and willingness to participate in the study. Patients who had preeclampsia, pre-gestational or gestational diabetes, fibromyalgia, anxiety disorder, depression, psychiatric, chronic diseases, etc. were excluded from the study. They were asked about the demographic features of the puerperium, the types of anesthesia, VAS scores (0-10), the nature of the pain they suffered, the place where they felt the most severe pain and other accompanying complaints (nausea, vomiting, headache, etc.) and these features were recorded in the case report form.

Statistical Analysis

The data obtained from the study were analyzed with the Statistical Package for the Social Sciences (SPSS), 21st version (SPSS Inc., Chicago, Illinois, USA).

Data: The number of samples (N), mean ($\bar{X}$),±standard deviation (SD), the minimum-maximum values and percentages of the values are given. Pairwise comparisons of the incision pain groups were made by two Independent Sample T-Test and multiple comparisons were made with ANOVA (one-way analysis of variance). The normal distribution of the data was effective in the selection of these methods. Turkey's Post-Hoc Tests was used to find the significance source of the data obtained from the comparison tests. Correlation relationships between parameters were determined with the Pearson method. For statistical significance level, $p<0.05$ was accepted. Comparisons in categorical data were made with Chi-Square ($\chi 2$) analysis.

RESULTS

The mean age of the 78 pregnant women included in the study was 30.85±5.24 and the mean body mass index (BMI) was 28.81±5.45. 61.5% of the pregnant women underwent the first cesarean delivery and 38.5% underwent the second and higher cesarean delivery. Emergency cesarean delivery was performed in 33.3% and elective cesarean delivery was performed in 66.7%. Spinal anesthesia in 35.9%, general anesthesia in 62.8% and combined spinal-epidural anesthesia in 1.3% are shown in **Table 1.**

Table 1. Characteristics of patients, distribution according to type of surgical intervention and type of anesthesia

Age (mean±std)	30.85±5.24
BMI (mean±std)	28.81±5.45
Type of surgical intervention (n:78)	
Emergency cesarean (%)	33.3%
Elective cesarean (%)	66.7%
Type of anesthesia	
Spinal	35.9%
General	62.8%
Combined spinal-epidural	1.3%

The smoking rate was 28.2% in pregnant women. The smoking rate among the spouses of the pregnant women was 32.1%. The mean VAS scores in the first 6 hours postoperatively were 5.56±1.31. The VAS score of patients was 3 in 5.1%, 4 in 20.5%, 5 in 14.1%, 6 in 37.2%, 7 in 16.7%, and 8 in 6.4%. Preoperative ASA scores were ASA 1 in 88.5% and ASA 2 in 11.5%. Body areas where the patients felt pain were 7.7% in the incision site, 14.1% under the umbilicus, 23.1% in the whole abdominal region, 50% on the right side of the incision, 1.3% on the left side of the incision, 3.8% on both sides of the incision. The pain was described as follows: 70.5% as flammable prickles and 29.5% as tingling are shown in **Table 2**.

Table 2. Pain places and description of the patients

Pain Place	Number of patients (n)	Percentage (%)
Incision site	6	7.7
Uterus recovery	11	14.1
Diffuse abdominal pain	18	23.1
Incision only right	39	50.0
Incision only left	1	1.3
Incision on two sides	3	3.8
Flammable prickles	55	70.5
Tingle	23	29.5

When VAS scores were compared based on types of anesthesia (general, spinal, epidural+spinal), no statistically significant difference was found between

the averages (p>0.05). When the body mass indexes and pain definitions of the patients were compared, no statistically significant difference was found between the pain definitions of the patients (p>0.05) as shown in **Table 3**.

Table 3. Comparison of visual analogue scale (VAS) scores and anesthesia types and comparison of BMI and pain definitions

Types of anesthesia	VAS score and BMI mean±std	p value
General VAS score	5.50±1.31	0.870
Spinal VAS score	5.63±1.31	
Epidural+spinal VAS score	6.00±**	
Flammable prickles BMI	28.57±4.474	0.559
Tingle BMI	27.91±4.563	

*p>0.05; no statistically significant
** test value is not calculated from the small number of data

There was no statistically significant difference between the number of cesarean delivery and pain sites (p>0.05). 61.5% of the patients experienced primary cesarean delivery and 38.5% experienced repeated cesarean delivery. Most of the patients were those who experienced pain on the right side of the incision and underwent primary cesarean delivery. No statistically significant difference was found between the pain sites of the patients based on the type of administered anesthesia (p>0.05) as shown in **Table 4.**

There was no statistically significant difference between the pain at the incision site and the number of cesarean deliveries (p>0.05) .There was no statistically significant difference between the pain at the incision site and the indications for cesarean delivery (emergency/elective) (p>0.05) .There was no statistically significant difference between the pain and the characteristic features of the incision site pain (p>0.05) as shown in Table 10. Of the patients who felt pain on the right side of the incision, 72.6% felt flammable tingling and 27.4% felt tingling as shown in **Table 5**.

In our study, a statistically significant relationship was found between the age of the patients and the pain felt at the incision site (p<0.05). There was a statistically significant relationship between postoperative mobilization hours and satisfaction scores of the patients (p<0.05).

Table 4. Comparison of pain location with obstetric history and anesthesia types

Comparison of pain location and obstetric history								
Obstetric history (number of cesarean) (n)		Pain location						p value
		incision site	Uterus recovery	Diffuse abdominal pain	Incision only on the right side	Incision only left side	Incision on two sides	
Primer	n:48	4	5	11	27	0	1	0.401
	Expected value	3.7	6.8	11.1	24.0	0.6	1.8	
	(61.5%)	66.7%	45.5%	61.1%	69.2%	0.0%	33.3%	
≥2	n:30	2	6	7	12	1	2	
	Expected value	2.3	4.2	6.9	15.0	0.4	1.2	
	(38.5%)	33.3%	54.5%	38.9%	30.8%	100.0%	66.7%	
Comparison of pain location and anesthesia types								
Anesthesia types		Pain location						p value
		Incision site	Uterus recovery	Diffuse abdominal pain	Incision only on the right side	Incision only left side	Incision on two sides	
Spinal	n:28	2	4	5	16	0	1	0.460
	Expected value	2.2	3.9	6.5	14.0	.4	1.1	
	35.9%	33.3%	36.4%	27.8%	41.0%	0.0%	33.3%	
General	n:49	3	7	13	23	1	2	
	Expected value	3.8	6.9	11.3	24.5	.6	1.9	
	62.8%	50.0%	63.6%	72.2%	59.0%	100.0%	66.7%	
Spinal + Epidural	n:1	1	0	0	0	0	0	
	Expected value	0.1	0.1	0.2	0.5	0.0	0.0	
	1.3%	16.7%	0.0%	0.0%	0.0%	0.0%	0.0%	

N: Number of patients

Table 5. Comparison of pain location with obstetric history and anesthesia types

Comparison of cesarean delivery types and incision site pain				
Obstetric story (number of cesarean delivery)		**Pain at the incision site**		**p value**
		yes	**no**	
Primer	n	41	7	0.089
	Expected value	38.2	9.8	
	%	66.1%	43.8%	
≥2	n	21	9	
	Expected value	23.8	6.2	
	%	33.9%	56.3%	
Comparison of cesarean delivery types and incision site pain				
Cesarean delivery indication		**Pain at the incision site**		**p value**
		yes	**no**	
Emergency	n	21	5	0.547
	Expected value	20.7	5.3	
	%	33.9%	31.3%	
Elective	n	41	11	
	Expected value	41.3	10.7	
	%	66.1%	68.8%	
Comparison of pain characteristic and pain at the incision site				
Description of pain		**Pain at the incision site**		**p value**
		yes	**no**	
Flammable prickles	n	45	10	0.540
	expected value	43.7	11.3	
	%	72.6%	62.5%	
Tingle	n	17	6	
	expected value	18.3	4.7	
	%	27.4%	37.5%	

DISCUSSION

It is important to establish the connection between mother and baby and encourage breastfeeding immediately after cesarean delivery. The recovery time and mobilization of the mother after cesarean delivery are closely related to postoperative pain. Pain that cannot be relieved in the postoperative period leads to unnecessary discomfort of the patient, delayed recovery, prolonged hospital stay, and reduced patient participation in treatment and care (20).

Preoperative information has an important role in coping with postoperative pain and anxiety as well as medical treatment and approaches. A sense of uncertainty added to the fears increases anxiety, especially when the necessary information about the operation is not provided. Increased anxiety and fear cause an increase in the severity of pain (21).

Generally, the highest pain score occurs at the postoperative 12th hour. In the current study, the resting VAS scores of the patients were found to be less than the movement state. When the factors affecting the intensity of pain were evaluated, high BMI, prolonged operation time, divorced women and general anesthesia administration were reported more (22,23).

Several studies have suggested that preoperative factors may predict postoperative pain. But there are conflicting results. For example, some researchers reported a correlation between postoperative pain and preoperative stress, anxiety, and personality traits, while others did not (24,25). Anesthesiologist's experience is also important (26). In the study conducted by Fecho K et al. (27), it was reported that the duration of surgery was a predictive factor in post-cesarean section pain and that prolongation of the surgery led to increased pain scores. Besides, it has been reported that as the complexity of surgery increases, pain scores increase. Kessous R et al. (28) reported that the meperidine requirement was higher in patients receiving general anesthesia in the first 24 hours postoperatively. In a study conducted by Gonano C et al. (29), it was reported that patients undergoing general anesthesia had higher pain scores in patients undergoing a postanesthesia care unit.

In our study, no statistically significant difference was found between the pain scores of the patients based on the type of anesthesia. In our study, patients reported that their pain often occurred on the right side of the incision. When we reviewed the literature, we could find limited edition work reporting pain localization after cesarean delivery. In the study conducted by Sousa L et

al. (30), it was reported that for 75% of the participants, the pain was located around the surgical delivery area and for 41.7%, pain was experienced in mixed areas and felt superficially and deeply. In the study conducted by Astepe B, no significant relationship was found between preoperative anxiety scores and VAS scores at 6th, 12th and 18th hours postoperatively (31). In the same study, post -operative pain- relief was found more in patients with high preoperative anxiety scores. In the study conducted in France, 78 births were evaluated and 60 of them stated that it was beneficial for them to have their spouses with them at birth. In the same study, pain scores were reported to be lower in patients with their spouses (32). Surgery can stimulate psychological and emotional reactions, causing stress for patients (33). The single-centered study is the limitation of the study in terms of the small sample size.

CONCLUSION

As a result of the study, the patients reported that the most common sensation of pain was felt at the right side of the incision after cesarean delivery. If the post-cesarean section pain is identified, evaluated and its characteristics are determined, appropriate interventions can be made to reduce or eliminate the pain. There is a need for new methods and investigations for the cause of pain and treatment of pain after cesarean delivery.

ETHICAL DECLARATION

Ethics Committee Approval: The study was carried out with the permission of Research Ethics Committee of Beykoz University (Permission granted /CAAE number: 2019/30.4, Decision no: 1).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Yanıkkerem UE, Kitapçıoğlu G, Karadeniz G. Women's view of birth methods, experience and satisfaction. Fırat Sağlık Hizmetleri Derg 2010; 5: 107-23.
2. Yanıkkerem UE, Göker A, Nicole Piro N. Women's opinions about mode of delivery and satisfaction with hospital care after cesarean delivery. Selçuk Tıp Derg 2013; 29: 75-81.
3. Çapık A, Sakar T, Yıldırım N, Karabacak K, Korkut M. Determining the satisfaction levels of the mothers according to their mode of birth. Anadolu Hemşirelik ve Sağlık Bilimleri Derg 2016; 19: 92-9.
4. Pınar G, Doğan N, Algıer L, Kaya N, Çakmak F. Factors that affecting mothers' postnatal comfort. Dicle Tıp Derg 2015; 36: 184-190.
5. Brown AK, Christo PJ, Wu CL. Strategies for postoperative pain management. Best Pract Res Clin Anaesthesiol 2004; 18: 703-17.
6. Shea RA, Brooks JA, Dayhoff NE, Keck J. Pain intensity and postoperative pulmonary complications among the elderly after abdominal surgery. Heart & Lung: J Acute Crit Care 2002; 31: 440-9.
7. Wang H-L, Keck JF. Foot and hand massage as an intervention for postoperative pain. Pain Manag Nurs 2004; 5: 59-65.
8. Huang SY, Sheu SJ, Tai CJ, Chiang CP, Chien LY. Decision-making process for choosing an elective cesarean delivery among primiparas in Taiwan. Matern Child Health J 2013; 17: 842–51.
9. Henriksen L, Grimsrud E, Schei B, Lukasse M. Factors related to a negative birth experience - A mixed methods study. Midwifery 2017; 51: 33-9.
10. Villar J, Valladares E, Wojdyla D, et al. Cesarean delivery rates and pregnancy outcomes: the 2005 WHO global survey on maternal and perinatal health in Latin America. Lancet 2006; 367:1819-29.
11. Eyi EGY, Mollamahmutoglu L. An analysis of the high cesarean delivery rates in Turkey by Robson classification. J Matern Fetal Neonatal Med 2019; 1: 1-11.
12. Güngör I, Kızılkaya Beji N. Development and psychometric testing of the scales for measuring maternal satisfaction in normal and cesarean birth. Midwifery 2012; 28: 348-5.
13. Saunders WB. Cesarean Delivery, High Risk Pregnancy. 2nd ed. Harcourt Publishers Limited. 1999; 1: 10-2.
14. Klopfenstein CE, Herrmann F, Mamie C, Van Gessel E, Forster A. Pain intensity and pain relief after surgery. Acta Anaesthesiol Scand 2000; 44: 58-62.
15. D'Arcy YM. Pain management: Evidence-based tools and techniques for nursing professionals: marblehead, MA: Hcpro Incorporated 2007; 2: 164.
16. Duncan GH, Bushnell MC, Lavigne GJ. Comparison of verbal and visual analogue scales for measuring the intensity and unpleasantness of experimental pain. Pain 1989; 37: 295-303.
17. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain 1986; 27: 117-26.
18. D'Arcy YM. Pain assessment in medical-legal aspects of pain and suffering. Lawyers & Judges Publishing Company. 2003.
19. Olofsson CI, Legeby MH, Nygards EB, Ostman KM. Diclofenac in the treatment of pain after cesarean delivery. An opioid-saving strategy. Eur J Obstet Gynecol Reprod Biol 2000; 88: 143-6.
20. Valente SM. Hypnosis for pain management. J Psychosoc Nurs Ment Health Serv 2006; 44: 22-30.
21. Coll MA, Jemel RM, Mead D. Postoperative pain assesment tools in day surgery: literature review. J Adv Nurs 2004; 46: 2.
22. Ngan Kee W, Khaw K, Wong E. Randomised double-blind comparison of morphine vs. a morphine–alfentanil combination for patient controlled analgesia. Anaesthesia 1999; 54: 629-33.

23. Vijayan R, Delilkan A. First years's experience with an acute pain service–University Hospital Kuala Lumpur. Med J Malaysia 1994; 49: 385-400.

24. Taenzer P, Melzack R, Jeans ME. Influence of psychological factors on postoperative pain, mood and analgesic requirements. Pain 1986; 24: 331-42.

25. Boyle P, Parbrook GD. The interrelation of personality and postoperative factors. Br J Anaesth 1977; 49: 259-64.

26. Chung F, Ritchie E, Su J. Postoperative pain in ambulatory surgery. Anesth Analg 1997; 85: 808-16.

27. Fecho K, Miller NR, Merritt SA, et al. Acute and persistent postoperative pain after breast surgery. Pain Med 2009; 10: 708-15.

28. Kessous R, Weintraub AY, Wiznitzer A, et al. Spinal versus general anesthesia in cesarean deliverys: the effects on postoperative pain perception. Arch Gynecol Obstet 2012; 286: 75-9.

29. Gonano C, Leitgeb U, Sitzwohl C, Ihra G, Weinstabl C, Kettner SC. Spinal versus general anesthesia for orthopedic surgery: Anesthesia drug and supply costs. Anesth Analg 2006; 102: 524-9.

30. SousaI L, Pitangui ACR, Gomes FA, Nakano AMS, Ferreira CHJ. Measurement and characteristics of post-cesarean delivery pain and the relationship to limitation of physical activities. Acta Paul Enferm 2009; 22: 6.

31. Astepe BS. The relationship between preoperative anxiety level and postoperative pain in patients with cesarean delivery. Kocaeli Med J 2018; 7: 64-9.

32. Niven C. How helpful is the presence of the husband at childbirth? J Reprod Infant Psychol 1985; 3: 45-53.

33. Granot M, Lowenstein L, Yarnitsky D, Tamir A, Zimmer EZ. Postcesarean delivery pain prediction by preoperative experimental pain assessment. Anesthesiology 2003; 98: 142-226.

Original Article

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Investigating anxiety, depression and obsessive-compulsive disorders among the pregnant women during Covid-19 pandemic

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ABSTRACT

Aim: Our study aimed to investigate anxiety, depression, and obsessive-compulsive disorders (OCDs) among pregnant women during the Covid-19 pandemic.

Material and Method: This cross-sectional study was conducted on 71 pregnant women who referred to Gynecology and Obstetrics Clinic between June and July 2020 for routine pregnancy examination. The Beck anxiety inventory (BAI), the Beck depression inventory (BDI), and the Maudsley obsessive-compulsive inventory (MOCI) were used to assess the rate of depression, anxiety, and OCD. The questionnaire containing information about smoking, working status, gravidity, and education was completed by the subjects.

Results: Mean age of the participants was 30 years and their mean body mass index (BMI) was 24.4. 76.1% of the participants were non-smokers. 71.8% were nulliparous. 62% of pregnant women had a high school degree. 80.3% were working. There was a positive significant relationship between BDI and BAI (r=0.405, 0.000) and MOCI scores (r=0.319, sig= 0.007). There was a negative statistically significant relationship between OCD and BMI (r=-0.268, sig=0.024). Anxiety, depression, and OCDs were not significantly different between smokers and non-smokers. Working pregnant women had significantly higher depression and OCDs than the non-working had. The pregnant women showed mild to severe anxiety and depression levels and also showed moderate to high OCDs under the Covid-19 pandemic. Most of the pregnant women showed mild depression, moderate anxiety, and high OCD. The results showed that the studied pregnant women experienced mental complications under the Covid-19 pandemic.

Conclusion: Since the mental health of pregnant women is highly important, one should pay special attention to the mental health of working pregnant women under the Covid-19 pandemic. The reason is that such women are more vulnerable to infectious diseases such as Covid-19.

Keywords: Anxiety, Covid-19, depression, obsessive-compulsive disorder, pandemic

INTRODUCTION

The history of humanity has been always affected by several fearsome epidemics of infectious disease (1). A distinctive type of coronavirus with an acute respiratory syndrome called Covid-19 appeared in Wuhan, China, and immediately extended to other states in 2020 (2,3). On March 11, 2020, Covid-19 was called pandemic as the World Health Organization (WHO) declared (4). Covid-19 is a beta virus which is transmitted to humans due to close physical contact (4). This pandemic has a fatality rate of 2.3% higher than influenza has and also is more contagious than severe acute respiratory syndrome (SARS) (5,6). Besides the significant increase in mortality rate due to the Covid-19 pandemic, the psychological status of the population was also negatively affected (7,8). The most common symptoms of Covid-19 are cough, fever, dyspnea, headache, sputum production, rhinorrhea, ageusia, myalgia, anosmia, and diarrhea (9,10). Besides, the patients infected with Covid-19 had shown symptoms of depression, post-traumatic stress disorder, and anxiety (11,12).

Among the vulnerable populations, pregnant women as well as their fetuses are highly exposed to infectious diseases during the outbreaks (13) but there are only 55 pregnant women infected with the 2019 coronavirus, and there has been no mortality among them due to the disease (14).

The focus of several studies and clinical measures is on the treatment and prevention of Covid-19 aiming

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at the reduction of the mortality rates, but only two investigations have been done on the health workers (15) and the general population (16) to assess the psychological effects of this pandemic.

Pregnant women who need more protections against the Covid-19 outbreak have been reported to be among the vulnerable population groups exposed to vertical transmission of Covid-19 during pregnancy (17,18). The pregnant women may be impacted by all aspects of the Covid-19 pandemic due to the effects of the related restrictions, the unpredictability of the pandemic, and the feeling of fear (19). There should be a focus on the different aspects of pregnancy during the Covid-19 pandemic and pregnant women should receive psychological support during this outbreak (20).

There is limited research on the psychological effects of a global pandemic such as Covid-19, particularly among pregnant women. Therefore, this study aims to investigate depression, anxiety, and OCDs among pregnant women during the Covid-19 pandemic to see the rate of such psychological impacts among them.

MATERIAL AND METHOD

This cross-sectional study was conducted on 71 pregnant women who referred to Gynecology and Obstetrics Clinic between June and July 2020 for routine pregnancy examination. Those who agreed to participate in the study did not have any psychiatric diagnosis before, and not use any drug that was included in the study. The informed consent was received from all pregnant women. The pregnant women who had previous mental disorders such as depression, anxiety, and obsessive-compulsive disorders were excluded from the study. Local academic committee number 09.06.2020/01 and the Turkish Republic dated 26.06.2020 after approval of the application for work by the Ministry of Health Scientific Research Platform seventy-one pregnant women who referred to Gynecology and Obstetrics Clinic between July and June 2020 for routine pregnancy examination participated in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Pregnant women responded to the BDI, a validated Turkish version of BAI and the MOCI. Beck Depression inventory (BDI) which was originally developed by Beck in 1961 (21), was carried out by Hisli in 1989 (22). The scale consists of 21 subscales with depressive symptoms. Each item is scored between 0 and 3. The cutoffs for normal range are 0–9, for mild to moderate depression 10–18, for moderate to severe depression 19–29, and for severe depression 30–63 (22). Beck Anxiety inventory (BAI) which was developed by Beck et al. in 1988 (23) consists of 21 questions. Each question is evaluated between 0 (none) and 3 (severely). The total score from this scale varies between 0 and 63. A validated Turkish version was carried out by Ulusoy (24). Maudsley obsessive-compulsive inventory (MOCI) was developed by Hodgson and Rachman (1977) to assess obsessive-compulsive symptoms (25). Turkish version of MOCI was applied by Erol et al. (26). The questionnaire containing information about smoking, working status, gravidity, and education was completed by the subjects.

Statistical analysis

The Kolmogorov–Smirnov test has been used to test the normality of the research variables. Considering that the significance level of the test related to all variables is above 0.05, the normality of the research variables has been accepted. To examine the relationship between variables of depression inventory, anxiety inventory score and obsessive-compulsive symptom and age, and BMI, considering the normality and quantitative variables, the Pearson correlation coefficient test was used.

RESULTS

The results show that the mean age of the participants was 30 years and the mean BMI was 24.4. 23.9% of the pregnant women were smokers and 76.1% were non-smokers. 71.8% of the pregnant women were nulliparous and 28.2% were multiparous. 62% of pregnant women had a high school degree, and 38% had a university degree. 80.3% were working and 19.7% were not working. **Table 1** shows the BDI, BAI, and MOCI scores of pregnant women. The mean depression score was 17.25, the mean anxiety score was 20.07, and the mean OCDs score was 16.77.

Table 1. Descriptive statistics related to research variables

	N	Min.	Max.	Mean	Std. deviation
Beck depression inventory	71	2	38	17.25	8.768
Beck anxiety inventory score	71	7	42	20.07	8.054
Maudsley obsessive-compulsive symptom scale	71	8	31	16.77	5.394

Table 2 shows that 16.9% of the pregnant women were normal, 46.5% had mild depression, 22.5% had moderate depression and 14.1% had severe depression. The anxiety rate of 31% of the respondents was mild, 45.1% was moderate and 23.9% was severe. The results also show that 25.4% of the respondents had a low probability of detecting OCD, 31% had OCD detection and 43.7% had a high probability of detecting OCD.

Table 2. Percentage and frequency of respondents based on research variables

Demographics		Frequency	Percentage	Accumulated percentage
Depression inventory	Normal level	12	16.9	16.9
	Mild depression	33	46.5	63.4
	Moderate depression	16	22.5	85.9
	Severe depression	10	14.1	100.0
Anxiety inventory score	mild anxiety	22	31.0	31.0
	Moderate anxiety	32	45.1	76.1
	severe anxiety	17	23.9	100.0
Obsessive-compulsive symptom	OCD is likely to be detected but low	18	25.4	25.4
	OCD detection	22	31.0	56.3
	High probability of detecting the obsessive-compulsive disorder	31	43.7	100.0

Table 3 shows that there was a positive significant relationship between BDI and BAI (r=0.405, 0.000) and MOCI scores (r=0.319, sig= 0.007). There was a negative statistically significant relationship between OCD and BMI (r=-0.268, sig=0.024). However, there was no statistically significant relationship between other variables.

Table 4 shows the relationship between BDI, BAI, and MOCI variables and smoking, working status, gravidity, and education. The mean depression score was 16.94 in the non-smokers and 18.24 in smokers. The mean anxiety score was 20.89 in the non-smokers and 17.47 in smokers. The mean score of obsessive-compulsive disorders was 16.59 in the non-smokers and 17.35 in smokers. Levene's Test for Equality of Variances has been used. In the Levene's Test, the significance level in the three variables was above 0.05. Therefore, it can be said with the confidence of 95% that no significant difference was found between smokers and non-smokers in anxiety, depression, and obsessive-compulsive disorders.

Regarding working status, the results show that the mean depression score was 18.49 in the working participants and 12.21 in the non-working participants. The mean anxiety score was 20.19 in the working participants and 19.57 in the non-working participants. The mean obsessive-compulsive disorder score was 17.53 in the working participants and 13.71 in the non-working participants. The significance level of the t-test in two variables of depression and obsessive-compulsive disorders was below 0.05. Therefore, it can be said with the confidence of 95% that there was a significant difference between the working participants and non-working participants in terms of depression, and obsessive-compulsive disorders while there was no significant difference between the working participants and non-working participants in terms of anxiety.

Regarding the gravidity, the mean depression score was 16.51 in the nulliparous participants and 19.15 in multiparous participants. The mean anxiety score was 19.57 in the nulliparous participants and 21.35 in multiparous participants. The mean OCD was 16.57 in the nulliparous participants and 17.30 in multiparous participants. The significance level of the t-test in three variables was above 0.05. Therefore, it can be said with the confidence of 95% that there was no significant difference between nulliparous and multiparous participants in terms of anxiety, depression, and OCD.

Regarding education, the mean depression score was 18.61 in the participants with high school education and 15.04 in participants with university education. The mean anxiety score was 20.55 in the participants with high school education and 19.30 in participants with university education. The mean OCD was 17.02 in the participants with high school education and 16.37 in participants with university education. The significance level of the t-test in three variables was above 0.05. Therefore, it can be said with the confidence of 95% that there was no significant difference between the participants with high school and university education in terms of anxiety, depression, and OCD.

Table 3. Pearson correlation test

		Depression inventory	Anxiety inventory score	Obsessive-compulsive symptom scale	Age	BMI
Depression inventory	Pearson correlation	1				
	Sig. (2-tailed)					
Anxiety inventory score	Pearson correlation	0.405**	1			
	Sig. (2-tailed)	0.000				
Obsessive-compulsive symptom scale	Pearson correlation	0.319**	0.176	1		
	Sig. (2-tailed)	0.007	0.141			
Age	Pearson correlation	0.131	-0.056	-0.021	1	
	Sig. (2-tailed)	0.276	0.640	0.860		
BMI	Pearson correlation	-0.216	-0.106	-0.268*	-0.048	1
	Sig. (2-tailed)	0.071	0.379	0.024	0.693	

**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).

Table 4. T-Test results between depression ınventory, anxiety ınventory score, obsessive-compulsive symptom scale and cigarettes, working status, gravidity, and education

Cigarettes		**N**	**Mean**	**Std. deviation**	**Levene's test for equality of variances**		**t-test for equality of means**		
					F	Sig.	t	df	Sig.
Depression inventory	No	54	16.94	8.996	0.206	0.651	-0.527	69	0.600
	Yes	17	18.24	8.182					
Anxiety inventory score	No	54	20.89	8.529	3.609	0.062	1.541	69	0.128
	Yes	17	17.47	5.778					
Obsessive-compulsive symptom scale	No	54	16.59	5.544	0.251	0.618	-0.504	69	0.616
Working		**N**	**Mean**	**Std. deviation**	**Levene's test for equality of variances**		**t-test for equality of means**		
					F	Sig.	t	df	Sig.
Depression inventory	Yes	57	18.49	8.919	3.127	.071	2.487	69	0.015
	No	14	12.21	6.104					
Anxiety inventory score	Yes	57	20.19	7.832	1.230	.271	0.257	69	0.798
	No	14	19.57	9.205					
Obsessive-compulsive symptom scale	Yes	57	17.53	5.471	1.643	.204	2.453	69	0.017
Gravidity		**N**	**Mean**	**Std. deviation**	**Levene's test for equality of variances**		**t-test for equality of means**		
					F	Sig.	t	df	Sig.
Depression inventory	Nulliparous	51	16.51	8.559	.292	.591	-1.144	69	.257
	Multiparous	20	19.15	9.230					
Anxiety inventory score	Nulliparous	51	19.57	8.050	.104	.748	-.837	69	.406
	Multiparous	20	21.35	8.126					
Obsessive-compulsive symptom scale	Nulliparous	51	16.57	5.438	.058	.810	-.511	69	.611
Education		**N**	**Mean**	**Std. deviation**	**Levene's test for equality of variances**		**t-test for equality of means**		
					F	Sig.	t	df	Sig.
Depression inventory	High school	44	18.61	8.890	1.046	.310	1.691	69	.095
	University	27	15.04	8.248					
Anxiety inventory score	High school	44	20.55	8.108	.000	.992	.632	69	.530
	University	27	19.30	8.057					
Obsessive-compulsive symptom scale	High school	44	17.02	5.781	1.783	.186	.492	69	.624

DISCUSSION

The present study investigated the effect of mental disorders such as anxiety, depression, and obsessive-compulsive disorders on pregnant women under the Covid-19 pandemic. The study showed a positive significant relationship between depression and anxiety and obsessive-compulsive disorders. There was a negative statistically significant relationship between obsessive-compulsive disorders and BMI. Anxiety, depression, and OCDs were not significantly different between smokers and non-smokers. Working pregnant women had significantly higher depression and OCDs than the non-working had. The pregnant women showed mild to severe anxiety and depression levels and also showed moderate to high OCDs under the Covid-19 pandemic. Most of the pregnant women showed mild depression, moderate anxiety, and high OCD. The findings show that the studied pregnant women experienced mental complications under the Covid-19 pandemic.

All people all over the world are fighting against the Covid-19 pandemic which is the most threatening power of the twenty-first century. Almost all countries are affected by all aspects of this outbreak, encouraging the researchers to investigate the treatment and prevention of the disease and deal with the mortality risk caused by the outbreak. Besides, the psychological effect of the outbreak on the susceptible people particularly pregnant women should be taken into account (19). Durankuş F et al. (19) found that pregnant women experienced higher depression and anxiety scores during the pandemic and that most of the case groups reported that the pandemic affected their pregnancy. They also revealed that the BAI and BDI scores, and also the effects of Covid-19 on social isolation and mental health statistically significantly affected the Edinburgh postnatal depression scale (EPDS) scores while our study found that most of the pregnant women showed mild depression rate, moderate anxiety level, and high OCD.

Mirzadeh et al. (20) found prenatal depression, anxiety, and stress to be the prevalent issues of the public health of pregnant women. The Covid-19 outbreak made mothers concerned about their and their babies' health due to stress or anxiety. The nulliparous pregnant women showed the adverse mood symptoms as well as childbirth

fear which may irreversibly affect the health of mother and child, while our study found no significant difference between nulliparous and multiparous participants in anxiety, depression, and OCDs under the pandemic.

Our study is in line with the results of the study by Saccone et al. (27) who found moderate to the severe psychological impact of the Covid-19 outbreak on pregnant women and showed higher than normal anxiety levels of more than two-thirds of the women.

Spiniello et al. found that pregnant women experienced high levels of anxiety and stress due to the adverse obstetrical outcomes including fetal abnormalities and intrauterine fetal death and also due to infectious disease outbreaks (28).

Our study supports the results of the study by Grigoriadis et al. (29) who found the relationship between increased anxiety during pregnancy and postpartum depression or other mood disorders and suggested continual monitoring of the depression as well as other mood disturbances (30).

Corbett et al. (31) found that the pregnant population showed rising anxiety during the Covid-19 pandemic and were almost concerned about their children, unborn children and their relatives and were at least worried about their health, while more than half of women showed significant health anxiety, which is consistent with our study results.

Wu Y et al. (32) found the increased risk of anxiety and depression symptoms during the outbreak among the pregnant women who were underweight before becoming pregnant, had only one child and below the age of 35, working on a full-time basis, earning middle income, and those who have suitable appropriate living space, while our study found that working pregnant women had higher depression, anxiety and OCD scores than the non-working.

Brooks et al. (33) stated that some extensive public health measures which are taken to reduce the speed of SARS-CoV-2 infections, such as travel restrictions, and physical distancing can reduce the pressure on health-care systems but such measures may lead to some unintended consequences for women and families, including family and gender-based violence, increased depression after childbirth and the worsening other mental health issues, which is in line with our study which found the increasing depression levels among the pregnant women.

Wu et al. (32) found that the pregnant women who were primiparous, working on a full-time basis and were underweight before pregnancy were at higher risk of depressive and anxiety symptoms during the outbreak, which is in line with our study results which found a negative association between the low BMI and obsessive-compulsive disorders and that the working pregnant women were more mentally affected by the pandemic than the non-working ones were.

CONCLUSION

Pregnancy is a period that is known for its deep changes. Pregnant women should have adequate physical and mental health to protect them against mood disorders since some of the women may increase their vulnerability to psychiatric diseases such as anxiety, OCD, and depression. As a result, it is highly important to assess the psychological effect of the Covid-19 outbreak on pregnant women. Our study concluded that most of the pregnant women showed a mild to severe depression, mild to severe anxiety level, and moderate to high OCD level. A positive significant relationship was found between depression and anxiety and obsessive-compulsive disorders and A negative statistically significant relationship was found between obsessive-compulsive disorders and BMI. The working pregnant women had significantly higher depression and OCDs than the non-working pregnant women had.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Research Ethics Committee of Beykoz University (Permission granted /CAAE number: 2020/9.6, Decision no: 1).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Liu X, Kakade M, Fuller CJ, et al. Depression after exposure to stressful events: Lessons learned from the severe acute respiratory syndrome epidemic. Compr Psychiatry 2012; 53: 15–23.
2. Ahmad T, Khan M, Khan FM, Hui J. Are we ready for the new fatal Coronavirus: scenario of Pakistan? Hum Vacc Immunother. 2020: 1–3. doi: 10.1080/21645515.2020.1724000.
3. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (Covid-19) implicate special control measures. J Med Virol. 2020 Mar 5. doi: http: //10.1002/jmv.25748.

4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223): 497-506.
5. Bouey, Jennifer, From SARS to 2019-Coronavirus (nCoV): U.S.-China Collaborations on Pandemic Response: Addendum. Santa Monica, CA: RAND Corporation, 2020; https: //www.rand.org/pubs/testimonies/CT523z2.html.
6. Yang Y, Peng F, Wang R, Guan K, Jiang T, Xu G &Chang C. The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. J Autoimmun 2020; 102434.
7. World Health Organization Mental health and psychosocial considerations during the Covid-19 outbreak. https: //www.who.int/docs/default-source/coronaviruse/mental-health-considerations.pdf?sfvrsn=6d3578af_16
8. Robinson G. UK poll finds young people's mental health hit by coronavirus. The Guardian [Internet] 2020 Mar 30.
9. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (Covid-19): the epidemic and the challenges. Int J Antimicrob Agents. 2020; 55: 105924. doi: 10.1016/j.ijantimicag.2020.105924.
10. Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and ageusia: common findings in Covid-19 patients. Laryngoscope. 2020; doi: 10.1002/lary.28692. [Epub ahead of print].
11. Bo HX, Li W, Yang Y, Wang Y, Zhang Q, Cheung T, et al.Posttraumatic stress symptoms and attitude toward crisis mental health services among clinically stable patients with Covid-19in China. Psychol Med. 2020; 1–7. doi: 10.1017/S0033291720000999.
12. Kong X, Zheng K, Tang M, Kong F, Zhou J, Diao L, et al. Prevalence and factors associated with depression and anxiety of hospitalized patients with Covid-19. MedRxiv [preprint]. 2020. doi: 10.1101/2020.03.24.20043075.
13. Stockman LJ, Lowther SA, Coy K, et al. SARS during pregnancy, United States. Emerging Infect Dis. 2004; 10(9): 1689–1690.
14. Dashraath P, Jing Lin Jeslyn W, Mei Xian Karen L, et al. Coronavirus disease 2019 (Covid-19) pandemic and pregnancy. Am J Obstet Gynecol. 2020; In Press.
15. Li Z, Ge J, Yang M, et al. Vicarious traumatization in the general public, members, and non-members of medical teams aiding in Covid-19 control. Brain Behav Immun. 2020; doi: 10.1016/j.bbi.2020.03.007
16. Wang C, Pan R, Wan X, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (Covid-19) epidemic among the general population in China. IJERPH. 2020; 17: 1729.
17. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of Covid-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020; 395(10226): 809–15.
18. Liu W, Wang Q, Zhang Q, et al. Coronavirus disease 2019 (Covid-19) during pregnancy: a case series. Preprints. 2020; 2020020373.
19. Durankuş F, Aksu E. Effects of the Covid-19 pandemic on anxiety and depressive symptoms in pregnant women: a preliminary study. J Matern Fetal Neonatal Med. 2020: 1–7.
20. Mirzadeh M, Khedmat L. Pregnant women in the exposure to Covid-19 infection outbreak: the unseen risk factors and preventive healthcare patterns. J Matern Neonatal Med. 2020; 7: 1–2.
21. Beck At, Ward Ch, Mendelson M, Mock J, Erbaugh J. An inventory for Measuring Depression. Arch Gen Psychiatry. 1961; 4(6): 561–71.
22. Hisli N. Beck Depresyon Envanterinin üniversite öğrencileri için geçerliği, güvenirliği. Psikoloji Dergisi 1989; 23: 3-13.
23. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988; 56: 893–7.
24. Ulusoy M, Sahin N, Erkmen H. Turkish version of the Beck Anxiety inventory: Psychometric properties. J Cogn Psychother. 1998; 12: 163–72.
25. Hodgson RJ, Rachman S. Obsessional-compulsive complaints. Behav Res Ther. 1977; 15: 389-95.
26. Erol N, Savasir I. The Turkish version of the Maudsley Obsessional-Compulsive Questionnaire. Presented in the 2nd Regional Conference of the International Association of Cross-Cultural Psychology, Amsterdam, 1989.
27. Saccone G, Florio A, Aiello F, Venturella R, De Angelis MC,Locci M, et al. Psychological impact of coronavirus disease 2019 in pregnant women. Am J Obstet Gynecol 2020; S0002-9378(20)30527–5.
28. Spiniello L, Di Mascio D, Bianco C, Esposito O, Giangiordano I, Muzii L, Giancotti A, Brunelli R, Saccone G. All we know about Covid-19 in pregnancy: from perinatal to ethical and psychological perspective. Perinatal Journal 2020; 28(2): 120–6. doi: 10.2399/prn.20.0282008.
29. Grigoriadis S, Graves L, Peer M, et al. A systematic review and meta-analysis of the effects of antenatal anxiety on postpartum outcomes. Arch Womens Ment Health. 2019; 22: 543-56. doi: 10.1007/s00737-018-0930-2
30. Muzic M, Borovska S. Perinatal depression: implications for child mental health. Mental Health Fam Med. 2010; 7: 239–47.
31. Corbett GA, Milne SJ, Hehir MP, Lindow SW, O'connell MP. Health anxiety and behavioural changes of pregnant women during the Covid-19 pandemic. Eur J Obstet Gynecol Reprod Biol. 2020; 249: 96-7. doi: 10.1016/j.ejogrb.2020.04.022.
32. Wu Y, Zhang C, Liu H, et al. Perinatal depressive and anxiety symptoms of pregnant women along with Covid-19 outbreak in China [published online ahead of print, 2020 May 10]. Am J Obstet Gynecol. 2020; S0002-9378(20)30534-2. doi: 10.1016/j.ajog.2020.05.009.
33. Brooks SK, Webster RK, Smith LE, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet 2020; 395: 912–20.

Original Article

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Spectrum of eyelid lesions–a histopathological study in South India

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ABSTRACT

Aim: Eyelids are complex structures that protect the anterior surface of the globe. Eyelid lesions range from benign, self-limiting conditions to malignant, possibly metastatic tumors.

To assess the histomorphology of various eyelid lesions, determine their frequency, age and sex distribution in our study population and compare them with the other studies.

Material and Method: This is a retrospective study involving 122 patients of either sex presenting with lesions involving the eyelid, reporting to a tertiary care hospital in Karnataka.

Results: We came across 67.72% neoplastic, 28.34% inflammatory/infectious, and 3.94% miscellaneous lesions. There was a slight female predominance with a male to female ratio of 1: 1.18. The mean age at presentation was 43.7 years, range being 1-90 years. Majority were in their 3rd and 4th decades. Among the neoplastic lesions, 90.7% were benign. The most common benign, malignant and inflammatory lesions were nevus, sebaceous carcinoma and chalazion respectively. Uncommon stromal lesions, such as fibrous histiocytoma and a rare variant of basal cell carcinoma with sebaceous differentiation were encountered.

Conclusions: The frequency of eyelid lesions depends upon age group, source institution, racial and geographic factors. Histopathology remains the mainstay for diagnosis. In addition to determining the malignant potential of a lesion, it reveals its exact nature and structure, thereby influencing management and prognosis.

Keywords: Eyelid, nevus, chalazion

INTRODUCTION

Eyelid lesions are one of the many ophthalmologic conditions encountered in routine clinical practice. Eyelids are crucial to the health of the underlying eye.

Histologically, eyelid is composed of inner tarsal plate containing the meibomian glands, middle layer of orbicularis oculi muscle and surface epithelium. The cilia exit from the middle portion of the lid margin inferiorly. Eccrine and apocrine sweat glands, sebaceous glands of Zeis and hair follicles of the surface lanugo hair are also seen in the lids (1).

Any of the histologic elements can be the origin of the vast spectrum of eyelid lesions.

Most of the eyelid tumors are of cutaneous origin. Others include lymphoid neoplasms, hamartomas, and choristomas (1). Majority develop in adults (2).

Studies in different parts of the world have observed a variable incidence and distribution of eyelid lesions. The present study was conducted to evaluate the overall incidence, age and sex distribution and histopathology of different eyelid lesions in a tertiary care hospital in Karnataka; and compare our findings with published literature.

MATERIAL AND METHOD

The study was carried out with the permission of Kempegowda Institute of Medical Sciences, Institutional Ethics Committee (Permission granted: 06.12.2016, Decision no: KIMS/IEC/DUPLICATE01/M/2020). All procedures were performed adhered to the ethical rules and the Helsinki Declaration of Principles.

We undertook a three year retrospective hospital based study of 122 patients from January 2016 to December 2019 presenting with eyelid lesions. Purposive sampling was done. The surgically resected specimens were received in 10% formalin, grossed and processed. Five microns thick sections were taken, stained with haematoxylin&eosin (H&E) and evaluated. The identity of the patient was

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kept confidential. The data was subjected to descriptive statistical collation and analysis. Approval of the institution was obtained for the study.

RESULTS

127 histopathological specimens from 122 patients (few patients had more than one lesion) were analysed.

The mean age at presentation was 43.7 years, range being from 1-90 years. Peak was noticed in the third and fourth decades of life.

Most lesions were inflammatory/infectious amounting to 28.34%, closely followed by adnexal lesions (27.6%). Amongst the 86 neoplastic lesions, 90.7% (n=78) were benign and 9.3% (n=8) were malignant. The most common benign and malignant tumors were nevus and sebaceous gland carcinoma (SGC) respectively. Miscellaneous lesions included two cases of blepahrochalasis, one case each of ectropion, entropion and burn injury.

The distribution of various lesions is depicted in **Table 1.**

Table 1. Distribution of eyelid lesions

Origin	Benign	Malignant	Total
Epidermal	33	02	35
Adnexal	24	06	30
Mesenchymal	21	0	21
Inflammatory/infectious	36	0	36
Miscellaneous	05	0	05

The graph depicts the sex distribution of different lesions. Overall, a slight female predominance with a male to female ratio of 1:1.18 was observed. Benign epidermal tumors mainly affected 3rd and 4th decades of life, while benign adnexal tumors were most common between 41-60 years of age. Stromal lesions had a wide range of age distribution from 1-83 years. Infectious/inflammatory lesions peaked at 21-40 years.

Of the 33 benign epidermal lesions, nevi were the most common (48.5%, n=16) and affected females predominantly. This was followed by squamous papilloma (36.37%, n=12), which showed a male predominance. There were two cases each of seborrheic keratosis and cutaneous horn, and one case of lichen planus pigmentosus.

Microscopically, intradermal nevus shows clusters of round to spindle cells with small, regular nuclei in the dermis (**Figure 1a**). Compound nevus shows a junctional component along with intradermal clusters. We encountered 13 cases of intradermal nevi and three cases of compound nevi.

The most common benign adnexal tumor was epidermal inclusion cyst (33.33%, n=8) followed by eccrine cyst (16.67%, n=4). The other cystic lesions observed were sebaceous cyst (n=3), cyst of Moll (n=2); and one case each of retention cyst, tenon's cyst, cyst of Zeis, eccrine hidrocystoma and apocrine hidrocystoma. Amongst the sweat gland tumors, there was one case each of chondroid syringoma and nodular hidradenoma.

Benign vascular lesions comprising of seven cases of capillary hemangioma (**Figure 1b**) were the most common stromal lesions. Few cases of pyogenic granuloma, xanthelasma, hamartoma and neurofibroma were also noted. There was one case each of fibrous histiocytoma, xanthogranuloma and scar tissue.

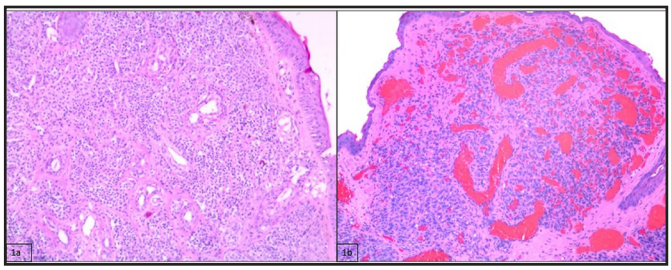

Figure 1. (a) Photomicrograph of intradermal nevus, H&E, 4x. **(b)** Photomicrograph of capillary hemangioma, H&E, 4x.

Figures 2 and 3 show the histologic images of few of the above lesions.

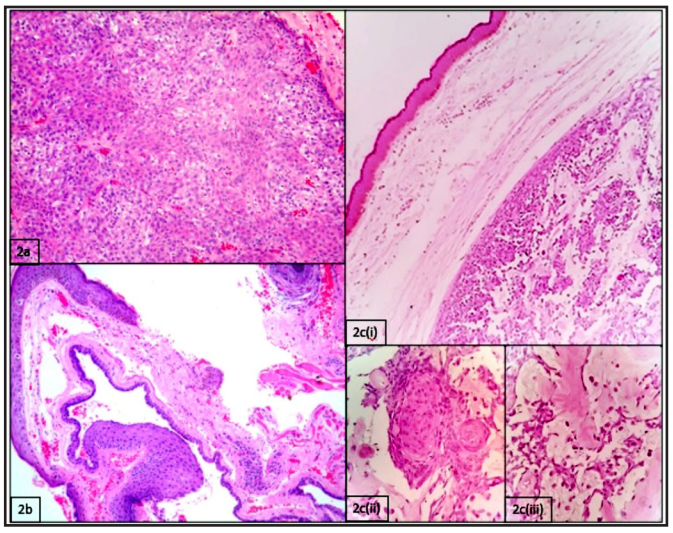

Figure 2. (a) Photomicrograph of nodular hidradenoma showing cells with clear to eosinophilic cytoplasm, H&E, 4x. **(b)** Photomicrograph of apocrine hidrocystoma, H& E, 4x. **(c(i))** Photomicrograph of chondroid syringoma, H&E, 4x. **(c(ii))** Photomicrograph of chondroid syringoma showing focal squamous differentiation H&E, 40x **(c(iii))** Photomicrograph of chondroid syringoma showing chondromyxoid matrix, H&E, 40x.

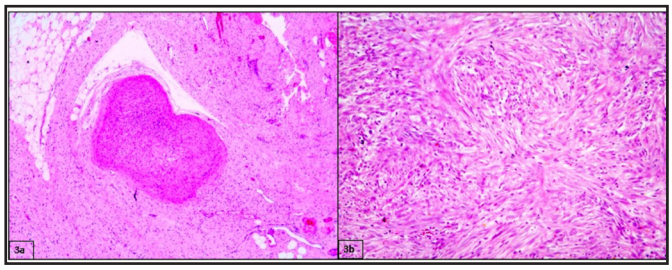

Figure 3. (a) Photomicrograph of plexiform neurofibroma, H&E, 4x. **(b)** Photomicrograph of fibrous histiocytoma, H&E, 4x.

We came across eight malignant eyelid tumors, six of which were sebaceous gland carcinoma (**Figure 4**). There was one case each of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). SGC involved only females above 40 years of age with predilection for right eyelid. SCC of the right eyelid as a contiguous spread of conjunctival ocular surface squamous neoplasia was seen in an 80 year old male. Specimen from right eyelid of a 65 year old female showed BCC with sebaceous differentiation, a rare variant of BCC.

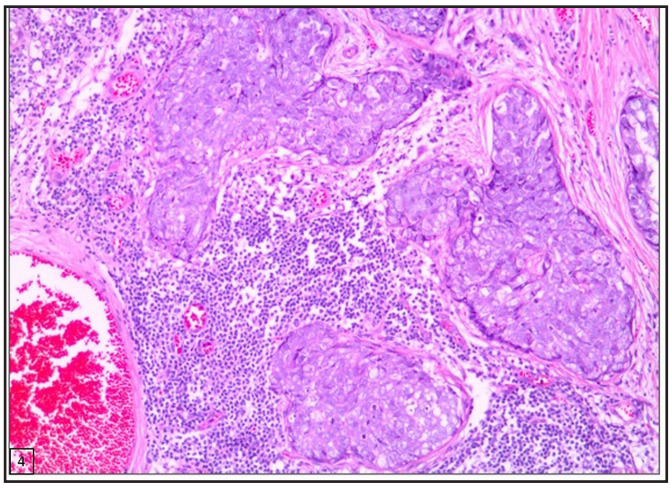

Figure 4. Photomicrograph of sebaceous carcinoma, H&E, 40x.

83.33% (n=30) of the lesions in infectious/inflammatory category were chalazia (**Figure 5a**), more common in males and affected individuals aged 21-40 years predominantly. We encountered three cases of molluscum contagiosum (**Figure 5b**), two of which were seen in children and one in a 28 year old male.

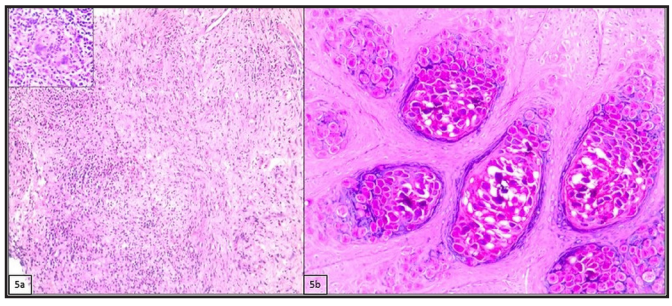

Figure 5. (a) Photomicrograph of chalazion, H&E, 4x. Inset – multinucleate giant cell, H&E, 40x. **(b)** Photomicrograph of molluscum contagiosum, H&E, 4x.

The miscellaneous cases included ectropion, entropion, blepharochalasis and burn injury.

DISCUSSION

Eyelid lesions encompass a variety of inflammatory and neoplastic growths.

Histologically, eyelid tumors can be classified based on the tissue or cell of origin into the following categories: epidermal, adnexal, stromal, secondary, metastatic, inflammatory/infections. Based on their behaviour, they can be benign or malignant (3). Significant majority of the neoplastic growths are benign and constitute 82–98% of all neoplasms (4).

In our study, the mean age at presentation of benign and malignant lesions were 45.9 years and 61.5 years respectively, correlating well with other studies (5-7).

The gender distribution is variable globally. Few studies (5,8,9) noticed a male predominance, but most studies (6,7,10-13) including ours have observed a female predominance. Amongst the 86 neoplastic lesions, 90.7% were benign, in accordance with published literature (3,4).

Melanocytic nevus was the most common benign lesion, similar to few other studies (5,6,9). However, Coroi MC et al. (10) and Gupta P et al. (11) observed squamous papilloma and sebaceous cyst to be more common respectively (**Table 2**).

Table 2. Comparison with other studies

Study	% Benign	% Malignant	% Inflammatory	Most common benign tumor	Most common malignant tumor
Deprez M. et al. (12)	84	16	-	Squamous papilloma	Basal cell carcinoma
Bagheri A. et al. (5)	45	55	-	Nevus	Basal cell carcinoma
Xu XL. et al. (6)	62.1	13.8	24.1	Nevus	Basal cell carcinoma
Asproudis I. et al. (22)	53.1	41.3	5.6	Cyst	Basal cell carcinoma
Coroi MC. et al. (9)	45.8	54.2	-	Squamous papilloma	Basal cell carcinoma
Gupta P. et al. (10)	64	36	-	Sebaceous cyst	Sebaceous carcinoma
Patel M. et al. (8)	56	44	-	Nevus	Sebaceous carcinoma
Present	61.42	6.3	28.34	Nevus	Sebaceous carcinoma

Epidermal inclusion cysts and sebaceous cysts were common cystic lesions with male predominance observed in our study as well as by Bagheri A et al. (5). The epithelial cells lining the sebaceous cyst possess no clearly visible intercellular bridges with amorphous eosinophilic material in the cavity, while in epidermal inclusion cyst, the cells are stratified squamous epithelium with loose laminated keratin in the lumen (1).

Benign tumours originating from skin appendages of the eyelid are rare and frequently have apocrine or eccrine differentiation (14), most common being hidrocystomas (1). We came across twenty four benign adnexal lesions. Very few other studies on eyelid neoplasms in our country have reported these (9).

Review of eyelid tumors by Jacob Pe'er (3) states capillary hemangioma and pyogenic granuloma to be the most common vascular and acquired vascular lesions of the eyelid respectively. A similar observation was made by us.

Chalazion is a chronic, localized swelling of the eyelid typically affecting the meibomian glands or glands of Zeis. In a review by Deprez et al. (15) , chalazia represented nearly half of all eyelid lesions in Switzerland. In ours as well as a retrospective study in Saudi population (13), they represented about one fourth of all the lesions.

The global distribution of eyelid malignancies is varied. It is reported that around 90% of the malignant eyelid tumors are basal cell carcinomas, while sebaceous gland and squamous cell carcinomas are uncommon. (16-18). However, studies from Asian countries report a higher incidence of SGC. (3,12,17). There is wide racial and probable geographical variation reported in the incidence of the eyelid tumors. (4). A study on sebaceous carcinoma of ocular adnexa (18) proposed that the incidence of SGC is higher in Asian population compared to Caucasians and this could be related to genetics and racial predisposition for SGC in Asians. However, a more recent study by Dasgupta et al. (19) proposed that Asian ancestry is not a risk factor for developing sebaceous carcinoma.

Indian studies (7,9,11) have observed SGC as the most common eyelid malignancy with a female predominance. This is exemplified by our study as well. SGC is generally a disease of elderly patients, more common in women (3). All cases of SGC were females, mean age at presentation being 57.8 years, similar to Kaliki S et al. (7) The results of two hospital based studies in Nagpur (19,20) showed BCC to be most common eyelid malignancy. Many studies in America and Europe have found BCC to be very common (10,15,22,23).

BCC with sebaceous differentiation is a rare variant, histopathologically characterised by nests of pleomorphic basaloid cells invading the dermis with peripheral palisading , retraction clefts at the tumor stroma interface, brisk mitotic activity and sebaceous duct-like structures. Vacuolated cells, with foamy, bubbly cytoplasm and scalloped or starry nuclei, suggestive of sebocytes (sebaceous differentiation) are scattered within the nests. These vacuolated cells are immunohistochemically positive for epithelial membrane antigen (EMA) (24,25). In contrast, sebaceoma shows monomorphic basaloid cells, minimal or absent mitotic activity and lack of peripheral palisading and retraction clefts. Sebaceous carcinoma also shows absence of peripheral palisading and retraction clefts (25,26).

Ectropion and entropion are structural abnormalities that can be congenital or senile. An accentuation of the aging changes may result in an ectropion (turning-out) or an entropion (turning-in) of the lower lid. Histologically, both ectropion and entropion show chronic non granulomatous inflammation and cicatrisation of the skin and conjunctiva (1). We encountered two such cases.

CONCLUSION

The eyelid is made up of different types of tissues, each of which can be pathologically affected. Most of the lesions are benign. The distribution of this wide spectrum of lesions shows racial and geographic variation. Data from published literature in our country show variable incidence of different types of eyelid tumors, thereby emphasising the need for further studies to determine the geographic pattern. Our study reiterates the geographic variation in the incidence of eyelid tumors, especially sebaceous carcinoma, which was the most frequent eyelid malignancy. Histopathologic examination enables accurate diagnosis, thereby enhancing patient care.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kempegowda Institute of Medical Sciences, Institutional Ethics Committee (Permission granted: 06.12.2016, Decision no: KIMS/IEC/DUPLICATE01/M/2020).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Yanoff M, Sassani JW. Ocular Pathology. 7th ed. Philadelphia: Elsevier Saunders; 2015.
2. Folberg R. Tumors of the eye and ocular adnexa. In: Diagnostic histopathology of tumors. Fletcher CDM. 4th ed. Philadelphia: Elsevier Saunders; 2013: 2086-116.
3. Peĕer J. Pathology of eyelid tumors. Indian J Ophthalmol 2016; 64: 177-90.
4. Singh U, Kolavali RR. Overview of eyelid tumors. In: Surgical ophthalmic oncology. Chaugule SS, Honavar SG, Finger PT (eds). Switzerland: Springer; 2019: 3-10.
5. Bagheri A, Tavakoli M, Kanaani A, et al. Eyelid masses: a 10-year survey from a tertiary eye hospital in Tehran. Middle East Afr J Ophthalmol 2013; 20: 187-92.
6. Xu XL, Li B, Sun XL, et al. Eyelid neoplasms in the Beijing Tongren Eye Centre between 1997 and 2006. Ophthalmic Surg Lasers Imaging 2008; 39: 367-72.
7. Kaliki S, Bothra N, Bejjanki KM, et al. Malignant eyelid tumors in India: a study of 536 Asian Indian patients. Ocul Oncol Pathol 2019; 5: 210-19. doi:10.1159/000491549
8. Lee SB, Eong KGA, Saw SM, Chan TK, Lee HP. Eye cancer incidence in Singapore. Br J Ophthalmol 2000; 84: 767–70
9. Patel M, Chavda BH, Shah Y, Bhavsar M. Study of incidence, occurrence, origin, and histological types of eyelid tumors at Tertiary Care Hospital in Ahmedabad. Int J Sci Stud 2019; 6: 16-9.
10. Coroi MC, Roşca E, Muţiu G, Coroi T, Bonta M. Eyelid tumors: histopathological and clinical study performed in County Hospital of Oradea between 2000-2007. Rom J Morphol Embryol 2010; 51: 111-5.
11. Gupta P, Gupta RC, Khan L. Profile of eyelid malignancy in a Tertiary Health Care Center in North India. J Can Res Ther 2017; 13: 484-6.
12. Wang JK, Liao SL, Jou JR, et al. Malignant eyelid tumors in Taiwan. Eye 2003; 17: 216-20.
13. Al-Faky YH. Epidemiology of benign eyelid lesions in patients presenting to a teaching hospital. Saudi J Ophthalmol 2012; 26: 211-6.
14. Ozdal PC, Callejo SA, Codère F, Burnier MN Jr. Benign ocular adnexal tumours of apocrine, eccrine or hair follicle origin. Can J Ophthalmol. 2003; 38: 357-63.
15. Deprez M, Uffer S. Clinicopathological features of eyelid skin tumors. A retrospective study of 5504 cases and review of literature. Am J Dermatopathol 2009; 31: 256-62.
16. Al-Buloushi A, Filho JP, Cassie A, Arthurs B, Burnier MN Jr. Basal cell carcinoma of the eyelid in children: a report of three cases. Eye 2005; 19: 1313-4.
17. Shields JA, Demirci H, Marr BP, Eagle RC Jr, Shields CL. Sebaceous carcinoma of the eyelids: Personal experience with 60 cases. Ophthalmology 2004; 111: 2151-7.
18. Ni C, Searl SS, Kuo PK, Chu FR, Chong CS, Albert DM. Sebaceous cell carcinomas of the ocular adnexa. Int Ophthalmol Clin 1982; 22: 23-61.
19. Dasgupta T, Wilson LD, Yu JB. A retrospective review of 1349 cases of sebaceous carcinoma. Cancer 2009; 115: 158-65.
20. Kale SM, Patil SB, Khare N, Math M, Jain A, Jaiswal S. Clinicopathological analysis of eyelid malignancies-a review of 85 cases. Indian J Plast Surg 2012; 45: 22-8.
21. Jahagirdar SS, Thakre TP, Kale SM, Kulkarni H, Mamtani M. A clinicopathological study of eyelid malignancies from central India. Indian J Ophthalmol 2007; 55: 109-12.
22. Paul S, Vo DT, Sikliss RZ. Malignant and benign eyelid lesions in San Francisco: Study of a diverse urban population. Am. J. Clin Med 2011; 8: 40-6.
23. Asproudis I, Sotiropoulos G, Gartzios C, et al. Eyelid Tumors at the University Eye Clinic of Ioannina, Greece: A 30-year Retrospective Study. Middle East Afr J Ophthalmol 2015; 22: 230-2.
24. Misago N, Suse T, Uemura T, Narisawa Y. Basal cell carcinoma with sebaceous differentiation. Am J Dermatopathol 2004; 26: 298-303.
25. Steffen CH, Ackerman AB. Basal-cell carcinoma with sebaceous differentiation. In: Steffen CH, Ackerman AB, editors. Neoplasms with Sebaceous Differentiation. Philadelphia, PA: Lea&Febiger; 1994. pp 577-96.
26. Steffen CH, Ackerman AB. Sebaceous carcinoma. In: Steffen CH, Ackerman AB, editors. Neoplasms with sebaceous differentiation. Philadelphia, PA: Lea&Febiger; 1994. pp 487–74.

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Clinical features and laboratory values associated with disease severity in Covid-19 patients: a single center experience

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ABSTRACT

Background: To date, several studies were published about clinical features and laboratory values associated with disease severity in Covid-19 patients. We aimed to show the relationship between disease severity and clinical and laboratory characteristics of the patients as a single center experience.

Material and Method: Clinical features and laboratory data of fifty patients diagnosed with Covid-19 by PCR was evaluated at diagnosis. These patients divided into 2 groups as early and advanced disease. Clinical features and laboratory data were compared in terms of severity of disease.

Results: In all patients, the most common accompanying disease was coronary artery disease. Cough and headache were the most common complaints. Laboratory values showed low lymphocyte count and high CRP levels in all patients. Twenty four patients in early stage and 26 patients in advanced stage were compared in terms of clinical features and laboratory values. In advanced stage, it was observed that body weight, number of comorbid diseases, age, CRP, procalcitonin, BUN, GGT, fibrinogen, D-dimer and ferritin levels of patients were higher whereas height, serum total protein, albumin and potassium levels were lower when compered with early stage patients ($p<0.05$).

Conclusions: Our data showed that older age, having cough, increased number of comorbid diseases, CRP, BUN, GGT, fibrinogen, D-dimer and ferritin and decresed serum total protein, albumin, potassium levels at the time of diagnosis in Covid-19 patients were associated with advanced stage disease.

Keywords: Covid-19, disease severity

INTRODUCTION

Coronaviruses (CoV) are a large family of viruses showing wide clinical variation from common gribal infection to more serious diseases such as the Middle East Respiratory Syndrome (MERS-CoV) and severe Acute Respiratory Syndrome (SARS-CoV). Since December 8, 2019, several cases of pneumonia of unknown etiology have been reported in Wuhan, a city within the Hubei province of China. The disease and the virus that causes it have been named as Covid-19 and SARS-COV-2, respectively and ultimately it was declared as a pandemic disease by WHO on March 11, 2020 (1-3). Most patients eventually made a recovery after careful treatment, but, some developed more severe and even critical illness (4,5). Although early diagnosis and timely treatment of critical cases is very crucial, factors related to disease severity are still unclear.

To date, the severity of the disease has been shown to be related to many clinical futures and laboratory parameters, such as age, presence of co-morbidities, (like diabetes, obesity, heart disease), elevated blood urea nitrogen (BUN), creatinine, procalcitonin, lactate dehydrogenase, D-dimer, C-reactive protein (CRP), neutrophil, lymhocyte counts and pro-inflammatory

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cytokines, such as interleukin-6, respectively (6-8). So, we aimed to show correlation between clinical and laboratory data and the severity of Covid-19 infection in adults as a single center experience.

MATERIAL AND METHOD

Patients

The data of Covid-19 patients diagnosed with polymerase chain reaction (PCR), between June 10, 2020 and june 30, 2020 were analyzed retrospectively.

Fifty Covid-19 patients were included in this study. Early and advenced stage patients included to this study were compared in terms of their age, gender, body surface area, symptoms (for instance fever, cough, sputum, sore throat, diarrhea, headache), leukocytes, neutrophils, hemoglobin, hematocrit, lymphocytes, eosinophils, monocytes, platelets, CRP, BUN, creatinine, total protein, albumin, procalcitonin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), sodium, potassium, International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT), fibrinogen, D-dimer, ferritin, hospitalization time and mortality rates.

Laboratory Analysis

Real-time reverse transcriptase-polymerase chain reaction (PCR) tests for SARS-CoV-2 RNA were performed using nasopharyngeal swabs. Total nucleic acid extraction of nasopharyngeal swabs of viral isolates was performed using a biospeedy and coyote extraction system (Bioeksen ltd and Coyote Bioscience ltd). Real-time PCR (RT-PCR) assays for SARS-CoV-2 RNA detection were performed using Biospeedy Covid-19 RT-qPCR Detection Kit (Bioeksen, Istanbul, Turkey).

Disease Severity

Patients were divided into 4 stage according to their clinical status. Stage 1; asymptomatic (without any symptoms), stage 2; symptomatic without lung involvement, stage 3; symptomatic with lung involvement, stage 4; acute respiratory distress syndrome, intubation, multiorgan failure (9,10). Stage 1, 2 patients were accepted as early stage and 3,4 patients were accepted as advanced stage patients.

Statistical Analysis

Data analysis was performed using IBM SPSS v26 software. Descriptive statistics were used to summarize data. Variables assessed for normal distribution with the Kolmogorov Smirnov test. Categorical data were presented as number-percentages, and numerical data were presented as median, minimum, and maximum. Differences between categorical variables were analyzed with the Chi-Square test, and numeric variables were compared with the Mann-Whitney U test. A two-sided p-value ≤0.05 was considered statistically significant.

The study was approved by the research ethics committee (date/reference number: 30-06-2020/892). All analyses were performed in accordance with the principles of the Declaration of Helsinki.

RESULT

Fifty patients were included in the study. When the comorbid diseases of the patients were evaluated, most common accompanying disease was coronary artery disease and second was hypertension. Cough and headache were the most common complaints in hospital admissions. Laboratory values showed low lymphocyte count and high CRP levels (**Table 1**).

Twenty four patients in early stage and 26 patients in advanced stage were compared in terms of clinical features and laboratory values (**Table 2**). In advanced stage, it was observed that body weight, number of comorbid diseases, age, CRP, procalcitonin, BUN, GGT, fibrinogen, D-dimer and ferritin levels of patients were higher whereas height, serum total protein, albumin and potassium levels were lower when compered with early stage patients ($p<0.05$).

DISCUSSION

In our study clinical and laboratory features evaluated in Covid-19 patients were compatible with the literature. Rodriguez-Morales et al. (6) performed a systematic literature review with meta-analysis, using three databases to assess clinical, laboratory, imaging features, and outcomes of Covid-19 confirmed cases. They showed that fever (88.7%), cough (57.6%) and dyspnea (45.6%) were the most prevalent manifestations. Cough and headache were the most common symptoms in our study. Three patients included in our trial had dyspnea. They reported that the mean age of patients across 18 studies was 51.97 (46.06–57.89), and male sex was 55.9 (51.6–60.1). Patients presented comorbidities were 36.8% of all cases. Most prevalent comorbid diseases were hypertension (18.6%), cardiovascular disease (14.4%), and diabetes (11.9%). In our study, the median age was 44 years, the ratio of women to men was equal, and the most common comorbid disease was coronary artery disease. Gürbüz P. reported that obesity has been obtained to be an independent and important risk factor for Covid-19 process in nearly all researches (11). Higher BMI but not significantly was evaluated in advanced disease in our study.

Table 1. Clinical features and laboratory values of all the patients

Characteristics and labratory values (normal range)			All patients median (min-max)
Total number of patients			50
Median age			44 (18-88)
Gender (Number/percent)	Female		25 (50)
	Male		25 (50)
Height (centimeter)			162 (153-185)
Weight (kilogram)			70 (50-110)
Body surface area (/m²)			1.77 (1.47-2.1)
Number of comorbid disease	Hypertension (HT)		4
	Coronary artery disease (CAD)		5
	Diabetes mellitus (DM)		1
	Asthma/chronic obstructive pulmonary disease (COPD)		2
	DM+HT		2
	COPD+HT		2
	CAD+HT		3
	Number of all comorbid disease		25
Symptoms (number, (%))	Fever		23 (46)
	Cough		34 (68)
	Sputum		11 (22)
	Throat ache		7 (14)
	Diarrhea		15 (30)
	Headache		34 (68)
Stage (number, (%))	Early	Stage I	1 (2)
		Stage II	23 (46)
	Advanced	Stage III	24 (48)
		Stage IV	2 (4)
Complete blood count (median)	Leukocyte (4-10 x10³/µL)		5.19 (2.83-20.36)
	Neutrophil (2-6 x10³/µL)		3.27 (0.86-18.81)
	Hemoglobin (13.6-17.2 gr/dL)		13.95 (8.5-17.9)
	Hematocrit (39-50%)		40.75 (25.6-52.7)
	Lymphocyte (1.3-3.5 x10³/µL)		1.28 (0.39-2.53)
	Monocyte (0.3-0.9x10³/µL)		0.47 (0-1.16)
	Eosinophil (0-0.5x10³/µL)		0.02 (0-0.6)
	Platelet (150-400x10³/µL)		210 (116-389)
C-reactive protein (0-0.35 mg/dL)			0.56 (0-15.7)
BUN (5.1-16.8 mg/dL)			31 (13-98)
Creatinine (0.57-1.25 mg/dL)			0.75 (0.43-1.81)
Total protein (6.4-8.3 g/dL)			7 (5.62-8.7)
Albumin (3.5-5 gr/dL)			4.2 (2.59-5.04)
Procalcitonin (0-0.5 ng/mL)			0.05 (0.01-3.51)
AST (5-34 U/L)			27 (11-89)
ALT (0-55 U/L)			21 (7-93)
ALP (40-150U/L)			78 (11-210)
GGT (9-64 U/L)			19 (8-189)
Sodyum (136-145 mmol/L)			138 (126-142)
Potasyum (3.5-5.1 mmol/L)			4.1 (3.4-5.4)
INR (0.8-1.2)			1.2 (0.92-2.80)
APTT (23-35 sn)			24.78 (18.6-58)
Fibrinogen (150-350 mg/dL)			295 (2.48-743)
D-dimer (0-0.55 mg/L)			0.17 (0-3.98)
Ferritin (22-322 ng/mL)			105.5 (7.69-1475)
Lenght of stay in hospital (day)			5 (1-17)
Mortality (number/percent)			2 (4)

Table 2. Comparison of laboratory values and clinical features of early and advanced stage patients

Characteristics and labratory values (normal range)			Early stage median (min-max)	Advanced stage median (min-max)	p
Total number of patients			24	26	-
Median Age (year)			27.5 (18-52)	57.5 (27-88)	<0.001
Gender	Female (number/percent)		10 (41.7)	15 (57.7)	0.396
	Male (number/percent)		14 (58.3)	11 (42.3)	
Height (centimeter)			166 (158-185)	160 (153-180)	0.047
Weight (kilogram)			69.0 (55-82)	80.5 (50-110)	0.035
Body Surface area (/m²)			1.76 (1.56-2.02)	1.87 (1.47-2.1)	0.213
Number of comorbid diseases	Hypertension (HT)		1	3	-
	Coronary artery disease (CAD)		-	5	-
	Diabetes mellitus (DM)		-	1	-
	Asthma/chronic obstructive pulmonary disease (COPD)		1	1	-
	DM+HT		-	2	-
	COPD+HT		1	1	-
	CAD+HT		-	3	-
	Number of all comorbid diseases		3	22	p<0.043
Symptoms (number, (%))	Fever		9 (37.5)	14 (53.8)	0.382
	Cough		10 (41.7)	24 (92.3)	<0.001
	Sputum		2 (8.3)	9 (34.6)	0.057
	Throat ache		6 (25)	1 (3.8)	0.055
	Diarrhea		8 (33.3)	7 (26.9)	0.853
	Headache		16 (66.7)	18 (69.2)	1.000
Stage (number, (%))	Early	Stage I	1 (4.2)	-	-
		Stage II	23 (95.8)	-	-
	Advanced	Stage III	-	24 (92.3)	-
		Stage IV	-	2 (7.7)	-
Complete blood count	Leukocyte (4-10 x10³/µL)		5.54 (3.25-9.09)	5.13 (2.83-20.36)	0.398
	Neutrophil (2-6 x10³/µL)		3.33 (1.63-6.84)	3.26 (0.86-18.81) 0.614	0.614
	Hemoglobin (13.6-17.2 gr/dL)		14.3 (10.5-17.2)	13.65 (8.5-17.9)	0.244
	Hematocrit (39-50%)		41.25 (35.2-52.2)	40.25 (25.6-52.7)	0.541
	Lymphocyte (1.3-3.5 x10³/µL)		1.21 (0.61-2.53)	1.39 (0.39-2.32)	0.778
	Monocyte (0.3-0.9x10³/µL)		0.49 (0.00-1.12)	0.43 (0.32-1.16)	0.122
	Eosinophil (0-0.5x10³/µL)		0.05 (0.00-0.60)	0.01 (0.00-0.21)	0.058
	Platelet (150-400x10³/µL)		221 (152-389)	196 (116-309)	0.062
C-reactive protein (0-035 mg/dL)			0.26 (0.01-1.84)	2.27 (0.00-15.7)	<0.001
BUN (5.1-16.8 mg/dL)			27 (15-38)	36 (13-98)	0.005
Creatinine (0.57-1.25 mg/dL)			0.72 (0.43-1.25)	0.8 (0.55-1.81)	0.083
Total protein (6.4-8.3 g/dL)			7.35 (6.3-8.7)	6.7 (5.62-8.2)	0.033
Albumin (3.5-5 gr/dL)			4.3 (3.8-5.0)	3.8 (2.59-4.7)	<0.001
Procalcitonin (0-0.5 ng/mL)			0.042 (0.02-0.26)	0.063 (0.1-3.51)	0.046
AST (5-34 U/L)			25 (11-73)	28.5 (14-89)	0.052
ALT (0-55 U/L)			21.5 (7-86)	20.5 (9-93)	0.351
ALP (40-150U/L)			81.5 (11-210)	77 (42-120)	0.331
GGT (9-64 U/L)			15.5 (8-189)	27 (10-130)	<0.001
Sodyum (136-145 mmol/L)			138 (134-142)	138 (126-142)	0.747
Potassium (3.5-5.1 mmol/L)			4.18 (3.30-5.08)	3.98 (3.1-5.4)	0.040
INR (0.8-1.2)			1.08 (0.97-1.97)	1.13 (0.92-2.80)	0.524
APTT (23-35 sn)			22.7 (18.6-26.5)	24.05 (20-58)	0.056
Fibrinogen (150-350 mg/dL)			251 (2.5-356)	371 (50.9-743)	<0.001
D-dimer (0-0.55 mg/L)			0.08 (0-0.56)	0.28 (0.05-3.98)	<0.001
Ferritin (22-322 ng/mL)			57 (7.7-268)	169 (33-1475)	0.002
Lenght of stay in hospital (day)			5 (1-17)	10 (1-16)	0.037
Mortality (number,%)			0 (0)	2 (7.7)	0.491

Weiliang Cao et al. (7) compared patients that aged between 21~50, 51~65, over 66 years who were accounted for 44.5%, 35.1%, 18.8%, respectively. Fever (89.8%) and cough (67.2%) were common clinical symptoms. The rate of patients with sore throats (14.1%) was rare. White blood cell counts in the normal range of overall patients, but severe group patients were increased significantly ($p<0.01$). Lymphocytes of overall patients were decreased. ALT and AST levels were in the normal range of overall patients, but were elevated in the severe group. Serum creatinine and BUN levels of all patients were in the normal range. CRP level of all patients were increased markedly, which was significantly higher in severe disease group ($p<0.01$). In our study, patients in advanced stage were found to be statistically older. The most common symptoms were cough and fever,whereas the least common was chest pain. There was no significant difference in both leukocyte and lymphocyte counts between disease stages. Higher serum GGT and BUN levels were noted especially in advanced stage patients. Creatinine levels were increased, but could not reach to statistically significance. CRP level was increased in all patients. It was significantly increased in advanced stage disease compared to early stage. Gao et al. (8) reported that a comparison of the hematological parameters between the mild and severe groups showed significant differences in interleukin-6 (IL-6), D-dimer, glucose, thrombin time, fibrinogen, and CRP ($p<0.05$) (8). We could not eveluate interleukin-6 level in our study. In our study, D-Dimer, fibrinogen and CRP levels were statistically higher in advanced stage disease. Moreover, potassium levels, which was not evaluated in these two studies, was significantly lower disease and the length of hospital stay was longer in advanced stage in our study. Although no mortality was observed in early stage patients, 2 patients died due to infection in advanced stage group. The present study has several limitations. The study was retrospective and had a small sample size. For this reason, we did not associate clinical data with disease prognosis.

CONCLUSION

Our data showed that older age, having cough, increased number of comorbid diseases, CRP, BUN, GGT, fibrinogen, D-dimer and ferritin and decresed serum total protein, albumin, potassium levels at the time of diagnosis in Covid-19 patients were associated with advanced stage disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the research ethics committee (date/reference number: 30-06-2020/892).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020; 382: 1199-207. doi:10.1056/NEJMoa2001316.
2. Pal M, Berhanu G, Desalegn C, Kandi V. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2): an update. Cureus 2020; 12: e7423. doi:10.7759/cureus.7423.
3. World Health Organization Press Conference. The World Health Organization (WHO) has officially named the disease caused by the novel Coronavirus as Covid-19. Available online: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (accessed on 18 May 2020).
4. Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020; 395: 514-23. doi:10.1016/S0140-6736(20)30154-9.
5. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020; 382: 727-33. doi:10.1056/NEJMoa2001017.
6. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of Covid-19: A systematic review and meta-analysis. Travel Med Infect Dis 2020; 34: 101623. doi:10.1016/j.tmaid.2020.101623.
7. Weiliang Cao, Li Shi, Lin Chen, Xuemei Xu, Zirong Wu. Clinical features and laboratory inspection of novel coronavirus pneumonia (Covid-19) in Xiangyang, Hubei. medRxiv 2020.02.23.20026963
8. Gao Y, Li T, Han M, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe Covid-19. J Med Virol 2020; 92: 791-6. doi:10.1002/jmv.25770
9. Lauer SA, Grantz KH, Bi Q, et al. The Incubation Period of Coronavirus Disease 2019 (Covid-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med 2020; 172: 577-82. doi:10.7326/M20-0504
10. Ferguson NM, Laydon D, Nedjati-Gilani G, et al. Impact of non-pharmaceutical interventions (NPIs) to reduce Covid-19 mortality and healthcare demand. Imperial College Covid-19 Response Team 2020; 10: 77482.
11. Gürbüz P. Covid-19 and obesity: a systematic review. İnönü Üniversitesi Sağlık Hizmetleri Meslek Yüksekokulu Derg 2020; 8: 506-14. doi: 10.33715/inonusaglik.735600.

Original Article

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Evaluation of ferric carboxymaltose treatment efficacy in women with postpartum iron deficiency anemia

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ABSTRACT

Aim: Most women in the Turkish population have iron deficiency anemia. Particularly among the pregnant women, its rate increases. In this study, we aimed to evaluate the efficacy of intravenous ferric carboxymaltose administration in anemic women in the postpartum period.

Material and Method: The hemoglobin (Hb) and hematocrit (Htc) values of 64 patients who received intravenous ferric carboxymaltose treatment between January 1, 2020 and July 1, 2020 in Mardin State Hospital, Gynecology and Obstetrics Clinic were retrospectively evaluated. Patients who received intravenous iron carboxymaltose treatment for postpartum iron deficiency anemia were compared after treatment. The length of stay in the hospital and whether the patient priorly received an erythrocyte suspension were evaluated.

Results: Patients who received intravenous (IV) ferric carboxymaltose mostly due to anemia after cesarean section and normal delivery (NSD) were included in the study. Pregnancy week and hospitalization duration means were significantly higher in the C/S group ($p<0.05$). A statistically significant increase was observed in Hb and Htc values after intravenous iron treatment administered after cesarean delivery. ($p<0.05$). The birth rate was significantly higher in the young and normal delivery groups ($p<0.01$). A significant increase in control hemoglobin values was observed after 10 days in patients who received intravenous iron therapy.

Conclusion: During the postpartum period, IV ferric carboxymaltose use for moderate anemia is safe and efficient.

Keywords: Anemia, ferric carboxymaltose, hemoglobin, iron deficiency anemia, intravenous iron

INTRODUCTION

Iron deficiency anemia is an important public health problem. It develops in cases where the need for elemental iron required for hemoglobin synthesis increases, such as during pregnancy or the post-operative period, in other words, when negative iron balance occurs in the body. The World Health Organization has stated that female individuals with hemoglobin values below 12 g/dl have iron deficiency anemia (1). Although the rate is higher in developing countries, considering the general population, the rate of iron deficiency is approximately 25% (2). The World Health Organization states that the rate of iron deficiency anemia during pregnancy increases even more. Iron deficiency anemia should be corrected after delivery in women, for it is responsible for 20-40% of maternal deaths after cesarean section or normal spontaneous vaginal delivery (3).

If iron deficiency is detected in a woman, it should be treated. It is essential to treat this condition quickly and safely. Oral iron should be preferred to intravenous iron treatment, except in special cases, because it is safe and cheap. In oral iron treatment, side effects such as nausea, vomiting, peptic complaints, gastroesophageal regurgitation, diarrhea, constipation, stool discoloration affect the treatment and may lead to discontinuation (4,5). Accompanying symptoms such as tachycardia, dizziness and headache in severe anemias require urgent treatment. Intravenous iron therapy may be appropriate in patients who cannot tolerate oral therapy or need urgent treatment (6,7).

In this study, we aimed to determine the effectiveness of the treatment with intravenous ferric carboxymaltose and control hemogram and hematocrit values after 10 days in patients with hemogram values below 9 g/ml

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after cesarean and normal delivery. Patients were also asked to evaluate their hospital stay. Practical and current treatment approaches for anemia, which must be treated after birth, were evaluated.

MATERIAL AND METHOD

Ethics committee approval was received from Mardin Provincial Health Directorate on 27.08.2020 with the permission number 806.02.02-E.1333. All procedures were performed adhered to the ethical rules and the Helsinki Declaration of Principles.

Intravenous ferric carboxymaltose was administered in Mardin State Hospital, Gynecology and Obstetrics Clinic between 1 January 2020 and 15 July 2020 to patients with hemoglobin values below 9 mg/dL, who had given birth with caesarian section or via spontaneous vaginal route, who were incidentally determined to have anemia during routine outpatient visits. Those who had chronic anemia before, those who received intravenous iron treatment during pregnancy, those with anemia not caused by iron deficiency, those with severe liver disease, those with known allergy to any substance contained in the intravenous ferric carboxymaltose preparation were not included in the study. Control hemogram and hematocrit values obtained after 10 days were compared with pre-treatment values. Oral iron therapy was continued during these 10 days. A total of 64 anemic women with postpartum period were included in this retrospective cohort study. The gestational status of the patients, the weeks of gestation of the pregnant women, whether they underwent an operation, whether blood was priorly transfused, control hemogram and hematocrit values before and after treatment, and duration of hospital stay were analyzed. Each patient was given 1000 mg intravenous ferric carboxymaltose in 250 ml of 0.9% isotonic for 15 minutes. None of the patients experienced allergies, rash, itching, anaphylaxis or similar side effects.

Statistical Methods

Scale parameters were described with mean and standard deviations, whereas nominal parameters were described with frequency analysis. Kolmogorov Smirnov Test was used for normality distribution test of scale parameters. Independent samples T-Test was used for differences between normally distributed parameters, and Mann Whitney U test was used to evaluate differences between non-normally distributed parameters. Chi Square Test was used for comparison of categorical parameters. Spearman's rho correlation was used for relational analysis. SPSS 17.0 for Windows was used, and analysis was performed with 95% confidence interval and an alpha level of 0.05.

RESULTS

Some baseline characteristics of patients are presented in the **Table 1.**

Table 1. Some baseline characteristics of patient groups

Parameters	C/S (n=42)	NSD (n=22)	p
Age, mean±SD	29.24±6.48	28.73±5.55	0.754[a]
Pregnancy week, mean±SD	36.40±3.76	31.68±6.06	0.001[b]
ES, n (%)	9 (21.4)	3 (13.6)	0.439[c]
ES Amount, mean±SD	3.00±1.12	1.67±0.58	0.082[a]
Hospitalization duration, mean±SD, (day)	2.12±1.04	1.14±0.35	0.000[b]

a. Independent Samples T-Test, b. Mann Whitney U Test, c. Chi-Square Test, SD: Standard Deviation.

Pregnancy week and hospitalization duration means were significantly higher in the C/S group ($p<0.05$). Age, ES transfusion and its amount were similar between patient groups ($p>0.05$).

Initial and final Hb and Htc values and difference analysis results between patient groups are presented in **Table 2**.

Table 2. Initial and final Hb and HTC values and difference analysis results between patient groups

Parameters, mean±SD	C/S (n=42)	NSD (n=22)	p[a]
Initial Hb	7.93±0.58	8.00±0.51	0.598
Initial HTC	24.95±2.06	25.50±1.82	0.301
Final Hb	10.91±0.96	10.51±0.78	0.093
Final HTC	35.26±2.85	33.31±2.57	0.009

a. Independent Samples T-Test, SD: Standard Deviation.

Final Htc value was significantly higher in the C/S group ($p<0.05$). Initial Hb, Htc and final Hb differences between groups were insignificant ($p>0.05$). Final Htc distribution of patient groups is shown in the **Figure 1**.

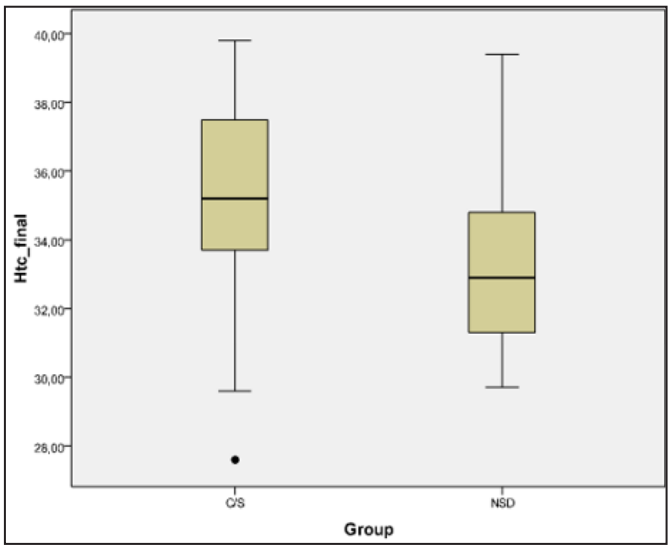

Figure 1. Final HTC distribution of patient groups

According to **Figure 1**, both mean and range of final Htc of C/S patients were higher those of NSD patients.

Spearman's rho correlation analysis results of baseline Hb and Htc values are presented in **Table 3**.

Table 3. Spearman's rho correlation analysis results between baseline characteristics with Hb and HTC

Parameters	C/S (n=42)		NSD (n=22)	
	Final Hb	Final HTC	Final Hb	Final HTC
Age	0.029	0.064	-0.555**	-0.331
Pregnancy week	0.191	0.167	0.188	0.177
ES	0.283	0.141	-0.157	-0.178
ES Amount	0.291	0.158	0.500	0.866
Hospitalization duration	-0.033	-0.086	0.178	0.230

**p<0.01

Only final Hb and age relation in NSD group was statistically and negatively significant (p<0.01). On the other hand, this correlation was insignificant in the C/S group (p>0.05). Pregnancy week, erythrocyte suspension (ES) transfusion, its amount and hospitalization duration were not correlated with final Hb and Htc in both groups (p>0.05).

DISCUSSION

Iron deficiency anemia is confirmed by a measurable hemoglobin concentration of less than 12 g/dl for women or a ferritin level of less than 30 ml/ng (8). Erythrocytic changes such as hypochromia, microcytosis, anisocytosis and poikilocytosis can be seen in the examination of the blood sample with light microscopy. As a result of these changes, a series of symptoms such as fatigue, shortness of breath, vertigo, syncope, PICA, palpitations, angina, headache, cognitive dysfunction, and restless leg syndrome may occur due to the inadequate supply of tissues (8). It is known that intravenous iron use is superior to oral use in pregnancy, chronic renal failure, and inflammatory bowel disease (9-14). Oral iron therapy is also associated with frequent gastrointestinal side effects, and this is one of the most important reasons for non-compliance (15).

Ferric carboxymaltose was approved by the European Medicines Agency in 2007 for use in iron deficiency anemia (16). In July 2013, intravenous ferric carboxymaltose was approved by the United States Food and Drug Administration (FDA) for the treatment of iron deficiency anemia in adult patients with inadequate response to oral iron therapy.

During the Covid-19 pandemic, the operation room at Mardin State Hospital was reserved only for emergency cases. While cesarean section was performed in 42 of the patients included in our study, 22 patients had a normal delivery. Before the administration of intravenous ferric carboxymaltose, 12 units of erythrocyte suspension was required: Following caesarian section in 42 patients, following had a hysterectomy in 1 patient.

In this study, when Hb and Htc levels were examined before and after intravenous ferric carboxymaltose administration, a statistically significant increase was observed in both variables after cesarean operations (p<0.05). An increase was observed in mean final Hb (10.91±0.96 mg/dL) (3 mg/dL-fold) and final Htc values (%35.26±2.85). During the pandemic, there were difficulties in obtaining erythrocyte suspension. All patients were prescribed oral iron treatment to be used for 1 month following discharge. Although the number of patients participating in the current study population is small, our study may be a modest guiding point for the treatment process of severe anemia pre- and postoperatively during the pandemic.

Richard F. Pollock et al. found a significant improvement in the initial Hb value after treatment, as in our study (8). They recommended intravenous iron treatment without concern in patients who cannot tolerate oral iron therapy (8). Although medical and economic considerations regarding the administration of erythrocyte suspension (RBC) advocate restricting its use, it is widely used for the correction of anemia (17). It has been shown that RBC transfusion significantly increases morbidity and mortality, and negatively affects the remaining survival after treatment in colorectal cancer patients (18). Infection and autoimmune events can also occur after RBC transfusion. Moreover, RBC transfusion increases the risk of nosocomial infections and is highly associated with increased mortality in hospitalized patients (19). In anemia, erythrocyte increase will be attained within a brief period with iron infusion only, and treatment success will be achieved.

The cost-effectiveness of intravenous iron therapy was evaluated especially in UK publications. In a 5-center study conducted on surgical patients in Europe and the United States, RBC transfusion was not found to be cost-effective (20). In a study conducted in Sweden, it was reported that the side effects developing after RBC transfusion and the cost resulting from the increase in the hospitalization of the patients constituted 35% of the total treatment cost (6). In our study, after cesarean operation, the average length of stay after intravenous iron treatment was 2.12±1.04 day, and significantly higher than the NDS group. The Ministry of Health of The Republic of Turkey published a guideline, recommending at least 48 hours of hospital stay following caesarian delivery.

We determined that as gestational week increased, Hb value decreased significantly, due to the physiological increase in maternal intravascular volume. In addition, iron uptake in the placenta is high, regardless of the Hb level, the iron absorbed by the fetus from the circulation continues unabated. Therefore, as the gestational week progresses, the Hb values decrease.

It has been shown that intravenously administered iron increases Hb levels more effectively than oral iron (21). Some studies offer intravenous carboxymaltose as an additional treatment option in the treatment of iron deficiency anemia (22). Serious acute hypersensitivity reactions to intravenous iron formulations are rare but may occur, and most allergic reactions seen in the past were due to the high-molecular iron dextran complex (23). Ferric carboxymaltose is administered in a single visit. Considering the patient and length of stay, it promises a shorter treatment period for patients diagnosed with anemia (24). However, anaphylaxis, allergy and not being used in the first trimester of pregnancy are the limitations of this treatment.

This current study has some limitations. First of all, our study population is relatively small. Moreover, this study was a single center, retrospective research.

CONCLUSION

As disease awareness of iron deficiency anemia continues to develop over the next few years and the benefit-risk ratio encouraging the patients from different populations to comply is considered, treatment options for iron supplementation will be open to evolution and change. Future modeling efforts may further clarify the frequency and consequences of events such as side effects and allergies, in addition to the initial administration costs of iron formulations.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was received from Mardin Provincial Health Directorate on 27.08.2020 with the permission number 806.02.02-E.1333.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Moore RA, Gaskell H, Rose P, Allan J. Meta-analysis of efficacy and safety of intravenous ferric carboxymaltose (Ferinject) from clinical trial reports and published trial data. BMC Blood Disord 2011; 11: 4.
2. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011 (WHO/NMH/NHD/MNM/11.1) (http://www.who.int/vmnis/indicators/haemoglobin. pdf, accessed [25.09.2020]).
3. Prakash S, Yadav K. Maternal anemia in pregnancy: an overview. IJPPR 2015; 4: 164-79.
4. Johnson-Wimbley TD, Graham DY. Diagnosis and management of iron deficiency anemia in the 21st century. Therap Adv Gastroenterol 2011; 4: 177-84.
5. Percy L, Mansour D, Fraser I. Iron deficiency and iron deficiency anaemia in women. Best Pract Res Clin Obstet Gynaecol 2017; 40: 55-67.
6. Glenngard AH, Persson U, Soderman C. Costs associated with blood transfusions in Sweden-the societal cost of autologous, allogeneic and perioperative RBC transfusion. Transfus Med 2005; 15: 295–306.
7. Low MS, Grigoriadis G. Iron deficiency and new insights into therapy. Med J Aust 2017; 207: 81-7.
8. Pollock RF, Muduma G. A patient-level cost-effectiveness analysis of iron isomaltoside versus ferric carboxymaltose for the treatment of iron deficiency anemia in the United Kingdom. J Med Econ 2020; 23: 751-9. doi:10.1080/13696998.2020.1745535.
9. Avni T, Bieber A, Steinmetz T, Leibovici L, Gafter-Gvili A. Treatment of anemia in inflammatory bowel disease--systematic review and meta-analysis. PLoS One 2013; 8: e75540.
10. Bonovas S, Fiorino G, Allocca M, et al. Intravenous Versus Oral Iron for the Treatment of Anemia in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Medicine (Baltimore) 2016; 95: e2308.
11. Avni T, Leibovici L, Gafter-Gvili A. Iron supplementation for the treatment of chronic heart failure and iron deficiency: systematic review and meta-analysis. Eur J Heart Fail 2012; 14: 423–9.
12. O'Lone EL, Hodson EM, Nistor I, Bolignano D, Webster AC, Craig JC. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. Cochrane Database Syst Rev 2019; 2: CD007857.
13. Susantitaphong P, Alqahtani F, Jaber BL. Efficacy and safety of intravenous iron therapy for functional iron deficiency anemia in hemodialysis patients: a meta-analysis. Am J Nephrol 2014; 39: 130–41.
14. Reveiz L, Gyte GM, Cuervo LG, Casasbuenas A. Treatments for iron-deficiency anaemia in pregnancy. Cochrane Database Syst Rev 2011; 10: CD003094.
15. Lindgren S, Wikman O, Befrits R, et al. Intravenous iron sucrose is superior to oral iron sulphate for correcting anaemia and restoring iron stores in IBD patients: A randomized, controlled, evaluator-blind, multicentre study. Scand J Gastroenterol 2009; 44: 838–45.
16. Linda M Mundy, Stefan Wohlfeil ; A comment on the comparative safety of intravenous ferumoxytol versus ferric carboxymaltose in iron deficiency anemia ; Am J Hematol 2018; 93: 231-2.
17. Hreinsson JP, Jonasson JG, Bjornsson ES. Bleeding-related symptoms in colorectal cancer: a 4-year nationwide population-based study. Aliment Pharmacol Ther 2013; 39: 77–84.
18. Auerbach M, Macdougall IC. Safety of intravenous iron formulations: facts and folklore. Blood Transfus 2014; 12: 296–300.
19. Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. Crit Care Med 2008; 36: 2667–74.

20. Shander A, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn DR. Activity-based costs of blood transfusions in surgical patients at four hospitals. Transfusion 2010; 50: 753–65.
21. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl 2012; 2: 280–335.
22. Breymann C, Honegger C, Hösli I, Surbek D. Diagnosis and treatment of iron-deficiency anaemia in pregnancy and postpartum. Arch Gynecol Obstet 2017; 296: 1229-34.
23. Macdougall IC, Vernon K. Complement activation-related pseudoallergy: a fresh look at hypersensitivity reactions to intravenous iron. Am J Nephrol 2017; 45: 60–2.
24. Kant S, Kaur R, Ahamed F, Singh A, Malhotra S, Kumar R. Effectiveness of intravenous ferric carboxymaltose in improving hemoglobin level among postpartum women with moderate-to-severe anemia at a secondary care hospital in Faridabad, Haryana - An interventional study. Indian J Public Health. 2020; 64: 168-72.

Original Article

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Retrospective analysis of urine culture results in our clinic: determination of pathogen types and antibiotic resistance in our region

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ABSTRACT

Aim: Untreated urinary tract infections and increasing resistance to antibiotics are important health problems in pregnant and non-pregnant women. The aim of this study is to determine "*Escherichia coli*" (*E. Coli*) strains and other growing microorganisms isolated from urine samples sent from pregnant and non-pregnant patients in the Gynecology and Obstetrics outpatient clinic in Mardin State Hospital, and evaluate the antimicrobial susceptibility profile.

Material and Method: The results of reproduction in midstream urine samples obtained from pregnant and non-pregnant women who were sent to Mardin State Hospital Microbiology Laboratory with the suspicion of urinary system infection from the Gynecology and Obstetrics Outpatient Clinic between January 1, 2018 and June 17, 2020 were retrospectively evaluated.

Results: The mean age of pregnant patients was significantly lower than that of the non-pregnant group. While *E. Coli* and *Klebsiella* were prominent in the pregnant group, the incidence of *E. Coli* and *Enterococcus spp*. had increased in the non-pregnant group.

Conclusion: Urinary tract infection remains an important public health problem. To prevent the adverse obstetric consequences of urinary tract infection during pregnancy, it is important to investigate local susceptibility of microorganisms, especially common factors such as *E. Coli*, at certain periods.

Keywords: Urinary tract infection, pregnancy, *Escherichia coli*, antibiotic sensitivity, bacteriuria

INTRODUCTION

Symbiotic bacterial cells found in the skin, mucosa, intestine and oral cavity in humans constitute the human microbiota. Microbiota protect tissues from pathogenic microorganisms by increasing mucosal barrier resistance. During pregnancy, changes occur in the female body, especially in the vaginal microbium. Changes in vaginal acidity are also one of the important reasons for the increase in the frequency of urinary tract infections during pregnancy.

All bacterial infections considered, while urinary system infections are the most common, the most frequently isolated microorganism in laboratories is "*Escherichia coli*" (*E. Coli*). Urinary infection occurs when microorganisms move retrogradely towards the bladder through the urethra. *E. Coli*, the most common agent in urinary system infections, is a member of *Enterobactericeae*, and found in the intestinal flora (1,2). Extended spectrum beta-lactamase (ESBL) production is one of the principal resistance mechanisms developed by *Enterobactericeae* members (3). In addition to the typical clinical symptoms, the diagnosis is made by showing the reproduction of the pathogen in urine culture (4). The presence of pyuria, hematuria, or bacteria in the microscopy of the urine is the main data suggesting urinary tract infection. However, the visualization of leukocyte casts suggests pyelonephritis. The presence of abundant squamous cells indicates that the urine sample is contaminated, and the culture result may be misleading.

Urinary tract infection in non-pregnant women is usually a self-limiting condition if there is no secondary disease such as diabetes mellitus, conditions that cause immunosuppression, ureter stone, or renal failure. Urinary

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tract infection in pregnant women can lead to complications with serious morbidity and mortality, such as preterm labor, pyelonephritis, premature rupture of membrane, and chorioamnionitis. Although urinary tract infection during pregnancy is usually asymptomatic, pathogenic microorganisms can grow more conveniently with the decrease of ureter peristalsis due to progesterone, decrease in the bladder capacity with the compression of the uterus on the bladder, and the change of vaginal flora, which is the reason urinary tract infection can rapidly progress to acute pyelonephritis (5). The American College of Obstetricians and Gynecologists (ACOG) reports that pregnant women should be given appropriate treatment for urinary tract infections, or serious maternal and fetal complications may occur (6).

An increasing resistance is observed against antibiotics used in empirical treatment in symptomatic patients (7). The widespread use of antibiotics in our country, the patients' compliance problem and the use of advanced generation antibiotics as the first choice in treatment are the primary causes of resistance development. In the European Association of Urology (EAU) manual, it is stated that if a resistance exceeding 20% is detected against an antibiotic used in urinary tract infection, that drug should not be used in empirical treatment (8).

The aim of this study is to determine *E. Coli* strains and other bacteria isolated from urine samples obtained in the outpatient clinics in our hospital, their antimicrobial susceptibility profile, and investigate their resistance against antibiotics commonly used in empirical treatment in clinical practice.

MATERIAL AND METHOD

A total of 158 samples with growth in midstream urine samples obtained from pregnant and non-pregnant women who were sent to Mardin State Hospital Microbiology Laboratory with the suspicion of urinary tract infection from the Gynecology and Obstetrics Outpatient Clinic between 1 January 2018 and 17 June 2020 were retrospectively investigated. Ethics approval was obtained from Mardin Provincial Directorate of Health's Ethics Committee (Document no: 37201737-806.02.02-1332, Date: 27/08/2020) and the research was carried out in accordance with the Helsinki Declaration, published by the World Medical Association. Urine samples were inoculated on Eosin Methylene Blue (EMB) and 5% sheep blood agars. Microorganisms grown after 24 hours of incubation were conventionally pre-defined. After that Gram staining method was performed. According to Gram staining properties, chemical properties were determined by tests such as catalase, sugar fermentation, citrate use, indole test, urea test, oxidase test, PYR test. After the pre-identification, the automated system VİTEK 2® (Biomerieux, France) was identified. Conventional methods and VITEK 2® (Biomerieux, France) automated bacterial identification system were used for identification of isolated microorganisms. VITEK 2® (Biomerieux, France) automated susceptibility system was used for antibiotic susceptibility tests, which were performed in accordance with the recommendations of CLSI (Clinical and Laboratory Standards Institute) and EUCAST (European Committee on Antimicrobial Susceptibility Testing). CLSI criteria and recommendations were used only for the first six months of 2018. Among the materials available by the current laboratory, in accordance with the CLSI recommendations, MHA and 5% sheep blood agars were used for rare bacteria, and not the MH-F agar, which was recommended by the EUCAST. The CLSI criteria were used for the minimum inhibitory concentration of nitrofurantoin for enterococci other than Enterococcus faecium, as that was not available in the EUCAST.

Based on the studies of Belete et al. (9) (2020), the minimum number of patients for each group was 45, with 95% confidence interval and 1.6448536 effect size.

Statistical Methods

Nominal and ordinal data were described with frequency analysis, and scale parameters were described by mean and standard deviations. Chi-Square Test and Chi-Square Likelihood ratio were used for differences between categorical parameters. Kolmogorov Smirnov test was used for normality of age. Mann Whitney U test was used for age difference, since the distribution was non-nornal. SPSS 17.0 for windows was used with 95% Confidence Interval.

Table 1. Age, gravida, parity and gestational week distribution of patients

	Non-pregnant (n=74; 46.8%)	Pregnant (n=84; 53.2%)	p
Age	41.34±16.46	27.30 ±6.47	0.000a
Gravida	-	2.60 ±1.37	-
Parity	-	1.32±1.16	-
Gestational week	-	13.82±8.97	-

a. Mann Whitney U Test.

RESULTS

Age, gravida, parity and gestational week distribution of patients were given in the **Table 1.**

Seventy-four non-pregnant and 84 pregnant women were subjected to the study. Age mean of non-pregnant group was statistically higher than age mean of pregnant group ($p<0.05$). Gravida mean of pregnant patients was 2.60±1.37, parity mean was 1.32±1.16, and gestational week mean was 13.82±8.97.

Microorganism distribution based on groups was given in the **Table 2.**

Table 2. Microorganism distribution based on groups

	Non-pregnant (n=74; 46.8%)	Pregnant (n=84; 53.2%)	Total (n=158)
E. Coli	44 (59.5)	51 (60.7)	95 (60.1)
Staphylococcus saprophyticus	2 (2.7)	1 (1.2)	3 (1.9)
Staphylococcus epidermidis	2 (2.7)	-	2 (1.3)
Streptococcus agalactiae	4 (5.4)	3 (3.6)	7 (4.4)
Klebsiella pneumoniae	5 (6.8)	11 (13.1)	16 (10.1)
Staphylococcus aureus	4 (5.4)	2 (2.4)	6 (3.8)
Enterococcus sp.	5 (6.8)	1 (1.2)	6 (3.8)
Enterobactericeae Spp.	1 (1.4)	1 (1.2)	2 (1.3)
Coagulase (-) negative staphylococcus	3 (4.1)	4 (4.8)	7 (4.4)
Other	4 (5.4)	10 (11.9)	14 (8.9)
p=0.223>0.05			

In both patient groups, *E. Coli* was the most common species among other microorganisms, followed by *Klebsiella pneumoniae*. *Enterococcus spp*. was higher in the non pregnant group. Difference analysis results showed that differences between patient groups were insignificant (p>0.05). Antibiotic resistances and sensitivity results were given in the **Table 3.**

According to antibiotic resistance and sensitivity analysis results Amikacin, Aztreonam and Rifampisin results were significantly different between patient groups (p<0.05).

DISCUSSION

Urinary tract infections are common among women. Among the entire population, 50% of women suffer from urinary tract infection at least once in their lifetime and 25% tend to recur (10). In addition pregnancy increases the incidence of urinary tract infections. Physiological changes occur in kidney, ureter, bladder and renal pelvis from the eighth week of pregnancy; Bladder capacity increases, minimal dilatation of the renal pelvis occurs and ureteral peristalsis decreases with the effect of increasing progesterone. In the second and third trimester of pregnancy, secondary to the growth of the uterus, a compression effect occurs on the ureter and a physiological stasis is observed in the urinary system (11-12). This provides a basis for the development of infection. Despite the availability of multiple treatment options, urinary tract infections continue to pose a significant financial and social burden. It is extremely important to know and follow

Table 3. Antibiotic resistances and sensitivity results

	Non-pregnant (n=74; 46.8%)			Pregnant (n=84; 53.2%)			p
	LS	S	R	LS	S	R	
Amikacin	-	16 (80.0)	4 (20.0)	2 (9.1)	20 (90.9)	-	0.013[a]
Ampicillin	-	6 (25.0)	18 (75.0)	-	2 (7.7)	24 (92.3)	0.090[a]
Ampicillin/Sulbactam	-	11 (68.8)	5 (31.3)	-	11 (55.0)	9 (45.0)	0.400[b]
Aztreonam	-	1 (50.0)	1 (50.0)	-	2 (100.0)	-	<0.05
Cefazolin	1 (6.7)	8 (53.3)	6 (40.0)	1 (5.3)	12 (63.2)	6 (31.6)	0.846[a]
Cefepime	2 (11.8)	9 (52.9)	6 (35.3)	1 (4.3)	17 (73.9)	5 (21.7)	0.363[a]
Cefotoxin	-	7 (87.5)	1 (12.5)	-	5 (100.0)	-	0.312[a]
Ceftazidime	2 (8.7)	12 (52.2)	9 (39.1)	-	18 (66.7)	9 (33.3)	0.160[a]
Ceftriaxone	2 (12.5)	11 (68.8)	3 (18.8)	-	9 (64.3)	5 (35.7)	0.188[a]
Cefuroxime	-	13 (61.9)	8 (38.1)	-	15 (60.0)	10 (40.0)	0.895[b]
Chloraphenicol	-	-	-	-	-	-	-
Ciprofloxacin	-	17 (65.4)	9 (34.6)	-	13 (86.7)	2 (13.3)	0.124[a]
Clindamycin	-	2 (25.0)	6 (75.0)	-	3 (60.0)	2 (40.0)	0.207[a]
Colistin	-	2 (100.0)	-	-	2 (66.7)	1 (33.3)	0.276[a]
Erythromycin	-	2 (16.7)	10 (83.3)	-	3 (50.0)	3 (50.0)	0.144[a]
Gentamicin	1 (4.0)	17 (68.0)	7 (28.0)	-	14 (87.5)	2 (12.5)	0.269[a]
Imipenem	-	23 (92.0)	2 (8.0)	-	26 (100.0)	-	0.087[a]
Levofloxacin	2 (8.0)	22 (88.0)	1 (4.0)	-	22 (84.6)	4 (15.4)	0.096[a]
Linezolid	-	15 (100.0)	-	-	6 (100.0)	-	>0.05
Meropenem	-	22 (95.7)	1 (4.3)	-	27 (100.0)	-	0.209[a]
Nitrofurantoin	-	21 (87.5)	3 (12.5)	-	21 (84.0)	4 (16.0)	0.726[a]
Penicillin G	-	-	4 (100.0)	-	-	4 (100.0)	>0.05
Piperacillin Tazobactam	-	18 (78.3)	5 (21.7)	-	25 (92.6)	2 (7.4)	0.142[a]
Rifampisin	-	3 (75.0)	1 (25.0)	-	3 (100.0)	-	<0.05
Tetracycline	-	4 (33.3)	8 (66.7)	-	-	6 (100.0)	0.051[a]
Tigecycline	-	16 (100.0)	-	-	8 (88.9)	1 (11.1)	0.146[a]
Trimethoprim Sulfamethoxazole	-	8 (80.0)	2 (20.0)	-	2 (40.0)	3 (60.0)	0.125[a]
Vancomycin	-	12 (100.0)	-	-	7 (100.0)	-	>0.05

a. Chi-square Likelihood Ratio, b. Chi-Square Test, LS: Less sensitive, S: Sensitive, R: Resistant

the regional resistance rates to decide on the appropriate antibiotic selection. For this reason, one of the aims of this study was to determine the agent and resistance to drugs used in the treatment in the province of Mardin.

In the pregnant and non-pregnant group, *E. Coli* was the most common species among other microorganisms, followed by *Klebsiella pneumoniae* in pregnant women. The rate of *Enterococcus sp*. was higher in the non-pregnant group. However, none of these differences were statistically significant (p>0.05). Today, an increasing resistance to antibiotics among uropathogenic bacteria draws attention. In particular, the susceptibility rates of *E. Coli* strains isolated from urine cultures to combinations of oral betalactam-beta lactamase inhibitor and quinolones are gradually decreasing (13,14). In their systematic study, Belete et al. (15) screened patients between 2005 and 2016 to find that *E. Coli* ranked first in urinary tract infections with a rate of 55.2%, followed by *Klebsiella spp*. (14.6%). Our study is in parallel with other studies. Forson et al. (16) attributed the difference in prevalence of *E. Coli* to genital hygiene and socioeconomic differences between communities.

Antibiotic resistance and sensitivity analysis results of amikacin, aztreonam and rifampisin were significantly different between patient groups. When considering treatment in pregnant women, these 3 drugs must be excluded. Considering socially acquired urinary tract infection, resistance to nitrofurantoin and cephalosporin groups affects empirical treatment. A need to regulate the treatment based on the antibiogram of the urine culture of the patients has emerged due to the above-mentioned resistance pattern. Some studies report that treatment change is required in one third of the patients based on the results of the urine culture and a body temperature higher than 38.5°C in the first trimester may have side effects on the fetus (17).

In a study conducted in Uganda, it was observed that pregnant women with a low socio-economic level, need more frequently treatment for urinary tract infections (18). The income level of people living in Mardin is low compared to other regions. Well water is still used in the villages. Hence, frequent urination, burning while urinating, and malodorous urine, which are the symptoms of general urinary tract infection, are common complaints in pregnant women in Mardin. Therefore, treatment should be given to symptomatic pregnant women. In order to be able to give empiric treatment, it is necessary to know the urinary tract infection agents of the general population and their antibiotic resistance.

In a study conducted in England, maternal age, gestational status and week, body mass index, obese women were also evaluated. There was no statistically significant association between parity and the risk of urinary tract infection (19). In our study, the average parity in the population in which this study was conducted is above three.

Brazilian Society of Infectious Diseases (SBI) and Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO) recommend the treatment of urinary tract infection in pregnancy which was a study conducted throughout Brazil. It also draws attention to the differences in microorganisms that cause regional urinary tract infections. They state that there may be differences in development of resistance in antibiotics used regionally (20). In this study in the province of Mardin, a general evaluation was made in order to determine the regional antibiotic resistance and to guide the treatments in this region.

CONCLUSION

When choosing antibiotics in the empirical treatment of community-acquired urinary tract infections, we need to know the rates of resistance in our country and our region. To prevent the adverse obstetric consequences of urinary tract infections during pregnancy, it is important to investigate local susceptibility of microorganisms, especially common factors such as *E. Coli*, at certain periods. Low socio-economic level is a risk factor for urine culture contamination and further research into this topic is essential given trends in obesity worldwide. There is need to do urine culture and sensitivity from women diagnosed with in pregnancy so that appropriate antimicrobial agents are used in order to reduce the associated complications. Further work examining screening methods for the asymptomatic pregnant woman is required.

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ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics approval was obtained from Mardin Provincial Directorate of Health's Ethics Committee (Document no: 37201737-806.02.02-1332, Date: 27/08/2020).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Winn W Jr, Allen S, Janda W, Koneman E, Procop G, Schreckenberger P, Woods G. Koneman's color atlas and textbook of diagnostic microbiology, 6th edition. Lippincott Williams & Wilkins, Baltimore, MD. 2006.
2. Coskun USS, Coskun G. Determination of the prevalence and antibiotic susceptibilities of extended spectrum beta-lactamase positive Escherichia coli strains ısolated from urine of outpatient patients of a state hospital. Kocatepe Tıp Derg 2015; 16: 25-30.
3. Mert D, Çeken S, Ertek M; İdrar yolu enfeksiyonlarında kültürden izole edilen bakteriler ve antibiyotik duyarlılıkları.Turk Hij Den Biyol Derg 2020; 77: 25-32.
4. Forbes BA, Sahm DF, Weissfeld AS, Bailey WR. Bailey & Scott's Diagnostic Microbiology. 12th Edition, Elsevier Mosby, St. Louis. 2007
5. Atalay CR, Ertürk NK. Gebelikte üriner sistem enfeksiyonları; Turkiye Klinikleri J Urology-Special Topics 2018; 11: 92-5.
6. Committee on Obstetric Practice. Committee Opinion No. 717: sulfonamides, nitrofurantoin, and risk of birth defects. Obstet Gynecol 2017; 130: 150-2.
7. Budak G, Budak S, Arı A, et all. Investigating the distribution of the bacteria that lead to urinary tract infections and antibiotic susceptibility of *E. Coli*. J Clin Anal Med 2015; 6: 216-8.
8. Johansen TE, Naber KG. Urinary Tract Infections. Antibiotics (Basel) 2014; 3: 375-7.
9. Belete MA. Bacterial Profile and ESBL Screening of Urinary Tract Infection Among Asymptomatic and Symptomatic Pregnant Women Attending Antenatal Care of Northeastern Ethiopia Region. Infect Drug Resist 2020; 13: 2579-92.
10. Marcon J, Stief CG, Magistro G. Urinary tract infections : What has been confirmed in therapy? Der Internist 2017; 58: 1242-9.
11. McCormick T, Ashe RG, Kearney PM. Urinary tract infection in pregnancy. Obstet Gynaecol 2008; 10: 156–62.
12. Glaser AP, Schaeffer AJ. Urinary tract infection and Bacteriuria in pregnancy. Urol Clin North Am 2015; 42: 547–60.
13. Kahlmeter G, Poulsen HO. Antimicrobial susceptibility of Escherichia coli from community-acquired urinary tract infections in Europe: the ECO·SENS study revisited. Int J Antimicrob Agents 2012; 39: 45-51.
14. Zhanel GG, Karlowsky JA, Harding GK, et al. A Canadian national surveillance study of urinary tract isolates from outpatients: comparison of the activities of trimethoprim-sulfamethoxazole, ampicillin, mecillinam, nitrofurantoin, and ciprofloxacin. The Canadian Urinary Isolate Study Group. Antimicrob Agents Chemother 2000; 44: 1089-92.
15. Belete MA, Saravanan M. A systematic review on drug resistant urinary tract ınfection among pregnant women in developing countries in Africa and Asia; 2005-2016. Infect Drug Resist 2020; 13: 1465-77.
16. Forson AO, Tsidi WB, Nana-Adjei D, Quarchie MN, Obeng-Nkrumah N. Correction to: Escherichia coli bacteriuria in pregnant women in Ghana: antibiotic resistance patterns and virulence factors. BMC Res Notes 2019; 12: 29.
17. Dautt-Leyva JG, Canizalez-Román A, Acosta Alfaro LF, Gonzalez-Ibarra F, Murillo-Llanes J. Maternal and perinatal complications in pregnant women with urinary tract infection caused by Escherichia coli. J Obstet Gynaecol Res 2018; 44: 1384-90.
18. Nteziyaremye J, Iramiot SJ, Nekaka R, Musaba MW, Wandabwa J, Kisegerwa E, Kiondo P. Asymptomatic bacteriuria among pregnant women attending antenatal care at Mbale Hospital, Eastern Uganda. PLoS One. 2020; 15: e0230523.
19. O'Leary BD, Armstrong FM, Byrne S, Talento AF, O'Coigligh S. The prevalence of positive urine dipstick testing and urine culture in the asymptomatic pregnant woman: A cross-sectional study. Eur J Obstet Gynecol Reprod Biol 2020; 253: 103-7. doi:10.1016/j.ejogrb.2020.08.004
20. de Rossi P, Cimerman S, Truzzi JC, et al. Joint report of SBI (Brazilian Society of Infectious Diseases), FEBRASGO (Brazilian Federation of Gynecology and Obstetrics Associations), SBU (Brazilian Society of Urology) and SBPC/ML (Brazilian Society of Clinical Pathology/Laboratory Medicine): recommendations for the clinical management of lower urinary tract infections in pregnant and non-pregnant women. Braz J Infect Dis 2020; 24 110-9. doi:10.1016/j.bjid.2020.04.002

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Investigation of the contribution of concentrated growth factor (CGF) and processed lipoaspirate (PLA) to wound healing in diabetic rats

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ABSTRACT

Aim: The aim of the study is to show the effectiveness of concentrated growth factor (CGF) and processed lipoaspirate (PLA) in wound healing in diabetic rats.

Materyal and Method: A total of 30 rats were used in the study. It was divided into 3 groups as concentrated growth factor, processed lipoaspirate and control group. The rats were made diabetic using Sreptozotocin IP. A 5mm diameter wound was created on one of the hind legs of all rats by using a punch. Concentrated growth factor and processed lipoaspirate were applied to the lesions. Daily wound size and wound condition were recorded on days 3, 5 and 10. At the end of the study, blood samples were taken for TNF-α, TGF-β, IL-1, PDGF, FGF and VEGF measurements before the rats were sacrificed.

Results: The mean wound diameters measured on the 3rd day in the study were 4.6±0.06 mm in the control group, 4.1±0.05 mm in the concentrated growth factor group, and 4.4±0.07 mm in the processed lipoaspirate group. The wound diameters measured on the 5th day were 3.1±0.04 mm in the control group, 1.6±0.05 mm in the concentrated growth factor group and 2.7±0.06 mm in the processed lipoaspirate group ($p<0.01$). The mean closure time of wounds was 5.3±1.1 days in the concentrated growth factor group, 7.1±1.4 days in the processed lipoaspirate group, and 9.4±0.5 days in the control group. All of the wounds were healed in all groups on the 10th day. This improvement rate in the concentrated growth factor group was statistically significant compared to the other two groups ($p<0.01$). Concentrated growth factor and PLA increased the speed of wound healing in diabetic rats. Inflammatory marker levels (TNF-α, TGF-β, IL-1, PDGF, FGF, VEGF) obtained from blood samples were higher than normal in all rats and there was no significant difference between the groups ($p>0.05$).

Conclusion: In this study, it was shown that concentrated growth factor application was more effective than processed lipoaspirate application in wound healing in diabetic rats.

Keywords: CGF, PLA, diabetic rat, ulcer

INTRODUCTION

Wound is the disruption of the tissue integrity of the skin or mucosa for many different reasons such as abrasions, cuts, stings, bruises, burns, venous ulcers, surgical incisions and diabetic ulcers. Damaged tissue repair begins with hemostasis. Then the inflammatory period begins and is completed in 24-48 hours. It is completed in 3 stages as proliferative and maturation stages (1,2).

When the vessel wall is damaged, thrombocytes contact the collagen in the opened vessel wall and form a temporary clot and hemostasis is achieved. Inflammatory cells migrate towards the wound area and begin to remove apoptotic cells and bacteria from the wound area. Cytokines are released immediately after tissue damage in the inflammatory period. Cytokines guide the healing process (3).

Proliferation Phase is a process that starts on the 2nd day after the injury and continues for 3 weeks. At this stage, a basically permeable barrier is created. Epithelialization and contraction develop (4).

In response to cytokines and growth factors released from inflammatory cells in the wound area, fibroblasts begin to synthesize new extracellular matrix and immature Type III collagen. Epithelial cells originating from the basal layer at the edges of the wound create a new surface on the wound.

The remodelization phase starts in the 3rd week after the proliferation phase. At this stage, the number of fibroblasts in the wound area decreases. Collagen production reaches equilibrium and epithelization is completed. (5).

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Especially thrombocytes stimulate angiogenesis by secreting transforming growth factor beta (TGF-β), platelet derivated growth factor (PDGF), interlokin 1 (IL-1), platelet aktivated growth factor (PAF), transforming growth factor alfa (TGFα), tumor nekroz factor (TNFα), fibroblast growth factor (FGF), epidermal growth faktor (EGF) (6).

In order to increase these effects, the use of platelet-enriched plasma-rich platelet (PRP) and plasma-rich fibrin (PRF) or the collection and injection of these directly activated factors are techniques used to accelerate wound healing (7).

Growth factors in platelet cells provide healing. Platelet cells injected rupture when they encounter calcium in the body. The Growth Factors in it repair the damaged tissues in the injected area. However, not all Platelet cells have a chance to encounter Calcium. In fact, this is the feature that distinguishes CGF from PRP. CGF is obtained by separating minimum 97% of the growth factors from the Platelet and bringing it to high density (8).

Concentrated growth factor has the isolation of a fibrin matrix denser in terms of growth factors compared to PRP and PRF (9). Therefore, CGF can be expected to have regenerative potential and better properties for clinical manipulation (10). CGF and PRF contain almost the same components; however, the high tensile strength and viscosity of CGF protect growth factors better than proteolysis (11).

Another method for wound healing is MSC injection. In theory, cells that are not limited in their ability to reproduce and renew themselves and transform into any cell are defined as stem cells (12).

While embryonic stem cells can be obtained from early blastocysts, adult stem cells can also be obtained from non-embryonic tissues. These are cord blood, hematopoietic stem cells, fat and skin cells (13).

There are local and systemic factors affecting wound healing. Factors such as blood flow in the area of the wound, cytokines and growth factors, genetic and immunological disorders, diabetes, infection, radiotherapy, chemotherapy, inappropriate nutrition, steroid drug use affect wound healing (14)

Microvascular disorder, which is one of the important complications of diabetes, neuropathy causing loss of sensation in the skin, and weakening of the ability to fight infection are the main factors that delay wound healing (15).

An excisional wound model is used in DM-induced rats to observe wound healing. An open wound is created and the time-dependent closure rate of the wound is recorded. Granulation formation, collagen deposition, reepithelization and constriction can be investigated with this model (16).

Our aim in this study is to compare the effectiveness of CGF and PLA on wound healing in the excisional wound model created in diabetic rats.

MATERIAL AND METHOD

A total of 30 male Wistar albino rats weighing between 300-350 g were used in this study. Experimental animals were obtained from Kırıkkale University Hüseyin Aytemiz Experimental Research and Application Laboratory. The experiment was carried out in accordance with the principles of "Guide for the Care and Use of Laboratory Animals". Approval was obtained from Kırıkkale University Animal Experiments Local Ethics Committee for the study. (Date: 02.05.2016/Issue: 16/54).

Diabetic Rat: Rats were carried out diabetic using Sreptozotocin (STZ, Sigma Mo, USA) 55 mg/kg intraperitoneally (9). It was confirmed that morning fasting sugars were higher than 250 mg/dL with blood taken from the tail 1 week after the injection. Three groups were formed with 30 rats at 12 weeks of age. Groups consisted of 10 male rattan. One of the groups was given CGF (CGF group), the other was PLA (PLA group). Group 3 was the control group (Control group).

Wound: A full-thickness skin wound was created on the legs of all rats under anesthesia with xylazine HCl (1 mg/kg i.m.) + ketamine HCI (50 mg/kg i.m.) using a 5 mm punch under sterile conditions. The diameters were recorded by examining the wound areas on the 0, 3, 5 and 10 days after treatment.

Treatment Method: 1 day later, mesenchymal stem cells (MSC) were applied to PLA group, CGF was applied to CGF group and no medication was given to control group.

CGF preparation: Commercial kit (Truecell®) was used. The kit consists of two tubes with citrate as anticoagulant substance in A-tube and calcium chloride in tube B for platelet activation. 4 ml of blood taken from a rat was put into A-tube and centrifuged at 2500 rpm/min for 10 minutes. BuffyCoat layer containing dense thrombocytes and leukocytes on the surface and serum plasma part were transferred from A-tube to B-tube. It was centrifuged for 5 minutes at 4000 rpm/min. 2 ml CGF was collected, which was released from activated platelets, passed into plasma and accumulated on the surface. Then, 0.2 ml was injected into the wound area of each rat.

PLA Preparation: Stem cells obtained from rat adipose tissue were prepared as $5x10^6$ cells/ml. It was supplied under cold chain conditions. (Live laboratories Hospital, Istanbul, Turkey). Lipoaspirate was washed with buffer

solutions (PBS: phosphate buffer solution was used for this purpose). Enzymatic destruction was performed with collagenase. The cell layer was obtained by separating the supernatant layer by centrifugation. It was carried out by cell culture and passaging after this step to obtain PLA alone.

Sacrification: On the 12th day, subjects were sacrificed and blood samples were taken.

ELISA: TNF-α, TGF-β, IL-1, PDGF, FGF and VEGF levels were measured from the blood samples taken by ELISA method.

During the experiments, five rats per cage were followed up. Maintained under standard environmental conditions (12-hour light/dark cycle, temperature ~ 21°C). It was fed ad libitum with standard rat chow and water.

Statistical Analysis

SPSS version 20.0 (SPSS; Chicago, IL, USA) software was used for statistical analysis. Normally distributed data were given as means±standard deviation and non-normally distributed data as mean±25%. Chi-square and Fisher's exact tests were used to compare categorical variables. Mann-Whitney U-test (MWU) and Kruskal-Wallis test (Bonferroni-adjusted) were used to compare continuous data with non-normal distributions. A p value of <0.05 was considered statistically significant.

RESULTS

The study was conducted on 30 diabetic rats. The rats were divided into 3 groups and there were 10 rats in each group (n=10). A full thickness wound was created with a 5 mm punch. PLA was given to the wound in group 1. CGF was given to the wound in group 2. Group 3 was the control group. Wound diameters were measured and recorded on the 3rd day, 5th day and 10th day. Blood samples were taken on the 12th day and the rats were sacrificed. TNF-α, TGF-β, IL-1, PDGF, FGF and VEGF levels were measured to show the severity of the inflammatory process. Blood levels of inflammatory markers were higher than normal. However, there was no significant difference between the groups (p>0.05). The data are shown in **Table 1**.

Table 1. Inflammatory markers

n = 10	CGF group	PLA group	Control group	P
TNF-α (pg/ml)	13.4±1.4	14.3±2.6	13.1±1.5	0.369
TGF-β (ng/ml)	20.1±2.9	18.7±3.7	20.8±3.8	0.481
IL-1 (pg/ml)	0.8±0.2	1.0±0.3	0.90±0.2	0.122
PDGF (pg/mL)	39.8±4.7	37.9±6.7	42.47±4.9	0.21
FGF (ng/mL)	17.8±4.7	17.6±3.4	15.5±3.6	0.202
VEGF (pg/ml)	201.1±4.7	198.9±8.6	197.7±6.3	0.525

Abbreviations: CGF: Concentrated growth factor, PLA: Processed lipoaspirate, PDGF: Platelet-derived growth factor, TGF-β: Transforming growth factor, TNF-α: Tumor necrosis factor, VEGF: Vascular endothelial growth factor, FGF: Fibroblast growht factor, IL-1: Interlökin 1

The mean wound diameters measured on the 3rd day were 4.6±0.06 mm in the control group, 4.1±0.05 mm in the CGF group, and 4.4±0.07 mm in the PLA group. Wound diameters measured on the 5th day were 3.1±0.04 mm in the control group, 1.6±0.05 mm in the CGF group, and 2.7±0.06 mm in the PLA group. There was a significant difference in wound diameters measured on both days between CGF and PLA and control group (p<0.01). In addition, a significant difference was found between CGF and PLA groups (p<0.01). The fastest improvement was in the PLA group. The data are shown in **Table 2** and **Figure 1**.

Table 2. Wound diameter on the 3rd and 5th days

n=10	3rd day (mm)	5th day (mm)	P
CGF group	4.1±0.06	1.6±0.004	<0.001
PLA group	4.4±0.05	2.7±0.05	<0.001
Control group	4.6±0.07	3.1±0.06	<0.001

Abbreviations: CGF: Concentrated growth factor, PLA: Processed lipoaspirate

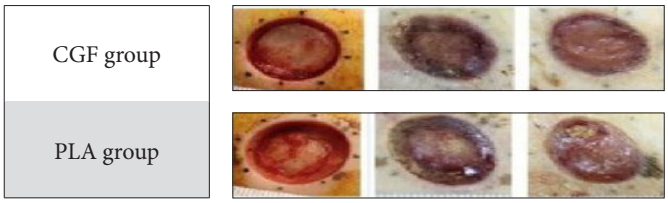

Figure 1. Wound healing status on the first, 5th and 7th days

The mean closure time of wounds was 5.3±0.32 days in the CGF group, 7.1±0.51 days in the PLA group, and 9.4±0.4 days in the control group. A significant difference was found between the mean healing time of wounds, CGF and PLA and the control group (p<0.01). There was also a significant difference between CGF and PLA groups (p<0.01). It was observed that the fastest closure was in the CGF group and the slowest closure was in the control group. In the 10-day follow-up period, the wounds on the legs of all rats made diabetic healed. The data are shown in **Table 3** and **Figure 2**.

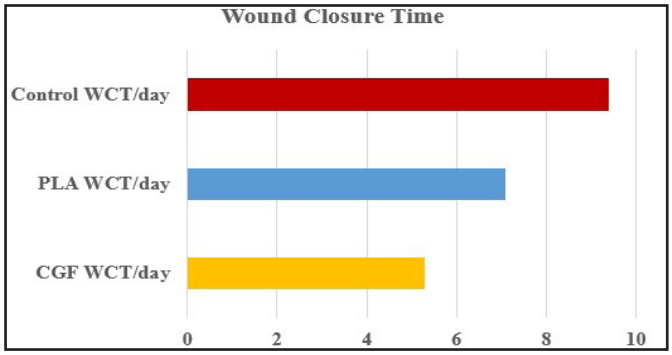

Figure 2. Wound closure time (WCT)

Table 3. Wound closure time

n=10	CGF group	PLA group	Control group	p
WCT (mean±std)	5.3±0.32	7.10±0.51	9.4±0.4	<0.01

Abbreviations: WCT: Wound closure time, CGF: Concentrated growth factor, PLA: Processed lipoaspirate

DISCUSSION

Wounds can be acute (surgery, burns, penetrating injuries) or chronic (pressure sores, venous stasis ulcers, diabetic wounds, ischemic wounds, etc.).Chronic wounds are an important health problem affecting a significant portion of the population in developed countries and impairing the quality of life. In addition, its treatment brings a serious financial burden (17).Wound healing is the process of restoring the anatomical and functional properties of the tissue by regularly completing certain wound healing phases. It is known that various factors affect the wound healing process negatively. These; malnutrition, infections, diabetes, hypoxia, circulatory disorder, immunosuppression, aging and chronic diseases (18).

In vivo wound models are incisional, excisional, burn and frozen models.Models applied for cases where wound healing is impaired are malnutrition, ischemia, infection, compression and diabetes models. In this experiment, we investigated wound healing in diabetic rats using an excisional wound model (19).

It has been shown that a significant part of the proliferation, migration and vascular formation promoting effects of PRP are achieved through exosome-like molecules released from platelets into the plasma (20). The effect of PRP on wound healing has been mainly associated with growth factors released from platelets (21). CGF is more intense in terms of growth factors compared to PRP and PRF (22). In our study, instead of PRP, growht factors (GF) released from leukocyte-free and activated PRPs were applied to the wound area.

The most important inflammation cytokines in wound healing are TNF-α, TGF-β, IL-1, PDGF, FGF and VEGF. (23). Blood levels in the groups were measured by ELISA method. All were found higher than normal levels. But there was no statistically significant difference between them ($p>0.05$). The similar inflammatory mediator levels were interpreted as similar rates of local and systemic inflammation in the treatment groups. The high levels were interpreted as tissue repair and healing continued. It has been shown that the proliferation phase, which is the last phase of wound healing, can continue for up to 6 weeks (24). Towards the end of this process, it was thought that there might be a differentiation between the treatment group and the treatment group.

In wound healing, epithelial cells migrate from the beginning of the injury until the entire damaged surface is covered. Wound contraction begins to occur 7 days after injury, and myofibroblasts play an important role at this stage. Many factors affect the healing and contraction process at a rate of approximately 0.75 mm/day (5-7). In this study, the mean wound diameters on the 3rd day were 4.6±0.06 mm in the control group, 4.1±0.05 mm in the CGF group, and 4.4±0.07 mm in the PLA group. Wound diameters measured on Day 5 were 3.1±0.04 mm in the control group, 1.6±0.05 mm in the CGF group, and 2.7±0.06 mm in the PLA group ($p<0.01$). These results show that both PLA and CGF increase wound repair in diabetic rats compared to the control group. The fastest recovery seems to be in the CGF group.

In an animal study where the reconstruction of bone defects was evaluated using CGF, PRP and PRF, they were compared in terms of their osteogenic potential, but no statistically significant difference was found between them (25). First developed by Sacco (26) in 2006, CGF, one of the second-generation platelet concentrations, demonstrated the potential to accelerate osteogenesis when used in sinus augmentation.

In the rat calvarial bone defect regeneration study of Khojasteh et al. (27) it was reported that MSC application yielded more successful results than PRP.

It has been shown in different studies that stem cell application will contribute to the treatment of difficult-to-heal wounds such as diabetic ulcers (28).

Walter et al. (20) MSCs associated their contribution to wound healing with the chemotactic mediators they secrete, such as TGF-1β, IL-6, and IL-8. The clinical benefits of MSCs can be summarized as stimulation of cellular repair, attenuation of inflammation, enhancement of angiogenesis and therapeutic cell migration (29).

The mean closure time of the wounds in the study was 5.3±0.32 days in the CGF group, 7.1±0.51 days in the PLA group, and 9.4±0.4 days in the control group. A significant difference was found between the mean healing time of wounds, CGF and PLA and the control group ($p<0.01$). There was also a significant difference between CGF and PLA groups ($p<0.01$). It was observed that the fastest closure was in the CGF group and the slowest closure was in the control group. In the 10-day follow-up period, the wounds on the legs of all rats made diabetic healed. These results in diabetic rats have shown that CGF and PLA are effective in wound healing as in other studies. In the study, it was found that CGF is more effective than PLA. We think that the reason for CGF's effectiveness is its active and long effect.

CONCLUSION

In this study, CGF and PLA applications are two important methods that increase wound healing, but CGF application has been shown to be a more effective method than PLA in wound healing.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval was obtained from Kırıkkale University Animal Experiments Local Ethics Committee for the study. (Date: 02.05.2016/Issue: 16/54).

Referee Evaluation Process: External double-blind referee assessment.

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Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Harper D, Young A, McNaught CE. The physiology of wound healing. Surgery (Oxford) 2014; 32: 445-50.
2. Macdonald J, Asiedu K. WAWLC: World Alliance for Wound and Lymphedema Care. Wounds 2010; 22: 55-9.
3. Sayek İ, Ozmen MM, Temel Cerrahi El Kitabı, Güneş Tıp Kitabevleri, Ankara, 2009.
4. Coşkun Ö, Uzun G, Dal D, ve ark. Kronik yarada tedavi yaklaşımları. Gülhane Tıp Derg 2016; 58: 207-28.
5. Rajpaul K. Biofilm in wound care. Br J Community Nurs; Suppl Wound Care: 2015; 6: 10-1.
6. Broughton G, Janis JE, Attinger CE. The basic science of wound healing. Plast Reconstr Surg 2006; 117: 125-34.
7. Jeffcoate J.W, Price P, Harding G.K.Wound healing and treatments for people with diabetic foot ulsers. Dıabetes/Metabolısm Research and Reviews 2004; 20: 78–89.
8. Martino MM, Tortelli F, Mochizuki M, al. Engineering the growth factor microenvironment with fibronectin domains to promote wound and bone tissue healing. Sci Transl Med 2011; 3: 100-89.
9. Rodella LF, Favero G, Boninsegna R, et al. Growth factors, CD34 positive cells, and fibrin network analysis in concentrated growth factors fraction. Microsc Res Tech 2011; 74: 772-7.
10. Chen Y, Cai Z, Zheng D, et al. Inlay osteotome sinus floor elevation with concentrated growth factor application and simultaneous short implant placement in severely atrophic maxilla. Scientific reports 2016; 6: 273-8.
11. Kim T-H, Kim S-H, Sándor GK, Kim Y-D. Comparison of platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and concentrated growth factor (CGF) in rabbit-skull defect healing. Archives of oral biology 2014; 59: 550-8.
12. İnan S, Ozbilgin K. Kok Hucre Biyolojisi. Sağlıkta Birikim. Cilt 1, Sayı 5, 2009: 11-23.
13. Kok IJ, Peter SJ, Archambault M, et al. Investigation of allogeneic mesenchymal stem cell-based alveolar bone formation: preliminary findings. Clin Oral Implants Res 2003; 14: 481-9.
14. Öztopalan DF, Işık R, Durmuş AS. Yara iyileşmesinde büyüme faktörleri ve sitokinlerin rolü. Dicle Üniv Vet Fak Derg 2017; 10: 83-8.
15. Greenhalgh DG. Wound healing and diabetes mellitus. Clin Plastic Surg 2003; 30: 37-45.
16. Galiano RD, Michaels VJ, Dobryansky M, Levine JP, Gurtner GC. Quantitative and reproducible murine model of excisional wound healing. Wound Repair Regen 2004; 12: 485-92.
17. Blakytny R, Jude E. The molecular biology of chronic wounds and delayed healing in diabetes. Diabet Med 2006; 23: 594-608.
18. Larsen JA, Overstreet J. Pulsed radio frequency energy in the treatment of complex diabetic foot wounds: two cases. J Wound Ostomy Continence Nurs 2008; 35: 523-7.
19. Reid RR, Said HK, Mogford JE, Mustoe TA. The future of wound healing: Pursuing surgical models in transgenic and knockout mice. J Am Coll Surg 2004; 199: 578-85.
20. Guo SC, Tao SC, Yin WJ, Qi X, Yuan T, Zhang CQ. Exosomes derived from platelet-rich plasma promote the re-epithelization of chronic cutaneous wounds via activation of YAP in a diabetic rat model. Theranostics 2017; 7: 81-96.
21. Yuan T, Guo SC, Han P, Zhang CQ, Zeng BF. Applications of leukocyte- and platelet-rich plasma (L-PRP) in trauma surgery. Curr Pharm Biotechnol 2012; 13: 1173–84.
22. Wang F, Sun Y, He D, Wang L. Effect of Concentrated Growth Factors on the Repair of the Goat Temporomandibular Joint. J Oral Maxillofac Surg 2017; 75: 498-507.
23. Shih B, Garside E, McGrouther DA, Bayat A. Molecular dissection of abnormal wound healing processes resulting in keloid disease. Wound Repair Regen 2010; 18: 139-53.
24. Ulaşlı AM. Kas iskelet sistemi yaralanmalarında plateletten zengin plazma tedavisi. Kocatepe Tıp Derg 2012: 13; 1-3.
25. Kim JM, Sohn DS, Bae MS, Moon JW, Lee JH, Park IS. Flapless transcrestal sinus augmentation using hydrodynamic piezoelectric internal sinus elevation with autologous concentrated growth factors alone. Implant Dent 2014; 23: 168-74.
26. Sohn D, Moon J, Moon Y, Park J, Jung H. The use of concentrated growth factors (CGF) for sinus augmentation. J Oral Implant 2009; 38: 25-38.
27. Khojasteh A, Eslaminejad MB, Nazarian H. Mesenchymal stem cells enhance bone regeneration in rat calvarial critical size defects more than platelete-rich plasma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008; 106: 356-63.
28. Falanga V, Iwamoto S, Chartier M, et al. Autologous bone marrow-derived cultured mesenchymal stem cells delivered in a fibrin spray accelerate healing in murine and human cutaneous wounds. Tissue Eng 2007; 13: 1299–312.
29. Walter MN, Wright KT, Fuller HR, MacNeil S, Johnson WE. Mesenchymal stem cell-conditioned medium accelerates skin wound healing: an in vitro study of fibroblast and keratinocyte scratch assays. Exp Cell Res 2010; 316: 1271-81.

Original Article

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Evaluation of craniometric measurements in human skulls

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ABSTRACT

Aim: We aimed to provide a source of information that could contribute to the determination of normal values in our country and to reveal possible variations by comparing our results with the literature.

Material and Method: Our study was carried out on 60 skulls of unknown gender and age found in the Laboratory of the Department of Anatomy. Measurements were made directly on the skull using an inelastic and soft measuring tape, Holtain Harpenden anthropometric set, and a digital sliding caliper (Mitutoyo). In our study, using direct anthropometric measurement techniques, the measurements of the head and face regions were taken by a single researcher three times and their averages were calculated. 19 anthropometric points were determined and used for 22 measurements.

Results: As a result of our study, the head and face data were generally lower than the literature. Apertura piriformis height (APH), orbital length (OL) and orbital width (d-ec) results were compared as left and right asymmetry percentages, respectively; it was calculated as 1.35, 0.25, 0.26. Left measurement results were found more than right side.

Conclusion: In our study, it was observed that the mean values of skulls in our country were generally lower than those of other studies in the literature. At the same time, we think that comparing data with different nationalities will be important in determining the structural craniometric properties for social diversity. In addition, we believe that our findings will shed light on future research.

Keywords: Craniometry, skull, anthropometry

INTRODUCTION

Anthropometric studies are a scientific method for showing different measurements and observations on human and skeleton (1). Craniofacial anthropometry; it is a branch of anthropometry that includes head and face measurements in living, cadaver and radiological samples. These measurements are important data for craniofacial surgery, plastic surgery, genetic counseling and forensic applications (2).

Using anthropometric methods in clinical practice to measure changes in craniofacial structures, features that distinguish various races or ethnic groups have been discovered (3). Cephalographers investigated human head and face profiles by measuring angles or lengths of soft tissues or dry bones using two-dimensional photogrammetry or direct measurements (4,5). Craniometry, which was developed in the 19th century, is a method of measuring skull and facial structure. Craniometry and other anthropometric measurements enable the widely accepted theories to be re-evaluated by arguing that standing upright and brain growth occur at the same time in human development (6). Measurement of cranial bones plays an important role in the determination and classification of population history, analysis of skeletal variation (7).

In recent years, craniometric measurements have become an important tool used by opticians, anthropologists, forensic experts and reconstructive surgeons. In this context, the importance of anthropometric studies in both our health and social life is indisputable. Although craniofacial studies in humans are abundant in our country, there are few studies on craniometric analysis of skulls.

By addressing the information gap in craniometric indices of human skulls, we aimed to provide a source of information that can contribute to the determination of normal values in our country with the findings of our study.

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MATERIAL AND METHOD

Our research was carried out on 60 skulls of unknown gender and age found in the Laboratory of the Department of Anatomy, Faculty of Medicine, Kırşehir Ahi Evran University. Skulls, which are the fixtures of the Anatomy department, are used as educational materials in the relevant department. Measurements were made directly on the skull using an inelastic and soft measuring tape, Holtain Harpenden anthropometric set, and a digital sliding caliper (Mitutoyo). In our study, using direct anthropometric measurement techniques, the measurements of the head and face regions indicated in **Table 1** were taken by a single researcher three times and their averages were calculated. 19 anthropometric points were determined and used for 22 measurements (**Table 1, Figure 1-4**).

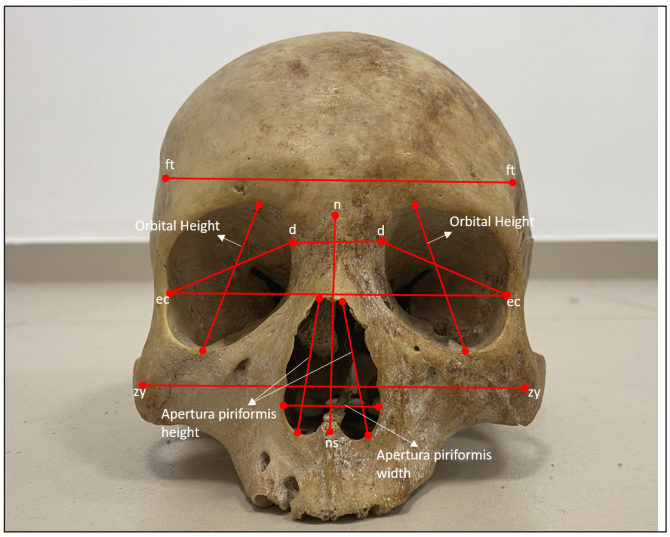

Figure 1. Craniometric measurements and landmarks. ft: Frontotemporale, n: Nasion, d: Dacryon, ec: Ectoconchion, zy: Zygion, ns: Nasospinale.

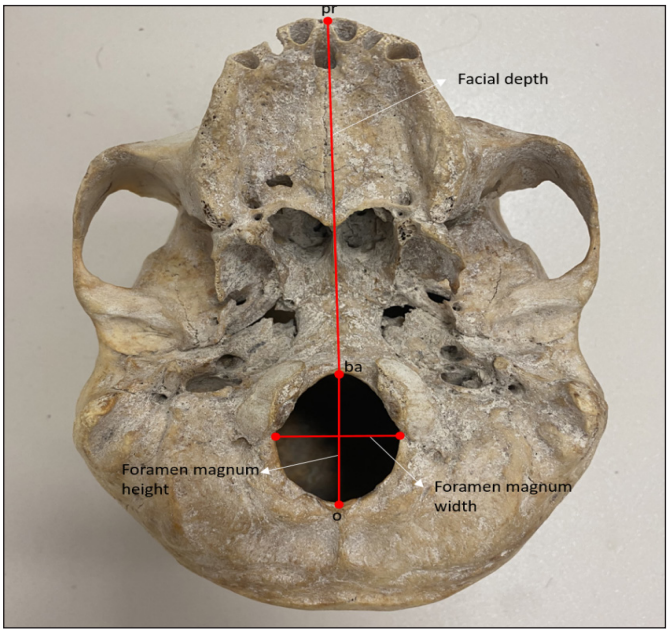

Figure 2. Craniometric measurements and landmarks. pr: Prosthion, ba: Basion, o: Opisthion.

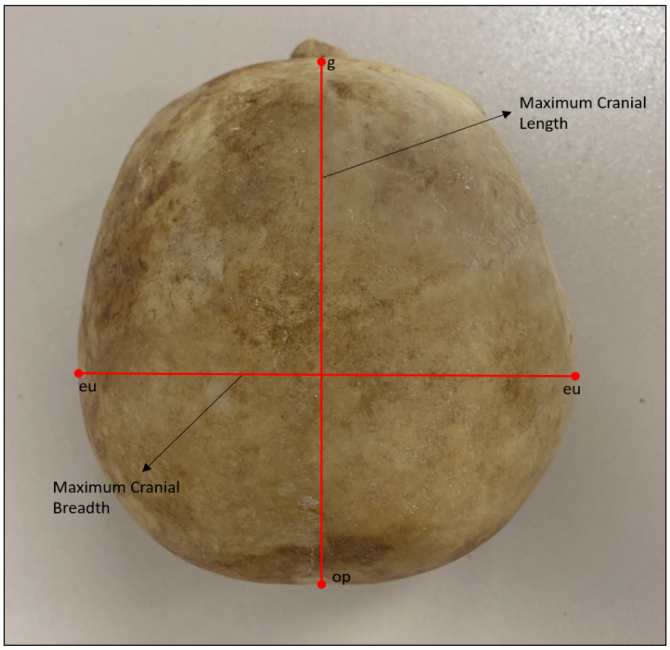

Figure 3. Craniometric measurements and landmarks. g: Glabella, op: Opisthocranion, eu: Euryon.

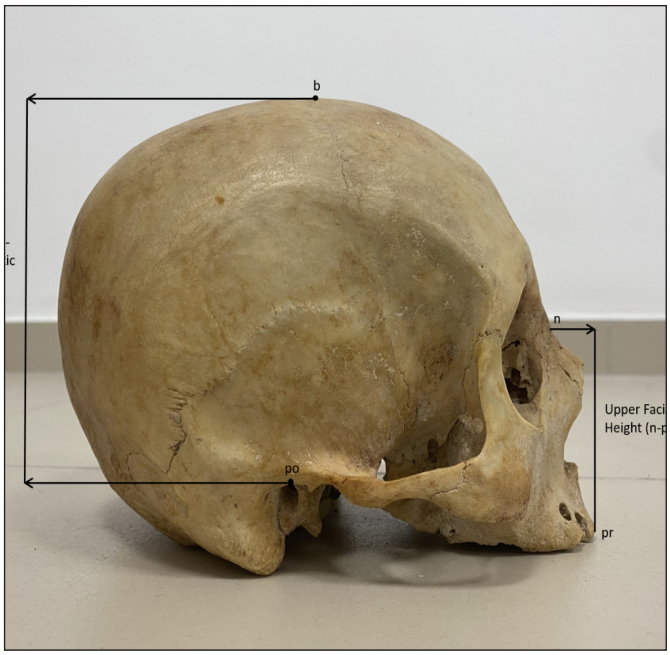

Figure 4. Craniometric measurements and landmarks. b: Bregma, n: Nasion, po: Porion, pr: Prosthion.

Statistical Analysis

The data were tabulated in Microsoft Excel worksheet and the analysis of the data was performed using SPSS 22.0 package program. The results of the craniometric measurements are given as mean, standard deviation (SD), minimum and maximum values. The compatibility of right-left measurement data to normal distribution was evaluated by Histogram, Q-Q graphics and Shapiro-wilk test. Variance homogeneity was tested with the Levene test. Independent two samples t-test was used for quantitative variables in comparisons between pairs. Significance level was accepted as $p<0.05$.

Table 1. Craniometric measurements (2,8,9)

No	Measurements	Abbreviation	Definition
1	Maximum cranial length	g-op	Length from glabella (g) in the midsagittal plane to opisthocranion (op) in the occipital bone
2	Maximum cranial width	eu-eu	The length between the most protruding points in the parietal and temporal bones on both sides of the skull
3	Maximum face width	zy-zy	Distance between the most lateral points of zygomatic (zy) arcs
4	Basion-bregma height	ba-b	Length between the projections of the basion (ba) and bregma (b) at the front edge of the foramen magnum
5	Minimum frontal width	ft-ft	The shortest distance between two frontotemporale (ft) point on either side of the forehead
6	Upper face height	n-pr	Length between nasion (n) and prosthion (pr)
7	Basi-nasal length	n-ba	Length between nasion (n) and basion (ba)
8	Facial depth	ba-pr	Length between basion (ba) and prosthion (pr)
9	Orbital width (left-right)	d-ec	Distance from Dacryon (d) to ectoconchion (ec)
10	Orbital length (left-right)	OL	Length between upper and lower orbital boundaries
11	Biorbital width	ec-ec	Distance between right and left ectoconchion (ec) points
12	Interorbital width	d-d	Distance between right and left dacryon (d) points
13	Nasal height	n-ns	Distance between nasion (n) and spina nasalis anterior (ns)
14	Apertura piriformis height (left-right)	APH	Apertura piriformis height from the distance between the lower point of the sutura nasalis and the most protruding points on either side of the spina nasalis anterior
15	Apertura piriformis width	APW	Apertura piriformis width from the furthest points in the midline in the transverse direction
16	Foramen magnum (FM) length	ba-o	Length from basion (ba) to opisthion (o)
17	Foramen magnum width	FMW	The farthest distance between the side edges of the foramen magnum
18	Horizontal circumference of the skull	g-op-g	Length of the horizontal circumference of the skull from glabella (g) to glabella (g) via opisthocranion (op)
19	Auriculo-bregmatic height	po-b	Length between porion (po) and bregma's projections

RESULTS

The mean±standard deviation values of craniometric measurements used in our study are shown in **Table 2** and **Table 3.**

Apertura piriformis height (APH), orbital length (OL) and orbital width (d-ec) results were compared as left and right asymmetry percentages, respectively; It was calculated as 1.35, 0.25, 0.26. Left measurement results were found more than right side. There was no statistically significant difference between the left and right measurements of these parameters showing normal distribution (p>0.05).

DISCUSSION

In forensic and anthropological sciences, cranial analyses, whether morphognostic or morphometric, have played an important role in examining age at death, ancestry, biodistance, cranial variation and geographical relationships, cranial development, and, of course, sex differences (10). In addition, the information obtained from these analyzes can also be used in planning the surgical process to be performed in the cranial region.

Cranial length or maximum cranial length (g-op) is the distance between the glabella point and the opisthacranion point, which is the most posterior point of

Table 2. Cranial measurements of skulls, mean (mean)±standard deviation (SD), minimum and maximum values (mm)

Measurements	n=60		
	Mean±SD	Min.	Max.
Glabella-opisthocranion (g-op)	162.45 ±6.20	151.00	178.50
Euryon-euryon (eu-eu)	129.45±4.99	117.00	138.00
Frontotemporale-frontotemporale (ft-ft)	99.46±4.42	89.09	106.57
Basion-bregma (ba-b)	125.19±5.33	115.07	134.73
Nasion-basion (n-ba)	91.43±4.27	82.00	101.00
Basion-prosthion (ba-pr)	88.18±4.76	77.65	100.18
Basion-opisthion (ba-o)	35.81±7.57	30.17	90.84
Foramen magnum width	28.65±1.78	23.52	31.74
Porion-bregma-porion (po-b-po)	295.21±9.34	270.00	320.00
Glabella-opisthocranion-glabella (g-op-g)	486.43±13.27	460.00	510.00
Porion-bregma (po-b)	109.71±4.00	101.14	121.00

the cranium, and reaches its size in adults around the age of 10 for females and about 14 years for males (11). In our study, the maximum cranial length value was measured as 162.45±6.20 mm. This measurement average stands out as lower (approximately 10%) when compared with the findings of other studies in the literature (**Table 4**) (7,9,12-17). The maximum cranial width (eu-eu) is the distance between the most lateral points of the skull (11). In our study, the maximum cranial width findings were similar to the findings of the study conducted by Ramamoorthy et al. (14) in India, but it was found to be lower than the findings of other studies (7,9,12,13,15,16) (**Table 4**). Auriculo-bregmatic height is the height measured from the porion (po) to bregma (b) by taking the head in the Frankfurt Horizontal Plane. Tritsarol (18) reported this measurement as 128±6.9 mm, and Todd (19) reported as 115.2±0.3 mm. In our study, this height was measured as 109.71±4.00 mm. These findings of our study were found to be lower than the findings of studies in the literature.

Cranial length, cranial width and auriculo-bregmatic height measurements are linear cranial measurements and constitute the basic data in the calculation of cranial capacity. In this context, it is understood that the cranial capacities of the skulls in our study are lower than the studies in the literature.

The minimum frontal width (forehead width, ft-ft) reaches adult size at the age of 13 for females and about 15 for males (11). The minimum frontal width measurement (99.46±4.42 mm) obtained from our study was found to be higher than the results of similar studies in the literature (9,14,16,17) as indicated in **Table 4.**

The horizontal circumference of the skull is measured from glabella to glabella (g-op-g) via opisthocranion (20). The horizontal circumference of the skulls obtained in our study was measured as 486.43±13.27 mm. Ziylan et al. (12) measured this measurement as 502.2±15.8 mm in male and 496.9±19.5 mm in female. Ramamoorthy et

Table 3. Facial measurements of skulls, mean (mean)±standard deviation (SD), minimum and maximum values (mm)

Measurements	n=60		
	Mean±SD	Min.	Max.
Zygion-zygion (zy-zy)	112.07±4.91	96.52	123.71
Nasion-nasospinale (n-ns)	49.59±3.33	41.26	56.02
Apertura piriformis height (APH) (left)	36.26±3.58	28.33	42.59
Apertura piriformis height (APH) (right)	35.77±3.53	27.56	42.30
Apertura piriformis width (APW)	24.25±1.56	21.32	28.40
Orbital length (OL) (left)	36.31±2.40	32.04	41.86
Orbital length (OL) (right)	36.22±2.11	32.20	41.31
Dacryon-Ectoconchion (d-ec) (left)	38.28±1.77	34.33	43.11
Dacryon-Ectoconchion (d-ec) (right)	38.19±1.61	33.23	43.12
Dacryon-dacryon (d-d)	22.67±2.27	18.31	27.26
Ectoconchion-ectoconchion (ec-ec)	94.30±2.61	86.14	99.77
Nasion-prosthion (n-pr)	63.98±4.15	56.09	75.97

Table 4. Comparison of cranial measurements (mm) of skulls with the literature

Author	Sex	n	g-op	eu-eu	ft-ft
Orish and Ibeachu (Nigeria)	F	22	167.5±7.88	127.5±3.53	-
	M	78	180.4±8.12	137.2±7.95	-
Mahakkanukrauh et al. (Thailand)	F	100	164.02±6.76	138.68±5.33	89.43±4.25
	M	100	172.64±6.23	144.44±5.69	92.94±5.02
Vidya et al. (India)	F	39	167.7±17.3	132.8±14.5	-
	M	41	168.1±16.1	132.9±19.3	-
Kranioti et al. (Crete)	F	88	172.89±6.48	133.92±5.85	93.23±4.50
	M	90	181.07±6.63	137.64±6.63	96.33±4.52
Ziylan et al. (Turkey)	F	45	168.8±7.1	134.6±6.3	-
	M	40	170.0±8.8	134.8±7.3	-
Padala and Khan (India)	F	19	171.0±7.7	129.0±4.6	-
	M	31	179.2±6.0	134.0±9.6	-
Ramamoorthy et al. (India)	F	27	170.5±6.8	128.0±6.2	94.2±3.5
	M	43	178.3±8.1	133.0±6.2	96.4±4.7
Steyn and Iscan (South Africa)	F	47	179.0 ±5.85	-	93.6± 4.78
	M	44	187.7± 5.45	-	97.8±3.87
Present Study (Turkey)	-	60	162.45±6.20	129.45± 4.99	99.46±4.42

al. (14) measured the same measurement as 509.0±19.39, 492.3±14.1 mm in male and female, respectively. The result of our study was lower than the results of other studies.

The results of basion-bregma (ba-b) measurements in the skulls of Thai (9), South African whites (17), Indian (14), and Japanese (21) were higher than the same measurement result in our study (**Table 5**).

Basi-nasal length is the length between nasion (n) and basion (ba) and it was found as 91.43±4.27 mm in our study. When compared with the studies in the literature, it was found higher than female skulls and lower than male skulls (**Table 5**) (7,9,13,14,17,21), Basi-nasal length was consistent with the average values in the literature. Facial depth, the length between basion (ba) and prosthion (pr), has been measured to be lower than other studies in the literature (7,13,14,17).

The foramen magnum (FM) is an important landmark of the base of skull and is of particular interest to many fields of medicine. The dimensions of FM have clinical importance because the vital structures that pass through it may suffer compression as in cases of FM achondroplasia and FM brain herniation (22). Although the FM length obtained in our study was found higher than some studies in the literature, it was found to be lower than the measurements made by Ramamoorthy et al. (14). Although our FMW measurement is lower than the data of Ramamoorthy et al. (14) and Mahakkanukrauh et al. (9), there are also higher data in the literature (23,24) (**Table 5**).

One of the facial measurements, the maximum face width (bi-zygomatic diameter, upper face width) is the distance between the most protruding lateral points of the right and left zygomatic arches (zy-zy), and it completes its development at the age of 15 for males and 13 for females (2,25). Although the maximum face width data obtained from our study were lower compared to some studies in the literature, it was found higher than the data of Padala and Khan (9,11-14) (**Table 6**).

The interorbital width (d-d) and biorbital width (ec-ec) in the orbital region constitute important data for the harmony of the face (2). The interorbital width measurement result obtained from our study was found higher than the results of Mahakkanukrauh et al. (9) and Ramamoorthy et al. (14) and lower than the measurements of Farkas (11). Our biorbital width measurement result (94.30±2.61 mm) was found to be lower than the results of Mahakkanukrauh et al., Ziylan et al. and Ramamoorthy et al. (9,12,14) (**Table 6**).

In our study, orbital width (d-ec) was measured as left and right separately, and the left orbital width was found to be greater than the right orbital width. Orish and Ibeachu (7) and Farkas (11), in their similar study, reported that the left orbit is wider than the right orbit. In this respect, our work is similar to the work of Farkas and Orish. Although these measurement results obtained from our study were lower than the results of other studies (9,11,13,14) in the literature, they were higher than the same measurement results of women in the study of Orish and Ibeachu (7). Orbital length (OL) is the straight and widest distance between the upper and lower edges of the orbital cavity. Although these measurement results obtained from our study were higher than the results of other studies (9,13,14) in the literature, they were found lower than the same measurement results of men in the study of Orish and Ibeachu (7) (**Table 6**). The higher orbital length measurement obtained in our study than the measurements in other studies may be due to genetic and racial factors.

Table 5. Comparison of cranial measurements of skulls with the literature

Author	Sex	n	ba-b	n-ba	ba-pr	ba-o	FMW
Ogawa et al. (Japan)	F	40	134.0 ±3.79	96.3± 4.04	-	-	-
	M	73	142.2 ±5.47	103.8± 4.74	-	-	-
Steyn and Iscan (South Africa)	F	47	130.5±5.3	96.2±4.10	90.0±5.03	-	-
	M	44	136.8±4.08	102.4±4.48	95.4± 5.39	-	-
Ramamoorthy et al. (India)	F	27	130.2±4.69	98.0±5.36	91.8±4.81	36.5±2.43	30.7±3.0
	M	43	135.7±6.14	102.0±5.17	94.4±5.58	36.6±3.16	31.3±2.92
Padala and Khan (India)	F	19	-	97.2±5.9	90.3±5.1	-	-
	M	31	-	102.0±4.0	95.0±5.0	-	-
Orish et al. (Nigeria)	F	22	-	98.00±4.22	96.80±2.66	-	-
	M	78	-	101±5.53	100.5±5.95	-	-
Mahakkanukrauh et al. (Thailand)	F	100	132.2±4.41	93.07± 4.03	-	33.44±2.03	28.89±1.84
	M	100	138.55±4.73	99.64 ±3.44	-	35.72±2.41	30.63±1.81
Radhakrishna et al.(India)	F	45	-	-	-	31.72±2.14	26.59±1.64
	M	55	-	-	-	34.04±2.36	28.63±1.89
Singh et al. (India)	F	24	-	-	-	32.31±3.24	27.21± 2.99
	M	26	-	-	-	33.54±2.80	27.77±2.10
Present Study (Turkey)	-	60	129.45± 4.99	99.46±4.42	88.18±4.76	35.81±7.57	28.65±1.78

Table 6. Comparison of the facial measurements of skulls with the literature

Author	Sex	n	zy-zy	d-d	ec-ec	d-ec	OL
Mahakkanukrauh et al. (Thailand)	F	100	124.72±4.82	19.46±1.97	92.76±4.42	38.23±2.1	33.57±1.55
	M	100	133.81±3.97	20.14±2.26	98.45±3.71	40.49±1.82	34.69±1.73
Farkas et al. (Canada)	-	25	131.5±5.1	24.4±1.7	98.6±4.1	40.3±3.1 (L) 40.1±3.0 (R)	-
Ziylan et al. (Turkey)	F	45	120.3±7.2		99.0±6.1	-	-
	M	40	129.2±6.0		102.9±5.1	-	-
Orish and Ibeachu (Nigeria)	F	22	-	-	-	Left 37.8±2.3 (L) Right 37.65±3.18	Left 32.75±2.23 Right 32.94±2.21
	M	78	-	-	-	Left 40.50±3.20 Right 40.01±3.20	Left 36.59±5.72 Right 36.45±3.00
Padala ve Khan (India)	F	19	49.7 ±3.3	-	-	41.0±2.4	33.0±1.9
	M	31	54.7±5.2	-	-	42.0±2.8	31.5±3.6
Ramamoorthy et al. (India)	F	27	108.8±5.73	12.9±3.07	94.6±4.24	43.8±4.25	34.6±1.69
	M	43	113.6±6.1	13.4±3.11	97.0±4.21	45.1±4.9	34.1±2.42
Present Study (Turkey)	-	60	112.07±4.91	22.67±2.27	94.30±2.61	Left 38.28±1.77 Right 38.19±1.61	Left 36.31±2.40 Right 36.22±2.11

Apertura piriformis forms the bone entrance of the nasal cavity. Uygur et al. measured the height of the apertura piriformis (APH) as 35.95±3.14 mm and its width (APW) (lower part) as 23.99±2.62 mm in their study on 38 skulls (26). In the study conducted by Aksu et al. in 101 skulls, APH was measured as 33.03±4.36 mm and APW as 23.24±2.00 mm (27). Ofodile (28) measured APW in the skulls of black people from different ethnic groups; 26.50 mm in Ashanti (West Africa), 21.60 mm in Austrians, 25.20 mm in American Indians and 23.40 mm in Americans. In the same study, APH was found to be 25.80 mm, 31.40 mm, 28.60 mm and 28.20 mm, respectively. When the findings of our study regarding these measurements are compared with other studies in the literature, the APH result in our study (left: 36.26±3.58 mm, right: 35.77±3.53 mm) was found to be higher than other studies, while the APW (24.25±1.56 mm) result is similar to other studies.

Nasal height (n-ns) is the most important measurement of nose in craniometry. Orish and Ibeachu examined 100 skulls in their study and measured the nasal height as 48.48±0.78 mm in female and 55.56±3.52 mm in male (7). Mahakkanukrauh et al. (9) measured this measurement as 48.78±2.69 mm in female and 53.53±3.06 mm in male in the 200 skulls they examined. In our study, this measurement result was found to be 49.59±3.33 mm, which stood out as a lower value compared to the measurement results in the literature.

The upper face height is the distance between nasion and prosthion (n-pr) (20). The measurement of upper face height (63.98±4.15 mm) in our study was found to be lower than the results of Ziylan et al., Kranioti et al. and Steyn and Iscan (12,16,17).

When the data we obtained are compared with the literature, it is observed that the data of other studies are higher than the data obtained in our study. Genetic, racial, developmental factors, geographical location and dietary habits can be listed among the reasons for these differences. To get more accurate information about the variation of the human skull, further research should focus on comparing different analytical methods applied to the same data set.

CONCLUSION

As a result of our study, the head and face data were generally lower than the literature. Right and left bilateral apertura piriformis height, orbital length and orbital width measurements showed right-left asymmetry, and the left side measurement results were higher than the right side.

Since it is important for radiologists, forensic anthropologists, aestheticians and neurosurgeons to know the variations of skull bones well, we think that this study will contribute to the existing knowledge about craniometric measurements and will guide the surgical interventions in this area. At the same time, we think that comparing data with different nationalities will be important in determining the structural craniometric properties for social diversity. In addition, we believe that our findings will shed light on future research.

ETHICAL DECLARATIONS

Ethics Committee Approval: Skulls, which are the fixtures of the Anatomy department, are used as educational materials in the relevant department. Therefore, ethical approval is not required.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Choudhary A, Chowdhary DS. Comparative anthropometric study of nasal parameters between two ethnic groups of Rajasthan state. Int J Med Public Health 2012; 2: 46-8.
2. Ulcay T, Kamaşak B. Sex Based Comparative Examination of Craniofacial Anthropometric Measurements in Medical School Students. Antropoloji 2020; 39: 66-73. Doi: 10.33613/antropolojidergisi.731186
3. Farkas LG, Katic MJ, Forrest CR. International anthropometric study of facial morphology in various ethnic groups/races. J Craniofac Surg 2005; 16: 615-46.
4. Taşkınalp O, Erdem N. Some vertical proportions of the face in Turkish adults. Balkan Med J 2009; 26: 49-52.
5. Porter JP, Olson KL. Anthropometric facial analysis of the African American woman. Arch Facial Plast Surg 2001; 3: 191-7.
6. Deniz M. Yetişkin kadınlarda orbital bölgenin antropometrik analizi ve yaşa bağlı değişiklikler. phD Thesis, Harran University, Şanlıurfa; 2011.
7. Orish CN, Ibeachu PC. Craniometric indices of Nigeria skulls. Int J Anat Appl Physiol 2016; 2: 6-13.
8. Farkas LG (Editor). Examination. In: Anthropometry of the head and face. Raven Press; 1994: 3-56.
9. Mahakkanukrauh P, Sinthubua A, Prasitwattanaseree S. Craniometric study for sex determination in a Thai population. Anat Cell Biol 2015; 48: 275-83.
10. Gapert R, Black S, Last J. Test of age-related variation in the craniometry of the adult human foramen magnum region: implications for sex determination methods. Forensic Sci Med Pathol 2013; 9: 478-88.
11. Farkas LG, Posnick JC, Hreczko TM. Anthropometric growth study of the head. The Cleft Palate-Craniofacial Journal 1992; 29: 303-8.
12. Ziylan T, Karabulut AK, Murshid KA, Yücel N, Çiçekçibaşı AE. İnsan kafa iskeletlerinin antropometrik analizi. S.Ü. Tıp Fakültesi Derg 2001; 17: 1-6.
13. Padala SR, Khan N. Assessment of craniometric indices of adult human skulls of South Indian origin. Int J Med Sci 2017; 3: 155-60.
14. Ramamoorthy B, Pai MM, Prabhu LV, Muralimanju BV, Rai R. Assessment of craniometric traits in South Indian dry skulls for sex determination. J Forensic Leg Med 2016; 37: 8-14.
15. Vidya CS, Prashantha B, Gangadhar MR. Anthropometric Predictors for Sexual Dimorphism of Skulls of South Indian Origin. Int J Sci Res Pub 2012; 2: 1-4.
16. Kranioti EF, İşcan MY, Michalodimitrakis M. Craniometric analysis of the modern Cretan population. Forensic Sci Int 2008; 180: 110.e1–110.e5
17. Steyn M, Iscan MY. Sexual dimorphism in the crania and mandibles of South African whites. Forensic Sci Int 1998; 98: 9-16.
18. Tritsaroli P. Artificial cranial modification on a female skeleton from the Byzantine site of Maroneia (Thrace, Greece). Int. J. Osteoarchaeol 2011; 21: 464-78.
19. Todd TW. The comparison of auricular height determinations. J Anat 1925; 59 : 390-3.
20. Sinha R, Venkatramana P (Editors). Unit 2 Craniometry, Mandibulometry, Used Somatoscopy and Somatometry. In: Practical in Physical Anthropology. IGNOU; 2017: 32.
21. Ogawa Y, Imaizumi K, Miyasaka S, Yoshino M. Discriminant functions for sex estimation of modern Japanese skulls. J Forensic Leg Med 2013; 20: 234- 8.
22. Chethan P, Prakash KG, Murlimanju BV, et al. Morphological analysis and morphometry of the foramen magnum: an anatomical investigation. Turk Neurosurg 2012; 22: 416-9.
23. Radhakrishna SK, Shivarama CH, Ramakrishna A, Bhagya B. Morphometric analysis of foramen magnum for sex determination in South Indian Population. NUJHS 2012; 2: 20-2.
24. Singh G, Talwar I. Morphometric analysis of foramen magnum in human skull for sex determination. Human Biol Rev 2013; 2: 29-41.
25. Farkas LG, Posnick JC, Hreczko TM. Growth patterns of the face: a morphometric study. Cleft Palate Craniofac J 1992; 29: 308-15.
26. Uygur M, Ertür M, Akcan A, Kayalıoğlu G. Apertura piriformis ve os nasale'nin morfometrik özellikleri. Göztepe Tıp Derg 2006; 21: 174-7.
27. Aksu F, Mas NG, Kahveci O, Çırpan S, Karabekir S. Apertura Piriformis ve Choana çapları: anatomik bir çalışma. Deü Tıp Fakültesi Derg 2013; 27: 1-6.
28. Ofodile FA. Nasal bones and pyriform apertures in blacks. Ann Plast Surg 1994; 32: 21-6.

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The relationship between renal resistive index and simple hematologic indices in patients with chronic kidney disease

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ABSTRACT

Introduction: The renal resistive index (RRI) in Doppler ultrasonography is a useful marker for measuring the blood flow changes in kidney diseases as well as showing tubulointerstitial damage. Although there have been many studies on the relationship between RRI increase and kidney damage, only a few provide information on RRI and inflammation markers. This study aimed to compare RRI with blood inflammatory markers derived from hemogram in patients with chronic kidney disease (CKD).

Material and Method: Ninety (33 female, 57 male) CKD patients who followed up at a nephrology clinic between January 2017 and December 2018 were included in this retrospective study. The RRI, serum creatinine, C-reactive protein (CRP), complete blood count results, leukocyte count (WBC), neutrophil to lymphocyte ratio (NLR), monocyte or lymphocyte (MLR), platelet to lymphocyte ratio (PLR), mean platelet volume (MPV) and red cell distribution width (RDW) values of each patient were recorded. The eGFR was calculated with a CKD-EPI formula. Nonparametric tests were used to compare age, gender, RRI, biochemistry and hemogram values for the study patients.

Results: The mean age of the patients was 55.24±14.35 years. Regarding the comparison of the RRI with age and serum CRP, a statistically significant positive relationship was found (r=.398, p<.001; r=.365, p<.001, respectively). The mean eGFR was found to be 42.47±26.57 ml/min/1.73 m^2. A statistically significant negative correlation was found between the RRI and the eGFR (r=-.312, p=.003). When the RRI was compared with the WBC and the PLR, no statistically significant relationship was found (p=.229, p=.45, respectively). However, statistically significant positive relationships were found when the RRI was compared to the NLR and the MLR, a (r=.259, p=.014/r=.228, p=.031, respectively). Additionally, there was a statistically significant positive relationship between the RRI and the RDW (p<.001, r=.383). In contrast, there was no relationship between the MPV and the RDW (p>.05).

Conclusions: The negative relationship between the RRI and the eGFR in CKD patients show that the resistive index may determine the level of renal damage.

Keywords: Renal resistive index, simple hematologic indices, chronic kidney disease

INTRODUCTION

Chronic kidney disease (CKD) is a chronic inflammatory process (1). Many factors such as increased pro-inflammatory cytokines, oxidative stress, acidosis and recurrent infections contribute to chronic inflammation in CKD patients (2). Chronic inflammation affecting tubulointerstitium increases nephron loss (3). A renal resistive index (RRI) of Doppler ultrasonography is a useful parameter for measuring blood flow changes in kidney diseases and can show damage in tubulointerstitium (4). A renal resistive index can be used in the early diagnosis of chronic tubulointerstitial nephritis in patients with preserved kidney function (5). An increased serum C-reactive protein (CRP) level has been reported in CKD when compared to healthy individuals (6,7). Mean platelet volume (MPV), the neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) increase during chronic inflammation (8-10). The monocyte to lymphocyte ratio (MLR) is an independent predictor for risk of CKD (11). The red cell distribution width (RDW) elevates during oxidative stress, inflammation, malnutrition, dyslipidemia and hypertension (12). There have been a limited number of studies in the literature comparing the RRI with inflammatory serum markers in CKD (13). The purpose of our study was to investigate whether there would be a relationship between the RRI and serum inflammatory markers in CKD patients.

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MATERIAL AND METHOD

The study was carried out with the permission of Çanakkale Onsekiz Mart University Clinical Research Ethics Committee (Permission granted 13.03.2019 Decision No. 2019-06).

In this retrospective study, the medical records of the patients that presented to the nephrology clinic of Çanakkale Onsekiz Mart University, Medical Faculty Hospital hospital between January 2017 and December 2018 were examined. Patients with CKD whose ages were between 18 and 80 years were included in the study. Patients with an age of fewer than 18 years or more than 80 years and patients with active signs of infection, chronic systemic disease history that could effect the CRP value and malignities at the time of the RRI measurement were excluded from the study. Blood was taken in vacuum gel tubes for CRP measurement. CRP was analyzed using the nephelometric method. The RRI measurement of each patient was obtained by a radiology specialist using a doppler USG device for recording. The RRI value was determined according to an average of three different measurements obtained as a result of examining the interlobar artery in the upper, middle and lower regions of the kidney. A Toshiba Aplio XG doppler USG device was used with a convex transducer (PVT-375BT) for the determination of the RRI value. The RRI value was calculated by using the following formula: "peak systolic velocity-end-diastole velocity/peak systolic velocity" (4). The complete blood count was examined with a Beckman Coulter LH-780 (Beckman Coulter Ireland Inc Mervue, Galway, Ireland). In CKD patients, the eGFR measurement was determined with the CKD-EPI formula (14).

Statistical Analysis

The data from this research was electronically transferred to the SPSS 20.0 statistics program, and data control and analysis were performed. In evaluating the normal distribution of data, Kolmogorov-Smirnov test was used. The average, standard deviation, median, minimum and maximum values were used to evaluate continuous variables. A Spearman correlation analysis was used to compare the markers examined for statistical evaluation. The $p<.05$ value was accepted as proof of statistical significance.

RESULTS

Ninety CKD patients (33 females, 57 males) were included in this study. The demographic features and serum markers of the patients are shown in **Table 1**. Statistically significant positive correlations were found between the RRI of CKD patients and age, as well as serum CRP level ($r=.398$, $p<.001$; $r=.365$, $p<.001$, respectively). Conversely, a statistically significant negative correlation was found between the RRI and the eGFR ($r=-.312$, $p=.003$). Additionally, there was a statistically significant positive relationship between the RRI and the NLR ($r=.259$, $p=.014$). When the RRI and the MLR were compared, a statistically significant positive relationship was further found ($r=.228$, $p=.031$). There was no statistically significant relationship between the RRI and the MPV or the RRI and the PLR ($p=.141$, $p=.45$, respectively). There was a statistically significant positive relationship between the RRI and the RDW ($r=.383$, $p<.001$). The relationship between renal resistive index and hematologic parameters of the patients are shown in **Table 2**.

Table 1. Demographic findings and serum markers of patients

Demographic findings and serum markers	Mean±standard deviation	Median (min-max)
Age (years)	55.24±14.35	55.5 (26-79)
RRI	0.70±0.09	0.70 (0.50-0.85)
Serum creatinine (mg/dL)	2.09±1.26	1.8 (0.6-9.0)
eGFR (mL/min/1.73 m^2)	42.47±26.57	35.5 (5-127)
Serum uric acid (mg/dL)	6.41±1.8	6.1 (1.2-11.0)
Serum albumin (g/dL)	4.24±0.65	4.3 (2.3-5.4)
Serum CRP (mg/dL)	1.79±2.92	0.6 (0.1-16.5)
Serum total cholesterol (mg/dL)	180.5±43.1	166 (110-328)
Serum triglyceride (mg/dL)	158.6±76.2	130 (45-449)
WBC (mm^3)	8133±2654	8065 (1260-17240)
Hemoglobin (g/dL)	11.89±2.24	12.0 (6.4-16.7)
PLT (mm^3)	258500±95348	241000 (59000-528000)
MPV (fL)	8.57±1.35	8.4 (6.4-15.5)
RDW	15.16±2.16	15 (12-23)
NLR	7.12±9.13	4.15 (0.7-55.33)
PLR	357.78±475.54	199.45 (36.3-2677.8)
MLR	0.67±0.73	0.42 (0.04-5.1)

RRI, renal resistive index; eGFR, estimated glomerular filtration rate; WBC, white blood cell; PLT, platelet count; MPV, mean corpuscular volume; RDW, red blood cell distribution width; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; MLR, monocyte lymphocyte ratio.

Table 2. The relationship between renal resistive index and hematologic parameters

	RRI	
Hematologic parameters	**r**	**p**
WBC	0.129	0.229
Hemoglobin	-0.225	0.034
PLT	-0.87	0.419
MPV	-0.157	0.141
RDW	0.383	<0.001
Neutrophil	0.150	0.160
Lymphocyte	-0.126	0.259
Monocyte	0.118	0.271
NLR	0.259	0.014
MLR	0.228	0.031
PLR	0.081	0.450

RRI, renal resistive index; WBC, white blood cell; PLT, platelet count; MPV, mean corpuscular volume; RDW, red blood cell distribution width; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; MLR, monocyte lymphocyte ratio.

Regarding the serum CRP of CKD patients, statistically significant correlations were determined between the CRP and the NLR, PLR, MLR and RDW ($p<.05$). However, no statistically significant relationship was found between the CRP and the MPV ($p=.258$).

DISCUSSION

In chronic kidney disease, the NLR, PLR, MLR, RDW, MPV and serum CRP increase relative to inflammation (6,8-11,13,15). In some studies, a positive correlation was found between the RRI and serum CRP in CKD patients (13,16). Apart from this study, we did not find other studies comparing the RRI with serum inflammatory markers such as the NLR, PLR, MLR, RDW and MPV in chronic kidney disease. In our study, we found a positive significant relationship between the RRI and the CRP, NLR, MLR, and RDW in CKD patients. In contrast, there was no association between the RRI and the PLR or between RRI and the MPV.

Chronic inflammation affects tubulointerstitium and increases nephron loss (3). The RRI has been found useful in chronic nephropathy and in demonstrating tubulointerstitial damage (4,5). In our study, we found a negative correlation between the RRI and the eGFR and a positive correlation between the RRI and age. This result was consistent with that of the literature (4,5,13). In end-stage renal failure, the elevation of serum hs-CRP is accompanied by an increase in the NLR and the PLR (10). In our study, the serum CRP levels of the patients were found to correlate positively with each of the other inflammatory markers, including the NLR, PLR, MLR and RDW and excluding the MPV.

In our study, we did not find a relationship between the serum CRP level and the MPV or between the RRI and the MPV in CKD patients. Although Yilmaz et al. (7) have reported an inverse correlation between the MPV and fibrinogen in stage 3–4 CKD patients, the authors have not shown an MPV increase in the case of disease progression. In patients with hypertensive CKD (stage 1–3), the PLR has not been demonstrated to have an impact on the progression of the disease (17). These findings suggest that an increase in the MPV and PLR may not be expected with the progression of CKD.

There were several factors that limited our study. Our retrospectively planned study included a limited number of patients. Body mass index, blood pressure measurement, serum glucose, fibrinogen, electrolytes and total protein in urine were not assessed simultaneously for patients. Additionally, a control group could not be included in this study.

CONCLUSION

In addition to determining the degree of vascular occlusion, the RRI can be useful when evaluating the chronic inflammatory response accompanying tubulointerstitial injury for CKD patients. Prospective studies are needed on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Çanakkale Onsekiz Mart University Clinical Researchs Ethics Committee (Permission granted: 13.03.2019, Decision no. 2019-06).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Tonelli M, Wiebe N, Culleton B, et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol. 2006; 17: 2034-47.
2. Akchurin OM, Kaskel F. Update on inflammation in chronic kidney disease. Blood Purif 2015; 39: 84-92.
3. Schnaper HW. The tubulointerstitial pathophysiology of progressive kidney disease. Adv Chronic Kidney Dis 2017; 24: 107-16.

4. Pontremoli R, Viazzi F, Martinoli C, et al. Increased renal resistive index in patients with essential hypertension: a marker of target organ damage. Nephrol Dial Transplant 1999; 14: 360-5.
5. Boddi M, Cecioni I, Poggesi L, et al. Renal resistive index early detects chronic tubulointerstitial nephropathy in normo- and hypertensive patients. Am J Nephrol 2006; 26: 16-21.
6. Bolton CH, Downs LG, Victory JG, et al. Endothelial dysfunction in chronic renal failure: roles of lipoprotein oxidation and pro-inflammatory cytokines. Nephrol Dial Transplant 2001; 16: 1189-97.
7. Yilmaz G, Sevinc C, Ustundag S, et al. The relationship between mean platelet volume and neutrophil/lymphocyte ratio with inflammation and proteinuria in chronic kidney disease. Saudi J Kidney Dis Transpl 2017; 28: 90-4.
8. Ju HY, Kim JK, Hur SM, et al. Could mean platelet volume be a promising biomarker of progression of chronic kidney disease? Platelets 2015; 26: 143-7.
9. Kocyigit I, Eroglu E, Unal A, et al. Role of neutrophil/lymphocyte ratio in prediction of disease progression in patients with stage-4 chronic kidney disease. J Nephrol 2013; 26: 358-65.
10. Ahbap E, Sakaci T, Kara E, et al. Neutrophil-to-lymphocyte ratio and platelet-tolymphocyte ratio in evaluation of inflammation in end-stage renal disease. Clin Nephrol 2016; 85: 199-208.
11. Zhang M, Wang K, Zheng H, Zhao X, Xie S, Liu C. Monocyte lymphocyte ratio predicts the new-onset of chronic kidney disease: a cohort study. Clin Chim Acta 2020; 503: 181-9.
12. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: a simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci 2015; 52: 86-105.
13. Lai S, Ciccariello M, Dimko M, et al. Cardio-renal syndrome type 4: the correlation between cardiorenal ultrasound parameters. Kidney Blood Press Res 2016; 41: 654-62.
14. GFR Calculator. National Kidney Foundation. 2020. Available online: https: //kidney.org/professional/kdoqi/ gfr_calculator.cfm
15. Zhang T, Li J, Lin Y, Yang H, Cao S. Association between red blood cell distribution width and all-cause mortality in chronic kidney disease patients: a systematic review and meta-analysis. Arch Med Res 2017; 48: 378-85.
16. Ozmen ND, Mousa U, Aydin Y, Deren T, Unlu EB. Association of the renal resistive index with microvascular complications in type 2 diabetic subjects. Exp Clin Endocrinol Diabetes 2015; 123: 112-7.
17. Sevencan NO, Ozkan AE. Associations between neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, albuminuria and uric acid and the estimated glomerular filtration rate in hypertensive patients with chronic kidney disease stages 1-3. Arch Med Sci 2019; 15: 1232-9.

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An evaluation of risk factors affecting amputation in patients with diabetic foot infection

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ABSTRACT

Introduction: Diabetic foot infections are one of the most common complications of diabetes and generally result in lower extremity amputations.

Aim: The purpose of this study is to investigate risk factors affecting amputation in patients diagnosed with diabetic foot ulcer.

Material and Method: This prospective cohort study involved 137 patients diagnosed with diabetic foot infection in a university hospital diabetic foot clinic.

Results: The mean age of the participants was 60.5±10.1 years, and 70.8% (n=97) were men. The majority of patients (62.0%) were educated to elementary or middle school level, while 26.3% were illiterate. Mean duration of diabetes was 13.3±6.2 years. Hypertension was present in 48.2% of patients, hypercholesterolemia in 31.4%, cardiovascular disease (CVD) in 38%, peripheral artery disease (PAD) in 21.2%, peripheral venous insufficiency in 10.2%, and polyneuropathy in 70.1%, and 9.5% were receiving hemodialysis. According to the PEDIS classification, moderate foot ulcers were present in 60.6% of patients, mild ulcers in 34.3%, and severe ulcers in 5.1%. Forty-six percent of patients were diagnosed with osteomyelitis during follow-up. Amputation was present in 28.5% (n=39) of the patients followed-up due to foot ulcers. PAD increased the risk of amputation 2.7-fold (95% CI: 1.02-7.14), osteomyelitis 2.6-fold (95% CI: 1.10-6.16), and repeated hospitalizations 5.9-fold (95% CI: 2.25-15.33). Growth was observed in 72.6% of patients without amputation, 76.5% were polymicrobial, and 65.9% of antibiogram results were multidrug resistant. No significant difference was observed among the patients in terms of multidrug resistance (p=0.468).

Conclusion: PAD, osteomyelitis, and history of repeated hospitalizations are separate risk factors for amputation in patients with diabetic foot ulcers.

Keywords: Diabetic foot, amputation, risk factors, infection, multidrug resistance

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease affecting approximately 425 million individuals worldwide. Hyperglycemia is a condition caused by a problem in the effect and/or production of insulin (1). Diabetic foot ulcer (DFU) is one of the most common diabetic complications. The lifetime prevalence of DFU in diabetic patients is estimated at 19-34% (2). DFU arising from peripheral neuropathy (PNP), peripheral vascular disease, and poor glycemic control results in lower extremity amputations (3). DFU causes amputation at different levels at a rate of approximately 20% (4). DFU therefore has an adverse impact on patients' quality of life and increases treatment costs. Several factors causing increased morbidity and mortality in diabetic patients have been identified. These include the duration of the disease, coronary artery disease, smoking, male gender, diabetic nephropathy, and peripheral artery disease (PAD) (5). Diabetic foot infections are also associated with increased amputations rates, morbidity, and mortality (6,7).

Polymicrobial infections can make healing of the ulcer less likely and can lead to amputation and death (8). The purpose of this study was to evaluate risk factors affecting amputation in the light of data obtained prospectively in patients under follow-up in our clinic with diagnoses of diabetic foot infection.

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MATERIAL AND METHOD

The study was carried out with the permission of Atarürk University Clinical Researches Ethics Committee (Permission granted: 07.05.2020, Decision no: 04-04, Ethics approval certificate: B.30.2.ATA.0.01.00/200). One hundred thirty-seven patients aged 18 or over, with type 2 DM and hospitalized for treatment of foot ulcer in our clinic were included in this study that commenced in May 2019. This is a prospective study with a sample of 137 patients with DFU and infected. Patients were followed-up for one year. Repeat hospitalizations during the follow-up process were disregarded and considered as a single case.

Demographic data including age, sex, place of residence, and education level, and duration of disease, treatment received and presence of amputation, and comorbid conditions including hemodialysis, cardiovascular disease (CVD), hypercholesterolemia, hypertension (HT), PAD, peripheral venous insufficiency (PVI), peripheral neuropathy (PNP), smoking, and osteomyelitis, tissue culture results, polymicrobial growth, and multidrug resistance (MDR) of growing agents were evaluated.

All open lesions on the feet of patients with diabetes were defined as ulcers and we hospitalized patients diagnosed with DFUs whose general condition was so poor that outpatient clinic-based treatments were not possible. All ulcers were analyzed according to the severity of infection using the PEDIS (Perfusion, Extent/size, Depth/tissue loss, Infection) classification (9). According to this classification, absence of signs and findings of infection is defined as "Grade 1". Local infection involving only the skin and subcutaneous tissue (rim of erythema around the ulcer of 0.5-2 cm) is defined as "Grade 2". Involvement of structures extending deeper than the skin and subcutaneous tissue (abscess, osteomyelitis, septic arthritis, fasciitis) without systemic infection findings, and with a rim of erythema around the ulcer >2 cm is defined as "Grade 3". The presence, in addition to local infection, of at least two inflammatory response syndrome markers (body temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20/min or $PaCO_2$ <32 mmHg, or white cell count >12,000 or 4000 cell/uL or ≥10% band formation) is defined as "Grade 4".

Osteomyelitis was diagnosed via magnetic resonance imaging. Presence of PNP was evaluated on electromyography (EMG) test. Vascular evaluations were made by means of palpation of distal pulses, and using Doppler ultrasound. Cultures in which there was no bacterial growth were considered negative. Cultures that grew two or more different bacteria were considered polymicrobial. The fact that the factors isolated from patients were resistant to at least one of three or more antibiotic groups was defined as MDR (10). Amputations were defined as under-ankle amputations as minor, and above-ankle amputations as major amputations. HbA_{1c} levels were employed to assess patients' diabetic control. Laboratory values at time of presentation to the clinical were employed at statistical analysis

Statistical Analysis

Data analysis was performed on SPSS for Windows version 22 software (Statistical Package for the Social Sciences). Categorical variables were expressed as number and percentage, and numerical variables as mean plus standard deviation. Normality of distribution of numerical variables was investigated using the Kolmogorov Smirnov test, z values calculated for skewness and kurtosis, and charts/tables. The t test was used to compare normally distributed numerical variables between the groups, the Mann Whitney U test to compare non-normally distributed numerical variables between the groups, and the χ^2 test to compare the distribution of categorical variables in the groups. Binary logistic regression analysis was applied to identify risk factors affecting amputation. Independent variables identified as significant at univariate regression analysis were included in the regression model. The backward LR method was used at regression analysis. p levels <0.05 were regarded as significant for all analyses.

RESULTS

The mean age of the 137 cases included in the study was 60.5±10.1 years, and 70.8% (n=97) were men. Mean ages were 62.5±11.9 years for women and 59.6±9.2 men, and the difference was not statistically significant (p=0.132). The majority of patients (62.0%) were educated to elementary or middle school level, and 26.3% were illiterate.

Mean duration of diabetes was 13.3±6.2 years. While 48.9% (n=67) of patients were using insulin alone for DM, 37.2% were using insulin together with oral hypoglycemic drugs. A history of smoking was present in 36.5% of patients, and 20.4% were still smokers.

Mean blood leukocyte count (WBC) at time of admission to the clinic was 9982.9±4172.8, C-reactive protein (CRP) 64.6±65.4 mg/L, sedimentation rate 55.7±29.5 mm/h, HbA_{1c} 9.5±2.6 mg/dL, and creatinine 1.4±1.5 mg/dL.

HT was present in 48.2% of patients, hypercholesterolemia in 31.4%, CVD in 38%, PAD in 21.2%, PVI in 10.2%, and PNP in 70.1%, and 9.5% were receiving hemodialysis. According to the PEDIS classification, "grade 3" foot ulcers were present in 60.6% of patients, "grade 2" ulcers in 34.3%, and "grade 4" ulcers in 5.1%. Forty-six percent

of patients were diagnosed with osteomyelitis during follow-up. Amputation was present in 28.5% (n=39) of patients followed-up due to foot ulcers. 34 of the cases were minor and 5 were major amputation. No mortality occurred during the follow-up period.

Patients with amputation were compared with those without amputation. PAD was present in 21.2% (n=29) of cases, and the distribution of amputations was significantly higher these patients than in those without PAD (p=0.037). Osteomyelitis developed in 46.0% (n=63) of patients, and the distribution of amputation was also higher among these patients (p=0.004).

Growth was observed in 27.4% of tissue cultures in amputated patients and in 72.6% among non-amputated patients, of which 23.5% and 76.5%, respectively, were polymicrobial. Growth in culture and polymicrobial culture results were similar among the amputated and non-amputated patients (p=0.518, and p=0.462, respectively). However, antibiogram results of 34.1% of amputated patients and 65.9% of non-amputated patients were reported as MDR (+), and no significant difference in MDR distributions was observed among the patients (p=0.468). The agents most commonly isolated from cultures were *Staphylococcus spp*. (36.7%) in amputated patients and *Escherichia spp*. (35.3%) in non-amputated patients.

Demographic characteristics of the patients with and without amputation, comorbid characteristics, a comparison of various laboratory parameters, and distributions of foot ulcers according to the PEDIS classification are shown in **Table 1**.

Logistic regression analysis was applied in order to evaluate risk factors for amputation. Major and minor amputations were included in the regression model as a dependent variable. Risk factors identified as significant at univariate analysis were added to the multivariate regression model. PAD, osteomyelitis, and history of repeated hospitalizations were found to make a significant contribution to the final model obtained using the backward elimination method with presence of amputation as the dependent variable. PAD increased the risk of amputation 2.7-fold (95% CI: 1.02-7.14), osteomyelitis 2.6-fold (95% CI: 1.10-6.16), and repeated hospitalizations 5.9-fold (95% CI: 2.25-15.33) (**Table 2**).

Table 2. Logistic regression analysis results

Variable	Wald	OR	95% CI	p value
Hemodialysis	3.113	3.394	0.873-13.193	0.078
PAD	3.977	2.695	1.017-7.142	0.046
Osteomyelitis	4.800	2.611	1.106-6.163	0.028
Repeated hospitalization	13.128	5.881	2.255-15.335	<0.001

R2= 0.28 (Nagelkerke). χ^2 (5)= 1.12 (Hosmer&Lemeshow)

DISCUSSION

Diabetic foot ulcer is a complication involving severe outcomes, such as psychosocial problems, the need for prolonged hospitalization for treatment, and amputation. Some recent studies have reported that DFU is an important independent predictor of mortality and frequently leads to lower extremity amputation (11,12). It is of great importance to identify risk factors in order to prevent extremity losses in patients with DFUs. In the present study, PAD, osteomyelitis, and a history of repeated hospitalizations were identified as independent risk factors for amputation at logistic regression analysis.

The mean age of the patients undergoing amputation was 61. One population-based study reported an approximate mean age of 65 (13). While some studies have reported a significant effect of age on amputations others, including the present research, have reported no such effect (14,15).

Sex was reported as a risk factor in Moon et al.'s study of risk factors for major amputation in DFU patients (16). Studies have also shown that major amputation rates in DFUs are significantly higher among men than in women (17,18). In the present study, although the amputation rate was higher among male DFU patients, sex was not identified as a risk factor at regression analysis. Men are generally taller, and PNP is more common among men. In addition, joint mobility and the pressure to which the feet are exposed are also greater in men (19,20). In contrast, women pay more attention to personal care, and engage in more active wound care (21). These factors may account for the higher prevalences of DFU and amputation among men.

Orneholm et al. reported a significant association between age and wound healing in patients with DFUs (22). Studies have also reported that advanced age and duration of diabetes exceeding 10 years increase the risk of mortality (23). On the other hand, it is also possible to encounter studies reporting that age is not a risk factor for amputation (16). The findings of the present study suggest that patient age and duration of diabetes are not risk factors for amputation (p>0.05).

Several studies have described weak glycemic control as a risk factor for amputation in diabetic patients (16, 24,25). In contrast to Selvin et al.'s study describing an increase in HbA_{1c} levels as increasing the risk of major amputation, Winkley et al. reported that low HbA_{1c} levels were associated with higher mortality (26,27). HbA_{1c} was also not reported as a predictive factor for amputation in Cardoso et al.'s study (28). Serum HbA_{1c} levels were also not identified as a risk factor for amputation in the present study.

Table 1. Demographic characteristics, diabetic treatment, comorbid characteristics, a comparison of various laboratory parameters, and distributions of foot ulcers according to the PEDIS classification of the patients with and without amputation

Variables		Amputated (n=39)	Non-amputated (n=98)	p value
Age (years)		60.7±11.6	60.4±9.5	0.845
Sex [n (%)]	Female	13 (32.5)	27 (67.5)	0.502
	Male	26 (26.8)	71 (73.2)	
Education [n (%)]	Not literate	15 (41.7)	21 (58.3)	0.068
	Elementary/middle school	22 (25.9)	63 (74.1)	
	High school/university	2 (12.5)	14 (87.5)	
	Duration of diagnosis (years)	13.2±6.5	13.3±6.2	0.914
Diabetes treatment [n (%)]	Insulin	18 (26.9)	73.1	0.253
	Oral hypoglycemic drugs	3 (15.8)	84.2	
	Insulin and oral hypoglycemic drugs	18 (35.3)	64.7	
Smoking history [n (%)]	Yes	14 (28.0)	36 (72.0)	0.815
	No	26 (29.9)	61 (70.1)	
Hypertension [n (%)]	Yes	21 (31.8)	45 (68.2)	0.515
	No	19 (26.8)	52 (73.2)	
Hypercholesterolemia [n (%)]	Yes	10 (23.3)	33 (76.7)	0.301
	No	30 (31.9)	64 (68.1)	
Cardiovascular disease [n (%)]	Yes	15 (28.8)	37 (71.2)	0.944
	No	25 (29.4)	60 (70.6)	
Peripheral artery disease [n (%)]	Yes	13 (44.8)	16 (55.2)	0.037
	No	27 (25.0)	81 (75.0)	
Peripheral venous insufficiency [n (%)]	Yes	4 (28.6)	10 (71.4)	0.957
	No	36 (29.3)	87 (70.7)	
Peripheral neuropathy [n (%)]	Yes	31 (32.3)	65 (67.7)	0.233
	No	9 (22.0)	32 (78.0)	
Hemodialysis [n (%)]	Yes	7 (53.3)	6 (46.2)	0.054
	No	33 (26.6)	91 (73.4)	
Osteomyelitis [n (%)]	Yes	26 (41.3)	37 (58.7)	0.004
	No	14 (18.9)	60 (81.1)	
PEDIS classification [n (%)]	Grade 2	7 (14.9)	40 (85.1)	0.056
	Grade 3	29 (34.9)	54 (65.1)	
	Grade 4	3 (42.9)	4 (57.1)	
	WBC	10345.4±4299.1	9838.6±4135.1	0.523
	Sedimentation (mm/h)	62.7±22.3	52.9±31.6	0.043
	CRP	75.5±74.4	60.3±61.4	0.317
	Creatinine (mg/dL)	1.8±2.2	1.3±1.1	0.588
	HbA1c1 (mg/dL)	9.7±2.8	9.4±2.5	0.901
Growth in culture [n (%)*]	Yes	34 (87.2)	90 (91.8)	0.518
	No	5 (12.8)	8 (8.2)	
Polymicrobial culture result [n (%)*]	Yes	8 (20.5)	26 (26.5)	0.462
	No	31 (79.5)	72 (73.5)	
Multipl drug resistance [n (%)*]	Yes	14 (48.3)	27 (40.3)	0.468
	No	15 (51.7)	40 (59.7)	
Pathogens growing in culture [n (%)*]	*Enterococcus spp*	2 (5.9)	8 (8.9)	
	Staphylococcus spp	7 (20.6)	33 (36.7)	
	Streptococcus spp	1 (2.9)	5 (5.6)	
	Acinetobacter spp	2 (5.9)	9 (10.0)	
	Citrobacter spp	3 (8.8)	5 (5.6)	
	Escherichia spp	12 (35.3)	17 (18.9)	
	Enterobacter spp	2 (5.9)	3 (3.3)	
	Klebsiella spp	1 (2.9)	6 (6.7)	
	Proteus spp	3 (8.8)	3 (3.3)	
	Pseudomonas spp	1 (2.9)	1 (1.1)	

*: Column percentage

A low level of education can adversely effect patients' possession of adequate information about diabetes and its complications, and also the prevention of such complications (28). No association was determined between patients' education levels and amputation status in the present study, and education did not emerge as a risk factor in progression to amputation.

Osteomyelitis was identified as a risk factor increasing progression to amputation 2.6-fold in patients with DFUs (p=0.028). Namgoong et al. reported that ulcers with bone involvement were an important risk factor for major amputation (29). Based on the study findings, the treatment decision being taken in the early period appears to be very important in preventing the progression of DFUs and amputation.

Hypertension, PNP, nephropathy and dyslipidemia also appear among the risk factors for amputation in the literature (29,30,31). However, no significant relationship between amputation and HT, hypercholesterolemia, CVD, PNP, or neuropathy was observed in the present study. The presence of PAD has been described as one of the important risk factors for amputation in diabetics (29,32). In the present study, presence of PAD increased the risk of amputation 2.7-fold (p=0.046).

Diabetic patients are generally hospitalized for treatment due to other comorbid diseases and foot ulcers. In the present study, a history of repeated hospitalization increased the risk of amputation 5.9-fold (p<0.001). While this study was planned as prospective single-center research involving only patients under follow-up by the infectious diseases clinic, the short follow-up period of one year represents its principal limitation. In addition, the effectiveness in terms of progression to amputation of multidisciplinary diabetic foot management could not be evaluated. We think that multi-center and multidisciplinary studies are now needed to assess risk factors for amputation in patients with DFUs.

The type of bacterium isolated from infected ulcers of diabetic feet was not identified as a risk factor for amputation in this study. The most commonly isolated bacteria in the amputated patient group were E. coli (35.39%) and *Staphylococcus spp.* (20.6%). In a study conducted in our country, it was reported that the most common bacteria isolated from diabetic wound infections are Staphyloccus aureus, group B hemolytic streptococci and *Klebsiella spp*. (33). In Cardoso et al.'s study, the most commonly isolated micro-organisms in DFUs in patients with amputation and resulting in mortality were *Acinetobacter spp*. (33.3%), *Morganella spp.* (33.3%) and *Proteus spp*. (27.8%). The type of bacterium isolated was reported not to constitute a risk factor associated with mortality (28). In another, retrospective, study, 65% of cases resulted in amputation, and the most common bacteria were *Staphyloccus spp*. (34).

Polymicrobial cultures may also occur in patients with DFUs, and this can delay the ulcer healing process (8). No polymicrobial culture dominance (23.5%) was observed in amputated patients in this study, and polymicrobial culture was not identified as a risk factor for amputation. Polymicrobial growth is frequently present in patients with severe infection and prolonged DFUs. Knowing the microbiological etiology is an important factor in managing the treatment of DFUs.

Multidrug resistant infections are a significant and growing global problem. Resistant strains prolong patients' hospital stays and increase treatment costs (35). Although the prevalence of MDR was higher in our non-amputated patient group (65.9%), there was no significant difference among the patients in terms of MDR distributions. Prolonged DFUs can result in repeated hospitalizations and multidrug resistant infections. Knowledge of antibiotic susceptibility and multidrug resistance status will be helpful to physicians in prescribing effective medications in the treatment of DFUs.

CONCLUSION

Peripheral artery disease, osteomyelitis, and a history of repeated hospitalizations emerged as risk factors for amputation in patients with DFUs. The identification of risk factors can serve as a useful guide to physicians in the management of such patients. The ability to control diabetic foot and its complications depends on the establishment of a multidisciplinary clinical team and the development of public health-based protection strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Atarürk University Clinical Researches Ethics Committee (Permission granted: 07.05.2020, Decision no: 04-04).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. International Diabetes Federation, IDF Diabetes Atlas, International Diabetes Federation, Brussels, Belgium, 8th edition, 2017.
2. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. Ann Med 2017; 49: 106-16.
3. Apelqvist J, Larsson J. What is the most effective way to reduce incidence of amputation in the diabetic foot? Diabetes Metab Res Rev 2000; 16 Suppl 1: S75-S83.
4. Chronic Complications of Diabetes, Diabetes and Foot. National Diabetes Consensus Group. TURKDIAB Diabetes Diagnosis and Treatment Guideline. 2019; 121-30.
5. Brownrigg JRW, Griffin M, Hughes CO, et al. Influence of foot ulceration on cause-specific mortality in patients with diabetes mellitus. J Vasc Surg 2014; 60: 982–6.
6. Turhan V, Mutluoglu M, Acar A, et al. Increasing incidence of Gram-negative organisms in bacterial agents isolated from diabetic foot ulcers. J Infect Dev Ctries 2013; 7: 707-12.
7. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med 2017; 376: 2367-75.
8. Spicler A, Hurwitz BL, Armstrong DG, Lipsky BA. Microbiology of diabetic foot infections: from Luis Pasteur to 'crime scene investigation'. BMC Med 2015; 13: 1-13.
9. The International Working Group on the Diabetic Foot. International consensus on diagnosing and treating the infected diabetic foot. 4th International symposium on the diabetic foot. Noordwijkenhout-The Netherlans. 22-24 May 2003. Schaper NC. Diabetes Metab Res Rev 2004; 20: 90-5.
10. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012; 18: 268-81.
11. Barwell ND, Devers MC, Kennon B, et al. Diabetic foot infection: Antibiotic therapy and good practice recommendations. Int J Clin Pract 2017; 71: 10.1111/ijcp.13006.
12. Apelqvist J, Larsson J. What is the most effective way to reduce incidence of amputation in the diabetic foot? Diabetes Metab Res Rev 2000; 16: 75-83.
13. Baba M, Davis WA, Norman PE, Davis TM. Temporal changes in the prevalence and associates of diabetes-related lower extremity amputations in patients with type 2 diabetes: the Fremantle Diabetes Study. Cardiovasc Diabetol. 2015; 14: 1-10.
14. De Jesus-Silva SG, De Oliveira JP, Colepicolo Brianezi MH, De Moraes Silva MA, Krupa AE, Cardoso RS. Analysis of risk factors related to minor and major lower limb amputations at a tertiary hospital. J Vasc Bras 2017; 16: 16-22.
15. Namgoong S, Jung S, Han SK, Jeong SH, Dhong ES, Kim WK. Risk factors for major amputation in hospitalised diabetic foot patients. Int Wound J 2016; 13: 13-9.
16. Moon KC, Kim SB, Han SK, Jeong SH, Dhong ES. Risk factors for major amputation in hospitalized diabetic patients with forefoot ulcers. Diabetes Res Clin Pract 2019; 158: 107905.
17. Al-Mahroos F, Al-Roomi K. Diabetic neuropathy, foot ulceration, peripheral vascular disease and potential risk factors among patients with diabetes in Bahrain: a nationwide primary care diabetes clinic-based study. Ann Saudi Med 2007; 27: 25-31.
18. Bruun C, Siersma V, Guassora AD, Holstein P, de Fine Olivarius N. Amputations and foot ulcers in patients newly diagnosed with type 2 diabetes mellitus and observed for 19 years. The role of age, gender and co-morbidity. Diabet Med 2013; 30: 964-72.
19. Larsson LG, Baum J, Mudholkar GS. Hypermobility: features and differential incidence between the sexes. Arthritis Rheum 1987; 30: 1426-30.
20. Cheng YJ, Gregg EW, Kahn HS, Williams DE, De Rekeneire N, Narayan KM. Peripheral insensate neuropathy--a tall problem for US adults? Am J Epidemiol 2006; 164: 873-80.
21. Hjelm K, Nyberg P, Apelqvist J. Gender influences beliefs about health and illness in diabetic subjects with severe foot lesions. J Adv Nurs 2002; 40: 673-84.
22. Orneholm H, Apelqvist J, Larsson J, Eneroth M. High probability of healing without amputation of plantar forefoot ulcers in patients with diabetes. Wound Repair Regen 2015; 23: 922-31.
23. Al-Rubeaan K, Youssef AM, Ibrahim HM, et al. All-cause mortality and its risk factors among type 1 and type 2 diabetes mellitus in a country facing diabetes epidemic. Diabetes Res Clin Pract. 2016; 118: 130-9.
24. Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG. A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. Diabetes Care 1999; 22: 1036-42.
25. Shatnawi NJ, Al-Zoubi NA, Hawamdeh HM, Khader YS, Garaibeh K, Heis HA. Predictors of major lower limb amputation in type 2 diabetic patients referred for hospital care with diabetic foot syndrome. Diabetes Metab Syndr Obes 2018; 11: 313-9.
26. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004; 141: 421–31.
27. Winkley K, Stahl D, Chalder T, Edmonds ME, Ismail K. Risk factors associated with adverse outcomes in a population-based prospective cohort study of people with their first diabetic foot ulcer. J Diabetes Complications 2007; 21: 341–9.
28. Cardoso HC, Zara ALSA, Rosa SSRF, et al. Risk factors and diagnosis of diabetic foot ulceration in users of the Brazilian public health system. J Diabetes Res 2019; 2019: 5319892.
29. Namgoong S, Jung S, Han SK, Jeong SH, Dhong ES, Kim WK. Risk factors for major amputation in hospitalised diabetic foot patients. Int Wound J 2016; 13 Suppl 1: 13-9.
30. Al-Rubeaan K, Al Derwish M, Ouizi S, et al. Diabetic foot complications and their risk factors from a large retrospective cohort study. PLoS One 2015; 10: e0124446.
31. Khawaja N, Abu-Shennar J, Saleh M, Dahbour SS, Khader YS, Ajlouni KM. The prevalence and risk factors of peripheral neuropathy among patients with type 2 diabetes mellitus; the case of Jordan. Diabetol Metab Syndr 2018; 10: 8.
32. Faglia E. Characteristics of peripheral arterial disease and its relevance to the diabetic population. Int J Low Extrem Wounds 2011; 10: 152–66.
33. Bozkurt F, Tekin R, Çelen MK, Celal A. Diyabetik ayak enfeksiyonlu hastalarda Wagner sınıflaması ve kültür sonuçlarının değerlendirilmesi. Dicle Tıp Dergisi. 2011; 38: 31-4.
34. Oliveira AFD, Oliveira Filho HD. Microbiological species and antimicrobial resistance profile in patients with diabetic foot infections. J Vasc Bras 2014; 13: 289-93
35. Oliva A, Giacobbe DR, Di Luca M, Miller NS. New insights into infections due to multidrug resistant gram negative Bacteria: The Interplay between Lab and Clinic. Biomed Res Int 2018; 2018: 8905874.

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Risk of malnutrition in general surgical patients

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ABSTARCT

Aim: The aim of this study is to determine the malnutrition risk of patients hospitalized in the general surgery clinic and to evaluate the relationship between malnutrition risk and anthropometric measurements.

Material and Method: The study was carried out with 228 adults who were hospitalized in the general surgery clinic. Weight, body mass index (BMI), waist circumference, upper middle arm circumference (MUAC), triceps skinfold thickness (TSF) and handgrip strength measurements were taken. The nutritional status of the patients was evaluated with Nutritional Risk Screening (NRS)-2002 and Subjective Global Assessment (SGA).

Results: According to the NRS-2002, 30.3% of patients had a risk of malnutrition; according to the SGA 34.2% had moderate and 12.3% had severe malnutrition. The anthropometric measurements evaluated in the study and the length of hospital stay (LHOS) were found to be related to the NRS-2002 score and SGA level ($p<0.05$). The parameter that most affected the NRS-2002 score was MUAC (19.6%), the LHOS was the most affected by the NRS-2002 score (8.6%) ($p<0.05$).

Conclusion: The determination of malnutrition risk in general surgery clinics by using practical screening tools such as NRS-2002 and SGA and evaluating anthropometric measurements at certain intervals will enable early nutritional support to be initiated, thereby preventing the risk of developing malnutrition and its complications and contributing surgical procedures' success.

Keywords: Anthropometric measurements, general surgery, length of hospital stay, malnutrition, Nutritional Risk Screening-2002, Subjective Global Assessment

INTRODUCTION

Malnutrition, which is an important public health problem for developed and developing countries, occurs with decreased food intake and deterioration in nutritional status, and causes loss of weight in a short time involuntarily (1,2). Nutritional deficiencies are largely due to the direct loss of nutrients, an increase in nutritional requirements and insufficient nutrient consumption required to meet these requirements. However, nutritional problems such as medications, restrictive diets, prolonged hunger, anorexia, nausea and vomiting also contribute to the development of malnutrition (3).

Although malnutrition is common in hospitalized patients, it is an important health problem that is often ignored (4). It has been reported that the prevalence of hospital malnutrition exceeds 70% in low and middle-income countries and up to 50% in high-income countries (5). However, it has been stated that the frequency of malnutrition seen in patients may change between 20-50% after admission to the hospital, and more weight loss is observed during the initial stay in patients with undernourishment (4). Hospital malnutrition; it causes worsening prognosis, increased risk of developing nosocomial infections, decreased quality of life, prolonged hospital stay, increased morbidity and mortality risk and health expenditures (1). In addition, it has been reported that nutritional support in the early stage improves mucosal atrophy arising from malnutrition and increases anastomotic collagen accumulation and strength (6). Therefore, it is important for patients to have adequate nutritional levels, especially in areas where extensive surgical procedures are applied, to reduce the risk of operative trauma (7). It has been stated that even if the necessary interventions for malnutrition are not performed, even well-performed surgical procedures

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may result in negative results (8-10). In this context, evaluation of nutritional status is important for proper nutrition practices (11). For this reason, many screening and assessment tools have been developed that evaluate nutritional status based on various parameters (12). Among these tools, Nutritional Risk Screening (NRS)-2002 and Subjective Global Assessment (SGA) are among the most commonly used tools (13,14). This study was carried out to determine the risk of malnutrition with NRS-2002 and SGA screening tools and to the evaluation of the relationship between malnutrition risk status and anthropometric measurements in adults who were hospitalized in the general surgery clinic.

MATERIAL AND METHOD

The research is used in accordance with the Helsinki Declaration principles with 228 individuals (aged ≥19) who were in the general surgery clinic of Ankara University Research and Training Hospital, who are not bedridden, do not use a pacemaker and are between the ages of 19-90. Ethics Committee Approval which dated 22/05/2018 and numbered 07-449-18 was obtained in order to conduct the research from Ankara University Clinical Research Ethics Committee.

Evaluation of Nutrition

NRS-2002 and SGA forms were used to evaluate the nutritional status of individuals.Nutritional Risk Screening-2002, which is recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) for the assessment of nutritional status, is a tool that identifies patients at risk of malnutrition quickly and effectively (15,16). The NRS-2002 scoring system consists of two sections as 'nutritional status' and 'disease severity' and scoring between 0-3 points for each section. Patients with a total score of ≥3 are considered to be at risk of malnutrition (15).

Subjective Global Assessment; is an easy-to-apply and reliable nutritional assessment method based on weight change, change in nutrient intake, gastrointestinal symptoms, functional capacity and physical examination (17). The subjective view of the assessor determines the level of malnutrition. According to this result, individuals are classified into three groups: good nutritional status (SGA-A), moderate nutritional deficiency (SGA-B) and severe malnutrition (SGA-C) (18).

Anthropometric Measurements

The height of the individuals was determined with Tanita height meter; weight (kg), body fat percentage (BFP,%), lean body mass (LBM, kg) with Tanita Bc 601 Innerscan body analyzer. In addition, individuals' body mass index (BMI), waist circumference, upper-middle arm circumference (UMAC), triceps skinfold thickness (TSF) and handgrip strength measurements were taken. However, anthropometric measurements could not be made to the entire study group due to individuals with a lack of physical strength and various limitations. BMI levels of individuals with anthropometric measurements are determined according to WHO criteria (19); UMAC level is based on British Association for Parenteral and Enteral Nutrition (BAPEN) criteria (20), TSF level is based on National Center for Health Statistics (NCHS) percentile values (21), and the handgrip strength is evaluated according to the criteria determined by the study conducted by Dodds et al. (22), which is also used by the European Elderly Sarcopenia Study Group (EWGSOP2) (23). Body mass index <18.5 kg/m2 for both sexes, UMAC <23.5 cm, TSF <5 percentile, handgrip strength <16 kg for women, <27 kg for men are included in the risk group.

Statistical Analysis of Data

The analysis of the data was done in SPSS for Windows package program. Descriptive statistics are shown as mean (X) and standard deviation (SD) for variables with normal distribution; median and quartile difference (IQR) values for non-distributed variables; number of cases (n) and percentage (%) for nominal variables. In the study, statistical analysis between qualitative variables was done using Student's t-test if normal distribution assumptions were provided, and the Mann-Whitney U test if not provided. In terms of a quantitative variable, the difference between the categories of variables with ≥3 categories was evaluated using the One Way ANOVA test if normal distribution assumptions were provided, or the Kruskal Wallis test if not provided. The relationship between the two quantitative variables was evaluated with the Pearson Correlation Coefficient when both variables provided normal distribution assumptions, if at least one of the variables did not provide normal distribution assumptions the Spearman Correlation Coefficient was used. Linear regression analysis was applied to the data with a statistically significant correlation. In all statistical tests, the confidence interval was accepted as 95.0% and was evaluated at $p<0.05$ significance level.

RESULTS

Fifty-two point 2 percent (52.2%) of the individuals participating in the study are male and 47.8% are female and the median value of patients' ages is 56.0 (24.0) years. The median value of the length of hospital stay (LHOS) of the patients is 4.0 (8.0) days, and the majority of the reasons for the stay in the general surgery clinic are gastrointestinal tract diseases (63.1%). Weight loss has been observed in 22.8% of patients in the last 6 months and the median value of the weight loss percentage is 11.4% (13.55). Although 25.4% of individuals expressed

that their food intake decreased, only 8.8% stated that they received nutritional support. As a nutritional supplement, enteral nutrition is taken most frequently (65.0%). According to the NRS-2002 evaluation, 30.3% of patients have a risk of malnutrition; according to the SGA assessment, 34.2% had moderate and 12.3% had severe malnutrition (**Table 1**).

Table 1. General characteristics of patients and their distribution according to their nutritional status

	n	%
Gender		
Male	119	52.2
Female	109	47.8
Reason for hospital stay		
Gastrointestinal tract diseases	144	63.2
Endocrine system diseases	25	10.9
Cancer	23	10.1
Non-tumor mass	23	10.1
Other	13	5.7
Weight loss in the last 6 months		
Yes	52	22.8
No	176	77.2
Change in nutritional intake		
Increase	8	3.5
No change	162	71.1
Reduction	58	25.4
Nutritional support status		
Yes	20	8.8
No	208	91.2
Way of nutritional support	-	-
Enteral (oral/tube)	13	65.0
Parenterally	2	10.0
Combination	5	25.0
SGA level		
SGA-A	122	53.5
SGA-B	78	34.2
SGA-C	28	12.3
NRS score		
<3	159	69.7
≥3	69	30.3
Age (year)		
Median (IQR)	56.0 (24.0)	
Percentage of weight loss in the last 6 months (%)		
Median (IQR)	11.4 (13.55)	
LHOS (day)		
Median (IQR)	4.0 (8.0)	

Distribution of patients' ages, anthropometric measurements, and LOHS by NRS are given in Table 2. According to NRS, compared to those without malnutrition risk, ages and LOHS of patients at risk of malnutrition are statistically significantly higher; weight, BMI, UMAC, TSF, LBM, right and left handgrip strength levels are lower ($p<0.05$). However, the percentage of individuals in the risk group for BMI, TSF, left and right handgrip strength is higher among those with an NRS score of ≥3 ($p<0.05$) (**Table 2**).

Distribution of patients' ages, anthropometric measurements, and LHOS according to SGA are given in **Table 3**. There is a statistically significant difference in all parameters evaluated with SGA levels of patients. This difference arising from age, weight, BMI, UMAC, TSF, BFP, left handgrip strength and the LHOS is due to the differences between SGA-A and SGA-B groups, and SGA-C groups; the difference in waist circumference and LBM is due to the differences between SGA-A and SGA-C groups; the difference in right handgrip strength is due to differences between SGA-A and SGA-B groups ($p<0.05$). In addition, the rate of individuals in the risk group for BMI, UMAC, TSF, and right handgrip strength was higher in the SGA-C group ($p<0.05$) (**Table 3**).

The correlation of the NRS score, LHOS; ages and anthropometric measurements of the patients are given in **Table 4**. It was found that a positive correlation between the NRS score and age; a negative correlation between weight, BMI, waist circumference, UMAC, TSF, LBM, left and right handgrip strength ($p<0.05$). There was a positive correlation between LHOS, age, and NRS score; a negative correlation between weight, BMI, UMAC, TSF and LBM ($p<0.05$).

Linear regression of parameters with significant correlation in **Table 4** is given **Table 5**. While the NRS score of the patients is mostly explained with UMAC, the LHOS is explained with the NRS score ($p<0.05$).

DISCUSSION

Malnutrition is among the most common health problems in hospitalized patients. Studies in developed countries report that 20-60% of patients in the hospital are malnourished (24-26). However, malnutrition is associated with medical complications, prolonged recovery time and increased mortality rate. Therefore, identifying patients who are malnourished or at risk of malnutrition is an important requirement for early implementation of nutritional intervention and improving health outcomes (12). While 30.3% of individuals participating in the research are at risk for malnutrition according to NRS-2002, 34.2% have moderate malnutrition and 12.3% have severe malnutrition according to SGA (**Table 1**). In a study conducted by Ryu and Kim (27) with gastric cancer patients who underwent surgery, it was determined that 43% of patients had malnutrition risk according to NRS-2002, and 31% had moderate and severe malnutrition according to SGA. In the research conducted in various clinics by Tangvik et al. (28), the risk of malnutrition was found to be 30.8% in the general surgery clinic according to NRS-2002. In the study conducted by

Velasco et al. (29), it was stated that 34.5% of patients hospitalized in internal medicine and general surgery clinics according to NRS-2002 and 35.3% of patients according to SGA had malnutrition risk. In the study conducted by Güler and Tireli (30), in which the patients were evaluated with SGA in the general surgery clinic, it was found that 17.3% of the patients had moderate and severe malnutrition; in the study of Lim et al. (31), it was found that 29% of the patients had moderate and severe malnutrition. In addition to the burden of the disease for patients hospitalized in surgical clinics, surgery is a stress factor that causes metabolic and physiological changes. In response to stress, basal metabolic rate increases, nitrogen stores are used and negative nitrogen balance may occur. Furthermore, increased intestinal permeability and decreased villi height in the surgical process causes malabsorption and impaired barrier of the intestines against endogenous bacteria and toxins (32). For these reasons, the risk of developing malnutrition in patients hospitalized in the surgical clinic to be high has been confirmed by this and other research results. Given that nutritional deficiencies can directly affect mortality and morbidity in patients undergoing surgical intervention, it is extremely necessary to evaluate the nutritional status of patients in the preoperative period and to plan, implement and monitor early nutritional support when necessary.

Advanced age brings many health-related problems, including malnutrition (33). Many studies have found that malnutrition increases with age (28,34-36). It is stated that compared to younger patients, older individuals use more drugs and have comorbidities that affect their appetite, food intake, and absorption of nutrients. In this context, as elderly individuals show lower tolerance for malnutrition, another score is added to the total score for individuals aged 70 years in the NRS-2002 tool (28). In addition, it has been reported that malnutrition is associated with prolonged hospital stay (31,37,38). In a study conducted by Leandro-Merhi and de Aquino (39), it was determined that the LHOS was extended in case of patients having malnutrition risk according to NRS and advanced malnutrition levels according to SGA. In the study conducted by Wu et al. (40), it was determined that the duration of hospitalization and medical expenses increased with the increase of the SGA score ($p<0.05$). In this study, when age and LHOS of the patients were evaluated according to the NRS-2002 score (**Table 2**) and the SGA level (**Table 3**), it was found that the NRS score and the SGA level increased statistically significantly with increasing age and LHOS ($p<0.05$). The positive correlation of the NRS score with age and LHOS supports these results ($p<0.05$) (**Table 4**). According to linear regression analysis, the factor that best explains the LHOS at a statistically significant level is the NRS score ($p<0.05$) (**Table 5**). Patients may have malnutrition at the time of hospitalization, and some of them develop during their stay in the hospital. Therefore, as the LHOS increases, the risk of developing malnutrition increases. Factors such as pain, anxiety, depression, environmental change, different food intake, unusual medication and mealtimes can affect food consumption. Studies show that 30-60% of food prepared in the hospital is not taken and waste because of meal plans that are not tailored to the needs of patients. For this reason, patients generally receive energy, protein, and micronutrients that are well below their basal needs (41,42). This iatrogenic malnutrition can be largely prevented by appropriate nutrition policies, raising awareness of the healthcare team about malnutrition, screening and patient monitoring at regular intervals.

Anthropometric measurements are important in evaluating the nutritional status as it is an indicator of the amount of adipose tissue and lean body tissue and the distribution of these tissues in the body. In this context; measurements such as weight, BMI, waist circumference, UMAC, skinfold thickness are frequently used methods (43). When the anthropometric measurements of the patients were evaluated according to the NRS-2002 score (**Table 2**) and SGA level (**Table 3**), in the presence of malnutrition and at the level of increased malnutrition, it was determined that the weight, BMI, UMAC, TSF, LBM, right and left handgrip strength levels of the patients were lower and the ratio of those in the risk group was higher ($p<0.05$). However, while the NRS score was negatively correlated with weight, BMI, waist circumference, UMAC, TSF, LBM, left and right handgrip strength; the length of stay in hospital had a negative correlation with weight, BMI, UMAC, TSF and LBM ($p<0.05$) (**Table 4**). According to linear regression analysis, the parameter that most explains the NRS score of the patients is UMAC ($p<0.05$) (**Table 5**). In parallel with the results of this research, in studies nutritional status was evaluated with NRS; it was found that increased NRS score and decreased weight (44), BMI, UMAC (38,44,45), TSF (38,44) values were associated. Likewise, in the studies conducted with SGA, it was determined that the level of weight, BMI (12,36,40), TSF (36,40), UMAC (12), handgrip strength (12,36) decreased and weight loss increased with increasing SGA level. Based on this information, it is thought that anthropometric measurements are a good indicator in the screening and evaluation of malnutrition status, and measurements to be taken at certain intervals may be a guide for nutritional status and disease prognosis.

Table 2. Distribution of patients' ages, anthropometric measurements and LOHS by NRS score

	NRS score					
	<3 (n:159)		**≥3 (n:69)**		**t/Z**	**p**
Age (year)	54.0 (23.0)		64.0 (20.0)		-5.077	0.000*
Weight (kg)	77.7±13.45		68.6±12.82		4.182	0.000*
BMI (kg/m²)	28.1 (6.6)		25.5 (6.9)		-3.603	0.000*
Waist circumference (cm)	99.8±12.47		96.9±11.03		1.589	0.114
UMAC (cm)	31.0 (5.0)		28.0 (6.0)		-4.284	0.000*
TSF (mm)	23.3 (11.6)		17.6 (10.4)		-3.903	0.000*
BFP (%)	30.3±9.85		27.2±11.35		1.786	0.076
LBM (kg)	50.3±10.00		47.0±7.85		2.379	0.018*
Left handgrip strength (kg)	20.3 (18.0)		17.5 (13.8)		-2.700	0.007*
Right handgrip strength (kg)	21.3 (20.0)		17.7 (9.2)		-2.719	0.007*
LHOS (day)	3.0 (4.0)		9.0 (11.5)		-5.201	
	n	**%**	**n**	**%**	**X²**	**p**
BMI (kg/m²) αβ (n:183)						
Risk group	1	0.8	4	7.7	5.916	0.024*
Non-risk group	130	99.2	48	92.3		
UMAC (cm) αβ (n:185)						
Risk group	4	3.0	4	7.5	1.692	0.193
Non-risk group	128	97.0	49	92.5		
TSF (cm) αβ (n:185)						
Risk group	4	3.0	7	13.2	6.204	0.013*
Non-risk group	128	97.0	46	86.8		
Left handgrip strength αγ (n:183)						
Risk group	58	36.5	39	75.0	14.107	0.000*
Non-risk group	73	45.9	13	25.0		
Right handgrip strength αγ (n:184)						
Risk group	55	41.7	35	67.3	9.815	0.002*

α The evaluation has been carried out on individuals who can be measured.
β Likelihood chi-square test γPearson chi-square test was used. *p<0.05

Table 3. Distribution of patients' ages, anthropometric measurements and LHOS by SGA

	SGA-A[1] (n:122)		**SGA-B[2] (n:78)**		**SGA-C[3] (n:28)**		**t/Z**	**p**
Age (year) [1-2, 1-3]	52.0 (19.25)		64.0 (21.7)		64.5 (31.5)		35.028	0.000*
Weight (kg) [1-2, 1-3]	80.3±12.31		69.7±12.80		63.3±12.70		21.633	0.000*
BMI (kg/m²) [1-2, 1-3]	28.7 (6.6)		25.7 (5.3)		21.9 (8.5)		30.074	0.000*
Waist circumference (cm) [1-3]	101.3±12.29		97.1±10.97		91.6±12.16		5.882	0.003*
UMAC (cm) [1-2, 1-3]	32.0 (5.0)		29.0 (5.0)		25.0 (5.2)		43.958	0.000*
TSF (mm) [1-2, 1-3]	24.9±7.43		19.8±6.57		16.1±6.78		18.074	0.000*
BFP (%)[1-2, 1-3]	31.5±9.71		27.5±10.00		23.5±13.06		5.728	0.004*
LBM (kg) [1-3]	51.0±9.91		47.4±8.73		47.2±8.48		3.685	0.027*
Left handgrip strength (kg) [1-2, 1-3]	22.2 (16.8)		17.4 (14.2)		14.6 (11.2)		11.952	0.003*
Right handgrip strength (kg) [1-2]	23.3 (20.1)		17.5 (9.8)		14.7 (8.2)		12.033	0.002*
LHOS (gün) [1-2, 1-3]	2.0 (3.2)		6.0 (9.2)		9.5 (11.7)		32.025	0.000*
	n	**%**	**n**	**%**	**n**	**%**	**X2**	**p**
BMI (kg/m2) αβ (n:183)								
Risk group	-	-	2	3.1	3	20.0	6.725	0.024*
Non-risk group	103	100.0	63	96.9	12	80.0		
UMAC (cm) αβ (n:185)								
Risk group	1	1.0	4	6.1	3	20.0	9.877	0.004*
Non-risk group	103	99.0	62	93.9	12	80.0		
TSF (cm) αβ (n:185)								
Risk group	2	1.9	5	7.6	4	26.7	11.386	0.002*
Non-risk group	102	98.1	61	92.4	11	73.3		
Left handgrip strength αγ (n:183)								
Risk group	40	38.5	45	70.3	12	38.5	20.915	0.000*
Non-risk group	64	61.5	19	29.7	3	61.5		
Right handgrip strength αγ (n:184)								
Risk group	38	36.5	41	63.1	11	73.3	15.171	0.001*
Non-risk group	66	63.5	24	36.9	4	26.7		

α The evaluation has been carried out on individuals who can be measured.
β Fisher exact chi-square test γPearson chi-square test was used. *p<0.05
[1-2] Statistical significance is due to the difference between SGA-A and SGA-B groups.
[1-3] Statistical significance is due to the difference between SGA-A and SGA-C groups.

Table 4. The correlation between the NRS score and LHOS; ages and anthropometric measurements of patients

	Correlation with NRS score		Correlation with LHOS	
	r	p	r	p
Age (year)	0.428	0.000*	0.143	0.031*
Weight (kg)	-0.411	0.000*	-0.188	0.011*
BMI (kg/m^2)	-0.342	0.000*	-0.161	0.029*
Waist circumference (cm)	-0.153	0.038*	-0.062	0.398
UMAC (cm)	-0.453	0.000*	-0.194	0.008*
TSF (mm)	-0.351	0.000*	-0.212	0.004*
BFP (%)	-0.143	0.054	-0.010	0.892
LBM (kg)	-0.249	0.001*	-0.208	0.005*
Left handgrip strength (kg)	-0.291	0.000*	-0.108	0.144
Right handgrip strength (kg)	-0.290	0.000*	-0.116	0.115
NRS score	-	-	0.407	0.000*

Spearman correlation was used. *p<0.05

Table 5. Linear regression of patients' NRS score and LHOS; ages and anthropometric measurements

	B	%95 (CI)	β	R^2	p
Regression with NRS score					
Age (year)	0.043	0.030-0.056	0.396	0.157	0.000*
Weight (kg)	-0.053	-0.069--0.036	-0.432	0.187	0.000*
BMI (kg/m^2)	-0.102	-0.143--0.062	-0.350	0.123	0.000*
Waist circumference (cm)	-0.026	-0.046--0.010	-0.188	0.035	0.010*
UMAC (cm)	-0.176	-0.228--0.124	-0.442	0.196	0.000*
TSF (mm)	-0.082	-0.112--0.053	-0.377	0.142	0.000*
LBM (kg)	-0.041	-0.066--0.016	-0.236	0.056	0.001*
Left handgrip strength (kg)	-0.044	-0.067--0.022	-0.275	0.076	0.000*
Right handgrip strength (kg)	-0.042	-0.063--0.021	-0.282	0.080	0.000*
Regression with LHOS					
Age (year)	0.038	-0.051--0.128	0.056	0.003	0.399
Weight (kg)	-0.075	-0.190-0.040	-0.095	0.009	0.202
BMI (kg/m^2)	0.035	-0.243-0.312	0.018	0.000	0.806
UMAC (cm)	-0.119	-0.495-0.256	-0.046	0.002	0.531
TSF (mm)	-0.112	-0.317-0.094	-0.079	0.006	0.286
LBM (kg)	-0.245	-0.409--0.080	0.214	0.046	0.004*
NRS score	1.867	1.071-2.662	0.294	0.086	0.000*

*p<0.05

CONCLUSION

The rate of malnutrition in patients hospitalized in the general surgery clinic is quite high. In surgical patients, delaying the postoperative oral intake for more than seven days, not starting early nutritional support, not understanding the increasing nutritional requirements, and not being able to provide perioperative nutritional support in the patient with impaired nutrition are important factors in the development of malnutrition. Malnutrition causes deterioration of disease prognosis, increased susceptibility to infections, prolonged hospital stay, increased unnecessary treatment expenditures, resulting in significant economic losses and an increase in morbidity and mortality rates. In order to protect against malnutrition, which is a common but preventable condition, it is an important requirement that raising awareness of patients and training involving healthy nutrition, developing and implementing disease-specific nutrition guides, screening and monitoring the nutritional status of risky groups systematically, and providing adequate and balanced nutrition principles as part of the basic and vocational training of all health personnel. Nutritional support to be provided in the early period will help to improve inflammatory and metabolic responses after surgery and reduce the risk of postoperative complications. In this context, in clinics with a high risk of malnutrition, it is essential to have Nutritional Support Teams and provide nutritional support to patients as soon as possible.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Ethics Committee Approval which dated 22/05/2018 and numbered 07-449-18 was obtained from Ankara University Clinical Research Ethics Committee.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Suárez-Llanos JP, Benítez-Brito N, Vallejo-Torres L, et al. Clinical and cost-effectiveness analysis of early detection of patients at nutrition risk during their hospital stay through the new screening method CIPA: A Study Protocol. BMC Health Serv Res 2017; 17: 292.
2. Correia MI, Peman MI, Waitzberg DL. Hospital malnutrition in Latin America: a systematic review. Clin Nutr 2017; 36: 958-67.
3. Bucay AJ, Machiavelo MA, Alvarez-Altamirano K, et al. Hospital malnutrition: food services need to be improved in Mexico. Int J Clin Nutr 2017; 1: 13-7.
4. Weiss ARR, Wassermann U, Brennfleck F, et al. Prevalence of malnutrition in general surgery applying the nutritional risk screening 2002. J Surg Pract 2018; 1: 5.
5. Nakahara S, Nguyen DH, Bui AT, et al. Perioperative nutrition management as an important component of surgical capacity in low - and middle - income countries. Trop Med Int Health 2017; 22: 784-96.
6. Tang Z, Cai H, Cui Y. Influence of early postoperative feeding in gastrointestinal anastomotic fistula formation and healing time in rabbits. Biomed Res Int 2018; 2018: 8258096.
7. Horowitz M, Neeman E, Sharon E, et al. Exploiting the critical perioperative period to improve long-term cancer outcomes. Nat Rev Clin Oncology 2015; 12: 213-26.
8. Starke J, Schneider H, Alteheld B, et al. Short-term individual nutritional care as part of routine clinical setting improves outcome and quality of life in malnourished medical patients. Clin Nutr 2011; 30: 194-201.
9. Yeh DD, Fuentes E, Quraishi SA, et al. Adequate nutrition may get you home: effect of caloric/protein deficits on the discharge destination of critically ill surgical patients. J Parent Enteral Nutr 2016; 40: 37-44.
10. Zhong JX, Kang K, Shu XL. Effect of nutritional support on clinical outcomes in perioperative malnourished patients: A meta-analysis. Asia Pac J Clin Nutr 2015; 24: 367-78.
11. Mueller C, Compher C, Ellen DM. A.S.P.E.N. clinical guidelines: nutrition screening, assessment, and intervention in adults. J Parent Enteral Nutr 2011; 35: 16–24.
12. Flood A, Chung A, Parker H, et al. The use of handgrip strength as a predictor of nutrition status in hospital patients. Clin Nutr 2014; 33: 106-14.
13. Lomivorotov VV, Efremov SM, Boboshko VA, et al. Evaluation of nutritional screening tools for patients scheduled for cardiac surgery. Nutr 2013; 29: 436-42.
14. Lomivorotov VV, Efremov SM, Boboshko VA, et al. Prognostic value of nutritional screening tools for patients scheduled for cardiac surgery. Interact Cardiovasc Thorac Surg 2013; 16: 612–8.
15. Kondrup J, Allison SP, Elia M, et al. ESPEN guidelines for Nutrition Screening 2002. Clin Nutr 2003; 22: 415-21.
16. Alhaugi J, Gay CL, Henriksen C, et al. Pressure ulcer is associated with malnutrition as assessed by Nutritional Risk Screening (NRS 2002) in a mixed hospital population. Food Nutr Res 2017; 61: 1324230.
17. Bauer J, Capra S, Ferguson M. Use of the scored patient-generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. Eur J Clin Nutr 2002; 56: 779–85.
18. Gupta D, Lammersfeld CA, Vashi PG, et al. Prognostic significance of Subjective Global Assessment (SGA) in advanced colorectal cancer. Eur J Clin Nutr 2005; 59: 35–40.
19. WHO. Waist Circumference and Waist–Hip Ratio: Report of a WHO Expert Consultation. http://apps. who. int/iris/bitstream/10665/44583/1/9789241501491_eng. pdf. Accessed April 6, 2017.
20. BAPEN. Malnutrition Universal Screening Tool. https://www.bapen. org. uk/pdfs/must/must_full. pdf. Accessed March 9, 2020.
21. Bishop CW, Bowen PE, Ritchey SJ. Norms for nutritional assessment of American adults by upper arm anthropometry. Am J Clin Nutr 1981; 34: 2530–9.
22. Dodds RM, Syddall HE, Cooper R, et al. Grip Strength across the life course: normative data from twelve British studies. PLoS One 2014; 9: e113637.
23. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019; 48: 16–31.
24. Correia MI, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. Clin Nutr 2003; 22: 235-9.
25. Norman K, Schütz T, Kemps M, Josef Lübke H, Lochs H, Pirlich M. The Subjective Global Assessment reliably identifies malnutrition-related muscle dysfunction. Clin Nutr 2005; 24: 143-50.
26. Westergren A, Torfadóttir O, Ulander K, et al. Malnutrition prevalence and precision in nutritional care: an intervention study in one teaching hospital in Iceland. J Clin Nurs 2010; 19: 1830-37.
27. Ryu W, Kim H. Comparison of different nutritional assessments in detecting malnutrition among gastric cancer patients. World J Gastroenterol 2010; 16: 3310–7.
28. Tangvik RJ, Tell GS, Guttormsen AB, et al. Nutritional risk profile in a university hospital population. Clin Nutr 2015; 34: 705-11.
29. Valesco C, Garcia EV, Rodríguez V, et al. Comparison of four nutritional screening tools to detect nutritional risk in hospitalized patients: a multicentre study. Eur J Clin Nutr 2011; 65: 269–74.
30. Guler Y, Tireli M. Malnutrition frequency in surgical patients and its effect on morbidity and mortality. Acta Medica Alanya 2018; 2: 35-9.
31. Lim SL, Ong KC, Chan YH, et al. Malnutrition and its impact on cost of hospitalization, length of stay, readmission and 3-year mortality. Clin Nutr 2012; 31: 345-50.
32. Abunnaja S, Cuviello A, Sanchez JA. Enteral and parenteral nutrition in the perioperative period: state of the art. Nutrients 2013; 5: 608-23.
33. Leij-Halfwerk S, Verwijs MH, van Houdt S, et al. Prevalence of protein-energy malnutrition risk in European older adults in community, residential and hospital settings, according to 22 malnutrition screening tools validated for use in adults ≥65 years: A systematic review and meta-analysis. Maturitas 2019; 126: 80-9.
34. Imoberdorf R, Meier R, Krebs P, et al. Prevalence of undernutrition on admission to Swiss hospitals. Clin Nutr 2010; 29: 38-41.
35. Kyle UG, Kossovsky MP, Karsegard VL, et al. Comparison of tools for nutritional assessment and screening at hospital admission: a population study. Clin Nutr 2006; 25: 409-17.
36. Pham NV, Cox-Reijven PL, Wodzig WK, et al. SGA and measures for muscle mass and strength in surgical Vietnamese patients. Nutr 2007; 23: 283-91.
37. Agarwal E, Ferguson M, Banks M, et al. Malnutrition and poor food intake are associated with prolonged hospital stay, frequent readmissions, and greater in-hospital mortality: results from the Nutrition Care Day Survey 2010. Clin Nutr 2013; 32: 737-45.
38. Knappe-Drzikova B, Maasberg S, Vonderbeck D, et al. Malnutrition predicts long-term survival in hospitalized patients with gastroenterological and hepatological diseases. Clin Nutr ESPEN 2019; 30: 26-34.
39. Leandro-Merhi VA, Braga de Aquino JL. Comparison of nutritional diagnosis methods and prediction of clinical outcomes in patients with neoplasms and digestive tract diseases. Clin Nutr 2015; 34: 647-51.
40. Wu B, Yin TT, Cao W, et al. Validation of the Chinese version of the Subjective Global Assessment scale of nutritional status in a sample of patients with gastrointestinal cancer. Int J Nurs Stud 2010; 47: 323-31.

41. Hiesmayr M, Schindler K, Pernicka E, et al. Decreased food intake is a risk factor for mortality in hospitalised patients: the NutritionDay survey 2006. Clin Nutr 2009; 28: 484-91.

42. Naber TH, Schermer T, de Bree A, et al. Prevalence of malnutrition in nonsurgical hospitalized patients and its association with disease complications. Am J Clin Nutr 1997; 66: 1232-9.

43. Pekcan G. Determination of nutritional status. Republic of Turkey Ministry of Health Publication Nu: 726, Ankara; 2008.

44. Maasberg S, Knappe-Drzikova B, Vonderbeck D, et al. Malnutrition predicts clinical outcome in patients with neuroendocrine neoplasia. Neuroendocrinology 2017; 104: 11-25.

45. Turkoglu I, Ilgaz A, Yalcin T, et al. Prevalence of malnutrition in hospitalized adult patients: a comparison of four nutritional screening tools. J Nutr Diet 2015; 43: 135-42.

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Awareness among patients taking oral non-steroidal anti-inflammatory drugs as analgesics: a cross-sectional study

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ABSTRACT

Aim: Non-steroidal anti-inflammatory drugs (NSAIDs), the most used drugs for pain management, are among the most commonly prescribed drugs both in the world and in Turkey. NSAIDs have a serious side effect profile, and their inappropriate use can result in adverse outcomes, including mortality. This study aimed to determine consciousness level of drug use among patients who used oral NSAIDs for pain relief.

Material and Method: This was a cross-sectional and descriptive study. The universe of the study consisted of patients aged ≥18 years who presented to the Ankara City Hospital Family Medicine Outpatient Clinic at the end of 2019 for any reason who used at least one type of oral NSAID for pain relief. Data were collected using a questionnaire developed by the researchers. Awareness was measured via a survey concerning knowledge and attitude, and knowledge and attitude scores were calculated for each participant. Significance was determined at a $p<0.05$ level.

Results: There were 210 participants. The most used NSAID was diclofenac. The most common reasons for analgesics use were headache and musculoskeletal pain. Participants had poor knowledge of the diseases associated with NSAID use, and the most well-known diseases were stomach ulcer and bleeding and kidney failure. Participants' average knowledge scores were low, and average attitude scores were relatively higher. Women had significantly higher knowledge scores than men. Knowledge and attitude scores were positively associated with education and income status. Analgesics use was positively correlated with age and negatively correlated with attitude scores. Participants with chronic diseases had lower attitude scores than those without chronic diseases. Knowledge and attitude scores were positively correlated.

Conclusion: We conclude that participants lacked knowledge about the general characteristics of and risks associated with NSAIDs, widely used, over-the-counter drugs that are found in almost every home. A more cost-effective, knowledgeable, and rational approach is required for NSAID use.

Keywords: Analgesics, pain management, non-steroidal anti-inflammatory agents, rational drug use, family medicine

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs), the most used drugs for pain management, are among the most prescribed drugs around the world. In addition to their analgesic properties, NSAIDs are widely used as antipyretic and anti-inflammatory agents, and their utility in colorectal cancer prophylaxis has also been demonstrated by recent studies. Low dose of acetylsalicylic acid, also known as aspirin, is used for cardiovascular and cerebrovascular prophylaxis.

Prescriptions for ibuprofen and naproxen, both among the most commonly used NSAIDs, reached 40 million in the USA in 2009 (1). In Europe, NSAIDs account for 7.7% of all prescriptions (1). Like the rest of the world, NSAID use is common in Turkey. According to 2017 data, analgesics constituted 7.1% of 2.2 billion boxes of drugs sold in Turkey, the majority of which consisted of NSAIDs (2). NSAIDs are also prominent due to being available over the counter and easy to access.

Studies have proven that NSAIDs can have serious and mortal consequences, including gastrointestinal, renal, cardiovascular, hematological, pulmonary, allergic, and anaphylactic side effects. The prominent gastrointestinal side effects of NSAIDs include dyspepsia, peptic ulcer disease, and bleeding. At least 25% of chronic NSAID users develop peptic ulcers, while 2-4% of these ulcers are complicated by bleeding or perforation (3). Serious renal side effects, on the other hand, occur in about 1-5% of all patients taking NSAIDs (4). This number can reach 20% for patients under

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increased risk due to concomitant diseases (5). NSAIDs also have various side effects on the cardiovascular system. NSAIDs have been shown to increase the risk of adverse vascular events, such as myocardial infarction and stroke, and can also exacerbate heart failure (6).

In primary care, NSAIDs are frequently requested by patients and prescribed by physicians irrespective of indication. It was statistically demonstrated that 39.9% of all prescriptions written by family practitioners in Turkey in 2017 included analgesics (7). NSAIDs have also been shown to have the largest share of sales among all analgesics. It is estimated that $6.8 billion has been spent on NSAIDs worldwide each year (5).

To summarize, NSAIDs have many serious side effects and are also a significant economic burden. NSAID availability over the counter sets the stage for inappropriate use. Physicians should inform patients at the point of access to health care. Moreover, it is important to determine patients' level of NSAID knowledge to try and prevent possible side effects. In our study, we aimed to determine awareness concerning NSAIDs, drugs that are widely used and can have serious side effects.

MATERIAL AND METHOD

Prior to data collection, the scientific and ethical aspects of the protocol were reviewed by the local hospital research ethics committee, and the study was granted ethical approval (date 07/11/2019, decision number E-19-115). All procedures were performed adhered to the ethical rules and the Helsinki Declaration of Principles.

This was a cross-sectional, descriptive, and comparative observational study. The universe of the study consisted of patients aged ≥18 years with good cognition (no neurological or psychiatric disorders that may affect the results of the questionnaire) who presented to the Ankara City Hospital Family Medicine Outpatient Clinic between 10/11/2019–31/12/2019 for any reason and who used at least one type of oral NSAID for pain relief. The analysis conducted using G Power 3.1.5 software revealed that a sample size of 207 was required with a medium effect size and an alpha-type error of 0.05.

Data were collected using a 20-item questionnaire, which included descriptive questions concerning sociodemographic characteristics (gender, age, occupation, income status, education status, any illnesses) and painkiller use, and questions measuring attitude and knowledge of painkillers. Moreover, we calculated knowledge and attitude scores to evaluate our participants' NSAID awareness levels. Than the "Overall Knowledge Score" and "Overall Attitude Score" were compared with sociodemographic features of the participants.

When assessing knowledge, "one" point was assigned to all correct answers. These points were summed up to determine the Overall Knowledge Score. The highest possible score was 16 and the lowest possible score was 0.

To determine attitude, participants were given 12 statements that reflected positive or negative behavior. The statements were scored as a 5-point Likert-type scale (4 always, 3 often, 2 sometimes, 1 rarely, 0 never). Negative propositions were scored in reverse. The scores from all propositions were added to determine the Overall Attitude Score. The highest possible score was 48 and the lowest possible score was 0.

The questionnaire was applied using the face-to-face interview method.

Data were analyzed using IBM SPSS Statistics 18© Copyright SPSS Inc. 1989, 2010. Fit to normal distribution was investigated using the Kolmogorov–Smirnov test. Categorical variables were presented as frequencies and percentages, and continuous variables as means, medians, standard deviation, and minimums and maximums. Chi-square and Fisher's chi-square significance tests were used to analyze categorical variables. When parametric assumptions were met, one-way ANOVA was used to compare means between two or more independent groups. When parametric assumptions were not met, the Mann Whitney U test was used to compare means between two groups and the Kruskal-Wallis test to compare means between more than two groups. Correlations between continuous variables were examined using Spearman's correlation analysis. The level of statistical significance was accepted as 0.05. The internal consistency of the questionnaire items was analyzed using Cronbach's alpha. Cronbach's alpha coefficient was calculated as 0.671.

RESULTS

There were a total of 210 volunteer participants. The mean age was 41.23±13.96 years, and the median age was 39 years (range 19-82). **Table 1** presents the participants' sociodemographic characteristics.

The number of participants with chronic diseases was 92 (43.8%). The most common chronic diseases were hypertension (12.9%), diabetes (8.1%), asthma (7.1%), goiter (6.7%), gastritis, and depression (6.2%). Average painkiller use was 5.83±3.53 units per month (range 1-25). Reasons for using painkillers and the most used painkillers are presented in **Table 2**.

78.6% (n=165) of participants stated that they never used aspirin, and 17.1% sometimes and 4.3% regularly used aspirin. Among participants who used aspirin, 22 (48.9%) did so because they believed that taking aspirin every once in a while was good for their health, 14 (31.1%) for

pain relief, 7 (15.6%) due to having cardiovascular disease as heart attack prophylaxis, and 2 (4.4%) due to having cerebrovascular disease as stroke prophylaxis.

Table 1. Sociodemographic data of the participants

	Number (n)	Percent (%)
Gender (n=210)		
Female	129	61.4
Male	81	38.6
Educational status (n=210)		
University and above	100	47.6
High school	80	38.1
Middle school	16	7.6
Elementary school	13	6.2
Illiterate	1	0.5
Marital status (n=210)		
Married	120	57.1
Single	66	31.4
Widowed/divorced	24	11.4
Occupation (n=210)		
Government officer	47	22.4
Housewife	43	20.5
Worker	34	16.2
Unemployed	25	11.9
Retired	24	11.4
Other	18	8.6
Tradesman	12	5.7
Medical staff	7	3.3
Households income status (n=210)		
Income=expenses	108	51.4
Income<expenses	89	42.4
Income>expenses	13	6.2

Table 2. Reasons for using analgesics and distribution of used analgesics

	Number (n)	Percent (%)
Reasons for using analgesics		
Headache	120	57.1
Other joint and muscle pain	72	34.3
Low back pain	62	29.5
Dysmenorrhea	47	22.4
Toothache	24	11.4
Knee pain	17	8.1
Abdominal pain	13	6.2
Cancer pain	2	1.0
Used analgesics		
Diclofenac	87	41.4
Dexketoprofen	79	37.6
Paracetamol	76	36.2
Flurbiprofen	72	34.3
Naproxen	64	30.5
Etodolac	21	10.0
Indometacin	9	4.3
Mefenamic acid	8	3.8
Nimesulide	8	3.8
Metamizole	2	1.0
Ibuprofen	2	1.0
Morphine/tramadol	2	1.0
Meloxicam	1	0.5

A total of 77 participants (36.7%) reported painkiller-related side effects. The observed side effects and participants' reactions to side effects are presented in detail in **Table 3.**

Table 3. Participants' characteristics regarding side effects related to analgesics

	Number (n)	Percent (%)
Any side effects (n=210)		
No	133	63.3
Yes	77	36.7
Side effects (n=117) *		
Heartburn	46	21.9
Stomach pain	28	13.3
Nausea	18	8.6
Allergic reaction	7	3.3
Fatigue	4	1.9
Rash	4	1.9
Palpitation	4	1.9
Headache	2	1.0
Drowsiness	2	1.0
Dizziness	1	0.5
Vomiting	1	0.5
Visual impairment	0	0.0
Tinnitus	0	0.0
Confusion	0	0.0
Anaphylaxis	0	0.0
Reaction to Side Effects (n=77)		
Waiting it out	51	66.2
Consulting a doctor	14	18.2
Using other medication to reverse side effect without consulting a doctor	12	15.6
Other methods	0	0.0

*Multiple items could be selected.

Answers to the Knowledge Score item "What diseases do you know that are at increased risk or triggered by painkillers?" are presented in **Table 4.** The presented answers are correct according to the literature. 12.4% (n=26) of the participants answered this question as "I don't know".

Answers to another Knowledge Score item "Where do painkillers need to be stored?" were as follows: almost half (49.5%) of all participants correctly answered the question by indicating that painkillers need to be stored "at room temperature in a cool and dry environment", whereas 28.6% indicated "in the refrigerator" and 21.9% indicated that "painkillers do not require specific storage conditions".

Lastly, the correct answers given to the remaining Knowledge Score items concerning the properties of painkillers are also presented in **Table 4.** Knowledge scores were calculated by assigning 1 point to each item. The mean overall knowledge score of the participants was calculated as 3.72±2.11 points (range 0-12) over 16.

Table 4. Number of correct answers to knowledge questions

Parameters that determine the Overall Knowledge Score	Number of correct answers given (n)	Percent (%)
Increased risk of stomach ulcers/ bleeding	123	58.6
Increased risk of kidney failure	100	47.6
Increased risk of liver failure	47	22.4
Increased risk of heart attack	37	17.6
Increased risk of intestinal ulcers/ bleeding	31	14.8
Increased risk of clot formation in blood vessels	25	11.9
Increased risk of hypertension	15	7.1
Increased risk of depression	7	3.3
Increased risk of asthma attacks	6	2.9
Increased risk of hepatitis	5	2.4
Increased risk of various blood diseases	5	2.4
Increased risk of epilepsy	2	1.0
Where do painkillers need to be stored?	104	49.5
"Painkillers interact with certain other drugs when taken together"	72	34.3
"Painkillers can reduce fever."	129	61.4
"Painkillers have anti-inflammatory properties."	74	35.2

Table 5 presents the distribution of participants' responses to the overall painkiller attitude score parameters. Accordingly, the mean overall attitude score was calculated as 26.24±5.88 (range 11-42) over 48.

Table 6 presents the relationship of knowledge and attitude scores with age and painkiller use. Correlation analysis revealed a weak positive correlation between knowledge and attitude scores (r=0.219, p<0.01).

Table 6. Relationship of knowledge and attitude scores with age and analgesics use

Correlation test results	Knowledge score	Attitude score	Age	Amount of analgesics
Knowledge score	1			
Attitude score	0.219**	1		
Age	-0.007	-0.050	1	
Amount of analgesics	-0.032	-0.362**	0.217**	1

** p<0.01

Mean overall knowledge and attitude scores and their comparisons according to sociodemographic data are presented in **Table 7**. Statistical analysis revealed that the mean overall knowledge score of participants who had experienced side effects (4.27±2.25) was significantly higher than that of participants who had not (3.41±1.96) (p=0.005). Also, patients who had chronic diseases that required chronic medication had significantly lower attitude scores compare to participants who did not (p=0.005).

Table 5. Distribution of participants' responses to the overall analgesics attitude score parameters

Parameters that determine the overall attitude score	Always		Often		Sometimes		Rarely		Never	
	n	%	n	%	n	%	n	%	n	%
When I have pain, I take painkillers without seeking a medical opinion.	43	20.5	91	43.3	60	28.6	12	5.7	4	1.9
I buy painkillers over the counter at the pharmacy.	18	8.6	48	22.9	92	43.8	30	14.3	22	10.5
I ask my doctor to prescribe painkillers so that I have them available at home.	18	8.6	42	20.0	78	37.1	54	25.7	18	8.6
I always carry painkillers with me.	28	13.3	30	14.3	75	35.7	57	27.1	20	9.5
I use any leftover painkillers later if I have any pain.	81	38.6	77	36.7	23	11.0	21	10.0	8	3.8
I am careful to take painkillers after eating.	77	36.7	65	31.0	53	25.2	15	7.1	0	0.0
I am careful about the expiration dates of painkillers.	104	49.5	65	31.0	25	11.9	15	7.1	1	0.5
I read medication package inserts before using painkillers.	45	21.4	40	19.0	75	35.7	39	18.6	11	5.2
I take painkillers together with other drugs I am using.	3	1.4	17	8.1	69	32.9	67	31.9	54	25.7
I take painkillers together with herbal/ supplement products.	3	1.4	20	9.5	66	31.4	121	57.6	0	0.0
I take gastroprotective agent together with painkillers.	8	3.8	17	8.1	54	25.7	66	31.4	65	31.0
When painkillers have side effects, I seek medical help.	45	21.4	22	10.5	54	25.7	60	28.6	29	13.8

Table 7. Mean overall knowledge and attitude scores and their comparisons according to sociodemographic data

	Mean overall knowledge score	p value	Mean overall attitude score	p value
Gender (n=210)				
Female	4.01±2.07	0.008*	26.42±6.06	0.839*
Male	3.27±2.09		26.13±5.79	
Educational status (n=210)				
University and above	4.60±2.26	0.0001&	27.48±6.17	0.022&
Elementary school	3.38±1.50		25.69±4.73	
High school	3.04±1.63		23.88±6.85	
Middle school	2.13±1.20		23.69±6.88	
Illiterate	1.0		18.00	
Marital status (n=210)				
Married	3.76±2.16	0.979&	26.93±6.42	0.034&
Single	3.73±2.24		25.92±4.91	
Widowed/divorced	3.54±1.38		23.67±4.81	
Occupation (n=210)				
Medical staff	6.43±2.87	0.001&	28.06±6.22	0.231
Government officer	4.49±2.18		26.82±5.75	
Retired	3.54±1.86		26.13±6.32	
Tradesman	3.42±1.78		25.86±5.64	
Unemployed	3.40±2.39		25.80±4.87	
Worker	3.15±2.07		24.83±3.18	
Housewife	3.05±1.17		24.70±6.07	
Other	4.28±2.29		25.94±6.52	
Households income status (n=210)				
Income<expenses	3.34±1.95	0.012&	31.00±7.80	0.063
Income=expenses	3.89±2.19		26.40±5.47	
Income>expenses	5.00±1.87		25.36±5.77	

* Mann Whitney U test, & Kruskal Wallis test

DISCUSSION

In our study, we aimed to determine the level of NSAID awareness among patients who presented to the family medicine outpatient clinic who used NSAIDs for pain relief.

In our study, the mean frequency of painkiller use was 5.83±3.53 per month. In other words, participants used 6 units of painkillers per month and 1-2 per week on average. A similar thesis study concerning hypertensive patients found that 4.28% of the participants used NSAIDs every day, 6.61% used 3-6 units per week, 8.17% 1-2 units per week, and 22.57% 1-3 units per month (8). A study from Saudi Arabia reported that 3.8% of the participants used painkillers once a day, 6.9% once a week, 12.1% once a month, and 77.2% as needed (9). As evidenced, painkiller use is high among our participants. Our participants were relatively young. That said, we found that painkiller use increased with age. Given that advanced age is associated with increased conditions that cause pain, such as rheumatic diseases, it is expectable that painkiller use will increase with age. However, it is curious that we found high painkiller use throughout our patient group. We infer that patients may not be aware of the potential consequences of frequent and inappropriate painkiller use, which are available over the counter and already present in many homes.

Among our participants, the most common reason for using painkillers was headaches (57.1%), followed by other joint and muscle pain, low back pain, dysmenorrhea and toothache, and knee pain, respectively. In our study, we classified musculoskeletal pain under three separate categories, and we preferred to ask the participants about the most common musculoskeletal pains (low back and knee pain) individually, and included "other joint and muscle pain" as a third option. In total, these three options amount to 71.9%. Therefore, it can be said that musculoskeletal pain was the most common reason for painkiller use. Balabanlı indicated that the most common reasons for painkiller use were headaches (76.7%), followed by musculoskeletal pain (43.1%) (10). A similar study from the Sivas province of Turkey indicated that, among patients aged 65 and over, the most common reason for using NSAIDs was diffuse musculoskeletal pain and gonarthrosis (11). Hopayılmaz reported that the most common reason for using NSAIDs was rheumatic pain (50%), followed by headache (30.8%) and low back pain (13%) (12). Accordingly, we inferred that the most common reasons for using NSAIDs are headache and musculoskeletal pain, with varying rates depending on age.

In our study, the most used painkiller was an NSAID, diclofenac (41.4%). This was followed by dexketoprofen, paracetamol, flurbiprofen, and naproxen. Balabanlı (10) indicated that the most used NSAIDs were flurbiprofen (51%) and diclofenac (40.3%). It should be noted that this study did not investigate paracetamol use. Roshi et al. (13) reported the most commonly used painkillers to be paracetamol, ketoprofen, and ibuprofen, respectively. A similar study from Greece found that paracetamol and ibuprofen, respectively, were the most commonly used painkillers, followed by diclofenac and meloxicam (14). Karami et al. (9) similarly found that the most used painkillers were paracetamol (73.4%) and ibuprofen (13.1%). Hopayılmaz (12) and Yılmaz (8) reported that paracetamol, diclofenac and flurbiprofen, respectively, were the most commonly used painkillers among patients aged 65 years and older. As illustrated, paracetamol is consistently the most used painkiller in studies where it was included. This is a favorable result since paracetamol is a milder and more tolerable drug compared to NSAIDs in terms of potential side effects. In our study, paracetamol was the third most used painkiller. We ascribe this finding to the fact that the universe of our study consisted of patients using at least one type of NSAID (excluding paracetamol) and did not include patients who used paracetamol alone. This is both a distinguishing and limiting factor for our study.

Answers to the Knowledge Score item "List all diseases that you know painkillers to increase the risk of or trigger." included stomach ulcer/bleeding, kidney failure, liver failure, heart attack, intestinal ulcer/bleeding, and blood clot formation in descending order; hypertension, depression, asthma attacks, various blood disorders, and epilepsy were less common responses. Yılmaz reported that the most well-known side effects of NSAIDs were gastrointestinal problems and kidney failure. This study reported that more than half of the participants did not know of any side effects and only 14.7% knew about the risk of hypertension (8). Contrarily, Roshi et al. (13) found that 31.7% of their participants knew that NSAIDs could lead to hypertension, 30.2% to gastrointestinal ulcers, 27.1% to kidney damage, and 18.1% to cardiac damage. Karakitsiou et al. (14) demonstrated that the most well-known NSAID side effects were hypertension, peptic ulcer, and kidney damage, while hepatopathy was less well-known. In our study, a very small percentage (7.1%) of participants indicated knowing NSAIDs could lead to hypertension. That said, the percentages were similarly low for other diseases also, with 12.4% of the participants indicating that they did not know of any diseases associated with NSAID use. This suggests that patients should be better informed about the side effects of NSAIDs.

In our study, almost half of all participants indicated that painkillers should be stored in a cool and dry environment at room temperature, while 28.6% said that they should be stored in the refrigerator. Ilhan et al. (15) conducted a study concerning rational drug use and found that 60.3% of the participants stored unused drugs in the refrigerator. A Belgian study showed that one-third of households stored drugs in inappropriate conditions (16). Oral NSAIDs are recommended to be stored at room temperature, but research shows that misinformation and incorrect applications are abundant.

In our study, 63.8% of participants stated 'always' or 'often taking painkillers without seeking a medical opinion' when they have pain. 52.6% of Hopayılmaz's participants indicated taking painkillers without visiting the doctor's office when they had pain (12). Multiple studies reported that the vast majority of drugs used without consulting a doctor are painkillers (17,18). This is most likely largely due to the easy availability of painkillers over-the-counter. In our study, 31.5% of participants indicated that they 'always' or 'often buy painkillers over the counter at the pharmacy'. Önder et al. (19) reported a comparatively higher rate of buying over-the-counter painkillers with 57.8%. A similar US study indicated that 65% of the participants used over-the-counter painkillers (20). The National Health and Nutrition Examination Survey III (NHANES-III), also from the United States, reported that 76% of the population used over-the-counter analgesics (21). In our study, the prevalence of buying over-the-counter painkillers was lower compared to the literature. On the other hand, 28.6% of our participants 'always' or 'often asked [their] doctor to prescribe painkillers so that [they] have them available at home'. Balabanlı (10) reported a higher rate, with 40.7% of participants indicating that they requested prescriptions for NSAIDs, even though they had no complaints. These results demonstrate the need for increased public awareness on this issue.

In our study, knowledge and attitude were separately evaluated. The mean overall knowledge score was 3.72±2.11 out of 16, and the mean overall attitude score was 26.24±5.88 out of 48. These scores were below expected. The mean knowledge score was considerably lower compared to the mean attitude score. Most of the knowledge questions concerned the diseases and side effects associated with NSAIDs, therefore the low mean knowledge score suggests that patients need to be better informed about the side effects of NSAIDs. Moreover, the correlation analysis revealed a weak but significant positive relationship between knowledge and attitude scores. Accordingly, we concluded that increased NSAID knowledge was associated with better attitude.

In our study, participants who had completed university education or higher had the highest knowledge and attitude scores. Balabanlı similarly found that educational status was positively correlated with the rational use of NSAIDs (10). A thesis study on rational drug use also observed that increased education was associated with better knowledge of drug side effects (22).

Participants who developed NSAID-related side effects had significantly higher knowledge scores than those who did not. This suggests that experiencing NSAID-related side effects may have resulted in more cautious use.

Correlation analysis revealed a weak but significant negative relationship between attitude scores and painkiller use. This suggests that participants using fewer painkillers had a better attitude, or that a better attitude was associated with reduced NSAID use.

Our results indicated that attitude scores were higher among participants who knew the correct storage conditions for painkillers and those who knew of NSAIDs' drug interactions and antipyretic properties. That said, we found that participants with chronic diseases had lower attitude scores than those without chronic diseases. Balabanlı (10) similarly found that individuals without chronic diseases had better knowledge about NSAIDs. These results are curious since people with chronic diseases who require chronic medication are expected to know more about NSAIDs, and their interactions and side effects.

Among the limitations of this study are the single-center and cross-sectional design, and the limited number of subjects, all of which reduce the generalizability of our results. Hence, the comments presented in the discussion section mostly reflect the attitudes of the participating population.

CONCLUSION

Participants' average knowledge scores were low, and average attitude scores were relatively higher. Women, medical staff, and participants with higher education and income statuses had significantly higher knowledge scores. Moreover, participants with higher education and income statuses, and government officers had significantly higher attitude scores.

We conclude that patients lack information about the general characteristics and risks of NSAIDs, and further education is required.

Furthermore, among our results are increased painkiller use with age, and poor conscious level of drug use among patients with chronic diseases. The elderly and individuals with chronic diseases more frequently require medical care and are at higher risk for side effects and drug interactions; therefore, it is crucial to improve medication awareness in this population. Family physicians are the most likely to receive NSAID prescription requests and also the most likely to prescribe painkillers. As the first line of health care, to provide community-oriented, comprehensive, and person-centered care, family physicians should provide accurate information about NSAIDs to the population they are responsible for. Moreover, due to over-the-counter availability, physician-pharmacist-patient cooperation is also vital for a successful outcome in the context of rational drug use of analgesics.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Clinical Research Ethics Committee of Ankara City Hospital (Date 07/11/2019, Decision number E-19-115).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Tielemans MM, van Rossum LG, Eikendal T, et al. Gastrointestinal symptoms in NSAID users in an 'average risk population': results of a large population-based study in randomly selected Dutch inhabitants. Int J Clin Pract 2014; 68: 512-9.
2. "Türkiye ilaç sektörü 2017" Access URL address: http: //ieis.org.tr/ieis/tr/sektorraporu2017/#1, İlaç Endüstrisi İşverenler Sendikası (İEİS), Access Date: 11.09.2020
3. Lanza FL, Chan FK, Quigley EM, Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol 2009; 104: 728-38.
4. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. Am J Med 1999; 106: 13-24.
5. Harirforoosh S, Jamali F. Renal adverse effects of nonsteroidal anti-inflammatory drugs. Expert Opin Drug Saf 2009; 8: 669-81.
6. Ardoin SP, Sundy JS. Update on nonsteriodal anti-inflammatory drugs. Curr Opin Rheumatol 2006; 18: 221-6.
7. Türkiye Cumhuriyeti Sağlık Bakanlığı, "Sağlik istatistikleri yıllığı," 2016.

8. Yılmaz N. "Ankara Atatürk Eğitim ve Araştırma Hastanesi Aile Hekimliği Polikliniklerine Başvuran Hipertansif Hastaların Kan Basıncı Regülasyon Durumları ile Ağrı Kesici Kullanım Profilleri ve Non-steroid Antiinflamatuar İlaç Yan Etki Bilgi Düzeylerinin Karşılaştırılması" phD Thesis, Department of Family Medicine, Ankara; 2018
9. Karami NA, Altebainawi AF, Alfarki SA, et al. Knowledge and attitude of analgesics use among Saudi population: A cross-sectional study. Int J Med Sci Public Health 2018; 7: 137-42.
10. Balabanlı H. "Investigation of knowledge levels and attitudes of patients using NSAİD about those medications who applied to Ankara Training and Research Hospital Family Practice Polyclinics" phD Thesis, Department of Family Medicine, Ankara; 2019
11. Öksüz A, Atadağ Y, Aydın A, Kaya D. The frequency of analgesic drug use and causes in 65 years old and above; A family medicine unit experience. J Surg Med 2017; 1: 12–4.
12. Hopayılmaz Ö. "Centers in burdur province 65-85 age group conscious non-steroidal anti-inflammatory in humans determination of levels of drug use" Master Thesis, University of Burdur Mehmet Akif Ersoy, Department of Pharmacology and Toxicology, Burdur; 2018
13. Roshi D, Toçi E, Burazeri G, Schröder-Bäck P, Malaj L, Brand H. Users' Knowledge About Adverse Effects of Non-steroidal Anti-inflammatory Drugs in Tirana, Albania. Mater Sociomed 2017; 29: 138-42.
14. Karakitsiou M, Varga Z, Kriska M, Kristova V. Risk perception of NSAIDs in hospitalized patients in Greece. Bratisl Lek Listy 2017; 118: 427-30.
15. İlhan MN, Aydemir Ö, Çakır M, Aycan S. Akılcı olmayan ilaç kullanım davranışları: Ankara'da üç ilçe örneği," Türkiye Halk Sağlığı Derg 2014: 12: 188.
16. De Bolle L, Mehuys E, Adriaens E, Remon JP, Van Bortel L, Christiaens T. Home medication cabinets and self-medication: a source of potential health threats?. Ann Pharmacother 2008; 42: 572-9.
17. Özçelikay G. Akılcı İlaç Kullanımı Üzerinde Bir Pilot Çalışma. Ankara Üniversitesi Eczac. Fakültesi Derg 2001; 30: 9–18.
18. Beggi B, Aşık Z. Evaluation of Rational Drug Use in Patients Applying to Family Medicine Outpatient Clinic. Ankara Med. J 2019: 19.
19. Önder E, Koçıa O, Öztürk S, Sabuncu Z, Soyutemiz Ö, Altıntaş H. Yunus Emre Sağlik Ocağı bölgesinde yaşayan 18 yaş ve üstü bireylerin ağrı kesici kullanımı ve bu konudaki bazı bilgilerinin saptanması," Hacettepe Toplum Hekim Bülteni, 2002; 23: 16–28.
20. Palos GR, Mendoza TR, Cantor SB, Aday LA, Cleeland CS. Perceptions of analgesic use and side effects: what the public values in pain management. J Pain Symptom Manage 2004; 28: 460-73.
21. Paulose-Ram R, Hirsch R, Dillon C, Losonczy K, Cooper M, Ostchega Y. Prescription and non-prescription analgesic use among the US adult population: results from the third National Health and Nutrition Examination Survey (NHANES III). Pharmacoepidemiol Drug Saf 2003; 12: 315-26.
22. Türker Ö. Status of the polypharmacy and the rational drug usage who applied to the polyclinics of the Ankara Training and Research Hospital, phD Thesis, Department of Family Medicine, Ankara; 2017

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Outcomes of mTORi-involving minimized immunosuppression protocols in renal transplantation

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ABSTRACT

Aim: Immunosuppression lowering protocols are commonly involving low-dose calcineurin inhibitors (CNIs) and the mammalian target of Rapamycin inhibitor (mTORi). In renal transplant (RT) recipients, due to various factors (the development of polyoma B-K virus [BKV] and cytomegalovirus [CMV] infections, malignancy, and CNIs nephrotoxicity), immunosuppression lowering comes up mandatory. Here, we present the outcomes of renal allografts after switching from a standard immunosuppression protocol to mTORi-containing lower immunosuppression protocol.

Material and Method: This single-center, retrospective, and observational study includes RTs performed between 2014-2016. Three hundred twenty-two recipients were evaluated and 231 proper recipients were enrolled in the study. Recipients who received mTORi for at least 12 months were included in mTORi arm. Recipients who did not have a BKV and/or CMV screening test, and allograft biopsy were excluded. The remains were enrolled in mTORi-free arm. Allograft survival rate and function before mTORi and at 1, and 3-year under mTORi treatment were compared.

Findings: A total of 231 recipients were followed-up approximately for 5-years. In mTORi arm CMV and BKV viremia positivity rates were higher than mTORi-free group; p=0.001. Additionally, acute rejection (AR) rate was higher in mTORi arm (p=0.001). Estimated glomerular filtration rate (eGFR) at 1 and 3-year after mTORi arm was less than mTORi-free arm (p=0.001). However, 1 and 3-year recipient and allograft survival rates were similar among two groups; p=0.23 and p=0.06, p=0.52 and p=0.72, respectively.

Conclusion: In renal allograft recipients, mTORi is commonly considered in the cases that require lowering immunosuppression, such as BKV and CMV viremias, and CNI nephrotoxicity. Despite these disadvantages, it may provide a similar allograft survival rate compared to mTORi-free group. However, mTORi use is associated with more AR episodes and may not prevent the development of a worse eGFR.

Keywords: mTORi, renal allograft, renal transplantation

INTRODUCTION

Mammalian target of Rapamycin (mTOR) inhibitors; sirolimus and everolimus, are used in the kidney transplantation to prevent allograft rejection. They exert their effects via inhibiting a signaling pathway executed by mTORCs (mTOR complex 1 and 2) which results in inhibition of the immune response by disruption of the proliferation of T lymphocytes and induce immune cells apoptosis (1,2).

Calcineurin inhibitors (CNIs) are the most potent drugs in preventing acute allograft rejection in renal transplantation (RTx) recipients. However, CNIs use is associated with acute and chronic allograft dysfunctions (3-5). The majority of immunosuppressant minimizing protocols involve CNI dose reduction and adding mTORi (5-6). Other potential factors that might have negative impacts on allograft functions are cytomegalovirus (CMV) and polyoma BK virus (BKV) infections which are directly or indirectly associated with over immunosuppression (7,8). In CMV and BKV infections, minimizing immunosuppression is the main approach of the treatment; while mycophenolate mofetil (MMF) is ceased, CNI dose is reduced and mTOR inhibitors are added (9,10). On the other hand, minimizing CNI dose is bearing acute rejection (AR)

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risk, especially when is realized in the first year post-transplant (11,12). Additionally, CNIs-induced acute and chronic allograft nephrotoxicity and malignancy are two other causes that require immunosuppression lowering.

The outcomes of allografts are controversial, in minimized immunosuppression protocols, due to the variability of the study designs. In our study, we present the outcomes of the immunosuppression protocol that consists of low-dose CNI and mTORi, in RTx recipients.

MATERIAL AND METHOD

This single-center, retrospective observational study involved all kidney transplant recipients between the years 2014-2016. Data of 507 recipients were evaluated and 322 of those were enrolled in the study. A brief study design is depicted in **Figure 1**. Recipients who were on mTORi for at least 12months were enrolled in mTORi arm. Recipients who did not have BKV and CMV real-time polymerase chain reaction (PCR) testing results and at least one allograft biopsy were excluded. Recipients who have CMV and/or BKV positivity, and/or CNI nephrotoxicity but had high immunological risk were not switched to mTORi and received various treatment protocols. Those were addressed in mTORi-free arm. Early mortalities (mortality within 3 months posttransplant) and recipients with primary nonfunction grafts were excluded.

Two groups were defined as follow;

- mTORi group: low-dose CNI (target: 2-4 ng/dL for tacrolimus and 25-50 ng/mL for cyclosporine-A) + mTORi (target: 5-7 ng/dL); dose reductions were performed due to CMV, BKV positivitity or CNI nephrotoxicity.
- mTORi-free group: standard dose CNI (target: 5-12 mg/dL) + MMF (1-2 gr/day). Recipients who received mTORi less than 6 months also included in this group.

Allograft functions before the onset of mTORi, 1 and, 3–year allograft functions, and allograft losses were evaluated. CMV and BKV viremias were investigated in blood samples, by using reverse transcriptase quantitative PCR. Biopsy-proven AR episodes, donors' and recipients' ages were noted.

Ethics committee approval was obtained from "The University Scientific Research and Ethic Committe" of the Yeni Yuzyil University with IRB; 2020/06-478.

Statistical Analysis

Data were analyzed by using the Statistical Package for Social Sciences (S.P.S.S.) for Windows version 15. Numeric variables were presented as mean±standard deviation, and median (minimum and maximum). Categorical variables compared by using the Chi-Square test. Parametric variables were compared among the two groups, by using independent samples T-test. Allograft and patient survival rates were analyzed by Kaplan Meier survival curves. Cox-regression was used to demonstrate the impact of the potential factors on recipient and allograft survival. $p<0.05$ was accepted significant in a 95% confidence interval.

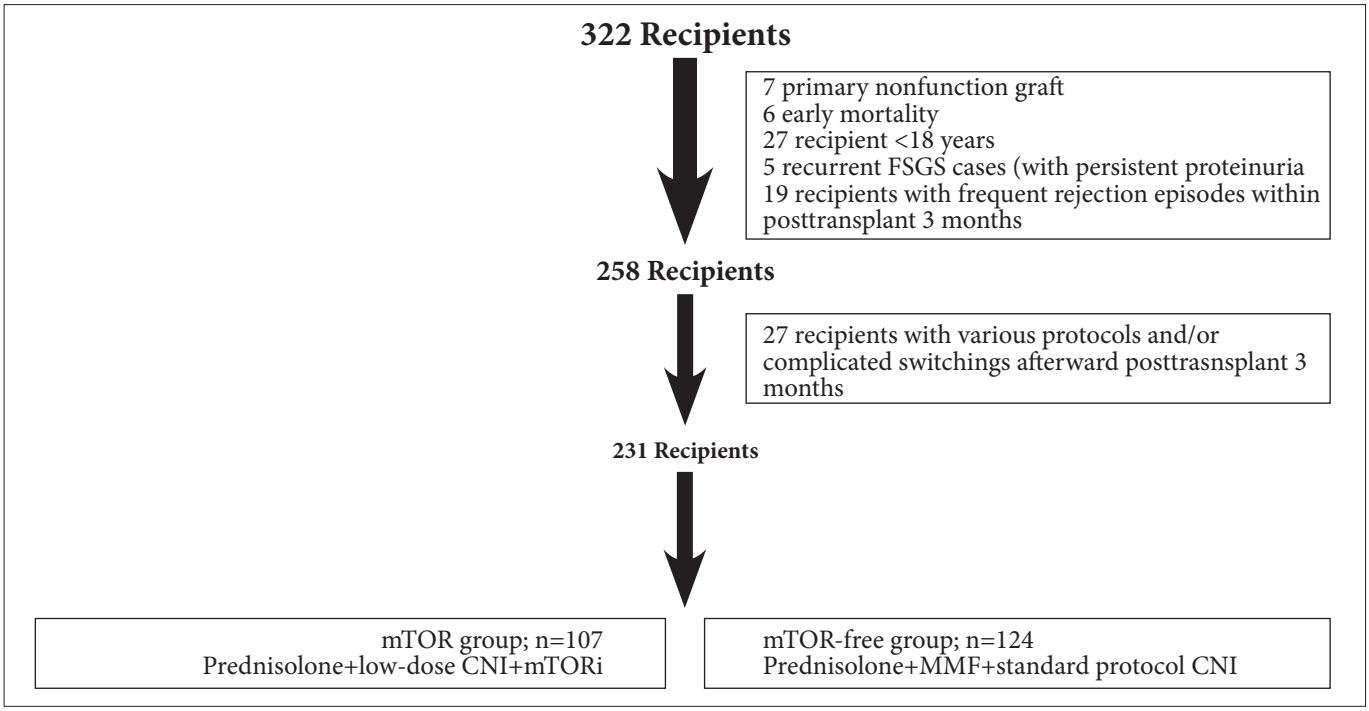


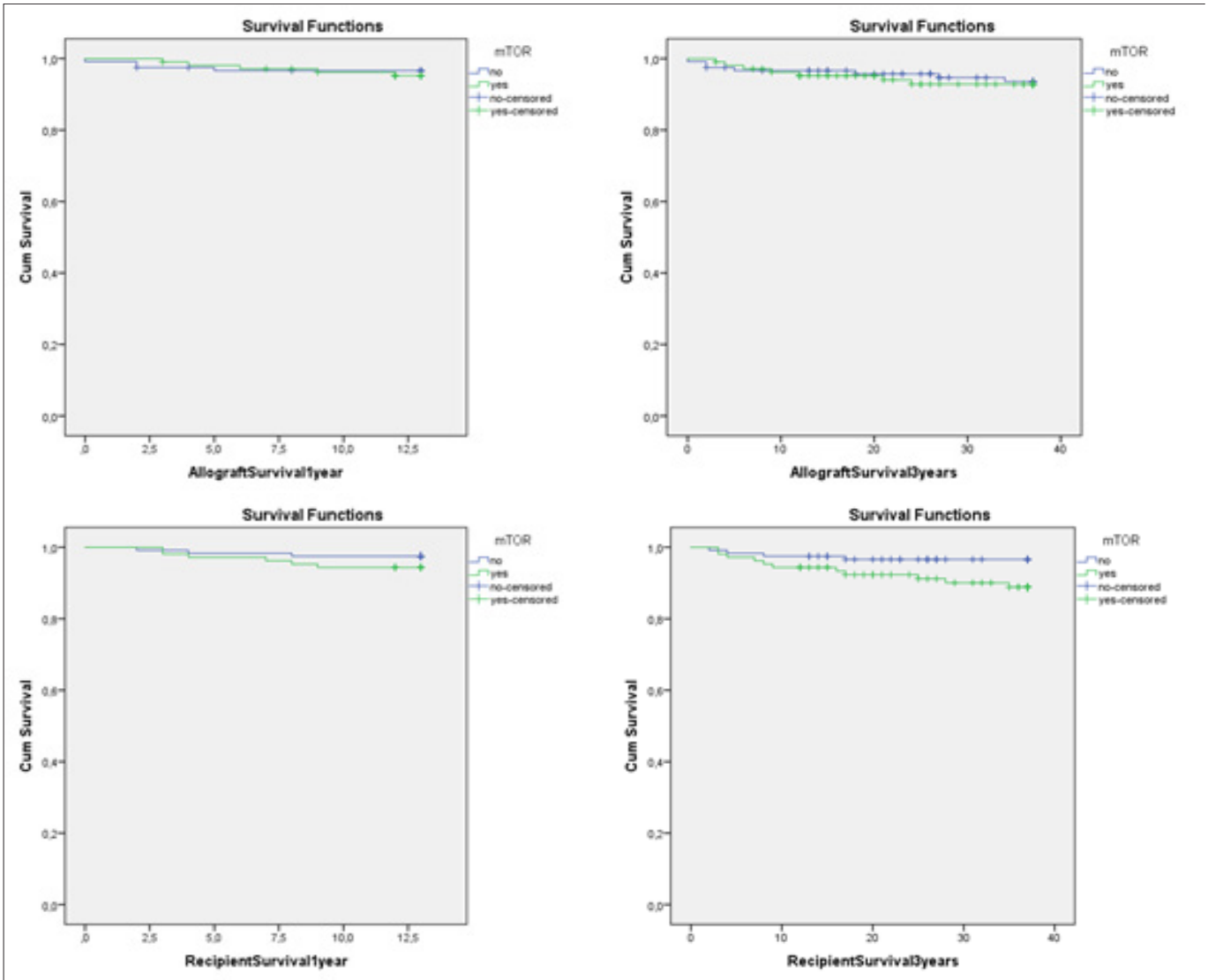
Figure 1. The recipient and allograft survival rates of two groups.

RESULTS

A total of 231 recipients, 132 males, and 99 females were evaluated, and the mean age was 45.79±11.10. One hundred-seven recipients received mTORi and 124 recipients received mTORi-free protocol. **Table 1** demonstrates the clinical and laboratory features of recipients and donors. 83.9% of the allograft donation was from living donors. 32.9% of recipients experienced at least one AR episode. The average follow-up duration was 54.82±20.23 months.

In mTORi arm, CMV and BKV infections and AR episodes were in higher rate compared to mTORi-free arm (p=0.001 for all). 89.1% of CMV and 89.5% of BKV viremias were in mTORi arm. 1 and 3-year allograft functions (eGFR) were worse in mTORi arm (p=0.001 and p=0.001, respectively) (**Table 2**). eGFR before switching to mTORi was 57.28±22.17 ml/dk/1.73m2 and was similar to the 12-month and 36-month eGFR, p=0.37 and p=0.11, respectively.

Allograft survival rates were similar in mTORi and mTORi-free arms at posttransplant 1 and 3-year (p=0.52 and p=0.72, respectively) (**Figure 2**). Cox-regression analysis demonstrated CMV and BKV viremia positivities had no impact on 1 and 3-year allograft survival rates (p=0.525 and p=0.876, p=0.982 and p=0.905) (**Table 3**). Besides AR episodes had a negative impact on 3-year allograft survival (p=0.014 and OR=3.996). Donor age had an impact both in 1 and 3-year allograft survival rates (p=0.022 and OR=1.039, and p=0.001 and OR=1.055).



	mTORi	mTORi-free	P value
Recipient survival rate;			
• **1 year**	94.3%	97.5%	0.23
• **3 years**	89.6%	96.6%	0.06
Allograft survival rate;			
• **1 year**	92.3%	96.6%	0.52
• **3 years**	90.4%	94.1%	0.72

Figure 2. Study design and case selection
FSGS; focal segmental glomerulosclerosis, mTOR; mammalian target of rapamycine, CNI; calcineurin inhibitör.

Table 1. Clinical and laboratory features of recipients and donors.

	N=231
Male/female	132/99
Age, year	45.79±11.10
Recipient BMI, kg/m^2	24.06±4.24
Donor BMI, kg/m^2	26.20±4.15
Donor type; living/deceased	194 (83.9%)/37 (16.1%)
BKV positivity, yes/no	48 (20.7%)/183 (79.3%)
CMV positivity, yes/no	46 (19.9%)/185 (80.1%)
Acute rejection, yes/no	76 (32.9%)/155 (67.1%)
Average allograft survival, month (5-year)	47.36±24.03
Average recipient survival, month (5-year)	52.82±20.23
eGFR, ml/dk/min/1.73m^2;	
3 months	62.38±33.26
1 year	71.21±24.87
3 years	63.06±24.09
5 years	59.28±26.43
Recipient survival rate;	
1 year	96.0%
3 years	93.3%
5 years	91.2%
Allograft survival rate;	
1 year	96.0%
3 years	93.8%
5 years	91.1%

BMI; body mass index, BKV; polyoma B-K virus, CMV; cytomegalovirus, eGFR; estimated glomerular filtration rate.

Table 2. Comparison of two groups for eGFR and risk factors

	mTORi; n=107	mTORi-free; n=124	P value
Recipient age, year	45.63±12.01	44.86±10.20	0.602
Male/female	62/45	74/50	0.589
Recipient BMI, kg/m^2	23.75±3.92	24.06±4.16	0.662
CMV positivity, yes/no	41/66 (38.3%/61.2%)	5/119 (4.0%/96.0%)	0.001
BKV positivity, yes/no	43/64 (40.1%/59.9%)	5/119 (4.0%/96.0%)	0.001
Acute rejection, yes/no	40/67 (37.38%/62.62%)	22/102 (17.7%/82.3%)	0.001
CNI induced nephrotoxicity (biopsy proven); yes/no	28.6%/71.4%	17.4%/78.6%	0.603
eGFR, ml/dk/1.73 m^2;			
1 year	59.36±25.69	71.85±25.72	0.001
3 years	54.41±23.21	70.96±27.00	0.001
Immunological risk assessment			
Low risk	82.4%	77.0%	0.751
High risk	17.6%	23.0%	
CNI induced nephrotoxicity			
Yes	28.6%	17.4%	0.603
No	71.4%	82.6%	

The one and 3-year recipient survival rates were similar in the two groups (p=0.23 and p=0.06) (**Figure 2**). Cox-regression analysis demonstrated CMV and BKV infections and AR episodes had no impact on 1 and 3-year recipient survival rates (p=0.235 and p=0.872, p=0.202 and p=0.593, and p=0.559 and p=0.943, respectively). However, recipient age was associated with worse 1 and 3-year recipients survival rates (p=0.010 and OR=1.094, and p=0.001 and OR=1.096, respectively).

Subgroup analysis revealed that 3-month posttransplant eGFRs were similar in mTORi and mTORi-free arm,63.44±32.16 vs 61.18±29.15, p=0.10. However, in mTORi arm, eGFR at the switching time was lower compared to eGFR at posttransplant 3-month, 63.44±32.16 vs57.28±22.17, p=0.04. eGFR at 1 and 3 years posttransplant in recipients with CMV and/or BKV positivity and AR episodes are compared in **Table 4.** 3-year eGFR was worst in CMV viremia positive recipients compared to the CMV viremia negative individuals (p=0.005) (**Table 4**). AR rates in CMV and BKV viremia positive recipients were given in **Table 5**.

Table 4. Estimated glomerular filtration rates at posttransplant 3, 12, and 36 months in CMV, BKV viremia positive recipients and in recipients with AR episodes.

	3-month posttransplant eGFR	1-year eGFR	3-year eGFR
CMV;			
Negative	67.39±26.65	71.47±24.57	70.22±22.42
Positive	59.37±28.81	65.21±25.92	40.40±13.95
	p=0.08	p=0.19	**p=0.005**
BKV;			
Negative	65.45±27.53	70.93±25.29	64.31±25.30
Positive	72.49±19.18	69.19±18.58	58.08±20.11
	p=0.11	p=0.68	p=0.61
AR;			
No	67.91±24.99	70.68±23.10	67.89±23.46
Yes	60.59±31.45	67.33±25.11	49.88±25.22
	p=0.06	p=0.38	p=0.11

Table 5. Acute rejection and calcineurin inhibitör nephrotoxicity in CMV and BKV infections

	Acute rejection rates[a]	CNI nephrotoxicity[b]	p value
CMV; positive/ negative	18.5%/11.0%	17.4%/28.6%	0.13[a], 0.60[b]
BKV; positive/ negative	18.4%/7.2%	12.5%/22.7%	0.03[a], 0.99[b]

Table 3. Impact of factors on 1 and 3-year recipient and allograft survival rates.

	CMV	BKV	AR
	p value, 95% CI, and odds ratio		
1-year recipient survival	0.235 (0.533-13.083) 2.640	0.202 (0.061-1.809) 0.331	0.559 (0.126-3.068) 0.622
3-year recipient survival	0.872 (0.295-4.219) 1.116	0.593 (0.220-2.375) 0.723	0.943 (0.349-3.107) 1.041
1-year allograft survival	0.525 (0.298-10.696) 1.787	0.982 (0.164-5.865) 0.980	0.080 (0.865-13.136) 3.370
3-year allograft survival	0.876 (0.221-5.887) 1.140	0.805 (0.185-3.707) 0.828	*0.014* (1.331-11.997) 3.996

CMV; cytomegalovirus, BKV; poliyoma B-K virus, AR; acute rejection.

DISCUSSION

Renal transplantation (RTx) is the favorable choice of treatment in end-stage kidney disease due to having better patient survival advantages. Additionally, a logical posttransplant immunosuppression therapy has vital importance, since the over-immunosuppression is related to serious life-threating infections, malignancies, and allograft toxicity whereas low-immunosuppression is related to a higher rate of allograft rejection episodes. Clinicians commonly are forced to CNI minimizing approaches, due to BKV, CMV infections, and the existence of the evidence piece of the biopsy-proven CNI toxicity. In this study, we indicated switching to mTORi due to various compelling issues (CMV and BKV viremias and CNI toxicity) might have no adverse outcomes on allograft survival and function.

The evolution in immunosuppressants has advanced with the introduction of the CNI. CNIs have been associated with reduced AR rates over time, however, long-term allograft survival and function have not improved to a satisfactory extent (13,14). It is thought that CNI induced acute and chronic nephrotoxicity might have some adverse impact on allograft survival and function (14,15). CNI induced nephrotoxicity is at a high rate in RTx recipients, up to 94% (16). mTORi-involving immunosuppressant protocols have been used to avoid CNI induced nephrotoxicity (either CNI dose reduction or complete withdrawal of CNI). This approach carries the risk of higher AR episodes, however, the previous studies reported conflictive outcomes. Additionally, given the available studies which demonstrated antiviral activities of mTORi against BKV, make mTORi a good option in enhancing the immunosuppression modifications, both via allowing CNI dose reduction, and via its antiviral activity (17,18). Additionally, as an important part of the overall immunosuppressant dose reduction in the treatment of CMV viremia, switching to mTORi may provide some benefits. In our study, mTORi arm substantially was consisted of cases with CMV and BKV viremias positivities. One and 3-year allograft survival rates were similar in mTORi and mTORi-free groups. However, in the surviving allografts 1 and 3-year, eGFRs were worse in mTORi groups. Higher prevalences of CMV, BKV, and AR rates all might have an overall impact on reduced eGFR, in mTORi group. Subgroup analysis revealed CMV has associated with reduced 3-year eGFR.

Allograft survival rate and function depend on various potential adverse factors such as CMV and BKV infection, and acute rejection episodes. CMV is one of the most important infectious causes associated with substantial morbidity and mortality after organ transplantation (19,20). CMV prevalence has a great variation among RTx studies (ranging from 5% to 100%) due to different population serostatus, immunosuppression protocols, and testing methods (21,22). Immunosuppression level is the most important influent on the development of CMV infection, and lowering immunosuppression along with valganciclovir/ganciclovir therapy is the main first-line approach in the disease control (20,23-25). In our cohort, CMV prevalence is 19.9%, and 89.1% of those were in mTOR group. 1-year eGFR in CMV positive and negative groups were similar. In CMV viremia positive recipients, after immunosuppression lowering and CMV disease treatment with valganciclovir/ganciclovir therapy, allograft function did not recovery at 3-year posttransplant (the worst eGFR). AR seems to have an impact on 3-year allograft functions. AR rate was higher in recipients with CMV viremia but statistically was not significant. However, the regression analysis revealed that AR episodes had an impact on the 3-year allograft survival in mTORi arm. CMV viremia and AR development are well-known and interrelated issues in RTx (26,27). However, allograft survival rates were at 1 and 3-year were similar in mTORi and mTORi-free groups, and surprisingly, CMV viremia positivity had no impact on allograft survival in our cohort. We think this preferable outcome might be associated with mTORi use and less CNI induced nephrotoxicity (biopsy-proven CNI nephrotoxicity has been found less in CMV positive recipients) (17.4% vs 28.6%). Posttransplant 1 and 3-year recipients' survival rates were also similar in both groups, and CMV viremia existence had no impact on the recipient survival.

Polyoma B-K virus (BKV) is highly prevalent in the general population with over 80% of individuals having serological positivities against BKV (28,29). BKV reactivation is a common problem after therapeutic immunosuppression in RTx. BKV viremia occurs in up to 13% of RTx and BKV associated nephropathy prevalence is approximately 10% (30-32) The prolonged persistent BK viremia is associated with the development of ClassII donor-specific antibodies and higher AR rates (33,34). BKV nephropathy has been associated with reduced 3-year overall allograft survival (35). The immunosuppression level is the main promotor factor in the development of BK viremia, and lowering immunosuppression (dose adjustment, drug withdrawal, substituting with another drug) is the key point of the treatment (36). In our cohort, BKV prevalence is 20.7%, and 89.5% of the cases were in mTORi arm. One and 3-year allograft and recipient survival rates were similar among BKV viremia positive and negative recipients. Cox-regression analysis revealed that BKV had no impact on overall allograft and recipient survival. AR rates were found higher in BKV positive recipients, as previous studies reported.

CONCLUSION

The low-dose CNI + mTORi protocol which is established due to many mandatory factors, has not worse outcomes compared to the protocols involving standard dose CNI.

Limitations of the study; the treatments of CMV and BKV infections and AR episodes and the impacts of the success or failure of those treatment protocols were not included in the study. Additionally, lacking assessment of the induction protocols, of the immunological risk, and of the adverse drug reactions were some other limitations of the study.

ETHICAL DECLARATIONS

Ethics Committee Approval: The University Scientific Research and Ethic Committe of the Yeni Yuzyil University; 2020/06-478.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: Mehmet Emin Demir: Project designer, writer, coordianator, Ozgur Merhametsiz: Data collection, Murat Sevmis: Statistical analyzes, Murathan Uyar: Advisor, Sema Aktas: Advisor, Sinasi Sevmis: Advisor

REFERENCES

1. Kajiwara M, Masuda S. Role of mTOR Inhibitors in Kidney Disease. Int J Mol Sci 2016 Jun 21; 17: 975.
2. Badve SV, Pascoe EM, Burke M, et al. Mammalian target of rapamycin inhibitors and clinical outcomes in adult kidney transplant recipients. Clin J Am Soc Nephrol 2016; 11: 1845-55.
3. Farouk SS, Rein JL. The many faces of calcineurin inhibitor toxicity-what the FK? Adv Chronic Kidney Dis 2020; 27: 56-66.
4. Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. N Engl J Med 2003; 349: 2326-33.
5. Prashar R, Venkat KK. Immunosuppression minimization and avoidance protocols: when less is not more. Adv Chronic Kidney Dis 2016; 23: 295-300.
6. Farkas SA, Schnitzbauer AA, Kirchner G, Obed A, Banas B, Schlitt HJ. Calcineurin inhibitor minimization protocols in liver transplantation. Transpl Int 2009; 22: 49-60.
7. Rostaing L, Wéclawiak H, Mengelle C, Kamar N. Viral infections after kidney transplantation. Minerva Urol Nefrol 2011; 63: 59-71.
8. Malvezzi P, Jouve T, Rostaing L. Negative impact of CMV and BKV infections on kidney-allograft function at 1-year post-transplantation: can it be changed by modifying immunosuppression? EBioMedicine 2018; 34: 2-3.
9. Tedesco-Silva H, Felipe C, Ferreira A, et al. Reduced incidence of cytomegalovirus infection in kidney transplant recipients receiving everolimus and reduced tacrolimus doses. Am J Transplant 2015; 15: 2655-64.
10. Jouve T, Rostaing L, Malvezzi P. Place of mTOR inhibitors in management of BKV infection after kidney transplantation. J Nephropathol 2016; 5: 1-7.
11. Malvezzi P, Rostaing L. Renal transplantation in 2016: Novel approaches to improve recipient and allograft outcomes. Nat Rev Nephrol 2017; 13: 73-74.
12. Sawinski D, Trofe-Clark J, Leas B, et al. Calcineurin inhibitor minimization, conversion, withdrawal, and avoidance strategies in renal transplantation: a systematic review and meta-analysis. Am J Transplant 2016; 16: 2117-38.
13. Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. Am J Transplant 2004; 4: 378-83.
14. Tantravahi J, Womer KL, Kaplan B. Why hasn't eliminating acute rejection improved graft survival? Annu Rev Med 2007; 58: 369-85.
15. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol 2009; 4: 481-508.
16. Zununi Vahed S, Ardalan M, Samadi N, Omidi Y. Pharmacogenetics and drug-induced nephrotoxicity in renal transplant recipients. Bioimpacts 2015; 5: 45-54.
17. Moscarelli L, Caroti L, Antognoli G, et al. Everolimus leads to a lower risk of BKV viremia than mycophenolic acid in de novo renal transplantation patients: a single-center experience. Clin Transplant 2013; 27: 546-54.
18. Hirsch HH, Yakhontova K, Lu M, Manzetti J. BK polyomavirus replication in renal tubular epithelial cells is inhibited by Sirolimus, but activated by tacrolimus through a pathway involving FKBP-12. Am J Transplant 2016; 16: 821-32.
19. Ramanan P, Razonable RR. Cytomegalovirus infections in solid organ transplantation: a review. Infect Chemother 2013; 45: 260-71.
20. Selvey LA, Lim WH, Boan P, et al. Cytomegalovirus viraemia and mortality in renal transplant recipients in the era of antiviral prophylaxis. Lessons from the western Australian experience. BMC Infect Dis 2017; 17: 501.
21. Cordero E, Casasola C, Ecarma R, Danguilan R. Cytomegalovirus disease in kidney transplant recipients: incidence, clinical profile, and risk factors. Transplant Proc 2012; 44: 694-700.
22. Durlik M, Siennicka J, Litwińska B, et al. Clinical manifestations and diagnosis of cytomegalovirus infection in renal allograft recipients. Transplant Proc 2001; 33: 1237-9.
23. Avery RK. Low-dose valganciclovir for cytomegalovirus prophylaxis in organ transplantation: is less really more? Clin Infect Dis 2011; 52: 322-4.
24. Asberg A, Jardine AG, Bignamini AA, et al. VICTOR Study Group. Effects of the intensity of immunosuppressive therapy on outcome of treatment for CMV disease in organ transplant recipients. Am J Transplant 2010; 10: 1881-8.
25. Anglicheau D, Lautrette A, Scieux C, Flamant M, Morinet F, Legendre C. Efficacy and safety of lowering immunosuppression to treat CMV infection in renal transplant recipients on valaciclovir prophylaxis: a pilot study. Nephrol Dial Transplant 2003; 18: 1654-6.
26. Hasanzamani B, Hami M, Zolfaghari V, Torkamani M, Ghorban Sabagh M, Ahmadi Simab S. The effect of cytomegalovirus infection on acute rejection in kidney transplanted patients. J Renal Inj Prev 2016; 5: 85-8.

27. Sagedal S, Nordal KP, Hartmann A, et al. The impact of cytomegalovirus infection and disease on rejection episodes in renal allograft recipients. Am J Transplant 2002; 2: 850-6.

28. Stolt A, Sasnauskas K, Koskela P, Lehtinen M, Dillner J. Seroepidemiology of the human polyomaviruses. J Gen Virol 2003; 84: 1499-504.

29. Knowles WA. Discovery and epidemiology of the human polyomaviruses BK virus (BKV) and JC virus (JCV). Adv Exp Med Biol 2006; 577: 19-45.

30. Hirsch HH, Knowles W, Dickenmann M, et al. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N Engl J Med 2002; 347: 488-96.

31. Brennan DC, Agha I, Bohl DL, et al. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. Am J Transplant 2005; 5: 582-94.

32. Hirsch HH. BK virus: opportunity makes a pathogen. Clin Infect Dis 2005; 41: 354-60.

33. Sawinski D, Forde KA, Trofe-Clark J, et al. Persistent BK viremia does not increase intermediate-term graft loss but is associated with de novo donor-specific antibodies. J Am Soc Nephrol 2015; 26: 966-75.

34. Haas M, Loupy A, Lefaucheur C, et al. The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. Am J Transplant 2018; 18: 293-307.

35. Schold JD, Rehman S, Kayle LK, Magliocca J, Srinivas TR, Meier-Kriesche HU. Treatment for BK virus: incidence, risk factors and outcomes for kidney transplant recipients in the United States. Transpl Int 2009; 22: 626-34.

36. Sawinski D, Goral S. BK virus infection: an update on diagnosis and treatment. Nephrol Dial Transplant 2015; 30: 209-17.

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Urinary tract stone surgery in patients with urinary diversion and vesicostomy: a single center experience

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ABSTRACT

Objective: To report our experience in percutaneous nephrolithotomy and endoscopic urinary tract stone surgery in patients with urinary diversion or vesicostomy.

Material and Method: Data of 21 patients with urinary diversion or vesicostomy who underwent surgery for urinary tract stones in our clinic between January 2008 and January 2020 were retrospectively analyzed. Eight patients (38%) underwent percutaneous nephrolithotomy, 2 patients (9.5%) underwent antegrade flexible ureteroscopy, 4 patients (19.0%) underwent retrograde semi-rigid or flexible ureteroscopy, 5 patients (23.8%) underwent retrograde pouch lithotripsy and 2 patients (9.5%) underwent percutaneous cystolithotripsy with vesicostomy tract entrance. Preoperative and postoperative data of the patients were evaluated.

Results: The male to female ratio was 16/5.The mean age of the patients was 54.6±10.1 years and mean preoperative stone diameter was 2.8±4.5 cm. It was determined that 14 patients (66.6%) had ileal conduit (Bricker anastomosis), 5 patients (23.8%) had ureterocutaneostomy, and 2 patients (9.5%) had vesicostomy. Stone-free rate was 85.7% after single session of treatment. In the postoperative period, febrile urinary tract infection was observed in 4 (19.0%) patients, urinary system obstruction secondary to stone in 3 (14.2%) patients and anastomotic leakage in 1 (4.7%) patient.

Conclusion: Percutaneous nephrolithotomy, antegrade ureterorenoscopy, retrograde ureterorenoscopy and vesicostomy entry cystolithotripsy are highly effective and safe methods in patients with urinary diversion and vesicostomy. The most important factors affecting the success are the experience of surgical team that can apply procedural options together with careful preoperative preparation and correct instrumentation.

Keywords: Urinary diversion, stone formation, stone surgery

INTRODUCTION

Ureterosigmoidostomy procedure was first applied after radical cystectomy by Simon et al. (1) and following this, different types of urinary diversion such as cutaneous conduit, orthotopic neobladder and continent urinary diversion were developed. Stone formation in the upper urinary tract as well as in the reservoir or conduit is one of the most common complications in patients with urinary diversion (2). The incidence of stone formation in patients with ileal conduit was reported to be from 9%to 11%, while it was reported that 17% patients with Koch pouch and from 11% to 12.9% of patients with Indiana pouch developed urinary tract stones in the long term follow-up period (3-5). Similar to patients with urinary diversion, it is known that both bladder stones and upper urinary tract stones are frequently develop in patients with neurogenic bladder developing secondary to spinal cord injury (6).

Stone surgery in patients with urinary diversion presents various difficulties for urologists. Difficulties in visualizing the ureter orifices through the pouch and entering the ureter during both imaging and retrograde approach due to the impaired anatomical structure constitute the main problem in this area (7-9). On the other hand, stone recurrence reported in 33% to 63% of patients with urinary diversion within 3-5 years after the first surgical intervention significantly limits the option of the open stone surgery (10). Therefore, in patients with urinary diversion, percutaneous nephrolithotomy (PNL), semi-rigid or flexible antegrade ureteroscopy (URS) performed through percutaneous tract, or

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combined antegrade and retrograde approaches constitute the preferred surgical options (11). Although successful results of extracorporeal shoch wave lithotripsy (ESWL) have been reported in stone patients with urinary diversion in stones smaller than 2 cm, it is known that the success rate of ESWL decreases in larger stones (10).

As the literature data and our clinical experience indicate, urinary system stone stone surgery in patients with urinary diversion and vesicostomy requires preoperative instrumentation preparation and surgical team experience, which allows all options to be applied during the operation.

In this study, we aimed to share our experiences in urinary system stone surgeries performed in patients with urinary diversion and vesicostomy in our clinic, which is one of the centers working intensively on urinary system stone surgery.

MATERIAL AND METHOD

The study was carried out with the permission of Keçiören Training and Research Hospital Health Application Research Center Medical Specialty Education Board (Date: 08.12.2020 IRB: 2012-KAEK-15/2202) of our institution, the data of 21 patients with urinary diversion or vesicostomy who underwent surgical intervention for urinary tract stones between January 2008 and January 2020 were retrospectively analyzed. All procedures were performed adhered to the ethical rules and the Helsinki Declaration of Principles.

During the preoperative preparation period, all patients were evaluated with routine preoperative blood tests, urine analysis, urine culture, and non-contrast abdominal computed tomography (CT). Intravenous urography (IVU) was performed to evaluate the anatomical structure of kidney. Possible anatomical variations were evaluated according to the type of operation and diversion the patients had, and the possible difficulties to be encountered during the operation were discussed and necessary and sufficient instrumentation was provided according to these possibilities. In the preoperative evaluation, it was determined that 14 (66.6%) patients had Bricker-type ileal conduit diversion, 5 (23.5%) had ureterocutaneostomy performed during radical cystectomy, and 2 (9.5%) patients had vesicostomy due to neurogenic bladder developing secondary to spina bifida. Appropriate prophlylactic and therapeutic antibiotic was administered to patients according to preoperative urine culture results. Intravenous 1 g 3rd generation cephalosporin was administered to all patients for preoperative prophylaxis. The operations included in the study were performed by a total of six surgeons working in the same center.

Surgical Procedures

Percutaneus nephrolithotomy (PNL): All patients with renal stones were evaluated primarily in lithotomy position in terms of performing retrograde ureteral catheterization and, if possible, retrograde intrarenal surgery (RIRC). Patients whose ureter orifices cannot be seen and retrograde access was not possible were prepared for percutaneous intervention, a 16-18 fr foley catheter was inserted into the pouch from the stoma, the balloon was inflated with 5-6 cc saline, and the patient was turned to the prone position. After the appropriate position was given, radiopaque liquid diluted with 50% saline was given into the pouch through the foley catheter, and it was tried to pass from the ureter to the kidney to visualize the renal collecting system. In cases which sufficient radiopaque material could not reached into the kidney and the renal collecting system, the ultrasound-guided entry technique was used. An 18-gauge percutaneous needle was used to enter the renal collecting system, and the needle was removed so that the outer sheath remained in the renal collecting system by providing the targeted renal calix entry. Afterwards, radiopaque fluid was injected into the renal collecting system through the outer sheath of the percutaneous needle, and the collecting system was visualized, and the entrance location and anatomical structure were evaluated. In cases where it was seen that proper calix entry could not be achieved, re-entry was made with a second needle and the outer sheath of the first entry needle was not removed and used for radiopaque fluid infusion into the renal collecting system in order to ensure adequate visualization. After proper renal calix insertion was provided, a 0.035-inch hydrophilic guide wire was advanced into the renal collecting system through the outer sheath of the needle, followed by percutaneous dilatation with percutaneous dilatators ranging from 24fr-30fr, allowing percutaneous access to the renal collecting system with rigid nephroscope (Karl-storz®-22 fr). Following the percutaneous entry, the stone was fragmented and removed with use of an ultrasonic lithotripter (EMS®), or pneumatic lithotripter (EMS®). A flexible cystoscope (Olympus®-21 fr) was used in some calix stones that cannot be reached with rigid nephroscope. Following the procedure, a 16-fr catheter was placed in all patients as a nephrostomy, and the catheter had placed in the pouch was removed.

Antegrade URS: Antegrade URS procedure was used in upper ureteral stones where retrograde intervention was not possible and for stones that could not be reached with a rigid or flexible nephroscope. At the entrance, the same procedure was applied as the PNL entry and percutaneous entry to the kidney through the appropriate calix was provided. Then, a 0.035-inch hydrophilic guide wire was advanced antegradely into the ureter and then the stone was reached by entering the ureter with

a flexible ureteroscope (Olympus®-9.5 fr) through the nephrostomy tract. The stone was fragmented with using a 200 µm or 500 µm Ho:YAG laser energy (StoneLight®) and removed with a 2.2 fr nitinol stone basket. After the stone was removed, imaging was performed by antegrade ureterography in terms of possible obstruction and anostomosis integrity, and a 5 fr doule-j stent was placed through the nephrostomy tube up to the reservoir pouch. Subsequently, a 16 fr nephrostomy catheter was inserted and the procedure was terminated. The nephrostomy tube was removed on the postoperative day 3, and then on the 7th day, the duoble-j stend was removed through the pouch using a rigit (Karl-Storz®-17 fr) or flexible cystoscope.

Retrograde URS: Except for patients with vesicostomy, ureteral catheterization for PNL or URS was tried in all 19 patients with urinary diversion, but only in 4 (21.0%) of the patients procedure wassuccessful. Retrograde URS was performed in cases that the ureter orifice can be seen through the diversion pouch. Using a 17 fr rigit cystoscope or 9.5-fr semi-rigid ureterorenoscope (Olymus® 9.5 fr), a 0.035-inch hydrophilic guidewire was advanced to the ureter under direct visualition of the ureter orifice of the stone side. Subsequently, the ureter was entered by using a semi-rigid or flexible ureterorenoscope under the guidance of a hydrophilic guidewire. The stone was fragmented with a 200 µm or 500 µm Ho: YAG laser energy and removed using a 2.2 fr nitinol stone basket. At the end of the procedure, a 5 fr double-j stent was placed over the hydrophilic guidewire into the ureter and the procedure was terminated.The double-j stent was removed on the postoperative day 7 by retrograde route using a rigit or flexible cystoscope.

Retrograde pouch lithotripsy with stomal entry: Retrograde pouch lithotripsy with stomal entry was applied in patients with reservoir stones. For this purpose, the pouch was inserted retrograde from the stoma with using a 22 fr nephroscope and the stone was fragmented with a pneumatic or ultrasonic lithotriptor and removed with the aid of a stone basket. During the procedure, the presence of stone fragments between the mucosal folds was checked by fluroscopy, and possible fragmented stones were removed. At the end of the procedure, radiopaque fluid was injected into the pouch and the presence of possible anastomotic leakage was checked, and at the end of the procedure, a 16-18 fr foley catheter was placed in the pouch and the procedure was terminated. The foley catheter in the pouch was removed on the second postoperative day.

Percutaneous cystolithotripsy with vesicostomy entry: In patients with vesicostomy, which was performed due to neurogenic bladder developing secondary to spina bifida, percutaneous cystolithotripsy with vesicostomy entry was applied for bladder stone. In this procedure, the bladder was entered through the vesicostomy tract with a 22-fr nephroscope, and then the stone was fragmented using an ultrasonic or pneumatic lithotripter and removed using a stone basket. When necessary, 200 µm or 500 µm Ho: YAG laser energy was also used for stone fragmentation. At the end of the procedure, a 16-18 fr foley catheter was inserted through the vesicostomy tract into the bladder and removed on the second postoperative day.

Statistical Analysis

All statistical analyses were performed with SPSS 24.0 (IBM Corp., Chicago) for Windows. The mean±standard deviation was used for parametric data and the median and minimum-maximum values were used for nonparametric data.

RESULTS

The male to female ratio was 16/5. The mean age of the patients was 54.6±10.1 (16-71) years. The most common comorbidity factor detected in the preoperative period was hypertension which was seen in 14 (66.6%) patients. The mean preoperative creatinine level was 1.1±0.3 (80.7-2.2) mg/dL. The most common stone localization was kidney in 11 (52.3%) patients, while it was found in the reservoir pouch in 5 (23.8%) patients and in the ureter in 3 (14.2%) patients. Bladder stones were detected in the other 2 (9.5%) patients with vesicostomy included in the study. Preoperative patient characteristics are shown in **Table 1.**

Table 1. Preoperative patient's characteristics

Age, mean±SD (minimum-maximum),years	54.6±10.1 (16-71)
Gender (n,%)	-
Male	16 (76.1%)
Female	5 (23.8%)
Comorbidities (n,%)	-
Hypertension	14 (66.6%)
Diabetes mellitus	4 (19.0%)
Dyslipidemia	5 (23.8%)
Chronic obstructive pulmonary disease	2 (9.5%)
Rheumatoid arthritis	1 (4.7)
Preoperative serum creatinine level (mg/dL)	1.1±0.3 (0.7-2.2)
Stone localization (n,%)	-
Kidney	11 (52.3%)
Ureter	3 (14.2%)
Reservoirpouch	5 (23.8%)
Bladder	2 (9.5%)
Stone size (cm)	2.8±4.5 (1.4-8.5)
Diversion type (n,%)	-
İleal conduit (Bricker type)	14 (66.6%)
Ureterocutaneostomy	5 (23.8%)
Vesicostomy	2 (9.5%)

It was observed that the mean operation time was 74.5±14.6 (40-130) minutes and the most common operationtype was PNLthat was performed in 8 (38.0%) patients. Other procedures performed were antegrade URS in 2 (9.5%) patients, retrograde URS in 4 patients (19.0%), retrograde pouch lithotripsy with stomal entry in 5 patients (23.8%) and percutaneous cystolithotripsy with vesicostomy entry in 2 patients (9.5%). In the early postoperative period, febrile urinary tract infection was developed in 4 (19.0%) patients. In total of 3 (14.2%) patients, 2 (9.5%) who underwent PNL and 1 (4.7%) who underwent antegrade URS, urinary obstruction was developed due to residual stones in the postoperative period and secondary surgical intervention was required. Minimal anastomotic leakage was found at the end of the procedure in 1 (4.7%) of the patients who underwent retrograde URS, and it was observed that the urinary leakage spontaneously recovered by a double-j stent without additional surgical intervention. Postoperative findings of the patients are shown in **Table 2.**

Table 2. Surgical procedures and postoperative results

Surgical procedure (n,%)	-
Percutaneus nephrolithotomy	8 (38.0%)
Antegradeureteroscopy (flexible)	2 (9.5%)
Retrogradeureteroscopy (semi-rigid or flexible)	4 (19.0%)
Retrograde pouch lithotripsy (transstomal)	5 (23.8%)
Percutaneus cystolithotripsy (vesicostomy-entry)	2 (9.5%)
Operation time (minutes)	74.5±14.6 (40-130)
Postoperative serum creatinine level (mg/dL)	0.8±0.4 (0.7-1.9)
Complication (n,%)	-
Febrile urinary tract infection	4 (19.0%)
Urinary obstruction and secondary surgery	3 (14.2%)
Anastomotic urine leakage	1 (4.7%)
Stone composition (n,%)	-
Calcium-oxalate	9 (42.8%)
Struvite	10 (47.6%)
Calcium-phosphate	1 (4.7%)
Urine-acite	1 (4.7%)

DISCUSSION

The most common postoperative complication seen in patients with urinary diversion is urinary stone formation with a prevalence of 2.6% to 15.3% (12,13). The main cause of urinary system stone disease in these patients is the presence of increased chronic infection and metabolic changes, as well as the structural and mechanical differentiation in the urinary system (14). Stasis in the upper urinary system and the presence of hydronephrosis developing secondary to this, together with the change of the anatomical structure as a result of urinary diversion, are seen with a frequency of up to 80% in these patients (15). Mucus production originating from the intestinal mucosa and the foreign body reaction caused by it, stomal stenosis and urinary retention are also important factors that cause stone formation in the pouch (16). Metabolic changes are characterized by systemic acidosis, hypercalciuria, hyperoxaluria, and hypocitraturia (17). These factors increase the risk of calcium-containing stones (17). However, the most common factor causing stone formation in patients with urinary diversion is the presence of increased chronic infection (18). Therefore, struvite stones are the most common stone formation in patients with urinary diversion. In our study, similar to the literature, struvite stones were found to be the most common stone formation.

In patients with urinary diversion with asymptomatic small size urinary stone, ESWL is recommended as a non-invasive initial treatment option in order to reduce potential surgical difficulties and complication (19). Ahmed et al. (20) reported that they were performed ESWLin 27 patients with urinary diversion with stones smaller than 1 cm. According to this study, the success rate of upper urinary tract stones in urinary diversion patients with single session ESWL treatment was reported as 81.5% (22/27). However, in this study, it was also reported that the stone-free status could not completely reached in 2 (7.4%) patientsand 1 (3.7%) had a significant residual stone, 2 (7.4%) patients developed renal obstruction after ESWL and 5 (18.5%) patients had PNL, antegrade URS or a secondary procedure such as open operation is required. The fact that the stone fragments after ESWL enters into the intestinal folds in the pouch and do not drain spontaneously and cause the formation of large stones again by undergoing reformation is considered as an important factor limiting the effectiveness of this procedure, especially in stones larger than 1 cm (18-20).

Percutaneous nephrolithotomy is one of the most important options in the surgical treatment of large stones in the upper urinary system in patients with urinary diversion, and its success rate has been reported to be from 60% to 80% (21). In a study conducted by Lindsay et al. (22) involving 77 patients, the effectiveness of PNL, retrograde URS and ESWL in the treatment of upper urinary tract stones in patients with urinary diversion was compared. In this study, it was stated that the average stone size in the PNL group was significantly higher than the URS and ESWL groups (2.1 vs 0.9 and 1.0 cm,respectively, $p<0.0001$).In this study, although the mean stone size was significantly larger, the total stone-free rate was significantly better in PNL than the URS and ESWL groups (83.3% vs 33.3% and 30%, respectively, $p<0.0001$). Total complication rates were reported to be similar between the groups ($p=0.900$). In another similar study by Zhong et al. (23) including 20 patients with urinary diversion, 8 patients underwent PNL, 3 patients had antegrade URS, 6 patients had percutaneous pouch lithotripsy, 2 patients

had transurethral neo-bladder lithotripsy, 1 patient had open stone surgery. It was reported that 18 (90%) patients werestone-free at the end of the procedures. According to this study, an insignificant residual stone remained in 1 (5%) patient who underwent PNL and 1 (5%) patient who underwent percutaneous pouch surgery, and only 2 (15%) patients had postoperative fever and 1 (5%) patient had postoperative urinary extravasation. In our study, it was seen that the most common surgical procedure used in patients with urinary diversion was PNL, and similar to the literature, a high rate of stone-free was achieved. In our study, secondary intervention was required due to urinary obstruction in only 1 of the patients who underwent PNL. This result supports the idea that PNL should be the preferred surgical method for the surgical treatment of upper urinary tract stones in patients with urinary diversion due to its high success rate. The most common problem encountered when performing PNL in patients with urinary diversion is that the retrograde catheterization cannot be performed most of the time due to the difficulty in visualizing the ureter orifices through the pouch (17). Ultrasonographic approach can be used in these patients for achieving proper access to the collecting system (24). At this stage, proper preoperative preparation and equipment competence, as well as surgical team experience come to the fore. In our study, there was no access problem in any urinary diversion patient who underwent PNL, and therefore, there was no need to switch to another surgical method.

The most important problem with retrograde URS in patients with urinary diversion is the difficulty in identifying the ureteral orifices within the reservoir (3,4,19,20,23). Singla N et al. (25) reported the results of retrograde URS intervention performed in 45 neobladder patients due to several upper urinary tract anomalies. According to this study, it was reported that retrograde URS intervention was successful in 2 of 4 urinary system stone patients. In the study of Delveccio et al. (11) it was reported that retrograde URS can be performed more easily under the guidance of the guidewire advanced into the neo-bladder from antegrade route, but the procedure is very time consuming. Therefore, antegrade URS is recommended for upper ureteral stones or renal calix stones that cannot be reached with PNL in urinary diversion patients, and the procedure can be successfully performed with a semi-rigid or flexible ureterorenoscope (26). In our study, retrograde URS intervention was largely unsuccessful because the ureteral orifices could not be clearly visualized so the procedure changed to antegrade URS or PNL in these patients. This result indicates that the antegrade URS or PNL should be the more preferred choice rather than retrograde URS in patients with urinary diversion with upper urinary tract stones due to the loss of time and effort.

In several studies, it has been reported that stones in the diversion pouch can be successfully treated with transurethral lithotripsy, percutaneous pouch lithotripsy or stomal entry pouch lithotripsy in patients with both orthotopic urinary diversion and cutaneous urinary diversion (7,11,15). The surgical method to be chosen depends on the type of diversion and the size of the stone. In our study, stomal entry pouch lithotripsy was applied to all patients with stones in the reservoir pouch and complete stone-free was achieved in all patients without complications, similar to the literature.

Various studies have reported that the risk of bladder stone formation is increased in neurogenic bladder disorder that develops in patients with spinal cord injury (27). Ordet al. (28) reported that the risk of bladder stone formation was significantly increased in patients with spinal cord injury, both in patients who underwent intermittent urethral catheterization, and in patients with vesicostomy and cystostomy. In our study, bladder stones were detected in 2 patients who had vesicostomy due to neurogenic bladder secondary to spina bifida, and complete stone-free was achieved with vesicostomy-entry cystolithotripsy.

Limitations

The most important limitation of our study is its retrospective nature. In addition, the fact that urinary system stone surgery is one of the rare cases in patients with urinary diversion and therefore the low number of patients in the study can be considered as another limitation. The fact that no comparison was made due to the absence of a control group in our study can be considered as another limitation.

CONCLUSION

Surgical treatment of urinary tract stones in patients with urinary diversion and vesicostomy varies according to the type of diversion, stone location and stone size. In upper urinary tract stones, antegrade URS and PNL should be the primary choice due to their short operation time and effort advantage. Retrograde URS should be preferred in patients where ureter orifices can be clearly visualized through the diversion pouch. Stones in diversion pouch can be easily treated with both stomal entry and percutaneous stomal entry, and high stone-free rate can be achieved. Surgical treatment of bladder stones in patients with vesicostomy can be successfully performed with vesicostomy entry. The most important factors in the success of urinary tract stone surgery in patients with urinary diversion and vesicostomy are the correct management of the preoperative surgical preparation process and instrumentation preparation in which all interventions can be performed, as well as surgical team experience.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Keçiören Training and Research Hospital Health Application Research Center Medical Specialty Education Board (Date: 08.12.2020 IRB: 2012-KAEK-15/2202).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. Simon J. Extrophia vesicae (absence of the anterior walls of the bladder and pubic abdominal parietes); operation for directing the orifices of the ureters into the rectum; temporary success; subsequent death; autopsy. Lancet 1852; 2: 568.
2. Urh A, Soliman PT, Schmeler KM, et al. Postoperative outcomes after continent versus incontinent urinary diversion at the time of pelvic exenteration for gynecologic malignancies. Gynecol Oncol 2013; 129: 580-5.
3. Turk TM, Koleski FC, Albala DM. Incidence of urolithiasis in cystectomy patients after intestinal conduit or continent urinary diversion. World J Urol 1999; 17: 305–7.
4. Ginsberg D, Huffman JL, Lieskovsky G, Boyd S, Skinner DG. Urinary tract stones: a complication of the Kock pouch continent urinary diversion. J Urol 1991; 145: 956–9.
5. Arai Y, Kawakita M, Terachi T, et al. Long-term follow up of the Kock and Indiana pouch procedures. J Urol 1993; 150: 51–5.
6. Ku JH, Jung TY, Lee JK, Park WH, Shim HB. Risk factors for urinary stone formation in men with spinal cord injury: a 17-year follow-up study. BJU Int 2006; 97: 790-3.
7. Okhunov Z, Duty B, Smith AD, Okeke Z. Management of urolithiasis in patients after urinary diversions. BJU Int 2011; 108: 330–6.
8. Fernandez A, Foell K, Nott L, Fernandez A. Percutaneous nephrolithotripsy in patients with urinary diversions: A case-control comparison of perioperative outcomes. J Endourol 2011; 25: 1615–8.
9. Franzoni DF, Decter RM. Percutaneous vesicolithotomy: an alternative to open bladder surgery in patients with an impassable or surgically ablated urethra. J Urol 1999; 162: 777–8.
10. Cohen TD, Streem SB, Lammert G. Long-term incidence and risks for recurrent stones following contemporary management of upper tract calculi in patients with a urinary diversion. J Urol1996; 155: 62–5.
11. Delvecchio FC, Kou RL, Iselin CE, et al: Combined antegrade and retrograde endoscopic approach for management of urinary diversion-associated pathology. J Endourol 2000; 14: 251–6.
12. Terai A, Arai Y, Kawakita M et al. Effect of urinary intestinal diversion on urinary risk factors for urolithiasis. J Urol 1995; 153: 37.
13. Shimko MS, Tollefson MK, Umbreit EC, et al. Long-term complications of conduit urinary diversion. J Urol 2011; 185: 562.
14. Beiko DT and Razvi H: Stones in urinary diversions: update on medical and surgical issues. Curr Opin Urol 2002; 12: 297.
15. el-Nahas AR, Eraky I, el-Assmy AM, et al. Percutaneous treatment of large upper tract stones after urinary diversion. Urology 2006; 68: 500-4.
16. Haselhuhn GD, Kropp KA, Keck RW, Selman SH. Photochemical ablation of intestinal mucosa for bladder augmentation. J Urol. 1994; 152: 2267-71.
17. Cohen TD, Streem SB, and Lammert GK: Selective minimally invasive management of calculi in patients with urinary diversions. J Urol 1994; 152: 1091–4.
18. Razvi HA, Martin TV, Sosa ER, et al. Endourologic management of complications of urinary intestinal diversion. AUA Update Series 11(lesson 22): 174 –9, 1996.
19. Cass AS, Lee JY, Aliabadi.Extracorporeal shock wave lithotripsy and endoscopic management of renal calculi with urinary diversions. J Urol 1992; 148: 1123–5.
20. El-Assmy A, El-Nahas AR, Mohsen T, et al. Extracorporeal shock wave lithotripsy of upper urinary tract calculi in patients with cystectomy and urinary diversion. Urology 2005; 66: 510-3.
21. Madbouly K. Large orthotopic reservoir stone burden: Role of open surgery. Urol Ann 2010; 2: 96–9.
22. Hertzig LL, Iwaszko MR, Rangel LJ, Patterson DE, Gettman MT, Krambeck AE. Urolithiasis after ileal conduit urinary diversion: a comparison of minimally invasive therapies. J Urol 2013; 189: 2152-7. .
23. Zhong W, Yang B, He F, Wang L, Swami S, Zeng G. Surgical management of urolithiasis in patients after urinary diversion. PLoS One 2014; 31: 9.
24. Desai M. Ultrasonography-guided punctures-with and without puncture guide. J Endourol 2009; 23: 1641–3.
25. Singla N, Montie JE, Lee CT, Wolf JS Jr, Faerber GJ. Experience with 45 Consecutive Patients with Neobladders Undergoing Retrograde Ureteroscopy for Upper Tract Abnormalities. Urol Pract 2015; 2: 244-9.
26. Li X, He Z, Wu K, Li SK, Zeng G. Chinese minimally invasive percutaneous nephrolithotomy: the Guangzhou experience. J Endourol 2009; 23: 1693–7.
27. Yamamoto M, Kashiwai H, Hirayama A, et al. [Long-term follow-up of female tetraplegic patients with cutaneous vesicostomy]. Hinyokika Kiyo1997; 43: 263-6.
28. Ord J, Lunn D, Reynard J. Bladder management and risk of bladder stone formation in spinal cord injured patients. J Urol 2003; 170: 1734-7.

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The cultural attitudes of nurses and the analysis of the interactive relation between the nurse and the patient

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ABSTRACT

Aim: This study was aim to determine the effects of nurses' cultural approach on the patient care, to reveal the relation between the nurse and the patient, and to determine the factors that affect this relation.

Material and Method: A cross-sectional descriptive study was conducted in a hospital. 300 nurses participated in the study. Multicultural Attitude Scale and Care Oriented Nurse-Patient Interaction Scale were used to obtain data that was collected between March 2016 and June 2016. Descriptive statistics and independence t-test corelation were used to analyse the data.

Result: The attitudes and behaviors of the nurses concerning care oriented nurse-patient interaction are positive (significance is 297.4±56.9, sufficiency is 284.8±60.7, and practicality is 281.3±70.7); however, it was found that the cultural attitudes of the nurses were not positive. The relation between total sufficiency and practicality points of curing oriented nurse-patient interaction scale and multiculturalism attitude scale were evaluated as positive and medium level (r:0.248, $p<0.05$, r:0.302, $p<0.05$)

Conclusions: This study creates a resource for an education plan on developing cultural awareness among nurses. To increase the quality of patient and individual patient care, the cultural attitudes of nurses should be improved.

Keywords: Nursing, culture, attitudes, care, health

INTRODUCTION

The removal of borders, increase in migration rate, traveling becoming easy and common, and increase in dialogues among people from different backgrounds led to coexistence with people from different cultures. Thus, the societies turned into multicultural structures. This result increased the importance of transcultural nursing. Transcultural nursing is a field of study that deals with the differences and similarities of people's cultures, gathers information by focusing on the cultural beliefs and standart of judgements, and uses these knowledge in determining convenient ways for providing nursing care (1-4). Social and cultural differences and intolerance against cultural differences cause an increase in the cost of the care, poor people not benefiting from the health care, gender apartheid, inequalities, cultural conflicts, and racism. Moreover, when the healthcare personnel are not familiar with the culture of the individuals that they give care service, when there is a cultural differences between the nurse and the patient, or when the nurse uses complex technology, it causes fear, resistance, impatience, and disappointment towards the nurse. For this reason, patients' and nurse's self confidence can only be increased and high-quality nursing care can only be provided by transcultural nursing (2,5-7).

Giving culturally susceptible nursing service is vocationally multidimensional. Knowing and understanding the culture of the patient and having cultural awareness are very important when giving care by the nurse (8,9). Cultural awareness is exploring one's own cultural background and making self-assessment. Previous studies were conducted on the approach of the individuals from different cultures and these studies put forth the cultural structures of patients (4,7,9-11). However, there are no studies on how the cultural attitudes affect the relation between the patient and the nurse or on the factors that affect this relation.

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Background

People have the ability of developing solutions by using cultural means when they comply with their environment. The understanding of the cultural dimension is achieved by the field of "anthropology". Anthropology describes human and culture from the point of a holistic (integrative) view. For this reason, the cultural basis of human behaviors has great importance for the nursing practices. All the aspects of culture are effective in nursing practices. One of the most important functions of nursing is care. Human caring is seen as the origin and essence of nursing (2,3). Giving care is the center of nursing knowledge and practices and involves helping, supportive, and facilitator roles for the individual or the group to meet present or expected needs. Caring of nurse is an interactive and interpersonal process occurring in moments of caring between nurse and patient (12). Leininger stated that care is basic for the health of the individual and is the most important dimension that distinguishes nursing from other disciplines. Consequently, there can be no cure without care, while there is caring without cure (12). Comparative studies show that professional nursing care gathers in itself the scientific and humanistic helping types for the continuation of the conditions needed to continue living at the desired level. Therefore, to be able to give good care, a professional nurse should know the importance and meaning of physical, psychological, cultural, and social values of the individual or a group (2,13,14).

Aim of the Study

This syudy aimed to determine the relation between the nurse and the patient and the cultural attitudes of the nurses, to provide awareness about the subject, to make the care based upon culture irreplaceable, and to create a resource for the future studies that will focus on the subject matter. However, to the best of our knowledge, there is no studies dealing with the effects of nurses' own cultures on the patient care. This study proves that why transcultural nursing is irreplaceable. When the literature is reviewed, it is seen that there are studies focusing on preparing, practicing, and evaluating the patient care plans according to the cultures of patients. Green and Davis (14) showed a positive correlation between patient perceptions of nurse caring behaviours and patient satisfaction. Wolf, Miller and Hajynezhad and their colleagues (12,13) also showed a significant correlation between patient reports of nurse caring and their satisfaction with nurse curing. Knowledge, attitude and skills of nurses are the three most important factors in evaluating the quality of nursing care behaviors. In this context, the following hypotheses were tested:

Hypothesis 1. As the attitudes of the nurses that are based upon culture are increased, the interaction between the nurse and the patient will be at higher quality.

Hypothesis 2. The cultural attitudes of the nurses are affected by their socio- demographic characteristics.

Hypothesis 3. Care oriented nurse- patient interaction is affected by nurses' socio- demographic characteristics.

MATERIAL AND METHOD

Design

This study is a cross-sectional descriptive research.

The Period of the Study

This study was carried out between March and June 2016 and was designed as a cross-sectional descriptive research. The population and sample of the study involves 1137 nurses working at hospitals and primary care clinics in a city in the southeastern Anatolia region, Turkey. The research sample size is calculated with α=0.05 significance level and with d=0.05 sampling error at p=0.5, q=0.5 column as minimum 278 people (16). To represent the population, the minimum sample size is increased to 300. The nurses in the sampling group were selected by using stratified sampling method.

Study Setting

First of all, the aim of the study was explained to the nurses and the points to consider during filling in the survey were indicated. This session lasted for 15-20 minutes. The survey was filled in by the nurses who accepted to participate in the study and who were working during working hours (from 08 am to 4 pm) under researcher's supervision.

Data Collection Tools

Individual Data Collection Form was used for the socio-demographic characteristics of the nurses, Multicultural Attitude Scale was used to determine the cultural approach of the nurses, and Care-Oriented Nurse-Patient Interactive Relation Scale was used to determine the interactive relation of the patient-nurse.

Individual Data Collection Form

The Individual Data Collection Form was prepared by the researchers, that composed of 8 questions about socio-demographic characteristics and 7 questions about the nursing profession.

Multicultural Attitude Scale (MAS)

Multiculturalism attitude scale was first developed by Munreo and Perseon (2006) and improved based upon the components made up of multicultural approach of Banks (2007). The attitude scale has 5 dimensions. It is composed of 5 dimensions as flexibility, social

enterprise, empathy, emotional stability, and explicitness. Likert type collection tool was scaled between "(1) strongly disagree to (5) my thoughts exactly". At the end of the study, the Alpha Reliability Coefficient of the confidence test was found as 0.65. As the points increase, it was inferred as the attitudes based upon cultures of nurses were increased.

Care-Oriented Nurse-Patient Interactive Relation Scale (CONPIRS)

This scale was developed by Cossette, Caraa, Ricarda, and Pepin (2005) to evaluate the attitudes and behaviorsof the nurses related to care which is based upon Watson's Care Hypothesis. The scale was adapted to Turkish by Atar and Aştı (2012). The scale is composed of 3 dimensions (significance, sufficiency, and practicality), 10 subscales (humanism, hope, susceptibility, contributing to the relation, expressing the emotions, problem solving, education, environment, requirement, and spirituality) and 70 articles. Atar and Aştı (2012) found the Cronbach Alpha Reliability Coefficient is A=0.99 for significance dimension, α=0.98 for sufficiency dimension, and α=0.99 for practicality dimension. The minimum point was find 70 and maksimum point was find 350 from Likert type CONPIRS that is composed of 70 articles. The statements in the Likert type with five articles are scaled from Strongly Disagree (1), Disagree (2), Neutral (3), Agree (4), and Strongly Agree (5). It is evaluated that as the score taken from CONPIRS increases, the attitudes and behaviors of the nurses about care oriented nurse-patient interaction are affected positively. Cronbach's Alpha Reliability Coefficient of the scale in this study was found for significance, sufficiency, and practicality dimensions respectively 0.94, 0.96, 0.98.

RESULT

Sixty percent of the nurses are older than 25, the youngest is 19 years old while the oldest is 54 years old. The 73.0% of the nurses are women. The 44.3% of them are single and 37.5 of them are from Şanlıurfa. The 55.7% of them are Turkish origin and 36.0% are Kurdish. 74.3% of the nurses' native language is Turkish. 56.5% of the nurses have been working as a nurse from one to five years. 64.2% of them indicated that they have chosen this profession willingly. 93.0% of them told that they have knowledge about cultural differences.

According to **Table 1**, when the total average points of care oriented nurse- patient interaction scale is evaluated, the average of total points for significance, sufficiency, practicality are 297.4±56.9, 284.8±60.7, 281.3±70.7 respectively. The data show that the attitudes and behaviors related to care-oriented nurse-patient interaction are positive.

According to the results of humanism, subdimension of care oriented nurse-patient interaction scale, average point of significance is determined as 25.7±4.3; average point of sufficiency is 24.5±4.5; and average point of practicality is 23.3±5.0. Therefore, it is determined that the manners and behaviors of the nurses relating to humanism are positive.

For hope subdimension, the average point of significance is determined as 30.0±5.5, the average point of sufficiency is determined as 28.6±6.0, and the average point of practicality is determined as 28.6±5.3. According to the average points of subdimension hope, it is determined that the manners and behaviors of the nurses relating to hope are positive.

For susceptibility subdimension, the average point of significance is determined as 24.9±4.6, the average point of sufficiency is determined as 19.3±4.6, and the average point of practicality is determined as 24.0±5.7. According to average points of subdimension susceptibility, it is determined that the attitudes and behaviors of the nurses relating to susceptibility are positive for significance and practicality but not for sufficiency.

Table 1. The average points that the nurses take from total points and points taken from subdimensions of care oriented nurse-patient ınteraction scale

Scale and the sub dimensions	Momentousness		Sufficiency		Workableness	
Subdimensions	Min-Max	X±SS	Min-Max	X±SS	Min-Max	X±SS
1:Humanism	6-30	25.7±4.3	6-30	24.5±4.5	6-30	23.3±5.0
2: Hope	7-35	30.0±5.5	7-35	28.6±6.0	7-35	28.6±5.3
3: Susceptibility	6-30	24.9±4.6	6-30	19.3±4.6	6-30	24.0±5.7
4: Contributing relation	7-35	30.0±5.1	7-35	28.3±5.4	7-35	29.0±6.6
5: Expressing the emotions	6-30	25.4±6.2	6-30	23.5±6.5	6-30	24.3±5.2
6: Problem solving	6-30	24.8±4.8	6-30	23.4±6.0	6-30	23.7±6.5
7: Education	9-45	38.2±7.0	9-45	37.1±8.3	9-45	35.3±7.2
8: Environment	7-35	29.6±5.1	7-35	28.8±5.5	7-35	28.3±7.3
9: Requirement	10-50	43.4±7.9	10-50	41.6±8.6	10-50	41.1±8.9
10: Spirituality	6-30	25.4±6.4	6-30	24.3±5.3	6-30	23.7±6.5
TOTAL	70-350	297.4±56.9	70-350	284.8±60.7	70-350	281.3±70.7

According to **Table 2**, it isdetermined that the nurses have taken 21.6±3.5 points from the social enterprise that is the subdimension of multicultural attitude scale and this means that the attitudes of the nurses according to social enterprise are good. It is also determined that the nurses have taken 24.0±6.6 points from emphaty that is the subdimension of multicultural attitude scale and this means that the attitudes of the nurses according to social enterprise are low. The average points for the subdimension of emotional stability of the nurses are 25.6±5.6 and this average point is low. The average points for the subdimension of explicitness of the nurses are 19.0±3.6 and the average points for the subdimension of flexibility of the nurses is 13.5±2.1. According to these average points, it is determined that the attitudes of the nurses for both explicitness and flexibility are good. When the total points of multicultural attitude scale are evaluated, the nurses have taken 82.3±7.5 points and this average point shows us that the attitudes of the nurses are low.

Tablo 2. The average points that the nurses take from total points and points taken from subdimensions of multicultural attitude scale

Multicultural attitude scale	The number of the title	Max-Min	X±SS
Subdimensions	1: Social enterprise	8-30	21.6±3.5
	2: Empathy	14-60	24.0±6.6
	3: Emotional stability	7-68	25.6±5.6
	4: Explicitness	5-25	19.0±3.6
	5: Flexibility	7-19	13.5±2.1
	Total	63-126	82.3±7.8

The correlation between the average points of care oriented nurse-patient interaction scale and multicultural attitude scale are given in **Table 3**. There are no significant relations between the sufficiency points of care oriented nurse-patient interaction scale and total points of multiculturalism attitude scale (r: 0.100; p›0.05). However, there are is a positive relation between the sufficiency and practicality points of care oriented nurse-patient interaction scale and total points of multicultural attitude scale (r: 0.248, p<0.05; r: 0.302, p<0.05).

The socio-demographic characteristics of the nurses are themale nurses have taken 295.1±49.2 for average points of momentousness from CONPIRS and 278.0±45.0 for sufficiency and 287.9±44.5 for workableness. These values are respectly 298.8±40.4, 280.0±43.7 and 286.8±47.4 for female nurses. When the statistical differences are evaluated, there aren't meaningfull difference between the three values of the two sexualities (p>0.05). When the relation between the culture and sexualities is evaluated the male nurses have taken lower points from female nurses and as a result it's determined that the manners of male nurses related to culture is negative(p>0.05). When the relation between the age and the scale are evaluated, the nurses aged 25 and lower are taken more points for sufficiency and workableness except momentousness at CONPIRS and as a result the manners of this aged nurses are determined as positive. But the statistical difference for all is not meaningful(p>0.05). At the study the question; "nurses should have cultural knowledge" is answered as yes or no by the nurses. It's determined that the average points of all the answers by nurses for this question are the same (p>0.05).

DISCUSSION

The health necessities of individuals are different according to cultural structures (1). The worthy of notice during the patient care with cultural approach is to find an answer to the question: "Is this group culturally different from my cultural group and how much is the dimension of this difference?" In this study, which explores the relation between the nurse and the patient, it isevaluated that there is a mean relation between the sufficiency and practicality total points of CONPIRS and MAS (**Table 3**, p<0.05). As the attitudes of the nurses based upon their culture increase, the attitudes and behaviours during patient/ individual care are also affected positively (Hypothesis 1).

As the cultural awareness level of the personnel increases, the sufficiency during patient care also increases. In one study, the patients evaluated the behaviours of the nurses e.g. saying "how are you today?", sharing time with them, being there for them, communicating with them,being willing to help them, caring about them and the patients indicated that they feel happy for that (2).

Tablo 3. The correlation between care oriented nurse-patient ınteraction scale and multicultural attitude scale

Care orianted nurse patient scale total points	Multiculturalism attitude scale total points		Social enterprise		Empathy		Emotional stability		Explicitness		Flexibility	
	r	p	r	p	r	p	r	p	r	p	r	p
Momentousness	0.100	0.86	0.320	0.00	–0.150	0.009	0.777	0.000	0.664	0.00	0.584	0.00
Sufficiency	0.248	0.00	0.348	0.00	-0.354	0.00	0.312	0.00	0.306	0.00	0.233	0.00
Workableness	0.302	0.00	0.348	0.00	0.327	0.00	0.330	0.00	0.312	0.00	0.291	0.00

In a more recent study, it is indicated that the hardest requirements to meet between the nurse and the patient are the necessities based upon cultural differences (11). In another study, nurses indicated that they have problems because of language differences (76%), dialect differences (4.6%), and privacy issues (40.4%) (17).

In studies that were conducted by collating the care service given by the nurses and the requirements for the patients, it is reported that the patients want nurses to talk to them, to let them talk and tell their feelings, to listen to them, to try to understand them, to worry about them, to inform them, to be reachable, and to be facilitative. The patients indicate that these expectations are not met. In addition, supporting these studies, in our study, the average points of empathy and emotional stability that are the subdimensions of multiculturalattitude scale are low (**Table 2**).

It may be expected that growing cultural differences between the nurse and the patient affect the care provided and the nurses cannot fulfill the requirements. The patients can easily communicate with the nurses who understand the culture of the patient, who can communicate with the patient with simple words, and who knows both his/her own culture and the patients' culture and do not deny them. However, it is disappointing to see that there is an average relation between the understanding the culture and the care nurses give in this study. That is why it isimportant to increase the number of trainings about servicing based upon cultural awareness to improve the quality of the care provided (Hypothesis 1).

Although 93.0% of the nurses told that they know about cultural awareness from books and school, it is found out that their cultural attitudes are low (**Table 2**). In the study by Aktaş et al. when the knowledge levels of the nurses about transcultural nursing are evaluated, it is seen that 26.9% of them do not have any knowledge at all about the subject. The nurses described transcultural as "gathering of different cultures" and transcultural nursing as "servicing patients from different cultures"(11). On the contrary to the findings of our study, Leung and Bond determined that 65% of the students of nursing know the term of transcultural nursing (18). The findings may show that nurses are not culturally sensitive enough. Culturally insensitive nurses may perform wrong applications or may disservice the patient. Not giving beneficial care to the patients from different cultures and giving wrong messages e.g. some cultures are less important than others show the healthcare personnel's insufficiency about cultural awareness. These findings show us that the transcultural nursing is not emphasized enough in education programs in our country. When the average points of care and culture scale are evaluated, the nurses who have cultural knowledge and who do not took nearly the same points (**Table 4**, $p>0.05$). This result makes us think that the nurses do not have sufficient cultural knowledge.

The attitudes and behaviors related to care-oriented nurse-patient interaction are determined as positive (**Table 1**). In a study, nursing is defined as "an interpersonal interaction process". Nursing may be defined as a science and art of giving care and care may be defined as an interpersonal process (19). Individuals from different cultural characteristics affected from beliefs and traditions when perceiving health and illness. The cultural values, beliefs, and approaches affect how the patients benefit from the nurse care (20). As indicated in the literature, health care professionals should use their problem-solving skills to help the individuals, increase the quality of the care, and to satisfy the patients. To give sufficient health care to individuals, to family, and to the society, nurses should have knowledge about underlying cultural characteristics about health and illness. When the nurses interract with the individuals, they should make the evaluation culturally sensitive. This evaluation may be indept and may provide a basis for future evaluations. People who are looking at communication from a cultural point of view may distinguish differences between cultures, try to give correct messages, and try to make contribution for efficient communication between members of different cultures (20-22).

It is evaluated that 73.0% of the nurses participating in the study are women. Nursing is not only a woman occupation anymore both in our country and in the world and there are increasing tendencies and ambitions supporting this aim. Thus, the number of male nurses is increasing day by day. The number of male students of nursing increased as the number of male students were only 27 in 2006-2007 academic year while it reached to 14.929 in 2015 (23,24).

According to gender of the nurses, the total points of multiculturalism attitude scale of male nurses are lower than of female nurses ($p>0.05$, Hypothesis 2). In the study of Çelik et al. (2012) (25), the patients who have not been given care by male nurses before think that nursing is a woman occupation and that males should not be nurses. In addition, they do not want to be given service by a male nurse and think that both she and her relatives would be annoyed because of it. Besides, the patient thinks that she would have difficulty to tell her problem and that male nurses should give service to male patients. Similarly, the patients who have not been given care by male nurses stated that they are indecisive about male nurses' providing good care or not, about changing the negative thoughts about nursing, about male nurses' being as polite and tolerant as female nurses or not (27). When the care oriented nurse-patient interaction scale is evaluated, it is seen that the male nurses have lower

average points than female nurses do on significance and sufficiency and that male nurses have higher points on practicality (p>0.05, Hypothesis 3).In the study by Ünver et al (26), the female students of nursing department thought that the female patients would be shy while the male students of nursing department thought that they would not be shy before the clinical practice. After the clinical practice, all the female students reported that the female patients were not shy during the applications while the male students stated that the female patients were acting shy during the applications (28). In opposite, in the study by Potur and Bilgin (2014) (27), the male students of nursing department stated that when the patients discriminate,it makes them stressful and that when the patient is female and makes sexual discrimination, they feel stressed. Although the male nursing students thought that they may be discriminated, there were not too much adverse events during clinical practices. After clinical practices, the male nursing students determined to work at clinics of obstetrics and gynecology.

Among the nurses who participated in the study, 60.0% of the nurses are older than 25, the youngest of the nurses is 19 years old and the oldest is 54 years old. In CONPIRS, it is determined that, according to sufficiency and practicality, the age is a positive variable for the nurses aged under 25 (p>0.05). The same is seen in MAS. The cultural aproach of the nurses under 25 is positive (p>0.05). These results indicate that the nurses of under age 25 believe that the care-oriented nursing and patient interaction is important and they find themselves sufficient and practical. In the study by Kostak et al. (2010), most of the nurses stated that they do not provide moral care (28). Similar to the findings of our study, in the study by Aktaş et al., as the average age and the number of years of experience of the nurses increase, the thought of "giving health care apppropriate to culture" decreases (11). In the study by Eğlence and Şimşek, there are no statistically significant differences among the age of the nurses, their education level, and the number of years of experience (29). In another study, the statistical difference among the average of ages of nurses, their marital status, field experience, and the average of moral points are not significant (30). The main reasons for not fullfilling the care requirement may be the lack of time, the working environment, lack of personnel, lack of knowledge, or lack of opportunities. The reasons for the differences among the studies might stem from the differences in the qualities of the hospitals and the characteristics of the nurses.

Restrictions: The questionnaire form used in this study was too long that damages the credibility of the answers. Conducting observations with an in-dept analysis will increase the validity of the results.

CONCLUSION

The most important result obtained from this study is the interaction between the nurse and the patient: even though their attitudes and behaviors are positive, their cultural approaches are not sufficient enough. Another significant result of the study is about the effect of cultural approaches of the nurses to patient's care. The effect of the cultural approach of nurses to patient's care is positive or average that is unsettling. Therefore, precautions should be taken to prevent it both during the education of nurses and during in-service trainings. To increase the quality of the patient/individual care, the cultural attitude of the nurses should be improved. This article forms a basis to improve cultural awareness and to revise education plans based upon improving cultural awareness.

What is already known about this topic?

•Giving culturally-susceptible nursing service is vocationally multidimensional.

•Knowing and understanding the culture of the patient and having cultural awareness are very important when giving care by the nurse

•Previous studies were conducted on the approach of the individuals from different cultures and these studies put forth the cultural structures of patients.

•When the literature is reviewed, it is seen that there are studies focusing on preparing, practicing, and evaluating the patient care plans according to the cultures of patients.

What this paper adds?

•This Study explained how the cultural attitudes affect the relation between the patient and the nurse or on the factors that affect this relation.

•This study proves why transcultural nursing is irreplaceable.

•With this study, it isaimed to determine the relation between the nurse and the patient and the cultural attitudes of the nurses, to provide awareness about the subject, to make the care based upon culture irreplaceable, and to create a resource for the future studies that will focus on the subject matter.

The implications of this paper:

•To increase the quality of patient/ individual care, the cultural attitudes of nurses should be improved.

•This study creates a resource for an education plan on developing cultural awareness among nurses.

The Evaluation of the Data

Statistical Package Social Sciences (SPSS) 16.0 program was used to evaluate the data. For the evaluation, numerical percentage distribution, average, and standart deviation data were used in the computer program. The data analysis for the three dimensions of socio-demographic characteristics scale was calculated by the

independence t-test and corelation. Moreoever, normal distributional corelation between total point averages of all the subscales of them is evaluated by Shapiro- Wilk test.

ETHICAL DECLARATIONS

Ethics Committee Approval: For applicability of the study, a writen permission was obtained (25/02/2016, Session 01 and no. 74059997.050.04/23) from Unıversity Medical Faculty Ethics Committee

Informed Consent: The study was the consent of the nurses who accepted to participate in the study was taken.

Referee Evaluation Process: Externally peer-reviewed. Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support. Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Prosen M. Introducing transcultural nursing education: Implementation of transcultural nursing in the postgraduate nursing curriculum. Procedia Soc Behav Sci 2015; 174: 149-55.
2. Stevenson N. Developing cultural understanding through storytelling. JTTT 2019; 19: 8-21.
3. Leininger M. Cultural care theory: A major contribution to advance transcultural nursing knowledge and practices. J Transcult Nurs 2002; 13: 189-92.
4. Bekar M. Kültürlerarası (transkültürel) hemsirelik. Toplum ve Hekim Derg 2001; 16, 136-41.
5. Temel A. Çok kültürlülük ve kültürlerarası iletişimin sağlık hizmetlerinin sunumuna etkileri. (Edit), Esen E, Yazıcı Z. Onlar bizim hem şehrimiz uluslararası göç ve hizmetlerin kültürlerarası açılımı. Erek Ofset Matbaacılık, 2011; Ankara, 48.
6. Özcan A. İletişim Uluslararası Kültür. (Edit). Seviğ E, Tanrıverdi G. Intercultural Nursing. Kayhan Yayıncılık. 1. Basın 2014; İstanbul, 86.
7. Jones ME, Cason CL, Bond ML. Cultural attitudes, knowledge, and skills of a health workforce. J Transcult Nurs 2004; 15: 283-90.
8. Atkins M, Stone KS. Undergraduate and graduate students partnering in a short-term transcultural experience in Honduras. ABNF Journal 2006; 17: 147-51.
9. Başalaniz F, Bayık T. Hemşirelikte Kültürel Yeterlik. Aile ve Toplum 2009; 11: 17.
10. Tanrıverdi G, Seviğ Ü, Bayat M, Birkök MC. Hemşirelik bakımında kültürel özellikleri tanılama rehberi. J Hum Sci 2009; 6: 793-806.
11. Aktaş YY, Uğur HG, Orak SO. Hemşirelerin kültürlerarasi hemşirelik bakimina ilişkin görüşlerinin incelenmesi. UHD 2016; 8: 120-35.
12. Hajinezhad ME, Azodi P. Nurse caring behaviors from patients' and nurses' perspective: European Online. J Nat Soc Sci 2014; 3: 1010-7.
13. Ünsal A. Türk kültüründe geleneksel hasta bakımı: Anadolu örneği. Y.Y.Ü. Sosyal Bilimler Enstitüsü Derg Special Edition 2017; 2: 1-12.
14. Green A, Davis S. Toward a predictive model of patient satisfaction with nurse practitioner care. J Am Acad Nurse Pract 2005; 17: 139-48.
15. Wolf ZR, Miller PA, Devine M. Relationship between nurse caring and patient satisfaction in patients undergoing invasive cardiac procedures. Med Surg Nurs 2003; 12: 391-6.
16. Yazıcıoğlu Y, Erdoğan S. SPSS uygulamalı bilimsel araştırma yöntemleri. Detay Yayıncılık, 2004; Ankara, 50.
17. Ayaz S, Bılgılı N, Akın B. The transcultural nursing concept: a study of nursing students in Turkey. Int Nurs Rev 2010; 57: 449-53.
18. Leung K, Bond MH. Social axioms: A model for social beliefs in multi-cultural perspective. Adv Exp Soc Psychol 2004; 36: 119–97.
19. Kumcağız H, Yılmaz M, Balcı ÇS, Aydın Aİ. Hemşirelerin iletişim becerileri: Samsun ili örneği. Dicle Tıp Derg 2011; 38: 49-56.
20. Yalçın N, Aştı T. Hemşire-hasta etkileşimi. İstanbul Üniversitesi FNJN 2011; 19: 54-9.
21. Kelleci M, Gölbaşı Z, Doğan S, Tuğut N. Entegre eğitim programında öğrenim gören hemşirelik öğrencilerinin problem çözme becerileri: Bir izlem çalışması. İstanbul Üniversitesi FNJN 2011; 19: 23-8.
22. Halk Sağlığı Kurumu. Sağlık araştırmaları ve sağlık hizmet sunumunda kültürel yaklaşım 2016; Ankara.
23. Şahin NH, Bayram GO, Avcı D. Kültürlere duyarlı yaklaşım: transkültürel hemşirelik. HEAD 2009; 6: 2-7.
24. Dinç L. Bakım kavramı ve ahlaki boyutu. HÜSBFD 2010; 74–82.
25. Çelik AS, Pasinlioğlu T, Çilek M, Çelebi A. Kadın doğum servislerinde yatan hastaların erkek hemşireler hakkındaki düşüncelerinin belirlemesi. Ana Hemş Sağ Bil Derg 2012; 5: 254-61.
26. Ünver S, Avcıbaşı İM, Özkan ZK, Motör D. Hemşirelik bölümünde okuyan erkek öğrencilerin sosyal çevrelerinde yaşadıkları sorunlar. ITOBIAD 2016; 5: 1636-48.
27. Potur DC, Bilgin NÇ. Assessment of clinical stress in male and female nursing students, as measured on the first and last day of the obstetrical nursing clinic course. KASHED 2014; 1: 93-106.
28. Kostak MA, Çelikkalp Ü, Demir M. Hemşire ve ebelerin maneviyat ve manevi bakıma ilişkin düşünceleri. MÜ Hem. Bilim ve Sanatı Derg Sempozyum Özel Sayısı 2010; 218-25.
29. Eğlence R, Şimşek N. Hemşirelerin maneviyat ve manevi bakım hakkındaki bilgilerinin değerlendirilmesi. ACU Sağlık Bil Derg 2014; 5: 48-53.
30. Özbaşaran F, Ergül Ş, Bayık TA, Gürol AG, Çoban A. Turkish nurses' perceptions of spirituality and spiritual care. J Clin Nurs 2011; 20: 3102–10.

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The view of #schizophrenia on Twitter (a splitting of the mind in 280 characters)

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ABSTRACT

Aim: Posts about an important public health problem, schizophrenia, are increasing on Twitter, whose user number is multiplying every day. This disorder of complex aetiology is often stigmatized with society. In this study, we investigate the perspectives and attitudes of the community surrounding the terms "schizophrenia", "schizophrene", "schizophrenic", and "paranoiac" on Twitter in Turkey.

Material and Method: For approximately one month, a total of 1200 tweets containing the terms "schizophrenia", "schizophrene", "schizophrenic" or "paranoiac" were analysed and compared to their usage in a pilot sample . After establishing inter-rater reliability, the contexts of these terms were sorted into five main categories: a) mocking/humorous b) negative c) inappropriate d) anti-psychiatric e) medically appropriate. When possible, the age and gender of the posters were also recorded.

Results: It was seen that these four words were usually used in "mocking/humorous" (39.2%) or "negative" (26%) contexts. The predominant use of the words was in a non-medical manner, with the most medically appropriate usage belonging to "schizophrenia" (26.7%) and the most "negative" and "mocking/humorous" usage belonging to "schizophrenic" (33.2% and 45.8%, respectively). In terms of gender, the four words were used mocking/humorous nearly equally by both genders (39.5% and 38.8%, respectively). Medically appropriate use was seen more often in posts by women than in posts by men (14.8% vs 7.5%, respectively).

Conclusion: Our findings reveal a great deal of misuse of the term "schizophrenia" and its related words on Twitter. This misuse is quite pronounced in the "schizophrenic", which is adjective forms of the word schizophrenia . At this time, where information is readily available, the stigma, ignorance and attitude problems towards schizophrenia are at an notable level.

Keywords: schizophrenia, social media, Twitter, stigma, stigmatization, paranoiac

INTRODUCTION

Since Twitter entered our lives in 2006, it has provided its ever-increasing user base with participation, openness and speech opportunities without any space or time limitations. Twitter users can easily share their thoughts, experiences and images about any subject, including schizophrenia, an important public health problem. These posts, as well as the medical uses of the term "schizophrenia" and its related words, can offer a quick reflection of people's feelings and thoughts towards the disorder and its sufferers .

Stigmatization based on differentness diminishes the dignity of the victim, and elicits negative emotions and prejudiced behaviours in others towards them (1). Stigmatization is frequently associated with disorders with complex aetiologies such as schizophrenia. To combat this stigmatization, it is not enough to have knowledge about stereotypes surrounding schizophrenia sufferers (i.e., that they are dangerous, weak in character, incurable, etc.) (2). Biased individuals endorse negative stereotypes (e.g. "That's right! Schizophrenia patients are prone to violence") and, as a result, display negative emotional reactions (e.g. "They scare me!") (3,4). Contrary to stereotypes , prejudiced attitudes usually contain a negative assessment and cause emotional reactions (fear, anger, etc.) towards the stigmatized individuals. Prejudice leads

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to discriminatory behaviours (e.g., avoiding the prejudiced individual, preventing them from taking advantage of opportunities such as working, housing), and sometimes hostile behaviours against individuals with schizophrenia may be displayed due to negative emotions caused by prejudice (5).

Medically inappropriate explanations and statements about schizophrenia also increase the stigma. In addition, the words "schizophrenic" or "schizophrene", which are the adjective forms of schizophrenia, cause more negative emotions than the word "schizophrenia". These adjectives elicit a qualitative perception of the patients and consequently generate cognitive division in the form of "us" and "them", which is the essence of stigmatization. Humour and jokes made in social settings marginalize individuals diagnosed with schizophrenia, spread stereotypes and the reinforce hostile attitudes (6–8).

In studies conducted on societal perceptions , it was reported that half of the population felt that people with severe mental illness should be afraid of people with severe mental disorders; that these patients should be removed from society; that these patients were irresponsible; that it was appropriate for others to make decisions about the patients' lives; and that the patients were childish and needed serious care (9,10). A study conducted by Arkar (1991) found that the participants had a tendency to interrupt or reduce interactions with individuals diagnosed with schizophrenia in environments requiring social intimacy, especially in cases such as sharing a house, being a next-door neighbour, working in the same workplace, or taking part in a social activity together.

It is possible to access publications and articles from the printed or visual media from the past that examine the attitudes, beliefs and perspectives of society towards schizophrenia and compare them with media sources of today, where information can be near instant via the internet. In the historical articles, negative attitudes, beliefs and stigmatization towards schizophrenia and patients diagnosed with schizophrenia are mentioned. In a study conducted in the USA in 2005, it was determined that 39% of the newspaper news about mental illnesses referred to dangerousness and violence (12). Crisp et al. (2000) stated that the violent news in the media caused the public to believe that individuals with schizophrenia are aggressive . The media's inaccurate and harmful information about mental disorders negatively affects the public's attitude towards patients and increases prejudice and stigmatization tendencies in society.

In this study, the perspective of society on schizophrenia and the issue of stigmatization was examined via Twitter, one of the most preferred social media outlets. Our data was sourced in a social environment where participants could express their thoughts in 280 character posts without outside influence, thus reflecting the belief and perspective of society in a natural way. In addition, since the majority of Twitter users are teenagers and young adults, who are a high-risk group for the onset of schizophrenia, it is very important to understand their knowledge, perceptions and attitudes regarding schizophrenia. As we noticed in Turkey, this forum's demographic increases the value of our study, which is the first work to be done in this area.

MATERIAL AND METHOD

This study was conducted over one month using a total of 1200 Twitter posts (tweets) containing the words "schizophrenia", "schizophrenic", "schizophrene", or "paranoiac". Tweets were selected by inputting these four keywords in the search tab of Twitter and noting the number of tweets containing each word (approximately 300 tweets per word). None of these tweets were retweets, and only those written in Turkish were taken into consideration.

The tweets were categorised into five separate groups:

1) Mocking/humorous use: Sentences ending with positive emojis (:), :)), :D); use of reference words such as "LOL", "haha", "hehe"; humorous, mocking or sarcastic tweets.

2) Negative use: Tweets with negative words such as "die", "hate", "torment", "mad", "maniac", "idiot", "dangerous", "terrible"; other tweets used to insult.

3) Inappropriate use: Misinformation about the disease; puzzling and ambiguous expressions; tweets attributing schizophrenia with symptoms of other diseases but not for negative or humorous purposes.

4) Anti-psychiatric opinion: Content indicating that psychiatric science is useless and unnecessary; that drugs make the condition worse and should not be used; or that a doctor should not be visited, etc.

5) Medically appropriate: Correct medical references to the disease; correct use of the signs or symptoms of this disease such as delusion, psychosis, cognitive impairment, hallucination, paranoia, correct information about treatment options; references or links to printed media reporting about individuals with the disease.

After grouping, the inter-rater reliability rates of these groups were examined by two researchers (ŞAK and YD). The inter-rater reliability analysis found high inter-peer reliability in over 206 tweets (Cohen Kappa=0.804; p=0.001; CI=95% 0.732-0.867). In addition, the profiles of the posters were examined one by one, and any shared information about age and gender was recorded. Then, statistical analyses were made using SPSS 18.0.

RESULTS

We found that the contexts of these four words are most frequently "mocking/humorous" (n=470, 39.2%) or "negative" (n=312, 26%). Inappropriate use was seen in 21.75% (n=261) of the tweets, and medically appropriate information in 11.4% (n=137). We found that the least number of tweets (1.7%) were in an anti-psychiatric manner context (n=20) (**Figure 1**).

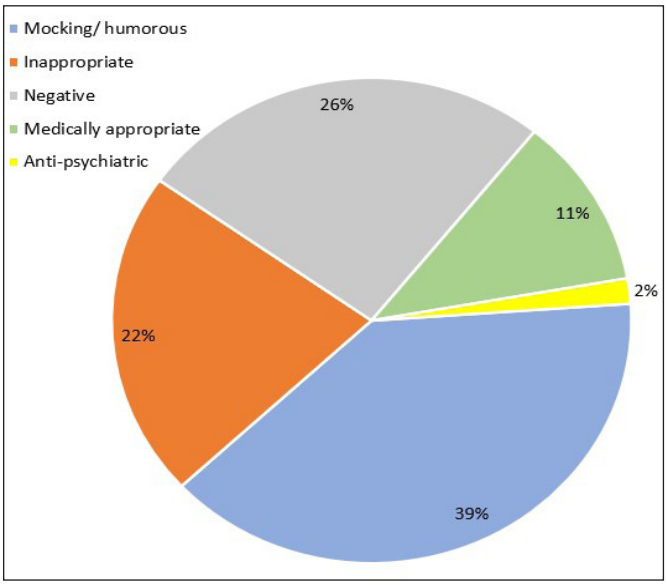

Figure 1. The proportion of 4 words according to the stigma type

When each word was examined separately, the most common negatively used word was "schizophrenic" (33.2%). "Schizophrene" 29.4% was the second most frequent (**Figure 2**). It was observed that "schizophrenic" (45.8%) and "paranoiac" (39.3%) were used most frequently in mocking/humorous contexts. We found that "schizophrenia" (26.7%) was used most within a medically appropriate context .

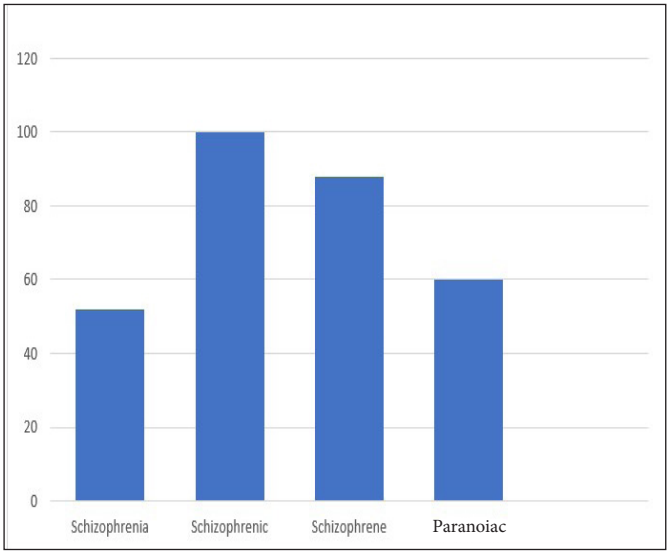

Figure 2. The proportion of 4 words according to "negative" type (n)

When evaluated in terms of gender, males mostly used these four words within mocking/humorous and negative contexts (39.5% and 33.8%, respectively), while females mostly used them in the contexts of mocking/humorous posts (38.8%) or inappropriate use (25.6). It was found that medically appropriate use of these terms was twice as high by women as it was by men (14.8% and 7.5%, respectively) (**Figure 3**).

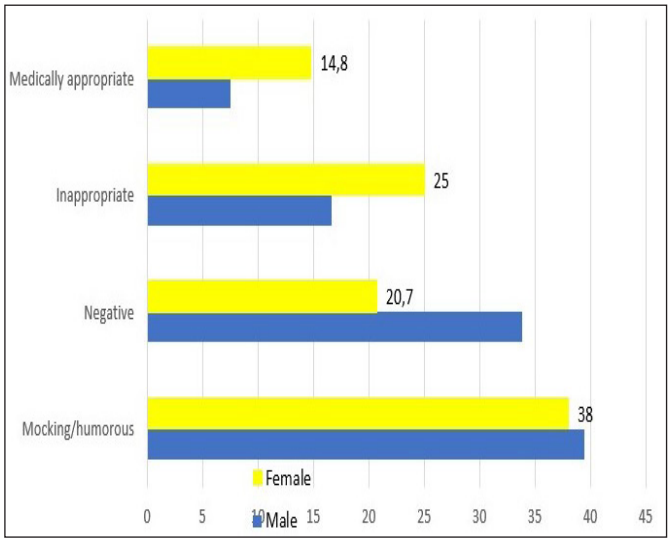

Figure 3. The proportion of 4 words usage according to gender (%)

DISCUSSION

Our findings show that all four words—schizophrenia, schizophrene, schizophrenic, and paranoiac—are misused. It is also seen that misuse is more common in the word "schizophrenic", which is the adjective form of the word "schizophrenia". Although the medically appropriate use of "schizophrenia" is higher than other words, this word is also frequently used in a non-medical way. Our findings coincide with previous studies conducted abroad in printed and social media (14,15). In a similar study comparing schizophrenia and diabetes references on Twitter in 2015, it was noted that "schizophrenia" is generally used for negative, medically inappropriate, sarcastic and stigmatizing purposes compared to "diabetes", while "schizophrenic" is used more negatively and inappropriately than "schizophrenia" (15). In addition, Reavley et al. (2014) published a study on Twitter comparing schizophrenia and depression. They found that there was significantly more stigma against schizophrenia, and that 5% (n=451) of the detected schizophrenia tweets were stigmatizing. Our findings show that the main uses of the term "schizophrenia" on social media were inappropriate, negative, stigmatizing, and non-medical.

In our study, it was observed that mocking/humorous use of these terms was quite common. This form of use,

especially in daily language, becomes an important part of the stigmatization process of individuals diagnosed with schizophrenia. With mocking or humorous use, the burden of the disease on the patient and their family is undervalued, and the individuals with schizophrenia are marginalized. The higher non-medical use of "schizophrenic" and "schizophrene" than "schizophrenia" may indicate that society does not know the name of the disorder correctly and that these uses are actually a part of stigmatization. Similarly, it can be said that the adjective forms of "schizophrenia" are used more negatively than "schizophrenia" itself. This kind of usage creates the cognitive fission of "us" and "them". It should also be kept in mind that the more frequent non-medical use of these four words may devalue the destructive symptoms of chronic mental diseases, which may add to stigmatization. As a result of the disconnection of "schizophrenia" and its related words from their medical contexts, the basic symptoms of schizophrenia become incomprehensible and may delay or prevent individuals and their families from seeking treatment (15,17).

It was observed that men use these four words in a negative manner more often than women. Considering that women use the terms in a medically appropriate context at a higher rate than men, this may reflect the gender difference in social media users' perspectives on schizophrenia.

In a natural environment without influence on the individuals, the attitudes seen in the posts may be accurate reflections of the poster's thoughts and attitudes. The results of such studies are less affected by social attractiveness bias than the studies conducted on questionnaires, and can thus be very useful in terms of evaluating stigmatizing attitudes and attitudes (18). That the most common uses of the four key words of this study were non-medical may also indicate a deviated terminology usage.

One of the limitations of the study is that the sociodemographic characteristics of those who do not share the tweets are unknown. Twitter is mostly used by young people and young adults who live in cities and have a computer culture; thus, the sample may not reflect the whole society. However, we maintain that research on Twitter is a valuable means of understanding the attitudes and beliefs of adolescents and young adults .

Our analysis found that schizophrenia and related words were used in a stigmatizing way on Twitter. It is argued in the literature that other words should be used instead of schizophrenia to reduce stigmatization. However, Passerello et al. (2019) investigated the use of the words "psychosis" and "schizophrenia" in over 1120 tweets and found that the word "psychosis" is more stigmatized than "schizophrenia". This result refutes the claim that using the word "psychosis" instead of "schizophrenia" will reduce the risk of stigmatization.

CONCLUSION

This study shows that our society is lacking in knowledge about schizophrenia and that awareness of the effects of the disease is insufficient. In a period when accessing information and using social media has become so much easier, the lack of knowledge and attitude problems regarding mental disorders are an important issue. With the increasing importance of social media, the results of this study can help the efforts towards raising awareness, reducing stigma and providing information on helpful and accurate resources. In the fight against stigma, we believe that educating society, raising awareness and providing accurate information about the disease by collaborating with the media is an important responsibility of psychiatric associations and their colleagues. Attempts to end stigmatization on social media can play key roles in increasing the awareness of young people (future leaders), and can thus reduce stigmatization in future generations.

ETHICAL DECLORATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Sontag S. Ilness as Metaphor and AIDS and its Metaphors. UK, Blackstone Publishing; 2008.
2. Hamilton DL, Sherman JW. Stereotypes. In: Wyer RS Jr, Srull TK, editors. Handbook of social cognition, 2nd ed. Hillsdale, Lawrence Erlbaum; 1994.
3. Devine PG. Stereotypes and prejudice: their automatic and controlled components. J Pers Soc Psychol 1989; 56: 5–18.
4. Eagly AH, Chaiken S. The social psychology of attitudes. Fort Worth, Harcourt Brace Jovanovich; 1993, p: 794.

5. Crocker J, Major B, Steele C. Social stigma. In: Gilbert D, editor; Fiske ST, editor; Lindzey G, editor. The handbook of social psychology, 4th ed. Vol. 2. New York, McGraw- Hill; 1998.
6. Ford TE, Ferguson MA. Social consequences of disparagement humor: a prejudiced norm theory. Personal Soc Psychol Rev 2004; 8: 79–94.
7. Rüsch N, Angermeyer MC, Corrigan PW. Mental illness stigma: concepts, consequences, and initiatives to reduce stigma. Eur Psychiatry 2005; 20: 529–39.
8. Jorm AF, Oh E. Desire for social distance from people with mental disorders. Aust NZ J Psychiatry 2009; 43:183–200.
9. Taylor SM, Dear MJ. Scaling community attitudes toward the mentally ill. Schizophr Bull 1980; 7: 225–40.
10. Brockington I. Hall P. Levings J, Murphy C. The community's tolerance of the mentally ill. Br J Psychiatry 1993; 162: 93–9.
11. Arkar H. Akıl hastasının sosyal reddedilimi. Düşünen Adam Derg 1991; 4: 6-9.
12. Corrigan PW, Watson AC, Gracia G, Slopen N, Rasinski K, Hall LL. Newspaper stories as measures of structural stigma. Psychiatr Serv 2005; 56: 551-6.
13. Crisp AH, Gelder MG, Rix S, Meltzer HI. Stigmatisation of people with mental illnesses. Br J Psychiatry 2000; 177: 4-7.
14. Link, BG, Yang LH, Phelan JC, Collins PY. Measuring mental illness stigma. Schizophr Bull 2004; 30: 511–41.
15. Joseph AJ, Tandon N, Yang LH, et al. #Schizophrenia: use and misuse on Twitter. Scizophr Res 2015; 165: 111-5.
16. Reavley NJ, Pilkington PD. Use of Twitter to monitor attitudes toward depression and schizophrenia: an exploratory study. Peer J 2014; 2: e647
17. Link BG, Phelan JC. Conceptualizing stigma. Annu Rev Sociol 2001; 27: 363–85.
18. Reavley NJ, Jorm AF. Stigmatizing attitudes towards people with mental disorders: findings from an Austrialian National Survey of Mental Health Literacy and Stigma. Aust N Z J Psychiatry 2001; 48: 1086-93.
19. Passerello GL, Hazelwood JE, Lawrie S. Using Twitter to assess attitudes to schizophrenia and psychosis. BJPsych Bull 2019; 43: 158-66.

Original Article

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Is mean platelet volume better than other long-used non-invasive parameters in assessing severe fibrosis in patients with chronic hepatitis B?

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ABSTRACT

Aim: This study was aimed at i-) investigating the correlation between the severity of hepatic fibrosis and mean platelet volume (MPV) ii-) comparing the accuracy rate of MPV with that of other long-used non-invasive parameters in predicting severe hepatic fibrosis in patients with chronic hepatitis B (CHB).

Material and Method: Ninety-nine patients with CHB were enrolled. The patients were assigned to two groups, based on their hepatic fibrosis scores. Those with scores ranging from 0 to 3 (mild to moderate fibrosis) were assigned to Group 1, and those with scores ranging from 4 to 6 (severe fibrosis) were included in Group 2.

Results: The mean age of the patients was 42±13, and 69 (70%) of them were male. Twenty two patients (22%) were in Group 2. Patients in Group 2 displayed significantly lower albumin and platelet count ($p<0.001$), and significantly higher aspartate aminotransferase-to-platelet ratio index (APRI) and MPV ($p<0.001$). Among the parameters in detecting severe fibrosis, the most sensitive (90%) test was MPV at a cut-off value of ≥10 fl, whilst the most specific (95%) test was platelet count at a cut-off value of ≤150x10^3/mm^3. The accuracy rates of albumin, platelet count, MPV, and APRI were 79%, 91%, 90%, and 77%, respectively.

Conclusions: Among the parameters for the detection of severe fibrosis in patients with CHB, the most sensitive test was MPV and the most specific test was platelet count. When assessed for their accuracy rates, it was determined that platelet count was superior to the other parameters.

Keywords: Albumin, aspartate aminotransferase to platelet ratio index, chronic hepatitis B, fibrosis, mean platelet volume, platelet count

INTRODUCTION

According to data published by the World Health Organisation (WHO), it is estimated that worldwide 257 million people are chronically infected with hepatitis B virus (HBV), which is a major cause of hepatic cirrhosis and hepatocellular carcinoma (HCC) (1-3).

The risk of developing HCC and other liver-related complications is higher in chronic hepatitis B (CHB) patients with advanced hepatic fibrosis or cirrhosis. Therefore, the accurate prediction of the severity of hepatic fibrosis in these patients is of major significance (2,4).

Liver biopsy remains the gold standard of detecting hepatic fibrosis. However, being an invasive procedure, liver biopsy is associated with the risk of several complications. To exemplify, following liver biopsy, the risk of developing severe haemorrhage is 3/1000 and the risk of mortality is 3/10000. Furthermore, biopsy specimens represent only a very small portion (1/50000) of the total hepatic volume. Moreover, the examination results of liver biopsy specimens may present with intraobserver and interobserver variability (5). In view of these limitations of liver biopsy, several non-invasive models have been tried to be developed for the assessment of hepatic fibrosis in patients with CHB, and several literature reports have been published (6-8). However, as most of these models have been tested by different researchers in different groups of patients, standardisation has not been achieved. Further to that, some of these models involve the use of expensive blood tests. Thus, it has not been possible to put these non-invasive models into routine clinical use.

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Albumin is a significant plasma protein synthesized in the liver, and its production decreases in the event of chronic hepatic failure and hepatic fibrosis (9,10). Similar to the measurement of the serum albumin level, the platelet count is also a simple and inexpensive laboratory method. Cases of chronic hepatic diseases may be associated with thrombocytopenia due to several reasons, including the splenic sequestration of platelets, the suppression of the bone marrow and the decrease of thrombopoietin production (11). In this respect, both serum albumin level and platelet count have long served as two simple and inexpensive laboratory methods for the demonstration of chronic hepatic failure and hepatic fibrosis.

Mean platelet volume (MPV) is a standard component of routine complete blood counts, and recently, it has been used to determine the severity of inflammatory disorders, and has been suggested as a potential biomarker for proinflammatory and prothrombotic diseases (12). Studies have been carried out on the correlation between non-alcoholic fatty liver disease (NAFLD) and MPV (13,14). However, only very few studies are available on the correlation of hepatic fibrosis and hepatic inflammation level with MPV in CHB patients, and a complete standardisation has not been able to be established for the results of these studies.

Another simple, non-invasive and inexpensive parameter, known to be available before the use of MPV, for the detection of hepatic fibrosis and inflammation, is the aspartate aminotransferase-to-platelet ratio index (APRI) (15).

In this study, we aimed to i-) assess the correlation of hepatic fibrosis level with MPV in CHB patients and ii-) compare the accuracy rate of MPV with that of other long-used parameters (serum albumin, platelet count, and APRI) in predicting severe hepatic fibrosis.

MATERIAL AND METHOD

The study was conducted pursuant to the approval of the Local Ethics Committee. This study was performed at the outpatient clinic of the Department of Gastroenterology of Bursa Yüksek İhtisas Training and Research Hospital. Ninety-nine treatment-naive patients with CHB were enrolled in the retrospective study.

The demographic, clinical, laboratory, and histopathological data of the patients were obtained from a computerized patient registry database. It was confirmed that all laboratory measurements had been performed within one month before or after the liver biopsy.

Hepatic fibrosis staging and histological activity index (HAI) score were assessed according to the Modified Ishak Scoring System (16). The APRI score was calculated with the formula: (Aspartate aminotransferase/40)/ platelet (10^9/L)×100 (15). The patients were divided into two groups, namely, Group 1 and Group 2, according to their hepatic fibrosis scores. Those with scores ranging from 0 to 3 (mild to moderate fibrosis) were assigned to Group 1, and those with scores ranging from 4 to 6 (severe fibrosis) were included in Group 2. The patients were also divided into two groups on the basis of their HAI scores. Those with scores ranging from 0 to 9 (mild to moderate inflammation) were assigned to Group A, and those with scores ranging from 10 to 18 (severe inflammation) were included in Group B.

Patients, who had undergone liver biopsy with a diagnosis of chronic HBV infection and for whom laboratory data was available within one month before or after the biopsy, were included in the study.

Patients, who had a history of atherosclerotic heart disease, diabetes mellitus, hypertension, renal failure, asthma, chronic obstructive pulmonary disease, peripheral/cerebral vascular disease, haematological disorders, cirrhosis, portal hypertension, splenectomy, rheumatic diseases, pregnancy, malignancies, and any medication use capable of influencing platelet function (e.g., aspirin, heparin), were excluded from the study.

Statistical Analyses

The data were analysed using the Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, Illinois, USA). The Kolmogorov-Smirnov test was used to assess the normal distribution of the continuous variables. Values were expressed as mean ± standard deviation (SD) for normally distributed variables, as median and 25^{th}-75^{th} percentiles for non-normally distributed variables, and count and percent for categorical variables. In univariate analysis, variables were compared using the independent t-test for normally distributed data, the Mann–Whitney U-test for non-normally distributed data, and the chi-square test for categorical data. The Pearson correlation coefficient was used to assess the association between the variables. Receiver-operating characteristic (ROC) curve analysis with a 95% confidence interval (CI) was used to establish optimal cut-off value, sensitivity, specificity, and accuracy rate for MPV, APRI, platelet, and albumin for the detection of severe fibrosis. For all analyses, a P value less than 0.05 was considered to be statistically significant.

RESULTS

Out of the 99 patients enrolled in this study, 69 (70%) were male and their mean age was 42±13 years (range: 18-76). The number of patients found to be positive

for hepatitis B early antigen (HBeAg) and anti-HBeAg were 7 (7%) and 92 (93%), respectively. The median HBV-DNA, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, APRI, and fibrosis of the patients were 60x10³ IU/ml, 32 U/L, 44 U/L, 4.3 g/dl, 0.46, and 2, respectively. Furthermore, the mean total bilirubin, prothrombin time, platelet, MPV, and HAI values of the patients were 0.7 mg/dL, 12.4 s, 200x10³/mm³, 9.5 fl, and 7, respectively (**Table 1**).

Table 1. Demographic and laboratory parameters of the patients (n: 99)

Parameters	Value
Age±SD (years)	42 (±13)
Gender (M/F), n (%)	69/30 (70/30)
HBeAg positivity, n (%)	7 (7)
Anti-HBe positivity, n (%)	92 (93)
HBV DNA* (x10³ IU/mL)	60 (8-3010)
AST* (U/L)	32 (24-51)
ALT* (U/L)	44 (22-81)
Total bilirubin±SD (mg/dL)	0.7 (±0.3)
Protrombin time±SD (s)	12.4 (±1.7)
Albumin* (g/dl)	4.3 (4.0-4.5)
Platelet±SD (x10³/mm³)	200 (±63)
MPV±SD (fl)	9.5 (±1.3)
APRI*	0.46 (0.28-0.76)
HAI±SD	7 (±3)
Fibrosis*	2 (1-3)

SD: Standard deviation, M: Male, F: Female, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, MPV: Mean platelet value, APRI: AST to Platelet Ratio Index, HAI: Histologic activity index, *: Median (25th-75th percentiles)

Based on their hepatic fibrosis scores, 77 (78%) of the patients were assigned to Group 1, and 22 (22%) were assigned to Group 2. The mean age of the patients was 39±12 years in Group 1 and 51±13 years in Group 2. Patients with severe fibrosis were older than those with mild to moderate fibrosis (p=0.01). Group 1 and Group 2 did not differ for sex distribution. The number of HBeAg-positive patients was 3 (4%) in Group 1 and 4 (18%) in Group 2, and the percentage of HBeAg positivity was higher in the group with severe fibrosis (p=0.02). Groups 1 and 2 showed no significant difference for anti-HBe positivity, HBV-DNA, total bilirubin, and ALT levels (p>0.05). In Group 2, the prothrombin time was longer, the AST level was higher and the albumin level and platelet count were lower, when compared to Group 1 (p<0.05). The median APRI value was 0.4 in Group 1 and 0.8 in Group 2 (p<0.001). HAI scores and MPV values were 6.4 and 8.9 fl, respectively, in Group 1, and 10 and 11 fl, respectively, in Group 2. The HAI score and MPV value were significantly higher in the group with severe fibrosis (p<0.001) (**Table 2**).

Based on the HAI, 76 (77%) of the patients were assigned to Group A and 23 (23%) were assigned to Group B. The mean age of the patients was higher in Group B (p=0.01). The HBV-DNA, AST, and ALT levels were significantly higher in Group B, compared to Group A (p<0.05). No difference was detected between the two groups for gender, HBeAg/anti-HBeAg positivity, prothrombin time, and total bilirubin levels. Platelet counts and albumin were significantly lower in Group B, when compared to Group A (p<0.05). MPV, APRI, and fibrosis score were significantly higher in Group B, compared to Group A (p<0.05) (**Table 3**).

Hepatic fibrosis was determined to be positively correlated with MPV (r=+0.77) and APRI (r=+0.50), and negatively correlated with albumin level (r=-0.43) and platelet count (r=-0.42) (p<0.001) (**Figure 1**).

Table 2. Comparison of the patients according to liver fibrosis scores

Parameters	Group 1, n: 77 (78%)	Group 2, n: 22 (22%)	p
Fibrosis score range	0-3	4-6	
Age±SD (years)	39 (±12)	51 (±13)	0.01
Gender (M/F), n (%)	50/27 (65/35)	19/3 (86/14)	0.06
HBeAg positivity, n(%)	3 (4)	4 (18)	0.02
Anti-HBe positivity, n(%)	73 (95)	19 (86)	0.2
HBV DNA* (x10³ IU/ml)	40 (8-1411)	76 (7-11420)	0.25
AST* (U/L)	32 (23-42)	51 (28-150)	0.01
ALT* (U/L)	42 (11-70)	50 (27-149)	0.1
Total bilirubin±SD (mg/dL)	0.6 (±0.3)	0.8 (±0.5)	0.1
Protrombin time±SD (s)	13 (±1.4)	15 (±1.8)	0.001
Albumin* (g/dl)	4.4 (4.2-4.5)	3.8 (3.6-4.0)	<0.001
Platelet ±SD (x10³/mm³)	218 (±56)	136 (±41)	<0.001
MPV±SD (fl)	8.9 (±0.9)	11 (±0.9)	<0.001
APRI*	0.4 (0.3-0.6)	0.8 (0.5-3)	<0.001
HAI±SD	6.4 (±1.7)	10 (±2.4)	<0.001

SD: Standard deviation, M: Male, F: Female, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, MPV: Mean platelet value, APRI: AST to Platelet Ratio Index, HAI: Histologic activity index, *: Median (25th-75th percentiles)

Table 3. Comparison of the patients according to liver histologic activity index scores

Parameters	Group A, n: 76 (77%)	Group B, n: 23, (23%)	p
HAI score range	0-9	10-18	
Age±SD (years)	40 (±13)	48 (±12)	0.01
Gender (M/F), n (%)	51/25 (67/33)	18/5 (78/22)	0.3
HBeAg positivity, n(%)	4 (3)	5 (13)	0.2
Anti-HBe positivity, n(%)	71 (93)	21 (91)	0.7
HBV DNA* (x10³ IU/ml)	24 (7-1487)	693 (45-8560)	0.02
AST* (U/L)	30 (23-41)	74 (31-157)	0.001
ALT* (U/L)	38 (21-68)	91 (28-158)	0.01
Total bilirubin±SD (mg/dL)	0.7 (±0.3)	0.8 (±0.5)	0.1
Protrombin time±SD (s)	13 (±1.4)	14 (±2)	0.1
Albumin* (g/dl)	4.4 (4.2-4.5)	3.9 (3.8-4.2)	0.001
Platelet ±SD (x10³/mm³)	211 (±60)	164 (±65)	0.02
MPV±SD (fl)	9 (±1.1)	11 (±0.9)	0.001
APRI*	0.37 (0.3-0.5)	0.96 (0.4-3.3)	0.001
Fibrosis*	2 (1-3)	3 (2-3)	0.001

SD: Standard deviation, M: Male, F: Female, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, MPV: Mean platelet value, APRI: AST to Platelet Ratio Index, HAI: Histologic activity index, *: Median (25th-75th percentiles)

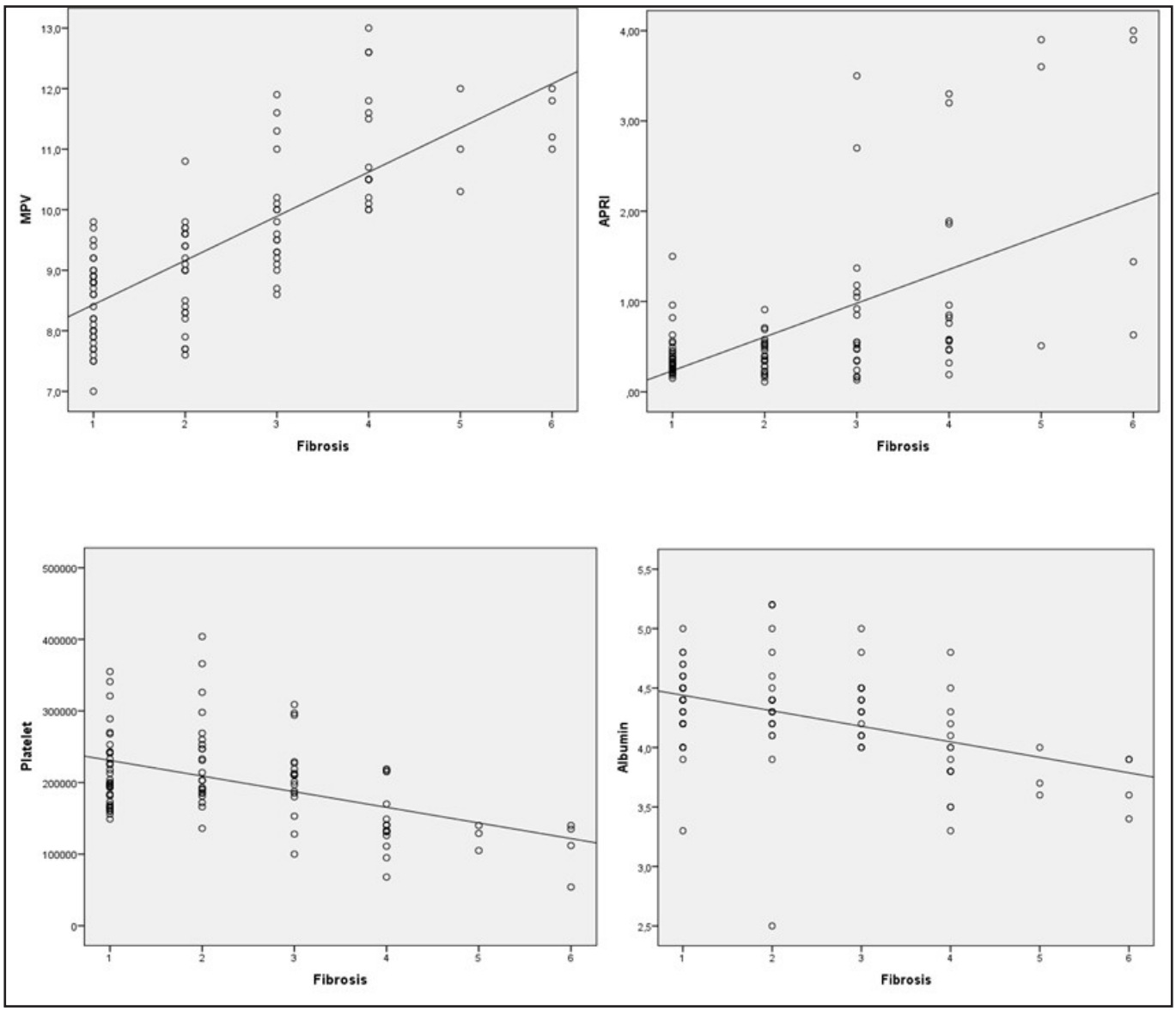

Figure 1. Scatter diagrams showing correlation between fibrosis and different values (MPV: mean platelet value, APRI: Aspartate aminotransferase to Platelet Ratio Index, platelet count, and albümin, respectively). Coefficients (r) and p values were calculated using Spearman correlation analysis. Coefficients (r)/p values for MPV, APRI, platelet, and albumin were +0.77, +0.50, -0.42, and -0.43, respectively (p<0.001).

The ROC analysis performed to determine the accuracy rates of albumin level, platelet count, MPV, and APRI in detecting severe fibrosis revealed area under the curve (AUC) values of 0.86 (0.75-0.96), 0.89 (0.80-0.98), 0.95 (0.92-0.99), and 0.81 (0.71-0.92), respectively, for these parameters (**Figure 2**).

The cut-off values established for albumin level, platelet count, MPV, and APRI for detecting severe fibrosis were ≤4.0 g/dl, ≤150x10^3/mm^3, ≥10 fl, and ≥0.55, respectively. Accordingly, the parameter most sensitive in detecting severe fibrosis was found to be MPV (90%), and the most specific parameter was proven to be platelet count (95%). The accuracy rates were 79%, 91%, 90%, and 77% for albumin level, platelet count, MPV, and APRI, respectively (**Table 4**).

Table 4. Statistical diagnostic measures of different noninvasive variables in the detection of severe fibrosis

Diagnostic measures	Variables and cut-off values			
	Albumin (≤4.0 g/dl)	**Platelet (≤150x10^3/mm^3)**	**MPV (≥10 fl)**	**APRI (≥0.55)**
AUC (95% CI)	0.86 (0.75-0.96)	0.89 (0.80-0.98)	0.95 (0.92-0.99)	0.81 (0.71-0.92)
SEN (%)	81	82	90	77
SPE (%)	80	95	91	78
AR (%)	79	91	90	77
p value	<0.001	<0.001	<0.001	<0.001

MPV: Mean platelet value, APRI: Aspartate aminotransferase to Platelet Ratio Index, AUC: Area under the ROC curve, SEN: Sensitivity, SPE: Specifity, AR: Accuracy rate.

DISCUSSION

Due to liver biopsy being an invasive diagnostic method associated with the risk of several complications, research has been carried out on alternative non-invasive, easily applicable, inexpensive models that can be used for the detection of hepatic fibrosis and inflammation (17). One of the most common models tested for this purpose is APRI (17,18). APRI was first described as a simple, easily detectable and inexpensive marker that could be used to detect significant fibrosis in patients with chronic hepatitis C (CHC) (15). Later, it was also reported as a reliable marker of significant fibrosis in patients with CHB (19). Shoaei et al. determined that APRI was significantly correlated with the Knodell histological activity index and the Ishak fibrosis score in 137 patients with CHB, and suggested that this index would be of use in detecting severe fibrosis and necroinflammation (20). Similarly, the present study demonstrated that APRI values were significantly correlated with advanced hepatic fibrosis and marked necroinflammation.

Serum albumin level and platelet count, both of which have also been long-used as simple, inexpensive, and non-invasive markers similar to APRI in detecting chronic hepatic diseases, have been demonstrated to be negatively correlated with the severity of these diseases (9-11). Likewise, in the present study, both serum albumin levels and platelet counts were observed to be significantly and negatively correlated with hepatic fibrosis and necroinflammation.

Platelets have an essential role in the development of inflammation and the immune response, and antiplatelet treatment is known to reduce mortality rates caused

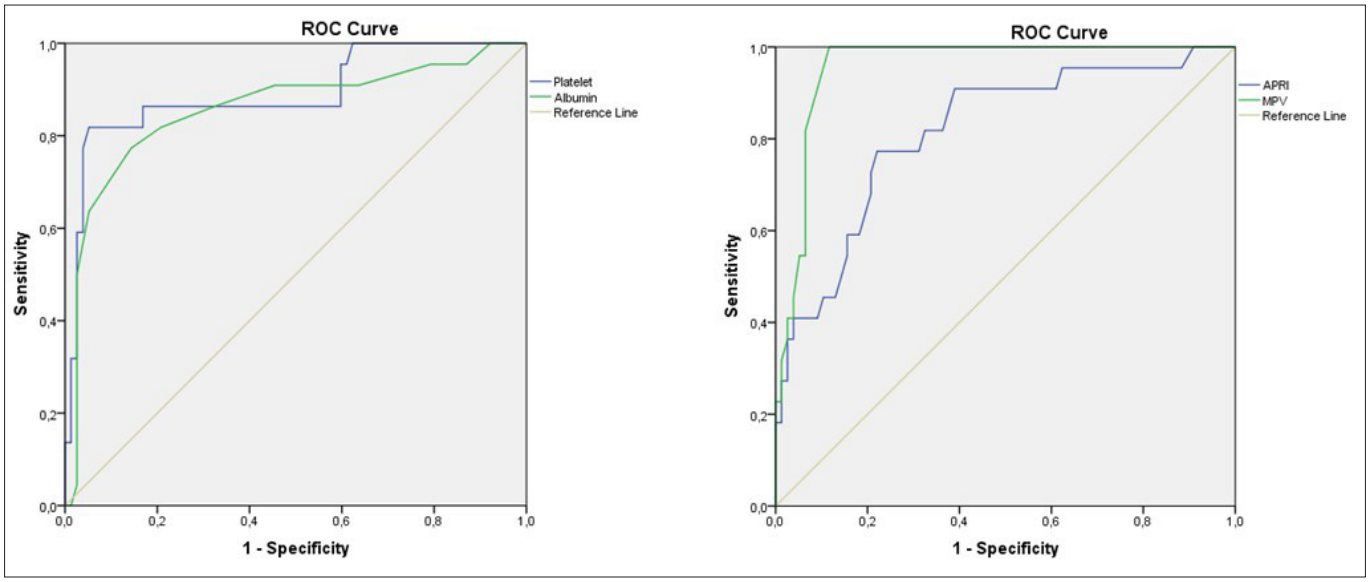

Figure 2. Comparison of receiver operating characteristic curves of albumin, platelet, mean platelet value (MPV), and Aspartate aminotransferase to Platelet Ratio Index (APRI) values in identifying severe fibrosis. For severe fibrosis area under receiver operating characteristic (ROC) curves were 0.86 (0.75-0.96), 0.89 (0.80-0.98), 0.95 (0.92-0.99), and 0.81 (0.71-0.92) for albumin, platelet, MPV, and APRI, respectively and the differences between four areas were statistically significant.

by sepsis and infection (12,21,22). In recent years, the involvement of platelets in inflammation has drawn much interest. MPV, which is a platelet parameter, has been reported to increase in the event of inflammatory diseases, including rheumatoid arthritis (23-25), ulcerative colitis (26), Crohn's disease (27), and acute pancreatitis (28). On the other hand, only very few literature reports are available on the correlation between MPV and chronic hepatic damage. Further to that, the number of studies on the correlation of MPV with hepatic fibrosis and inflammation in CHB patients is particularly low. Research investigating the correlation of NAFLD with MPV has shown that MPV values are higher in cases of NAFLD (13). Abdel-Razik et al. (14) reported that in patients with NAFLD, MPV was positively correlated with the NAFLD activity score, and also determined that MPV was higher in the group with advanced fibrosis (fibrosis=3-4). Therefore, these researchers suggested that MPV could be used in determining advanced cases of hepatic fibrosis. Similarly, in the present study, MPV values were significantly higher in the group with severe fibrosis, in comparison to the group with mild to moderate fibrosis. Different from the study of Abdel-Razik et al. (14), the patients enrolled in the present study had been diagnosed with CHB. In a previous study on patients with chronic inactive hepatitis B and healthy controls, it was determined that MPV values were significantly higher in chronic inactive hepatitis B patients (29). Based on their comparative assessment of 17 patients with acute hepatitis B, 62 patients with CHB, 41 patients with severe chronic hepatitis B, and 58 healthy volunteers, Hu et al. (30) ascertained that MPV values were higher in the patients with CHB and were correlated with the severity of the infection. In another study on patients diagnosed with CHB and CHC, it was observed that in the group with CHC, MPV values were higher in the patients with advanced fibrosis, compared to the patients in the early stage of hepatic fibrosis, yet no such difference was detected in the patients with CHB. Another report on CHB patients indicated that, although statistically insignificant, MPV values were lower in patients with advanced hepatic fibrosis, compared to those with early-stage fibrosis (31). In a more recent study conducted by Hamidi et al. (32) on CHB patients, who had undergone liver biopsy, MPV values were observed to be higher in patients with advanced fibrosis (stages 3-6), compared to those with early-stage fibrosis (stages 1-2). In another study on the correlation between fibrosis and MPV in CHB patients, the comparison of 59 patients with CHB and 25 healthy volunteers demonstrated that MPV values were higher in the infected group. The subgroup analysis of the patients, based on METAVIR scoring, similar to the results of the present study, demonstrated that MPV values were higher in the group with advanced fibrosis (fibrosis=3-4), compared to patients with insignificant fibrosis (fibrosis=0-2), and were also correlated with the severity of hepatic fibrosis (33). In a previous study by Karagoz et al. (34), in agreement with the present study, MPV values were found to be higher in CHB patients with advanced fibrosis (fibrosis=3-6), compared to patients with mild fibrosis (fibrosis=0-2). Differently, in the present study, the group with severe fibrosis included patients with fibrosis scores ranging from 4 to 6, according to the Modified Ishak Scoring Method. Ceylan et al. (35) reported that, in their research on 238 patients diagnosed with CHB, of which those with a HAI score of 0-9 had been assigned to the group with mild to moderate inflammation and those with a HAI score of 10-18 had been assigned to the group with severe inflammation, MPV was proven to be a reliable marker in detecting the severity of inflammation. In the present study, the comparison of the group with the same inflammation score showed that MPV values were higher in the patients with severe inflammation.

The major limitations of the present study are it being a retrospective study covering a relatively small number of patients.

CONCLUSION

Among the simple, non-invasive, and inexpensive parameters (serum albumin level, platelet count, MPV, and APRI) tested in detecting severe fibrosis in treatment-naive CHB patients, the most sensitive test was MPV at a cut-off value of ≥10 fl, whilst the most specific test was platelet count at a cut-off value of $\leq 150x10^3/mm^3$. However, when compared for accuracy rate in predicting severe fibrosis, it was demonstrated that platelet count ($\leq 150x10^3/mm^3$) was superior to the other parameters (serum albumin, MPV, and APRI).

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital (Date: 09 December 2020, Protocol no: 2011-KAEK-25 2020/12-06).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed. Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Global Hepatitis Report 2017. Geneva: World Health Organization; 2017. Available at: http: //apps.who.int/iris / handle/10665/255016. Accessed October 01, 2020.
2. Karagoz E, Tanoglu A. Clinical usefulness of HBsAg quantification in patients with chronic hepatitis B infection. Hepat Mon 2017; 17(4): e12293.
3. Hyun Kim B, Ray Kim W. Epidemiology of Hepatitis B Virus Infection in the United States. Clin Liver Dis (Hoboken) 2018; 12: 1-4.
4. Konerman MA & Lok AS: Epidemiology, diagnosis, and natural history of hepatitis B. In Sanyal AJ, Boyer TD, Lindor KD & Terrault NA (Eds.), Zakim and Boyer's Hepatology: A textbook of liver disease, 7th edition, Philadelphia; Saunders/Elsevier; 2018: pp. 474-84.
5. Bedossa P, Dargere D, Paradis V: Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology. 2003; 38: 1449-57.
6. Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection. Geneva: World Health Organization; 2015 Mar.
7. Xiao G, Yang J, Yan L. Comparison of diagnostic accuracy of aspartate aminotransferase to platelet ratio index and fibrosis-4 index for detecting liver fibrosis in adult patients with chronic hepatitis B virus infection: a systemic review and meta-analysis. Hepatology 2015; 61: 292-302.
8. Leroy V, Sturm N, Faure P, et al. Prospective evaluation of FibroTest®, FibroMeter®, and HepaScore® for staging liver fibrosis in chronic hepatitis B: comparison with hepatitis C. J Hepatol 2014; 61: 28-34.
9. Astegiano M, Sapone N, Demarchi B, Rossetti S, Bonardi R, Rizzetto M. Laboratory evaluation of the patient with liver disease. Eur Rev Med Pharmacol Sci 2004; 8: 3-9.
10. Krier M, Ahmed A. The asymptomatic outpatient with abnormal liver function tests. Clin Liver Dis 2009; 13: 167-77.
11. Peck-Radosavljevic M. Thrombocytopenia in chronic liver disease. Liver Int 2017; 37: 778-93.
12. Korniluk A, Koper-Lenkiewicz OM, Kamińska J, Kemona H, Dymicka-Piekarska V. Mean Platelet Volume (MPV): New Perspectives for an Old Marker in the Course and Prognosis of Inflammatory Conditions. Mediators Inflamm 2019; 2019: 9213074.
13. Madan SA, John F, Nonalcholic fatty liver disease and mean platelet volüme: A systemic review and meta-anaysis. J Clin Gastroenterol 2016; 50: 69-74.
14. Abdel-Razik A, Mousa N, Shabana W, et al. A novel model using mean platelet volume and neutrophil to lymphocyte ratio as a marker of nonalcoholic steatohepatitis in NAFLD patients: multicentric study. Eur J Gastroenterol Hepatol 2016; 28: e1-9.
15. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003; 38: 518–26.
16. Ishak KG, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. J Hepatol. 1995, 22: 696-99.
17. Lurie Y, Webb M, Cytter-Kuint R, Shteingart S, Lederkremer GZ. Non-invasive diagnosis of liver fibrosis and cirrhosis. World J Gastroenterol 2015; 21: 11567-83.
18. Lin ZH, Xin YN, Dong QJ, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology 2011; 53: 726–36.
19. Shin WG, Park SH, Jang MK, et al. Aspartate aminotransferase to platelet ratio index (APRI) can predict liver fibrosis in chronic hepatitis B. Dig Liver Dis 2008; 40: 267-74.
20. Shoaei SD, Sali S, Karamipour M, Riahi E. Non-invasive histologic markers of liver disease in patients with chronic hepatitis B. Hepat Mon 2014; 14: e14228.
21. Margraf A, Zarbock A. Platelets in Inflammation and Resolution. J Immunol 2019; 203: 2357-67.
22. Thomas MR, Storey RF. The role of platelets in inflammation. Thromb Haemost 2015; 114: 449-58.
23. Milovanovic M, Nilsson E, Järemo P. Relationships between platelets and inflammatory markers in rheumatoid arthritis. Clin Chim Acta 2004; 343: 237-40.
24. Yazici S, Yazici M, Erer B, et al. The platelet indices in patients with rheumatoid arthritis: mean platelet volume reflects disease activity. Platelets 2010; 21: 122-5.
25. Kisacik B, Tufan A, Kalyoncu U, et al. Mean platelet volüme (MPV) as an inflammatory marker in ankylosing spondylitis and rheumatoid arthritis. Joint Bone Spine 2008; 75: 291–94.
26. Yüksel O, Helvaci K, Basar O, et al. An overlooked indicator of disease activity in ulcerative colitis: Mean platelet volume. Platelets 2009; 20: 277–81.
27. Liu S, Ren J, Han G, et al. Mean platelet volume: a controversial marker of disease activity in Crohn'sdisease. Eur J Med Res 2012; 17: 27.
28. Mimidis K, Papadopoulos V, Kotsianidis J, et al. Alterations of platelet function, number and indexes during acute pancreatitis. Pancreatology 2004; 4: 22-7.
29. Turhan O, Coban E, Inan D, Yalcin AN. Increased mean platelet volume in chronic hepatitis B patients with inactive disease. Med Sci Monit 2010; 16: 202–05.
30. Hu Y, Lou Y, Chen Y, Mao W. Evaluation of mean platelet volume in patients with hepatitis B virus infection. Int J Clin Exp Med 2014; 7: 4207-13.
31. Eminler AT, Uslan MI, Ayyildiz T, et al. Mean platelet volume is an important predictor of hepatitis C but not hepatitis B liver damage. J Res Med Sci 2015; 20: 865-70.
32. Hamidi AA, Oncul A, Ozguven BY, et al. Diagnostic accuracy of different noninvasive scores for detecting advanced fibrosis in chronic hepatitis B. Eur J Gastroenterol Hepatol 2019; 31: 1439-43.
33. Ekiz F, Yüksel O, Koçak E, et al. Mean Platelet Volume as a Fibrosis Marker in Patients With Chronic Hepatitis B. Journal of Clinical Laboratory Analysis 2011, 25: 162–65.
34. Karagoz E, Ulcay A, Tanoglu A, et al. Clinical usefulness of mean platelet volume and red blood cell distribution width to platelet ratio for predicting the severity of hepatic fibrosis in chronic hepatitis B virus patients. Eur J Gastroenterol Hepatol 2014; 26: 1320-4.
35. Ceylan B, Fincancı M, Yardımcı C, et al. Can mean platelet volume determine the severity of liver fibrosis or inflammation in patients with chronic hepatitis B? Eur J Gastroenterol Hepatol 2013, 25: 606–12.

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Sleep quality and social support in people over 65 years old who have had a quarantine process due to Covid-19

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ABSTRACT

Background and Aim: We aimed to investigate the effects of anxiety or social support on sleep quality in patients with Covid-19 who were older than 65 years of age and undergoing quarantine process.

Material and Method: The study included the patients ≥65 years of age who had a quarantine process for 14 days during the Covid-19 outbreak. The sociodemographic features and comorbidities were recorded in all patients. Geriatric anxiety scale (GAS), multidimensional perceived social support scale (SS), and Pittsburgh sleep quality index (PSQI) questionnaires were applied.

Results: Totally 198 patients (123 male and 75 female) were included in the study. Among patients, 115 (58.1%) patients were living in a nursing home. All GAS scores and the total PSQI were significantly higher and all SS scores were significantly lower in PCR positive patients compared with the negative ones (p=0.001). Moreover, all GAS scores and the total PSQI were significantly higher and all SS scores were significantly lower in patients living in nursing homes compared with the others (p=0.001).

Conclusion: In elderly patients faced with the Covid-19, social support was negatively associated with the sleep disturbances. We suggest that, increasing social support is important in elderly patients in the clash against Covid-19.

Keyword: Anxiety, Covid-19, elderly people, social support, sleep quality

INTRODUCTION

The coronavirus disease 2019 (Covid-19) was first recognized in Wuhan, China, in December 2019. It rapidly spread across mainland China and became a global threat. As of January 2021, the causative pathogen, namely severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected millions of people and caused thousands of deaths globally.

Unfortunately, the coronavirus disease 19 (Covid-19) pandemic affected all over the world within a short period. Even though Covid-19 infection may be severe in all age groups, older adults (65-year-old or older) may experience a higher mortality rate (1,2). Exposure to chronic and daily stressors such as quarantine or life-threatening conditions can affect the emotional experience of the patients. With many unknowns and leading to long quarantine periods, Covid-19 may cause an emotional burden to the patients. With higher mortality rates, elderly patients constitute a special group in this pandemia period, requiring special attention (3,4). Covid-19 can cause various mental disorders and worsening of existing mental symptoms. Anxiety, panic attacks, and depression are some of these symptoms. Sleep is another area where problems may occur in relation to these symptoms.

It is noteworthy that sleep disturbances are prevalent especially in individuals who are forced to medical isolation due to infection or exposure to SARS-CoV-2, demonstrating features of difficulty to fall asleep and early wake-up. In addition to sleep loss, there are people who experience other sleep disturbances, of which SDB is one of the most frequently encountered, and poses a significant burden not only for the affected patients but also for the patient's close contacts. Along those lines, various associations and scientists have recommended activities and exercises that can be applied at home to protect individuals who were separated in their homes from isolation due to the epidemic from mental illnesses such as depression, anxiety and sleep disorders. Sleep

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disturbances are associated with anxiety and depression and should be defined and treated as soon as possible (5,6). In fact, in many studies conducted both in our country and around the world, the relationship between covid 19 pandemic and sleep has been investigated in many ways; reported a high incidence of sleep disturbance, lifestyle change, satisfaction, and increased anxiety, regardless of gender and current employment status (7,8).

The aim of the study is to investigate the effects of anxiety or social support on sleep quality in patients with Covid-19 who were older than 65 years of age and undergoing quarantine process. To the best of our knowledge, this is the first study in the literature evaluating the effects of quarantine period due to Covid-19 on anxiety level and sleep quality in geriatric patients.

MATERIAL AND METHOD

All patients who agreed to participate in the study were included in the study. The study was approved by Turkish Ministry of Health and Bezmialem Vakıf Üniversitesi non-interventional research ethics committee with the number of 2011-KAEK-42 2018703-01. All procedures were performed adhered to the ethical rules and the Helsinki Declaration of Principles.

The study was conducted in 198 patients who applied to two different health centers in Izmir between 15 March 2020 and 30 May 2020 and had a quarantine process for 14 days during the Covid-19 outbreak. The study included patients ≥65 years of age who were treated at hospital due to Covid-19 disease and quarantine was recommended at home after discharge, or who were under quarantine at home for suspected infection or suspicious contact.

The sociodemographic features and comorbidities were recorded in all patients. Geriatric Anxiety Scale, Multidimensional Perceived Social Support Scale, and Pittsburgh Sleep Quality Index questionnaire were applied in all patients face to-face or on the internet.

Geriatric Anxiety Scale includes 23 self-report items used for scoring and 5 additional items to define the common topical concerns of anxiety among older adults. The total score is calculated as well as the 3 subscale scores, measuring cognitive, affective, and somatic symptoms. The patients were asked for the symptoms of anxiety by indicating how often they have experienced each symptom during the past week on a Likert-type scale that ranges from 0 (not at all) to 3 (all the time). The total score ranges from 0 to 75, with higher scores representing the existence of more severe anxiety (9,10).

Multidimensional Perceived Social Support Scale is a 12-item scale designed to determine the perceived social support from three sources: Family, Friends, and a Significant Other (for example, dating, engaged, verbal, relative, neighbor, doctor ...) (11). Higher scores represent better social support presence.

The Pittsburgh Sleep Quality Index (PSQI) is a 19-item survey that defines the global sleep quality in the past month. The Responses are calculated on a four-point, Likert-type scale ranging from 0 to 3. PSQI includes seven components (sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleep medication use, daytime dysfunction) and the component scores are summed to form a global score (12). The total PSQI score ≥5 was defined as the presence of sleep disturbances.

Statistical Analyses

In statistical analysis, demographic definitions regarding the individuals participating in the survey were given in Frequency (n) and Percentage (%). The mean and Standard Deviation (SD) values related to the questions in the scales were given in the tables. Kolmogorov-Smirnov test was applied to determine the suitability of the data for normal distribution. The relationship between the questionnaire scales was analyzed with the Pearson Correlation Coefficient because the variables showed normal distribution. Two group comparisons were performed with the student's t-test. IBM SPSS Amos 21 Statistical Package Program was used for statistical analysis. For statistical significance, $p < 0.05$ was used.

RESULTS

Totally 198 patients (123 male and 75 female) were included in the study. Polymerase chain reaction (PCR) test for Coronovirus-19 was obtained in 152 of the patients and it was positive in 123 of them. Among patients, 183 (92.4) were married and 15 (7.6%) were single. 115 (58.1%) patients were living in a nursing home. Clinically, fever, cough, and dyspnea were determined in 121 (61.1%) patients and the remaining 77 (38.9%) patients were asymptomatic. Thorax CT was obtained at admission in all patients and tomographical features of the Covid-19 was present in half of the patients (n:99). The demographic, educational, and social features of the patients are summarized in **Table 1**.

The results of Geriatric Anxiety Scale, Multidimensional Perceived Social Support Scale, and Pittsburgh Sleep Quality Index questionnaire are summarized in **Tables 2, 3 and 4**, respectively. Regarding the total PSQI score, 96.9% of the participants were having sleep disturbances.

The correlation analysis was performed between the total PSQI and the findings of other surveys performed (**Table 5**). Regarding these findings, there were significant positive correlations between total GAS, GAS-somatic, GAS-cognitive and GAS-affective and total PSQI (p=0.001), while there were significant negative correlations between SS-total, SS- family, SS- friend and SS- significant other and the total PSQI (p=0.001).

We compared the overall findings of the surveys between PCR positive and negative subjects to determine the effects of PCR positivity on these parameters **(Table 6).** Regarding these findings, total GAS, GAS-somatic, GAS-cognitive, GAS-affective and the total PSQI were significantly higher and SS-total, SS- family, SS- friend and SS- significant other were significantly lower in PCR positive patients compared with the negative ones (p=0.001).

Table 1. Demographic, educational and social features of the patients

Feature	Number of patients (%)
Age groups (years)	
65-70	45 (22.7)
71-75	26 (13.1)
76-80	79 (39.9)
>80	48 (24.2)
Treatment modality	
Quarantine was proposed at home without swab sampling	46 (23.2)
A swab sample was taken and quarantine was proposed at home	40 (20.2)
Hospitalized in wards	88 (44.5)
Hospitalized in ICU	24 (12.1)
Living place	
Urban	157 (79.3)
Rural	41 (20.7)
Alcohol	
Never drunk	177 (89.4%)
Stopped	21 (10.6%)
Smoking	
Never smoked	75 (37.9)
Quitted	71 (35.9)
Daily one package or less	45 (22.7)
Daily more than one package	7 (3.5)
Living with	
A nurse or care-giver	112 (56.6)
Family	62 (31.4)
Single	24 (12.1)
Educational level	
Primary school	35 (17.7)
High school	152 (76.8)
University	11(5.6)
Daily Routines are performed	
With the help of care-giver or family members	25 (12.6)
With the help of tools such as walker	105 (53)
Without help	68 (34.3)
Comorbidities	
Asthma-COPD	46 (23.2)
Diabetes mellitus type 2	82 (41.4)
Hypertension	151 (76.2)
Cardiovascular diseases	81 (40.9)
Osteoporosis	47 (23.7)
Osteoarthritis	41(20.7)

ICU: Intensive care unit, COPD: Chronic obstructive pulmonary disease

Table 2. The results of Geriatric Anxiety Scale

	Mean±SD	Median	Minimum-Maximum
Somatic	11.72±4.32	12.00	4.00 -20.00
Cognitive	10.31±3.78	10.00	5.00-20.00
Affective	10.97±4.58	12.00	3.00-22.00
Total GAS*	33.02±11.96	36.00	12.00-60.00

*GAS: Geriatric Anxiety Scale

Table 3. The results of multidimensional perceived social support scale

	Mean±SD	Median	Minimum-Maximum
*SS-family	17.56±9.21	17.00	4.00-28.00
SS-friends	18.07±6.25	20.00	4.00-28.00
SS-significant other	17.56±7.02	20.00	4.00-27.00
SS-total	53.20±21.24	57.50	12.00- 80.00

*SS: Social Support

Table 4. The results of PSQI

		Frequency
Sleep Quality	0	10 (5.1)
	1	58 (29.3)
	2	99 (50.0)
	3	31 (15.7)
Sleep Latency	0	6 (3.0)
	1	59 (29.8)
	2	97 (48.9)
	3	36 (18.2)
Sleep Duration	0	63 (31.8)
	1	93 (47.0)
	2	30 (15.2)
	3	12 (6.1)
Sleep Efficiency	0	30 (15.2)
	1	82 (41.4)
	2	78 (39.4)
	3	8 (4.0)
Sleep Disturbances	0	97 (49.0)
	1	82 (41.4)
	2	19 (9.6)
Sleep Medication Use	0	95 (48.0)
	1	63 (31.8)
	2	32 (16.2)
	3	8 (4.0)
Daytime Dysfunction	0	11 (5.6)
	1	87 (43.9)
	2	74 (37.4)
	3	26 (13.1)
Total Score	<5	6 (3.1)
	≥5	192 (96.9)

Table 5. Correlation Analysis performed between the other parameters and the total PSQI

	r	p
Total GAS	0.773	0.001
*GAS-somatic	0.757	0.001
GAS-cognitive	0.681	0.001
GAS-affective	0.742	0.001
**SS-total	-0.765	0.001
SS- family	-0.822	0.001
SS- friend	-0.651	0.001
SS- significant other	-0.655	0.001

*GAS: Geriatric Anxiety Scale, **SS: Social Support

Table 6. Comparison of the survey results between PCR positive and negative subjects

	PCR positive (n: 123)	PCR negative (n:29)	p
Total GAS	39.50±8.91	22.93±5.55	0.001
*GAS-somatic	13.87±3.49	8.65±1.81	0.001
GAS-cognitive5	12.14±3.36	7.31±1.64	0.001
GAS-affective	13.47±3.18	6.96±3.08	0.001
**SS-total	45.01±12.32	67.62±12.24	0.001
SS- family	14.39±6.60	23.72±4.92	0.001
SS- friend	17.30±5.13	21.82±4.16	0.001
SS- significant other	15.31±5.13	22.06±3.93	0.001
Total PSQI***	23.29±7.69	9.62±5.39	0.001

*GAS: Geriatric Anxiety Scale, **SS: Social Support, ***PSQI: Pittsburgh Sleep Quality Index

We compared the overall findings of the surveys between the patients living in nursing homes and the others to determine the effects of living in nursing homes on these parameters (**Table 7**). Regarding these findings, total GAS, GAS-somatic, GAS-cognitive, GAS-affective, and total PSQI were significantly higher and SS-total, SS- family, SS- friend, and SS- significant other were significantly lower in patients living in nursing homes compared with the others (p=0.001).

Table 7. Comparison of the survey results between the patients living in nursing homes and the others

	Patients living in nursing homes (n:115)	Patients living with their families (n:83)	p
Total GAS	39.05±10.30	24.66±8.63	0.001
GAS-somatic	13.92±3.61	8.68±3.27	0.001
GAS-cognitive	12.28±3.38	7.57±2.31	0.001
GAS-affective	12.84±4.19	8.39±3.80	0.001
SS-total	43.24±18.55	67.00±16.54	0.001
SS- family	12.16±6.74	25.04±6.58	0.001
SS- friend	15.86±6.23	21.13±4.86	0.001
SS- significant other	15.20±6.80	20.81±5.96	0.001
Total PSQI	21.46±8.98	14.38±7.75	0.001

*GAS: Geriatric Anxiety Scale, **SS: Social Support, ***PSQI: Pittsburgh Sleep Quality Index

DISCUSSION

In this study, we determined that, in patients older than 65 years of age who faced with the quarantine process due to Covid-19 pandemic with some reasons; 1. Sleep quality was disturbed in 96.9% of the participants; 2. Total and subscale anxiety scores were positively correlated with the sleep disturbances, while increased social support was associated with a decreased sleep disturbance; 3. PCR positivity increased the anxiety scores and sleep disturbances with a decrease in social support; 4. Living in a nursing home increased the anxiety scores and sleep disturbances with a decrease in social support.

In this study, we analyzed a special group of patients who were ≥65 years of age and who were faced with a quarantine process of 14 days due to Covid-19. More than 60% of our patients were male and about 40% of the patients were aged between 76-80 years. Most of our patients were living an urban areas and about 25% of the participants were still smoking. The most common comorbidity was hypertension.

In a retrospective case series of 1591 patients with laboratory-confirmed Covid-19 referred for ICU admission, the median age was 63 (56-70) and 82% of the patients were male and approximately half of the patients were hypertensive (13). However, Wang et al reported that, among 339 patients with Covid-19 with a mean age of 71±8 years; 51% were female and hypertension was still the most common comorbidity (14).

The data regarding the anxiety level of the patients due to Covid-19 is limited. In 1210 people from different cities of China, Wang et al reported that 53.8% of the respondents rated the psychological impact of the outbreak as moderate or severe; and 28.8% reported moderate to severe anxiety symptoms (15). In a study performed on medical college students, Cao et al reported that, among 7,143 responses, 0.9% were experiencing severe anxiety, 2.7% moderate anxiety, and 21.3% mild anxiety and they also reported that social support was negatively correlated with the level of anxiety (16). Lei et al compared the prevalence and associated factors of anxiety and depression among the public, people affected by quarantine and those unaffected and reported that in the affected group, the prevalence of anxiety and depression was significantly higher than that of the unaffected people and having no psychological support was significantly associated with higher anxiety and depression scores (19). In another study from our country, 45.1% of the participants scored above the cut-off point for anxiety (20). Similar with our results, Xiao et al investigated 170 individuals who were self-isolated at home for 14 days with self-reported

questionnaires and determined that low levels of social relationships were associated with increased levels of anxiety and stress and decreased sleep quality (19).

Sleep disturbances may affect the whole mental health. We defined that more than 96% of patients older than 65 years of age who met with Covid-19, reported some level of sleep disturbances. Using a web-based cross-sectional survey, Huang et al reported the rate of sleep disturbances as 18.2% during Covid-19 outbreak (20). However, our patients were compromising the most risky group and all were met with the disease previously. Those factors may be the reason of such high sleep disturbance rates.

Sleep disturbances showed a negative correlation with the social support. With an increase in social support, increased sleep quality and decreased degree of anxiety and stress were reported in medical staff during the Covid-19 pandemia (21). Similarly, we also determined a negative correlation between sleep disturbances and social support.

Viral nucleic acid test by RT-PCR assay plays an essential role in determining hospitalization and isolation for individual patients. However, many factors may affect the results of RT-PCR assay such as sampling operations and timing, and its positivity was defined as 30-60% at initial presentation of patients with Covid-19 (22). For the first time in literature we determined that PCR positivity increased the anxiety scores and sleep disturbances with a decrease in social support in elderly patients. Though it is not a highly sensitive test, we can suggest that PCR positivity may be thought as the main factor proving the disease prevalence and infectivity; and patients getting this test result reported higher anxiety levels with decreased social support.

We also determined that living in a nursing home was associated with increased anxiety scores and sleep disturbances with a decrease in social support. Recently, increased risk for COVID-19 infections was reported for both community-dwelling older persons as well as those residing in nursing homes (23). The high prevalence of functional and cognitive impairment and behavioral symptoms may also increase the risk posed to nursing home residents. Moreover, high transmission rate for infectious diseases due to sharing some common areas also increase the risk of infection (24,25).

There are some limitations of the study that should be mentioned. First are that this is a cross-sectional study without any follow-ups. We do not analyze the effects of these factors on outcomes, which may be the topic of another study. Secondly, this is a survey-based study, carrying the bias of self-reported surveys.

CONCLUSION

In conclusion, we determined sleep disturbances as high as 96% of elderly patients who met with Covid-19. It should also be highlighted that social support was negatively associated with the sleep disturbances. PCR positivity and living in nursing homes were associated with increased sleep disturbances, anxiety level, and decreased social support. Since elderly patients are compromising a special group with increased mortality rates, high rates of sleep disturbances should be taken into account during management and the effects of these factors on outcomes should be investigated in further studies. We suggest that increasing social support is important in elderly patients in the clash against Covid-19, which may improve the outcomes with improving sleep disturbances.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Turkish Ministry of Health and Bezmialem Vakıf Üniversitesi non-interventional research ethics committee with the number of 2011-KAEK-42 2018703-01.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Data available statement: The data that support the findings of this study are available from the corresponding author [G.D.I.], upon reasonable request.

REFERENCES

1. Wang C. A novel coronavirus outbreak of global health concern. Lancet. 2020; 395:470–3. doi: 10.1016/S0140-6736(20)30185-9.
2. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. The epidemiological characteristics of an outbreak of an outbreak of 2019 novel Coronavirus Diseases (Covid-19) in China. Zhonghua Liu Xin Bin 2020; 41: 145–51.
3. Sher L. Covid-19, anxiety, sleep disturbances and suicide. Sleep Med 2020; 70: 124.
4. Cullen W, Gulati G, Kelly BD. Mental health in the Covid-19 pandemic. QJM 2020; 113: 311-2.
5. Peteet JR. Covid-19 Anxiety. J Relig Health 2020: 1-2.

6. Mazza M, Marano G, Antonazzo B, et al. What about heart and mind in the covid-19 era? [published online ahead of print, 2020 May 12]. Minerva Cardioangiol 2020; 10.23736/S0026-4725.20.05309-8.

7. Stanton R, To QG, Khalesi S, et al. Depression, anxiety and stress during Covid-19: associations with changes in physical activity, sleep, tobacco and alcohol use in Australian adults. Int J Environ Res Public Health 2020; 17: 4065.

8. Demir Ü. The effect of COVID-19 pandemic on sleeping status. J Surg Med 2020; 4: 334-9.

9. Segal DL, June A, Payne M, Coolidge FL, Yochim B. Development and initial validation of a self-report assessment tool for anxiety among older adults: the Geriatric Anxiety Scale. J Anxiety Disord 2010; 24: 709-14.

10. Yochim BP, Mueller AE, June A & Segal DL. Psychometric properties of the geriatric anxiety scale: comparison to the beck anxiety ınventory and geriatric anxiety ınventory. Clin Gerontol 2011; 34: 21-33.

11. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The multidimensional scale of perceived social support. J Pers Assess 1988; 52: 30-41.

12. Buysse DJ, Hall ML, Strollo PJ, et al. Relationships between the Pittsburgh sleep quality index (PSQI), Epworth sleepiness scale (ESS), and clinical/polysomnographic measures in a community sample. J Clin Sleep Med 2008; 4: 563-71.

13. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA 2020; 323: 1574-81.

14. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. J Infect 2020; 80: 639-64.

15. Wang C, Pan R, Wan X, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (Covid-19) epidemic among the general population in China. Int J Environ Res Public Health 2020; 17: 1729.

16. Cao W, Fang Z, Hou G, et al. The psychological impact of the Covid-19 epidemic on college students in China. Psychiatry Res 2020; 287: 112934

17. Lei L, Huang X, Zhang S, Yang J, Yang L, Xu M. Comparison of prevalence and associated factors of anxiety and depression among people affected by versus people unaffected by quarantine during the covid-19 epidemic in Southwestern China. Med Sci Monit 2020; 26: e924609.

18. Özdin S, Bayrak Özdin Ş. Levels and predictors of anxiety, depression and health anxiety during Covid-19 pandemic in Turkish society: The importance of gender. Int J Soc Psychiatry. 2020 8: 20764020927051.

19. Xiao H, Zhang Y, Kong D, Li S, Yang N. Social capital and sleep quality in individuals who self-isolated for 14 days during the coronavirus disease 2019 (COVID-19) outbreak in January 2020 in China. Med Sci Monit 2020; 26: e923921.

20. Huang Y, Zhao N. Generalized anxiety disorder, depressive symptoms and sleep quality during Covid-19 outbreak in China: a web-based cross-sectional survey. Psychiatry Res 2020; 288: 112954.

21. Xiao H, Zhang Y, Kong D, Li S, Yang N. The effects of social support on sleep quality of medical staff treating patients with coronavirus disease 2019 (Covid-19) in January and February 2020 in China. Med Sci Monit. 2020; 26: e923549.

22. Yang Y, Yang M, Shen C, et al. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. 2020. Doi:10.1101/20 20.02.11.20021493.

23. Applegate WB, Ouslander JG. Covid-19 Presents High Risk to Older Persons. J Am Geriatr Soc 2020; 68: 681.

24. Fallon A, Dukelow T, Kennelly SP, O'Neill D. Covid-19 in Nursing Homes. QJM. 2020: hcaa136.

25. Davidson PM, Szanton SL. Nursing homes and Covid-19: We can and should do better. J Clin Nurs 2020: 10.1111/jocn.15297.

Original Article

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Outcomes of delayed graft function in deceased donor kidney transplantation: a single center experience

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ABSTRACT

Objective: Delayed graft function (DGF) is related to enhanced acute rejection attacks in the short-term and reduced graft survival and reduced overall survival in the long-term. In this study, we desired to ascertain the outcomes of DGF.

Material and Method: This study is a retrospective cohort study. Two hundred seventy-four patients who underwent a kidney transplant from a deceased donor were included. DGF was described as obtaining dialysis treatment within the first week of transplant. The kidney recipients were divided into groups DGF+ (Group 1) and DGF- (Group 2). Two groups were compared in terms of risk factors which were based on donor and recipient characteristics. Short-term outcomes, long-term graft survival and recipient survival results were compared.

Results: The incidence of DGF was 50.3%. The rate of donors with expanded criteria donor (ECD) was 37.3%. Mean glomerular filtration rate (GFR) at one year after kidney transplantation was 57.5 ml/dk/1.73m² for Group 1, and 73 ml/dk/1.73m² for Group 2 ($p<0.001$). There was no statistically significant difference between the groups in terms of graft loss and mortality at one year. There was no statistically significant difference between groups in terms of graft and recipient survival.

Conclusion: DGF did not negatively impact graft survival and recipient survival at one year and long-term, although it was associated with prolonged hospitalization and increased acute rejection in the early period.

Keywords: Delayed graft function, kidney transplantation, graft survival

INTRODUCTION

The need for dialysis in the first week after kidney transplantation is described as delayed graft function (DGF). Although the incidence of DGF varies widely due to various definitions in the literature (19-70%), it is around 25-30% (1,2). The activation of immunological pathways triggered by ischemic damage is one of the best-known mechanisms of DGF. The main physiopathological factors affecting the development of DGF are; donor-related (ischemic injury, inflammatory response) and recipient-related (reperfusion injury and immune response) (3).

In the last few decades, the use of allografts from marginal deceased donors to expand the cadaveric organ pool is a mandatory tendency by kidney transplant teams around world (3). Allograft donation from deceased donors after cardiac arrest is not applied routinely in our country; however, the use of those allografts results in an increased risk of DGF development (4). DGF is associated with prolonged hospitalization, worse kidney function, and increased acute rejection attacks in the early postoperative period (5,6). In a meta-analysis, DGF has been associated with 38% increased risk of acute rejection and 41% increased risk of graft loss in an average follow-up of 3.2 years. While many studies have shown that DGF is associated with decreased graft survival and decreased recipient survival (7-9), some other studies was found no association between DGF and graft survival, although it was associated with reduced kidney function (10,11).

Many risk factors have been argued to cause in DGF development, such as transplant-related (cold and warm ischemia time, sensitization, HLA mismatch), donor-related (age, body mass index, ethnicity, deceased donor after cardiac death, method of operation), recipient-related (age, sex, duration of dialysis, previous transplant history, presence of PRA, diabetes mellitus) and perioperative processes related (induction, anesthesia) (4,12).

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In this retrospective cohort study, we aimed to reveal the impact of DGF on short-term and long-term outcomes of kidney transplant recipients who received grafts from deceased donors.

MATERIAL AND METHOD

The study was approved by Yeni Yüzyil University Science, Social and Non-Invasive Health Sciences Research Ethics Committee (2020/06-473). All procedures were performed adhered to the ethical rules and the Helsinki Declaration of Principles.

In our retrospective cohort study, we contained patients who had kidney transplants from deceased donors, between 2008-2020. Kidney transplant patients who were followed for more than one year were included in the study. Patients with hyperacute rejection, primary nonfunctioning kidney, and multiple organ transplants were excluded. Kidney recipient and donor characteristics were obtained from medical records. Renal recipients were divided into two groups: DGF+ (group 1) and DGF- (group 2). Donor data included age, sex, body mass index (BMI), cause of death, history of diabetes mellitus (DM) and hypertension (HT), number of days in intensive care, creatinine level that belongs to a patient at admission time to hospital, and most recent creatinine level. Recipient data included age, sex, BMI, disease-causing end-stage renal disease, dialysis modality, dialysis duration, Class I-II PRA, HLA mismatch, cold ischemia time (CIT), biopsy-proven acute rejection (BPAR), length of hospital stay after transplantation, graft survival and recipient survival.

Definitions

Delayed graft function: The need for dialysis in the first week after kidney transplantation is described as DGF.

Expanded criteria donor (ECD): ECD was described as the presence of one of the following characteristics (13).

1.Donor aged ≥60 years,

2.Donor aged 50-59 years and additionally, in the presence of two of the following three features,

a. Cerebrovascular cause of death
b. Creatinine>1,5 mg/dl
c. Hypertension

Clinical Outcomes

In the present study the outcomes were biopsy-proven acute rejection (within 100 days after kidney transplantation), GFR (Glomerular Filtration Rate) at one year post-transplantation, graft loss within one year, short-term mortality (the patients who died within one year after kidney transplantation), the time it took to reach the best kidney function graft survival, and recipient survival.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 21.0. The variables were investigated using visual (histograms, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they were normally distributed. The Mann-Whitney U test was used to compare donor and recipient characteristics that they were not normally distributed between groups. The effect of DGF on graft survival and recipient survival was investigated using the Log-Rank test. The Kaplan-Meier survival estimates were calculated. A 5% type-1 error level was used to infer statistical significance.

RESULTS

In the present study, the incidence of DGF was 50.3% (n=135). The mean donor age and median donor age of Group 1 and Group 2 were 50.82±18.4 and 52 (12-87) years, 41.3±21.1, and 42 (1-86) years, respectively. Mean recipient age and median recipient age of Group 1 and Group 2 were 45.3±12 and 46 (10-66) years, and 40.3±16.3 and 43 (2-68) years, respectively. When kidney recipients age and donors age were compared according to groups, there was a statistically significant difference between Group 1 and Group 2 ($p<0.001$ and $p=0.036$).

When Group 1 and group 2 were compared according to donor BMI, a statistically significant difference was found. Median BMIs of groups 1 and 2 were 26.1 (16.5-41) and 25.1 (13.9-47), respectively ($p=0.012$). A statistically significant difference was found when Group 1 and 2 were compared according to kidney recipient BMI. Median BMIs of groups 1 and 2 were 23.6 (13.9-35) and 23.6 (12.9-38.3), respectively ($p=0.036$).

When the groups were evaluated in terms of donor diseases, Group 1 had a higher prevalance of DM and HT more than Group 2 ($p=0.001$). When creatinine level at admission time to hospital and recent creatinine values were evaluated, recent creatinine was statistically significant in terms of DGF development ($p=0.004$). The rate of donors with ECD was 37.3% (100/268). In Group 1, 59% of donors (n=59) were ECD, and this difference between the two groups was statistically significant ($p=0.029$).

Mean duration of dialysis 112.2±65 months. Duration of dialysis in Group 1 higher than in Group 2 ($p=0.018$). In terms of dialysis modality, we found that DGF developed statistically significantly more often in HD patients than in PD patients ($p=0.001$).

Mean and median duration of cold ischemia time of all patients were 14.7±4.3 and 14 (7-32) hours, respectively.

Cold ischemia time was statistically significant in the development of DGF (p=0.002). The presence of HLA mismatch, Class I, and Class II PRA in kidney recipients were not statistically significant in the development of DGF. Donor and recipient characteristics according to groups are given in **Table 1.**

Table 1. Donor and recipient characteristics according to groups

	Grup 1 (n=135)	Grup 2 (n=133)	
Donor Related Risk Factors**			
Age, years	52 (12-87)	42 (1-86)	0.000*
Sex, female/male (m%)	83/52 (38.5%)	78/55 (41.3%)	0.636
BMI (kg/m^2)	26.1 (16.5-41)	25.1 (13.9-47)	0.012
Cause of death			
CVE	68 (52.3%)	62 (47.7%)	0.119
Head trauma	48 (46.6%)	55 (53.4%)	
Hipoxia	9 (81.8%)	2 (18.2%)	
Other	10 (41.7%)	14 (58.3%)	
Comorbidities			
HT	31 (56.4%)	24 (43.6%)	0.001
DM	19 (86.4%)	3 (13.6%)	
No	56 (41.5%)	79 (58.5%)	
Unknown	29 (51.8%)	27 (48.2%)	
Creatinine level (mg/dl)			
Admisson to hospital cr	0.82 (0.37-3.6)	0.78 (0.19-3.7)	0.073
Terminal cr	1.23 (0.3-8)	1.01 (0.2-5.7)	0.004
Intensive care stay (days)	4 (2-45)	4 (1-10)	0.562
Expanded Criteria Donor			
Yes	59 (59%)	41 (41%)	0.029
No	76 (45.2%)	92 (54.8%)	
Recipient Related Risk Factors			
Age, years	46 (10-66)	43 (2-68)	0.027
Sex, female/male (m%)	81/54 (40%)	72/61 (45.8%)	0.332
BMI (kg/m^2)	23.6 (13.9-35)	23.6 (12.9-38.3)	0.036
Primary Disease			
DM	19 (61.3%)	12 (38.7%)	0.218
HT	28 (54.9%)	23 (45.1%)	
GN	19 (61.3%)	12 (38.7%)	
Other	68 (45.9%)	80 (54.1%)	
Dialiysis Modality			
PD	4 (17.4%)	19 (82.6%)	0.001
HD	130 (54.4%)	109 (45.6%)	
Duration of dialysis (months)	120 (39-264)	108 (6-264)	0.018
HLA Mismatch			
0	4 (50%)	4 (50%)	0.409
1-5	127 (49.8%)	128 (50.2%)	
6	4 (80%)	1 (20%)	
PRA Categories			
Class I and Class II negative	100 (54.1%)	85 (45.9%)	0.150
Class I or Class II positive	19 (38.8%)	30 (61.2%)	
Class I and Class II positive	16 (47.1%)	18 (52.9%)	
Graft Related Risk Factor			
Cold ischemia time (hours)	14 (7-21)	14 (8-23)	0.002

*p<0.001 **Numbers are given as median and minimum, maximum, and percentages by row.
CVE:Cerebrovascular event, HT: Hypertension, DM:Diabetes mellitus, GN:Glomerulonephritis,
PD:Peritoneal dialysis, HD:Hemodialysis, HLA:Human leukocyte antigen, PRA:Panel reactive antibody, cr:Creatinine

There was no difference between the two groups in terms of induction therapy (ATG or IL-2 Ab) and maintenance immunosuppressive treatments (p=0.051 and p=0.349). When the two groups were compared in terms of the time it took to reach the best kidney function, we found that patients in Group 1 took longer to reach the best kidney function than patients in Group 2. (p<0.001). After kidney transplantation, the length of hospital stay of Group 1 was 23.5 (5-46) days, while the duration of hospitalization of Group 2 was 10 (6-23) days. This difference was statistically significant (p<0.001). Biopsy proven acute rejection developed in 24 out of 135 patients (17.8%) in Group 1, and 10 out of 133 patients (7.5%) in Group 2 in the early period, and this difference was found to be statistically significant (p=0.019). The short-term outcomes are given in **Table 2** by groups. At one year, Group 1 had a mean (range) GFR of 57.5 ml/dk/1.73m^2 (8-132) and Group 2 had a mean (range) GFR of 73 ml/dk/1.73m^2 (20-133) and the difference was statistically significant (p <0.001). There was no statistically significant difference between the groups in terms of graft loss and mortality at one year.

Table 2. Short-term clinical outcomes according to groups

**	Grup 1 (n=135)	Grup 2 (n=133)	
Time it took to reach best kidney function (days)	195 (6-1320)	62 (5-490)	0.000*
Length of hospital stay (days)	23.5 (5-46)	10 (6-23)	0.000*
Biopsy proven acute rejection			
Yes	24 (70.6%)	10 (29.4%)	0.019
No	111 (47.4%)	123 (52.6%)	
GFR at one year (ml/dk/1.73 m^2)	57.5 (8-132)	73 (20-133)	0.000*
Mortality at one year			
Yes	13 (48.1%)	14 (51.9%)	0.967
No	122 (50.6%)	119 (49.4%)	
Graft loss at one year			
Yes	8 (53.3%)	7 (46.7%)	1.0
No	127 (50.2%)	126 (49.8%)	

*p<0.001 **Numbers are given as median and minimum, maximum, and percentages by row. GFR: glomerular filtration rate

Mean and median of follow-up time in all recipients and in recipients with DGF were 56.9±35.7, 50 (0-143) months, 54.4±35.7, 49 (0-143) months, respectively. While graft loss developed in 13.4% (36/268) of all patients, this rate was 17% (23/135) and 9.8% (13/133) in Group 1 and Group 2, respectively. While 17.9% (48/268) of all patients died, mortality rate was 20% (27/135) and 15.8% (21/133) in Group 1 and Group 2, respectively.

Figure 1 shows the Kaplan-Meier analysis results in terms of graft survival, and there was no statistically significant difference between the groups (p=0.141). **Figure 2** shows the Kaplan-Meier analysis results in terms of recipient survival, and there was no statistically significant difference between the groups (p=0.665).

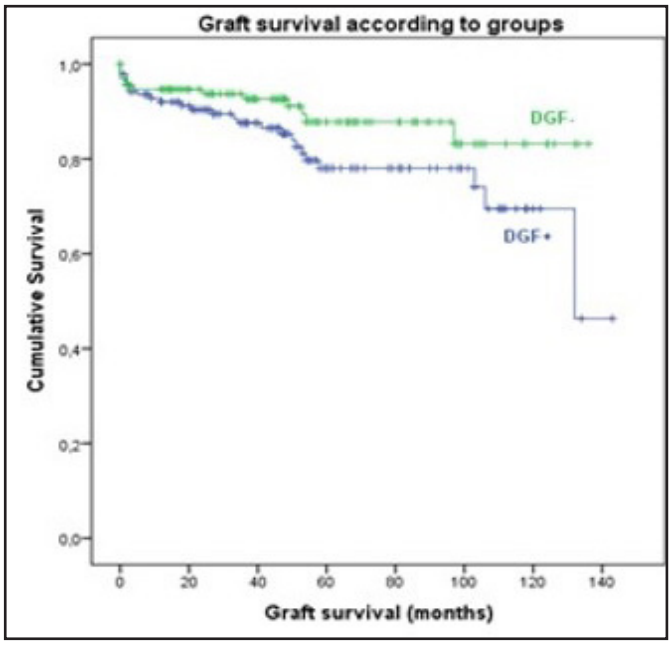

Figure 1. Graft survival according to delayed graft function

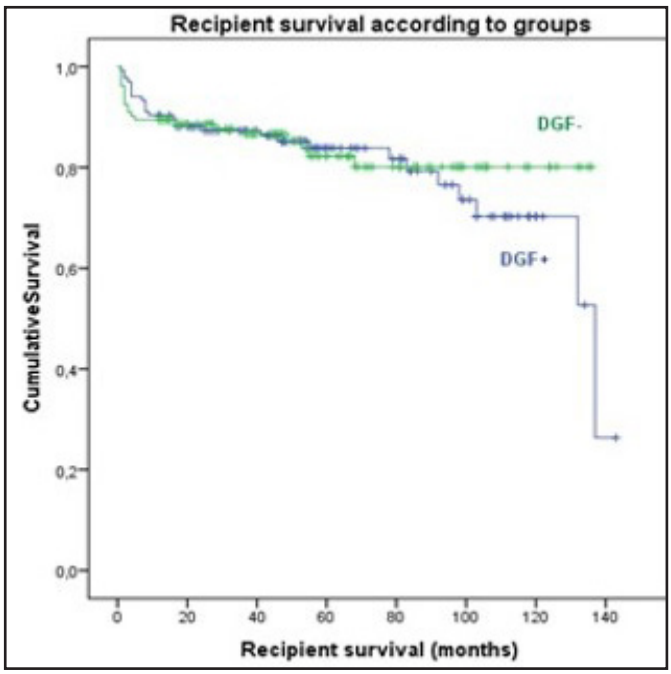

Figure 2. Recipient survival according to delayed graft function

DISCUSSION

Delayed graft function appears as a clinical outcome of all processes in the pre-harvesting period, organ protection phase, and reimplantation phase. Donor-related factors such as low perfusion, infection, and cytokine release triggered by brain death result in adverse effects on the kidney. Low perfusion during the organ preservation period creates ischemic damage, especially in the tubular area, and also causes the release of various proteins and antigens that activate immune pathways as a result of vascular endothelial damage. DGF develops as a result of processes such as tubular damage caused by ischemia,

complement activation, accumulation of free radicals, and increased proinflammatory cytokines as a result of reperfusion injury developed after reimplantation (3,4).

Although many studies have shown the associations between DGF and prolonged hospitalization, early acute rejection, and loss of graft in the short term after kidney transplantation (5-9), these are not apparent in the long-term. In the present study, we have shown that despite the high frequency of DGF (50.3%), it did not negatively affect graft loss and mortality rate within the first year, long-term graft survival, and recipient survival.

The incidence of DGF was significantly higher in studies from our country (20-57.8%) (10,14-18) than the incidence reported in international literature (25-30%) (1,2). In our study, the incidence of DGF (50.3%) was found to be similar to our national studies. The higher frequency of DGF in our transplant center may have been due to the more acceptance of kidney donors with ECD. While the frequency of ECD varies from 28 to 40.5% in international literature (19-21), in our study, it was 39.5% in all patients and 59% in the group that developed DGF.

One of the negative consequences of DGF is prolonged hospitalization after transplantation. In this study, we found the length of hospital stay was significantly longer in DGF+ group, similar to the data in the literature (5-9).

In the present study, BPAR rate that developed within 100 days after kidney transplantation was found to be higher in the group with DGF compared to the group without DGF (17.8% vs 7.5%). Yarlagadda et al. (5) found that the development risk of BPAR was 38% in the group that developed DGF, and in the study conducted by Lai et al. (6) BPAR developed in 60.8% of the group that developed DGF.

One of the most important results of our study is that kidney function continues to recover after the early period in both groups. Patients with DGF achieved the best kidney function an average of 133 days later compared to those without DGF. This effect may have been due to the long-term healing of inflammatory damage resulting from ischemic injury and the immune system response mounted by the recipient. Induction therapy used in the kidney transplant procedure and early maintenance high immunosuppressive therapy may also impair the recovery process.

In the present study, we found that GFR at one year post-transplantation of the DGF group was significantly lower than the group without DGF, but the graft loss was not different among the two groups at one year. Similarly, we did not find any difference between the two groups in terms of recipient survival at one year. In a recent meta-analysis, DGF was found to be a risk factor for graft loss in the 1st year (HR 1.89, 95% CI, 1.46-2.47) (22). In this meta-analysis, six factors were found to be associated with graft loss: donor age, deceased donor, number of HLA mismatches, recipient age, and DGF as a risk factor for one year graft loss. In this meta-analysis, DGF was considered a moderate level risk factor due to serious inconsistencies in the studies included in the analysis. Also, authors commented that each of the identified risk factors had a small effect.

In this study, as shown in **Figures 1 and 2**, DGF+ group accured more graft loss (23 vs 13) and patient death (27 vs 21). However, there was no statistically significant difference between the two groups in the long-term.

In the meta-analysis that Yarlagadda et al. (5) analyzed 33 studies, DGF was found to be associated with graft loss after 3.2 years of follow-up, however they also showed that it didn't negative impact recipient survival after 5 years of follow-up. Lai et al. (6) determined that graft survival was lower in the group with DGF at 1st year and 3rd years, but they did not find difference in terms of recipient survival. In the previously reported study from Turkey by Kara et al. (10), there was no difference in graft survival and recipient survival between the groups with and without DGF in the 1st year. Helfer et al. (7) determined that GFR was found to be statistically significantly higher in the group with DGF in the first 4 years after kidney transplantation, while 5 years later this difference was reduced and became insignificant. They demonstrated that longer DGF duration (>14 days) was associated with graft loss and worse kidney function.

Although the short-term negative results of DGF have been revealed in many studies, its effects on graft survival and recipient survival in the long term do not yet remain clear. There are many factors affecting graft survival and recipient survival, such as infection, acute rejection, recipient age, immunological risk status, and comorbidities. In our study, although GFR was lower in the group that developed DGF at one year, there was no significant difference between two groups in terms of graft loss. The reason may have been due to high number of ECDs in both groups. In our study, we showed that improvement in kidney function lasted longer in the group that developed DGF (195 versus 62 days). The fact that the recovery period of DGF continues beyond the early stage of kidney transplant may signify that the adverse effects of DGF are less common in the long term.

The present study has a few limitations. First, it is a retrospective study accomplished at a single center. Furthermore, although we have used the most widely preferred definition of DGF in the literature, postoperative dialysis indication is a subjective decision. The fact that DGF definition is not standardized in the literature has led to significant differences in center-specific incidences

of DGF, and this directly affects the results. Therefore, our DGF definition in this study directly affected our results. Some studies have revealed that patients with shorter DGF duration have similar results with patients that did not develop DGF and that patients with longer DGF duration have worse kidney outcomes (6,23,24). With more studies evaluating the effect of DGF duration on kidney and patient outcomes, the uncertainty generated by various DGF definitions in this area can be reduced. If the DGF duration were included in our study, the results would most likely be different.

CONCLUSION

Our study showed that DGF did not negatively affect graft survival and recipient survival in the first year and long-term, although it was associated with prolonged hospitalization and increased acute rejection in the early period.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Yeni Yüzyil University Science, Social and Non-Invasive Health Sciences Research Ethics Committee (2020/06-473).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Wang CJ, Wetmore JB, Israni AK. Old versus new: progress in reaching the goals of the new kidney allocation system. Hum Immunol 2017; 78: 9–15.
2. Samoylova ML, Nash A, Kuchibhatla M, Barbas AS, Brennan TV. Machine perfusion of donor kidneys may reduce graft rejection. Clin Transplant 2019; 33: e13716.
3. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. Am J Transplant 2011; 11: 2279–96.
4. Bahl D, Haddad Z, Datoo A, Qazi YA. Delayed Graft Function in Kidney Transplantation. Curr Opin Organ Transplant 2019; 24: 82-6.
5. 5.Yarlagadda SG, Coca SG, Formica Jr RN, Poggio ED, Parikh CR. Association between delayed graft function and allograft and patient survival: a systemic review and meta-analysis. Nephrol Dial Transplant 2009; 24: 1039e47.
6. Lai Q, Pretagostini R, Poli L, et al. Delayed graft function decreases early and intermediate graft outcomes after expanded criteria donor kidney transplants. Transplant Proc 2009; 41: 1145-8.
7. Helfer MS, Pompeo JC, Costa ORS, Vicari AR, Ribeiro AR, Manfro RC. Longterm effects of delayed graft function duration on function and survival of deceased donor kidney transplants. J Bras Nefrol 2019; 41: 231-41.
8. Tapiawala SN, Tinckam KJ, Cardella CJ, et al. Delayed graft function and the risk for death with a functioning graft. J Am Soc Nephrol 2010; 21: 153-61.
9. Lim WH, McDonald SP, Russ GR, et al. Association between delayed graft function and graft loss in donation after cardiac death kidney transplants-a paired kidney registry analysis. Transplantation 2017 ; 101: 1139-43.
10. Melih KV, Boynuegri B, Mustafa C, Nilgun A. Incidence, risk factors,and outcomes of delayed graft function in deceased donor kidney transplantation. Transplant Proc 2019; 51: 1096-100.
11. Boom H, Mallat MJ, de Fijter JW, Zwinderman AH, Paul C. Delayed graft function influences renal function, but not survival. Kidney Int 2000; 58: 859-66.
12. Mannon RB. Delayed Graft Function: The AKI of Kidney Transplantation. Nephron 2018; 140: 94-8.
13. Port FK, Bragg-Gresham JL, Metzger RA, et al. Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. Transplantation 2002; 74: 1281–6.
14. Emiroğlu R, Yagmurdur MC, Karakayali F, et al. Role of donor age and acute rejection episodes on long-term graft survival in cadaveric kidney transplantations. Transplant Proc 2005; 37: 2954-6
15. Sert I, Colak H, Tugmen C, Dogan SM, Karaca C. The effect of cold ischemia time on delayed graft function and acute rejection in kidney transplantation. Saudi J Kidney Dis Transpl 2014; 25: 960-6.
16. Uysal E, Gurer OA, Yuzbasioglu MF, Guzel H, Ulutasdemir N, Dokur M. Evaluation of renal transplantations performed in the Transplantation Center at Sanko University Medical School. Transplant Proc 2015; 47: 1117-21.
17. Yazici B, Oral A, Gokalp C, Akgün A, Toz H, Hoscoskun C. A new quantitative index for baseline renal transplant scintigraphy with 99mTc-DTPA in evaluation of delayed graft function and prediction of 1-year graft function. Clin Nucl Med 2016; 41: 182-8.
18. Tugmen C, Sert I, Kebabcı E, et al. delayed graft function in kidney transplantation: risk factors and impact on early graft function. Prog Transplant 2016; 26: 172-7
19. Hamed MO, Chen Y, Pasea L, et al. Early graft loss after kidney transplantation: risk factors and consequences. Am J Transplant 2015; 15:1632-43.
20. Park WY, Choi MS, Kim YS, et al. Impact of acute kidney injury in expanded criteria deceased donors on post-transplant clinical outcomes: multicenter cohort study. BMC Nephrol 2019; 20: 39.
21. Kwon JA, Park H, Park SJ, et al. Factors of acute kidney injury donors affecting outcomes of kidney transplantation from deceased donors.Transplant Proc 2019; 51: 2575-81.
22. Foroutan F, Friesen EL, Clark KE, et al. Risk factors for 1-year graft loss after kidney transplantation: systematic review and meta-analysis. Clin J Am Soc Nephrol 2019; 14: 1642-50.
23. Renkens JJ, Rouflart MMJ, Christiaans MHL, van den Berg-Loonen EM , van Hooff JP, van Heurn LW. Outcome of nonheart-beating donor kidneys with prolonged delayed graft function after transplantation. Am J Transplant 2005; 5: 2704-9.
24. Lim WH, Johnson DW, Teixeira-Pinto A, Wong G. Association between duration of delayed graft function, acute rejection, and allograft outcome after deceased donor kidney transplantation. Transplantation 2019; 103: 412-9.

Case Report

HEALTH SCIENCES
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Severe hypokalemia and rhabdomyolysis caused by Conn syndrome

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ABSTRACT

Hypokalemia is a common electrolyte abnormality. Generally being asymptomatic, muscular fatigue, paresis and arrhythmia can be seen as the severity of hypokalemia increases. Severe rhabdomyolysis and neuromuscular findings can be seen in severe hypokalemia cases. Presence of hypokalemia can be a precursor of secondary hypertension in hypertensive patients, and also should bring hyperaldosteronism into consideration. Mild hypokalemia is usually seen in primary hyperaldosteronism. However, deficient potassium levels are also seen in some cases. We here presented a case of a hypertensive patient, who attended to the emergency department with findings of rhabdomyolysis and neuromuscular findings secondary to severe hypokalemia. The potassium level of our patient was 1.3 mmol, and it was one of the lowest potassium levels reported up to today.

Keywords: Conn sydrome, hypertension, hypokalemia

INTRODUCTION

Potassium is a major in-cell cation, and it is one of the most frequently seen electrolyte anomalies. Generally, alongside being asymptomatic, the patient may complain of a lack of strength, muscular pain. Patients with deep hypokalaemia might end up with paraplegia and rhabdomyolysis. Gastrointestinal loss, use of diuretic agents, primary or secondary hyperaldosteronism, hypomagnesemia, Liddle, Bartter and Gitelman syndromes are some of the main reasons of hypokalaemia (1). As hypokalaemia in hypertensive patients can relate to diuretic agents, it can also be related to hyperaldosteronism, which is one of the significant reasons for secondary hypertension. Rarely, hyperaldosteronism can be seen alongside with hypokalaemia and rhabdomyolysis secondary to urinary potassium loss. While evaluating patients, who are assessed regarding hypertension, the first disease which comes to mind on the presence of hypokalaemia should be primary hyperaldosteronism (PH). In these cases, the patient should be checked for plasma aldosterone and plasma renin activity, and plasma aldosterone/plasma renin activity (PA/PRA) ratio should be evaluated. PA/PRA (ng/dl/dl) <20 does not suggest PH. However, if the rate is higher than 30%, PH can be considered with 90% sensitivity and 91% specificity. If the rate is above 50%, the possibility of the diagnosis of PH is much higher (2,3). We here presented a case of a hypertensive patient, who attended to the emergency department with findings of rhabdomyolysis and neuromuscular findings due to severe hypokalemia.

CASE REPORT

Forty-eight years old female patient presented to the emergency department, with complaints of inability to walk, inability to lift her arms, diffuse myalgia and severe fatigue. The patient stated that especially fatigue and myalgia have worsened in the last 15 days, the myalgia got worse after working in high heels for an extended period the day before, also started to fall during walking and could not move her arms and legs. The patient also stated that she was under follow-up and using valsartan 320 mg 1x1 and bisoprolol 5 mg 1x1 secondary to hypertension for the last four years, and her blood pressure (BP) was still elevated, despite the medication. The patient did not have any additional history; familial history had shown that her mother also had hypertension. Physical examination findings of the patient were; BP was 160/90 mmHg, heart rate was 88 bpm.

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Diffuse muscular sensitivity and grade 1/5 muscle strength were noted in upper and lower extremities. On laboratory work-up results: potassium level was 1.3 mmol/L (3.5-5.5 mmol/L), sodium level was 141 mmol/L (136-145 mmol/L), magnesium level was 1.8 mg/dL (1.6-2.6), urea was 19 mg/dL (15-40 mg/dL), creatinine was 0.52 mg/dL (0.57-1.11 mg/dL), aspartat aminotransferase (AST) was 221 U/L (5-34 U/L), alanine aminotransferase (ALT) was 85 U/L (0-55 U/L), Ph:7.65, pCO_2:34.7 mmHg, pO_2:117 mmHg, HCO_3:40.4 mmol/L, creatine kinase (CK) was 14248 U/L (≤145 U/L)), 24 hour urine potassium was 98 mmol/24h (25-125 mmol/24h), TSH was 1.513 IU/mL (0.4-4.9 IU/ml), free T4 was 0.99 ng/dL (0.6-1 ng/dl), cortisol was 15.1 ug/dL (5-20 ug/dl). The patient had deep hypokalaemia, metabolic alkalosis, elevated AST, ALT and significantly elevated CK levels. The cause of neuromuscular symptoms was related to hypokalaemia and rhabdomyolysis secondary to hypokalaemia. The patient was started on fluid and 120 mmol/day potassium replacement treatment. Starting from the second day of treatment, potassium level was noted as 2.2 mmol/mL and neuromuscular complaints started to normalise. During this process, as combined hypokalaemia and HT, hyperaldosteronism and Liddle syndrome were considered, plasma aldosterone, plasma renin activity, urinary sodium and potassium levels were evaluated. Elevated urinary potassium and normal sodium levels were found. No significant finding, consistent with renal artery stenosis was noted on renal doppler USG. Abdominal MRI was planned, as the patient had a severe elevation of aldosterone (887 pg/mL), plasma renin activity (0.27 ng/mL), PA/PRA level was (328.5 ng/ml) pointed to the presence of an aldosterone synthesis related adrenal mass lesion. A well-circumscribed lesion, measuring 33x20 mm in size, which appeared homogeneous hyperintense on T1-Weighted sequences and heterogenous hyperintense appearance on T2-Weighted sequences. Located in the superior segment of the right adrenal gland, was noted on Abdominal MRI. The lesion showed contrast uptake on post-contrast slices, and no significant wash-out was seen in late phases. The current findings were primarily considered in favour of adenoma (**Figure**). The presence of hypokalaemia and HT combination, elevated plasma Aldosterone level, PR/PRA elevation and unilateral adrenal adenoma led to the diagnosis of Conn Syndrome. The potassium level of the patient was elevated up to 3.3 mmol/mL with replacement, and the CK levels returned to normal. Neuromuscular complaints recovered and the patient was discharged with spironolactone treatment at the dose of 100 mg. On the follow-up after one week the findings were noted as; K:3.4 mmol/mL, Blood pressure with only spironolactone: 125/80 mmHg. The patient had been referred to surgery secondary to unilateral adenoma, which causes aldosterone synthesis. Written informed consent was obtained from the patient.

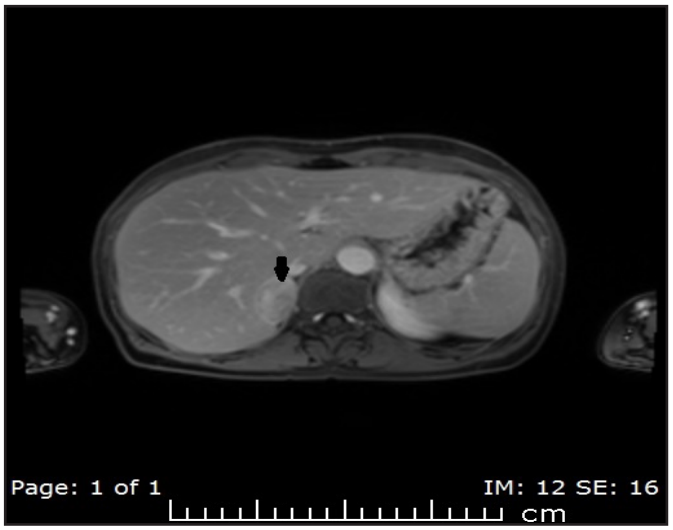

Figure. Contrast enhanced abdominal computerized tomography: arrow indicated surrenal adenoma.

DISCUSSION

Hypokalemia is one of the common findings of Conn syndrome. However, hypokalemia may not be present in all cases if present usually mild hypokalemia can be seen, rarely presents with severe hypokalemia (4). In the case of Yandle et al. (5) the patient's potassium level was 1.5 mmol/L but the patient was asymptomatic. Hypokalemia is a common finding in emergency departments and the main causes of hypokalemia are malnutrition and use of diuretics (6). But if hypertensive patients is presenting with hypokalemia other rare conditions should be considered.

Hypokalemic patients usually present with complaints of myalgia, and chronic hypokalaemia is often well tolerated, and patients may not have significant complaints. However, rhabdomyolysis risk increases when potassium levels drop below 2 mmol/mL (7). Our patient also had a significant increase of complaints within the last 15 days, and excessive work the day before had increased the severity of muscular damage and, the patient has presented to the Emergency department with primary secondary to neuromuscular symptoms. In two cases reported by Wen et al. (8) potassium levels were 1.38 and 1.98 mmol/ml. Patients were admitted with neuromuscular symptoms as in our case. Even though the elevation of potassium levels was expected due to rhabdomyolysis, potassium levels were noted at a deficient level as 1.3 mmol/ml. To the best of our knowledge this is one of the lowest potassium level reported up to today. This condition was considered as related to the potassium-exerting effect of aldosterone. Urinary potassium level was also high. The presence of combined HT, hypokalaemia and metabolic alkalosis brought hyperaldosteronism and Liddle Syndrome in mind. Due to this reason, plasma aldosterone and

plasma renin levels and urinary sodium levels were checked. Urinary sodium levels were within the normal range, but aldosterone levels were severely elevated. As the PA/PRA ratio was >50, it brought primary hyperaldosteronism into consideration. Because this level of PA/PRA indicates Conn syndrome (9). Also, the MRI findings, which shown unilateral adenoma, was a significant fact to support our diagnosis. Dramatical recovery was noted following fluid and potassium replacement and the patient, who presented in tetraplegic state started to walk without aid on the third day. CK levels returned to normal on the sixth day, and potassium level was brought up to 3.4 mmol/ml. On the background evaluation of the patients' old test results, the potassium level of the patient, when diagnosed with HT, was 3.3 mmol/mL. It was considered as a detail which was unnoticed during the evaluation of secondary HT. Especially the presence of hypokalaemia is a significant factor during the aetiology of hypertension, and it should bring Conn Syndrome into consideration. The patient started to be in a normotensive state with spironolactone at the dose of 100 mg 1x1, when not under control of the dual anti-hypertensive agent.

CONCLUSION

Hypokalaemia is an electrolyte abnormality which has fatal complications. Patients, who present to the emergency department with complaints of myasthenia, myalgia and neuromuscular symptoms should be primarily evaluated for this matter. The presence of hypokalemia should be considered after ruling out the factors such as vomiting, diarrhoea and use of diuretics in hypertensive patients.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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REFERENCES

1. Vilela LAP, Almeida MQ.Diagnosis and management of primary aldosteronism. Arch Endocrinol Metab 2017; 61: 305-12.
2. Morimoto R, Omata K, Ito S, Satoh F. Progress in the Management of Primary Aldosteronism. Am J Hypertens 2018 13; 31: 522-31.
3. Tun HN. Severe Hypokalemia with premature ventricular contraction. EC Cardiology 5.4 2018: 224-8.
4. Buffolo F, Monticone S, Burrello J, et al. Is Primary Aldosteronism Still Largely Unrecognized? Horm Metab Res 2017; 49: 908-14.
5. Yandle G, Vonderhaar DJ, Thayalakulasingam T, et al. Clinical case of the month: persistent hypertension in a young woman: a classic presentation of Conn's syndrome. J La State Med Soc 2016; 168: 23-6.
6. Marti G, Schwarz C, Leichtle AB, et al. Etiology and symptoms of severe hypokalemia in emergency department patients. Eur J Emerg Med 2014; 21: 46-51.
7. Williams TA, Reincke M. Management of endocrine disease: diagnosis and management of primary aldosteronism: the Endocrine Society guideline 2016 revisited. Eur J Endocrinol. 2018; 179: R19-R29.
8. Wen Z, Chuanwei L, Chunyu Z, Hui H. Rhabdomyolysis presenting with severe hypokalemia in hypertensive patients: a case series. BMC Res Notes 2013; 6: 155.
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