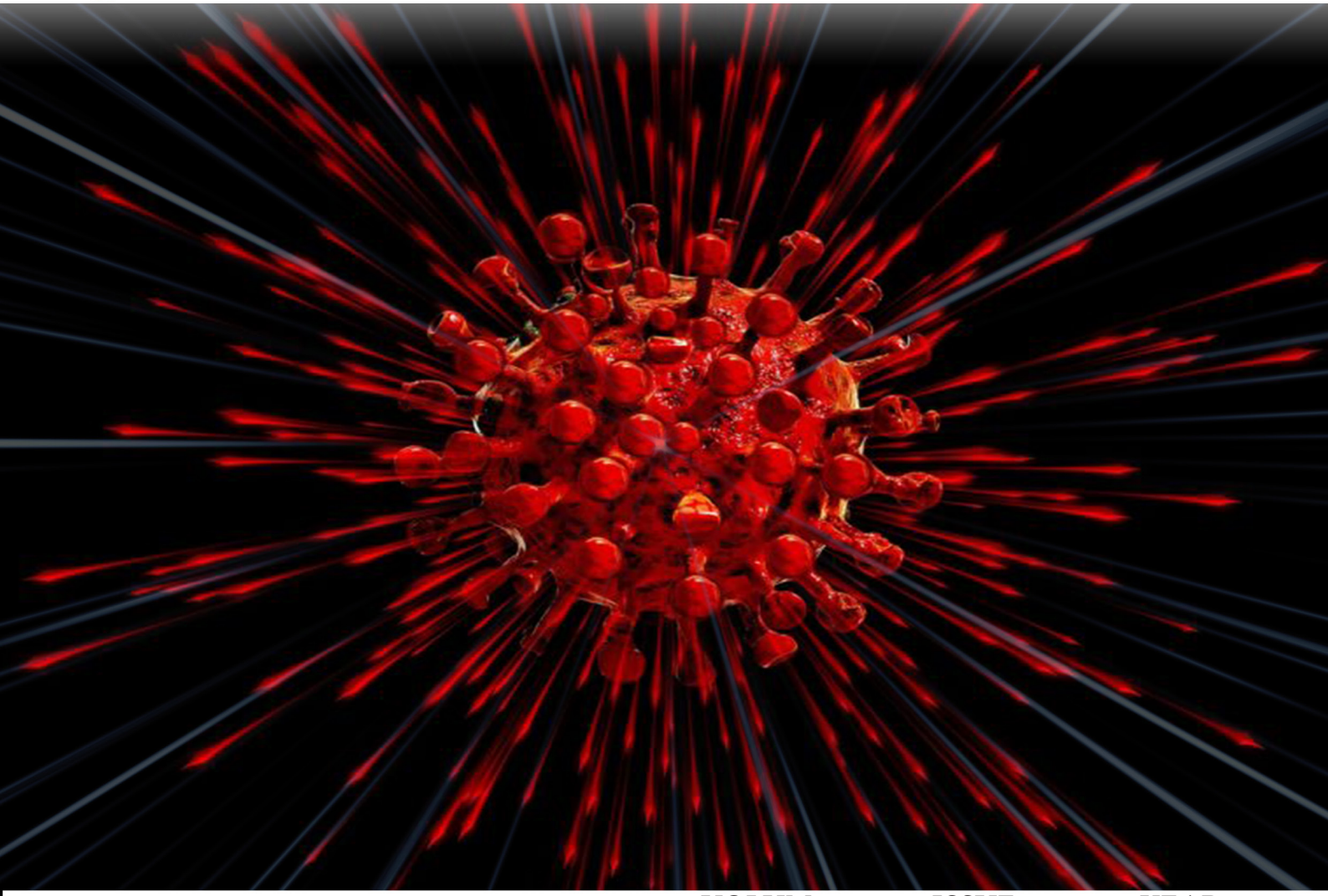
e-ISSN: 2718-0115

ACMJ

Anatolian Current Medical Journal



VOLUM: 3 ISSUE: 2 YEAR: 2021

PUBLICATION BOARD

FRANCHISE OWNER

MediHealth Academy Publishing
(***www.medihealthacademy.com***)

DESIGN

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EDITORIAL

Our dear readers,

We are proud to publish the second issue of our journal for 2021 with 19 articles. In this issue, there are 17 research articles and 2 case reports. We increase the scientific quality of our journal day by day. We have followed by a wider audience over time. Principally, we want to contribute to international literature at an increasing level and to increase the success bar of our journal by entering indexes such as PubMed, SCI and SCI-Expanded. I would like to thank all authors for submitting articles contributing to both domestic and international literature with their comprehensive scientific content for publication in our journal. We hope that this issue will be useful to our readers.

Sincerely yours.

Assoc. Prof. Dr. Alpaslan TANOGLU
Editor in Chief

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ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.826454

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Surgical nurses' knowledge levels about hemodynamic monitoring

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Cite this article as: Özkan E, Kulakaç N, Uzun Şahin C, Çilingir D. Surgical nurses' knowledge levels about hemodynamic monitoring. Anatolian Curr Med J 2021; 3(2); 85-92.

ABSTRACT

Aim: This study was carried out to determine surgical nurses' knowledge levels about hemodynamic monitoring.

Material and Method: The research was carried out in a descriptive design to determine the knowledge levels of surgical nurses related to hemodynamic monitoring. Nurses working in the surgical clinics of three hospitals in the Eastern Black Sea Region. 156 surgery nurses took part in the study. The data were collected through a questionnaire developed by the researchers. Percentage, mean, standard deviation, median, Kolmogorov-Smirnov test, t-test in independent groups, and variance analysis in multiple groups were used to evaluate the data in the research.

Results: The mean score of the nurses' knowledge about hemodynamic monitoring was 65.3±7.9. There was a significant difference between nurses' receiving education on monitoring, gender, marital status, education level and the mean scores of their knowledge about hemodynamic monitoring ($p<0.05$).

Conclusion: The study revealed that nurses had a lack of knowledge about hemodynamic monitoring, which was reflected in nursing care and practices. It is recommended that surgical nurses are provided detailed and regular training on hemodynamic monitoring methods and follow-up including nursing care.

Keywords: Surgical nurse, hemodynamic monitoring, invasive, non-invasive

INTRODUCTION

The term "hemodynamic" is defined as the branch of science that deals with blood circulation and the physical factors affecting it while monitoring refers to watching or following. In the field of health care, this concept indicates monitoring or following the vital functions of a patient (1,2).

The main purpose of monitoring including invasive and non-invasive methods is to advance the diagnosis, follow-up, and treatment. In this way, many subjective and numerical data such as vital signs, urinary flow, mechanical ventilation, blood gases, hematological and biochemical parameters, coagulation, intake and output follow-up, and physical examination findings can be monitored (3).

Hemodynamic monitoring is an important clinical decision that may be an indication for the intensive care admittance of high-risk surgical patients. It covers a wide range of procedures including monitoring of blood volume and blood circulation by placing an invasive catheter into the patient's vascular system, monitoring of hourly urine output, electrocardiography (ECG), laboratory examinations such as arterial blood gas monitoring, and hematocrit monitoring. Therefore, it provides a significant contribution to healthcare professionals to interpret patient outcomes and to ensure the necessary medical treatment and care (4,5).

Postoperative problems are important for surgical patients. Systematic application of hemodynamic monitoring before and after surgery will contribute positively to correct nursing interventions and will also facilitate the reduction of patient-specific problems (6). In maintaining nursing care after surgery, effective use of hemodynamic monitoring, when necessary, will help prevent complications in the cardiovascular system, respiratory system, fluid-electrolyte balance,

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Received: 16.11.2020 **Accepted:** 22.01.2021

and adequate renal perfusion that may develop in the patient. The ability of the nurse to apply and interpret hemodynamic monitoring skills correctly and effectively enables the care to be guided and helps make an effective decision about the health status of a patient (7).

Although there are studies on hemodynamic monitoring in the literature, fewer studies have been conducted with surgical nurses on the subject. For this reason, the study is thought to contribute to the knowledge, attitude, and practices of the surgical nurses related to hemodynamic monitoring.

MATERIAL AND METHOD

Type of the Study

The research was carried out in a descriptive design to determine the knowledge levels of surgical nurses related to hemodynamic monitoring.

The Universe and the Sample of the Research

The data were collected between 1 and 30 June 2019. The universe of the research consisted of all the nurses working in the surgical clinics of one public hospital and two research and training hospitals in the Eastern Black Sea Region. It was aimed to reach the entire universe without using a sampling method; however, twelve nurses who were not in the hospital (on sick leave, on leave) or refused to participate in the study were not included in the study, so the study was completed with 156 nurses who agreed to take part in the research and completed the data collection form.

Data Collection Tools and Data Collection

The data were collected by a questionnaire that prepared by the researchers the literature rewiev (9,10). The form consists of three sections and 48 questions. In the first section, there are six questions about the descriptive characteristics of nurses. The second section includes 26 questions about non-invasive monitoring, and the third section contains 16 questions about invasive monitoring. The questions regarding monitoring are responded as "right", "wrong" and "I don't know" and are evaluated as 2, 1, and 0 points respectively. The lowest and highest scores to be obtained from the information form on non-invasive hemodynamic monitoring and invasive hemodynamic monitoring are 0-52 and 0-32 respectively. Cronbach Alpha reliability coefficient of the questions was found 0.71. In evaluating the content validity of the prepared questions, expert opinions were received from the academic staff in the field of nursing. Necessary changes were made in the data collection form in line with the suggestions of the experts. After informing the surgical nurses about the purpose and duration of the research, the data were collected from the voluntary nurses through the face-to-face interview method. It took 10-15 minutes to complete the questionnaire.

Evaluation of the Data

SPSS 22.0 statistical package program was used for statistical analysis in the study. In the evaluation of the data, descriptive statistical methods such as percentage, mean, standard deviation, median, and Kolmogorov-Smirnov distribution test were used for the normal distribution. For the two-group comparison of quantitative variables, independent group t-test, and for the multiple groups, variance analysis was used. Statistical significance was accepted at the level of $p<0.05$.

Ethical Aspect of the Research

To conduct the study, permission numbered 05/2019 was obtained by the Scientific Research and Publication Ethics Committee of Gümüşhane University. Informed consent was received from the nurses in line with the principle of volunteering. The study was carried out in compliance with the ethical standards stated in the Helsinki Declaration.

RESULTS

The study showed that the mean age of the nurses was 32.1±1.2 (min=19, max=49), 76.3% were women. 54.5% were married, 66% were undergraduate graduates, the average working experience was 10.7±7.7 years, and 56.7% of the nurses received training on hemodynamic monitoring (**Table 1**).

Table 1. Descriptive characteristics of nurses (n = 156)

Descriptive characteristics	n	%
Gender		
Female	119	76.3
Male	37	23.7
Education level		
High school	16	10.3
Associate degree	37	23.7
Undergraduate degree	103	66.0
Marital status		
Married	85	54.5
Single	71	45.5
Status of receiving education about hemodynamic monitoring		
Yes	67	42.7
No	89	56.7
Working experience	10.9 ±7.7	
Age (year)	32.1±1.2	

The mean score of the nurses for non-invasive hemodynamic monitoring was found to be 43.7±4.6 (min=29, max=59). The nurses' knowledge level was determined to be high regarding the following items; ECG helps diagnose coronary insufficiency or myocardial infarction (97.4%), the patient's name, surname, date

and time must be written on the electrocardiogram obtained from ECG (97.4%), and monitoring is done to see the patient's response to treatment (96.2%). The number of correct answers given by nurses to the items of 'ECG provides information about the thickening of the heart muscle and enlargement of the heart cavities (%49.4), monitoring is done to determine the patient's organ reserves (48.1%), and ECG can be done in sitting position (34.6%)' were determined to be lower (**Table 2)**.

It was determined that the mean score of the nurses regarding invasive hemodynamic monitoring was 23.4±5.0 (min=9, max=41). Nurses had a high knowledge level regarding the questions such as 'Among the contraindications of the invasive arterial catheterization of nurses, regional infection, coagulation disorder and vasculature may develop (89.7%), sterile processing is not required for bladder catheterization, there is no need for a sterile procedure in bladder catheterization (84.6%), invasive catheterization is the most suitable method for blood pressure measurement of patients with unstable hemodynamics (82.7%), and the most effective way of urine monitoring is bladder catheterization (82.7%). However, the correct response rate of nurses to the following questions was found lower; in the catheter care used for central venous pressure, intravenous (IV) solution set buffers should be changed daily, and catheter entry dressing should be changed every 48-72 hours (67.9%), during central venous catheterization, air embolism and clot development should be monitored and in this case, the catheter should be washed with isotonic fluid (67.9%) and a separate urine bag must be used for each patient (66.7%) (**Table 3**).

Table 2. Responses and mean knowledge scores of the nurses to the questions regarding non-invasive hemodynamic monitoring (n=156)

Questions about non-invasive hemodynamic monitoring	Correct n %	Wrong n %	Don't know n %
1. Monitoring is done to collect data from the patient.	148 (94.9)	8 (5.1)	-
2. Monitoring is done to diagnose the patient.	88 (56.4)	64 (41.0)	4 (2.6)
3. Monitoring is done to determine the patient's organ reserves.	66 (42.3)	75 (48.1)	15 (9.6)
4. Monitoring is done to see the patient's response to treatment.	150 (96.2)	6 (3.8)	-
5. Monitoring is performed for the early identification of problems.	147 (94.2)	7 (4.5	2 (1.3)
6. ECG shows how the heart muscle contracts.	116 (74.4)	33 (21.2)	7 (4.5)
7. ECG gives information about the rhythm and conduction disorders of the heart.	147 (94.2)	9 (5.8)	-
8. ECG helps diagnose coronary insufficiency or myocardial infarction.	152 (97.4)	3 (1.9)	1 (0.6)
9. ECG provides information about the thickening of the heart muscle and enlargement of the heart cavities.	57 (36.5)	77 (49.4)	22 (14.1)
10. ECG gives information about the functions of an electronic pacemaker.	127 (81.4)	14 (9.0)	15 (9.6)
11. ECG gives information about the effects of some heart medications and electrolyte imbalance.	127 (81.4)	20 (12.8)	9 (5.8)
12. ECG gives information about the effects of non-cardiac diseases on the heart.	80 (51.3)	46 (29.5)	30 (19.2)
13. ECG can be done in sitting position.	94 (60.3)	54 (34.6)	8 (5.1)
14. Electrodes should not be located on diaphoretic skin.	146 (93.6)	10 (6.4)	-
15. Metal objects on the patient do not need to be removed.	104 (66.7)	52 (33.3)	-
16. A thin layer of electrode gel should be applied to the body surface where the electrode will be located.	143 (91.6)	13 (8.3)	-
17. ECG devices should be calibrated.	142 (91.0)	10 (6.4)	4 (2.6)
18. After the ECG device is switched off, the chest electrodes and then the limb electrodes must be removed.	98 (62.8)	27 (17.3)	31 (19.9)
19. The patient's name, surname, date, and time must be written on the electrocardiogram obtained from ECG.	152 (97.4)	3 (1.9)	1 (0.6)
20. Non-invasive arterial blood pressure is a quantitative measurement used to determine cardiovascular status.	133 (85.3)	12 (7.7)	11 (7.1)
21. Mismatches between the size of the cuff used to measure blood pressure and patient arm circumference affect the results.	146 (93.6)	9 (5.8)	1 (0.6)
22. Non-invasive arterial blood pressure is not a reliable method in critically ill patients with a poor general condition.	96 (61.5)	46 (29.5)	149.0
23. A pulse oximeter gives information about arterial oxygen value.	100 (64.1)	51 (32.7)	5 (3.2)
24. The pulse oximeter has limited reliability if there is a nutritional deficiency in the area measured in severe hypoxia.	138 (88.5)	15 (9.6)	3 (1.9)
25. With the capnograph, the level of carbon dioxide (CO2) in expiratory air can be measured by the non-invasive method.	95 (60.9)	15 (9.6)	46 (29.5)
26. Capnograph can evaluate the effectiveness of mechanical ventilation support.	102 (65.4)	3 (1.9)	51 (32.7)

It was found that the total mean score of the nurses regarding hemodynamic monitoring was 65.3±7.9 (min=39, max=82). The total knowledge scores of hemodynamic monitoring were significantly higher in male nurses and high school graduate nurses (p<0.05). Compared to married nurses, the knowledge scores of single nurses regarding invasive hemodynamic monitoring were also significantly higher. Besides, nurses who received education on hemodynamic monitoring were found to have significantly higher knowledge scores on non-invasive hemodynamic monitoring than those who did not (p<0.05) (**Table 4**).

Table 3. Responses of the nurses to the questions regarding invasive hemodynamic monitoring and the mean scores of their knowledge (n=156)

Questions on invasive hemodynamic monitoring	Correct n %	Wrong n %	Don't know n %
1. Invasive catheterization is the most suitable method for blood pressure measurement of patients with unstable hemodynamics.	129 (82.7)	15 (9.6)	12 (7.7)
2. The first method to be preferred for blood pressure measurement in a stable patient is invasive arterial monitoring.	102 (65.4)	50 (32.1)	4 (2.6)
3. The nurse is not at the forefront to follow the invasive arterial catheterization procedure.	100 (64.1)	43 (27.6)	13 (8.3)
4. It is the responsibility of the nurse to implement the invasive arterial catheterization procedure.	112 (71.8)	36 (23.1)	8 (5.1)t
5. It is the responsibility of the nurse to monitor the invasive arterial catheterization.	127 (81.4)	18 (11.5)	11 (7.1)
6. Contraindications for invasive arterial catheterization may include regional infection, coagulation disorder, and vasculitis.	140 (89.7)	6 (3.8)	10 (6.4)
7. Central venous pressure measures blood pressure in the thoracic vein at the end of the right atrium of the heart.	112 (71.8)	11 (7.1)	33 (21.2)
8. The central venous pressure normal value range is 8-12 mmHg.	100 (64.1)	27 (17.3)	29 (18.6)
9. The patient does not have to lie completely on the back during central venous pressure measurement.	87 (55.8)	48 (30.8)	21 (13.4)
10. In the catheter care used for central venous pressure, IV solution set buffers should be changed daily, and catheter entry dressing should be changed every 48-72 hours.	33 (21.2)	106 (67.9)	17 (10.9)
11. During central venous catheterization, air embolism and clot development should be monitored, and in this case, the catheter should be washed with isotonic fluid.	35 (22.4)	106 (67.9)	15 (9.6)
12. The most effective way of urine monitoring is bladder catheterization.	129 (82.7)	7 (4.5)	20 (12.8)
13. Sterile processing is not required for bladder catheterization.	132 (84.6)	21 (13.5)	3 (1.9)
14. Urine catheter should be regularly changed once a week.	101 (64.7)	44 (28.2)	11 (7.1)
15. A separate urine bag must be used for each patient.	45 (28.8)	104 (66.7)	7 (4.5)
16. Catheter and urine bags should be kept at the bladder level.	116 (74.4)	34 (21.8)	6 (3.8)

Table 4. Comparison of the knowledge mean scores of hemodynamic monitoring according to the descriptive characteristics of nurses (n=156)

	Knowledge mean scores		
Descriptive characteristics	**Non-invasive monitoring Mean±SD**	**Invasive monitoring Mean±SD**	**Total Mean±SD**
Gender			
Female	43.16±4.34	22.90±5.33	64.21±7.72
Male	45.56±4.98	25.27±3.34	69.08±7.45
	t=-2.83	t=-2.54	t=-3.37
	p=0.005	p=0.012	p=0.001
Education level			
High school	47.06±6.02	27.25±3.99	71.25±8.69
Associate degree	43.21±3.63	24.27±5.49	65.78±7.67
Undergraduate degree	43.40±4.49	22.59±4.70	64.31±7.51
	F=4.912	F=7.081	F=5.717
	p=0.009	p=0.001	p=0.004
Marital status			
Single	44.33±5.43	24.42±4.97	66.74±8.61
Married	43.23±3.73	22.67±4.95	64.22±7.12
	t=1.49	t=2.19	t=2.00
	p=0.137	p=0.030	p=0.047
The status of receiving education regarding hemodynamic monitoring			
Yes	44.86±8.6	23.22±5.41	64.41±6.68
No	44.39±5.17	23.65±4.73	66.08±8.69
	t=-2.073	t=-0.525	t=-1.30
	p=0.040	p=0.600	p=0.192

DISCUSSION

This research was conducted in a descriptive design to determine the knowledge levels of surgical nurses regarding hemodynamic monitoring. In this section, the results of the research are discussed with the literature findings.

Monitoring refers to the process of measuring and recording physiological parameters by use a modern catheter and electronic catheterization devices. The basic principle is the conversion of biophysical events in certain parts of the body into electrical signals, making them visible, measurable, and even recorded as a graphic. Clinical monitoring, starting with simple systemic blood pressure monitoring, varies considerably with hardware support in the development of permanent catheters and ensuring the accuracy of the data during the cardiovascular evaluation process (1,10). The term hemodynamics is defined as the branch of science that deals with blood circulation and the influencing physical factors, and monitoring is a technology that is used frequently in critical care, allowing rapid assessment and intervention, and continuous monitoring of the patient's general condition (11).

To ensure the hemodynamic stability of the patient, monitoring techniques and correct follow-up of patients are among the important issues that must be known by healthcare professionals (12). Conducted a study in an intensive care unit and noted that 43.3% of the nurses were in the 26-30 age group, 49.4% were associate degree graduates, and 38.9% had 0-5 years of working experience (13). In a study involving nurses working in the emergency and intensive care unit, it was stated that 64.6% of the nurses were between 23 and 32 years old, 52.1% of them were undergraduate graduates, and 50% had 0-4 years of working experience (14). In our study, the mean age of nurses was 32.1±1.2, 54.5% were married, 66% were undergraduate graduates, and the average working experience was 10.7±7.7 years. When our study was compared with the literature, there were some differences in the results obtained. It is thought that the differences depending on the mean age and working experience may be due to the employment of nurses in the emergency and intensive care unit in the first years of the profession, and the differences in the level of education are due to an increase in the number of undergraduates over the years.

The monitoring techniques that applied without disrupting the skin integrity and entering the vascular structures are called non-invasive methods. Electrocardiogram (ECG), non-invasive blood pressure, body temperature, respiratory rate, pulse oxymeter (SPO2), end-tidal carbon dioxide (EtCO2) are among the non-invasive techniques used in patient follow-up (15).

Due to coronary artery diseases that are likely to be encountered today, ECG monitoring and evaluation should be performed in most services, nurses working in all units should be able to recognize ECG findings in emergency heart diseases and evaluate appropriate treatment approaches. Doğan et al. (16) (2012) found that 80% of the nurses incorrectly determined the location of the chest derivations in the electrocardiography monitoring. In our study, 36.5% of the nurses gave the correct answer in response to the item of ECG provides information about the thickening of the heart muscle and enlargement of the heart cavities, 14% did not know the relationship between them and 34.6% stated that ECG can be done in sitting position. Another study reported that the majority of the nurses working in intensive care units and emergency departments did not receive training on ECG and ECG evaluations and interventions of trained nurses were not sufficient, but the same study also argued that the ECG/monitor should only be evaluated by the physician (17). Çelik et al. (14) stated that 58.3% of nurses did not participate in the in-service training. In the study conducted by Doğu et al. (18) it was emphasized that nurses working in clinics where monitoring was followed and cardiac rhythm problems were frequently encountered had insufficient information about ECG findings and interventions. Similar to the literature, in this study, nurses also had a lack of information in the questions regarding the ECG's determination of cardiac problems and the correct method of monitoring.

Organ perfusion is expressed as a sufficient blood flow that is required for the delivery of oxygen and substrates and for the excretion of metabolic waste with the formation of a high perfusion pressure in all organs and cells. Therefore, to provide tissue perfusion, maintaining body organ perfusion in intensive care conditions and perioperative care is a common goal (17). Among the methods used for the protection of organ perfusion, the priority is blood pressure measurement (19). Measuring the blood pressure is the most important diagnostic method used in the diagnosis of hypertension and hypotension. It is stated that the way to avoid misdiagnosis and improper treatment is to measure the blood pressure correctly (20). In a study, it was determined that the majority of nurses received information about the use of medical devices from other healthcare workers (17). In our study, it was determined that 42% of the nurses gave the correct answer to the question asked about the function of monitoring in the determination of the patient's organ reserves. Additionally, a lack of information about the materials used in the monitoring and the effect of the monitoring on the organ reserves was observed in nurses, and this situation is thought to affect the correct follow-up and care quality.

Current resuscitation guidelines suggest waveform capnography as an indication of indirect perfusion during cardiopulmonary resuscitation (CPR). ETCO2 is the partial carbon dioxide pressure at the end of expiratory and measured by a capnograph device. Parameters provided by respiratory gas monitoring, such as respiratory gas flow, are required to monitor the saturation level of the patient (21,22). In a study that retrospectively investigated the differences in arterial-end-tidal carbon dioxide in 799 pediatric patients undergoing general anesthesia with ventilation, it was determined that the decrease in PaCO2 was strongly related to the decrease in the PaCO2-ETCO2 difference (23). 29.5% and 32.7% of the nurses were found to have no knowledge about the function of the capnograph device and its effectiveness during the mechanical ventilator respectively. This situation suggests that nurses had a lack of knowledge of the evaluation of blood gas and follow-up for the respiratory system. As the result of the study, nurses' mean knowledge score for non-invasive hemodynamic monitoring was high, but there was a lack of knowledge in theory and practice.

Thanks to the cannula placed in an artery in the measurement of invasive arterial blood pressure, quick and instant information about arterial blood pressure are obtained. It is stated in the American Heart Society Guideline that inappropriate cuff sizes can cause serious deviations in blood pressure and result in inappropriate treatments. Although invasive monitoring is accepted as the reference method, non-invasive monitoring is advantageous due to fewer complications in terms of accuracy, precision, and rapid response change, so in critical situations, invasive methods should be preferred in patients (15,24,25). Similar to the literature, in our study, 82.7% of the nurses stated that invasive arterial blood pressure measurement is a reliable method in critically ill patients with a poor general condition. It was seen that there was a significant difference between the education level of the nurses and the knowledge scores of invasive monitoring and that there was no significant difference between the knowledge scores of invasive monitoring for the nurses who were trained for monitoring techniques and who were not.

In the infections developed due to catheters, the length of hospital stay of the patient is extended by an average of seven days, and the cost increase is reported to be 34.508-56.000 dollars (26). The UK National Institute for Health and Care Excellence (NICE) developed guidelines for the infection prevention and control in 2014, and according to this guideline the permanent catheter should be connected to the sterile urine drainage system and should not be separated from the closed drainage system unless necessary, and additionally, a separate drain pan should be used for each patient (27,28). In a study, it was pointed out that there is a 3-8% incidence of bacteriuria per day after bladder catheterization in hospitals (29). In another study, it was found that intensive care nurses had insufficient knowledge about the use of urine bags, changing urine bags, and using a separate drain pan for each patient (28). In the study of Köse et al. (30) found 26.4% of the nurses replied the question about replacing the bladder every week as 'correct', and 14.1% replied as 'I don't know'. In our study, the knowledge level of nurses was found high about the most effective way of urine monitoring which is bladder catheterization (82.7%), however, 64.7% expressed that the urinary catheter should be regularly changed once a week. Similar to the literature, in our study, nurses had a lack of knowledge related to bladder catheterization and care. It is thought that this situation may affect the development of an infection as a result of ongoing wrong practices due to a lack of information. It is thought nurses do not follow in-service training and evidence-based practices.

Central venous catheters (CVC) are used for different indications in hospitalized patients. Especially long term central venous catheters have an important place in the support treatment of cancer patients. It is a process of inserting a catheter with various features into a vein directly going to the heart. Although they have many benefits, their widespread use in recent years has also increased the incidence of some complications. The two most common major complications are indicated as infection and thrombosis, so it is recommended in the literature that attention should be paid not to contaminate the catheter inlet area during sponge change (31-34). In an observational study, it was seen that the nurses either did not clean or do the wrong application of hand hygiene, three-way tap cleaning with a disinfectant containing alcohol, treatment after drying of alcohol and washing the lumen after treatment (35). In our study, the item regarding the possibility of CVC infection is 'In the catheter care used for central venous pressure, IV solution set buffers should be changed daily and catheter entry dressing should be changed every 48-72 hours' and 67.9% of the nurses replied it as 'wrong', and 17.9% of them replied as 'I don't know'. Besides, 67.9% of the nurses gave the wrong answer to the item of 'During central venous catheterization, air embolism and clot development should be monitored and in this case, the catheter should be washed with isotonic fluid'. Similar to the literature, the nurses in our study had a lack of knowledge on CVC care and its possible complications.

CONCLUSION

The review of available literature revealed that the studies measuring the knowledge levels of nurses about hemodynamic monitoring have been infrequently conducted. Therefore, we think that our study is one of the unique studies performed to measure the knowledge level of surgical nurses on hemodynamic monitoring. It is thought to help fill the gap in the related literature. Hemodynamic monitoring is a guideline used to provide cell, tissue, and organ perfusion. Nurses, the practitioners of these guides, should have the correct information to ensure patient follow-up. As a result of the research, it was concluded that the nurses had a lack of knowledge about hemodynamic monitoring, the purpose of ECG and capnography, non-invasive hemodynamic monitoring, indication, central venous catheter care and its complications, urinary catheterization, and nursing care. In line with these results, it is recommended to give nurses working in surgical and intensive care clinics detailed and regular training on hemodynamic monitoring methods, nursing follow-up and care, and to evaluate the reflection of training on practice.

ETHICAL DECLARATIONS

Ethics Committee Approval: To conduct the study, permission numbered 05/2019 was obtained by the Scientific Resaerch and Publications Ethics Committee of Gümüşhane University.

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.

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.

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.835572

Anatolian Curr Med J 2021; 3(2); 93-103

Evaluation of spleen volume in thoracic computed tomography in patients with COVID-19 pneumonia

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Cite this article as: Samancı C, Saylan B, Gülsen G, Gülsen G, Yeşildal M, Çamurcuoğlu E, Ustabaşıoğlu FE. Evaluation of spleen volume in thoracic computed tomography in patients with COVID-19 pneumonia. Anatolian Curr Med J 2021; 3(2); 93-103.

ABSTRACT

Objectives: There is not enough data on the effect of COVID-19 on spleen volume in patients with COVID-19. Our aim was to compare the spleen volume of the COVID-19 patients with the control group.

Material and Method: 214 Patients (121 men, 93 women) who have a diagnosis of COVID-19 who have thorax CT were included in the study. In the patient group, there was evidence of viral pneumonia on thoracic CT or PCR was positive, all of them were patients who received treatment for Covid. The control group consisted of 185 patients (106 men, 79 women). Interobserver agreement was calculated. Analysis of the receiver operating characteristic (ROC) curve was used to identify a spleen volume cutoff value at which the accuracy for COVID-19 diagnosis was maximised.

Results: The mean spleen volume of the patient group was found to be 260 (range, 96.3-565, SD: 82.5) which was statistically significantly higher than the control group which was 220 (range, 125.9-331.9, SD: 34.5) ($p<0.05$). Excellent agreement was found between two blind observers and between intraobserver spleen volume measurements. In our study, the spleen volume for the diagnosis of COVID-19 pneumonia was 208.4 (AUC 0.639; 95% CI 0.584-0.695), sensitivity and specificity were 69.6% and 66.7%, respectively.

Conclusions: Quantitative evaluation of spleen volume can give an idea about the Covid diagnosis. Spleen volume is higher in Covid group than control group.

Keywords: Coronavirus disease, COVID-19, computed tomography, splenomegaly

INTRODUCTION

Novel coronavirus disease 2019 (COVID-19) is an infectious disease that first appeared in Wuhan province, People's Republic of China (1). In the following process, this disease spread all over the world and was declared as a pandemic by the World Health Organization (WHO) (2). Although the gold standard for diagnosis is the real-time reverse transcription polymerase chain reaction (RT-PCR) test, thorax computed tomography (CT) examination stands out as a very important modality, especially in patients with clinical symptoms and negative results of the test (3). The spleen is the largest organ of the reticuloendothelial system. Increased spleen size (splenomegaly) is an important clinical finding especially for liver diseases and various diseases such as immune system, hematopoietic system, portal hypertension, splenic vein thrombosis and lymphoma. Therefore, it seems necessary to properly evaluate the size of the spleen, both in order to initiate a diagnostic process and to make appropriate treatment decisions and to follow the treatment response in certain cases (4,5). Radiological imaging methods are widely used in the evaluation of spleen volume (6-9). In this study, it was aimed to measure the spleen size in thoracic CT of patients who were examined with non-contrast thorax CT with suspected COVID-19 and taking Covid treatment, to calculate the spleen volume and to evaluate the relationship between spleen volume and COVID-19.

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Received: 03.12.2020 **Accepted:** 14.01.2021

MATERIAL AND METHOD

Patient Population

Our study was approved by the Ümraniye Training and Research Hospital Ethics Committee (protocol number: B.10.1.TKH.4.34.H.GP.0.01). Patients who were examined with non-contrast thorax CT due to the suspicion of COVID-19 at the Haydarpaşa Sultan Abdulhamidhan Training and Research Hospital Radiology Department between April 4 and May 26 were retrospectively screened. Of the 360 patients found, 214 with radiological findings of infection or positive PCR were included in the study. 145 patients were excluded from the study. Of these 145 patients removed, 11 were not eligible for evaluation due to low image quality and 132 because the CT sections passing through the upper abdomen did not completely contain the spleen. Two patients were not included in the study due to their history of splenectomy. The control group consisted of 185 patients. All of them were patients who underwent thoracic CT for other reasons other than infection in 2019. In the patient group, there was evidence of viral pneumonia on thoracic CT or PCR was positive, all of them were patients who received treatment for Covid.

Technical Data

All patients were imaged in the supine position on 320 detector CT (Aquilion-ONE, Toshiba Medical Systems, Otawara, Japan). All images were obtained at 5 mm slice thickness in the lung window in the standard dose protocol. Standard protocol (120 kVp, auto-mA — maximal 350 mA) was used for thoracic CT scans. CT images were acquired at the end of the inspirium for a single breath-hold period. 1.25 mm collimation, 400 milliseconds (msec) rotation, 1.35 pitch, 120 kV in X-ray tube and 400–480 milliamper/second (mAs), section thickness; 1.25 mm and reconstruction interval; Parameters of 2.5 mm were used. Field of view (FOV) was adjusted according to the size of the patient and a 512x512 matrix was used.

Evaluation of Images

Spleen index measurements in thoracic CT of the patients included in the study were made by two radiologists with 8 years and 9 years of professional experience. Both radiologists measured the spleen size unaware of each other's results. After both radiologists made the measurements separately, the 1st radiologist made all measurements again 15 days later. Measurements were made using picture archiving and communication system (PACS).

Spleen Volume Calculation

The methodology in the study by Kucybała et al. (10) was used to calculate the spleen volume. First of all in axial section (**Figure 1a**), maximal length (L)—the longest dimension between poles of the spleen, the thickness (T) at the level of the hilum was obtained by measuring the distance between the inner and outer contours of the spleen. After that, the maximum height (H) of the spleen was measured by measuring the distance between the upper and lower pole of the spleen in coronal reformatted sections (**Figure 1b**). Spleen volume was calculated using the formula of "30 + 0.58 (LxTxH)" and the range of 110-340 mL was accepted as the normal range, while the value above 340 ml was evaluated as splenomegaly (10) (**Figure 2**).

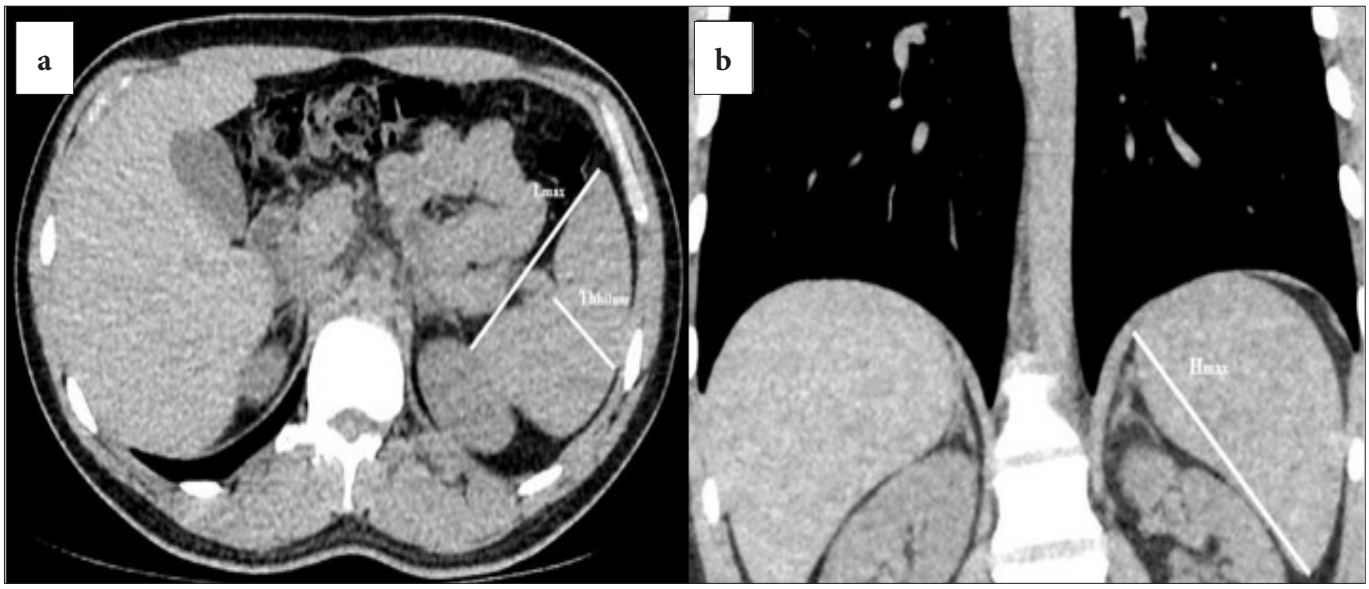

Figure 1. The method for calculating spleen volume on CT. First of all in axial section **(a)**, maximal length (L)—the longest dimension between poles of the spleen, the thickness (T) at the level of the hilum was obtained by measuring the distance between the inner and outer contours of the spleen. After that, the maximum height (H) of the spleen was measured by measuring the distance between the upper and lower pole of the spleen in coronal reformatted sections **(b)**.

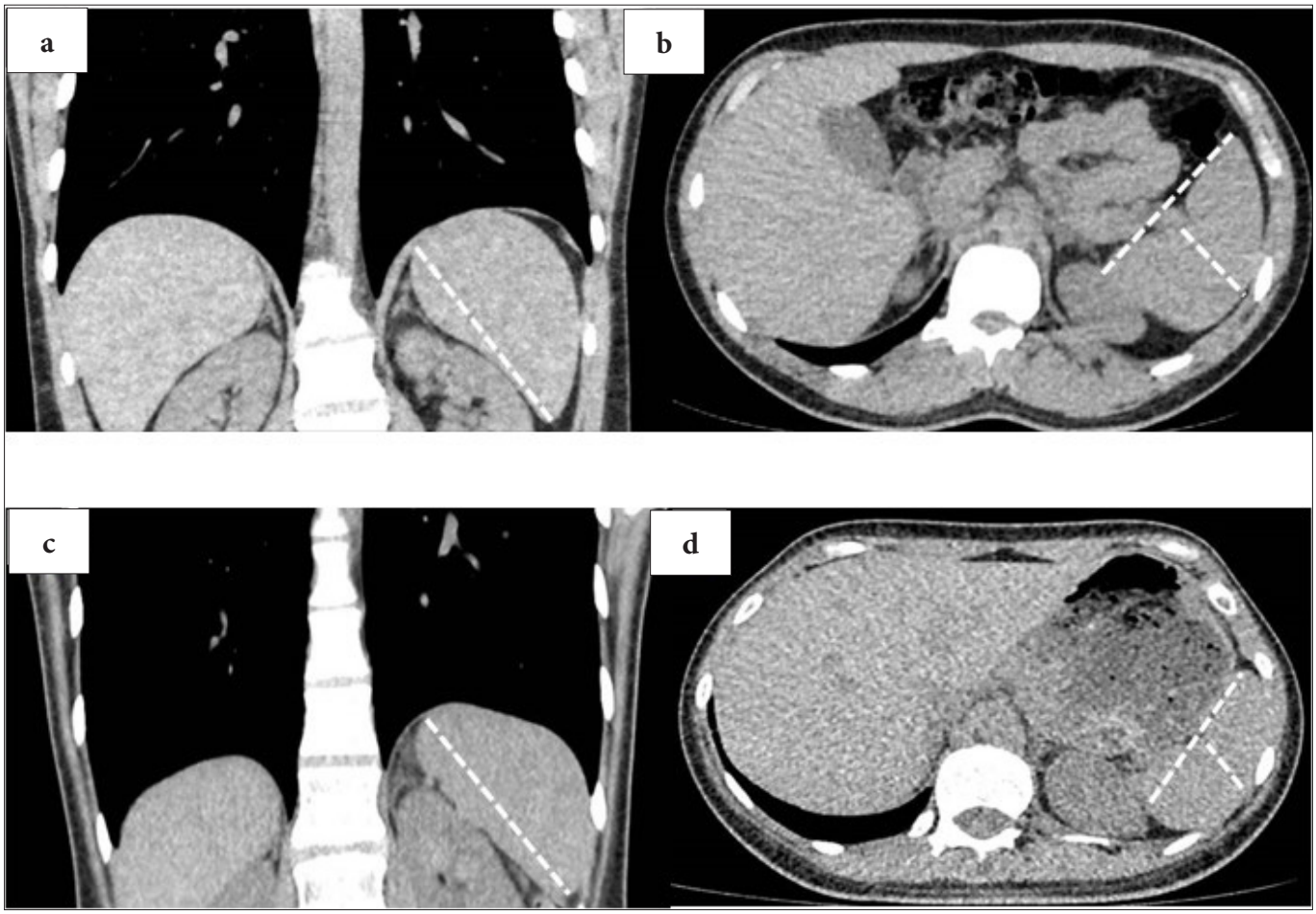

Figure 2. Spleen size in Covid-positive patient Hmax: 123mm Lmax: 98mm Th: 50mm, Volum: 349mm3 **(a-b)**, covid negative control group Hmax: 111mm Lmax: 94mm Th: 36mm Volum 218mm3 **(c-d)** in CT examination.

Statistical Analysis

Statistical Package for Social Science (SPSS, version 20.0) package program was used for statistical data analysis while evaluating the findings obtained in the study. Descriptive statistical methods were used while evaluating the study data. The results were evaluated at the 95% confidence interval and the significance level at $p<0.05$. The data were evaluated using the Kolmogorov-Smirnov test, which showed a normal distribution. Comparison of the control group and the patient group by gender was calculated using the Chi-square test, and the comparison of BMI and spleen volume was calculated using the Mann Whitney U test. In the measurements, the intraclass correlation coefficient (ICC) was used to show inter-observer and intra-observer agreement. A ICC value greater than 0.80 indicates a perfect agreement. Correlations between variables were evaluated using the Pearson correlation coefficient.

RESULTS

Two hundred and fourteen Covid patients (121 men, 93 women) and 185 controls (106 men, 79 women) were included in this study. The mean age was 50.6 years (range, 18-86 years) for the patient group and 52.4 years (range, 21-79) for the control group. Body mass index was calculated as 26.8 (range, 20-30) in the patient group and 26.6 (range, 19.9-30) in the control group. In the Mann Whitney U test, no difference was found between age and BMI values, which are variables that can affect spleen size in the patient group and the control group. The mean spleen volume of the patient group was 260 (range, 96.3-565, SD: 82.5), and the mean spleen volume of the control group was 220 (range, 125.9-331.9, SD: 34.5). Comparing the two groups with the Mann Whitney U test, the mean of the patient group was found to be statistically significantly higher than the control group ($p<0.05$) (**Table 1**). Interobserver variability results are shown in (**Table 2**). Excellent agreement was found between two blind observers and between intraobserver spleen volume measurements. In our study, spleen volume for diagnosis of COVID-19 pneumonia was 208.4 (AUC 0.639; 95% CI 0.584-0.695), sensitivity and specificity were 69.6% and 66.7%, respectively shows the ROC curve plotted for splenic volume values (**Figure 2**).

Table 1. Mean spleen volumes for Covid patients and the control group

	Covid patients (n=214)	Control Group (n =185)	P value
Spleen volume (mean±SD)	260±82.5	220±34.5	<0.05*

*Statistical comparison between groups with Mann Whitney U test

Table 2. Interobserver variability for spleen volume measurements

	Observer 1	Observer 2	ICC
	(mean±SD)	(mean±SD)	intraclass correlation coefficient
Spleen volume (n =399)	241.58±67.7	241.76±67.1	0.993 (0.992-0.994)

ICC: Intraclass Correlation Coefficients; SD: standard deviation

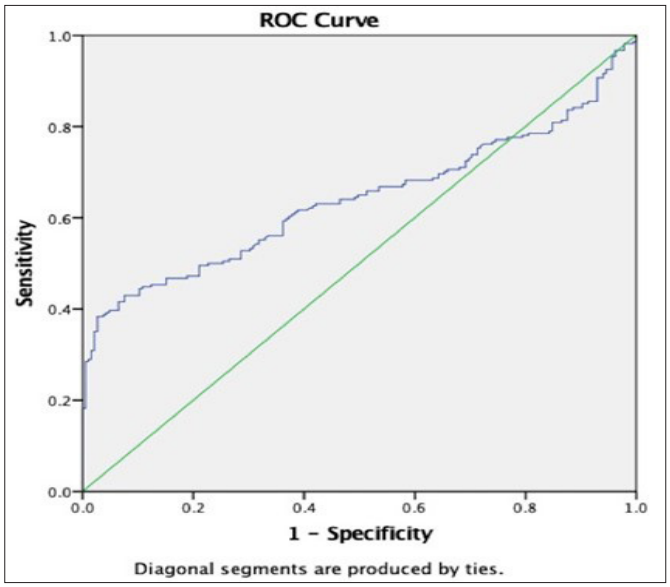

Figure 3. ROC curve for COVID-19 pneumonia diagnosis based on spleen volumes

DISCUSSION

The clinical features of COVID-19 range from asymptomatic to acute respiratory distress syndrome and multi-organ dysfunction. Common clinical features include fever (but not all), cough, sore throat, headache, fatigue, headache, myalgia, and shortness of breath. Conjunctivitis has also been described. Therefore, it cannot be distinguished from other respiratory infections. Sometimes at the end of the first week, the disease can progress to pneumonia, respiratory failure and death. The disease affects many systems (11,12). When we look at the blood tests, the white cell count is usually normal or low. There may be lymphopenia; Lymphocyte count less than 1000 has been associated with severe disease. The platelet count is usually normal or slightly low (13). The spleen may be one of the organs directly attacked by the virus in some patients who die from COVID-19. T and B lymphocytes in the spleen are reduced to varying degrees, lymphoid follicles are reduced, and the number of NK cells does not change significantly. Pathological changes of the spleen may be related to the direct attack of the virus and the immune system attacking its own tissues. The literature shows that although other imaging techniques such as ultrasonography (14,15) or magnetic resonance imaging (MRI) can be used, CT detects the varying splenic volume with the highest sensitivity and specificity (16). Additionally, a number of studies have demonstrated the significant accuracy of CT in the evaluation of the spleen in both pediatric and adult populations (17,18). We also used CT in our study. Because of the suspicion of Covid pneumonia thoracic CT was already performed, an additional scan was not performed for spleen so no additional dose was given. In our study, we showed that the spleen volume increased statistically significantly in patients diagnosed with Covid, but the average did not exceed the limit of splenomegaly. Xu et al. (13) studied the pathological changes of the spleen in post-mortem COVID-19 patients and analyzed the relationship between the weakened immune system and splenic lesions. They showed that the cell composition of the spleen was decreased in histopathological examinations. Since the Covid pandemic is very new, there is not enough data in the literature on the relationship between Covid infection and spleen volume. While calculating spleen volume, agreement between observers was excellent which shows that the volume measurements based on CT is highly reproducible.

There were some limitations in our study. Although patients with known infections, hematological diseases, infiltrative diseases, and diseases of the spleen that may enlarge the spleen were excluded from the study, patients were not tested for these diseases. Therefore, other reasons that may cause splenomegaly may still be in the study. Another limitation was the small number of patients.

It would be useful to re-evaluate the spleen volumes after a certain period of time in order to determine the change in spleen volume over time. Randomized controlled studies with larger patient groups are needed to demonstrate the effect of infection on splenic volume in COVID-19 patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The research was approved by Ümraniye Training and Research Hospital Ethics Committee (protocol number: B.10.1.TKH.4.34.H.GP.0.01).

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.

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.839213

Anatolian Curr Med J 2021; 3(2); 104-108

Monocyte/HDL ratio in women with polycystic ovary syndrome and healthy controls

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Cite this article as: Gürbüz T, Tanrıdan Okçu N, Dokuzeylül Güngör N. Monocyte/HDL ratio in women with polycystic ovary syndrome and healthy controls. Anatolian Curr Med J 2021; 3(2); 104-108.

ABSTRACT

Aim: To examine and compare various variables, especially monocyte/high-density lipoprotein (HDL) ratio (MHR), in women with polycystic ovary syndrome (PCOS) and healthy controls.

Material and Method: Data of patients who applied to Adana City Research and Training Hospital, Gynecology and Obstetrics Outpatient Clinic were analyzed retrospectively from the hospital database. The records of a total of 259 cases, including 194 with PCOS and 65 without PCOS who had normal menstrual cycles between the ages of 18-38, were examined.

Results: When compared with the control group, the overweight/obese PCOS group was found to have higher triglyceride value. Age and neutrophil values were significantly higher, whereas red blood cell distribution width was lower in the control group compared to both PCOS groups. Weight and body mass index values were significantly different for all three groups. The HDL value was detected to be significantly higher in the normoweight PCOS group compared to the overweight/obese PCOS group. Total cholesterol value was significantly higher in the overweight/obese PCOS group compared to the normoweight PCOS group. The MHR values was found to be similar in all groups.

Conclusions: Although the present study has various limitations, there are few studies on this subject and our findings represent an important difference from available results, suggesting the presence of underlying variations that necessitate further studies on this subject.

Keywords: Polycystic ovary syndrome, obesity, inflammation, monocyte, high-density lipoprotein

INTRODUCTION

Polycystic ovary syndrome (PCOS), one of the most common diseases among women, is a complex endocrine abnormality. It affects about 6–15% of all women of reproductive age (1,2). In recent studies, researchers have suggested that the effects of PCOS are not limited to reproductive functions, with studies demonstrating significant influences on metabolism and the cardiovascular system (3). Insulin resistance is an important pathological indicator of both PCOS and cardiometabolic syndrome. The cellular and molecular mechanisms of insulin resistance in PCOS are still not fully understood (4,5).

Many studies have examined various variables that play a role in the etiopathogenesis of PCOS. Although it is still unclear exactly what the underlying cause is, it has been suggested that imbalance at the level of luteinizing hormone and follicle-stimulating hormone, genetic factors and various environmental facilitators play important roles in the pathophysiology of PCOS (6-8). In addition to these factors, studies investigating the relationship between inflammation and PCOS have shown that there was a significant increase in almost all inflammatory markers in patients with PCOS (9,10). Although it is not clear whether the inflammation detected in PCOS cases is the cause or result of the disease, it is clear that chronic low-grade inflammation occurs in PCOS (10). The presence and severity of inflammation can be determined by various laboratory tests. Macrophages in tissues and monocytes in circulation contribute to inflammation. Increased monocyte activation is considered to be an indicator of

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Received: 11.12.2020 **Accepted:** 17.02.2021

increased inflammation (11). High-density lipoprotein (HDL) is involved in anti-inflammatory and antioxidant effects by preventing oxidation of low-density lipoprotein (LDL), altering the migration of macrophages, and activating monocytes. Therefore, while HDL increase suppresses inflammation, its decrease can be considered to be pro-inflammatory (12,13).

Researchers have recently reported that the ratio of monocyte count to HDL (MHR) can be used as an inflammatory index (14-16). There are only a few studies evaluating the role of MHR in PCOS patients (17-19). Therefore, in the present study, we aimed to evaluate women with PCOS who did not have any additional health problems (in two different groups based on body mass index (BMI)) and to compare MHR values in these groups with a control group of healthy subjects. In addition, we aimed to investigate biochemical parameters that demonstrated differences in the examined population.

MATERIAL AND METHOD

Ethics committee approval was obtained from the Ethics Clinical Researches Committee of Adana City Training and Research Hospital (Approval no: 878, Date: 2020/05.20). Informed consent was obtained from all individual participants included in the study. The trial was conducted in accordance with the Helsinki Declaration principles. Data of patients who applied to the Gynecology and Obstetrics Outpatient Clinic of Adana City Training and Research Hospital were analyzed retrospectively, with data drawn from the hospital database. The records of a total of 259 cases, including 194 with PCOS (103 overweight/obese, 91 normoweight) and 65 patients without PCOS (and with normal menstrual cycles) between the ages of 18–38, were examined.

Women aged between 18–38 years who were diagnosed with PCOS, were non-smokers, and did not have any additional diseases were included in the study. Pregnant women, smokers, women in early menopause, those in lactation, and women with hypertension, diabetes mellitus, autoimmune diseases, chronic infectious diseases or adrenal gland disease were excluded from the study. In addition to the absence of any other clinical cause leading to hyperandrogenism, PCOS was diagnosed based on the Rotterdam consensus criteria with at least two of the following three criterions: chronic oligomenorrhea (having an annual menstrual count of six or fewer), biochemical hyperandrogenism (defined as elevation in serum total testosterone concentration), polycystic ovarian morphology in clinical evaluation and pelvic ultrasonography (detection of 10 or more cysts of 0.8-1.2 cm in circumference in both ovaries) (7). Cases with regular menstrual cycles and serum total testosterone levels within normal limits who did not have polycystic morphology in pelvic ultrasonography examination were included in the control group with regard to age and BMI.

Statistical Analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). For the normality check, the Kolmogorov-Smirnov test was used. Data are given as mean±standard deviation or median (1st quartile – 3rd quartile) for continuous variables according to normality of distribution. Normally distributed variables were analyzed with the ANOVA test between groups, while non-normally distributed variables were analyzed with the Kruskal-Wallis test. Bonferroni correction was employed in post-hoc comparisons. $P<0.05$ values were accepted as statistically significant results.

RESULTS

While there was no statistically significant difference in terms of age between the two groups with PCOS, the control group had significantly higher age ($p<0.01$). When compared with the control group, the overweight/obese PCOS group was found to have higher triglyceride value ($p<0.05$). Age and neutrophil values were significantly higher, whereas red blood cell distribution width (RDW) was lower in the control group compared to both PCOS groups. Weight and BMI values were found to be significantly different for all 3 groups ($p<0.001$). HDL value was detected to be significantly higher in normoweight PCOS patients than the overweight/obese PCOS group ($P<0.01$). The total cholesterol value was significantly higher in the overweight/obese PCOS group compared to the normoweight PCOS group. The MHR value was found to be similar in all groups (**Table 1**).

We performed multiple linear regression analysis to determine factors significantly effective on monocyte count. None of the variables included in the model, age (p=0.189), BMI (p=0.626), triglyceride (p=0.551), HDL (p=0.614), total cholesterol (p=0.366), neutrophil (p=0.118) are RDW (p=0.283), were found to be significant (**Table 2**).

We performed multiple linear regression analysis to determine factors significantly effective on HDL value. We found that lower BMI was associated with higher monocyte level (OR: -0.617, 95%CI: -0.833--0.108). Other variables included in the model, age (p=0.698), triglyceride (p=0.162), total cholesterol (p=0.860), neutrophil (p=0.375), monocyte (p=0.614) and RDW (p=0.112) were found be non-significant (**Table 3**).

Table 1. Summary of individuals' characteristics with regard to groups

	Groups			
	Control	**PCOS (BMI<25)**	**PCOS (BMI≥25)**	**p**
N	65	91	103	N/A
Age (years)	31.80±5.58[a]	29.77±4.40[b]	29.35±4.72[b]	0.005
Height (cm)	166.25±6.06	166.70±6.08	166.67±7.44	0.899
Weight (kg)	66 (60-72)[a]	62 (57-65)[b]	86 (80-96)[c]	<0.001
BMI (kg/m^2)	23.81 (21.61-26.37)[a]	22.14 (20.94-23.51)[b]	30.85 (27.72-34.37)[c]	<0.001
Triglyceride (mg/dL)	96 (65-147)[a]	120 (88-148)[ab]	126 (96-153)[b]	0.014
LDL (mg/dL)	132 (76-152)	142 (108-164)	142 (115-162)	0.054
HDL (mg/dL)	64 (53-75)[ab]	72 (56-82)[a]	62 (48-74)[b]	0.001
Total Cholesterol (mg/dL)	204.02±57.42[ab]	185.52±50.56[a]	217.56±58.28[b]	<0.001
White blood cell (×1000)	7.55 (6.29-9.71)	7.30 (6.22-9.47)	6.87 (6.14-8.90)	0.189
Neutrophil (×1000)	4.82 (3.61-7.88)[a]	3.94 (3.19-5.82)[b]	4.07 (3.21-5.68)[b]	0.030
Lymphocyte (×1000)	2.25±0.81	2.09±0.85	2.35±0.96	0.125
Monocyte (×1000)	0.55±0.19	0.55±0.19	0.55±0.23	0.994
Basophil (×1000)	0.04 (0.03-0.07)	0.05 (0.03-0.06)	0.05 (0.03-0.07)	0.439
Hemoglobin (g/dL)	12.54±1.15	12.30±1.38	12.27±1.44	0.333
RDW (fL)	38.11±4.11[a]	35.41±3.27[b]	34.86±3.16[b]	<0.001
Platelet (×1000)	253.92±62.73	243.40±55.17	247.48±61.22	0.553
MPV (fL)	9.80±1.47	9.64±1.35	9.37±1.59	0.170
PDW (fL)	12.1 (10.3-17.2)	11.95 (10.3-16.5)	12.6 (10.9-18.5)	0.197
Monocyte/HDL Ratio	8.33 (6.48-10.86)	7.67 (5.76-10.36)	8.36 (6.35-11.61)	0.334

BMI: Body mass index, HDL: High density lipoprotein, LDL: Low density lipoprotein, MPV: Mean platelet volume, PDW: Platelet distribution width, PCOS: Polycystic ovarian syndrome, RDW: Red cell distribution width
Data are given as mean±standard deviation or median (1st quartile-3rd quartile) according to normality of distribution. Normally distributed variables were analyzed with the ANOVA test between groups, while non-normally distributed variables were analyzed with the Kruskal-Wallis test. Bonferroni correction was employed in post-hoc comparisons. Same letters denote the lack of statistically significant difference between groups.

Table 2. Results of linear regression analysis performed to determine factors effective on monocyte count

	Unstandardized β	**Standard Error**	**Standardized β**	**t**	**p**	**95.0% Confidence Interval for β**	
(Constant)	0.456	0.192		2.380	0.018	0.079	0.833
Age	-0.004	0.003	-0.085	-1.317	0.189	-0.009	0.002
BMI	-0.001	0.002	-0.033	-0.488	0.626	-0.006	0.003
Triglyceride	0.000	0.000	-0.038	-0.597	0.551	-0.001	0.000
HDL	0.000	0.001	0.032	0.505	0.614	-0.001	0.002
Total cholesterol	0.000	0.000	0.058	0.906	0.366	0.000	0.001
Neutrophil	0.008	0.005	0.098	1.568	0.118	-0.002	0.018
RDW	0.004	0.004	0.069	1.075	0.283	-0.003	0.011

Table 3. Results of linear regression analysis performed to determine factors effective on HDL

	Unstandardized β	**Standard Error**	**Standardized β**	**t**	**p**	**95.0% Confidence Interval for β**	
(Constant)	101.844	14.437		7.054	0.000	73.411	130.277
Age	-0.085	0.219	-0.025	-0.388	0.698	-0.515	0.346
BMI	-0.470	0.184	-0.167	-2.554	0.011	-0.833	-0.108
Triglyceride	-0.030	0.021	-0.089	-1.403	0.162	-0.072	0.012
Total cholesterol	-0.003	0.019	-0.011	-0.176	0.860	-0.040	0.034
Neutrophil	-0.374	0.420	-0.055	-0.890	0.375	-1.202	0.454
Monocyte	2.600	5.146	0.032	0.505	0.614	-7.535	12.735
RDW	-0.461	0.289	-0.101	-1.596	0.112	-1.031	0.108

Dependent Variable: HDL; R2=0.047; F=1.752; p=0.098
BMI: Body mass index, HDL: High density lipoprotein, RDW: Red cell distribution width

DISCUSSION

PCOS is an endocrine disorder with low-grade inflammation. In this study, in which various laboratory results were examined in PCOS, it was determined that MHR value was not affected by obesity or the presence of PCOS. Neutrophil count, as an inflammation marker, was found to be lower and RDW was higher in both PCOS groups compared to controls. In addition, triglyceride and total cholesterol were found to be elevated and HDL levels were decreased in the overweight/obese PCOS group. The results of the current study indicate that, despite causing adverse changes in lipid profile and inflammatory parameters, MHR cannot be utilized as a parameter that can quantify the relationship between these changes –even in the presence of obesity.

The presence of inflammation can be determined by examining different markers. Many different studies have shown the relationship between inflammation and increased monocyte count and decreased HDL (11-13). Studies that were based on the hypothesis of persistent inflammation in PCOS have shown an increase in the level of MHR as a result of an increase in monocyte count and a decrease in HDL, especially in obese individuals with PCOS. Usta et al. (18) reported that both monocyte count and MHR levels were significantly higher in PCOS cases compared to healthy women. They reported that these two variables were significant in terms of predicting inflammation in PCOS cases regardless of other risk factors. In addition, the obese control group, non-obese PCOS cases and obese PCOS cases were shown to have a significantly higher MHR value compared to the non-obese control group. In another study, Cakmak et al. (17) also showed that the MHR value was significantly higher in PCOS cases compared to healthy women. When compared to patients with PCOS who also had metabolic syndrome, women with PCOS who did not have metabolic syndrome and healthy controls were shown to have significantly lower MHR values. In a study examining monocyte activation and HDL function in healthy women and PCOS cases, Tedesco et al. (19) reported that macrophage response significantly decreased in PCOS cases compared to healthy controls. Furthermore, serum cholesterol efflux capacity (which is an indicator of HDL activity) was reportedly impaired in PCOS. Although the increased inflammation markers (including MHR) in patients with PCOS have been shown in previous studies, this relationship could not be shown in our study. It is possible that the lack of patients' medication data in the current study may have caused misinterpretation; however, a considerable effect that could alter the outcomes in such a large group is rather improbable.

When the neutrophil level was examined as a measure of inflammation in our study, it was found that neutrophil levels were significantly lower in both the normoweight and overweight PCOS groups compared to the control group. In a study on this subject, Herlihy et al. (20) reported that the frequency of elevated neutrophil levels were higher in patients with PCOS compared to controls (14% vs. 4%). In addition, they reported that neutrophil levels correlated positively with body fat mass. In many other studies, it has been shown that, when compared to healthy women, PCOS cases have an increased neutrophil level with adjustments for age and BMI (21-23). The neutrophil level has been shown to decrease with metformin and flutamide therapy and the use of various anti-inflammatory drugs (21,24). In our study, the drugs used by the patients for therapeutic purposes were not evaluated. Such drugs used in the treatment of PCOS cases may have affected neutrophil levels. In addition, the older age of the control group could also have contributed to this result.

Red blood cell distribution width, another widely-accepted marker of chronic inflammation, has been evaluated for many diseases. It has been reported that RDW value significantly changes in diseases that progress with chronic inflammation and oxidative stress (25,26). Since PCOS is a disease with chronic low-grade inflammation at its basis, RDW value is expected to be affected. Consistent with this expectation, Yilmaz et al. (27) reported that RDW value was significantly higher in PCOS cases compared to healthy controls. In addition, the study stated that a threshold for RDW (>12.5) could be used as a cut-off to identify PCOS. Similarly, Calan et al. (28) showed an increase in RDW in PCOS patients. In addition, RDW has been shown to increase significantly as a result of weight gain (29). In our study, contrary to the studies in the literature, it was determined that RDW value was higher in healthy women compared to the PCOS groups, and that there was no significant difference between the PCOS groups with regard to BMI-based groups. Parallel to our interpretation in the output of other inflammation markers, this may be due to the fact that additional inflammatory conditions were not evaluated in our study, and that the control group consisted of older individuals.

Regardless of other chronic/acute diseases, unhealthy weight gain is an undesirable condition that increases the level of total cholesterol and LDL and lowers the level of HDL; thereby creating a basis for different chronic diseases. When the studies conducted with PCOS cases on this subject were examined, Usta et al. (18) reported that total cholesterol and LDL levels were higher and HDL levels were lower in obese PCOS cases compared to obese controls. Cakmak et al. (17) reported that the

level of triglycerides was higher in patients with PCOS who had metabolic syndrome compared to those without metabolic syndrome, while the total cholesterol and LDL values were similar between the groups. In our study, triglyceride and total cholesterol values were higher and HDL values were lower in the overweight/obese PCOS group. Furthermore, it was thought that high levels of triglycerides, total cholesterol and low HDL levels identified in the overweight/obese PCOS group could be attributed to increased BMI rather than PCOS. However, it is also possible that these alterations could indicate an underlying change in endothelial function, since triglycerides have been suggested to be a marker of endothelial (dys)function in healthy individuals and also patients with metabolic syndrome (30).

It is an important limitation that our study has a retrospective design. Acute infectious diseases and the medication use of patients could not be assessed, and the lack of these evaluations may have affected the outcomes of our study –especially if the distribution of these characteristics were unequal between the groups. Also, the age of the control group was higher, which may be an important factor that altered results.

CONCLUSION

It was determined that MHR value was similar in healthy women and PCOS cases grouped on the basis of BMI. Although the importance of MHR was emphasized in predicting PCOS cases in previous studies, it was concluded that this relationship was not significant in our study. These results may indicate an underlying difference in patient characteristics, but may have also been caused by the baseline differences between groups. Nevertheless, it appears that MHR has little value in the clinical assessment of patients with PCOS, regardless of obesity. In addition, interestingly, neutrophil was lower and RDW was higher in PCOS cases. Although the study has various limitations, considering the number of studies on this subject, it can be said that it will be useful to clarify this issue with future studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was obtained from the Ethics Committee of Health Sciences University Adana City Training and Research Hospital (Approval no: 878, Date: 2020/05.20).

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.

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.848051

Anatolian Curr Med J 2021; 3(2); 104-108

COVID-19 pandemic and the quality of couples' sexual relationships

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Cite this article as: Karlı P, Gürbüz T, Şentürk M. COVID-19 pandemic and the quality of couples' sexual relationships. Anatolian Curr Med J 2021; 3(2); 104-108.

ABSTRACT

Aim: COVID-19 pandemic causes stress between individuals, and this stress can affect the quality of couples' sexual relationships. This study aimed to examine the quality of women's sexual life during the COVID-19 pandemic.

Material and Method: This prospective cross-sectional study was conducted at May-June 2020. 235 sexually active women aged 18 to 51 years participated in this study. The Female Sexual Function Index (FSFI) was used to examine women's sexuality from six different perspectives: desire, arousal, lubrication, orgasm, satisfaction, and pain. Due to quarantine restrictions, questionnaires were emailed to participants.

Results: The participants' age range was 18 to 51, with an average of 29.6±6.08 years. The total FSFI score with a minimum of 1 and a maximum of 26.75 had an average of 18.12±6.23. Since the cut-off value for female sexual dysfunction is 26.0, it can be concluded that, on average, participants had poor function and quality of sexual intercourse in the previous four weeks during the lockdown. The values of the FSFI score were significantly different according to the age of the woman (p-value=0.003), the age of the man (p-value=0.005), and duration of marriage (p-value=0.006). The woman's age (Sig.=0.008), the man's age (Sig.=0.004), and duration of marriage (Sig.=0.02) had a significant and negative correlation with the total FSFI score.

Conclusion: This study showed that the COVID-19 pandemic and lockdown reduced women's sex life quality. Our results also show that the older women and men are, the lower their sexual satisfaction will be, which may be due to the higher risk of COVID-19 for the elderly.

Keywords: COVID-19, FSFI, sexual quality of life, pandemic, lockdown

INTRODUCTION

The outbreak of COVID-19 was reported in late 2019 in Wuhan, China. With a high prevalence rate of fewer than four months, it affected almost every country in the world, with the World Health Organization declaring it a pantdemic on March 11, 2020 (1,2). This highly contagious viral disease has clinical manifestations such as fever, chills, sore throat, cough, difficulty breathing, nausea, vomiting, and diarrhea (3). As of December 2020, it has infected 77.6 million people worldwide caused 1.71 million deaths.

Psychological consequences such as fear and stress about this disease can be very severe and lead to intense emotions (4). Recent studies in China have also shown that the prevalence of COVID-19 disease is the most important public concern and has posed major challenges to individuals' physical and mental health (5). In general, in the face of a crisis that has targeted public health, people are prone to various psychological problems (3). It was shown that basic parameters such as gender, specific physical symptoms, chronic diseases, and poor health status were significantly associated with a wider range of physical and psychological due to the COVID-19 pandemic, such as more severe stress levels and depression (1,2,4,5).

Sexual desires are an important part of human life that can be affected by mental problems or crises (6,7). In 1998, the classification of female sexual dysfunction (FSD) was introduced by the American Urological Association (8). According to them, FSD is known in the form of impaired desire, sexual arousal, and pain during intercourse, and difficulty or inability to orgasm (9). Epidemiological studies have shown that FSD is a common problem in the community, and 20-25% of women are affected by it (10,11).

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Received: 27.12.2020 **Accepted:** 03.03.2021

Despite this high prevalence and recent research, the cause of FSD remains relatively unknown, possibly due to the complexity of its underlying physiological process (12). In addition to low objective measurement tools, there are a significant number of self-completion questionnaires that measure FSD. Among these tools, the Female Sexual Function Index (FSFI) is considered the gold standard for assessing female sexual function and has been translated and validated in more than 30 countries (12-14).

Many studies have focused on the pandemic effect on individuals' physical health. Few studies have been performed on the effects of the COVID-19 pandemic and quarantine conditions on sexual health. Therefore, in this study, it was decided to use the FSFI questionnaire to investigate these conditions' effect on female sexual function.

MATERIAL AND METHOD

This prospective cross-sectional study was conducted at Amasya University Gynecology and Obstetric Clinic. The study was approved by the Ethical Committee of Amasya University (07/05/2020-5/28) and the Turkish Republic dated 2020-05-07T15-56-23 after approval of the application for work by the Ministry of Health Scientific Research Platform. 235 women who referred to Gynecology and Obstetrics Clinic between May and June 2020 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.

Two hundred thirty five sexually active women aged 18 to 51 years participated in this study. Participants under the age of 18, diagnosed with COVID-19, had a history of pre-existing mental illnesses such as personality disorders or depression, and subjects who were taking medications reducing libido for up to three months before the study were excluded from the study. Those who agreed to participate in the study did not have any psychiatric diagnosis before, and did not use any drug that was included in the study. The informed consent was received from all women.

In this study, FSFI was used. This index is a 19-item questionnaire that examines women's sexuality from six different perspectives: desire, arousal, lubrication, orgasm, satisfaction, and pain. This assessment measures the respondent in the last four weeks and has a score range from 2 to 36. A score of less than 26 indicates sexual dysfunction. Due to quarantine restrictions, questionnaires were emailed to participants.

Information was collected on men and women's age, height, weight, duration of the marriage, pregnancy status, smoking, the emotional status between men and women, and income. The FSFI questionnaire was then presented to the participants to assess their sexual function.

Statistical Analyses

A Chi-square test was used to examine the significant difference between each of the qualitative variables. For quantitative variables, after examining their abnormality using the Kolmogorov-Smirnov test, the non-parametric equivalent of a one-way ANOVA test, the Kruskal-Wallis test was used. Statistical Package for Social Sciences (SPSS) version 26.0 (SPSS Inc., Chicago, IL, USA) was used to perform analysis.

RESULTS

The mean age of women participants 29.6 years. The mean age of male participants 32.9±6.3 years. Participants ranged in weight from 45 to 120, with an average of 71±13.4 kg, and height ranged from 145 to 185, with an average of 162±5.6 cm. 10 (4.3%) participants had primary education, 36 (15.3%) had secondary education, 79 (33.6%) had high school education, and 110 (46.8%) had university graduation.

In terms of previous duration of marriage, the minimum was 5 months, and the maximum was 336, with an average of 85.1±73.5 months. Among the participants, 168 (71.5%) were not pregnant, 17 (7.2%) were less than 12 weeks pregnant, 10 (4.3) were between 12 and 24 weeks pregnant, and 35 (14.9) were between 24 and 32 weeks pregnant. Participants also expressed their love for their husbands, with 166 (70.6%) expressing much love, 65 (27.6%) expressing normal love, and 4 (1.7%) expressing little love for their husband. 195 (83%) participants got married by agreement, and another 40 (17%) had an arranged marriage. **Table 1** shows the general characteristics of the study population.

The FSFI questionnaire results were as follows: Desire score had an average of 2.94±1.9, arousal score had an average of 2.97±1.32, lubrication score had an average of 2.91±1.25, orgasm score had an average of 3.2±1.42. The satisfaction score had an average of 3.48±1.5. Pain score had an average of 2.6±1.09. Finally, the total FSFI Score had an average of 18.12±6.23. The results of the FSFI questionnaire are shown in **Table 2**.

As shown in **Table 2**, the average total FSFI score is 18.12. Since the cut-off value for FSD is 26.0, it can be concluded that, on average, participants had poor function and quality of sexual intercourse in the previous four weeks during the lockdown.

Table 1. General characteristics of participants

Age [Years]	
Average	29.6±6.08
Education	
Primary	10 (4.3%)
Secondary	36 (15.3%)
High school	79 (33.6%)
University	110 (46.8%)
Pregnancy Status	
Not pregnant	168 (71.5%)
Less than 12 weeks	17 (7.2%)
Between 12-24 weeks	10 (4.3%)
Between 24-32 weeks	35 (14.9%)
Income	
Under 1500 TL	16 (6.8%)
1500-3000 TL	86 (36.6%)
3000-5000 TL	84 (35.7%)
Over 5000 TL	49 (20%)
Marriage form	
By agreement	195 (83%)
Arranged	40 (17%)
Job	
Housewife	130 (55.3%)
Employment	105 (44.7%)
Affection	
Love him a little	4 (1.7)
Love him normally	65 (27.6)
Love him so much	166 (70.6)

Table 2. Results of the FSFI questionnaire

Variable	N	Minimum	Maximum	Mean	SD
Desire	235	1	5	2.94	0.95
Arousal	235	0	5	2.97	1.32
Lubrication	235	0	5	2.91	1.25
Orgasm	235	0	5	3.2	1.42
Satisfaction	235	0	5	3.48	1.5
Pain	235	0	4.67	2.6	1.09
Total	235	1	26.75	18.12	6.23

The results of the Kolmogorov test show that not all quantitative variables have a normal distribution. With the FSFI score classification, the respondents were divided into low and medium categories. Participants with a score of ≤23 were placed in the low category, and participants with a score of >23 were placed into the medium category. **Table 3** examines the relationship between demographic variables with the total variable using Kruskal–Wallis test. Then **Table 4** examines the qualitative variables with the total variable using the Chi-square test.

The results of **Table 3** showed that the values of the FSFI score are significantly different according to the age of the woman (p-value=0.003), the age of the man (p-value=0.005), and duration of marriage (p-value=0.006). The results are shown in **Table 3**.

Table 3. Comparing the FSFI score categories with participant characteristics

	Total		p-value
Variable	**Low**	**Medium**	
Age of woman	30.2 (6.3)	27.3 (4.4)	0.003
Age of man	33.5 (6.4)	30.5 (5.3)	0.005
High (cm)	162.9 (5.8)	161.8 (4.5)	0.2
Weight	71.2 (13.4)	69.8 (13.6)	0.4
Duration of marriage	91.4 (76.5)	57.18 (49.7)	0.006

Table 4. Comparing the qualitative variables with the FSFI total score

Variable	Total		P-value
	Low	**Medium**	
Pregnancy			
Not pregnant	138 (71.9)	30 (69.8)	
Less than 12 weeks	12 (6.3)	5 (11.5)	
Between 12-24 weeks	8 (4.2)	2 (4.7)	0.6
Between 24-32 weeks	29 (15.1)	6 (14)	
Not pregnant	5 (2.6)	0	
Education			
Primary	9 (4.7)	1 (2.3)	
Secondary	62 (32.3)	17 (39.5)	0.7
High school	29 (15.1)	7 (16.3)	
University	92 (47.9)	18 (41.9)	
Affection			
Love him a little	4 (2.1)	0	
Love him normally	128 (66.7)	38 (88.4)	0.01
Love him so much	60 (31.3)	5 (11.6)	
Job			
Housewife	108 (56.3)	22 (51.2)	0.6
Employment	84 (43.8)	21 (48.8)	
Marriage form			
By agreement	157 (81.8)	38 (88.4)	0.3
Arranged	35 (18.2)	5 (11.6)	
Income			
Under 1500 TL	14 (7.3)	2 (4.7)	
1500-3000 TL	71 (37)	15 (34.9)	0.7
3000-5000 TL	66 (34.4)	18 (41.9)	
Over 5000 TL	41 (21.4)	89 (18.6)	

As shown in **Table 4**, the only factor influencing the FSFI total score of qualitative variables is the woman's affection for her husband. The correlation of participant characteristics with the total FSFI score was examined, and the results are shown in **Table 5**.

As shown in **Table 5**, the woman's age (Sig.=0.008), the man's age (Sig.=0.004), and duration of marriage (Sig.=0.02) have a significant and negative correlation with the total FSFI score. This means that the older a woman, man, and duration of marriage are, the lower the total FSFI score.

Table 5. Correlation of total FSFI score with participant characteristics

Variable	Correlation Coefficient	Sig.
Age of woman	-0.17	0.008
Age of man	-0.19	0.004
Height (cm)	-0.09	0.1
Weight (kg)	-0.03	0.6
Duration of marriage	-0.15	0.02

Table 6 also shows the comparison of pregnant and non-pregnant participants regarding their FSFI scores. It has been shown that there is no significant difference between the two groups regarding their FSFI score.

Table 6. Comparison of pregnant vs. non-pregnant participants

	Pregnancy	N	Mean	t	Sig.
FSFI scores	non-pregnant	168	18.3 (6.03)	0.71	0.4
	pregnant	67	17.6 (6.7)		

DISCUSSION

Our results showed that the overall FSFI score decreased significantly during the pandemic, which means that pandemic and lockdown had a negative impact on the women's quality of sexual life in our study. The results also showed that all six aspects of FSFI were significantly reduced among the participants. Our results were consistent with a study by Yuksel and Ozgor (15). They conducted a similar study in Turkey and found that women's quality of sexual life decreased significantly during the COVID-19 pandemic. However, their results showed that the number of intercourses and sexual desire increased during the lockdown. Their results also showed that during the COVID-19 pandemic, couples were less willing to have children (15).

One of the most important factors affecting the quality of couples' sexual health is their stress and level of anxiety (16). Hall, Kusunoki (17) studied 992 women aged 18 to 20 years and showed that stress and anxiety levels could negatively affect the quality of couples' sexual relationships. Another study by Liu Liu, Han (18) after the 2010 earthquake in Asia showed that individuals' sexual function is impaired after a natural disaster, and couples experience reduced sexual satisfaction. These results show that when bad things happen to everyone around and the level of anxiety and stress increases, sexual health quality decreases significantly (17,18).

Fear of the possibility of pregnancy can be considered as one of the factors reducing the number of intercourses during the lockdown (19,20). Research is currently underway to determine the effects of COVID-19 on pregnant women. Data are limited, but there is currently no evidence that pregnant women are more likely to develop the disease's severe form than the general population. However, due to physical and immune system changes in pregnant women, they can become seriously ill due to respiratory infections (16,19).

Micelli, Cito (21) examined the effect of COVID-19 on Italians' decision to have children. They did not find a significant difference between the number of intercourses before and after the COVID-19 pandemic between Italian couples. More than a third of couples who decided to have children decided to postpone the decision due to the pandemic. Factors influencing this decision include economic instability and lack of knowledge about pregnancy outcomes due to the prevalence of the disease. However, this study showed that 12% of couples decided to have children during the lockdown (21).

Other studies on couples' sexual satisfaction after natural disasters such as floods and earthquakes have shown that couples' desire for sex decreases (22-24). However, Yuksel and Ozgor (15) studied couples' sexual behaviors during the COVID-19 pandemic and concluded that the number of intercourses between couples has increased. This inconsistency can be due to two reasons: first, the COVID-19 pandemic has not destroyed people's living space, unlike floods and earthquakes, and second, the couple has more free time at home. However, their results showed that despite the increase in the number of intercourses, sexual satisfaction between couples has decreased, which is consistent with our study results (15).

This is the first study to look at the relationship between women's age and sexual satisfaction during the COVID-19 pandemic. Our results show that older men and women have decreased sexual satisfaction during the COVID-19 pandemic. This decrease may be due to the higher risk of COVID-19 for older people, and therefore older people are more prone to stress than younger people.

One of the most important limitations of this study was the lack of identical pre-pandemic data for comparison with post-pandemic data. Another limitation of this study was the small number of samples. Also, the FFSI questionnaire is usually answered physically and face-to-face, but due to COVID-19 pandemic limitations, the questionnaire was emailed to participants, which could affect participants' responses. Because sexual satisfaction is a complex matter, and many factors can influence it, including male sexual behavior, future studies should consider more influencing factors.

CONCLUSION

This study showed that the COVID-19 pandemic and lockdown reduced the quality of women's sex life. This result may be due to increased anxiety and stress in women during the pandemic. Our results also show that the older women and men are, the lower their sexual satisfaction will be, which may be due to the higher risk of COVID-19 for the elderly and thus the greater the stress on them. The results obtained in this study should be supported by prospective studies and a larger number of samples.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ethical Committee of Amasya University (07/05/2020-5/28) and the Turkish Republic dated 2020-05-07T15-56-23 after approval of the application for work by the Ministry of Health Scientific Research Platform.

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.

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

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.854866

Anatolian Curr Med J 2021; 3(2); 109-114

Determination of measles, rubella, mumps and chickenpox seropositivity of district public hospital healthcare workers

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Cite this article as: Yekenkurul D. Determination of measles, rubella, mumps and chickenpox seropositivity of district public hospital healthcare workers. Anatolian Curr Med J 2021; 3(2); 109-114.

ABSTRACT

Aim: Measles, rubella, mumps and chickenpox are the childhood diseases retain their importance in our country as well as all over the world. Healthcare workers have high probability of transmission due to their occupational risk; however by taking necessary protective measures, the risk can be reduced. Determining the seropositivity rates of healthcare workers; it was aimed to compare vaccination rates before and after screening.

Material and Method: The personnel cards of 160 healthcare workers who worked in Akçakoca State Hospital, from January 2018- December 2018 were retrospectively scanned. Information of 100 personnel has been reached. Demographic characteristics such as age and gender; infection or vaccination history; measles, rubella, mumps and chickenpox IgG results; old vaccination information and last vaccination status were recorded.

Results: Total of 100 staffs, 19 (19%) men and 81 (81%) women, were included in the study. 89 staffs (89%) were found to be immune to measles. After the scanning, 11 of the personnels who were not vaccinated or had incomplete vaccines saw that the measles IgG result was negative and eight of them agreed to be vaccinated. The seropositivity rate of rubella was 93%. Five of the seven personnels with rubella IgG negative, agreed to be vaccinated. The lowest seropositivity rate was in mumps (79%). 14 of the 21 people with mumps IgG negative were vaccinated. The highest seropositivity rate was in chickenpox (96%). Three of the four people with chickenpox IgG negative were vaccinated.

Conclusion: While the rate of vaccination for measles, rubella, mumps and chickenpox before screening is low (12%); our post-screening rate has increased (34%). For this reason, we think that healthcare workers should be screened for measles, rubella, mumps and chickenpox, and healthcare workers who are seronegative should be encouraged to vaccinate.

Keywords: Healthcare workers, measles, rubella, mumps, chicken pox

INTRODUCTION

Measles, rubella, mumps and chickenpox are the childhood diseases retain their importance in our country as well as all over the world. Undergoing these infections, which are highly contagious and generally symptomatic, in adulthood increases the morbidity and mortality rate (1). Healthcare workers (HCWs) are more likely to be exposed to infected materials such as blood, secretion, body fluid; therefore, they are people with an increased risk of infection compared to the community. Infections transmitted to HCWs put not only themselves, but also their families, other hospital staff and patients at risk. Therefore, vaccination of HCWs is a condition affecting public health (2).

Centers for disease control and prevention (CDC), according to current vaccine recommendations to healthcare professionals who are born in 1957 and later, with without serological evidence that has had the disease in; proposes two doses of measles and mumps, one or two doses of MMR vaccine for rubella, and two doses of chickenpox vaccine (3). Vaccination against infections such as measles, rubella and chickenpox reduces the incidence of the disease and significantly prevents health-related outbreaks (4). In our country, vaccines are recommended to against such infectious diseases and vaccines are provided free of charge; however, it is not mandatory. Vaccination of HCWs is also important in terms of health services not to be disrupted (5).

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Received: 06.01.2021 **Accepted:** 10.03.2021

Healthcare workers have a high probability of transmission due to their occupational risk; however, by taking necessary protective measures such as MMR and chickenpox vaccines, the risk can be reduced. Determining the seropositivity rates of HCWs; in addition, it was aimed to compare vaccination rates before and after screening test.

MATERIAL AND METHOD

After the approval of the hospital chief physician and the ethics committee approval was obtained from Düzce University Clinical Research Ethics Committee (permission granted: 07.01.2019, decision no: 244).The personnel cards of approximately 160 HCWs who worked in Akçakoca State Hospital, a secondary center hospital, from January 2018- December 2018 were retrospectively scanned. Health workers who had screening for measles, rubella, mumps and chickenpox were identified. Information and test results of 100 staff who had scanned were reached through personal health cards and hospital database. Those who have incomplete information and results from other staff or those who have not agreed to take the blood test are not included in the study; while working in our hospital between the same dates, staff who left our hospital for any reason were included. In the light of the information stated in the health cards, age, gender, occupation, professional year, unit of employment, educational status, history of infection or vaccination for MMR and chickenpox, MMR and chickenpox IgG result, recommended vaccine information and vaccination were recorded.

In our hospital, periodic healthcare worker surveillance is carried out every year and measles, rubella, mumps and chickenpox IgG tests are performed on every new health worker. Some tests as measles, rubella, mumps and chickenpox IgG are done in the form of external laboratory service. In the results that obtained, measles IgG value is positive if >11 NTU (Nephelometric Turbidity Unit), negative if <9 NTU, and borderline if it is between 9-11 NTU; rubella IgG value is positive if >10 IU/mL, negative if <10 IU/mL; mumps IgG value is positive if >11 NTU, negative if <9 NTU, and borderline if value between 9-11 NTU; varicella IgG value was positive if >11 NTU, negative if <9 NTU, and borderline if value between 9-11 NTU. In the results of staff, there was no need to control the values at the border in terms of cost and all of them were offered vaccination; therefore, those who are at the limit in the number and rate notifications are considered negative. Staff, those results were negative or borderline, who accepted the vaccine were vaccinated free of charge by the Ministry of Health in our hospital. No post-vaccination control IgG test was required. Staff who had the recommended vaccine (two doses one month apart) after the test were considered seropositive.

RESULTS

A total of 100 staff, 19 (19%) men and 81 (81%) women, were included in the study. The age range of employees was between 21 and 58, and the average age was 34.92±8.23 years. Considering the professional year, eight staff have not yet completed one year, and the longest employee has been working for 34 years; the average professional year of the employees was found to be 8.85±8.48 years. Demographic characteristics, occupation, professional year, unit of employment, educational status, numbers and percentages of the personnel are given in **Table 1**.

Table 1. The characteristics of healthcare workers

Characteristics	
Gender n (%)	
Male	19 (19%)
Female	81 (81%)
Average age	34.92±8.23 years
The average of professional year	8.85±8.48 years
Occupation n (%)	
Doctor	21 (21%)
Nurse and midwife	46 (46%)
Technician	10 (10%)
Cleaning staff	4 (4%)
Others1	19 (19%)
Unıt of employment n (%)	
Polyclinic	24 (24%)
Emergency	18 (18%)
Operating room	17 (17%)
Service	17 (17%)
Administration	9 (9%)
Others2	15 (15%)
Education status n (%)	
Primary school	5 (5%)
High school	12 (12%)
Associate degree	35 (35%)
License	48 (48%)

Others1: Healthcare workers who do not directly interfere to patient, including kitchen workers, secretaries, pharmacists, administrative officers
Others2: Healthcare workers who work in different units such as dialysis, kitchen, pharmacy

In total, 89 staffs (89%) were found to be immune to measles. The average age of the 11 negative staff is 31.72±7.15 years; those who were positive were 35.31±8.31 years. Seven negative staffs were under 35 years old, four staffs were over 35 years old (39, 40, 40, 42 years old) and none were born before 1957. In terms of profession, five of the 11 staff were midwives or nurses, one was a doctor, one was a radiology technician, one was a cleaning staff, two were data entry staff, and the risk of transmission was quite high. Since there was no single measles vaccine, those who did not have any contraindications were offered two doses of MMR vaccine at one-month intervals. One of the staff previously stated that they had a MMR vaccine, but the result was at the border (9.9 NTU). This personnel had been vaccinated by us, but the vaccination information of other personnels was anamnestic data. According to the information on the personnel health cards, 10 of the 11 staff were in the group who did not know whether they

had measles before or had no at all; however only one had been vaccinated; his level of protection was probably insufficient as he had vaccination once. However, eight of the 11 staff (73%), who saw that they were negative after the test, agreed to be vaccinated and received two doses of MMR vaccine (**Table 2**). No post-vaccination control IgG test was required and was considered seropositive. The other three people did not agree to be vaccinated for different reasons.

The overall seropositivity rate of rubella was 93% (**Table 3**). The mean age of rubella IgG values was calculated as 38.28±7.38 years and 34.59±8.23 years for positive ones. Only two of the seven were under 35 (28.33) and the other five were over 35 (38.40.42.43.51). The two did not agree to be vaccinated; Since five staff have MMR vaccine, we have received two doses of MMR vaccine at one month intervals. Of the seven negative people, one was a doctor, one was a civil servant and the other five were nurses.

Mumps IgG positivity rate was lowest with 79% (**Table 3**). The average age of IgG negative staff was 32.47±7.24 years, and positive ones were 35.56±8.4 years. Five of 21 staff with mumps negative IgG had already been vaccinated because the measles or rubella IgG test was also negative; The remaining 16 staff were offered two doses of MMR vaccine with one month intervals. However, the vaccine rate was low in this group, only 14 of 21 people agreed to be vaccinated. The reason for not being accepted was the probable of test insecurity; Five out of seven staff who did not get vaccinated had previously stated that they had the disease (**Table 2**). In our study, although male staff were few (19 in total), six of the seronegative mumps were male.

Chickenpox seropositivity rate was highest (96%). Four staff, aged 23, 34, 37, 42, were negative, and only one previously stated that they had chickenpox infection; his chickenpox IgG result was borderline. Four staff were offered two doses of chickenpox vaccine at one-month intervals; three agreed to be vaccinated. Thus, the number of seropositive staff rose to 99 (**Table 4**).

A total of 24 persons were vaccinated after the examination as MMR and varicella (**Table 5**); The seropositivity rates in all four groups after our vaccination were over 90% (**Table 4**). In our study, approximately one third of the staff did not know the history of measles (30%) or rubella (41%); in chickenpox (20%) and mumps (13%), this rate was lower (**Table 2**).

Table 4. IgG positive personnel numbers-ratios, before and after vaccination

Disease	Seropositivity before vaccination n (%)	Seropositivity after vaccination n (%)
Measles	89 (89%)	97 (97%)
Rubella	93 (93%)	98 (98%)
Mumps	79 (79%)	91 (91%)
Varicella	96 (96%)	99 (99%)

IgG: Immunglobulin G, Note: Vaccinated ones were considered IgG positive

Table 2. The numbers and rates of MMR and chickenpox infection history or vaccination history before screening; and vaccination rates after screening

Disease	Infection history before screening (n, %)			Vaccination history before screening (n, %)		Vaccination status after screening (n, %)	
	Yes	No	Not know	Yes	No	Yes	No
Measles (-)	1 (9%)	5 (45,5%)	5 (45,5%)	1 (9%)	10 (91%)	8 (73%)	3 (27%)
Measles (t)	40 (40%)	30 (30%)	30 (30%)	10 (10%)	90 (90%)	17 (17%)	83 (83%)
Rubella (-)	0	4 (57%)	3 (43%)	0	7 (100%)	5 (71%)	2 (29%)
Rubella (t)	26 (26%)	33 (33%)	41 (41%)	10 (10%)	90 (90%)	14 (14%)	86 (86%)
Mumps (-)	9 (43%)	7 (33%)	5 (24%)	1 (5%)	20 (95%)	14 (67%)	7 (33%)
Mumps (t)	65 (65%)	22 (22%)	13 (13%)	10 (10%)	90 (90%)	24 (24%)	76 (76%)
Chickenpox (-)	2 (50%)	2 (50%)	0	0	4 (100%)	3 (75%)	1 (25%)
Chickenpox (t)	65 (65%)	15 (15%)	20 (20%)	2 (2%)	98 (98%)	5 (5%)	95 (95%)
Total (-)				2 (6%)	32 (94%)	24 (71%)	10 (29%)
Total (t)				12 (12%)	88 (88%)	34 (34%)	66 (66%)

(-): IgG negative and borderline ones
(t): IgG negative, borderline and positive ones; the numbers were different due to the fact that some people had common vaccination rates (For example, there were 10 staff members who had the measles vaccine before the screening; but one staff member was re-vaccinated, so the number after our vaccination was calculated as 17, not 18)

Table 3. Number and rates of positive IgG results by age groups

Age range	Number of staff (n)	Measles IgG+ number/ percentage (n)/(%)	Rubella IgG+ number/ percentage (n)/(%)	Mumps IgG+ number/ percentage (n)/(%)	Chickenpox IgG+ number/percentage (n)/(%)
20-29	33	27 (82%)	32 (97%)	23 (70%)	32 (97%)
30-39	38	36 (95%)	36 (95%)	33 (87%)	36 (95%)
40-49	25	22 (88%)	22 (88%)	19 (76%)	24 (96%)
50-59	4	4 (100%)	3 (75%)	4 (100%)	4 (100%)
Total	100	89 (89%)	93 (93%)	79 (79%)	96 (96%)

IgG: Immunglobulin G

Table 5. Analysis of 34 people who were IgG negative or borderline for at least one disease

Feature	
Gender n (%)	
Male	7 (21%)
Female	27 (79%)
The average age	33.67±7.35 years
The average of professional year	9.32±7.82 years
Number of staff who accepted vaccination n (%)	24 (71%)
IgG negativity (accepted vaccination)	**Vaccinations made (n)**
Measles	MMR (4)
Rubella	MMR (3)
Mumps	MMR (10)
Varicella	C (2)
Mumps+rubella	MMR (1)
Mumps+measles	MMR (2)
Measles+rubella	MMR (1)
Mumps+measles+ chickenpox	MMR +C (1)
Total	24

IgG: Immunglobulin G, MMR: Measles, mumps, rubella, C: Chickenpox

DISCUSSION

Our Ministry of Health stated that, medical faculties, nurses and midwifery faculties, dentistry faculties, students of medical schools, all HCWs, including health institution cleaners, staff working in emergency service, emergency health vehicles, and National Medical Rescue Team staff, should receive MMR, chickenpox, Td, influenza, hepatitis A and B vaccines (6). Vaccination against these diseases prevents possible epidemics in health institutions; it prevents a great economic loss in terms of treatment costs (4). In our country, the adult vaccination rate (below 2%) is generally very low (7). However, in order to minimize the probability of an outbreak, the immunity rate should be above 95% (8). In our study, only the rate of seropositivity of chickenpox was found to be above 95% in all age groups (**Table 3**).

According to the results of surveillance studies in our country; 8042 of measles cases were detected in the outbreak in 2013, and 1.4% of them (96 cases) were reported to be HCWs (9). Epidemics can be seen not only in the unvaccinated population, but also in the population with reduced vaccine protection (reduced IgG) (10). In our country, some conditions are required for the healthcare professionals to be considered immune to measles. The first is that the history of measles is documented by a physician. Others are the presence of measles IgG positivity approved by a laboratory, born before 1957 or an official document indicating that two doses of measles were vaccinated (11). Turkey has been started measles vaccine after the 1970; while two doses were made between 1970-1987 and one dose between 1987-1998, they were increased to two doses again after 1998 (12,13). The fact that the lowest seropositivity rate was in the staff born between 1987-1998 in our study made us think that it may be due to insufficient vaccine dose. More research is needed on this subject. In the study conducted by Aypak et al. (14) as in our results, the lowest seropositivity rate (79.2%) was observed in the young group under 25 years of age, and the overall rate was found similar to our study with 90.8%. However, in the study of Özgüler et al. (15) the rate of measles seropositive staff is quite high with 99.1%.

Between 2006 and 2018, the number of confirmed rubella cases in our country was 1236, but an average of 95 cases per year are observed (9). In our study, the overall seropositivity rate of rubella was 93% (93 HCWs), and unlike measles, the lowest rate was in the 50-59 age group. It was noteworthy that the higher the age between the groups, the lower the positivity rate (**Table 3**). In some studies conducted in our country, this situation was found to be opposite and a partial increase in seropositivity was observed as the age progressed (14,16).

In our country, mumps vaccine has been included in the routine vaccination program since 2006 as a childhood vaccine (13). In our study, mumps IgG positivity rate was the lowest with 79%. In studies conducted in our country, seropositivity rates vary between 82.5-99.7% (14,16-19). According to these results, our rate is very low. The mumps IgG result was borderline in nine case, negative in 12; the most borderline was seen in mumps IgG. In addition, six of the nine staff previously declared that they had mumps infection. The history given in rash diseases such as measles and rubella could not be reliable; however, the history of the disease was more reliable because the symptoms of chickenpox and mumps were more specific (20). This made us think that even if it is naturally immune, there may be a decrease in mumps IgG titer over the years. However, more studies are needed on this subject.

In a study reported from a center with employees from different countries, chicken pox IgG positivity rate is quite low with 81.9%. The lowest rates; according to age was seen above 40 years (74.1%) and according to countries was seen at India (76.5%) (21). Studies in our country, it has been reported that the rate of seropositivity is between 98-99.7% (14,16-18). In our study, we found that the rate of chickenpox seropositivity was close to the general literature rates (96%).

Vaccines planned according to occupational hazards differ from country to country and even from center to center (22). Therefore, different results of seroprevalence studies are a concomitant. For example, in a study conducted in Italy, chicken pox IgG positivity rate was found as 97.9%; in another study conducted in Italy, 85.7% was detected (23,24). In a survey study on

occupational risks to health high school students; 94.5% of students knew that hepatitis B vaccine should be given to HCWs, while 72.7% knew that MMR vaccine should be given (25). This study made us think that one of the reasons for the low seropositivity rates may be the lack of information. Therefore, training about vaccines should be given to students and staff frequently.

The other subject; although the rate of not remembering the history of the disease is high in our group, the rate of vaccination is low. However, people who are recommended vaccines after the examination have a high rate of vaccination. Therefore, it is thought that the lack of information rather than distrust, neglect and seropositivity may be the reason for not being vaccinated. In a multicenter study conducted with HCWs in our country, it was reported that only a small group (15.5%) was vaccinated for MMR. In our study, our pre-screening vaccination rate is similar to 12%; however, this rate increased to 34% after screening (26). Although the use of live viral vaccines such as MMR mimics the natural infection that provides life-long protection; Studies have shown that immunity is reduced even in fully vaccinated individuals, especially in measles and mumps (27). In our results, the lowest rates belong to measles (89%) and mumps (79%).

Our study showed that our healthcare staff were at risk, especially in terms of mumps, and 29% (6/21) of the personnel who were seronegative for mumps were male. In addition, our seropositivity rate for measles was lower compared to the country average. It was noteworthy that most of the HCWs who were seronegative for measles, rubella, mumps and chickenpox did not have the vaccine before the examination, despite all the recommendations, but when the result was negative after the examination, most of them (71%) had the vaccine we recommended. Some of the people who did not have the vaccine were pregnant and some were people with chronic diseases. Others were sure that they had an illness, but did not have it because of a lack of confidence due to the negative test. Our high seropositivity rate for chickenpox and rubella were similar to those detected in other studies in Turkey. However, low seropositivity rates against mumps and measles were not consistent with these studies.

CONCLUSION

In a country with such a high rate of migration as Turkey, it should be noted that especially who work in high-risk places as a hospital must be vaccinated. Even before meeting the patient, vaccination should be recommended on the first day of starting work or in health-related schools, if they do not agree to have it, measles, rubella, mumps and chickenpox IgG tests should be requested. Our study can be an evidence for compliance with the vaccine recommendations of the Ministry of Health. In addition, the vaccination of the HCW is important in terms of not only being an example for the people who are against the vaccine, but also in terms of not interrupting the health service. Some studies suggest that HCWs should be vaccinated without screening because it is not cost-effective (18). Despite this, it has been observed that staff vaccination rates are low in many centers (26). Since our vaccination rate was low, we decided to screen our staff with the decision of the Infection Committee Control, and we saw a significant increase in the rate of vaccination afterwards. For this reason, we think that HCWs should be screened in order to increase vaccination rates and healthcare workers who are seronegative should be encouraged to vaccinate.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Non-Invasive Health Research Ethics Committee of Düzce University (permission granted: 07.01.2019, decision no: 244).

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.

Acknowledgments: I would like to thank Infection Committee Control of Akçakoca State Hospital for their contribution.

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.854759

Anatolian Curr Med J 2021; 3(2); 115-119

Evaluation of long-term effect of tuberculosis chemoprophylaxis in patients using anti tumor necrosis factor alpha agents

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Cite this article as: Başlılar Ş, Aydın M. Evaluation of long-term effect of tuberculosis chemoprophylaxis in patients using anti tumor necrosis factor alpha agents. Anatolian Curr Med J 2021; 3(2); 115-119.

ABSTRACT

Aim: There is an increased risk of tuberculosis (TB) in patients with rheumatoid diseases (RD) treated with antitumor necrosis factor (TNF) alpha agents. Screening and, if necessary, chemoprophylaxis is recommended in patients undergoing anti TNF alpha treatment. This study aimed to determine the incidence of active TB due to long term anti TNF alpha usage in patients with RD and to evaluate the effectiveness of tuberculosis chemoprophylaxis regimen.

Material and Method: Patients treated with anti TNF alpha agents for more than 5 years with RDs were evaluated retrospectively. Demographic and clinical characteristics, use of chemoprophylaxis, laboratory tests before and after anti TNF alpha treatment and development of TB were examined.

Findings: A total of 150 patients (79 male [52.7%], 71 female [47.3%]) with a mean age of 45±13 years were evaluated. The tuberculosis rate over 5 years follow up was found as 1.3%. One male developed pulmonary TB 5 years and 1 female developed miliary TB 10 years after the beginning of anti-TNF alpha therapy despite chemoprophylaxis with isoniazid. The mean number of neutrophils, lymphocytes ($p<0.05$) and the N/L ratio was significantly decreased after anti TNF alpha treatment ($p<0.0001$).

Conclusion: In an RD patient treated with anti TNF alpha agents, the risk of TB should be kept in mind even after 10 years. Regular monitoring should be considered for long term TNF antagonist therapy.

Keywords: Anti TNF alpha, tuberculosis, isoniazid, chemoprophylaxis, long term effectiveness.

INTRODUCTION

The role of TNF alpha in the pathogenesis of rheumatic diseases (RD) is immunomodulation, particularly as a proinflammatory cytokine (1).

The biologic antagonists of TNF alpha (anti TNF alpha), represent a major advance in the management of RD. However, an increased risk of tuberculosis (TB) in patients with RD who treated with anti TNF alpha agents has been demonstrated by several researchers (2,3). 2-fold elevated risk of TB by anti TNF alpha agents was reported at a systematic meta-analysis of randomized clinical trials (4). Guidelines recommends implementation of screening and, if necessary, chemoprophylaxis in patients undergoing anti TNF alpha treatment (5). Several studies reported higher incidence of TB among RD patients who treated with anti TNF alpha than without anti TNF alpha, despite chemoprophylaxis (6,7). This study aimed to determine the incidence of active TB due to anti TNF alpha usage in patients with RD for a long time period and to evaluate the effectiveness of an antituberculosis chemoprophylaxis regimen.

MATERIAL AND METHOD

This retrospective study included patients with RDs (Crohn's disease, rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis and psoriatic arthritis) that treated with anti TNF-α agents, admitted to University of Health Sciences, Ümraniye Training and Research Hospital, Chest Diseases Outpatient Clinic between January 10, 2010 and January 10,2020. The study was approved by University of Health Sciences, Ümraniye Training and Research Hospital Ethics Committee (235/ June 11, 2020). The trial was conducted in accordance with the Helsinki Declaration principles. Clinical, radiological and laboratory information were collected from our hospital's medical database. Each patient's data

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Received: 06.01.2021 **Accepted:** 07.03.2021

were observed for at least 5 years from the beginning of assignment, and patient's data were analyzed to evaluate the risk of TB development.

Demographic characteristics including age and gender, and clinical characteristics including RD and development of TB were examined. In order to determine active and latent TB, all patients had undergone a tuberculin skin test (TST) and a postero-anterior chest radiograph (CXR). According to national tuberculosis guideline, patients with latent tuberculosis infection (LTBI) received isoniazid (INH, H, 5 mg/kg with maximum dose 300 mg/d) for 9 months. LTBI was diagnosed as having a positive PPD (≥5mm)result or a positive quantiferon TB test in presence of a negative PPD (8). Anti TNF alpha treatment was started 1 month later than TB chemoprophylaxis.

Statistical Analysis

Patient data collected in the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 21.0 package program (Statistical Package for the Social Sciences, Chicago, IL, USA).

Discrete data were given as frequency and percentage. The mean±Standard deviation for continuous data was given as a descriptive value. The repeated measures of ANOVA test was used for evaluation of pre and post-treatment data. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

Among the 150 patients included in this study, 79 were male (52.7%), 71 were female (47.3%), and the mean age was 45±13 years. 63 (42.0%) had Crohn's disease, 41 (27.3%) had rheumatoid arthritis, 33 (22.0%) had ankylosing spondylitis, 6 (4.0%) had ulcerative colitis and 7 (4.7%) psoriatic arthritis.

There were 18 patients with hypertension (12%), 8 patients with diabetes mellitus (5.3%), 3 patients with asthma (2%), 2 patients with chronic obstructive pulmonary disease and 3 patients with coronary arterial disease.

Sixty six (44%) of the patients received adalimumab, 35 (23.3%) of the patients received infliximab, 17 (11.3%) of the patients received etanercept, 12 (8.0%) of the patients received golimumab, 10 (6.7%) of the patients received certolizumab. Ten patients (6.7%) received other anti TNF alpha agents such as tofacitinib, vedolizumab and abatacept. Additionally 61 (40.7%) of the patients received immunosuppressive drugs (**Table 1**). The mean number of peripheral blood cell counts and neutrophil/lymphocyte (N/L) ratio before and after anti TNF alpha treatment was shown in **Table 2**. The mean number of leukocytes were similar before and after treatment (p>0.05) while the mean number of neutrophils and lymphocytes were decreased significantly (p<0.05). The N/L ratio was significantly decreased after anti TNF alpha treatment (2.83±1.819 and 2.19±1.392 respectively, p<0.0001).

Table 1. Clinical, demographic and laboratory features of the patients

		n (%) or mean±SD*
Sex	Female	71 (47.3)
	Male	79 (52.7)
Age (years)		45±13
Follow up duration (years)		6±1
Rheumatoid disease	Crohn's disease	63 (42.0)
	Rheumatoid Arthritis	41 (27.3)
	Ankylosing Spondylitis	33 (22.0)
	Ulcerative colitis	6 (4.0)
	Pseuriatic arthritis	7 (4.7)
Anti-TNF alpha agent	Adalimumab	66 (44.0)
	Sertolizumab	10 (6.7)
	Etanercept	17 (11.3)
	Infliximab	35 (23.3)
	Golimumab	12 (8.0)
	Tofacitinib	4 (2.7)
	Vedolizumab	2 (1.3)
	Abatacept	4 (2.7)
INH chemoprophylaxis		124 (82.6)
TST	Negative (0-4 mm)	28 (18.7)
	Positive (≥5 mm)	122 (81.3)
Quantiferon TB	Not performed	136 (90.7)
	Negative	12 (8.0)
	Positive	2 (1.3)
Developed active TB		2 (1,3)
Additional immunosuppressive agent	None	89 (59.3)
	OCS**	6 (4.0)
	OCS+Leflunomide	5 (3.3)
	OCS+MTX***	7 (4.7)
	OCS+azathioprine	1 (0.7)
	Leflunomide	4 (2.7)
	Leflunomide+MTX	1 (0.7)
	MTX	6 (4.0)
	Azathioprine	27 (18.0)
	OCS+Leflunomide+MTX	4 (2.7)

*SD: Standard deviation, *OCS: Oral corticosteroid, **MTX: Methotrexate

Table 2. Laboratory values before and after anti TNF alpha treatment

	Pre-treatment (mean±SD)	Post-treatment (mean±SD)	p value
Number of leukocytes $\times 10^3$/ml	9758±17743	7604±2178	0.612
Number of neutrophils $\times 10^3$/ml	5367±2219	4440±1747	0.013
Number of lymphocytes $\times 10^3$/ml	2225±814	2415±950	0.003
N/L* ratio	2.83±1.819	2.19±1.392	0.0001

N/L: Neutrophil/lymphocyte.

Among the 150 patients, LTBI was diagnosed in 124 cases (122 had a positive PPD and 2 had a negative PPD but positive quantiferon test result) and were administered isoniazid. Two over 124 patients with LTBI developed active TB, one developed pulmonary TB 5 years after and one developed military TB 10 years after the beginning of anti TNF alpha therapy. Both of the patients had received chemoprophylaxis. Anti TNF alpha therapy was discontinued in patients immediately after the diagnosis of active TB. The characteristics of these patients are shown in the **Table 3**.

Table 3. Characteristics of patients with active TB

Characteristics	Patient 1	Patient 2
Age, years	38	49
Sex	Male	Female
Rheumatoid disease	Crohn's disease	Crohn's disease
Medication for RD	Adalimumab	Infliximab
TST (mm)	9	4
Quantiferon TB	Not perfomed	Positive
Chemoprophylaxis regimen	INH 9 months	INH 9 months
Site of active TB	Pulmonary	Miliary
Interval to active TB	5 years	10 years
Immunosuppressive drug	Yes (MTX)*	No
Number of lymphocytes, pre-treatment, $\times10^3$/ml	3410	780
Number of neutrophils, pre-treatment, $\times10^3$/ml	8690	4770
N/L ratio, pre-treatment	2.54	6.11
Number of lymphocytes, post-treatment, $\times10^3$/ml	3110	1150
Number of neutrophils, post-treatment, $\times10^3$/ml	4220	3820
N/L ratio, post-treatment	1.35	3.32

MTX: Methotrexate

DISCUSSION

To our knowledge this study is unique for the long duration of follow up the RD patients with anti TNF alpha therapy.

Adalimumab, infliximab and etanercept has been licensed and widely used in the treatment of rheumatoid diseases in our country. A nationwide study showed 6-fold increase in relative TB risk due to 2 years anti TNF alpha use in rheumatologic diseases and 4. 7-fold during 1 year anti TNF alpha therapy (9). In our study the patients who received anti TNF alpha therapy were followed at routine quarterly intervals for long term (5-10 years). Tuberculosis was diagnosed in two (1.3%) of 150 patients who were followed up regularly during anti TNF alpha treatment. One of the patient was on the 5th year of treatment and the other one was on the 10th year of treatment. This rate is higher than the incidence of tuberculosis in our country (8). Hanta et al. (10) reported 3 patients who were diagnosed with tuberculosis in the 3-year follow-up of 192 patients with RA, AS and PSA. The rate of active TB in this study (1.5%) was similar with our findings (1.3%). However, our follow up duration was longer than these studies.

Age older than 60 years was independent risk factor for TB among patients with anti TNF alpha treatment in previous studies that were higher than that in our study (11-13).

Tuberculosis is more common among men than women worldwide (14). In our study one of the patient was male and one of the patients was female.

It is reported in the systematic meta-analyses that RA patients treated with anti TNF alpha had increased risk of TB (15). While several studies reported no significantly increased risk of TB infection when anti TNF alpha were used to manage patients with Crohn's disease, a systematic meta-analysis found that the risk of TB was increased by using anti TNF alpha inhibitors in patients with Crohn's disease (16-18).

Most of our patients that we follow up, had Crohn's disease. The reason of the detection of TB, only in Crohn's disease patients, may be due to the clustering of the Crohn's disease cases in our study. The increased number of TB cases among Crohn's disease patients in our study needs to be further addressed in future studies.

The risk of TB according to the classes of anti TNF alpha drugs was found to different. A higher TB risk with infliximab or adalimumab was reported than with etanercept (19). In a study published in 2007 it was found that the risk of TB of patients with RA was 8.9 times higher than the general population. This rate was found to be 30.1 times higher in patients with RA who were treated with infliximab (20). In our study, the patient who received etanercept was diagnosed with miliary tuberculosis.

Latent TB was reactivated despite a chemoprophylaxis in two (1.3%) of the patients.

Our national TB guideline recommends 9 months of isoniazid prophylaxis for the treatment of latent TB infections defined as having a PPD result ≥5 mm or a positive interferon gamma release test such as quantiferon TB, prior to initiation of anti TNF alpha therapy. It was pointed out that the TB chemoprophylaxis could be effective for as long as 19 years and it must be repeated in case of a close contact with active tuberculosis patient (8). The two patients developed active TB denied a close contact with an active TB cases, so the INH prophylaxis was not repeated.

Researchers reported the active TB cases despite INH prophylaxis during maximum 3 years follow up. Sichletidis et al. (21) found that eleven patients developed active TB among 45 patients. In another study of the total

of 255 patients whom were diagnosed with latent TB, 5 patients developed active TB after LTBI treatment and the maximum duration of time to TB after anti TNF alpha initiation was 73,2 months (22).

It was previously shown that the decreased number of lymphocytes is a risk factor for developing TB (23,24). Berhane et al. (25) reported that N/L ratio over 2.7 is a predictive parameter in diagnosis of pulmonary tuberculosis. One of our patient developed TB had a N/L ratio over 2.7 but the other did not. In our study the mean number of neutrophils, lymphocytes and N/L ratio was decreased significantly ($p<0.05$) after anti TNF alpha treatment but as the number of patients developed TB was small we could not show a relation between neither number of peripheral blood cells nor N/L ratio and developing TB.

Compared to the studies in the literature, we observed the patients for longer duration. TB developed in two patients among 124 patients who received INH prophylaxis. It is possible that long-term anti TNF alpha therapy may predispose patients to both de novo TB infection and reactivation of latent TB. Periodic regimens may be more effective for these patients.

Limitations: Only 2 of 150 patients developed tuberculosis so the risk for developing active TB could not be analyzed.

CONCLUSION

As a result of this study, we want to draw attention to the risk of TB development in an RD patient without latent TB. In an RD patient without latent TB, the risk of TB should be kept in mind even after 10 years. Regular monitoring should be considered for long term TNF antagonist therapy.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by University of Health Sciences, Ümraniye Training and Research Hospital Ethics Committee (235/June 11,2020).

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.

Financial Disclosure: None.

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

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.860076

Anatolian Curr Med J 2021; 3(2); 120-123

Local plus sedoanalgesia or spinal analgesia in endovascular aortic aneurysm repair experiences in a single center

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Cite this article as: Doğukan M, Uludağ Ö, Duran M, et al. Local plus sedoanalgesia or spinal analgesia in endovascular aortic aneurysm repair experiences in a single center. Anatolian Curr Med J 2021; 3(2); 120-123.

ABSTRACT

Aim: In this study, we aimed to discuss the local anesthesia plus sedoanalgesia (LA-SA) and spinal anesthesia methods applied during endovascular aortic repair (EVAR) by retrospectively comparing the patients' data.

Material and Method: This study was carried out by retrospectively evaluating the data of 36 patients, who underwent endovascular surgery for aortic aneurysm, between 1 January 2013 and 31 December 2018. Three cases who were applied general anesthesia were not included in the study.The patients included in the study were divided into two groups according to the anesthesia method as LA-SA group (Group 1, n=19) and spinal anesthesia group (Group 2, n=14). This study was planned as a retrospective observational comparative study. Demographic data, comorbidities, American Anesthesiologists Association (ASA) risk classification scores, mortality rates, duration of anesthesia and surgery, length of stay in the hospital and intensive care unit, and laboratory values were analyzed.

Results: In current study, the mean age of 33 patients who underwent EVAR procedure was 69.04±13 (32-86). Local anesthesia plus sedo-analgesia was applied to 19 (52.7%) patients and spinal anesthesia was applied to 14 (38.8%) patients. No significant difference was found between demographic data, comorbidities and smoking rates in both groups. The length of stay in the hospital and the intensive care unit and the rates of death before discharge were similar in both groups (p=0.22), (p=0.15), (p=0.73), Anesthesia and operation times were shorter in the local anesthesia plus sedoanalgesia group compared to the spinal anesthesia group (p = 0.00, p = 0.004, respectively). Laboratory examinations of both groups were similar.

Conclusion: For arterial stents requiring percutaneous implantation, LA-SA provides a safe anesthesia method with stable hemodynamics, less invasive intervention and shorter operation times than neuraxial anesthesia.

Keywords: Endovascular aortic repair, local anesthesia sedoanalgesia, spinal anesthesia

INTRODUCTION

Abdominal aortic aneurysm (AAA) is very common among aortic pathologies. An enlargement of 1.5 times the normal segment or a total of more than 3 cm is considered an abdominal aortic aneurysm (1). The main risk factors for AAA can be stated as age, male gender, high blood pressure, smoking and family history (2). AAA is seen especially in the advanced age group. In the last thirty years, endovascular repair (EVAR) combined with neuraxial anesthesia or sedoanalgesia has been used instead of open surgery under general anesthesia, especially in patients with high complication rates (1). AAA's Endovascular Repair (EVAR) was introduced in 1990 to offer a lower-risk alternative to traditional open surgical repair (1). Although it was initially preferred in the patient group with high risk and systemic problems, many advantages such as providing lower mortality and morbidity rates, shortening the duration of hospital stay and reducing the use of blood products have enabled it to be used more and more (2-4). Sedoanalgesia is successfully used in EVAR (4,5). Although general anesthesia was used more frequently in the first years, LA-SA is used more frequently today (6). Today, local anesthesia plus sedoanalgesia and spinal anesthesia have largely replaced general anesthesia. Both methods have advantages and disadvantages. In this study, it was aimed to compare the methods of LA-SA and spinal anesthesia applied to patients during endovascular aortic repair.

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Received: 13.01.2021 **Accepted:** 27.01.2021

MATERIAL AND METHOD

After the approval of the Ethics Committee of Adıyaman University Faculty of Medicine was obtained (Meeting: 4, Decision No: 2018/4-29), the patient files and anesthesia records of 36 patients who underwent EVAR procedure with the diagnosis of aortic aneurysmbetween 1 January 2013 and 31 December 2018 were evaluated retrospectively. The trial was conducted in accordance with the Helsinki Declaration principles. A total of 33 cases who underwent neuraxial anesthesia and LA-SA were included in the study for Endovascular Aortic Repair on the specified dates. Aortic dissections were not included in the study. Again, it was understood from the file scan that all patients were taken by the same surgical team. The patients were divided into two groups. The LA-SA Group (GroupLA-SA, n=19), and the Spinal Anesthesia Group (GroupSA, n=14). It was determined that the electrocardiography, peripheral oxygen saturation, and noninvasive blood pressure measurements of all cases were monitored routinely. In sedation administrations, in addition to local anesthesia by the surgeon in the form of skin infiltration, 0.05-0.1 mg/kg Midazolam (Zolamide, Vem, Turkey), and 0.5-1 μg/kg Fentanyl (Talinat®, Vem, Turkey) were given intravenously (iv).The sedation scale of the patients was followed with the Ramsey-Sedation scale (RSS). No additional doses were administered to the patients with RSS≥4. It was determined that the patients with RSS<4 were administered with 1 μg/kg (iv) Remifental (Ultiva®, GlaxoSmithKline, Belgium) in 30-60 seconds. In the patient who underwent LA-SA, 0.5-1mg/kg tramadol hydrochloride and 20 mg Dexketoprofen were administered for postoperative analgesia. It was observed that 12.5 mg Bupivacaine (Heavy Marcaine®, Turkey), and 25 μg Fentanyl were administered for spinal anesthesia. The sensory blocks of the patients were evaluated with the Pin-Prick test, and Motor Block Level Bromagescale.

The intraoperative heparin administration was delayed approximately 1 hour after the spinal needle was inserted in the Neuraxial Anesthesia Group. The patient files, demographic data of the patients, concomitant diseases, American Anesthesiologists Association risk classification scores, anesthesia and surgery duration, length of hospital and intensive care stay, mortality rates, preoperative and postoperative hemoglobin, hematocrit, platelet, mean platelet volume, urea, creatinine and albumin values were examined.

Statistical Analysis

The SPSS (Statistical Package for Social Sciences) and Windows 17.0 program were used for the statistical analyses. Numerical data were expressed as median, standard deviation, and categorical data as percentages. These patients were divided into two groups as local anesthesia plus sedoanalgesia and spinal anesthesia. Intragroup comparisons were made by repeated measures analysis. Chi-square test is used for the comparison of categorical data. Independent t test was used to compare independent groups.p <0.05 was considered statistically significant.

RESULTS

In current study the mean age of 33 patients who underwent EVAR procedure was 69.04±13 (32-86). It was observed that local anesthesia plus sedoanalgesia was applied to 19 (52.7%) patients and spinalanesthesia was applied to 14 (38.8%) patients. No significant difference was found between the demographic data (p=0.77), comorbidities (p=0.61) and smoking rates (p=0.88) in both groups (**Table 1**). The length of stay in the hospital (p=0.22), the intensive care unit (p=0.15), and the pre-discharge rates (p=0.73) were similar in both groups. The duration of anesthesia administration (p=0.001) and operation times (p=0.004) were statistically shorter in the localanesthesia plus sedoanalgesia group (**Table 2**). Compared to the preoperative values, postoperative hemoglobin, hematocrit, and albumin values were statistically lower (p<0.05), whereas MPV values were statistically higher for both groups (p<0.05) (**Table 3**).

Table 1. The comparison of the demographic data and additional diseases of the cases undergoing EVAR

Group	Group LA-SA n=19	GroupSA n=14	p
Gender (Male/Female)	14/5	11/3	0.75
Age (year)	72.83	65.28	0.77
Hypertension	15 (78.9%)	10 (66.0%)	0.61
Diabetes	5 (26.3%)	6 (42.8%)	0.33
Pulmonary disease	4 (21.0%)	2 (40.0%)	0.68
Smoking	14 (73.6%)	10 (66.0%)	0.88
ASA II/III	9/10	7/7	0.59

LA-SA; localanesthesia plus sedoanalgesia, ASA; American Society of Aneshesiologists Chi-square was used for in-group comparisons

Table 2. The comparison of the cases undergoing EVAR in terms of hospital and ıntensive care unit stays, surgery durations and anesthesia durations

Group	Group LA-SA n=19	GroupSA n=14	p
Intensive care unit stay (day)	1.4	1.2	0.22
Hospital stay (day)	6	5	0.15
Anesthesia duration (minutes)	135	151	0.01
Surgery duration (minutes)	122	138	0.04
Mortality	2	1	0.73

p<0.05 statistically significant LA-SA; localanesthesia plus sedoanalgesia , SA; Spinal anesthesia, Chi-square was used for in-group comparisons.

Table 3. The comparison of the cases undergoing EVAR in terms of preoperative and postoperative hemoglobin, hematocrit, platelet, meanplatelet volume, urea, creatinine and albumin value

Group	Group LA-SA n=19	p	Group SA n=14	p
Preop./Postop. Hgb	11.9±1.6/10.9±1.4	0.008	12.1±1.4/11.0±1.2	0.007
Preop./Postop. Hct	36.5±4.6/33.1±4.5	0.001	36.8±4.2/34.4±4.3	0.015
Preop./Postop. Plt	259.3±50.0/238.4±65.9	0.108	200.4±62.7/173.2±68.9	0.204
Preop./Postop. Mpv	6.9±1.3/7.4±1.7	0.044	7.8±1.3/8.8±1.5	0.015
Preop./Postop. Urea	50.0±32.1/48.05±23.8	0.747	46.2±23.3/50.7±32.2	0.290
Preop./Postop. Cr	1.0±0.7/1.1±0.4	0.663	1.1±0.46/1.2±04	0.054
Preop./Postop. Alb	3.0±0.5/2.6±0.5	0.009	3.2±0.5/2.9±0.5	0.003

p<0.05 statistically significant, LA-SA; localanesthesi aplus sedoanalgesia, SA; Spinalanesthesia, Preop; preoperative, Postop; postoperative, Hgb;Hemoglobin, Hct; Hematocrit, Plt; Platelet, Mpv; MeanPlatelet Volume, Cr: Creatinine, Alb: Albumin I Independent T Test were used to compare the preoperative and postoperative laboratory values of the two groups

DISCUSSION

Abdominal aortic aneurysms, especially aneurysm ruptures, are life-threatening events that have high mortality. The introduction of endovascular aneurysm repair, which was developed as an alternative to traditional open repairs, led to a decrease in mortality and morbidity in such patients. In early years, EVAR applications were mostly applied to a higher-risk patient group. Since endovascular repair of abdominal aortic aneurysms is carried out with a less invasive technique compared to conventional open surgical repair, a lower-risk treatment alternative has been introduced for many patients with aortic aneurysms and aortic dissection in recent years. Local anesthesia, regional anesthesia and general anesthesia techniques are used for this procedure. Since early procedures usually require long surgical durations, general anesthesia is applied to improve patient compliance.

The EVAR procedure carried out in our hospital was performed under LA-SA at a rate of 52.7%, and under spinal anesthesia at a rate of 38.8%. The demographic data of the patients in bothgroups, hospital and intensive care stays, mortality rates before discharge were found to be similar. Anesthesia and operation durations were statistically longer in the spinal anesthesia group than in LA-SA group. Hypotension developed in four patients (28.5%) who underwent spinal anesthesia, and was resolved with the addition of 10 mg iv ephedrine. No other complications or epidural hematoma occurred because of spinal anesthesia in the spinal group.

Unlike our study, general anesthesia was applied mostly in the first studies. In a wide scale article in 2006, the patients underwent general anesthesia (69%), regional anesthesia (25%), and local anesthesia (6%). In the same study, it was shown that patients benefited more when local anesthesia technique was used for EVAR (7). In a literature review released in 2019, no differences were detected in mortality between local anesthesia for EVAR and general anesthesia group (8). In another article released in 2019, 30-day mortality of the patients who underwent general anesthesia was compared with local anesthesia group,and mortality was found to be less in the local anesthesia group (9). In another comprehensive article released in 2011, the anesthesia types were applied as general anesthesia (81%), spinal anesthesia (7%), epidural anesthesia (5.5%), and local anesthesia (6.5%). General anesthesia was used more in this study and general anesthesia was found to be associated with hospital stay and pulmonary morbidity compared to spinal and local anesthesia (10). Since the selection of anesthesia technique might be tolerated with neuraxial anesthesia, local anesthesia and sedation for arterial stents, which require percutaneous placement with limited incision, the general anesthesia application has gradually decreased. With increased experience of doctors, and with the development of more modern devices, the use of regional anesthetics as well as local anesthetics supported by mild sedation has increased (11-13).

In a study conducted in our country, a total of 77.1% of the patients underwent LA-SA, 22.8% general anesthesia was applied, and it was reported that local anesthesia plus sedation provided safe and comfortable environment for endovascular applications (14). In another study, the intensive care and hospitalization duration of patients in the local anesthesia group were shorter than regional and general anesthesia groups (15). The incidence of respiratory complications is lower in local anesthesia compared to local anesthesia and general anesthesia in patients who undergo EVAR.

The use of procedures regarding neuraxial anesthesia in these patients must be conducted after careful risk-benefit analysis, and after strict and guideline-compliant discontinuation of anticoagulant therapy (16). When using neuraxial anesthesia, intraoperative heparin administration is postponed approximately 1 hour after the epidural catheter insertion because of epidural hematoma risk (17,18). Although it is a rare complication of neuraxial blockade with epidural hematoma, neuraxial anesthesia is not applied in some centers because of the intraoperative heparin administration. In patients who undergo regional anesthesia, the request to wait 1 hour after the intraoperative heparin administration might affect the operation and anesthesia durations. In our study, the anesthesia and operation durations were statistically shorter in the LA-SA group than the regional anesthesia group.

The selection of anesthesia technique might vary depending on the planned surgical interventions, comorbid conditions of the patient, preoperative and on the intraoperative anticoagulation use. LA-SAfor arterial stents, which require percutaneous insertion with limited incision, has been used as a safe anesthesia method in recent years, and is well-tolerated by the majority of patients. The retrospective natureof our study and the fact that very few cases were taken in our hospital (an average of 5-6 cases a year) were the limitations of this study.

CONCLUSIONS

For arterial stents requiring percutaneous placement with minimally invasive methods, LA-SA provides a safe anesthesia as a less invasive method that provides shorter operation times than stable hemodynamic and neuraxial anesthesia.

ETHICAL DECLARATIONS

Ethics Committee Approval: After the approval of the Ethics Committee of Adıyaman University Faculty of Medicine was obtained (Meeting: 4, Decision No: 2018/4-29).

Informed Consent: Because the study was designed retrospectively, no written informed consentform 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.

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.861720

Anatolian Curr Med J 2021; 3(2); 124-129

The effect of adding morphine to intratecal bupivacaine on postoperative analgesia in patients with anorectal surgery

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Cite this article as: Babayiğit M. The effect of adding morphine to intratecal bupivacaine on postoperative analgesia in patients with anorectal surgery. Anatolian Curr Med J 2021; 3(2); 124-129.

ABSTRACT

Aim: Pain is the major problem in early postoperative period after anorectal operations. In this study, we aimed to evaluate the first analgesic requirement time and complications of intrathecal 5 mg hyperbaric bupivacaine, intrathecal 5 mg hyperbaric bupivacaine with intrathecal 50 µg and 100 µg of morphine combinations in anorectal surgery.

Material and Method: A total of 60 patients divided into 3 groups, including 20 patients in each group, were included for the study;Group 1: 5 mg 0.5% heavy bupivacaine (HB), Group 2: 5 mg 0.5% HB and 50 µg Morphine,Group 3: 5 mg 0.5% HB and 100 µg Morphine was intrathecally administered. Intraoperative and postoperative hemodynamics, time to urination and first analgesia requirement, perioperative and postoperative side effects were recorded

Results: The time to first analgesic requirement in Group 1 (305.40±143.86) was statistically significantly lower than Group 2 (435.50±171.70) and Group 3 (435.50±156.08) ($p=0.015$). No significant difference was found between urinary retention ($p>0.05$). It was determined that the postoperative nausea and vomiting percentages (25.0%) in Group 3 were statistically significantly higher than Group 2 (5.0%) and Group 1 (0.0%) ($p<0.05$).

Conclusions: The use of 50 µg of intrathecal morphine in patients undergoing anorectal surgery in saddle block anesthesia has the expected effect on postoperative analgesia and for this reason it is considered appropriate to be preferred in anorectal surgery thus to the minimal adverse side effects.

Keywords: Anorectal surgery, pain, bupivacaine, intratechal, morphine

INTRODUCTION

While 41% of the patients complained of severe or moderate pain on the first day after surgical interventions, more than half of the patients felt more pain than they expected in the early postoperative period after anorectal surgery (1,2). Therefore, in perianal operations, it is important to provide effective analgesia during the early postoperative period as well as during the operation.

Perianal operations performed for benign anal pathologies are short-term procedures and patients are usually discharged the next day. Therefore, neuraxial blocks, especially saddle spinal anesthesia is the safest and most preferred method in anesthesia management. Saddle block was found to be more effective than lumbar epidural or caudal block for depressing anal sphincter tone (3).In saddle spinal anesthesia, it is preferred to use low-dose, short-acting local anesthetic agents together with opioids to avoid motor block and provide adequate surgical anesthesia. Intrathecal addition of morphine to local anesthetics during spinal anesthesia also provided effective postoperative analgesia after a series of surgical procedures (4,5).

Morphine is preferred because of its long duration of action and its long postoperative analgesic effect (6). However, side effects such as nausea, vomiting, itching, fatigue, urinary retention, delayed respiratory depression and sedation are seen at various rates depending on the dose and disrupt patient comfort (7). Therefore, the lowest morphine dose with the incidence of side effects becomes important while providing effective analgesia.

In this study, we aimed to evaluate the effect of adding 50 µg or 100 µg of morphine (Morphine HCL) on intrathecal 5 mg hyperbaric bupivacaine (Bustesin spinal heavy 0.5%) on postoperative analgesia before anorectal surgery.

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Received: 15.01.2021 **Accepted:** 29.01.2021

MATERIAL AND METHOD

The study protocol was approved by the Ethics Committee of the Keçiören Training and Research Hospital (date/approval number: 27.08.2014/651). The trial was conducted in accordance with the Helsinki Declaration principles and all volunteers provided written informed consent.

American Society of Anesthesiologists (ASA) physical status I-II and patients over the age of 18 who were scheduled for anorectal surgery in our hospital were included in the study. Patients who did not accept regional anesthesia, ASA III-IV and patients who have coronary artery disease, hypertension, heart failure, arterial aneurysm, epilepsy, intracranial mass, liver failure, renal failure, abnormal coagulation profile, patients who were constantly using narcotic analgesics and allergic to study drugs were excluded from the study. The patients were divided into 3 groups using the closed envelope technique. The study was planned as double blind, and anesthesia application and intraoperative and postoperative patient follow-up were performed by different researchers. Following standard monitoring, saddle spinal anesthesia technique was applied with a 25 gauge spinal needle with a midline approach from the L3-4 interval in the sitting position. The patients were kept in this position for 5 min to achieve sufficient block. Sensory block was evaluated by the pin-prick method until sufficient block reached the S4 level. Motor block was evaluated according to a modified Bromage scale.

A total of 60 patients, including 20 patients in each group, were included for the study;

- Group 1: 5 mg 0.5% heavy bupivacaine (HB),
- Group 2: 5 mg 0.5% HB and 50 μg Morphine,
- Group 3: 5 mg 0.5% HB and 100 μg Morphine was intrathecally administered.

The patient, the anesthesiologist performing the saddle block, the anesthesiologist who followed the peroperative and postoperative patients and the surgeon were blind to the study.

Intramuscular 75 mg diclofenac sodium was administered when additional analgesic was required in the postoperative period.

Age, gender, height, body weight of patients during preoperative evaluation, intraoperative 1-10-20-30-40-60. systolic arterial pressure per minute, diastolic arterial pressure, mean arterial pressure (MAP), heart rate (HR), additional drug use and amounts were recorded. Spinal anesthesia time, surgery initiation time, and surgical ending time were recorded. Time to urination and first analgesia requirement were evaluated and recorded. Perioperative and postoperative side effects; Sedation, respiratory depression, nausea, vomiting, motor block and urinary retention were recorded.

Statistical Analysis

Expressions such as mean±standard deviation and median (min-max) were used for continuous variables, and numbers and percentages were used for categorical data. In the intergroup analysis of continuous variables, normality analyzes were performed using the Kolmogorov-Smirnov Goodness of Fit Test. In the analyzes between the three groups, the Oneway ANOVA (Post hoc: LSD) Test was used in cases where the variables fit the normal distribution, and the Kruskal Wallis Test (Mann Whitney U Test for further analysis) was used when it did not. Friedman Test was used for analysis between dependent groups, and comparison of categorical data was made using Chi-Square Test. The Pearson Correlation coefficient was used to determine the linear relationship (correlation) between variables. Analyzes were done with IBM SPSS Package Program version 24.0 (IBM Corporation, Armonk, NY, USA). Statistical significance level was taken as $p<0.05$.

RESULTS

No statistically significant difference was found between the groups in terms of age, gender, body mass index (BMI), mean operation time, ASA, type of surgery performed and position ($p>0.05$, **Table 1**).

Generally, Group 1 peroperative heart rate values were found to be lower than Group 2 and Group 3. While Group 3 beginning (0th minute) heart rate values (87.85±10.53) were significantly higher than Group 1 (78.95±11.63), it was determined that the 15th minute peroperative heart rate values were significantly higher in Group 2 (81.50±12.93) compared to Group 1 (73.15±9.33) ($p<0.05$). The peroperative heart rate levels (0-45 minutes) within the groups were not statistically significant ($p>0.05$). There was no significant difference in MAP values between the groups (**Table 2**).

The 6th hour HR values in Group 2 (81.65±9.42) were significantly higher than Group 3 (73.55±8.70). In addition, it was determined that the 24th hour MAP values were significantly higher in Group 3 (91.53±6.53) compared to Group 1 (85.79±5.76) ($p<0.05$). The postoperative HR levels (1-24 hours) within the groups made a significant difference in Group 3. In terms of HR values in Group 3, the 12th and 24th hour values increased significantly compared to the 1st to 6th hours ($p<0.05$, **Table 3**).

It was determined that the postoperative nausea and vomiting percentages (25.0%) in Group 3 were statistically significantly higher than Group 2 (5.0%) and Group 1 (0.0%) ($p<0.05$). Sedation, respiratory

depression, motor block was not developed in any patient, and no significant difference was found between the rates of headache, hypotension, bradycardia and urinary retention (p>0.05, **Table 4**).

The time to first analgesic requirement in Group 1 (305.40±143.86) was statistically significantly lower than Group 2 (435.50±171.70) and Group 3 (435.50±156.08) was determined (p=0.015, **Table 5**).

Table 1. Comparison of some descriptive characteristics of the groups

	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	Total (n=60)	p
Age (years) (Mean±SD)	39.55±11.9	38.60±12.78	40.35±13.08	39.50±12.39	0.908*
BMI (kg/m^2) (Mean±SD)	26.63±4.99	25.69±4.07	27.12±2.70	26.48±4.01	0.526*
Operation time (min) (Mean±SD)	27.60±8.27	28.45±11.07	32.80±11.16	29.62±10.61	0.255*
Gender (n,%)					0.918**
Female	6 (30.0%)	5 (25.0%)	5 (25.0%)	16 (26.7%)	
Male	14 (70.0%)	15 (75.0%)	15 (75.0%)	44 (73.3%)	
ASA (n,%)					0.415**
I	13 (65.0%)	15 (75.0%)	11 (55.0%)	39 (65.0%)	
II	7 (35.0%)	5 (25.0%)	9 (45.0%)	21 (45.0%)	
Operation type (n,%)					0.118**
Hemorrhoidectomy	6 (30.0%)	1 (5.0%)	6 (30.0%)	13 (21.7%)	
Fistulotomy	9 (45.0%)	8 (40.0%)	9 (45.0%)	26 (43.3%)	
Sphincterotomy	5 (25.0%)	11 (55.0%)	5 (25.0%)	21 (35.0%)	
Position (n,%)					0.166**
Jack knife	11 (55.0%)	16 (80.0%)	11 (55.0%)	38 (63.3%)	
Lithotomy	9 (45.0%)	4 (20.0%)	9 (45.0%)	22 (36.7%)	
Total	68 (100%)	88 (100%)	88 (100%)	156 (100%)	

* One-way ANOVA Test
** Chi-square Test

Table 2. Comparison of the peroperative HR and MAP values of the groups

	HR 0. min	HR 5. min	HR 10. min	HR 15. min	HR 20. min	HR 30. min	HR 45. min	p[1]
Group 1	78.95±11.63**a	76.05±11.59	75.50±13.61	73.85±11.55**a	73.15±9.33	73.00±10.23	75.00±6.37	0.663*
Group 2	84.05±11.81	82.45±12.13	82.75±14.14	81.65±11.20**a	81.50±12.93	78.56±15.58	85.75±12.71	0.981*
Group 3	87.85±10.53**a	85.50±12.14	82.10±10.74	78.90±9.29	78.75±9.22	77.86±9.08	78.86±7.96	0.143*
	p2=0.042**	p2=0.086**	p2=0.098**	p2=0.043**	p2=0.061**	p2=0.473**	p2=0.275**	
	MAP 0. min	**MAP 5. min**	**MAP 10.min**	**MAP 15. min**	**MAP 20. min**	**MAP 30.min**	**MAP 45.min**	
Group 1	101.15±15.78	97.25±22.22	92.90±14.36	90.60±17.20	89.90±13.63	92.09±14.18	90.00±9.79	0.528*
Group 2	99.40±16.76	91.45±23.69	90.30±8.46	93.50±8.18	90.18±7.06	91.09±9.04	91.00±4.69	0.461*
Group 3	103.45±12.70	90.65±22.59	93.30±6.64	91.70±8.41	90.25±7.94	90.71±6.79	89.29±1.25	0.253*
	p2=0.640**	p2=0.972**	p2=0.443**	p2=0.199**	p2=0.718**	p2=0.571**	p2=0.888**	

* Friedman Test; ** Kruskal Wallis Test (Post hoc:aMann Whitney U Test)
HR: Heart rate MAP: Mean arterial pressure

Table 3. Comparison of the postoperative HR and MAP values of the groups

	HR 1.st hour	HR 2.nd hour	HR 3.rd hour	HR 4.th hour	HR 12.th hour	HR 24.th hour	p[1]
Group 1	73.55±12.21	74.20±12.71	73.15±10.22	76.55±9.09	76.65±10.09	75.68±8.91	0.074*
Group 2	79.25±10.43	77.50±9.76	80.35±10.04	81.65±9.42**a	81.25±7.99	80.28±7.37	0.981*
Group 3	72.80±12.20*	74.45±9.92	72.45±8.71*	73.55±8.70**a	76.00±8.15*	75.11±7.07*	0.007*
	p2=0.131**	p2=0.509**	p2=0.055**	p2=0.046**	p2=0.120**	p2=0.133**	
	MAP 1.st hour	**MAP 2.nd hour**	**MAP 4.th hour**	**MAP 6.th hour**	**MAP12.th hour**	**MAP24.th hour**	
Group 1	85.10±12.75	85.20±13.50	84.85±11.20**a	83.95±12.30	84.90±6.72	85.79±5.76**a	0.745*
Group 2	92.50±13.21*	89.10±11.37*	90.65±8.46**a	89.20±7.99	88.10±8.12*	89.89±6.16*	0.036*
Group 3	113.90±131.21*	87.20±9.89	87.05±8.84	83.00±19.94*	88.55±6.21	*91.53±6.53**a	0.031*
	p2=0.135**	p2=0.333**	p2=0.058**	p2=0.062**	p2=0.227**	p2=0.027**	

* Friedman Test; ** Kruskal Wallis Test (Post hoc:aMann Whitney U Test)
HR: Heart rate , MAP: Mean arterial pressure

Table 4. Comparison of treatment groups according to postoperative side effects

	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	Total (n=60)	p
Nausea, vomiting (n,%)					0.020*
No	20 (100.0%)	19 (95.0%)	15 (75.0%)	54 (90.0%)	
Yes	0 (0.0%)	1 (5.0%)	5 (25.0%)	6 (10.0%)	
Headache (n,%)					0.322*
No	19 (95.0%)	18 (90.0%)	16 (80.0%)	53 (88.3%)	
Yes	1 (5.0%)	2 (10.0%)	4 (20.0%)	7 (11.7%)	
Hypotension (n,%)					0.596*
No	20 (100.0%)	19 (95.0%)	19 (95.0%)	58 (96.7%)	
Yes	0 (0.0%)	1 (5.0%)	1 (5.0%)	2 (3.3%)	
Bradycardia (n,%)					0.362*
No	20 (100.0%)	20 (100.0%)	19 (95.0%)	59 (98.3%)	
Yes	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (1.7%)	
Urinary retention (n,%)					0.108*
No	20 (100.0%)	18 (90.0%)	16 (80.0%)	54 (90.0%)	
Yes	0 (0.0%)	2 (10.0%)	4 (20.0%)	6 (10.0%)	
Total	68 (100%)	88 (100%)	88 (100%)	156 (100%)	

* Chi-square Test

Table 5. Comparison of some descriptive characteristics of the groups

	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	p
First urination time (min) (Mean±Sd)	194.25±53.63	205.50±57.42	190.25±57.86	0.676*
First analgesic time (min) (Mean±Sd)	305.40±143.86*	435.50±171.70	435.50±156.08	0.015*

* One way ANOVA Test (Post hoc:LSD)
** Kruskal Wallis Test

DISCUSSION

The anoderm consists of keratinized, stratified squamous epithelium and is extremely sensitive to pain because it has somatic nerve endings. Surgery of benign anorectal diseases such as hemorrhoids, anal fissure, and perianal abscess causes more pain than many other surgical procedures. Postoperative pain is the most common surgical complication of classical hemorrhoidectomy (8).High maximum resting pressure (MRP) values measured by anal manometry reflect the hyperactivity of the anal sphincter muscles and even spasm (9). It has been suggested that this spasm is a cause of severe pain after hemorrhoidectomy (10). The Saddle block we used in this study is effective in reducing anal sphincter tone and controlling postoperative pain.

Direct application of morphine to the intrathecal space provides spinal analgesia. Therefore, intrathecal morphine provides long-term pain relief in the postoperative period (7,11). Uchiyama Ave et al. (8) used 0.05, 0.1 and 0.2 mg of morphine intrathecally in cesarean sections and stated that pain control was better in the group using 0.1 and 0.2 mg morphine compared to the control group without morphine (12). In another study in which 0.1 and 0.2 mg morphine doses were used in cesarean sections, no significant difference was found between the two doses in terms of postoperative analgesia (13). Ozbek et al. (14) found that postoperative analgesic requirement was reduced in patients undergoing (transurethral resection of the prostate) TURP with spinal anesthesia who received 150 µg intrathecal morphine versus those who received 75 µg intrathecal morphine. Duman et al. (15) reported that in patients undergoing TURP, intrathecal morphine at a dose of 25 µg provides sufficient postoperative analgesia similar to a dose of 50 µg.In this study, it was observed that the time for the first analgesic requirement in the intrathecal morphine group was approximately two hours longer than the group without morphine. However, there was no difference between the 50 µg and 100 µg intrathecal morphine groups.

The usefulness of intrathecal morphine is limited at doses more than 300 µg due to its side effects (11). These side effects include nausea, vomiting, itching, weakness, urinary retention, delayed type respiratory depression and sedation. We did not experience itching or respiratory depression in any of the patients during this study.

In the study conducted by Baytas (16) on patients who underwent cesarean section, they did not find a significant difference between the groups at the 10^{th}, 20^{th}, 30^{th}, 50^{th}, 60^{th} and 70^{th} minutes of the operation in the comparison of the mean blood pressure of the patients according to the groups. They reported higher blood pressure values

in the 0.1 mg morphine group compared to the 0.05mg group. In a different study conducted between the groups in which 5 μg/kg intrathecal morphine was used and morphine was not used, no difference was found in terms of hemodynamic parameters (17). In this study, we found no significant difference between the groups in terms of peroperative MAP values. However, in terms of postoperative HR levels, a significant decrease was detected in group 3 in the first 6 hours.

It has been observed that nausea and vomiting, which are among the common postoperative side effects, increase to very high rates when the intrathecal morphine dose exceeds 100 μg, especially at 200 μg levels (18,19). Sakai et al. (20) showed that the use of 50 and 100 μg intrathecal morphine in TURP operations created a similar analgesic effect, and the frequency of side effects increased with the use of 100 μg morphine, increasing from 23% to 33%. In our study, in accordance with the literature, although both doses of morphine produced similar analgesic effects, it was observed that nausea and vomiting increased in group 3, where the intrathecal morphine dose was 100 μg, compared to the other groups. The frequency of nausea was 1% in Group 2 and 5% in Group 3, and it was found to be quite low compared to the study of Sakai et al. (20). We believe that the reason for this was the application of saddle spinal anesthesia with hyperbaric bupivacaine in our study, while a sensory block was created reaching T4-T8 levels with tetracaine. With the use of hyperbaric local anesthesia, the saddle spinal anesthesia technique prevents the cephalic spread of intrathecally administered drugs, and the frequency of side effects associated with these drugs decreases. In this way, in perianal surgeries such as hemorrhoidectomy, which is quite painful, the use of strong analgesic morphine together with intrathecal local anesthetics provides effective anesthesia and analgesia. In addition to reducing anal sphincter tone, this method is used by anesthetists especially in anorectal surgeries due to this advantage.

After anorectal surgery, urinary retention may occur due to temporary detrusor muscle dysfunction, secondary urethral spasm, and overhydration (21). It has been shown that it increases with age and the risk is 2.4 times higher in patients over 50 years old. After anorectal surgery, the incidence of postoperative urinary incontinence ranges between 2.3-21.9% (22).

The hydrophilic nature of morphine delays its systemic uptake resulting in a higher drug concentration in the lumbar region. As a result, while providing better analgesia, it also brings the risk of urinary retention (21-23). Moreira et al. (21) investigated the postoperative effects of intrathecal 7 mg of hyperbaric bupivacaine and 80 μg of morphine in hemorrhoidectomy surgery. They reported that while better analgesia was provided in the morphine group, 15% urinary retention developed, and there was no retention in the group without morphine. Similarly, in our study, it was determined that no urinary retention developed in the control group, while it was 10% in the 50 μg morphine group and 20% in the 100 μg morphine group. It is seen that as the morphine dose increases, the incidence of urinary retention increases depending on the dose.

One of the weak points of this study is the small number of patients. The number of patients was chosen based on the literature. In addition, we believe that it is very valuable since it is a prospective study and the number of studies on intrathecal morphine use in anorectal surgery is limited.

CONCLUSION

In this study, it was observed that the time for the first analgesic requirement in the groups in which intrathecal morphine was used was approximately two hours longer than the group without morphine. However, there was no difference between the 50 μg and 100 μg intrathecal morphine groups. In group 3, where the intrathecal morphine dose was 100 μg, it was observed that nausea and vomiting increased compared to the other groups.It is thought that the use of 50 μg of intrathecal morphine in patients undergoing anorectal surgery in saddle block anesthesia has the expected effect on postoperative analgesia and it is considered appropriate to be preferred in anorectal surgery because it causes minimal adverse side effects.

ETHICAL DECLARATIONS

Ethics Committee Approval: Appropriate Keçiören Training and Research Ethics Committee (IRB) approval has been obtained for the research reported (27.08.2014/651).

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.

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.

Acknowledgements: We would like to thank Assoc. Prof. Dr. Esra OZAYAR (Chief of Anesthesiology Clinic, University of Healh Science, Kecioren Training and

Research Hospital) and Assoc. Prof. Dr. Hakan BULUS (Chief of General Surgery Clinic, University of Healh Science, Kecioren Training and Research Hospital) for permissions and supports in our study. We also thank all the volunteers who participated in our study.

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.864261

Anatolian Curr Med J 2021; 3(2); 130-135

The relationship between health-related quality of life and demographic characteristics in patients with chronic hepatitis B

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Cite this article as: Alay H, Yılmaz S, Parlak M, Kesmez Can F, Pür N. The relationship between health-related quality of life and demographic characteristics in patients with chronic hepatitis B. Anatolian Curr Med J 2021; 3(2); 130-135.

ABSTRACT

Introduction: The evaluation of health-related quality of life at specific intervals in chronic hepatitis B (CHB) patients is important in terms of producing interventions aimed at raising quality of life.

Aim: The purpose of this study was to measure health-related quality of life in CHB patients and to evaluate its association with demographic characteristics.

Material and Method: The study was conducted with CHB patients presenting to the infectious diseases clinic between 01 January and 15 March 2020. Date were collected demographic characteristics, and with the short form-36 (SF-36).

Results: Two hundred fourteen patients diagnosed with CHB and receiving nucleos(t)ide therapy were included in the study. Patients' mean age was 41.9±12.9 years, 60.7% (n=130) were men, 83.6% were married, and 44.9% were educated to middle school level. Mean scores on all subscales were higher among men. Patients' SF-36 subscale scores differed significantly in terms of education. Unmarried individuals registered higher mean scales on the SF-36 subscales compared to married participants. The score distributions of housewives and clerical workers differed significantly on the physical functioning (PF), social functioning (SF), and physical role limitation (PRL) subscales ($p<0.001$, $p=0.004$, and $p=0.003$, respectively). Patients' mental health subscale scores were significantly differently distributed depending on smoking status ($p=0.015$). PF, PRL, social role limitation, and energy/fatigue subscale scores differed significantly between participants living in urban areas and those from outlying districts or villages ($p<0.01$).

Conclusion: It is of great importance for patients' demographic characteristics to be evaluated during follow-up and for appropriate clinical support to be provided when required.

Keywords: Chronic hepatitis B, quality of life, demographic characteristics

INTRODUCTION

Approximately 250 million people worldwide suffer from chronic hepatitis B (CHB) infection (1). CHB patients are at risk of developing end-stage liver disease such as cirrhosis, liver failure, and hepatocellular carcinoma. Antiviral therapy suppresses hepatitis B virus (HBV) replication in these patients, and survival rates rise. Nucleos(t)ide analogues used in treatment are safe and effective antiviral agents recommended in the first stage of treatment in most guidelines. Although these drugs powerfully inhibit HBV replication, they are unable to eliminate the virus (2-4).

Quality of life refers to the general perception of the individual's positive and negative aspects (5). Health-related quality of life (HRQoL) emerges as an important factor in chronic diseases, and especially CHB. The quality of life of CHB patients can be adversely affected by lengthy antiviral therapy and follow-up (6). The regular evaluation of HRQoL in CHB patients, even in the absence of advanced liver disease is important in the adoption of measures aimed at improving quality of life. The purpose of this study was to measure HRQoL in patients with CHB and to evaluate its associations with sociodemographic characteristics.

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Received: 21.01.2021 **Accepted:** 17.02.2021

MATERIAL AND METHOD

The study was approved by Atatürk University Faculty of Medicine Ethical Committee (Ethics approval certificate: B.30.2.ATA.0.01.00/95). All procedures were performed adhered to the ethical rules and the Helsinki Declaration of Principles.

The study was performed with CHB patients presenting to the infectious diseases clinic between 01 January and 15 March 2020. Patients aged over 18, receiving antiviral therapy with diagnoses of CHB, and consenting to take part were included in the study. Patients with cirrhosis and not receiving antiviral therapy were excluded.

Data were collected using a questionnaire developed by the author investigating various demographic characteristics (sex, age, marital status, place of residence, smoking status and/or alcohol use, duration of disease and accompanying diseases) and with the Turkish version of the short form of the quality of life questionnaire (SF-36). The questionnaires were completed using the face-to-face interview method.

The Short Form of the Quality of Life Questionnaire (SF-36).

This was developed in 1989 by Ware and Sherbourne for clinical application and research. The scale consists of 36 items under two main categories, physical and mental health. It consists of a number of subscales-general health, vitality, physical functioning, role physical, bodily pain, mental health, role emotional, and social functioning. Each heading is scored from a minimum of 0 to a maximum of 100.Higher scores indicate more favorable HRQoL (7). SF-36 was adapted into Turkish by Pınar et al. (8) and Koçyiğit et al. (9).

Statistical Analysis

Data analysis was performed on Statistical Package for the Social Sciences (SPSS v20) software. Categorical variables were expressed as number and percentage, and numerical variables as mean plus standard deviation. Normality of distribution of variables was evaluated using the Kolmogorov Smirnov test, z values for skewness and kurtosis, and charts. The Mann Whitney U test was applied to compare non-normally distributed numerical variables between two groups, the Kruskal Wallis test for comparisons between more than two groups, while the Mann Whitney U test with Bonferroni correction were applied at post-hoc analyses. Relationships between variables were investigated using Spearman's rho correlation analysis. p values <0.05 were regarded as significant for all analyses.

RESULTS

Sociodemographic and Clinical Characteristics

Two hundred fourteen patients diagnosed with CHB and receiving nucleos(t)ide therapy were included in the study. The patients' mean age was 41.9±12.9 years, 60.7% (n=130) were men, 83.6% were married, and 44.9% had been educated to middle school level. The mean number of children per participant was3.0±1.6. Cases' sociodemographic characteristics are shown in **Table 1.**

Table 1. Patients' sociodemographic characteristics

Variables	n	%
Sex		
Female	84	39.3
Male	130	60.7
Education level		
Primary school	10	4.7
Middle school	96	44.9
High school	48	22.4
University	60	28.0
Marital status		
Married	179	83.6
Single	35	16.4
Occupation		
Unemployed	38	18.0
Manual	69	32.7
Clerical	33	15.6
Housewife	61	28.9
Student	10	4.7
Smoking status		
Non-smoker	180	84.1
Smoker	34	15.9
Alcohol consumption		
No	210	98.1
Yes	4	1.9
Place of residence		
Urban area	148	69.2
District	53	24.8
Village	13	6.1
Additional disease		
No	192	89.7
Yes	22	10.3

The mean duration of disease was 102.7±104.0 months, and all participants consisted of CHB patients. Patients' mean hepatic activity index (HAI) was 5.6±3.3, and their mean fibrosis index was2.2±2.0.

Quality of Life Scores

The relationship between participants' SF-36 subscale scores and demographic characteristics was investigated. Men registered higher mean scores on all subscales, with physical functioning (p<0.001), social functioning (p=0.006), role physical (p<0.001), role emotional (p<0.001), vitality (p=0.024), and bodily pain (p=0.013) scores differing significantly from those of women. Significant differences were determined between education levels in terms of patients' SF-36 subscale scores. Significant differences in terms of physical functioning subscale scores were observed between primary school and university graduates, middle school and high school graduates, and middle school and university graduates (p=0.008, p=0.002, and p<0.001, respectively), while social functioning scores differed significantly between

middle school and university graduates (p<0.001). Role physical, role emotional, and general health subscale score distributions differed significantly between middle school and university graduates (p<0.001), and bodily pain subscale score distributions differed significantly between primary school and university graduates (p=0.006).

Mean scores on all SF-36 subscales were higher among unmarried participants compared to married individuals, with social functioning, bodily pain, and general health subscale scores being significantly higher (p<0.001, p=0.009, and p=0.012, respectively).

Significant differences were observed in SF-36 scores depending on patients' occupations. Physical functioning, social functioning, role emotional, and vitality subscale scores differed significantly between housewives and the unemployed (p<0.001). Physical functioning, role physical, and role emotional scores also differed significantly between housewives and the self-employed (p<0.001). Score distributions among housewives and clerical workers differed significantly in the physical functioning, social functioning, and role physical subscales (p<0.001, p=0.004, and p=0.003, relatively).

Mental health subscale scores differed significantly depending on smoking status (p=0.015). With the exception of role physical and role emotional, all mean SF-36 subscale scores were higher among patients who did not consume alcohol than among alcohol users, although statistical analysis could not be applied due to the insufficient number of alcohol users.

Physical functioning, role physical, role emotional, and vitality subscale scores differed significantly between participants living in urban areas and those living in outlying rural districts and villages (p<0.01). No significant difference was observed in participants' SF-36 subscale scores depending on presence or absence of additional disease (p>0.05). Patients' SF-36 subscale score distributions according to sociodemographic variables are shown in **Table 2.**

Correlations were investigated between a number of sociodemographic and clinical characteristics and SF-36 subscale scores. Interestingly, mental health subscale scores exhibited significant negative correlation only with duration of disease (r = -0.211, p=0.002). Correlations between SF-36 subscale scores and age, education level, number of children, duration of disease, HAI, and fibrosis are summarized in **Table 3.**

DISCUSSION

Patients with chronic liver disease have lower HRQoL than the general population (10). When the relationship between demographic, clinical characteristics and quality of life and fatigue was evaluated in CHD patients, it was seen that age, gender, education, employment, comorbidity and disease stage affect fatigue and quality of life (11). In a study examining both general and disease-specific measures of HRQOL in Chinese patients, lower scores were reported in CHB patients compared to controls, especially in patients with cirrhosis (12). Nucleos(t)ide analogues used in treatment are powerful inhibitors of HBV replication, but long-term use affects patients' quality of life (13). Patients' sociodemographic characteristics and quality of life must be considered before starting long-term treatment. The present study evaluated the relationship between quality of life scores and sociodemographic characteristics in the CHB patients receiving antiviral therapy.

Numerous studies have reported impairment of HRQoL in patients with CHB. In a study a study evaluating the quality of life in patients with chronic viral hepatitis, it was reported that the quality of life of patients with CHB was lower than that of other chronic liver problems (14). A separate study revealed comparable HRQoL between inactive HBV carriers and healthy controls, but that this worsened as liver disease progressed. Significant impairment of HRQoL occurs in patients with CHB (15). The HRQoL of CHB patients can vary depending on their sociodemographic characteristics. Significantly lower HRQoL has been reported in women, unmarried patients, and individuals with chronic disease (6). In

Table 3. Correlations netween SF-36 scores and various sociodemograhic variables and clinical characteristics (r/p)

Variables	Age	Education level	Number of children	Duration of disease	HAI*	Fibrosis
Physical functioning	-0.313/<0.001	0.332/<0.001	-0.401/0.006	-0.128/0.061	-0.194/0.031	-0.190/0.035
Social functioning	-0.307/<0.001	0.238/<0.001	-0.072/0.640	-0.306/<0.001	-0.122/0.178	-0.181/0.044
Role physical	-0.190/0.005	0.316/<0.001	-0.234/0.121	-0.037/0.585	-0.076/0.402	-0.102/0.258
Role emotional	-0.188/0.006	0.317/<0.001	-0.234/0.121	-0.046/0.501	-0.108/0.234	-0.108/0.231
Mental health	-0.090/0.189	0.122/0.075	-0.022/0.886	-0.211/0.002	-0.001/0.992	-0.042/0.645
Vitality	-0.171/0.012	0.172/0.012	-0.198/0.191	-0.125/0.067	0.044/0.628	-0.059/0.517
Bodily pain	-0.184/0.007	0.200/0.003	-0.193/0.204	-0.157/0.022	-0.139/0.124	-0.243/0.006
General health	-0.183/0.007	0.250/<0.001	0.044/0.776	-0.192/0.005	-0.011/0.905	-0.099/0.276

r/p: Correlation coefficient/p value *Hepatic Activity Index

Table 2. Distribution of SF-36 subscale scores in terms of sociodemographic variables

Variables	Physical Functioning	Social Functioning	Role Physical	Social Functioning	Mental Health	Vitality	Bodily Pain	General Health
Sex	p<0.001	p=0.006	p<0.001	p<0.001	p=0.936	p=0.024	p=0.013	p=0.090
Male	100.0 (90.0-100.0)	77.8 (55.6-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	60.0 (52.0-64.0)	50.0 (45.0-55.0)	44.4 (44.4-66.7)	52.0 (50.0-62.0)
Female	75.0 (55.0-100.0)	55.6 (55.6-100.0)	100.0 (0.0-100.0)	100.0 (0.0-100.0)	56.0 (52.0-64.0)	50.0 (40.0-50.0)	44.4 (44.4-60.8)	50.0 (50.0-62.0)
Education level	p<0.001	p=0.003	p<0.001	p<0.001	p=0.106	p=0.087	p=0.018	p=0.002
Primary school	75.0 (40.0-100.0)a	77.8 (55.6-90.0)	100.0 (0.0-100.0)	100.0 (0.0-100.0)	52.0 (40.0-60.0)	42.5 (35.0-50.0)	44.4 (44.4-44.4)a	52.0 (47.0-62.0)
Middle school	85.0 (60.0-100.0) b, c	55.6 (55.6-83.4)	100.0 (0.0-100.0)a	100.0 (0.0-100.0)a	56.0 (52.0-64.0)	50.0 (40.0-50.0)	44.4 (44.4-66.3)	50.0 (48.5-55.0)a
High school	100.0 (85.0-100.0)b	72.2 (55.6-100.0)	100.0 (75.0-100.0)	100.0 (66.7-100.0)	56.0 (52.0-64.0)	50.0 (40.0-52.5)	44.4 (44.4-66.7)	52.0 (50.0-66.0)
University	100.0 (90.0-100.0) a, c	77.8 (66.7-100.0)	100.0 (100.0-100.0)a	100.0 (100.0-100.0)a	60.0 (52.0-68.0)	50.0 (50.0-57.5)	55.6 (44.4-77.8)a	57.0 (51.0-67.0)a
Marital status	p=0.052	p<0.001	p=0.105	p=0.084	p=0.104	p=0.085	p=0.009	p=0.011
Married	90.0 (65.0-100.0)	66.7 (55.6-90.0)	100 (25.0-100.0)	100.0 (0.0-100.0)	56.0 (52.0-64.0)	50.0 (40.0-50.0)	44.4 (44.4-66.7)	52.0 (50.0-60.0)
Unmarried	100.0 (90.0-100.0)	100.0 (77.8-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	60.0 (52.0-68.0)	50.0 (45.0-65.0)	66.7 (44.4-88.9)	62.0 (50.0-75.0)
Occupation	p<0.001	p=0.002	p<0.001	p<0.001	p=0.611	p=0.029	p=0.065	p=0.040
Unemployed	100.0 (85.0-100.0)a	77.8 (55.6-100.0)a	100.0 (100.0-100.0)a	100.0 (100.0-100.0)a	56.0 (52.0-72.0)	50.0 (50.0-65.0)a	55.6 (44.4-77.8)	52.0 (50.0-72.0)
Self-employed	70.0 (55.0-100.0)b	55.6 (55.6-77.8)b	100.0 (0.0-100.0)	100.0 (0.0-100.0)b	56.0 (52.0-64.0)	50.0 (40.0-50.0)	44.4 (44.4-55.6)	50.0 (47.0-55.0)
Clerical	100.0 (85.0-100.0)c	77.8 (55.6-77.8)c	100.0 (100.0-100.0)b	100.0 (100.0-100.0)	60.0 (52.0-64.0)	50.0 (50.0-50.0)	44.4 (44.4-66.7)	57.0 (50.0-62.0)
Housewife	100.0 (90.0-100.0) a, b, c	77.8 (55.6-100.0) a, b, c	100.0 (100.0-100.0) a,b	100.0 (100.0-100.0) a, b	60.0 (52.0-64.0)	50.0 (45.0-50.0)a	44.4 (44.4-77.8)	52.0 (50.0-62.0)
Student	97.5 (90.0-100.0)	94.4 (77.8-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	52.0 (48.0-64.0)	42.5 (30.0-60.0)	44.4 (44.4-100.0)	59.5 (47.0-75.0)
Smoker	p=0.886	p=0.130	p=0.564	p=0.578	p=0.015	p=0.695	p=0.648	p=0.799
No	92.5 (65.0-100.0)	77.8 (55.6-100.0)	100.0 (25.0-100.0)	100.0 (33.3-100.0)	60.0 (52.0-64.0)	50.0 (40.0-55.0)	44.4 (44.4-66.7)	52.0 (50.0-62.0)
Yes	90.0 (70.0-100.0)	61.1 (55.6-77.8)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	52.0 (52.0-60.0)	50.0 (40.0-50.0)	44.4 (44.4-66.7)	52.0 (50.0-62.0)
Alcohol use								
No	90.0 (65.0-100.0)	77.8 (55.6-100.0)	100.0 (25.0-100.0)	100.0 (33.3-100.0)	56.0 (52.0-64.0)	50.0 (40.0-55.0)	44.4 (44.4-66.7)	52.0 (50.0-62.0)
Yes	87.5 (60.0-100.0)	50.0 (44.4-61.1)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	56.0 (52.0-60.0)	50.0 (42.5-50.0)	44.4 (44.4-66.7)	51.0 (50.0-52.0)
Place of residence	p=0.013	p=0.261	p=0.015	p=0.024	p=0.418	p=0.027	p=0.104	p=0.536
Urban center	95.0 (70.0-100.0)a	77.7 (55.5-100.0)	100.0 (50.0-100.0)a	100.0 (54.1-100.0)a	58.0 (52.0-64.0)	50.0 (40.0-55.0)a	44.4 (44.4-66.6)	52.0 (50.0-62.0)
Outlying district	90.0 (70.0-100.0)b	77.7 (55.5-100.0)	100.0 (100.0-100.0)b	100.0 (83.3-100.0)b	60.0 (52.0-64.0)	50.0 (42.5-55.0)b	44.4 (44.4-66.6)	52.0 (50.0-62.0)
Village	60.0 (55.0-87.5)a, b	66.6 (55.5-77.7)	0.0 (0.0-100.0)a, b	0.0 (0.0-100.0)a, b	56.0 (50.0-60.0)	40.0 (25.0-50.0) a, b	44.4 (38.8-44.4)	50.0 (845.0-61.0)
Additional disease	p=0.146	p=0.119	p=0.735	p=0.613	p=0.217	p=0.844	p=0.650	p=0.684
No	95.0 (67.5-100.0)	77.8 (55.6-100.0)	100.0 (38.0-100.0)	100.0 (41.7-100.0)	58.0 (52.0-64.0)	50.0 (40.0-55.0)	44.4 (44.4-66.7)	52.0 (50.0-62.0)
Yes	90.0 (60.0-100.0)	61.1 (55.6-77.8)	100.0 (25.0-100.0)	100.0 (0.0-100.0)	54.0 (52.0-60.0)	50.0 (45.0-50.0)	44.4 (44.4-55.6)	52.0 (50.0-57.0)

a, b, c : Indicate significant differences between subcategories.

addition, studies employed different quality of life scales have observed that education level, age, duration of disease, and antiviral therapy affect HRQoL (16).

In a study evaluating fatigue-related risk factors in chronic hepatitis B patients, it was shown that male patients were significantly lower than female patients in terms of physical fatigue, mental fatigue, and decreased motivation. The study emphasizes that there is a negative correlation between fatigue and quality of life (17). One multicenter study from Turkey reported significantly lower HRQoL scores in women and unmarried patients (6). In contrast, in the present study, HRQoL was significantly lower in women and married patients. The difference in HRQoL scores between the sexes may be attributed to factors such as women enjoying less social support, generally later access to medical care than men, to their returning to work early before they have entirely recovered, and to their assumption of responsibilities (18). Since being married increases social and individual responsibilities, it can also adversely impact on HRQoL. However, it can also provide a healthier life by providing economic and social support (19,20). There are striking differences between studies investigating the effect of marital status on HRQoL scores, and there are also studies reporting lower scores among unmarried patients (6).

Many studies have evaluated the effect of education level on quality of life in patients with chronic hepatitis B (6,13). One study comparing inactive hepatitis B patients, CHB patients, and a healthy population in terms of quality of life reported significant correlations between education level and role limitations and bodily pain associated with physical health problems (21). A multicenter study from Turkey showed statistically significant correlations between all quality of life component scores and education level (6). In the present study, SF-36 subscale score distributions differed significantly depending on CHB patients' education levels, and positive correlation was determined between patient education level and quality of life subscale scores.

Individuals' occupations are another factor affecting quality of life. One study assessing quality of life in CHB patients reported low physical functioning, role physical, general health, and role emotional scores in patients with CHB (22). Similarly, in the present study, quality of life scores varied significantly depending on patients' occupational groups.

Mental health scores in the present study were lower among patients who smoked than among non-smokers. Lam et al. (23) reported higher physical component scores among smoker CHB patients.

Individuals living in urban centers may have better social communication and lifestyles. Analysis of HRQoL in CHB patients in terms of place of residence in the present study revealed significant differences in physical functioning, role physical, role emotional, and vitality scores between those living in urban areas those resident in outlying districts and villages. However, one study of quality of life in patients with chronic hepatitis that place of residence had no effect on patients' quality of life (24).

No significant difference was also observed in the present study in any SF-36 subscale in terms of presence of additional disease. In contrast, however, some studies have reported lower quality of life scores in CHB patients with different chronic diseases than in those with no chronic disease (6).

Karacaer et al. (6) reported negative correlation between patient age and physical functioning subscale scores, and positive correlations between patient age and role emotional, mental health, and social functioning. In the present study, patient age was negatively correlated with physical functioning, social functioning, role physical, role emotional, vitality, bodily pain, and general health. Age-related decreases in numerous physical and mental abilities also result in a decrease in individuals' quality of life.

Negative correlation was detected in this study between duration of disease and mental and general health. Negative correlation was also detected between patients' HAI and physical functioning, and between fibrosis and physical functioning, social functioning, and bodily pain. However, one multi-center study reported no association between diagnosis of disease and duration of treatment and SF-36 scores. In addition, that study reported that since elevated alanine aminotransferase levels reduced quality of life scores, HBV DNA levels adversely affected subscales with the exception of vitality and physical and mental component scores (6).

Limitations

Significant increases have been reported in the physical components of quality of life, including physical functioning, role physical, bodily pain, and general health, following antiviral therapy (11). The present study analyzed quality of life of patients receiving antiviral therapy only in terms of sociodemographic characteristics. Comparative studies with patient groups not receiving antiviral therapy or inactive carriers might provide more extensive information about the effect of the treatment on quality of life. In addition, since a large proportion of the patients in this study were unwilling to disclose their monthly incomes, we were unable to assess the effect of economic status on quality of life.

CONCLUSION

The quality of life of the CHB patients in the study group varied depending on demographic characteristics. Quality of life is dependent on individual factors, and the course and duration of the disease. Knowing that factors such as age, sex, education, place of residence, and duration of disease affects quality of life in CHB patients, assessing quality of life at controls, and providing psychiatric support when required, will be useful in increasing such patients' quality of life.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Atatürk University Faculty of Medicine Ethical Committee (Ethics approval certificate: B.30.2.ATA.0.01.00/95).

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.

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

Author Contributions: : Concept-HA, SY, MP, FKC, NP; Design - HA, SY, MP, FKC, NP; Supervision - HA, SY, MP, FKC, NP; Resources-HA, SY; Materials-HA, SY, FKC; Data Collection and/or Processing-HA, MP, NP; Analysis and/or Interpretation-HA, SY, NP; Literature Search-HA, SY; Writing Manuscript-HA, SY; Critical Review-HA, SY

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.868495

Anatolian Curr Med J 2021; 3(2); 136-139

A comparative study between adolescent and adult patients with pilonidal sinus disease

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Cite this article as: Katı Ö, Kandur Y, Kaya M, Güler AG, Dalkıran T. Flap versus primary closure for treatment of pilonidal sinus disease: a comparative study between adolescent and adult patients. Anatolian Curr Med J 2021; 3(2); 136-139.

ABSTRACT

Objectives: The main targets of the treatment modalities for pilonidal sinus are to prevent recurrences, and to increase the quality of life. It is unknown whether there is a different treatment trend in pediatric patients as compared with adults. In this study, we aimed to evaluate the surgical methods in pediatric and adult patients with pilonidal sinus.

Material and Method: This retrospective study was conducted at the Departments of Pediatric Surgery and General Surgery Department of Necip Fazıl City Hospital, Kahramanmaraş from 2013 to 2017. A total of 66 pediatric patients and 68 adult patients were enrolled in this study.

Results: The number of pediatric patients was significantly higher than adults in mean of flap closure (21 (31.8%) vs 2 (2.9%), p≤0.01). However, primary closure was the most preferred method both in pediatric and adult patients, 45 (68.2%) pediatric patients and 63 (92.6%) adults. During a postoperative follow-up period of 1 month, 10 (15.2 %) pediatric patients and 12 (17.6%) adult patients developed wound infections (p=0.21). There was no significant difference between pediatric and adult patients with respect to mean recurrence rate (pediatric= 8 (%12.1) vs adult =9 (%13.2) (p=0.527)).

Conclusion: We believe that pediatric surgeons should increase their interest in treatment options of PS disease since its prevalence increases in pediatric age group especially in adolescents in recent years. Besides, there was a female prepondarance in pediatric patiens.

Keywords: Pilonidal sinus, flap, pediatric, adult

INTRODUCTION

Pilonidal sinus (PS) disease is usually seen in young age group, commonly between 17 and 38 years of age (1). The estimated prevalence is 26 per 100.000 people, affecting men 2 to 4 times as much as women (2,3). It was long considered that PS is predominantly a genetic disease (4).Today, PS is accepted as an acquired lesion in the natal cleft that results from burrowing of loose hair shafts into the distended hair follicles, that leads a suppurative sinus filled with hair (5,6). The nature of hairs, force of implantation, and vulnerability of the skin are important factors in the development of PS. Since overweight people have deeper inter-gluteal grooves and excessive hair they are more commonly affected(7).

The main target of the treatment modalities of PS are to prevent recurrences, and to increase the quality of life.There are different treatment modalities including letting the area open after excision, primary total or partial closure, closure with flap, injection of a sclerosing agent, destruction of sinus tract by heat or freezing cold application (8-10).In recent years the prevalence of PS in pediatric patients has been increasing (11). It is unknown whether there is a different treatment trend in pediatric patients as compared with adults.In this study, we aimed to compare the efficacy of the Limberg flap and tension-free primary closure between pediatric and adult patients.

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Received: 26.01.2021 **Accepted:** 05.02.2021

MATERIAL AND METHOD

This retrospective study was conducted at the Departments of Pediatric Surgery and General Surgery of Necip Fazıl City Hospital, Kahramanmaraş from 2013 to 2017. The study was carried out with the permission of Ethics Committee of Sütçü İmam University (permission granted: 16.05.2018, decision no: 06). The trial was conducted in accordance with the Helsinki Declaration principles. All of the patients who were operated on for sacrococcygeal PS were included in this study. A total of 66 pediatric patients and 68 adult patients were enrolled. All of the patients' age, gender, operational technique, and recurrence rate were recorded. Study data were analyzed using SPSS 17 (SPSS Inc., Chicago, IL, USA) software package. Descriptive analysis was done for demographic variables. Chi-square test was used for quantitative variables.

Patients were operated either by excision and reconstruction with the Limberg flap, primary closure, or marsupialization. The mean follow-up period was 20 months (range 6-42 months)to monitor surgical complications of the treatment, including post-operative infection and recurrence.

RESULTS

Overall, 50 (75.7%) of the pediatric patients and 12 (17.6%) of the adults were female. The two groups were significantly different with respect to gender distribution ($p<0.01$). The median age of the pediatric group was 14.4 years (range 12–17 years) and 24 years (range 18-53 years) of the adult group.The number of pediatric patients undergoing flap closure was significantly higher than adults (21(31.8%) vs 2 (2.9%), $p\leq0.01$). However, primary closure was the most preferred method both in pediatric and adult patients, 45 (68.2%) pediatric patients and 63 (92.6%) adults.Although 3(4.4%)adult patients underwent marsupialization, none of the pediatric patients were treated with this method. There was no significant difference between pediatric and adult patients in terms of the mean recurrence rate (pediatric group 8(12.1%)vs adult group 9 (13.2%)($p=0.527$)). There was no recurrence in patients undergoing flap closure.No post-operative complication other than wound infection developed in a total of 17 patients. They were treated with oral antibiotics. There was no significant difference between the groups in terms of the mean complication rate. During a postoperative follow-up period of 1 month, 10 (15.2 %) pediatric patients and 12 (17.6%) adult patients developed wound infections ($p=0.21$). Seven (15.5%) pediatric patients with primary closure and 3 (14.2%) with flap closure developed wound infection ($p=0.893$). Eight (12.1%) pediatric patients and 9 (13.2%) adult patients developed recurrence ($p=0.527$). Two (9.5%) pediatric patients with flap closure and 6 (13.3%) with primary closure developed recurrence ($p=0.650$).

DISCUSSION

The incidence of PS disease varies between populations. It is more common among people from Mediterranean countries (11). Pilonidal sinus has been increasing in recent years in pediatric population (12). In our opinion, the predisposing factors area history of local trauma due to excess body weight and increased hormonal factors in adolescence. Especially childhood obesity has reached epidemic levels in developed as well as in developing countries in recent decades (13).

Although the female/male ratio varies in many studies, it ranges between1/2 and 1/6 (14,15). Our results showed a girl preponderance in pediatric age group but a male preponderance in adult group. It is already known that the primary mechanism in the etiology of PS is the attachment of hair follicles to the epithelium of the deep intergluteal sulcus (6). We believe that this difference in the pediatric age group caused by the fact that female adolescents enter puberty earlier than boys; thus, local hair formation occurs earlier.In addition, hormonal changes starting with pulsatile secretion of GnRH (Gonadotropin releasing hormone) in adolescent girls is a major reason of the girl preponderance in the pediatric age groups since increased androgen hormones will affect pilosebaceous glands. As a result of late hormonal activity onset among boys, the process of sinus formation can occur after pediatric age (16).

Although different surgical methods have been proposed,there is no agreed optimal surgical procedure. The preference of the surgery type is dependent on patient specific factors and the width of the sinus area.Although we select the primary closure method mostly in both of pediatric and adult groups, the number of patients undergoing flap reconstruction in pediatric age group was significantly higher than the adult group. However various researchers have concluded that flap reconstruction was superior to excision and primary closure for PS (17) while other studies find no superiority (4).

Flap repair prevents tension of the wound and midline scar tissue. Recent studies have shown that recurrence rates for flap repair were very low in comparison to conventional primary closure (0-3% vs 7% to 42%) (18,19). Shabbir et al. (20) compared flap and primary closure in 60 adults. They found that flap closure have a advantage of 1.5 times less infection rate and 4 times less recurrence rate. In our study, we found no significant difference between the techniques in pediatric age group. We explained it by our shorter follow up period.

There was no significant difference between the adolescents and adults in terms of complications in our study. On the other way a recent study (21) found a higher incidence of complications (wound infection and recurrence) in pediatric age group compared with our study. We explained this conflict by the longer follow up period (median follow up 13 month).

Table 1. Comparison of pediatric and adult patients

		Pediatric group (n=66)	Adult group (n=68)	p
Gender (Female) n (%)		50 (75.7)	12 (17.6)	<0.01
Mean of age (year (range)		14.4 (12-17)	24.0 (16-53)	
Surgery type	Primary n (%)	45 (68.2)	63 (92.6)	<0.01
	Flap n (%)	21 (31.8)	2(2.9)	
	Marsupialization	0	3 (4.4)	
Recurrence		8 (12.1)	9(13.2)	0.527
Complication (wound infection) n (%)		10 (15.2)	12 (17.6)	0.21

An important conflict was the high rate of primary closure in adults. This study is not a concurrent prospective study. The technique was chosen according to the preference of the surgeon.

We are aware of the limitations. It was not possible to compare the lifestlye in the two groups. Additionally the indication for using a flap or doing a primary closure was subjective. Primary closure was preferered in small PS and flap large PS, especially in adolescents. Morover sinceour study was a retrospective study we were not able to compare the BMI values of the patients. Finally, our study deployed a relatively small sample size.

CONCLUSIONS

We are of the opinion that pediatric surgeons should increase their interest in treatment options of PS disease since its prevalence increases in pediatric age group especially in adolescents in recent years, due to increase of prevalence of obesity in children. Besides, there was a female prepondarance in pediatric patiens.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethics Committee of Sütçü İmam University (permission granted: 16.5.2018, decision no: 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.

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.

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.881784

Anatolian Curr Med J 2021; 3(2); 140-144

Recurrence rates and factors affecting recurrence after traumatic anterior shoulder dislocation

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Cite this article as: Büyükkuşcu MÖ, Kulduk A, Aydın A, Çetinkaya E, Gürsu ŞS. Recurrence rates and factors affecting recurrence after traumatic anterior shoulder dislocation. Anatolian Curr Med J 2021; 3(2); 140-144.

ABSTRACT

Objective: To investigate the factors affecting the recurrence of anterior shoulder dislocation, identify the patient group with the highest recurrence rates of shoulder dislocation, and determine the patient population to be recommended surgical treatment after the primary dislocation.

Materials and Method: We retrospectively screened the patients diagnosed with a primary shoulder dislocation and treated in our hospital between January 2005 and January 2017. Of the 1395 patients identified, we reached 1253 over phone calls to obtain follow-up information. The study excluded patients with no follow-up information, those with posterior dislocations, multidirectional instabilities, general joint hypermobility, traumatic nerve injury or shoulder fracture-dislocations (including greater tuberosity and glenoid fractures), and surgical treatment after a primary dislocation. We evaluated the general joint laxity of the patients using the Beighton scale. We recruited patients with a traumatic primary anterior shoulder dislocation and at least two years of follow-up data and divided them into three age groups: under 20 years, 20 to 40 years, and over 40 years.

Results: After applying the exclusion and inclusion criteria, 1,004 patients were included in the study. We detected recurrence in 408 patients (40.6%). The group under 20 years had the highest recurrence rate with 52% (88/170). We determined the recurrence rates as 43% (283/659) in the group aged 20-40 years and 21% (37/175) in the group over 40 years, respectively. However, except for age, we reached gender, presence of bone defects (Hill-Sachs lesion), and remaining parameters (immobilization time, injury mechanism, exercise habits and type of sports activity, dominant-side dislocation, and smoking) had no significant impact on the risk of recurrence after a primary dislocation.

Conclusion: The surgical treatment option should be presented to young male patients with bone defects after a primary dislocation. They also need to be informed about the possible difficulties due to recurrent instability.

Keywords: Shoulder dislocation, first, recurrence, risk factors, surgical treatment

INTRODUCTION

Shoulder joint dislocation is the most common joint dislocation encountered in emergency departments. Although its incidence reported in the literature varies depending on the population, this rate is estimated to be between 11-51/100,000 (1-5). Shoulder are more prone to redislocation following the first dislocation. In the literature, the rate of redislocation is generally reported as 17%-96% (6,7). The most consistent and significant factor affecting the prognosis of shoulder dislocation is the age of the patient at the time of the primary dislocation (8-10). Although still controversial, prognostic factors shown to affect recurrent instability also include low socioeconomic status, glenoid and/or humeral bone loss, exercise habits and type of sports, gender, and occupation (9,11,12).

This study aimed to investigate the factors affecting the recurrence of shoulder dislocation, identify the group of patients with the highest recurrence rates of shoulder dislocation, and determine the population to be recommended surgical treatment after the primary dislocation. We hypothesized that young people and those with bone defects would have higher rates of re-dislocation.

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Received: 17.02.2021 **Accepted:** 12.04.2021

MATERIALS AND METHOD

Before initiating the study procedures, we obtained the relevant approval from the Medical Specialty Ethics Committee of Health Science University Baltalimani Bone Diseases Education and Research Hospital (dated 01.19.2019, no. 22). Moreover, we conducted the study in accordance with the principles of the Declaration of Helsinki.

We retrospectively screened patients who presented to the emergency department of Baltalimani Bone Diseases Education and Research Hospital with an isolated primary shoulder dislocation between January 2005 and January 2017 and whose treatments and follow-ups were performed at this hospital. We were able to gather the information of 1253 of the 1395 patients via the electronic patient registration system and over phone calls. The study included patients with traumatic primary anterior shoulder dislocations and at least two years of follow-up. Nevertheless, we excluded 55 patients with unavailable patient information, 9 cases accompanied by nerve damages, 49 with posterior dislocations, 7 with multidimensional instabilities, 27 with general joint hypermobility, and 102 with shoulder fracture-dislocations (including bony Bankart lesions and greater tuberosity fractures). Considering the inclusion and exclusion criteria, we conducted the study with a total of 1,004 patients.

The retrospectively-reviewed data revealed all the procedures performed on the patients at the hospital. The patients were taken for vascular nerve examination after diagnosing shoulder joint dislocation in the emergency department based on physical examination and radiological imaging (anteroposterior and transthoracic shoulder joint radiography) findings. Then, closed reduction (Milch or Kocher Method) was applied, and immobilization was achieved with a shoulder arm sling. The vascular nerve examination and radiological imaging were repeated to check the state after reduction. In all patients, the shoulder joint was monitored at internal rotation at 0º abduction for one-three or four-six weeks with a shoulder arm sling. Outpatient controls were performed at the third and sixth weeks and third, sixth and twelfth months.

We evaluated the general joint laxity of the patients using the Beighton scale, accepting a score of ≥4 as general joint hypermobility (13). Besides, we extracted the anamnesis and physical examination findings of the patients during their visits to the emergency department and outpatient clinics from the patient registration system. We obtained the information which was not available in the patient registry system, (the mechanism of injury-causing primary dislocation, history of injury, smoking, exercise habits, presence of recurrent instability, and time and cause of redislocation and reason) over phone interviews. We utilized computed tomography to evaluate the shoulder joints of some patients (suspected fractures or bone defect measurements). Overall, we evaluated the shoulders of all patients with the help of magnetic resonance (MR) imaging at the sixth-week outpatient control.

In line with the previous research , we divided the patients into three age groups: under 20 years, 20 to 40 years, and over 40 years (5,11). We investigated the relationship between the likelihood of recurrence and patient age, gender, smoking, cause of primary dislocation, presence of a humerus bone defect (Hill-Sachs lesion), exercise habits, and effect of dominant-side dislocation.

Rehabilitation after Immobilization

The patients were allowed to move their elbows, wrists, and hand joints during shoulder fixation. Then, the patients were included in a physiotherapy program. The rehabilitation program covered scapular stabilization exercises and aimed to strengthen the rotator cuff and deltoid muscle. The patients started recommended exercises after the sixth week to ensure proprioceptive control. The patients were allowed to resume their sports activities after three months.

Statistical Analysis

We used Statistical Product and Service Solutions (SPSS) v. 22.0 for the statistical analyses. We presented the descriptive data as mean, standard deviation, median, maximum, minimum, frequency, and percentage. We run a Chi-square test to analyze independent qualitative data. A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1 shows the demographic characteristics and smoking status of the patients, recurrence rates and times, and the presence of bone defects. While the lowest patient age was 16 years, the highest was 64 years. After the primary dislocation, we could not detect recurrence in 596 (59.4%) of 1,004 shoulders. However, we determined more than one dislocation in 408 (40.6%) patients. Also, we identified that 62% (n=262) of the shoulders with more than one dislocation underwent surgery due to recurrent instability, but the remaining 161 patients were not operated on despite recurrent dislocation. The group aged under 20 years had the highest recurrence rate with 52%. We determined the recurrence rate as 43% in the group aged 20-40 years and 21% in the one aged over 40 years, respectively. There was no significant difference between the patients under 20 years and those aged 20-40 years by the rate of recurrent dislocations. However, these rates were significantly

higher in the groups aged under 20 years and 20 to 40 years compared to those aged over 40 years. Another striking finding was that the rate of recurrent dislocations was significantly higher in males than in females. The patients with bone defects were also more likely to have recurrent dislocation (**Table 2**). Finally, we found that immobilization time, injury mechanism, exercise habits and type of sports activity, dominant-side dislocation, and smoking had no significant impact on the recurrence risk after a primary dislocation (**Table 2**).

Table 1. Demographic and clinical characteristics of the patients

		n	%
Age	<20	170	17.0%
	20-40	659	65.8%
	>40	175	17.2%
Gender	Female	220	22.0%
	Male	784	78.0%
Smoking	(-)	613	61.0%
	(+)	391	39.0%
Dominant-side dislocation	(-)	425	42.0%
	(+)	579	58.0%
Sports activity	None	643	65.0%
	Contact sports	256	25.0%
	Non-contact sports/ Over-head sports	105	10.0%
Immobilization time	One-three weeks	697	69.4%
	Four-six weeks	307	30.6%
Injury mechanism	Falls	454	45.3%
	Sports injuries	341	34.0%
	Fight, battery	162	16.0%
	Motorbike accident	47	4.7%
Hill-Sachs lesion	(-)	321	32.1%
	(+)	683	68.2%
Recurrence	(-)	596	59.4%
	(+)	408	40.6%

DISCUSSION

In the literature, recurrence rate of traumatic primary anterior shoulder dislocations varies between 17% and 96% (14-16). In the current study, we found the recurrence rate of traumatic primary anterior shoulder dislocations, for which non-operative treatment had been applied, to be 40.6%. We also determined that young male patients with bone defects were at higher risk of recurrent instability compared to the general population. However, the remaining factors had no significant effect on the risk of recurrence.

In all current case series studies, the leading risk factor for recurrence is shown to be patient age at the time of primary dislocation (17-19). Lill et al. (20), investigating recurrent dislocation rates in 45 patients under 30 years and 46 patients over 30 years, found these rates to be 89% (n=40) in the former group and 26% (n=12 patients) in the latter group. The difference between the two groups was statistically significant. In a 25-year follow-up of patients with primary traumatic anterior shoulder dislocation, Hovelius et al. (21) reported that 39% of the patients aged 17-19 years (15 of 38 patients), 33% of the patients aged 20-25 years (19 of 57 patients), 26% of the patients aged 26-29 years (7 of 27 patients) and 14% of the patients aged 30-40 years (9 of 63 patients) had received operative treatment due to recurrent instability at the time of primary traumatic shoulder dislocation. In the current study, consistent with the literature, we found the recurrence rates to be significantly higher in patients aged under 20 years and 20 to 40 years compared to those over 40 years.

Table 2. Prognosis by demographic characteristics, smoking, immobilization time, sports activity, bone defect, and injury mechanism.

		Recurrence (-) (n : 596)	%	Recurrence (+) (n : 408)	%	p	
Age	<20	82	13.9%	88	27.1%	0.000	X^2
	20-40	376	63.0%	283	63.9%		
	>40	138	23.1%	37	9.0%		
Gender	Female	143	23.9%	77	18.8%	0.000	X^2
	Male	453	76.1%	331	81.2%		
Smoking	(-)	378	63.5%	235	57.6%	0.063	X^2
	(+)	218	36.5%	173	42.4%		
Dominant-side dislocation	(-)	294	49.3%	221	54.2%	0.084	X^2
	(+)	302	50.7%	187	45.8%		
Sports activity	None	431	55.6%	236	57.8%	0.104	X^2
	Contact sports	220	36.9%	146	35.9%		
	Non-contact sports	45	7.5%	26	6.3%		
Immobilization time	Three weeks	343	57.6%	262	64.3%	0.062	X^2
	Six weeks	253	42.4%	146	35.7%		
Injury mechanism	Falls	276	46.3%	178	43%	0.078	X^2
	Sports injuries	186	31.2%	155	40%		
	Fight, battery	121	20.3%	59	14%		
	Motorbike accident	13	2.2%	16	3%		
Bone defect	(-)	303	50.9%	18	4.5%	0.018	X^2
	(+)	293	49.1%	390	95.5%		

X^2 Chi-square test

In a systematic review that defined prognostic factors for recurrent instability, Wasserstein et al. (1) reported that none of the factors showed a significant relationship with recurrent instability, except for age. Shields et al. (11) stated that gender was not a risk factor for redislocation or recurrent instability. In addition to research indicating that gender does not affect recurrent instability, the literature bears many studies suggesting that male gender is an important prognostic factor (5,9,16,21,22). In a study releasing the 25-year long-term outcomes of 257 primary anterior shoulder dislocation cases, Hovelius et al. (23) reported no significant difference between females and males by recurrence rates. Similarly, we concluded recurrence rates of primary traumatic anterior shoulder dislocation to be significantly higher in males than in females.

In the long-term follow-up study of Hovelius (21), the primary anterior shoulder dislocation cases under 40 years of age were divided into three groups as those doing contact sports, those doing other sports, and those not engaged in any sports. As a result, there was no significant difference between the groups by recurrent dislocation rates. Both teSlaa (9) and Simonet (24) investigated the effect of engaging in sports on the risk of recurrent dislocation. Neither study reported a significant relationship between before the primary dislocation and recurrent dislocation by exercise habits. In the current study, we divided the patients into three groups as those engaged in contact sports, those engaged in non-contact sports, and those not performing any sports activities. As a result, we determined that neither the type of sports performed before primary dislocation nor exercise habits had any significant effect on recurrent dislocation.

Much of thinking in the literature concentrates on the effect of immobilization duration on recurrence. It was previously concluded that it did not alter the risk of recurrent dislocations (20,21,25,26). In the present study, we divided the patients into two groups (one-three weeks and four-six weeks) by the immobilization period. Consequently, the groups did not differ significantly by recurrent dislocation rates.

We did not encounter a study examining the relationship between smoking and recurrent dislocation in non-operatively treated traumatic primary anterior shoulder dislocation cases. In our study, we determined no significant relationship between smoking and redislocation among the patients.

Hovelius (27) reported that the injury mechanism causing primary traumatic anterior shoulder dislocation had no significant impact on recurrent dislocation. Sachs (28) and Robinson (5) also noted that the injury mechanism did not influence recurrence rates in conservatively treated traumatic shoulder dislocation cases. In our study, we accepted the injury mechanism as a fall even in patients that fell off a 2-meter height during sports activities. Other injury mechanisms were identified as sports injuries, fight-battery, motorbike accident, and seizure. Consistent with the literature, we also found no significant relationship between the injury mechanism and redislocation risk.

Kralinger (6), Hovelius (27), and Olds (29) reported higher recurrence rates in the presence of Hill-Sachs lesion after a primary anterior dislocation. Both Henry (30) and Safran (31) reported no significant difference in redislocation rates between those with and without Hill-Sachs lesions after a primary anterior shoulder dislocation. Also, Salomonsson (32) and Hoelen (33) found no significant difference between those with and without Hill Sachs lesions by the likelihood of recurrent instability. In the current study, we discovered that the presence of Hill-Sachs lesions having developed during the primary anterior dislocation had a significant impact on recurrence. In accordance with the relevant literature, dominant-side dislocation also did not have any impact on recurrence (33-35).

There are some limitations of this study. The first is concerned with the retrospective design and the absence of an extended follow-up. Another limitation is that the patients did not have any clinical scoring. Lastly, since we conducted the study retrospectively in a single-center, it was not a fully epidemiological study. Despite these limitations, it was the strength of the research that it included clinical and radiological examinations, as well as a large number of patients.

CONCLUSION

The surgical treatment option should be presented to young male patients with bone defects after a primary dislocation, and they need to be informed about the possible difficulties due to recurrent instability.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Medical Specialty Ethics Committee of Health Science University Baltalimani Bone Diseases Education and Research Hospital (dated 01.19.2019, no. 22).

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 declare that this study received no financial support.

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

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.884102

Anatolian Curr Med J 2021; 3(2); 145-150

The thorax tomography correlation in COVID-19 RT-PCR positive patients

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Cite this article as: Kesmez Can F, Alay H, Yılmaz S, et al. The thorax tomography correlation in COVID-19 RT-PCR positive patients. Anatolian Curr Med J 2021; 3(2); 145-150.

ABSTRACT

Aim: Although the RT-PCR test of pharyngeal swabs is the gold standard for diagnosing coronavirus disease 2019 (COVID-19), radiological imaging techniques, particularly thoracic computerized tomography (CT) were also used frequently as needed during the pandemic. The aim of this study is to investigate thorax CT findings in patients with COVID-19 confirmed by RT-PCR and to evaluate its relationship with clinical features.

Material and Method: This study included 311 consecutive patients who were hospitalized between April 1, 2020, and June 1, 2020, with COVID-19 diagnosis based on RT-PCR (+) results and underwent a thorax CT within 24-48 hours of admission. Symptoms, clinical status, co-morbidities of the patients were evaluated. Thorax CT findings were assessed by the Department of Radiology and the results were analyzed in relation to the clinical status of the PCR (+) patients.

Results: The study group consisted of 170 male (57.7%) and 141 female (42.3%) patients with mean age 46.7±33.7 years. Among the COVID-19 cases, 51 (16.4%) were asymptomatic, the clinical course was mild-moderate in 197 (63.3%) and severe in 63(20.3%). During follow-up 21 (6.8%) required intensive care and 10 (3.2%) died. The most common symptoms observed were cough (33.4%), weakness (30.2%) and fever (28%). The most commonly encountered co-morbidity in COVID-19 patients was hypertension (10.3%) followed by diabetes mellitus (7.7%), coronary artery disease (5.1%). Thorax CT findings were assessed as normal in 21.9% of the patients; viral pneumonia was detected in 20.9% and 27.7% were reported as compatible with COVID-19. Bilateral involvement was seen on CT scan in 49.2% of the patients. In regard to thorax CT imaging characteristics that suggest COVID-19 disease, the most common was ground-glass opacities observed in 181 (27.2%) and the least common was a vascular enlargement in 4(0.6%) of the patients.

Conclusion: COVID-19 is an air-borne disease that primarily affects the lungs. Thus, it is essential to define radiological lung involvement. The common CT findings of COVID-19 disease are similar to other viral pulmonary infections. The clinicians being familiar with common imaging features of COVID-19 would contribute to earlier detection and thus reduced mortality associated with the disease.

Keywords: Computed tomography, COVID-19, RT-PCR, emergency, infection

INTRODUCTION

The Coronavirus disease, which is a severe acute respiratory syndrome caused by a highly contagious coronavirus 2 (SARS-CoV-2), was reported firstly in Wuhan, State of Hubei, China in December 2019. The disease caused by this virus was defined as "Coronavirus Disease 2019 (COVID-19)" by the World Health Organization (WHO). The disease soon took hold of the whole world and the WHO announced that the disease progressed to become a pandemic on March 11, 2020 (1). Up to date, six coronavirus types known to cause infectious disease in humans have been defined. Among these, 229E, OC43, NL63, and HKU1 infections primarily cause common cold symptoms and have a mild course. The other two types including Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) cause severe disease (2). SARS-CoV-2 is the seventh coronavirus known to infect humans. The clinical spectrum of the SARS-CoV-2 infection includes a wide range of presentations from asymptomatic infection, mild upper respiratory infection to severe viral pneumonia leading to respiratory failure, multi-organ failure, and even death (3,4). The most common clinical symptoms are fever, cough, sore throat, headache, weakness, muscle pain, and shortness of breath. These symptoms are not specific to the disease and thus rapid diagnosis requires

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Received: 21.02.2021 **Accepted:** 22.03.2021

tests and imaging assessment (5). The gold standard for COVID-19 diagnosis is the detection of SARS-CoV-2 RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) from nasopharyngeal or oropharyngeal swab specimens. On the other hand, if the RT-PCR is negative and clinic features are highly suspicious for the disease, repeating RT-PCR test is recommended (6,7). It was reported that thorax computerized tomography is a relevant method for diagnosis, pneumonia grading, and disease monitorization. However, thorax CT is not a screening test for COVID-19 (8). Considering overlapping CT findings in respiratory infections due to various etiologies, thorax CT findings have high sensitivity (97%) but low selectivity (25%) (9). The most common CT findings in COVID-19 cases include ground-glass opacities, consolidations, reticular pattern, cobblestone pattern, vascular enlargement, nodules, cavitation, lymph node enlargement, and pleural effusion (10, 11). The aim of this study was to describe CT findings in relation to the clinical course in patients with RT-PCR confirmed COVID-19 infection.

MATERIAL AND METHOD

This study was designed and submitted to the T.R. Ministry of Health COVID-19 Scientific Research Committee and Ataturk University Medical School Clinical Research Ethics Committee for approval. Approval was granted by both committees (ethical approval no: B.30.2.ATA.0.01.00/276). All procedures were performed adhered to the ethical rules and the Helsinki Declaration of Principles.

Patient Groups

In this descriptive study, 311 consecutive patients who admitted to Ataturk University Medical School Research Hospital between April 1, 2020, and June 1, 2020, with a positive COVID-19 RT-PCR test, hospitalized at the COVID-19 clinic and underwent a thorax CT scan were included. The patients were divided into three groups based on their clinical status.

Group 1 asymptomatic: Asymptomatic patients found to be RT-PCR positive after high-risk contact.

Group 2 mild-moderate pneumonia: Includes patients with symptoms including fever, myalgia/arthralgia, cough, and sore throat, respiration rate <30/minute, SpO_2 level >90% on room air, and mild-moderate pneumonia (<50%) findings on tomography.

Group 3 severe pneumonia: Includes patients with symptoms including fever, myalgia/arthralgia, cough, and sore throat, tachypnea (respiration rate ≥30/minute), SpO_2 level ≤90% on room air and, bilateral extensive pneumonia (>50%) findings on tomography.

Unenhanced thorax CT scans were performed on all patients in the supine position using a 256 slice CT device (Aquillon; Toshiba Medical Systems, Tokyo, Japan). The tomography findings were assessed by the Department of Radiology. Patients over 18 years of age were included in the study. The clinical status and co-morbidities of the patients were evaluated. The distribution and patterns of lung lesions were assessed by subgroups. The thorax tomography findings of patients with RT-PCR (+) SARS-CoV-2 infection were evaluated.

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS v20) software. Categorical variables were presented as number and percent, numerical variables were presented as mean and standard deviation.

RESULTS

The study included RT-PCR confirmed 311 COVID-19 patients aged 18-77 years. The study group consisted of 170 male (57.7%) and 141 female (42.3%) patients with mean age 46.7±33.7 years. Among the COVID-19 cases, 51 (16.4%) were asymptomatic, the clinical course was mild-moderate in 197 (63.3%) and severe in 63 (20.3%). During follow-up 21 (6.8%) required intensive care and 10 (3.2%) died. The most common symptoms observed were cough 104 (33.4%), weakness 94 (30.2%) and fever 87 (28%). The most commonly encountered co-morbidity in COVID-19 patients was hypertension (10.3%) (**Table 1**).

Table 1. Distribution of symptoms, co-morbidities and clinical features of COVID-19 patients

Symptoms	**n**	**%**
Cough	104	33.4
Weakness	94	30.2
Fever	87	28.0
Dyspnea	55	17.7
Sore throat	35	11.3
Abdominal pain	26	8.4
Loss of appetite	14	4.5
Loss of taste/smell	13	4.2
Diarrhea	9	2.9
Nausea/vomiting	5	1.6
Co-morbidities		
HT	32	10.3
DM	24	7.7
CAD	16	5.1
COPD	15	4.8
Clinic		
Asymptomatic	51	16.4
Mild/moderate	197	63.3
Severe	63	20.3
Intensive care		
Yes	21	6.8
No	290	93.2
Mortality		
Yes	10	3.2
No	301	96.8

HT; Hypertension, DM; Diabetes mellitus, CAD; Coronary artery disease, COPD; Chronic obstructive pulmonary disease

Thorax CT findings were assessed as normal in 21.9% of the patients while viral pneumonia was detected in 20.9% and 27.7% was reported as compatible with COVID-19. Multiple findings were observed in some of the CT scans. In total, the detected CT findings were ground-glass opacities in 181 (27.2%), bilateral involvement in 153 (23.0%), peripheral localization in 80 (12.0%) (**Figure 1**), consolidation in 74 (11.1%), LAP/cavity/nodule in 50 (%7.5) (**Figure 2-3**), band formation in 56 (8.4%), cobblestone appearance in 22 (3.3%) (**Figure 4**), reticular pattern in 17 (2.6%), pleural thickening in 14 (2.1%), pleural effusion in 9 (1.4%), bronchiectasis changes in 5 (0.8%) and vascular enlargement in 4 (0.6%) (**Figure 5**) (**Table 2**).

Table 2. Distribution of thorax CT findings of COVID-19 patients

Thorax CT Findings	n	%
Grounded glass	181	27.2
Bilateral involvement	153	23.0
Peripheral involvement	80	12.0
Consolidation	74	11.1
Band formation	56	8.4
LAP/cavity/nodular pattern	50	7.5
Cobblestone appearance	22	3.3
Reticular pattern	17	2.6
Pleural thickening	14	2.1
Pleural effusion	9	1.4
Bronchiectasis changes	5	0.8
Vascular enlargement	4	0.6

* Distribution of CT findings exceed total number of cases based on evaluation of multiple findings.

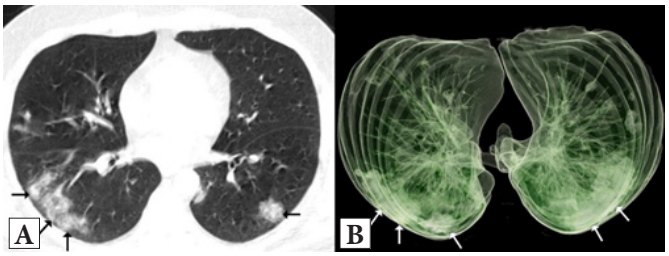

Figure 1. 46-year-old male patient who admitted with cough and back pain. The thorax CT axial parenchymal window (**A**) and three-dimensional pulmonary image (**B**) show multiple ground-glass density nodules (arrows) on lower lobes bilaterally.

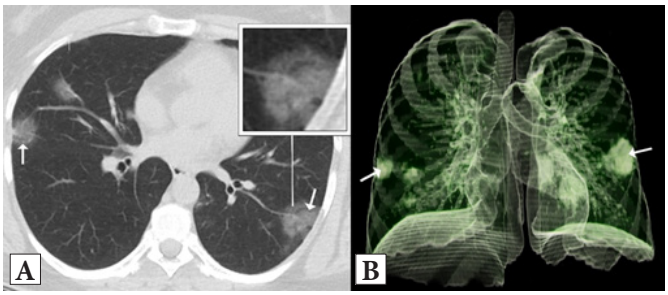

Figure 2. 46-year-old female patient who admitted with fever, generalized body pain and back pain. No co-morbidities reported. The thorax CT axial parenchymal window image (**A**) shows bilateral ground-glass density nodules (arrows). Three-dimensional chest CT image of the nodules (**B**).

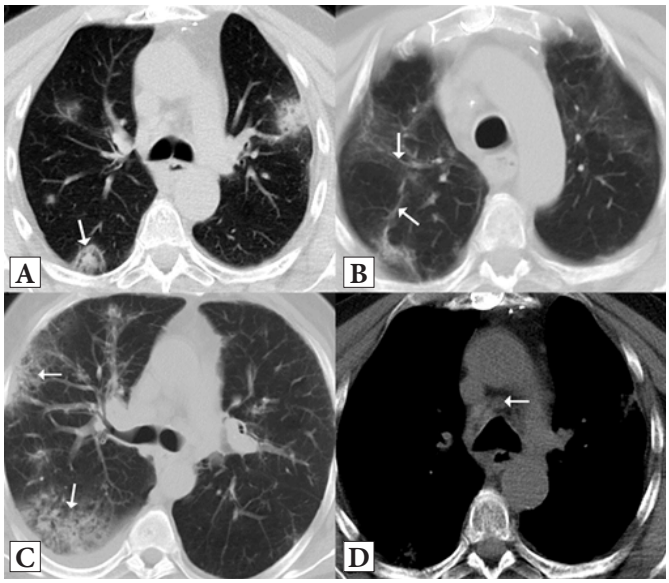

Figure 4. 72-year-old male patient who admitted with fever and cough had history of hypertension and coronary artery disease. The patient required intensive care during follow-up and was discharged following treatment in intensive care unit. On admission, thorax CT axial parenchymal window image (**A**) revealed nodular density with reverse halo adjacent to the pleura in right pulmonary lower lobe (arrow). At follow-up on Day 10, axial parenchymal window CT (**B**) showed diffuse ground-glass appearance in upper lobes bilaterally and fibrotic band formation on the right (arrow) and in lower sections (**C**) cobblestone appearance in right pulmonary middle and lower lobes (arrows) and lymph node in aortic-pulmonary area with mediastinal dose (**D**).

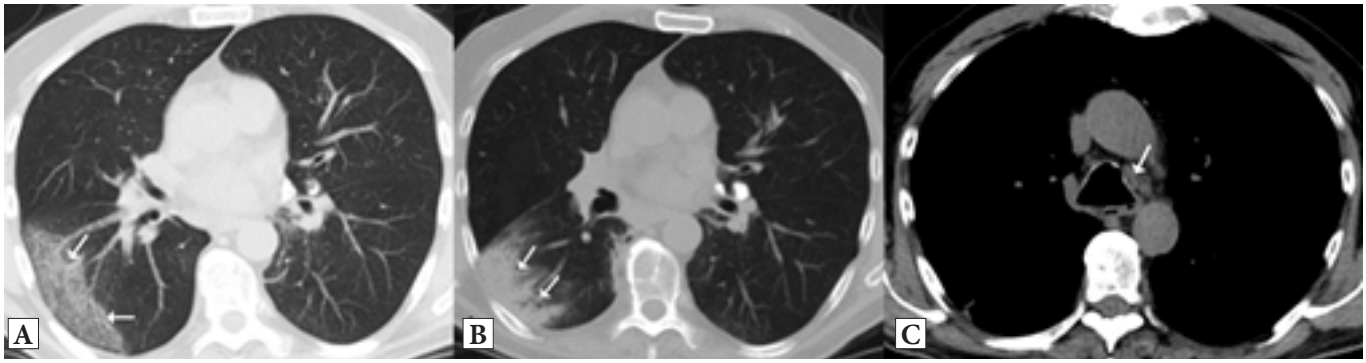

Figure 3. 50-year-old male patient with no known chronic disease admitted with a 5-day history of fever, sore throat and back pain. Thorax CT axial parenchymal window image (**A**) shows reticular-nodular densities adjacent to the pleura in right lower lobe and accompanying ground-glass appearance (arrows). Follow-up axial parenchymal window image at 1 week (**B**) shows consolidation area with air bronchogram at the same localization (arrows). Lymph node is observed in aortic-pulmonary window (arrow) on axial CT section with mediastinal dose (**C**).

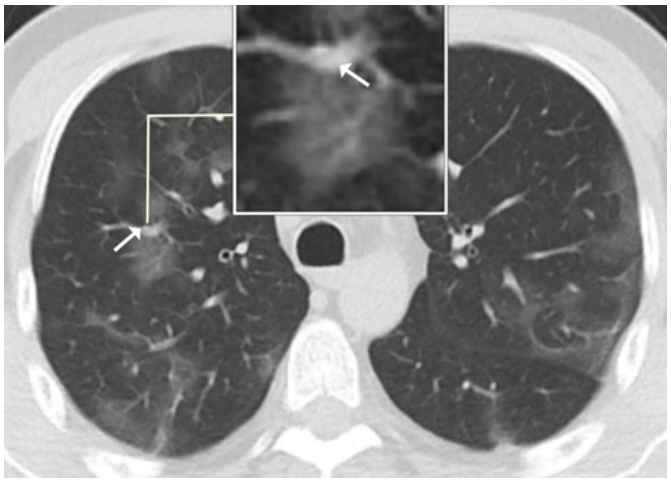

Figure 5. 47-year-old male patient who admitted with fever and back pain. The thorax CT axial parenchymal window image showed bilateral ground-glass appearance bilaterally and on the right, vascular enlargement adjacent to the ground-glass density (arrow).

DISCUSSION

Early recognition of COVID-19 is essential for treatment and disease control. The definitive diagnosis is possible by RT-PCR testing of respiratory specimens. In early cases, while tests are still negative and the patient is asymptomatic, thorax CT can reveal some findings which allow early detection of the disease.

In this study, among the 311 RT-PCR positive patients 51 (16.4%) were asymptomatic which suggests the absence of clinical symptoms cannot rule out the COVID-19 infection. In another study conducted with 90 patients, 7% were found to be asymptomatic (12). In asymptomatic patients, pulmonary findings appear to be less frequent and mild. On the contrary, symptomatic patients seem to admit with prominent consolidations, more generalized parenchymal involvement and pulmonary signs (13). In the study population, 197 (63.3%) had mild/moderate pneumonia and 63 (20.3%) had severe pneumonia. In a study conducted in China, the clinical presentation was mild in 80% and severe in 15% of the cases while 5% had highly severe conditions with high mortality such as respiratory failure, shock, organ failure; the reported mortality rate was 2.3% (14). Among our patients, 21 (6.8 %) required intensive care; 10 (3.2%) died, all from the seriously ill patient group. The clinical status and prognosis data of our study were compatible with the literature. Cardiovascular diseases, diabetes, hypertension, chronic pulmonary diseases, chronic renal failure, obesity, cancer, immune-suppression conditions, chronic liver disease and smoking were reported as factors that can affect the severity of COVID-19 disease (15,16). In this study, the most commonly encountered co-morbidity was hypertension in 32 (10.3%) followed by diabetes in 24 (7.7%), coronary artery disease in 16 (5.1%). The commonly reported symptoms were cough in 104 (33.4%), weakness in 94 (30.2%), fever in 87 (28%), dyspnea in 55 (17.7%) patients (**Table 1**). In previous studies, fever and cough were reported most frequently followed by weakness, myalgia and dyspnea (17, 18).

The involvement in COVID-19 pneumonia is similar to other viral pneumonia. In this study, among the CT scans 20.9% were reported as viral pneumonia and 27.7% as compatible with COVID-19 disease with atypical findings. The thorax CT was evaluated as normal in 21.9% of the patients. Particularly in early stage of the disease, it appeared thorax CT could be normal and this would not exclude the disease. The evaluation based on overall tomography findings; the most commonly observed finding was ground-glass appearance (n=181; 27.2%). In accordance with the literature, there was primarily bilateral involvement in 153 (23%) and peripheral involvement in 80 (12%). The frequency of ground-glass opacities is reported between 46-100%. In another study, ground-glass opacities were detected in 88% of 919 patients and described as the most common finding (19). Ground-glass opacities are suggested to occur as a result of increased capillary blood flow, partial filling of alveoli, shifting of air due to interstitial thickening. It is described as mildly increased lung density without disruption of bronchial and vascular threshold (20). In the study group, consolidation was the second common finding in the overall CT evaluation. According to the literature, consolidation was reported in 2-64% of COVID-19 infections. Initially, ground-glass involvement may accompany lung involvement and consolidation may supervene within 1-3 weeks which suggests progressing disease (20,21). Consolidation is increased parenchymal density that occurs as a result of replacement of alveolar air with pathological fluid, cells and tissue. The bronchial and vascular structures appear indistinct (22). SARS-CoV-2 was reported to use angiotensin-converting enzyme-2 as a cell entry receptor in humans which leads to initial pulmonary damage followed by parenchymal changes (23). Lymphadenopathy was reported in 4-8 % of COVID-19 patients; although rarely seen it was associated with critical disease (21). In this study, nodular appearance/LAP was detected 50 (7.5%) of the CT scan findings. Pulmonary parenchymal opacities with a diameter of ≤3 cm is defined as nodules and such nodules can be observed in viral pneumonia. Ground-glass opacity surrounding a nodule is defined as the "Halo sign" (22). Cobblestone appearance is defined as intralobular and interlobular septa accompanying ground-glass opacities. Alveolar edema and acute pulmonary damage may be due to interstitial inflammation. This appearance was reported in 5-36% of COVID-19 patients (22, 24). Overall, cobblestone appearance was detected in 22 (3.3%) of our findings. The reticular pattern was described as pulmonary interstitial thickenings such as inter-lobular septa and

intra-lobular lines. The occurrence of this pattern can be associated with interstitial lymphocyte infiltration which causes interlobular septal thickening. As the disease course is prolonged, the prevalence of reticular pattern may be increased in COVID-19 patients (21, 22, 25). In our patient group, 17 (2.6%) reticular patterns were observed. Pleural thickening (14; 2.1%), pleural effusion (9; 1.4%), bronchiectasis changes (5; 0.8%), vascular enlargement (4; 0.6%) were less frequently observed which was compatible with the literature.

CONCLUSION

Early detection, isolation and treatment are essential for control of the pandemic. Thorax CT is crucial for the early diagnosis of COVID-19. The most common CT findings include ground-glass appearance with consolidations. The findings may be variable among patients and different disease stages. In order to determine the guiding prognostic features for COVID-19, further investigation of the correlation between radiological and pathological findings is needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was designed and submitted to the T.R. Ministry of Health COVID-19 Scientific Research Committee and Ataturk University Medical School Clinical Research Ethics Committee for approval. Approval was granted by both committees (ethical approval no: B.30.2.ATA.0.01.00/276).

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.

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.

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.880037

Anatolian Curr Med J 2021; 3(2); 151-157

The effects of folic acid on vascular reactivity in a hyperhomocysteinemic rat model

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Cite this article as: Yılmaz M, Gemalmaz H, Yücel C, Ketenciler S, Gürcün U, Dişçigil B. The effects of folic acid on vascular reactivity in a hyperhomocysteinemic rat model. Anatolian Curr Med J 2021; 3(2); 151-157.

ABSTRACT

Objective: This study aimed to investigate the antioxidant effects of folic acid and its effects on contraction and relaxation responses in rat aorta in hyperhomocysteinemic rats.

Material and Method: Thirty-four male Wistar Albino rats were allocated into four groups. Rats in the hyperhomocysteinemia group (Group 1, n=9) received 1 g/kg/day methionine via orogastric gavage for 30 days and then injected with intraperitoneal saline for the next 7 days. In the hyperhomocysteinemia+folic acid group (Group 2, n=9), following the administration of methionine for 30 days, folic acid (4 mg/kg/day) was delivered intraperitoneally for 7 days. Sham group rats (Group 3, n=8) received orogastric saline for 30 days, which was followed by an IP injection of saline for another 7 days. Animals allocated into the folic acid group (Group 4, n= 7) had orogastric saline for 30 days and intraperitoneal folic acid for 7 days. After 5 weeks of treatment, blood samples were obtained, all animals were sacrificed, and hearts were harvested. Thoracic aortic segments were suspended on individual organ baths, and acetylcholine-induced (endothelium-dependent) relaxation responses of isolated aortic rings were evaluated.

Results: Relaxation responses in Group 1 through 4 were 73.88±9.96, 76.15±9.28, 76.61±8.83, and 69.26±15.68, respectively. There was no significant difference in the organ bath in terms of relaxation response to acetylcholine at a dose of 10-9 mM between the groups (p=0.550).

Conclusion: Folic acid therapy failed to produce a significant improvement in vascular reactivity.

Keywords: Hyperhomocysteinemia, folic acid, vascular reactivity

INTRODUCTION

Background/Rationale

Atherosclerotic cardiovascular diseases are among the leading causes of death in the world, as well as in Turkey (1,2). Hence, the effects of atherosclerosis at the cell level and their prevention continue to attract researchers.

Folic acid helps to make nucleic acids and convert some amino acids (such as the conversion of serine, glycine, and homocysteine to methionine, catabolism of histidine to glutamic acid) (3). In folic acid deficiency, especially in pregnant women, megaloblastic (macrocytic) anemia, cancers (such as colon, stomach, and uterus), and other pathologies (such as anencephaly, spina bifida, and cardiovascular disease) may occur together with elevated serum homocysteine level (4). It is stated that one of the most essential factors causing hyperhomocysteinemia (HHcy) is folic acid deficiency (5). In recent years, the link between folate homeostasis and homocysteine metabolism has been shown to play a crucial role in many vascular diseases (6).

HHcy is an independent risk factor for atherosclerotic vascular disease, stroke, and arterial as well as venous thromboembolism (5). Some mechanisms proposed for the formation of HHcy-related atherosclerosis can be listed as endothelial dysfunction, vasodilatation with an impaired flow, increased proliferation in vascular smooth muscle cells, and increased coagulation (7). Another undesirable effect of HHcy on vascular endothelium is reducing the production of nitric oxide (NO) and its bioavailability. NO is a critical molecule that plays an essential role in maintaining vital balance in all

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Received: 23.02.2021 **Accepted:** 25.03.2021

systems of the body (such as vascular reactivity, platelet aggregation, immune system, nerve conduction, and the production of various hormones) (8). We hypothesized that the demonstration of favorable effects of folic acid on contraction and relaxation responses can contribute to studies on the use of folic acid in vascular diseases.

Objectives

This study aimed to investigate the antioxidant features of folic acid and its effects on contraction and relaxation responses in rat aorta in hyperhomocysteinemic rats.

MATERIAL AND METHOD

Study Design

A randomized and controlled experimental animal study was designed. The study protocol was approved by Adnan Menderes University Animal Experiments Local Ethics Committee (IRB number: 2011-001, Date: 09.02.2011). The study was conducted in 2014 .The research institution is a third-level health center that provides specialized diagnosis, treatment, and service by using modern knowledge and technology.

Participants

Thirty-four Wistar albino male rats were obtained from the Adnan Menderes University Experimental Animal Production Laboratory. Rats were kept in their cages and were fed ad libitum with standard rat food and tap water until about 16 weeks old. A 12-hour day and night rhythm was applied. The animals were kept in a controlled room with a temperature of 20-25 degrees Celsius. Weights of the rats were measured weekly, starting from the first day of the study. The drug doses were adjusted accordingly (9). The animals were randomly allocated into four groups. Rats were kept in 4 different wire cages throughout the study. At the end of the ten-day adaptation period, the rats were weighed as 350-400 gr. Hyperhomocysteinemia was induced with a dose of 1 g/kg/day L-methionine (Sigma-Aldrich (M9625, USA) dissolved in 150 mM phosphate buffer (pH 7.4) given by oral gavage (9). Folic acid was given at a dose of 4 mg/kg/day dissolved in 1% sodium carbonate (10). Antioxidant levels were examined biochemically in tissue and blood samples in all groups.

The hyperhomocysteinemia (HHcy) group (Group 1, n=9): Animals in this group were given orogastric 1 g/kg/day L-methionine for 30 days. Then, intraperitoneal (IP) saline was given for a week, and a model of hyperhomocysteinemia was created in rats. The dose-response curves were assessed in the organ bath.

The hyperhomocysteinemia + folic acid group (Group 2, n=9): Rats in this group were given orogastric 1 g/kg/day L-methionine for 30 days. Then, 4 mg/kg/day IP folic acid was given for a week. Hyperhomocysteinemia was induced, and the effect of folic acid was assessed using dose-response curves in the organ bath.

The sham group (Group 3, n=8): Rats in this group were not medicated; orogastric saline was given for 30 days. Then, IP sterile saline was administered for a week, and dose-response curves were investigated in the organ baths.

The folic acid group (Group 4, n=8): Rats in this group were given IP folic acid for a week after feeding orogastric saline for 30 days. Dose-response curves were investigated in the organ bath.

One of the rats was lost before analysis. Accordingly, the number of rats used in the experiment was as follows: Group 1: 9, Group 2: 9, Group 3: 8, and Group 4: 8 (**Figure**).

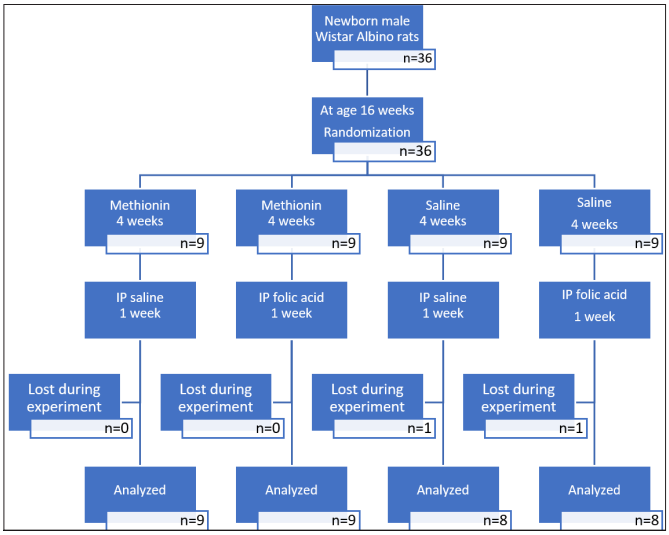

Figure. Participant flow diagram
IP: Intraperitoneal

Variables

Methionine is metabolized to form homocysteine (Hcy) over S-adenosine methionine and S-adenosine homocysteine. Additionally, methionine and its intermediate S-adenosyl homocysteine inhibits Hcy metabolism and causes an increase in plasma total Hcy levels (11). The commercial form of methionine was in the form of a sterile powder. The solution was prepared in weekly doses of 150 µM, pH 7.4, 0.25 mg/ml phosphate-buffered saline (PBS) mixture.

Folic acid was prepared at a dose of 4 mg/kg/day. Weekly doses were prepared by dissolving in 10 mg/ml PBS, and the solution was administered intraperitoneally with an insulin injector (26 G 0.45x10 mm).

The rats were enumerated by marking with picric acid. The experiment was started with four rats, and another four were added to the research every day. Thus, at the end of five weeks, the first four rats, which ended the experimental protocol for the organ bath, were sacrificed, allowing sufficient time for the organ bath.

At the end of five weeks, the rats were anesthetized with ketamine (100 mg/kg, IP) + xylazine (10 mg/kg, IP), and cervical dislocation was performed after intracardiac blood collection. Intracardiac 2-3 ml blood was taken and placed in tubes with EDTA. Later, the aorta was removed and prepared for the organ bath. The withdrawn blood was cooled in ice, centrifuged (3000 g) for 10 minutes, placed in plasma Eppendorf tubes (at least 2 separate tubes), and stored in -80°C until analysis. Heart tissue was also taken and immediately stored at minus eighty degrees for biochemical study. Organ bath experiments were carried out in the laboratory of the research institute.

Tissue homogenization was performed in a Braun Potter-S tissue homogenizer (B. Braun Biotech Co., Melsungen, Germany) with tissue homogenization buffer. The tissue homogenization buffer (1 mM, pH 7.4) was prepared using phenylmethylsulphonyl fluoride (C7H7FO25, SIGMA, catalog number P-7626), di-Natriumhydrogen-phosphate-Dihydrate (Na2HPO4.2H2O, MERCK, catalog number K25979680), potassium dihydrogen phosphate (H2KPO4, MERCK, catalog number A986373), and ethylenediaminetetraacetic acid disodium (EDTA, C10H14N2O8Na2.2H2O, SIGMA, catalog number E1644).

The primary variable of our study was defined as relaxation response to acetylcholine (%). Other variables were, substrates reacting with thiobarbituric acid (TBARS) in heart tissue and serum samples, nitric oxide (NO) (μM), superoxide dismutase (SOD) (ng/mL), glutathione peroxidase (GSH-Px) (U/L), glutathione reductase (GR) (mmol/min/ml), catalase (CAT) (mmol/min) in the heart tissue and hemolysate samples.

Glutathione determination was performed according to the method used by Tietz (12). By determining the level of nitrate, which is one of the cleavage products of NO, an indirect measurement of NO was done according to the method used by Cortas et al. (13). SOD activity determination was performed by the process of Yi Sun et al. (14). Glutathione peroxidase (GPx) activity was measured according to Paglia and Valentin's method (15). The technique developed by Carlberg and Mannervik and later by Kazim Husain was used for the determination of glutathione reductase (GR) activity (16). Catalase (CAT) activity analysis was done according to the Hugo Aebi method (17). The determination of homocysteine in the blood was made using an ELISA kit (Cusabio, Catalog No: CSB-E13376r).

Organ Bath: At the end of the five-week trial, after ketamine (100 mg/kg IP) and xylazine (10 mg/kg IP) anesthesia, the rib cage was opened with a median sternal approach, and cervical dislocations were performed after drawing intracardiac blood. Thoracic aorta, which stands at the same level as the thoracic vertebra, was carefully and rapidly removed along with the arcus aorta. Using a binocular magnifier (3.5 magnification), the aorta was cleared of the adipose and connective tissues on it and then cut through an appropriate incision to obtain isolated length aortic rings. During this process, an effort was given to preserving the endothelium.

Each aortic segment was cut into approximately 3 mm-wide rings. These rings were suspended in the carbonated (95% oxygen, 5% carbon dioxide) Krebs solution (118.3 mM NaCl, 4.7 mM KCl, 1.2 mM MgSO4, 1.22 mM KH2PO4, 2.5 mM CaCl2, 25.0 mM NaHCO3 and 11.1 mM glucose, Sigma-Aldrich), which was heated and circulated at 37 °C (Heater and Circulatory system - May WBC 3044V3), without delay (18). Each aorta ring was passed through two stainless steel hooks in a 25 ml organ bath filled with Krebs solution (May 99 IOBS Ankara, Turkey), and suspended to the organ bath.

Upperparts of the two hooks were attached to a transducer (May GTA0303, Biopac Systems Inc. Model MP 100), and their contractions in mg were measured (19). The Acq Knowledge 3.8.2 (Commat Ltd, Ankara, Turkey) was used as a computer program. The standard equilibrium stage was then performed for each aortic ring. Aortic rings initially were stretched with 1 g, waited for 10 min., then the tension was increased to 2 g, waited for 10 min., and then reached 3 g and waited for 10 minutes again.

Later, 0.1 ml of norepinephrine at 10-4 M concentration was added to the bath, and contraction responses were recorded. When the contraction curves were flat, the bath was washed twice with a Krebs solution. The bath was stretched up to 4 g and waited until it was stable. First, the contraction curve was taken with 0.1 ml of norepinephrine 10-4 M concentration, and then relaxation responses were obtained with 0.1 ml of Acetylcholine 10-4 M concentration. Finally, the bath was washed twice again with the Krebs solution, 45 minutes before starting the experiment. Baths without contraction and relaxation responses at these stages were not taken to the experimental phase (20). Then, the experiment phase was started. Norepinephrine 10-4 M was added 0.1 ml to each bath. Contraction responses in the baths were observed. Acetylcholine concentrations prepared when the plateau level formed and started to be stable in the contraction curve formed were given to the baths. First, 0.1 ml of

10-9 M concentration of acetylcholine was given, and a relaxation response was observed, acetylcholine was given 3.16 x10-9 M when non-relaxation was observed. When the relaxation response ended, another concentration of 10-8 M acetylcholine was given. Thus, 3.16x10-8 M, 10-7 M, 3.16x10-7 M, 10-6 M, 3.16x10-6 M, 10-5 M, 3.16x10-5 M, 10-4 M acetylcholine were given each 0.1 ml in an order. Relaxation responses at each dose were observed and recorded. Aortic rings were studied for each of the four groups in the organ baths.

Study Size

The sample size calculation was performed based on the primary outcome relaxation response to acetylcholine at a dose of 3.16 x10-9 M with the G Power program (21). Taking the effect size as 0.70 (large), α error as 0.05, power as 80%, number of groups as 4, a total of 28 subjects are required to compare the mean values with the one-way ANOVA.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) (SPSS for Windows, Version 25.0, Chicago, IC, USA). Results were presented as mean and standard deviation. The normal distribution of the continuous variables was examined with the Shapiro-Wilk test. The Kruskal-Wallis test was used to check for significant differences between groups. The Mann-Whitney U test was used for bivariate comparisons. The threshold for statistical significance was taken as $p<0.05$.

RESULTS

There was a substantial difference in the blood catalase levels between Group 1 and 2. Also, there were significant differences in blood homocysteine, blood catalase, tissue glutathione peroxidase, tissue glutathione reductase, and tissue glutathione levels between Group 1 and 3. There were significant differences in blood homocysteine, blood catalase, tissue glutathione peroxidase, tissue glutathione reductase, and tissue glutathione levels between Groups 1 and 4. Besides, there were significant differences in blood homocysteine, blood glutathione reductase, blood catalase, tissue glutathione peroxidase, tissue glutathione, tissue glutathione reductase, and tissue catalase levels between Group 2 and 3. Additionally, there were significant differences in blood homocysteine, blood catalase, blood TBARS, tissue glutathione, and tissue glutathione reductase levels between Group 2 and 4. However, there was no significant difference in the comparison of the biochemical results between Group 3 and 4 (**Table 1** and **Table 2**).

There was no significant difference in the organ bath analysis concerning relaxation responses between the groups. ($p>0.005$) (**Table 3**).

Table 1. Comparisons of the blood and tissue measurements between the groups

Variable	Group	Mean	SD	H	p
Blood homocysteine	1	18.20	4.91	24.558	<0.001
	2	17.33	1.84		
	3	8.32	1.52		
	4	9.75	2.12		
Blood glutathione reductase	1	61.09	5.35	478.887	<0.001
	2	22.39	1.97		
	3	8.25	1.35		
	4	15.10	2.13		
Blood glutathione	1	5.45	3.70	0.132	0.939
	2	5.83	3.18		
	3	6.22	2.15		
	4	5.40	2.61		
Blood catalase	1	417.44	171.66	17.907	<0.001
	2	665.40	137.31		
	3	1567.62	582.32		
	4	1530.84	560.81		
Blood nitric oxide	1	45.84	1.20	8.696	<0.001
	2	41.64	5.79		
	3	40.08	1.02		
	4	46.77	1.26		
Blood TBARS	1	8.73	4.15	14.963	<0.001
	2	11.82	1.05		
	3	4.05	1.51		
	4	4.42	3.23		
Tissue glutathione peroxidase	1	0.79	0.50	7.783	<0.001
	2	0.69	0.38		
	3	1.53	0.33		
	4	1.49	0.39		
Tissue glutathione reductase	1	1.25	0.28	4.613	0.009
	2	1.15	0.49		
	3	2.03	0.72		
	4	2.34	1.34		
Tissue glutathione	1	12.79	1.47	95.330	<0.001
	2	10.53	6.16		
	3	40.26	6.84		
	4	37.45	1.44		
Tissue catalase	1	0.57	0.14	6.210	0.002
	2	0.70	0.19		
	3	1.26	0.44		
	4	1.37	0.82		
Tissue nitric oxide	1	64.04	4.23	1.388	0.266
	2	71.43	5.85		
	3	70.92	4.17		
	4	66.90	5.43		
Tissue TBARS	1	3.57	1.85	15.484	<0.001
	2	4.99	2.10		
	3	1.03	0.28		
	4	0.92	0.44		

SD: Standard deviation. TBARS: tissue substrates that react with thiobarbituric acid H: Kruskal-Wallis test value. Group1: Hyperhomocysteinemia, Group 2: Hyperhomocysteinaemia+Folic acid, Group 3: Sham, Group 4: Folic acid.

Table 2. Post hoc comparison of the groups concerning the measured variables with significant differences

Variable	Group	Group	Z	p
Blood homocysteine	1	3	2.882	0.002
		4	2.558	0.010
	2	3	3.000	0.001
		4	2.646	0.006
Blood glutathione reductase	2	3	2.143	0.035
Blood catalase	1	2	2.286	0.022
		3	2.722	0.006
		4	2.558	0.011
	2	3	2.571	0.010
		4	2.646	0.008
Blood TBARS	1	3	2.009	0.045
	2	3	3.021	0.003
		4	2.670	0.008
Tissue glutathione peroxidase	1	3	2.598	0.009
		4	2.382	0.017
	2	3	2.941	0.003
		4	2.662	0.008
Tissue glutathione reductase	1	3	2.502	0.012
		4	2.276	0.023
	2	3	2.310	0.021
		4	1.967	0.049
Tissue glutathione	1	3	2.598	0.009
		4	2.699	0.007
	2	3	2.941	0.003
		4	3.125	0.002
Tissue catalase	1	3	2.598	0.009
	2	3	2.521	0.012
		4	2.646	0.008
Tissue TBARS	1	3	2.791	0.005
		4	2.699	0.007
	2	3	2.836	0.003
		4	2.662	0.008

Group 1: Hyperhomocysteinemia, Group 2: Hyperhomocysteinemia + Folic acid, Group 3: Sham, Group 4: Folic acid. Z: Mann-Whitney U test value.

Table 3. Comparison of relaxation responses between the groups

Acetylcholine dose (M)	Group	Mean	SD	H	p
10^{-9}	1	73.88	9.96	0.716	0.550
	2	76.15	9.28		
	3	76.61	8.83		
	4	69.26	15.68		
$3.16x10^{-9}$	1	85.78	7.95	0.361	0.781
	2	90.32	10.80		
	3	86.16	5.94		
	4	87.43	13.19		
10^{-8}	1	83.36	9.11	0.036	0.990
	2	83.84	9.88		
	3	83.75	6.74		
	4	84.89	12.87		
$3.16x10^{-8}$	1	82.92	9.28	0.021	0.995
	2	82.86	10.06		
	3	83.13	7.00		
	4	84.01	13.81		
10^{-7}	1	82.44	10.46	0.022	0.995
	2	81.89	10.19		
	3	82.55	7.64		
	4	83.28	14.16		
$3.16x10^{-7}$	1	80.99	10.51	0.012	0.998
	2	80.68	10.48		
	3	80.84	8.08		
	4	81.67	14.44		
10^{-6}	1	79.30	9.88	0.020	0.995
	2	79.48	10.82		
	3	80.13	8.46		
	4	80.47	14.06		
$3.16x10^{-6}$	1	77.87	9.95	0.009	0.998
	2	78.30	10.73		
	3	78.68	8.66		
	4	78.54	13.90		
10^{-5}	1	76.78	9.82	0.046	0.986
	2	77.59	9.78		
	3	75.59	10.09		
	4	76.92	13.82		
$3.16x10^{-5}$	1	74.95	9.85	0.022	0.995
	2	75.58	9.17		
	3	74.27	10.82		
	4	75.37	13.35		
10-4	1	74.04	9.79	0.028	0.993
	2	74.10	9.97		
	3	72.68	10.87		
	4	73.54	13.89		

SD: Standard deviation. H: Kruskal-Wallis test value

DISCUSSION

Key Results

This study demonstrated statistically significant differences in the mean blood glutathione reductase, blood glutathione peroxidase, blood catalase, blood TBARS, tissue glutathione peroxidase, tissue glutathione reductase, tissue glutathione, tissue catalase, and tissue TBARS levels between the groups. However, there was no significant difference in the organ bath in terms of relaxation responses between the groups.

Limitations

This was a well-conducted experimental study. However, there is a gap between study conduction and writing, which is due to the personal problems of the primary author. Also, the fact that the degree of endothelial damage was not measured can be considered as a limitation.

Interpretation

Hyperhomocysteinemia can cause several harmful effects in the body, some of which include acting as free radicals and causing endothelial damage. As a result, it causes coagulation-enhancing effects, such as platelet activation, coagulation factors, thrombus formation, oxidation in biological membranes, and induces atherosclerosis-enhancing effects by low-density lipoprotein (LDL) oxidation (22). Furthermore, hyperhomocysteinemia (HHcy) has been reported to increase aortic aneurysm and calcification in aortic valves (23,24).

HHcy can be defined as having total homocysteine (Hcy) above 15 μmol/L (25). There can be many causes of hyperhomocysteinemia. Some of these can be listed as folic acid, cyanocobalamin, pyridoxal phosphate deficiency, or various enzyme abnormalities (26,27).

There is a complicated relationship between plasma homocysteine, glutathione peroxidase (an antioxidant enzyme, containing selenocysteine), and endothelial dysfunction. It has been claimed that glutathione peroxidase may play a role in the harmful effects of homocysteine. It has even been suggested that homocysteine partially decreases GPx-1 expression and, therefore, may increase endothelial dysfunction. There is even evidence that increasing the level of GPx can reduce endothelial dysfunction (28). In our study, glutathione peroxidase levels were observed lower in homocysteine groups, in line with previous publications, which is an encouraging finding of the experiment.

Detoxification of hydrogen peroxide (H2O2), which passes from mitochondria to cytosol, is carried out by the enzyme catalase, synthesized by peroxisomes (29). It has been noted that increased hydrogen peroxide levels may have contributed to the emergence of the pathological effects of homocysteine because it inhibits catalase (30). In our study, the fact that the level of catalase in the homocysteine groups was lower than the other groups supports this view.

Biomembranes and intracellular organelles are susceptible to the attack of oxidants due to the unsaturated fatty acids in membrane phospholipids. Malondialdehyde (MDA), which is one of the vital products of lipid peroxidation, affects ion exchange through cell membranes, leads to cross-linking of the compounds in the membrane, and causes unwanted results, such as change of ion permeability and enzyme activity. MDA can react with the nitrogenous bases of DNA and is, therefore, mutagenic, genotoxic, and carcinogenic for cell cultures (31). On the other hand, in pharmacological doses, folic acid has been reported to lower MDA levels and increase antioxidant capacity (32).

Determination of MDA, one of the lipid peroxidation products, is based on the principle that thiobarbituric acid reacts with MDA to give rise to a colored compound that can be measured at a wavelength of 532 nm. In this method, substances that react with thiobarbituric acid are analyzed and included in the literature as TBARS (33). In our experiment, the lower TBARS levels in groups without hyperhomocysteinemia were evaluated as in harmony with the previous research.

Hyperhomocysteinemia causes vascular dysfunction mainly due to oxidative stress, reduced vasodilators such as nitric oxide, damaging the vascular matrix, supporting smooth muscle proliferation, and reducing vascular constriction (34). The fact that no significant difference was detected between the groups in both blood and tissue nitric oxide levels in our study suggested that the adverse effects of homocysteine may not have been fully revealed in our experiment.

In an animal study with pulmonary arteries, it was reported that hyperhomocysteinemia significantly affected both the contraction and relaxation responses of the vessels compared to the control group (26). It has been stated that high doses of folic acid improve endothelial function and vascular reactivity after four weeks of supplementation, which may reduce the risk of cardiovascular disease (35). It has been claimed that folic acid can improve endothelial function even without lowering homocysteine levels (36). Although interventions for reducing the increased homocysteine concentration to desired levels vary depending on the underlying causes, folic acid has been reported to be very useful (37).

Reviewing the studies on this issue has created an expectation that giving folic acid in rats with hyperhomocysteinemia should increase vascular reactivity. In our study, a moderate hyperhomocysteinemia model was created in rats. However, no significant improvement in vascular reactivity was observed in rats given folic acid compared to the control group. Perhaps the duration of the experiment was not sufficient for the reactive effects to occur in the vessels. On the other hand, the folic acid dose might not have been high enough, and the supposed damage caused by homocysteine could not have been adequately established.

CONCLUSION

In the moderate hyperhomocysteinemia model, five-week folic acid administration increases antioxidant levels and decreases levels of damaging agents such as TBARS. However, there was no significant decrease in vasodilating nitric oxide levels. Likewise, folic acid therapy failed to produce a substantial improvement in vascular reactivity. This result may be due to insufficient vascular damage or inadequate folic acid doses. To elucidate this speculation, further studies are needed with higher doses of folic acid, ensuring that sufficient damage is generated in the vascular endothelium.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by Adnan Menderes University Animal Experiments Local Ethics Committee (IRB number: 2011-001, Date: 09.02.2011).

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.

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.

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.885326

Anatolian Curr Med J 2021; 3(2); 158-164

Nosocomial infection rates of three-years in neurological intensive care unit and relationship to mortality

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Cite this article as: Bilge N, Yevgi R, Ceylan M, Parlak E, Şimşek F. Nosocomial infection rates of three-years in neurological intensive care unit and relationship to mortality. Anatolian Curr Med J 2021; 3(2); 158-164.

ABSTRACT

Aim: The risk of developing nosocomial infections (NI) is higher in intensive care units (ICU). Recognition and treatment of NI is important in reducing mortality and morbidity. The aim of this study was to investigate the clinical and demographic characteristics, rates of mortality and nosocomial infection, agents of infection and antibiotic resistance rates of patients the neurological ICU.

Material and Method: The study was carried out between the dates of 01/06/2015 and 01/06/2018 in Neurological ICU. Data of all patients aged were retrospectively analyzed in accordance with the National Nosocomial Infections Surveillance System. SPSS 23 software was used for statistical analysis.

Results: Throughout the 3-year period, a total of 641 patients were followed up in the Neurological ICU and the most common diagnosis was ischemic cerebrovascular disease. It was found that 641 NIs developed in 55 patients in 5334 days of hospitalization in three years and the mortality rate was significantly higher in those with a NI (83.6%) compared to patients without a NI. The rate of NI the mean rate in three years was 9.98% and the most common NI was device-associated infections. In the 3-year period, the most common pathogen was *A. baumannii* which was susceptible to colistin in 100% of the cases, and resistant to imipenem in 96% of the cases.

Conclusions: The use of invasive tools should be reduced in order to reduce nosocomial infection and mortality rates in the ICU. Each ICU should monitor its own nosocomial infection agents and resistance rates and develop a rational antibiotic use.

Keywords: Nosocomial infection, antibiotic resistance, mortality, neurological intensive care unit

INTRODUCTION

The presence of a neurological intensive care unit (ICU) in tertiary hospitals which are reference centers in the organization of contemporary health systems has become a necessity (1). In our country, the rate of presence of a neurological ICU in centers older than 10 years is 90% (2). Status epilepticus, acute stroke, infectious or inflammatory diseases of the central nervous system, primary neurological diseases such as peripheral nervous system disorders, neuromuscular junction or muscle diseases, anoxic ischemic encephalopathy, fat embolism, hyper/hypo-glycemia and secondary neurological diseases such as encephalopathies associated with nutritional insufficiency and organ failure and hypertensive encephalopathy should be followed up in a neurological intensive care unit (3,4). Severe clinical course, old age, weak immune system, multiple drug use, risk of developing metabolic disorders and the frequency of invasive ICU procedures lead to an increase in the incidence of infections in patients in Neurological ICU's. Nosocomial infection (NI) which develops after hospital admission and is not in the incubation period at the time of admission or that might develop after discharge is defined as infections acquired within 48-72 hours after admission and 10 days after discharge or 30-90 postoperative days after discharge (5). It was reported that 5-10% of the hospitalized patients and 20-25% of the ICU patients have a NI. Ventilator-associated infections, catheter infections and urinary tract infections are among the most common infections in a neurological ICU (6-8). It was shown that NI can be significantly reduced by careful infection control planning (9). Currently, the need for ICUs has been increased in parallel with the increase in elderly population, improvement in diagnosis and treatment processes and higher health expenditures. In ICU patients, recognition of infection agents and treatment of these infections play an important role in the prognosis of primary disease as well as in

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Received: 23.02.2021 **Accepted:** 01.04.2021

duration of hospital stay. Detection of the most common infectious agents in hospitals through surveillance studies provides an appropriate and successful treatment plan. In addition, it is important to determine the common infectious agents in order to obtain a successful empirical treatment planning. However, there is limited data on the incidence, factors and effective antibiotherapy approaches with respect to NIs acquired in Neurological ICUs.

The aim of this study was to determine rates of NI rates and mortality, agents of NI and their antibiotic resistance, and to contribute to take control measures for NIs and to plan empirical treatment and reduce the rates of NI.

MATERIAL AND METHOD

The data of all patients followed up in the tertiary level neurological ICU of The Hospital of School of Medicine, University of Atatürk, between 01/06/2015 and 01/06/2018 were analysed retrospectively. The study was carried out with the permission of Ethics Board of Atatürk University, Faculty of Medicine (Permission granted/decision no: 05/21-07.06.2018). The trial was conducted in accordance with the Helsinki Declaration principles.

Demographic and clinical characteristics and status of discharge or death of the patients were recorded. The number and rates of nosocomial infections, number of inpatient days, number and rate of device-associated infections (DAI), number of days/rate of use of mechanical ventilator (MV), urinary catheter (UC), central venous catheter (CVC); rates of catheter associated urinary tract infection (CAUTI), ventilator-associated pneumonia (VAP), CVC- associated blood circulation infection (BCI), isolated microorganisms, antibiotic resistance rates and hand hygiene compliance rates were analyzed in light of the data obtained from the daily follow-up visits of infection control nurses, consultations of infection control physicians and daily visits of responsible physicians in the ICU in accordance with National Nosocomial Infections Surveillance System.

The NI rate was calculated using the formula of "NI rate=total number of nosocomial infections/number of inpatients x 100". The device-associated NI rate was calculated using the formula of "Device-associated NI rate=device-associated NI number/days of invasive device ×1000".

Statistical Method

D'Agostino Pearson test was used to determine whether the parameters were normally distributed. The nominal data were compared using the chi-square test. The intergroup comparisons of the normally distributed data were performed using the independent t-test. The results were accepted significant when the two-way p-values were found below 0.05. All statistical calculations were performed using SPSS 23 software.

RESULTS

In this study, NI was detected in 55 of 641 patients who were followed up in the ICU throughout the three-year period between dates stated above. Of the patients with and without NIs, 56.8% and 60% were females, respectively. There was no statistically significant difference between the genders. The mean age was 71.5 (±8.0) and 76.9 (±8.3) years, respectively, and there was no statistically significant difference in age between the groups with and without NI. In both groups, patients were most frequently admitted for ischemic stroke, hemorrhagic stroke, epilepsy and other diagnoses, and the most common comorbidities were hypertension and diabetes mellitus. The 3-year mortality rates were higher in patients with NI with a statistically significant difference between the two groups (**Table 1**). It was determined that a total of 64 NIs were developed in 55 patients (including more than one NI epizode in a single patient) and all patients who had multiple NIs died. The rate of NI was 10.53% in the year of 2015, 12.03% in 2016 and 6.81% in 2017 (**Table 2**).

Table 1. Demographic and clinical characteristics of patients

	Not NI (n=586)	NI (n=55)	p
Gender n (%)			
Female	331 (56.8)	33 (60)	0.091
Male	255 (43.2)	22 (40)	
Age, year (Mean ±SD)	71.5±8.0	76.9±8.3	0.072
Mortality n (%)	282 (48.1)	46 (83.6)	<0.001
Diagnoses n (%)			
Ischemic stroke	414 (70.7)	41 (74.6)	0.882
Hemorrhagic stroke	69 (11.8)	11 (20)	
Epilepsy	34 (5.8)	2 (3.6)	
GBS	19 (3.2)	1 (1.8)	
ALS	9 (1.5)		
Muscle disease*	9 (1.5)		
Others**	32 (5.5)		
Additional disease n (%)			
Hypertension	312 (53.2)	36 (65.5)	0.648
Diabetes mellitus	133 (22.7)	15 (27.3)	
Atrial fibrillation	113 (19.3)	15 (27.3)	
CAD	76 (13)	11 (20)	
CHD	73 (12.5)	9 (16.3)	
COPD	59 (10.1)	3 (5.5)	
Malignancy	24 (4.1)	7 (12.7)	
CRF	21 (3.6)	5 (9.1)	

GBS: Guillain barre syndrome, ALS: Amyotrofik lateral skleroz *Myasteni gravis, primary muscle disease** Dementia, parkinson, subarachnoid hemorrhage, encephalitis. CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CHF: Congestive heart failure, CRF: Chronic renal failure.

Table 2. Distribution of NI rates and mortality rates by years

	2015	2016	2017	Total
Number of patients (n)	209	241	191	641
Number of NI patients (n)	22	29	13	64
NI patients rate (%)	10.53	12.03	6.81	9.98
Number of patients with NI (n)	15	27	13	55
Mortality n (%)	12 (80)	23 (85.1)	11 (84.6)	46 (83.6)

NI: Nosocomial Infection, NI rate=Nosocomial Infectionrate/Number of inpatients x 100

DAIs were the most common in each of the three years and in the of three years total. The at total of three years, catheter associated urinary tract infection (CAUTI) was the most common, VAP was the second, and laboratory proven BCI was the third. Considering the distribution by years, it was found that the most frequent CAUTI in 2015, CAUTI and VAP in 2016, and VAP in 2017. During these three years, it was seen that the use of mechanical ventilators, urinary catheters and central venous catheters increased. In the three years data, the rate of DAIs was highest in VAP (**Table 3**).

In the three-year period, 75 pathogenic microorganisms were isolated and the most common pathogenic agent was gram-negative bacteria (94.7%). In 2016 and 2017, all of the agents consisted of gram-negative bacteria. While *Escherichia coli* (*E. coli*) was the most common causative agent in the year 2015, *Acinetobacter baumannii* (*A. baumannii*) was the most common causative agent in 2016 and 2017, and the total three-year period (**Table 4**).

Table 3. Distribution of NI regions over the years and NI rates

	2015 (n=22)	2016 (n=29)	2017 (n=13)	Total (n=64)
Device-associated infection n (%)	14 (63.6)	20 (68.9)	10 (76.9)	44 (68.7)
VAP	3	9	5	17
CVC related BCI	-	2	2	4
CAUTI	11	9	3	23
Non ınstrument-associated infection n (%)	8 (36.4)	9 (31.1)	3 (23.1)	20 (31.3)
Proven by laboratory BCI	8	5	3	16
Clinically defined pneumonia	-	1	-	1
Pneumonia specific laboratory findings	-	2	-	2
Skin and soft tissue infection	-	1	-	1
Patient day/ Number of patients	1527/209	1947/241	1860/191	5334/641
MV used days n (%)	831 (54)	1251 (64)	1452 (78)	3534 (66)
VAP rate	3.61	7.19	3.44	4.81
UC used days n (%)	1523 (99.7)	1946 (100)	1858 (100)	5327 (100)
CAUTI rate	7.22	4.62	1.61	4.32
CVC used days n (%)	164 (10.7)	528 (27.1)	703 (37.8)	1395 (26.2)
CVC-associated BCI rate	-	3.79	2.84	2.87

Instrument associated infection rate: Number of device-associated infections /Number of invasive instrument days x1000 NI: Nosocomial infection, BCI: Blood circulation infection, VAP: Ventilator associated pneumonia, CVC: Central venous catheter, UTI: Urinary tract infection, MV: Mechanical ventilation, UC: Urinary catheter, CAUTI: Catheter associated urinary tract infection.

For the distribution of pathogen microorganisms by infection sites, the most common causative agent for CAUTI was found to be *E. coli*, *A. baumannii* for VAP and *Klebsiella pneumoniae* (*K. pneumoniae*) for CVC-associated BCI (**Table 4**) in the three-year period.

In our study, while *A. baumannii*, *E. coli*, *K. pneumoniae* were resistant to most antibiotics, *A. baumannii* and *K. pneumoniae* were 100% sensitive to colistin. The rates of resistance to various antibiotics for all three pathogens are shown in **Table 5**.

Table 4. Distribution of NI-causing microorganisms isolated by region and years

NI Location	2015 n=22	2016 n=36	2017 n=17	Total n=75
VAP n (%)	3 (13.6)	12 (33.4)	7 (41.2)	22 (29.3)
Acinetobacter baumannii	2 (9.1)	9 (25)	7 (41.2)	18 (24)
Pseudomonas aeruginosa	1 (4.5)	-	-	1 (1.3)
Klebsiella pneumoniae	-	2 (5.6)	-	2 (2.7)
Escherichia coli	-	1 (2.8)	-	1 (1.3)
CAUTI n (%)	11 (50)	11 (30.6)	5 (29.4)	27 (36)
Acinetobacter baumannii	2 (9.1)	1 (2.8)	3 (17.6)	6 (8)
Pseudomonas aeruginosa	1 (4.5)	2 (5.6)	1 (5.9)	4 (5.3)
Klebsiella pneumoniae	1 (4.5)	3 (8.3)	-	4 (5.3)
Escherichia coli	5 (22.7)	5 (18.9)	1 (5.9)	11 (14.7)
Enterococcus spp.	1 (4.5)	-	-	1 (1.3)
Proven by laboratory BCI n (%)	8 (36.4)	5 (13.9)	3 (17.6)	16 (21.3)
Acinetobacter baumannii	1 (4.5)	2 (5.6)	1 (5.9)	4 (5.3)
Pseudomonas aeruginosa	1 (4.5)	-	-	1 (1.3)
Klebsiella pneumoniae	-	1 (2.8)	2 (11.8)	3 (4)
Escherichia coli	2 (9.1)	1 (2.8)	-	3 (4)
Enterococcus spp.	1 (4.5)	-	-	1 (1.3)
Staphylococcus aureus	1 (4.5)	-	-	1 (1.3)
Enterobacter spp	1 (4.5)	-	-	1 (1.3)
Acinetobacter lwoffii	-	1 (2.8)	-	1 (1.3)
Candida tropicalis	1 (4.5)	-	-	1 (1.3)
CVC-associated BIC n (%)	-	2 (5.6)	2 (11.8)	4 (5.3)
Acinetobacter baumannii *Klebsiella pneumoniae*	- -	- 2 (5.6)	1 (5.9) 1 (5.9)	1 (1.3) 3 (4)
Skin and soft tissue infection n (%)	-	2 (5.6)	-	2 (2.7)
Acinetobacter baumannii *Enterobacter aerogenes*	- -	1 (2.8) 1 (2.8)	-	1 (1.3) 1 (1.3)
Clinically defined pneumonia n (%)	-	1 (2.8)	-	1 (1.3)
Escherichia coli	-	1 (2.8)	-	1 (1.3)
Pneumonia specific laboratory findings n (%)	-	3 (8.3)	-	3 (4)
Acinetobacter baumannii	-	3 (8.3)	-	3 (4)

NI: Nosocomial infection, BCI: Blood circulation infection, VAP: Ventilator associated pneumonia, CVC:Central venous catheter, UTI: Urinary tract infection, MV: Mechanical ventilation, UC: Urinary catheter, CAUTI: Catheter associated urinary tract infection.

Table 5. Antibiotic resistance rates of *A. baumannii*, *E. coli*, and *K. pneumoniae* in three years.

	A. baumannii n (%)	*E. coli* n (%)	*K. pneumoniae* n (%)
Antibiotic			
Amikacin	13 (73%)	5 (42%)	4 (50%)
Ampicillin	7 (100%)	9 (75%)	3 (100%)
Ampicillin-sulbactam	5 (100	7 (78%)	2 (100%)
Gentamicin	10 (42%)	3 (19%)	6 (60%)
Ertapenem	7 (100%)	-	-
Aztreonam	6 (100%)	-	6 (100%)
Imipenem	22 (96%)	2 (17%)	8 (80%)
Colistin	0	-	0
Levofloxacin	14 (100%)	-	7 (100%)
Meropenem	33 (100%)	4 (36%)	8 (100%)
Netilmicin	3 (60%)	1 (100%)	2 (50%)
Piperacillin	10 (100%)	4 (100%)	4 (100%)
Piperacillin-tazobactam	18 (95%)	5 (84%)	7 (87%)
Ceftazidime	4 (100%)	-	1 (100%)
Seftriakson	1 (100%)	-	1 (100%)
Ciprofloxacin	3 (100%)	-	1 (100%)
Cefepim	3 (100%)	1 (100%)	2 (100%)
Tigeksilin	1 (25%)	-	-

DISCUSSION

Infections acquired in ICUs cause a significant increase in morbidity, mortality and treatment costs (10). Neurological ICUs poses additional risk factors due to elderly patient population, immobility due to mental and motor regression and debilitation of the patients and long hospitalizations besides the increased risk of NI which is common in all ICUs. The cases followed up consisted of elderly patients. The mean age of patients with a NI was 76.9 (±8.3) years, whereas the mean age of those had no NI was 71.5 (±8.3) years with no statistically significant difference between the groups. The patients with and without NIs were most frequently treated for the diagnosis of ischemic cerebrovascular disease.

In the literature, different results were obtained regarding the rate of NI which was reported to be 5-10% in the overall hospital wards and 20-25% in the ICUs (11,12). The rate of NI developed in the ICUs varies between 5.3 and 56.1% in Turkey. A study performed in a reanimation unit reported the frequency of NI as 53.5% (13). Another study conducted in an ICU revealed that 17% of patients had NI (14). In our study, the 3-year NI rate was found to be 9.98% although it varied from year to year.

Various causes of NI have been reported in the literature. In addition to the studies reporting urinary tract infection as the most common cause of NI, pneumonia has also been reported as the most common cause in some other studies (15-18). In another study conducted in the Neurology ICU, the rates of urinary tract infection were found to be high, and 95% of the infections were reported to be associated with urinary catheters (19). Again, in the same study, it was observed that the most common cause of UTI was *E. coli* and the second was *K. pneumoniae*. In our study, we determined that the most common cause of NI in 2015 and 2016 was CAUTI, *E. coli* was the most common cause of CAUTI, and *A. baumannii* was the second. In 2017, the most common causative agent was *A. baumannii*. All of the factors were associated with the use of UC.

Vincent et al. (17) reported that the most common cause of NI was pneumonia with a rate of 46.9%. In a different study conducted in intensive care units, it was reported that pneumonia was the most common, followed by UTI, bacteremia, sepsis and catheter infections (18). In our study in three years, nosocomial pneumonia (VAP (n=17) + specific laboratory findings pneumonia (n=2) + clinically defined pneumonia (n=1)) was in the second place along with BCI (laboratory proven BCI (n=16) +CVC- associated BCI (n=4)) (Tablo 3). VAP was the most common among cases of pneumonia in a total of three years and each year. In 2015 and 2017, all pneumonia were VAP. Other rare types of pneumonia were observed only in 2016. Eren et al. (19) reported most frequently isolated that *A. baumannii* and P. aeruginosa were in VAP in the ICU. In our study, *A. baumannii* was the most frequently isolated pathogen in VAP.

In the study of Saltoğlu et al. (20), bacteremia rate among NIs was found to be 20.5 %. In our study, BCI (Laboratory-proven BCI+CVK- associated BCI) second among NIs in three years (**Tablo 3**). A previous study was determined that the most common causative agents of BCI were *Staphylococcus aureus* and coagulase-negative staphylococci (21). In our study, *A. baumannii* was found to be the most common cause of BCI. BCI is mostly associated with CVC and they can lead to severe sepsis. According to our findings, the most common laboratory-induced BCI was identified among bloodstream infections. While CVC- associated BCI was not seen in 2015, it was observed that it increased in 2016 and 2017. We thought that this situation might be due to the increase in CVC usage rates. In our study, the most common cause of CVC associated BCI was *K. pneumoniae*.

Skin and soft tissue infections are common in ICUs with long hospitalization periods, and *A. baumannii* and *S. aureus* are frequently isolated agents (19,22). Skin and soft tissue infections were detected in our neurology intensive care unit only in 2016, and the isolated agents were *A. baumannii* and *Enterobacter aerogenes*. Skin and soft tissue infections were not observed in 2015 and 2017.

In 2006, Üstün et al. (23) found that 83% of NI in neurology ICU was DAI. In our study, the rate of DAI among NI was in the first place with 68.7%. In DAI, CAUTI was the most common, followed by VAP and CVC- associated BCI. The high rate of DAI indicates the necessity of determining invasive procedure indications well, removing invasive devices as early as possible, and taking simple infection control measures such as hand hygiene.

The frequency and distribution of microorganisms responsible for NI may vary in different clinics (24). A study reported that 64% of the bacteria isolated in ICU were gram-negative bacteria and 27% were gram-positive bacteria, among which *A. baumannii*, *S. aureus*, and *E. coli* were the most frequently isolated species (25). Gram-negative bacteria were reported to be most frequently isolated in 49.4% of the cases in another study conducted in the ICU between 2014-2015 years and *A. baumannii* was the most common among them, followed by *K. pneumoniae* and *E. coli*, in descending order (26). In the same study, 47.8% gram-positive bacteria, and 2.7% Candida species were detected. In another study, *A. baumannii* (69.83%) was the most frequently isolated agent from ICU (27). As reported in studies, gram-negative bacteria are reported to be dominant in the flora (23-27, 28). In our study, 95% of the isolated agents were gram-negative bacteria, 4% were gram-positive cocci and 1% were fungal infections. In 2016 and 2017, all of the microorganisms isolated were gram-negative bacteria. It was found that the most common agent of NI was *E. coli* in 2015 and *A. baumannii* in 2016 and 2017. In the 3-year period, the most common cause of NI was *A. baumannii* (%43,9), followed by *E. coli* (%21,3) and *K. pneumoniae* (%16), in descending order. Our results demonstrated that gram-negative bacilli were the most commonly isolated agents in a Neurological ICU and that they dominated the flora. It is of great importance to knowledge the alterations of the pathogenic microorganisms compared to previous years when planning empirical treatment for the NIs in the fight against NIs.

The development of antibiotic resistance is a common problem in ICUs. ICUs are places where antibiotic-resistant bacteria rapidly emerge and spread. Multiple and long-term antibiotic use increases the risk of colonization with resistant microorganisms in ICUs (29,30). *A. baumannii* has been reported to be more susceptible to imipenem and amikacin compared to other antibiotics (31). Colistin, among the antimicrobial agents has been demonstrated to be the most effective agent against the pathogens P. aeruginosa and *A. baumannii* (32-35). According to the three-year data including the years 2015, 2016, and 2017 in this present study, *A. baumannii* was 100% susceptible to colistin, 75% susceptible to tigexyline and 58% susceptible to gentamicin, whereas it was 96% resistant to imipenem and 100% resistant to meropenem. *E. coli* was found to be 83% susceptible to imipenem, 81% to gentamicin and 64% to meropenem. *K. pneumoniae* was found to be 100% susceptible to colistin, whereas it was 80% resistant to imipenem and 100% resistant to meropenem. This present study revealed that gram-negative bacilli were most susceptible to colistin. The results of this present study demonstrated that the susceptibility of gram-negative bacilli to imipenem and meropenem was decreased compared to the previous studies. This demonstrates how much antibiotic resistance and susceptibility rates have changed over the years and we believe that detecting this change each year will play an important role in the planning of empirical treatment. Therefore, further resistance problems could be avoided with the development of more rational antibiotic administration strategies.

There are many factors affecting mortality in ICUs. In various studies, the mortality rate in ICU in our country has been reported at varying rates such as 24.5% and 61.5%. The mortality rate was found to be 60% in a study conducted in our country's neurology ICU between 1999-2000 (5). In our study, the mortality rate was found to be 51.2% which was consistent with the literature. The mortality rate of patients with NI was 83.6%, and without NI was 48.1%. The high mortality rates may be due to the fact that most of the patients accepted to the neurology ICU are admitted to the hospital with severe neurological diseases such as cerebral infarction and cerebral hemorrhage, and accompanying chronic diseases such as DM and coronary artery disease. In addition, patients followed up in the neurology ICU have additional risk factors such as elderly patient population, immobility, and debility. In this study, most of the patients who developed HE were hospitalized for severe diseases such as ischemic stroke and hemorrhagic stroke. In our study, the three-year mortality rate in neurology ICU was 48.1% in patients who did not develop HE, while this rate was 83.6% in patients with NI, and this difference was statistically significant. According to our results, we believe that NI prevention will decrease mortality rates.

CONCLUSION

In order to reduce NI and mortality in the ICU, it is necessary to reduce the use of invasive devices, increase training activities for infection control measures, and to implement a regular resistance tracking program. Recognition of NI, determination of pathogenic microorganisms and their antibiotic susceptibility are highly important for determining empirical treatment and reducing mortality and morbidity. Every center, like in our study, should determine the HE factors and resistance rates in its own intensive care units, and rational antibiotic use should be developed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethics Board of Atatürk University, Faculty of Medicine (05/21-07.06.2018).

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.

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.888222

Anatolian Curr Med J 2021; 3(2); 165-170

The effectiveness of percutaneous nephrolithotomy for the treatment of large impacted upper ureteral stones

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Cite this article as: Sarıkaya K, Şenocak Ç, Çiftci M, İbiş MA, Bozkurt ÖF. The effectiveness of percutaneous nephrolithotomy for the treatment of large impacted upper ureteral stones. Anatolian Curr Med J 2021; 3(2); 165-170.

ABSTRACT

Objective: To compare the efficacy of combined semi-rigid+ flexible ureterorenoscopic surgery (URS+RIRC) and percutaneous nephrolithotomy (PNL), which is the standard method for the surgery of ≥2 cm upper ureteral impacted stones.

Material and Method: The data of 123 patients who underwent stone surgery for ≥2 cm impacted ureteral stones in the upper ureter in our clinic were retrospectively analyzed. The patients were divided into two groups as URS+RIRC (n=59) and PNL (n=64) according to the type of operation. Patients with stones impacted in the ureter at the level between the L4 vertebra and ureteropelvic junction were included in the study. Preoperative demographic data and postoperative results of the patients in two groups were compared.

Results: Average operation time was similar in both groups (p=0.147). Mean hospital stay was significantly higher in the PNL group compared to the URS+RIRC group (3.28±0.57 days vs 1.11±0.32 days, p=0.001). Mucosal injury was developed in 10 (16.9%) patients in the URS+RIRC group during the operation, while it was only 3 (4.7%) in the PNL group (p=0.027). Postoperative urinary tract infection development was found to be similar in URS+RIRC and PNL groups (8.5% vs 4.7%, p=0.479).Postoperativestone-free rate was found to be significantly higher in the PNL group compared to the URS+RIRC group (95.3% vs 79.7%, p=0.008).

Conclusion: PNL is a very effective and safe procedure in the surgical treatment of stones ≥2 cm in diameter impacted in the upper ureter. The complication rate of PNL is comparable with URS+RIRC; however, it is seen that the PNL is more advantageous than URS+RIRC in terms of postoperative total stone-free rate.

Keywords: Urolithiasis, percutaneous nephrolithotomy, ureteroscopic surgery

INTRODUCTION

Urinary system stones are a common health problem affecting more than 12% of the general population (1). Completely obstructed stones impacted into the ureter cause symptoms such as pain, high fever,infection and result in loss of renal function in the later period (2). Although extracorporeal shock wave lithotripsy (ESWL) is recommended as the first-line treatment method in upper ureteral stones, it is known that its effectiveness is decreased, especially in stones with a ≥1.5 cm in diamater (3). Therefore, semi-rigid ureteroscopy (URS) and combined retrograde intrarenal surgery (RIRC) are used as the common treatment choice in many centers in the treatment of upper ureteral stones with a diameter of ≥1.5 cm (4). However, it has been reported that the effectiveness of only semirigid-URS decreases in stones larger than 1 cm and therefore additional surgery is required (5). Retrograde migration of stone fragmentsduring the operation into the kidney and the inability to find some stone fragments in the kidney is a common problem in semi-rigid URS (6). Therefore, in recent years, percutaneous nephrolithotomy (PNL) has been used more frequently in many centers in the surgical treatment of upper ureteral stones with a diamater of ≥1.5 cm and its successful results have been reported (7). When the literature is reviewed, it is seen that all of the studies in this area were carried out on upper ureteral stones with a diameter of ≥1.5 cm (2-4,6,7). Therefore, in this study, we aimed to report our experience with PNL in the surgical treatment of larger upper ureteral stones with a diameter of ≥2 cm in our clinic, which is one of the centers that urinary system stone surgery is performed intensively.

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Received: 28.02.2021 **Accepted:** 10.03.2021

MATERIAL AND METHOD

After obtaining the approval of the Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 23.02.2021, Protocol no: 2012-KAEK-15/2238), the data of 123 patients who were operated for upper ureteral stones larger than 2 cm in diameter between January 2012 and January 2020 in our clinic were retrospectively analyzed. The trial was conducted in accordance with the Helsinki Declaration principles. While 59 of the patients had retrograde URS+RIRC, 64 patients had PNL. Patients with stones impacted in the ureter with a diameter of ≥2 cm located between the lower border of the spinal L4 vertebra and the ureteropelvic junction were included in the study. The stone that did not allow any passage at contrast graphies or computed tomography (CT) and that stayed at the same localization for more than 1 month and which resulted with hydronephrosis was defined as impacted stone. Before the operation, patients were informed in detail about URS+RIRC and PNL procedures, and the choice of treatment was decided by mutual consensus between the patient and the physician. Patients with non-functioning kidney or stones <2 cm were excluded from the study.Patients with additional stones in the renal collecting system other than ureter stones were excluded from the study. Patients who were observed to have pus drainage from the obstructed urinary system during URS+RIRC or PNL and who were terminated by inserting a ureteral double-J Stent or nephrostomy for this situation were not included in the study. Patients with additional urinary tract anomaly, pregnancy, coagulopathy, and active urinary tract infection were also excluded from the study. Another exclusion criterion was the previous unsuccessful ESWL and the scattering of the stones into the ureter or renal collecting system.

All patients were evaluated preoperatively with routine blood tests, urine analysis, urine culture, and non-contrast abdominal computed tomography (CT). Excretory urography was performed if the serum creatinine was normal. Dynamic renal scintigraphy (Tc-99m-DTPA) was performed in patients with severe reduction of renal parenchyma thickness and renal functions were evaluated. According to the antibiogram results, appropriate antibiotic treatment was initiated for the patients whose bacterial growth was detected in the urine culture and the operations were delayed until the urine culture was cleared. All operations were performed by a total of 5 urologists working in the same clinic.

Surgical Procedures

URS+RIRC: All of the URS+RIRC operations were underwent under general anesthesia. Under direct vision, a 0.035-inch hydrophilic guide-wire was advanced into the kidney from the ureter orifice on the stone side. A 9.8F semi-rigid ureteroscope (Olympus®) was used for ureteroscopy and access was provided up to the stone. The stone was fragmented with a 200 µm or 500 µm Ho: YAG laser energy (Stone light®)and removed using a 2.2 F nitinol stone basket. In cases where the stone migrated into the renal pelvis or renal caliceal system, the stone was found and fragmentated using a flexible ureteroscope (Olympus®-9.5 F). A5-6 F double-j stent was placed in the ureter for spontaneous drainage of small fractured residual stone fragments and easy recovery of mucosal edema. However, double-j stentwas not placed in cases where there was no residual stone and no significant mucosal edema.An urethral 16-18F foley catheter was placed into the bladder and removed on postoperative day 1 and the double-j stent was removed on postoperative 3rd week.

PNL: Following given a lithotomy position an external 5 F ureteral catheter was inserted to the target ureter with direct vision under general anesthesia. Then the patient was rotated to the prone position with a pack under the ipsilateral hemi-pelvis. After the appropriate position was given, radiopaque liquid diluted with 50% saline was given into the renal collecting system through ureteral catheter and it was screened using fluoroscopy. In cases which sufficient radiopaque material could not reached intothe 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. In order to reach of the upper ureter with a nephroscope, a middle calix-tract entry was preferred and the the operation was performed in a single percutaneous axess. Mini-PNL was not preferred in patients with stone size >2 cm, as it would significantly prolong the operation time.

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. 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 24F-30 F, allowing percutaneous access to the renal collecting system with rigid nephroscope (Karl-storz® -22F). Following the percutaneous entry, the stone was fragmented and removed with use of an ultrasonic lithotripter (EMS®), or pneumatic lithotripter (EMS®). A flexible nephroscope (Olympus®-21F) was used in some stones that can not be reached with rigid nephroscope.As a result of fluroscopic control, antegrade double-j stent was placed in patients who had escaped stone fragments into the distal of the ureter or had significant mucosal edema.

Following the procedure, a 16F catheter was placed in all patients as a nephrostomy. Nephrostomy of the patients was taken on the 3rd postoperative day. Patients who were placed with double-j stents were called for control at postoperative 3rd week and their double-j stents were removed. Patients in both groups were called for control in the postoperative 1st month and evaluated with non-contrast CT. Successful treatment was defined as complete removal of the stone or the presence of <4 mm small insignificant stone. The authors state that residual stones <4 mm in size drain spontaneously and do not require additional intervention (8). On the other hand, ESWL or second session URS+RIRC was recommended for patients with residual stones greater than a ≥4 mm diamater.

Groups were compared according to sucess rates, perioperative outcomes and postoperative complication rates.

Statistical Analysis

All statistical analyses were performed using the SPSS 24.0 (IBM Corp., Chicago) software for Windows. In the univariate analysis, the Chi-Square Test was used for nominal data, while the Mann-Whitney U test was used for nonparametric variables. Mean±Standart deviation, Median, minimum, and maximum were used to define the variables. A p-value of <0.05 was considered as statistically significant.

RESULTS

The median age of the patients was 42 (23-75) years and the male/female (M/F) ratio was 72/51 (**Table 1**). The median age of the patients in URS+RIRC group was 43 (23-75) years, while the median age of the patients in PNL group was 41 (23-72) years (p=0.939). M/F ratios were also found to be similar between groups (URS+RIRC: 34/25 vs PNL: 38/26, p=0.844). While the mean stone diameter was 24.22±3.53 mm in URS+RIRC group, it was found to be 25.28±4.38 mm in PNL group (p=0.230). Mean Hounsfield unit of the stone was 790.37±138.30 in URS+RIRC group,and it was mean 816.94±155.55 in PNL group (p=0.320). Preoperative mean hydronephrosis degrees of the groups were similar (p=0.582). There was no difference between the groups in terms of mean operation times (URS+RIRC=69.49±21.02 min vs PNL=75.46±22.44 min, p=0.147). The average hospital stay was significantly lower in URS+RIRC group than PNL group (1.11±0.32 days vs 3.28±0.57 days, p=0.0001). While 10 (16.9%) patients had peroperative mucosal injury in URS+RIRC group, only 3 (4.7%) patients in PNL group had mucosal injury (p=0.027). On the other hand, there was no bleeding that would require transfusion in any patient in URS+RIRC group, while blood transfusion was required in 3 (4.7%) patients in PNL group; however, there was no significant difference between the groups (p=0.245). While in URS+RIRC group 17 (28.81%) of the patients had stone migration to the renal collecting system during the operation, there was no stone migration in PNL group (p=0.0001). While 91.5% of the patients in URS+RIRC group had a peroperative ureteral double-j catheter, only 20.3% of the patients in PNL group required a double-j catheter (p=0.0001). There was no significant difference between the groups in terms of postoperative complications according to Clavien grade system (p=0.168); however, postoperative stone-free rate was found to be significantly higher in PNL group than URS+RIRC group (95.3% vs 79.7%, p=0.008) (**Table 2**).

Table 1. Patient's characteristics and outcomes (n=123)

Age, median (minimum-maximum), years	42(23-75)
M/F ratio, n	72/51
Stone diameter (mm), mean±SD	24.77±4.02
Operation time (min), mean±SD	72.60±21.89
Hospital stay (days), mean±SD	2.24±1.18
Stone-free rate, n (%)	108 (87.8)

*M/F: Male/Female
*SD:Standart deviation

Table 2. Patient's characteristics and comparison of the groups

	URS+RIRC (n=59)	PNL (n=64)	p value
Age, median (minimum -maximum), years	43 (23-75)	41 (23-72)	0.939
M/F ratio, n	34/25	38/26	0.844
Stone diameter (mm), mean±SD	24.22±3.53	25.28±4.38	0.230
Previous ipsilateral renal surgery, n (%)	13 (22)	16 (25)	0.699
Preoperative HN, n (%)			**0.582**
Grade 1	15 (25.4)	16 (25.0)	
Grade 2	25 (42.4)	23 (35.9)	
Grade 3	19 (32.2)	25 (39.0)	
Preoperative Hounsfield Unit, mean±SD	790.37±138.30	816.94±155.55	0.320
Operation time (min), mean±SD	69.49±21.02	75.46±22.44	0.147
Hospital stay (days), mean±SD	1.11±0.32	3.28±0.57	0.001*
Preoperative serum creatinine (mg/d L), mean±SD	1.09±0.29	1.06±0.27	0.719
Postoperative serum creatinine (mg/d L), mean±SD	1.20±0.28	1.17±0.26	0.634
Peroperative outcomes, n (%)			
Mucozal injury	10 (16.9)	3 (4.7)	0.027*
Bleeding	0 (0)	3 (4.7)	0.245
D-J catheterization	54 (91.5)	13 (20.3)	0.001*
Stone migration	17 (28.8)	0 (0)	0.001*
Postoperative urinary tract infection, n (%)	5 (8.5%)	3 (4.7)	0.479
Postoperative complications by Clavien grade, n (%)			**0.168**
Grade0	49 (83)	61 (95.2)	
Grade1	2 (3.4)	1 (1.6)	
Grade2	4 (6.8)	1 (1.6)	
Grade3	4 (6.8)	1 (1.6)	
Grade4	0 (0)	0 (0)	
Grade5	0 (0)	0 (0)	
Stone-free rate, n (%)	47 (79.7)	61 (95.3)	0.008*

*M/F: Male/Female
*SD: Standart deviation
*D-J catheterization: Double-j stent catheterization
*HN: Hydroureteronephrosis

DISCUSSION

Stones impacted in the ureter cause complete obstruction that prevents urine flow from the ureter, resulting in hydronephrosis (2-4). The increased backflow resulting from intrapelvic pressure leads to a decline in renal blood flow with progressive focal ischemia, compression of the papillae with a decrease in the glomerular filtration rate, thinning of the parenchyma and decrease in renal functions due to a loss of nephrons (9). The main treatment options for upper ureteral stones are ESWL,semirigid or flexible URS, PNL, laparoscopic or open ureteral stone surgey (10). ESWL is widely preferred in the first-line treatment of upper ureteral stones with a diameter of <1.5 cm and not causing complete obstruction (3). Although ESWL is frequently preferred as a minimally invasive method in the treatment of ureteral stones, the success rate decreases significantly, especially in impacted ureteral stones with a diameter of ≥1.5 cm and (5). In addition to the stone size, the hounsfield units of the stone also play an important role in the success of ESWL.In the study performed by Çelik et al. (11) on 254 ESWL patients, it was reported that the stone-free rate was significantly higher in the patient group with low HU compared to the patient group with high HU. In our study, HU values were quite high in both groups. In addition, repeated multiple ESWL sessions can cause serious complications such as renal injury, subcapsular hematoma and renal scarring (12).

Success rates of semi-rigid or flexible URS have been reported up to 87% in minimally invasive surgical treatment option of ureteral stones (13). Using both pneumatic-ultrasonic lithotripter and Holmium YAG: laser technology individually or in combination when necessary increases the success rate of URS in ureter stones ≥1.5 in diameter (14). However, the difficulty of reaching the stone, which occurs as a result of the migration of the complete stone or fragments of the stone into the renal collecting system due to pressure effect of irrigation fluid or lithotripter during operation is one of the most important problems of semi-rigid URS (15).Although the use of stone cone prevents this situation, it is not always possible to pass the proximal of the stone and the risk of mucosal damage increases.In this situation, fragmentation of the stone seriously increases the stone-free rate of the operation by reaching the stone fragments migrated into the renal collecting system with the help of a flexible ureteroscope in the same session (16). In the present study, a flexible URS combination was used with semi-rigid URS, and similar to the literature, a high stone-free rate was obtained (79.7%).

Nowadays, PNL is the most preferred surgical treatment method, especially in the treatment of renal stones larger than 2 cm in diameter, and its success rate has been reported between 85% and 100% (17). In addition, stone-free rates of up to 86% to 98.5% and higher than all other treatment options have been reported in upper ureteral stones with a diameter of 1.5 cm in PNL (18). In the presentstudy, stone-free rate of PNL in upper ureteral stones with a diameter of ≥2 cm was found to be quite high (95.3%). Juan et al. (19) reported the results of their study, in which they performed PNL in 22 patients and URS in 31 patients in the treatment of ureter impacted stones >1.5 cm in diameter. According to this study, the mean operation time was 115.4±49.5 min in the PNL group and 88.6±28.5 min in the URS group (p=0.001).In the same study, the mean hospital stay was 4.7±2.0 days in the PNL group, while it was 1.9±1.1 days in the URS group (p=0.009). However, in the same study, stone free rate was found to be 95.4% in the PNL group and 58% in the URS group, and PNL was reported to be quite advantageous (p=0.001).In another similar study, Yang et al. (20) reported the results of their study involving a total of 182 patients in which they performed PNL in 91 patients and URS in 91 patients due to upper ureter impacted stones. Also according to this study,the mean operative time was found to be significantly higher in the PNL group than the URS group (27.4±2.3 min vs 45.2±3.1 min, p<0.001). In addition, in this study, it was reported that the mean blood loss in the PNL group was significantly higher than the URS group (40.2±5.3 ml vs 15.6±1.8 ml, p<0.001).On the other hand, it has been reported that the total stone clearance rate in the PNL group is considerably higher than the URS group (p<0.001).

Combination of semi-rigid URS with RIRC is known to reduce the postoperative stone-free rate. Mugiya et al. reported the results of 54 patients treated with URS+RIRC (13). According to this study, 48 of the patients were treated solely using retrograde ureteroscopy. In 47 patients (87%), the stones were fragmented completely by a single endoscopic procedure.İn their study, additional shock wave lithotripsy was performed after endoscopic debulking in 2 patients, and any stones remaining in the ureter were easily treated by shock wave lithotripsy. Pyelonephritis resulting from obstruction caused by ureteral stones was observed in 4 patients, 3 of whom required percutaneous nephrostomy and 1 of whom required stent insertion before the endoscopic procedure. They reported that,these patients then underwent retrograde endoscopic lithotripsy, which completely cleared the calculi in one session with any complication. In another recent study, Kozyrakis et al. reported the effectiveness of retrograde semirigid and flexible ureteroscopic lithotripsy for the treatment of large ureteral stones equal of or greater than 15 mm in 19 patients (21). According to their study, a subsequent RIRS during the same session was necessary in 2 cases. They satated that, after a single procedure a stone free state was achieved in 15 cases (78.9%), while 4 others required a second session (ESWL or second ureterolithotripsy, 2 cases each).İn their study, only 1 patient, the stone-free state was not achieved after a 1.2 procedure per patient (overall

success rate 94.7%). In precent study, no significant difference was found between the groups in terms of mean operation time, but similar to the literature, the length of hospital stay was significantly higher in the PNL group.In addition, in our study, similar to the literature, the stone-free rate was found to be significantly higher in the PNL group compared to the URS+RIRC group.This result indicates that PNL is quite advantageous in terms of stone-free rate compared to URS in the surgical treatment of upper ureteral stones with larger diameter (≥2 cm) as well as in ureter impacted stones with ≥1.5 cm diameter.

Karalar et al. (22) evaluated the effects of parenchymal thickness and stone density values on PNL outcomes. According to this study, no correlation was detected between stone density and success rate ($p>0.05$), but drop in Hb (%) was only correlated with parenchymal thickness ($p<0.01$). They were also stated that the stone-free rate in patients with thicker renal parenchyma was higher than in patients with lower parenchymal thickness ($p<0.01$). Also in our study it was considered that, in patients with low renal parenchymal thickness on CT images, bleeding will be more during the operation, and recovery is longer after nephrostomy removal.In present study, no blood transfusion was required due to bleeding in any of the patients underwent PNL.

Wang et al. (23) reported the results of their studies in which they performed URS, mini-PNL and laparoscopic ureterolithotomy (RPLU) at a ratio of 1: 1: 1 to 150 patients with stones >15mm in diameter impacted into the upper ureter. In their study, it was reported that mini-PNL and RPLU are more appropriate treatment options for upper ureteral stones with a diameter of >15 mm, and URS would be more appropriate for selected patients with high general anesthesia risk. In addition, this study reported that there was no significant difference between the three groups in terms of complication rates ($p>0.05$). In another similar study, Bozkurt et al.(24) performed URS in 41 and PNL in 45 of 86 patients with a ≥1.5 cm diameter impacted upper ureter stones. According to this study, PNL was found to be quite advantageous over URS in terms of stone-free rate (97.8% vs 82.9%, $p=0.025$), while postoperative complication rates were shown to be close to each other according to the Clavien grade system (Grade 0: 35/34%, Grade 1: 3/2%, Grade 2: 7/5%, Grade 3-4-5: 0/0%). Similar to literature data, in the present study, no significant difference was found between the groups in terms of postoperative complications according to Clavien grade system ($p=0.168$). This result indicates that both URS and PNL can be safely applied with low complication rate in the treatment of larger impacted upper ureteral stones with a diameter of ≥2 cm as well as in stones with a diameter of ≥1.5 cm.

Limitations: The most important limitation of our study is its retrospective nature and the lack of randomization. The small sample size due to the fact that it is a single center study can be considered as another limitation. In addition, the lack of long-term patient satisfaction status may be determined as another important limitation.

CONCLUSION

Combined URS+RIRC and PNL are very effective and safe treatment options in the treatment of stones ≥2 cm in diameter. The complication rates of both procedures are similar. URS+RIRC is a more minimally invasive treatment option and is more advantageous than PNL in terms of hospital stay. However, in terms of total stone free rate, PNL provides a significantly higher success rate than URS+RIRC. The operation option, the advantages and disadvantages of both procedures should be determined with the patient-physician consensus after discussing the patient in detail.

ETHICAL DECLARATIONS

Ethics Committee Approval: After obtaining the approval of Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 23.02.2021, Protocol no:2012-KAEK-15/2238).

Informed Consent: Because the study was designed retrospectively, no written informed consentform 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.

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.901628

Anatolian Curr Med J 2021; 3(2); 171-176

Relationship between vitamin D levels and mortality rates of critically ill patients in intensive care unit

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Cite this article as: Sağır M, Kaplan M, Tanoğlu A, Demirel F. Relationship between vitamin D levels and mortality rates of critically ill patients in intensive care unit. Anatolian Curr Med J 2021; 3(2); 171-176.

ABSTRACT

Introduction: Vitamin D has a pivotal role in bone metabolism. It regulates immunity and inflammation. In this current research, it was aimed to determine whether there is an association between the mortality rate and the vitamin D level of critically ill patients who were followed in intensive care unit (ICU).

Material and Method: Fifty two patients (30 (58%) female and 22 (42%) male) admitted to ICU with the diagnosis of respiratory failure, sepsis, acute renal failure, multiple organ failure, GIS bleeding were included in the study. During the admission to the ICU, all of the patients' complete blood count, C-reactive protein, serum calcium, albumin, urea, creatinine, 25-OH vitamin D, potassium, and arterial/venous blood gas levels were measured. Their acceptable mortality risk was calculated according to the APACHE II scoring system.

Results: The level of vitamin D was found at least 1 up to 78.6 range, and the average was 19.61 ng/dl. Eighteen (35%) patients were discharged and 34 (65%) of the ICU patients were died. Vitamin D deficiency was observed to be a very common issue in our critically ill patients (65.4%). The difference between the two groups of age, accepted mortality and urea levels were found to be statistically significant ($p<0.05$). According to the terms of the patient's vitamin D status, differences were not significant ($p=0.269$). Vitamin D deficiency in the multivariate analysis was not an independent risk factor for mortality.

Discussion: Vitamin D deficiency occurs quite often in patients with chronic, severe disease. These patients are admitted to the ICU with more serious acute problems. They have high Apache II scores as well as poor prognosis and high mortality rates during ICU. Our results suggest that although vitamin D deficiency is not a real risk factor, it is a supporting factor in explaining increased mortality rates.

Keywords: Vitamin D deficiency, critically ill, intensive care unit

INTRODUCTION

Critical illnesses are important public health problems due to high mortality rates, the growing use of the intensive care units (ICU), and high health expenditures. The patients admitted to ICU have low quality of life and high mortality risk. The nutritional needs of critical patients are not fully understood and differ in each stage of the disease. The primary goal of nutritional support is to change the course and consequence of the critical illness, even though the results have not been obtained adequately by randomized trials (1-3).

Vitamin D is a member of vitamins that melt in the oil. It is a sterol with hormone and hormone precursors which can be synthesized endogenously in suitable biological medium. Many foods naturally contain vitamin D, but it is mainly synthesized through the skin. If vitamin D level is below 20 ng/ml, it is called vitamin D deficiency. On the other hand, the level above 150 ng/ml is defined as intoxication (4). The most important effects of vitamin D are related with calcium and phosphorus metabolism, and bone mineralization. Recently, it has been shown that deficiency of vitamin D affects many kinds of cancers, cardiovascular diseases, metabolic diseases, infectious and autoimmune diseases in a negative way (3-5). However, the relationship between deficiency of vitamin D and risk of mortality in critical illnesses is unclear.

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Received: 23.03.2021 **Accepted:** 03.04.2021

In this study, it was aimed to determine whether there is a relationship between the mortality rate and the vitamin D level of critically ill patients in ICU.

MATERIAL AND METHOD

Fifty two patients admitted to GATA Haydarpaşa Training Hospital Internal Diseases ICU with the diagnosis of respiratory failure, sepsis, acute renal failure, multiple organ failure, GIS bleeding were included in the study. The study was completed between October 2015 and May 2016. The written consents of the patients were obtained after informing them about the study. Ethics committee approval for the study was received from GATA Haydarpaşa Training Hospital Ethics Committee meeting held on 05.11.2015 (2015/41). The trial was conducted in accordance with the Helsinki Declaration principles.

Cases that received vitamin D vitamin replacement in the last year and patients with primary bone metabolism disorders were not included in the study. During the admission to the ICU, all of the patients' complete blood count (CBC), C-reactive protein (CRP), serum calcium, albumin, urea, creatinine, 25-OH vitamin D, potassium, and arterial/ venous blood gas levels were measured and recorded. Quantitative determination of serum 25-OH vitamin D level was performed with chemiluminescent microparticle immunoassay (CMIA) method by using 3L52 artcihet reagent 25-OH vitamin D reagent kit. Also, acceptable mortality risk was calculated according to the APACHE II scoring system, which is one of the common intensive care predictive scoring systems, by detecting patients' vital signs, disease history, and Glasgow coma scores (4).

Statistical Analysis

The study was done using the SPSS version 15.0 program. Continuous variables, arithmetic mean±standard deviation; categorical variables were expressed as number and %. The distribution of continuous variables was examined by Kolmogorov-Simirnov test. While the comparison of normal distributed parameters according to D-vitamin groups was performed with the T-group comparison test, non-normal distributed parameters were compared with Mann Whitney U test. Pearson's correlation coefficient test as used to analyze correlations between variables.

RESULTS

The age distribution of the patients was found between 49 and 93 years with a mean and standard deviation as 77.94±10.2 years. Of the 52 participants included in the study, 30 (58%) were female and 22 (42%) were male. The Apache Score of the patients was found between 5 and 35 values with a mean and standard deviation as 17.73±6.09. The distribution of mortality risk of the patients according to Apache ll Score was found between 5.8 and 83 values with a mean and standard deviation as 30.63±16.47. The vitamin D distribution of the patients was found between 1 and 78.6 values with a mean and standard deviation as 19.61±15.89. The frequency of vitamin D deficiency in ICU was found 65.4%. lt was observed that this rate increased up to 84% when the vitamin D values between 20-30 ng/dl were also defined as vitamin D deficiency. This rate was 70% in females and 68% in males respectively.

The duration of hospitalization was found in the range of at least 2 and at most 57 days. Of the 52 participants who were included in the study 18 (35%) were discharged and 34 (65%) died. The distribution of biochemical and important disease variables according to hospital status (exitus/discharge) of 52 participants were examined. There were statistically significant difference between exitus and discharge groups according to age, Apache II score, mortality risk and urea values ($p<0.05$). The distribution of age of the patients in exitus and discharged groups was found to be 80.44±8.88 and 73.22±11.09 respectively. It was statistically significant that the patients in exitus group had older ages ($p=0.014$). The distribution of mortality risk according to the Apache II score was found to be 35.42±16.08 and 21.57±13.39 for the patients in exitus group and discharge group respectively. It was statistically significant that the exitus group had the higher distribution of mortality risk according to Apache II score ($p=0.004$). The distribution of urea was found to be 120.59±66.03 and 78.61±45.49 for patients in exitus and discharge group respectively. It was statistically significant that the urea distribution was higher in exitus group ($p=0.024$). There was no significant difference between exitus and discharge groups in terms of vitamin D distribution ($p=0.269$) (**Table 1**).

Table 1. Exitus/discharge distribution of the patients

	Exitus	Discharge	P value
Age (year)	80.44±8.88	73.22±11.09	0.014**
Apache score	19.74±5.25	13.94±5.88	0.003
Mortality risk according to Apache II score	35.42±16.08	21.57±13.39	0.004**
Vitamin D (mg/dl)	17.28±12.44	24±20.63	0.269
Calcium (mg/dl)	10.02±12.39	7.91±0.96	0.736
Albumin (mg/dl)	2.96±0.59	3.06±0.73	0.736
Urea (mg/dl)	120.59±66.03	78.61±45.49	0.024**
Creatinine (U/L)	2.35±1.49	1.79±1.18	0.229
CRP (mg/L)	112.12±103.76	136.78±140.33	0.788
Hemoglobin (g/dl)	10.63±2.09	10.65±2	0.847
Leukocyte ($\times10^3$/u)	15.24±6.95	12.73±4.24	0.308
Thrombocyte ($\times10^3$/u)	224.21±117.57	238.61±129.84	0.832
Duration of stay (day)	37.88±79.94	13.22±9.93	0.098

*:Mann Whitney U test; **: Statistically significant.

When 52 participants were considered in terms of Apache II score, statistically significant positive correlation was found between the mortality risk and Apache score (r= 0.98, p=0.0001), between urea and Apache score (r=0.613; p=0.0001) and between creatinine and Apache score (r=0.567; p=0.0001); but a negative correlation was found between albumin and Apache score (r=-292; p=0.036). There was a statistically significant positive correlation between vitamin D and platelet count (r=0.304; p=0.028), between hemoglobin and albumin (r=0.613; p=0.001), between urea and creatinine (r=0.739; p=0.0001) and between leucocyte count and platelet count (r=0.319; p=0.021). However there was a significant negative correlation between CRP and albumin (r=-275; p=0.049 (**Table 2**).

The effects of all variables that may affect the discharge status of patients were analysed by logistic regression analysis. The Bacwald (Wald) method was used to select the best model equation. In the last 10th step, the best model equation was attained. According to the statistical analysis of the last equation; the result of the model equation in step 10 is statistically significant (Hosmerand Lemeshow Test p=0.207). This model represented the recovery as 88.5%. According to this model, Apache score and Vitamin D level are statistically significant risk factors. Although CRP and duration of hospitalization are not statistically significant but they need to be regarded as important risk factors (**Table 3**).

According to the hospital status of 52 participants (exitus/discharge), the accepted mortality value affects the average duration of stay in hospital 1.026 times as statistically significant. The effects of all variables of this thesis study that may affect the duration of stay in hospital according to the hospitalization time were analyzed by Cox regression analysis. The Backward (Wald) method was used to select the best model equation. In the last 11th step, the best model equation was attained. Apache Score and calcium level are statistically significant factors according to the statistical analysis of the last equation; (**Table 4**).

Table 3. Regression analysis of C-reactive protein, duration of hospital stay, Apache II score and vitamin D levels

	B	S.E.	Wald	Sig.	Exp(B)	95% CI for Exp (B)	
						Lower	Upper
Apache score	-.275	.092	8.895	.003	.760	.634	.910
Vitamin D	.064	.026	5.941	.015	1.066	1.013	1.123
CRP	.007	.004	3.417	.065	1.007	1.000	1.015
Duration of hospital stay	-.065	.035	3.409	.065	.937	.875	1.004

Table 2. Pearson correlation analysis table

		Day of stay	Apache score	Acceptance mortality	Vitamin D	Calcium	Albumin	Urea	Creatinine	Crp	Hemoglobin	Leucocyte	Trombocyte
Day of stay	r*	1	.022	-.005	-.064	-.037	-.071	-.018	-.142	.049	-.010	.176	.237
	p		.875	.973	.653	.792	.617	.899	.317	.728	.942	.213	.090
Apache score	r*	.022	1	.979**	.086	-.050	-.292**	.613**	.567**	.108	-.209	.148	-.108
	p	.875		.000	.546	.726	.036	.000	.000	.447	.137	.295	.447
Acceptance mortality	r*	-.005	.979**	1	.073	-.099	-.263	.646**	.581**	.138	-.223	.137	-.117
	p	.973	.000		.609	.486	.060	.000	.000	.329	.112	.332	.410
Vitamin D	r*	-.064	.086	.073	1	-.017	.039	-.014	.039	-.161	-.162	.130	.304**
	p	.653	.546	.609		.906	.782	.919	.784	.255	.252	.359	.028
Calcium	r*	-.037	-.050	-.099	-.017	1	-.130	-.149	-.138	-.043	.057	.054	-.173
	p	.792	.726	.486	.906		.359	.292	.330	.761	.690	.704	.219
Albumin	r*	-.071	-.292*	-.263	.039	-.130	1	-.262	-.259	-.275**	.448**	-.155	-.044
	p	,617	,036	,060	,782	,359		,061	.063	.049	.001	.272	.758
Urea	r*	-.018	.613**	.646**	-.014	-.149	-.262	1	.739**	.242	-.139	.133	-.199
	p	.899	.000	.000	.919	.292	.061		.000	.084	.327	.346	.158
Creatinine	r*	-.142	.567**	.581**	.039	-.138	-.259	.739**	1	.177	-.192	.072	-.094
	p	.317	.000	.000	.784	.330	.063	.000		.209	.173	.610	.506
Crp	r*	.049	.108	.138	-.161	-.043	-.275**	.242	.177	1	-.060	.098	-.070
	p	.728	.447	.329	.255	.761	.049	.084	.209		.672	.491	.624
Hemoglobin	r*	-.010	-.209	-.223	-.162	.057	.448**	-.139	-.192	-.060	1	-.185	-.043
	p	.942	.137	.112	.252	.690	.001	.327	.173	.672		.190	.760
Leucocyte	r*	.176	.148	.137	.130	.054	-.155	.133	.072	.098	-.185	1	,319*
	p	.213	.295	.332	.359	.704	.272	.346	.610	.491	.190		.021
Trombocyte	r*	.237	-.108	-.117	.304**	-.173	-.044	-.199	-.094	-.070	-.043	.319*	1
	p	.090	.447	.410	.028	.219	.758	.158	.506	.624	.760	.021	

**: Statistically significant.

Table 4. Regression Analysis of Apache II score and calcium values

	B	SE	Wald	Sıg.	Exp (B)	95% CI for Exp (B)	
						Lower	Upper
Apache score	.087	.039	5.018	.025	1.091	1.011	1.177
Calcium	.034	.016	4.369	.037	1.034	1.002	1.067

DISCUSSION

Vitamin D deficiency has been charged with many kind of disorders such as infections, cardiac problems, autoimmune diseases, various pulmonary diseases and tuberculosis (5,6). Also vitamin D deficiency may cause negative consequences like increased infection rates, prolonged hospitalization in intensive care units, increased hospital mortality and increased health care expenses. Many recent papers showed a close association between vitamin D deficiency and some systemic diseases that have significant morbidity and mortality rates (5,6). However, Ralph et al. found no relationship between vitamin D and mortality risk in critically ill patients as in our study (7). For this reason, currently the consequences of vitamin D deficiency on mortality and morbidity in critically ill patients is still unclear.

In this current study, vitamin D deficiency was found as 70% in females and 68% in males. This high rate primarily may be related to the high age distribution of patients. The average age was 77.9 (min 49 and max 93). Another reason may be the study time that included the interval between September and May. One of the important factors for the synthesis of vitamin D3 in the skin is the zenith angle of the sunlight (8). The increase in this angle causes UVB photons to travel longer (more oblique). In this study, we used <20 ng/dL 25-OH D level as a threshold value to define vitamin D deficiency. And by using this threshold value vitamin D deficiency of patients in ICU was found with a frequency of 65.4%. It was seen that this ratio increased up to 84% when the vitamin D values between 20 to 30 ng/dl were accepted as inadequate. The vitamin D levels of the patients included in our study were examined in detail. It was seen that the lowest level was 1 ng/ml, the highest level was 78.6 ng/ml and the mean serum level was 19.6 ng/ml. Also, the mean serum vitamin D level was found as 17.28 ng/mL in patients resulted in death and 24.20 ng/mL in discharged patients respectively, but no statistically significant difference was found.

Most of the published studies have reported that vitamin D deficiency has a higher prevalence in women and in the elderly in the general population (8). Similarly, in our study, the mean age was 77.9 years and female gender was more dominant in the patient sampling used. The vitamin D replacement therapy was not routinely included in the intensive care treatment protocol. That is why in this study no vitamin D measurements were routinely performed and the decrease in vitamin D levels of patients in ICU was not showed in a comprehensive manner.

Standard vitamin D supplements included in nutritional support may be inadequate for the patients in ICU. Various studies prove that daily enteral and parenteral nutritional support is still insufficient. High doses of vitamin D supplements may be more effective in ICU patients. A number of recent studies in ICU have shown that high doses of vitamin D can be given to critical patients within a short time (few days) without complications (9). The replacement of vitamin D was not included in our treatment protocol, that's why the benefit of high doses of vitamin D supplements in critically ill patients could not be evaluated. More studies are needed to determine the effectiveness of vitamin D supplements in critically ill patients (9).

Vitamin D deficiency may increase hospital mortality rates in critically ill adult patients. Although the factors that cause this situation are still unclear today, various mechanisms are speculated. For example, many kind of biological responses involving the immune system, cell growth and proliferation can be affected by vitamin D (10,11). On the other hand, vitamin D affects the production of antimicrobial proteins such as cathelicidin (IL-37) and β-defensin which have important roles in the immune system (12-15). The close association between vitamin D deficiency and human infections has been exhibited in some previous papers (16,17). Liu et al. have showed the dose dependent katelicidin production in response to 1-25-dihydroxyvitamin D (18). Moreover, it is suggested that vitamin D is related with Toll-like receptor (TLR) activation (18-20). Therefore, vitamin D deficiency may suppress the body immunity and may expand the risk of sepsis in ICU patients (21,22).

Also, vitamin D provides the up-regulation of anti-inflammatory cytokines such as IL-4, IL-5 and IL-10 (23). For this reason, vitamin D deficiency may increase mortality by suppressing immunity in ICU patients. In addition, in critically ill patients the tissues may require more vitamin D and vitamin D deficiency may cause widespread tissue dysfunction (22,23). These effects may explain why systemic inflammatory response syndrome, organ failure and mortality rates due to metabolic dysfunction increase in critically ill patients. In our current study, there was a correlation between mortality and vitamin D deficiency in univariate analysis. However, vitamin D deficiency was not found as a solely mortality risk factor in multivariate analysis. Our results suggest that vitamin D deficiency is a consequence of chronic, severe diseases or comorbid conditions of the patients. Our results suggest that although vitamin D deficiency is not a real risk factor, it is a helpful factor in explaining increased mortality rates.

Our research has some potential limitations. First, it was originally designed as a single-center study with a relatively small sample size. Thus, the results of our research cannot be generalized. The 25 (OH) D levels obtained in patient admission are probably a reflection of preliminary insufficiency. No samples were taken for 25 (OH) D levels during clinical follow-up. Therefore, replacement was not made by following vitamin D levels during stay in ICU.

CONCLUSION

Consequences of vitamin D deficiency on mortality and morbidity in ICU patients, is still remains unclear. Our current study was carried out in an internal medicine ICU. Thus, there is a need for studies including cardiac, anesthesia, surgery and other ICUs in terms of the relationship between vitamin D levels and mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of GATA Haydarpaşa Training Hospital Ethics Committee (meeting held on 05.11.2015, decision number: 2015/41)

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

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 had 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.

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.903392

Anatolian Curr Med J 2021; 3(2); 176-180

Detected frequency of bacteremia in pressure ulcer and the decision to systemic antibiotic

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Cite this article as: Öztin H, Erdemir M, Öztürk İ. Detected frequency of bacteremia in pressure ulcer and the decision to systemic antibiotic. Anatolian Curr Med J 2021; 3(2); 176-180.

Abstract

Introduction: Pressure injuries are a significant cause of morbidity and mortality, and a source of considerable expense in health expenditures. Bacteremia is a frequently seen complication of pressure injury, although its incidence has yet to be well defined, and there are scarce studies on the subject. The aim in the present study is to assess the frequency of bacteremia of pressure ulcer origin as an indicator in decisions to start systemic antibiotics in patients with pressure injuries.

Material and method: Included in the study were all patients over the age of 18 years receiving palliative care in hospital, and with a pressure injury. Pressure injury samples of the patients were taken within the first 24 hours of admission to the hospital. All decubitus ulcers were washed with sterile saline and a sample was taken using a sterile cotton swab from the deepest and the most solid part of the ulcers. we included 76 patients whose 40 (52.6%) were male and 36 (47.4%) were female, with a mean age of 70.8±15.6 (18-95) years. 76 of 208 patients hospitalized in palliative care in 2018 had decubitus ulcers. We detected decubit ulcers infections in 75 of 76 patients. Among the 75 (65.2%) patient had pressure ulcers infections at 115 different sites of the body.

Result: The rate of bacteremia in Pressure injury was 13.9% (16/115) , and the agents were found to be polymicrobial in the ulcers cultures of 42 (55.2%) of the patients. The most common accompanying bacteria were *Acinetobacter*, *Pseudomonas aeruginosa* and *Escherichia coli*(E.coli). Among the pressure injurys, 49 (42.6%), 60 (52.4%) and 6 (5.2%) were evaluated as stage 4, 3 and 2 pressure injurys, respectively.

Conclusion: The causative agent of decubitus infections was found to be the agent causing bacteremia in 13.9% of the patients with pressure injury in the present study. The agent growing in the ulcer culture was rarely found to be the causative agent of bacteremia when deciding whether to treat pressure injury infections with systemic antibiotic.

Keywords: Pressure injury, palliative care, elderly, decubitus infections

INTRODUCTION

The term "pressure injury" refers to localized tissue damage in the skin or subcutaneous tissue resulting from tears and/or friction, generally together with pressure in areas of bone protrusion. Pressure injury can develop in any area where bone protrusions are exposed to pressure, and develop most frequently on the sacrum, coccyx or heels in supine position, on the hips and ankle joints of patients lying continuously on the same side, and most frequently on the hips in the sitting position (1). They are commonly found on bedridden patients with comorbidities or on those with limited mobility. The prevalence of Pressure injury has been reported in the range of 4.7–37.1% (2), and 11.7% in every 1000 day of hospitalisation in the intensive care units of hospitals (3). Pressure injury has been reported to be up to 33% in palliative care centers in Turkey (4). The prevalence of Pressure injury in hospitalized geriatric patients has been reported to be 5.8% (2). Pressure injury is a significant cause of morbidity and mortality, and a source of considerable expense in health expenditures (3).

It is a significant health problem in long-term bedridden patients, lowering their quality of life, despite the development of various preventive and treatment methods (5). Bacteremia is a frequently seen complication of pressure injury, although its incidence has yet to be well defined, and there are scarce studies on the subject (5-7).

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Received: 26.03.2021 **Accepted:** 09.04.2021

Studies investigating the bacteremia associated with Pressure injuries are rare, and ulcers mostly could not be documented as the source of bacteremia (6,8). Pressure injury may not be the focus of bacteremia, since many of the factors that could cause a growth in blood cultures are already present in this patient group (vascular access, catheters and tracheostomy, etc.) (3). The detection of the causative agent can aid in antibiotic selection and when making the decision whether or not to treat pressure injury infections. The causative agent is not always singular, and colonized bacteria are mostly detected, and there is therefore a lack of consensus whether or not to administer antibiotics every time a growing agent is detected in the culture. Systemic antibiotics are suggested for use in the presence of systemic signs such as a positive blood culture, cellulitis, fasciitis, osteomyelitis and sepsis, according to the International Pressure Injury Prevention panel (9,10).

The aim in the present study is to assess the frequency of bacteremia of pressure injury origin as an indicator in decisions to start systemic antibiotics in patients with pressure injuries. The aim in this regard is to demonstrate how frequent the agent causes a growth in the pressure injury when deciding to treat it with systemic antibiotics.

MATERIALS AND METHOD

The study was launched after permission was granted by the Republic of Turkey, Health Sciences University, Erzurum Region Education and Research Hospital (dated: 11.02.2018, number: 37732058-514.10. 208), patients were hospitalized in 2018. 132(%63,5) patients were excluded because they were using systemic antibiotics, ulcer stage, or using local antibiotics. 76(36,5) patients were included in the study. Included in the study were all patients over the age of 18 years receiving palliative care in hospital, and with a pressure injury stage 2 and above. Pressure injury samples of the patients were taken within the first 24 hours of admission to the hospital. All decubitus ulcers were washed with sterile saline and a sample was taken using a sterile cotton swab from the deepest and the most solid part of the ulcers. Patients using systemic antibiotic and local antibiotics for ulcers treatment were excluded from the study, as were patients with a positive urine, catheter or tracheal aspirate culture.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics (Version 22.0. Armonk, NY: IBM Corp.) software. Descriptive statistics, as mean and standard deviation for normally distributed continuous variables and relative frequencies for categorical (qualitative) variables, were generated for all variables. A p-value of <0.05 was considered statistically significant. Demographic data were presented as frequencies and percentages, and continuous variables were presented as mean and standard deviation (SD). For the descriptive analyses, mean and SD were used for continuous variables, and percentages for categorical variables.

RESULTS

In our study, We found the pressure injury in 76 (%36,5) patients of 208 of hospitalized in 2018 in the Palliative Care Service. 76 patients in the Palliative Care Service with various diagnoses, and who had clinical findings of Pressure injury during hospitalization and a positive ulcer swab culture that was considered clinically significant, were included in the study. Among these patients, 40 (52.6%) were male and 36 (47.4%) were female, with a mean age of 70.8±15.6 (18-95) years. Among the diagnoses of the patients, Alzheimer's disease, Cerebrovascular accident and cancer were the most frequently encountered. The distribution of the diagnoses of the patients is presented in **Table 1**.

Table 1. Distribution of the diagnosis of the patients and laboratory findings

	n	**%**
Age (Year)	70.8	±15.6
Sex (Male)	40	%52.6
Cerebrovascular accident	28	36.84%
Neurodegenerative diseases (Alzheimer's, Parkinson Etc.)	20	26.32%
Cancer	9	11.84%
Amyotrophic lateral sclerosis	4	5.26%
Peripheral vascular diseases	4	5.26%
Trauma-fracture	4	5.26%
Chronic obstructive pulmoner disease	3	3.95%
Heart failure	2	2.63%
Multiple sclerosis	1	1.32%
Botulism Intox	1	1.32%
	76	**100.00%**
	mean	**±sd**
Hospitalisation day	62.17	79.48
Urinary catheter (yes)	54	71
Cantral venoz catheter (yes)	38	50
Tracheostomy (yes)	39	51.3
White blood cell ($\times 10^3$ mm^3)	10.98	5.42
Hemoglobin (gr/dl)	11.07	2.30
Platelets ($\times 10^3$ mm^3)	296.071	128.70
Albumine (gr/dl)	2.82	0.52
Creatinine (mg/dl)	0.88	0.58
Blood urea nitrogen (mg/dl)	28.45	22.48
Vitamine D (ng/ml)	20.56	25.54
C-reactive protein (mg/dl)	51.92	52.33
Proteine (gr/dl)	5.88	0.94

Among the 76 patients, 75 (65.2%) had pressure injury infections at 115 different sites of the body. As expected, ulcers were generally found at the sacrum, costa and hips. The distribution of pressure injury infections in terms of location are presented in **Table 2**. The rate of bacteremia in Pressure injury was 13.9% (16/115) , and the agents were found to be polymicrobial in the ulcer cultures of 42 (55.2%) of the patients. The most common accompanying bacteria were *Acinetobacter*, *Pseudomonas aeruginosa* and *E. coli*.

Table 2. Pressure injury locations

Sacrum	55 (48%)
Costa	13 (12%)
Hip	16 (14%)
Heel	13 (12%)
Leg	15 (13%)
Scalp	3 (1%)
Total	**115 (100%)**

Among the pressure injurys, 49 (42.6%), 60 (52.4%) and 6 (5.2%) were evaluated as stage 4, 3 and 2 pressure injurys, respectively.

The microorganisms identified in the pressure injury and blood cultures are presented in **Table 3**.

Table 3. Microorganisms identified in ulcer and blood cultures.

Microorganisms	Ulcer Culture	Blood Culture	Bacteremia
Escherichia coli	12	2	2
Proteus spp.	2	1	1
Klebsiella spp.	8	3	3
Serratia spp.	1	-	-
Pseudomonas aeruginosa	18	4	2
Acinetobacter baumannii	14	5	2
Stenotrophomas maltophilia	1	1	1
Enterococcus spp.	5	3	1
Staf. aureus	7	5	4
Staf. epidermidis	4	3	-
Staf. haemolyticus	2	9	-
Candida albicans	1	3	-
Candida parapsilosis	-	6	-
Staf. cohnii	-	2	-
Staf. simulans	-	2	-
Corynebacterium macruthotii	-	1	-
burkholderia gladioli		2	
Total	**75**	**52**	**16**

DISCUSSION

Bacteria on the surface of the skin may invade the underlying tissue and cause infection. Signs of sepsis and cellulitis, and osteomyelitis due to sepsis, may be seen (8,11).

The diagnosis of pressure injury infection is challenging. A good microbiological and clinical evaluation, in addition to imaging studies and deep tissue biopsy, are recommended (12). A clinical examination is important for the determination of Pressure injury as occult foci of infection. Increased temperature, erythema, local tenderness, bad odor and purulent discharge are valuable signs during a clinical evaluation. Although tissue biopsy samples and aspiration fluid cultures have been recommended for the microbiological diagnosis of pressure ulcer infection, they are not generally preferred due to the difficulty in clinical use and their invasive nature (11,12). The obtaining of bacterial swab cultures is a noninvasive procedure that provides preliminary knowledge on the bacterial density of the ulcer. Surface ulcer cultures show colonization rather than infection, although the colonizing bacteria may cause local infection if they continue to proliferate, delaying ulcer healing (13). The rate of bacteremia due to the Pressure injury was found to be 13.9% in our study, but was reported to be higher in another study (3). This difference may be attributable to the stages of the pressure ulcer in the studies, as the frequency of bacteremia may be higher in advanced stages. There was a large number of patients with stage 3 ulcer in the present study.

Bacterial contamination on the surface of Pressure injury is most common, and such contaminations, in turn, may lead to serious life threatening problems such as bacteremia and sepsis by diffusing into deep tissues, resulting in infection (11). Bacteremia due to Pressure injury should be considered in patients presenting with fever and with no other focus of infection. The optimum approach to the diagnosis of ulcer site infection is tissue biopsy or aspiration (14). Sterile swabs were used in this present study, given their non-invasive ease of use.

The most common colonizing microorganisms in Pressure injuries are gram negative bacteria such as *Escherichia coli*, *Acinetobacter* baumanni, *Pseudomonas aeruginosa* and Enterobacteriaceae, and gram positive Enterococcus (15). The frequency of infection and/or colonization by microorganisms with multi-drug resistance is increasing gradually in pressure injurys. Aerobic cultures generally reveal methicillin resistant S. aureus or multi drug resistant gram negative bacilli, and may lead to local and systemic infection (13).

The sacrum was the most common location for Pressure injury in the present study, concurring with other studies in literature (8,16,17). The reason for this may be the elevated head position of patients due to alleviate the risks associated with aspiration. The risk of infection has been reported to be high in stage 3–4 Pressure injury (11). In line with previous studies, most Pressure injurywere found to be stage 3 (11). Due to the high risk of infection, the prevention of colonization in stage 3 and 4 Pressure injurymay decrease the risk of infection and bacteremia.

Pressure injury-associated bacteremia was identified in 16 of the 21 patients in the study by Jeffrey et al. (7), while pressure injury-associated bacteremia was found in six out of the 27 patients with Pressure injuryin the study by Peromet et al. (18). The rate of bacteremia in Pressure injury was 53,6% (3).

In our study, the incidence of polymicrobial bacteremia was found to be increased in accordance with the literature (6-8).

No clinical or epidemiological sign is present for the prediction of the causative agent of bacteremia in chronic ulcers, since the local infection of pressure injury is polymicrobial, and the risk of colonization with new microorganisms is high. Microorganisms of the flora may grow in the cultures (19). Accordingly, as a starting antibiotherapy, agents with antimicrobial effects against staphylococcus aureus, gram negative enteric bacilli and anaerobic microorganisms, including Bacteroides fragilis, taking into account also local resistance rates, should be considered (16). Antibiotic treatment should be adjusted based on blood culture results (8).

The most commonly isolated bacteria were gram negative enteric bacteria (klebsiella and *E. coli*), followed by staphylococcus aureus in second place, and pseudomonas and *Acinetobacter* in third place. A vast majority of the patients were transferred from hospital beds and had previously been admitted to the intensive care unit. In addition to the bacteria that cause bacteremia, many factors such as the patient's age, immune status, comorbid conditions, feeding, hospitalization period, frequency of interventional procedures etc. are effective (20).

CONCLUSION

Pressure injuries are a significant cause of mortality in long-term bedridden patients, with the most common causative agents being gram negative enteric bacteria, staphylococcus aureus, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. The recommended criteria for the start of treatment in such patients is the presence of systemic signs or positive blood cultures. The causative agent of decubitus infections was found to be the agent causing bacteremia in 13.9% of the patients with Pressure injury in the present study.

The agent growing in the culture was rarely found to be the causative agent of bacteremia when deciding whether to treat pressure injury infections. Accordingly, we recommend that the identification of the agent causing the pressure injury infection through a swab culture alone should not be a determinant.

Limitations

Our study has limited data due to single-center design. It needs to be supported by multi-center and prospective studies. we had a small number of patients and further studys is needed in this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was launched after permission was granted by the Republic of Turkey, Health Sciences University, Erzurum Region Education and Research Hospital (dated: 11.02.2018, number: 37732058-514.10. 208).

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

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 had 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.

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Case Report

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.846942

Anatolian Curr Med J 2021; 3(2); 181-184

Angiomyofibroblastoma of the uterine cervix in a patient with triple negative breast cancer: a case report

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Cite this article as: Özyiğit Büyüktalancı D, Yiğit S, Altındağ SD, Aydoğmuş H, Gençdal S. Angiomyofibroblastoma of the uterine cervix in a patient with triple negative breast cancer: a case report. Anatolian Curr Med J 2021; 3(2); 181-184.

ABSTRACT

Angiomyofibroblastoma is an uncommon, benign mesenchymal tumor which generally occurs in the vulvovaginal region. Uterine cervix localisation is uncommon. A 40-year-old female patient, who had been operated becasue of breast carcinoma, presented vaginal bleeding. Examination revealed a polypoid mass located in both vagina and cervix. She underwent total abdominal hysterectomy and bilateral salpingectomy. With the help of typical histopathology and immunohistochemical findings, a diagnosis of "angiomyofibroblastoma" was made. Angiomyofibroblastoma is a benign mesenchymal tumor of unknown pathogenesis. A recognition of this entity is important to avoid misdagnosis of other angiomyxoid neoplasms such as aggressive angiomyxoma.

Keywords: Angiomyofibroblastoma, cervix uteri, breast carcinoma

INTRODUCTION

Angiomyofibroblastoma (AMFB) is characterized myofibroblastic differentiation and neoplastic stromal cell proliferation (1). AMFB is usually seen perineal and vulva–vaginal region in females and scrotum in males (2). AMFB needs to be distinguished from other stromal tumors especially angiomyxoma which is aggresive behaviour (3). Uterine cervix localization is unexpected in this tumor. To the best of our knowledge, 5 cases have been reported and this is the second reported AMFB of the uterine cervix in a patient with breast cancer in English literature (1,2,4–6). Tamoxifen treatment is thought to be effective in the development of AMFB (7). In this report, we discussed the histogenesis, immunohistochemical features, differential diagnosis, and relationship with tamoxifen of this uncommon entity and reviewed the English literature.

CASE REPORT

A 40-year-old female patient admitted to the hospital with vaginal bleeding. In medical history, she had a triple negative invasive ductal breast carcinoma which was treated with conservative breast surgery with axillary dissection and adjuvant chemo and radiotherapy in 2007. The gynecologic examination revealed a polypoid mass located in both vagina and cervix. The patient was diagnosed with cervical leiomyoma and underwent total abdominal hysterectomy and bilateral salpingectomy (TAH+BS) and sent intraoperative consultation. Macroscopically, TAH +BS was 10x6x4 cm size and a well-defined mass which was 6x5 cm in size was detected in the posterior cervix. The mass cut surface was solid and light yellow in appereance **Figure 1**. As a result of intraoperative consultation, the mass was reported as a benign mesenchymal tumor except leiomyoma. Histologically, the tumor was characterized by hypocellular edematous areas mixed with thin walled small blood vessels. The tumor cells were uniform eosinophilic, spindle-shaped or epitheloid without mitotic figures or atypia (**Figure 2-3**). The immunohistochemistry tumor had shown a strong positivity with desmin, vimentin, estrogen receptor (ER), progesterone receptor (PR), focal positivity with CD117 and caldesmon but CD34 and smooth muscle actin (SMA) were negative. According to these findings, the tumor was diagnosed as a "angiomyofibroblastoma". No tumor recurrence was reported.

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Received: 25.12.2020 **Accepted:** 26.01.2021

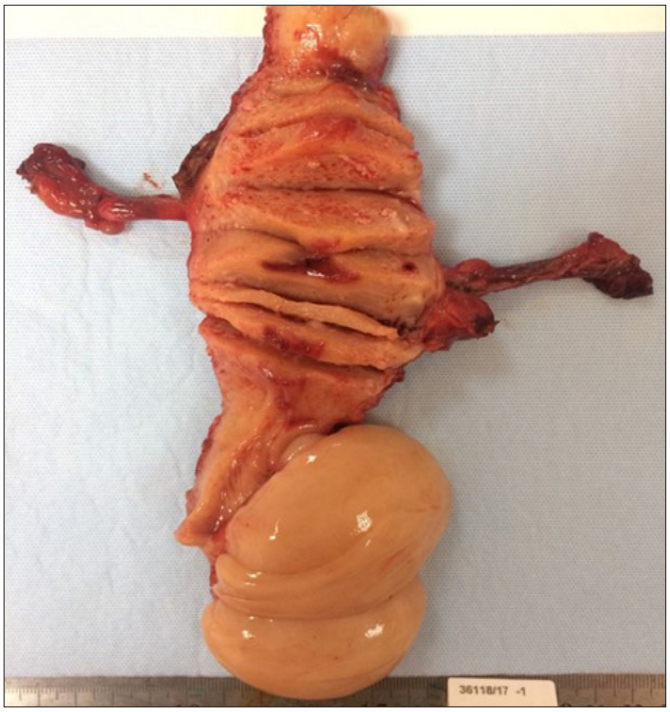

Figure 1. A well-defined mass which was 6x5 cm in size was detected in the posterior cervix

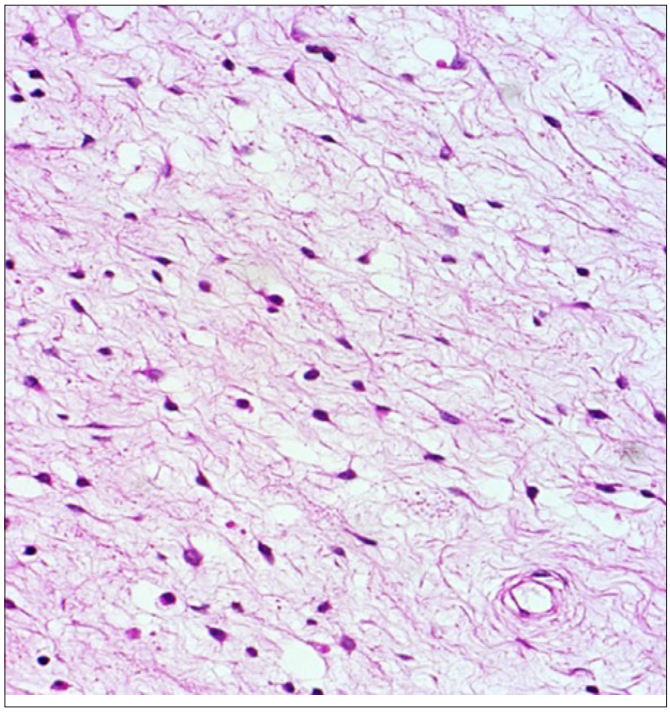

Figure 3. The neoplastic cells are bland-looking, spindle or oval shaped with scanty cytoplasm. H&E x400

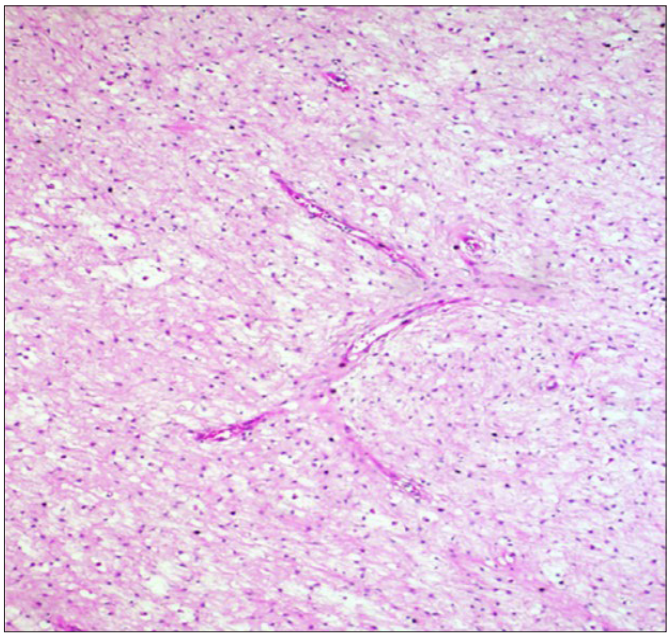

Figure 2. Tumor composed of hypocellularity in oedematous stroma and thin-walled blood vessels H&E x100

DISCUSSION

Angiomyofibroblastoma is frequently seen in vulva and vagina and between the ages of 20-50 (4,5). However, there are unusual cases reported in males (4,8). AMFB of the cervix is rarely seen with only 5 reports so far, ages range from 32- 53 and our case is 40 yearsold (1,2,4–6). The clinical and pathological features of AMFBs seen in cervix localization are shown in **Table 1**.

The tumor size varies between 10-40 mm (1,6). In our case, the tumor was the biggest diameter of 60 mm. Histologically, AMFB is characterized by variable hypocellular and hypercellular regions with spindle and round shaped cells (3,7). Stromal cells tend to collect around vessels. The immunohistochemistry shows strong positivity with desmin, vimentin, ER, PR, focal positivity with SMA and S100 protein, and negativity with cytokeratin and myoglobin (4,5). The imunohistochemical features of the cervical AMFB cases seen are listed in **Table 2.**

Table 1. The clinical and pathological features of AMFBs seen in cervix localization

Case Number	Age (Years)	Clinical Presentation	Treatment	Tumor size (cm)	Referance
1	53	Vaginal mass	Local excision	4x3	Lee CL et al. (1)
2*	43	Asymtomatic cervical mass	Local excision	3x3x2.5	Min Ji Kim et al. (2)
3	44	Polypoid mass	N/A	2	Babala et al. (4)
4	32	Vaginal spotting	N/A	1.2	Y.P.Wong et al. (5)
5	48	Intermens spotting	Cone biopsy	1	Roncati et al (6)
6*	40	Vaginal bleeding	TAH+BS	6x5	Present case

*breast carcinoma history cases, N/A: Not available, TAH+BS: Total abdominal hysterectomy and bilateral salpingectomy

Table 2. The imunohistochemical features of the cervical AMFB cases in the literature.

Case Number	Positive IHC	Negative IHC	Referance
1	Desmin CD 34 SMA	N/A	Lee CL et al. (1)
2	Desmin Vimentin	CD34 SMA	Min Ji Kim et al. (2)
3	Desmin Vimentin CD44	Ki67 Sarkomeric actin	Babala et al. (4)
4	ER PR	CD34 Desmin S100	Y.P.Wong et al. (5)
5	SMA Desmin ER PR	CD34 C Kit	Roncati et al. (6)
6	Desmin Vimentin ER PR	CD34 SMA	Present case

SMA: Smooth Muscle Actin, ER: Oestrogen receptor, PR: Progesterone receptor

The most important differential diagnosis is aggressive angiomyxoma (AAM). Other entities that should be considered in the differential diagnosis include cellular angiofibroma (CA), superficial myofibroblastoma (SM) fibroepithelial stromal polyp (FSP) (9). The clinical, histopathological, and immunohistochemical features of AMFB and differantial diagnosis are listed in the **Table 3.**

Aggressive angiomyxoma (AAM), described in 1983 by the first Steeper (4) and Rosai (9). AAM, with a high risk of recurrence, usually shows infiltrative growth with entrapped muscles, nerves, and mucous glands (5,10). AMFB has well circumscipred and benign clinical course. AAM is consisted of bland-looking stellate tumor cells with myxoid stroma, which has numerous variable-thickness blood vessels in contrast AMFB higher cellularity more numerous blood vessels more frequent plump, spindle shape cells (5). Dispersed inflammatory cells, especially neutrophils are always present (4). Immunohistochemistrically, AMFB and AAM express similar markers (5). Unlike AMFB, the CA occurs as a small and well-defined mass, grossly. The tumor consists of bland spindle cells arranged in intersecting fascicles mixed with wispy collagen bundles and hyalinised thickwalled blood vessels (4,5). CA is negative for desmin, and expresses variable estrogen receptor (ER), progesterone receptor (PR), CD34 and SMA (5). Superficial myofibroblastoma (SM) is composed of bland stellate or ovoid cells, within edematous and myxoid stroma (5,11). The neoplastic cells are separated by a non-neoplastic stromal band (Grenz zone) (5). SM shows variable immunoreactivity for ER, PR, CD34, desmin, and SMA (5,11). Fibroepithelial stromal polyp (FSP) is specific to the vulvovaginal region which is often incidentally encountered as a pedunculated polyp (5). It is overlied by squamous epithelium and typically contains central fibrovascular core (5).

Table 3. The clinical, histopathological, and immunohistochemical features of AMFB and differantial diagnosis.

	AMFB	AAM	CA	SM	FSP
Age (Years)	20-50	20-50	Middle-aged	40-70	Reproductive age
Clinical presention	Painless mass	Slow growing mass	Painless mass	Painless Mass	Asymptomatic
Tumor size (cm)	<5 cm	>10 cm	2-3 cm	<5 cm	1-3 cm
Margin	Well circumscipred	Infiltrative	Well circumscipred	Well circumscipred	Polypoid
Histological features	Alternating zone of cellularity Spindle-ovoid cells Stromal cells around vessels	Bland-looking stellate-spindle cells Myxomatous stroma Variable thickness blood vessels Inflammatory cells	Bland spindle cells Collagen bundles Hyalinised thick walled blood vessels	Bland stellate-ovoid cells Edematous or myxoid stroma (Grenz zone)	Overlied squamous epithelium Central fibrovascular core
Positive IHC	Desmin Vimentin ER, PR Focal positivity; SMA and S100	Desmin ER, PR Variable; CD34 and SMA	Variable; ER, PR CD34 SMA	ER, PR CD34 Desmin SMA	Desmin ER, PR Variable; CD34 and SMA
Negative IHC	Cytokeratin Myoglobin CD34	Cytokeratin S100 Myogenin	Desmin S100	Cytokeratin S100	Myogenin Myo D1
Treatment	Local excision	Surgical excision & Adjuvant chemotherapy	Local excision	Local excision	Simple excision

AMFB: Angiomyofibroblastoma, AAM: Aggressive angiomyxoma, CA: Cellular angiofibroma, SM:Superficial myofibroblastoma, FSP: Fibroepithelial stromal polyp

Histogenesis and pathogenesis of angiomyofibroblastoma have not been eluciated yet. However, some authors suggested that the neoplasm is probably derived from primitive mesenchymal cells of subepithelial myxoid stroma which may undergo differentiation to myofibroblasts under hormonal stimuli (12). The relationship between AMFB and tamoxifen which is used in treatment of breast cancer was firstly determined by Varras et al (7). In this study, it has been suggested that tamoxifen treatment may cause proliferation in mesenchymal cells of the vagina by estrogenic stimulation. Due to this effect, it has been reported to increase the incidence of endometriosis, adenomyosis, endometrial hyperplasia, leiomyoma, ovarian cysts, cervical and endometrial polyps especially in postmenopausal patients (7). Other previous studies have shown that in breast cancer patients, tamoxifen and similar drugs cause the development of vaginal AMFB (7,12–15). Although AMFB of the cervix is rare, cervical AMFB is much rarer due to tamoxifen and only 1 case has been reported in the literature so far.

CONCLUSION

Angiomyofibroblastoma located in uterine cervix is an unusual case, which creates a challenging diagnosis. The ethio-pathogenesis of AMFB is not clear yet. There are cases supporting the claim that says hormonal stimulation and usage of tamoxifen might have an effect on AMFB development. Since in our case the breast carcinoma is triple negative, there is no history of tamoxifen usage. As a result, more studies are needed to be made in order to show the relation between tamoxifen and AMFB development.

ETHICAL DECLARATIONS

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.

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.

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Case Report

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.886644

Anatolian Curr Med J 2021; 3(2); 185-187

Alopecia areata after hepatitis C virus infection treatment: a case report

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Cite this article as: Eroğlu E. Alopecia areata after hepatitis C virus infection treatment: a case report. Anatolian Curr Med J 2021; 3(2); 185-187.

ABSTRACT

Dermatological diseases may be the only early clinical manifestation of liver disease for patients. It has been shown that at least one skin manifestation develops in approximately 17% of chronic HCV infection patients. Dermatological manifestations have also been seen with antiviral therapy for HCV. It is difficult to distinguish that cutaneous adverse reactions are associated with antiviral therapy or cutaneous manifestations of HCV. Interferon-free direct-acting antiviral (DAA) therapies in the chronic hepatitis C virus (HCV) infections have low side effects. Sofosbuvir/ribavirin (SOF/RBV) therapy combination is among in the currently approved treatment regimens. Alopecia areata is a very rare side effect of this treatment. A case of alopecia areata developed after SOF/RBV combination therapy in a patient with chronic hepatitis C infection is presented.

Keywords: Alopecia areata, hepatitis C virüs, sofosbuvir/ribavirin

INTRODUCTION

It is estimated that 71 million people are infected with the hepatitis C virus (HCV) worldwide. It is the major cause of chronic liver disease in the world, including cirrhosis and hepatocellular carcinoma (HCC) (1). Interferon-free direct-acting antiviral (DAA) therapies in the chronic HCV infections are considered to be a significant improvement with a sustained virologic response, excellent tolerability and low side effects (2,3). The use of sofosbuvir/ribavirin (SOF/RBV) for genotype 3 for 24 weeks in the treatment of chronic hepatitis C is among the currently approved treatment regimens (4). Anemia (often due to ribavirin), weakness, nausea/vomiting, headache, rash, and alopecia are among the side effects (5). Alopecia areata is a very rarely reported side effect (6,7).

A case of alopecia areata developed after SOF/RBV combination therapy in a patient with chronic hepatitis C infection is presented.

CASE

A 52-year-old male with chronic hepatitis C genotype 3, treated with SOF/RBV, was being followed up at the infectious diseases outpatient clinic. He had hair loss in follow-up. Patient consulted with dermatology clinic. Dermatological examination revaled that; two sharply demarcated, 1-2 cm in size, alopecic areas with non-cicatricial ground were observed in the occipital region. The laboratory examination of the patient, complete blood count, biochemistry values routine thyroid stimulating hormone, free thyroxine hormone, total triiodothyronine, anti-thyroglobulin, antiperoxidase antibody, antiparietal cell antibody and vitamin B12 were found within normal limits. The patient had no comorbid disease. The patient was using sofosbuvir 400 mg/day +ribavirin 1000 mg/day due to chronic HCV infection. The 6th month of treatment was completed. The patient stated that the hair loss started in about a month. In the skin scrapings taken from the alopecic areas by the dermatologist, no pathogen, fungal or bacterial agent could be isolated. No different etiological agent causing alopecia was detected in the laboratory results of the patient. The treatment for chronic HCV infection was completed. His treatment was planned for alopecia areata and he was called for a control one month later. In the control examination of the patient, it was observed that the areas that developed alopecia regressed greatly. This situation was evaluated as alopecia areata that developed after SOF/RBV combination therapy. The treatment was arranged by the dermatology clinic and partially benefited from the treatment. There was no full recovery (**Table**).

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Received: 25.02.2021 **Accepted:** 17.03.2021

Table. The characteristics of the patient before and after chronic hepatitis C infection treatment

Patient Characteristics	
Age	46
Gender	M
HCV genotype	3
Underlying condition	None
Liver histopathology	
Stage	1
HAI	6
Laboratory results at admission	
HCV RNA (IU/ml)	497000
AST (U/L)	23
ALT (U/L)	45
Laboratory results after treatment (6 month)	
HCV RNA (IU/ml)	Negative
AST (U/L)	22
ALT (U/L)	28
Laboratory results 3 months after treatment was completed	
HCV RNA (IU/ml)	Negative
AST (U/L)	29
ALT (U/L)	27

ALT: Alanine aminotransferase, AST: Aspartate Aminotransferase, HAI: Histological Activity Index

DISCUSSION

Dermatological diseases may be the only clinical manifestation of liver disease for patients. It has been shown that at least one skin manifestation develops in approximately 17% of chronic HCV infection patients (8). Dermatological manifestations have also been seen with antiviral therapy for HCV. It is difficult to distinguish that cutaneous adverse reactions are associated with antiviral therapy or cutaneous manifestations of HCV (9-11).

In our study, a rare complication, alopecia areata developed after treatment of chronic hepatitis C was presented. Post-treatment alopecia of hepatitis C virus infection is often interferon-related. In addition, there are studies showing that alopecia developing after interferon therapy is reversible. Nowadays, Interferon-free DAA therapies are well tolerated drugs (12). In the treatment of chronic hepatitis C, SOF/RBV for genotype 3 for 24 weeks is among the currently approved treatment regimens (4). Current studies have shown that the SOF/RBV combination achieves very good response rates with a good safety profile in terms of side effects in patients infected with HCV genotype 2 or 3 (7, 13, 14). Alopecia developing in the treatment of hepatitis C virus infection has been frequently associated with interferon (14, 15), but an alopecia areata that developed after SOF/RBV treatment was presented in our case. It is an extremely rare side effect. In a study evaluating 58 patients with genotype 2 or 3 and using SOF/RBV for treatment in our country, one alopecia areata developed after the use of SOF/RBV was reported (6). In a study conducted in Russia, patients treated with the SOF/RBV combination were evaluated. Side effects of alopecia areata developing after the SOF/RBV combination have been reported (7). The exact pathogenesis of alopecia areata is not known, although substantial evidence exists to suggest roles for genetic factors, nonspecific immune and organ-specific autoimmune reactions, and environmental triggers (16). Our patient did not have a comorbid disease other than hepatitis C virus infection. In hepatitis C virus infection, the diagnosis of alopecia areata is made by examination (17-19). Alopecia due to other etiologies is not different from alopecia that develops after hepatitis C virus infection treatment (18). Alopecia that develops during hepatitis C virus treatment is usually a major cosmetic problem. Alopecia is an important side effect of the treatment that affects the patient's compliance with the treatment of hepatitis C virus infection (20).

CONCLUSION

Many studies have shown that the drugs used in the treatment of chronic hepatitis C infection have dermatological side effects. Alopecia areata is one of them and it should be kept in mind that alopecia areata may be the only skin symptom of chronic hepatitis C virus infection or may develop secondary to drugs used in the treatment of hepatitis C.

ETHICAL DECLARATIONS

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.

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.

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