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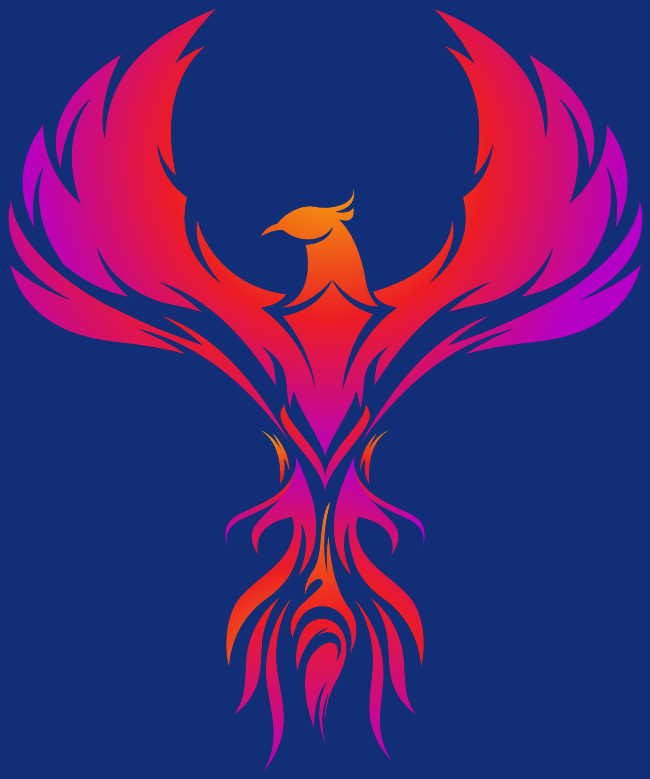

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Thesis
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ORIGINAL ARTICLE

Tonsillectomy Indications and Complications: 10 Years of Experience

Tonsillektomi Endikasyon ve Komplikasyonları: 10 Yıllık Deneyim

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ABSTRACT

Objective: *In this study, tonsillectomy indications and post-tonsillectomy complications were discussed in the light of the literature.*

Material and Method: *A retrospective file review of 775 patients who underwent tonsillectomy was performed between January 2014 and January 2024. Demographic data, preoperative indications, perioperative and postoperative complications of the patients were accessed from hospital records.*

Results: *Of the 775 patients who underwent tonsillectomy, 459 (59.2%) were male and 316 (40.8%) were female. Of the 630 pediatric patients, 404 (64.1%) were operated on for obstruction, 209 (33.1%) for recurrent tonsillitis, 11 (1.7%) for suspected malignancy, and 6 (0.9%) for Periodic Fever-Aphthous-Stomatitis-Pharyngitis-Adenitis (PFAPA) Syndrome. Of the 145 adult patients, 67 (46.2%) were operated on for recurrent tonsillitis, 39 (26.9%) for obstruction, 32 (22.1%) for suspected malignancy, 4 (2.7%) for peritonsillar abscess, and 3 (2.1%) for chronic caseous tonsillitis. In the postoperative period, bleeding was detected in 18 (2.8%) of 630 pediatric patients and oral intake disorder was detected in 4 (0.6%). Postoperative bleeding complications were observed in 15 (10.3%) of 145 adult patients.*

Conclusion: *In our study, obstruction was seen as the primary indication for surgical intervention in the pediatric patient group, while infectious causes were seen in the adult patient group. The most common complication was bleeding. Tonsillectomy is an operation in which good planning of surgical indications and good postoperative follow-up are important.*

Key Words: *Tonsillectomy, Indication, Complication, Bleeding*

ÖZET

Amaç: *Tonsillektomi, Kulak Burun Boğaz hekimlerinin en sık uyguladığı ameliyatlardandır. Bu çalışmada, tonsillektomi endikasyonları, tonsillektomi sonrası görülen komplikasyonlar literatür eşliğinde tartışıldı*

Yöntem ve Gereç: *Ocak 2014 ile Ocak 2024 arasında bademcik ameliyatı geçiren 775 hastanın retrospektif dosya incelemesi yapıldı. Hastaların demografik verilerine, ameliyat öncesi endikasyonlarına, ameliyat sırasındaki ve ameliyat sonrası komplikasyonlara hastane kayıtlarından ulaşıldı.*

Bulgular: *Tonsillektomi yapılan 775 hastanın 459'u (%59,2) erkek, 316'sı (%40,8) kadın idi. 630 pediatrik hastanın 404'ü (%64,1) obstrüksiyon, 209'u (%33,1) rekürren tonsillit, 11'i (%1,7) malignite şüphesi ve 6'sı (%0,9) PFAPA sendromu nedeniyle opere edildiği saptanmıştır. Yetişkin 145 hastanın 67'si (%46,2) rekürren tonsillit, 39'u (%26,9) obstrüksiyon, 32'si (%22,1) malignite şüphesi, 4'ü (%2,7) peritonsiller apse ve 3'ü (%2,1) kronik kazeöz tonsillit nedeniyle opere edildiği saptanmıştır. 630 pediatrik hastanın 18'inde (%2,8) kanama ve 4'ünde (%0,6) oral alım bozukluğu saptanmıştır.*

Sonuç: *Çalışmamızda pediatrik hasta grubunda obstrüksiyon, yetişkin hasta grubunda enfeksiyöz nedenlerin operasyon endikasyonları arasında ilk sırada olduğu görülmüştür. Komplikasyonlardan da kanama daha sık saptanmıştır. Bu ameliyatın, cerrahi endikasyonun iyi planlanmasının ve postoperatif takibin iyi yapılmasının önemli olduğu operasyonlardan biri olduğunu düşünüyoruz.*

Anahtar Kelimeler: *Tonsillektomi, Endikasyon, Komplikasyon, Kanama*

INTRODUCTION

Tonsillectomy is among the most common surgical procedures performed. Numerous studies have been conducted regarding the indications and complications associated with pediatric tonsillectomy; however, the literature on tonsillectomy in adults is limited. Tonsillectomy alone is rarely performed in children under three years of age, while adenoidectomy alone is seldom performed in individuals over 14 years of age. The rate of adenoidectomy is approximately 1.5 times higher in men than in women, whereas the rate of tonsillectomy is approximately one-third higher in women than in men (1,2) . Historically, the leading indication for tonsillectomy in the pediatric population has been recurrent/chronic tonsillitis. However, as the use of antibiotics has become more widespread, the surgical indication has shifted toward the relief of upper respiratory tract obstruction (3). In contrast to the pediatric population, the most common indication for tonsillectomy in adults is likely recurrent/chronic tonsillitis, possibly due to higher rates of antibiotic failure caused by resistant bacteria (4).

Although tonsillectomy is a frequently performed surgical procedure, its indications remain a topic of debate due to factors such as cost, impact on quality of life, postoperative complications, and potential psychological trauma. The literature has defined the accepted absolute and relative indications for tonsillectomy (5). The absolute indications include tonsil cancer, severe airway obstruction in the oropharynx due to tonsil hypertrophy, and persistent tonsil bleeding. Recurrent acute tonsillitis, chronic tonsillitis, and recurrent peritonsillar abscess or phlegmon are other relative

Table 1: Paradise Classification

Paradise Classification	
Classification	**Description**
Minimum frequency of some throat attacks	At least 7 attacks in the last year
	At least 5 attacks per year in the last 2 years
	At least 3 attacks per year in the last 3 years
At least one of the following clinical findings accompanies a sore throat attack	Fever > 38.3 °C
	Lymphadenopathy that is painful or greater than 2 cm
	Tonsillar exudate
	Culture positivity for Group A β-Hemolytic Streptococcus
Treatment	Receiving adequate antibiotic treatment with appropriate dose and duration
	Observation of all throat infection attacks by the physician and recording of their characteristics
Documentation	Observation of at least 2 attacks of throat infections described by the patient and/or relatives of patients who cannot be fully documented by the same physician and determination of the relationship between this evaluation and the initial history

indications. Additionally, the Paradise criteria have been defined for patients planned for tonsillectomy due to chronic and/or recurrent infections (6). However, the main issue in selecting patients for tonsillectomy lies in the variability of these criteria, which depend on the medical history provided by the patients and/or their families, as well as how frequently the physician evaluates the patient. This makes the indication for tonsillectomy more relative and potentially subject to change.

Although tonsillectomy is generally a safe procedure, the most common and serious complication is bleeding. Primary bleeding occurs within the first 24 hours after surgery and is rare, estimated to occur in less than 1% of patients. Secondary bleeding occurs after 24 hours and is estimated to occur in 2-4% of patients. Other common complications of tonsillectomy include pain, impaired oral intake, and dehydration. Dehydration, ear pain, fever, and edema of the uvula are also frequently encountered, but are generally less serious complications. In contrast, more serious but less common complications include atlantoaxial joint subluxation, mandibular condyle fractures, Eustachian tube injuries, velopharyngeal insufficiency, and nasopharyngeal stenosis (7, 8, 9).

In this study, we retrospectively reviewed the patients who underwent tonsillectomy and discussed the demographic information, indications, postoperative complications, and histopathological results of the patients in the light of current literature.

MATERIALS AND METHODS

The study was planned as retrospective. After obtaining approval from the local ethics committee (Meeting Number: 2024/21, Decision Number: 02), the research commenced. The study was conducted under the Helsinki Declaration and good clinical practices. In our study, we examined the files of 775 patients who underwent tonsillectomy, adenotonsillectomy. The procedures were performed in the Kahramanmaras Sutcu Imam University, Faculty of Medicine, Health Practice and Research Hospital, Ear, Nose, and Throat Diseases Clinic, between January 2014 and January 2024. The patient files were analyzed for age, sex, indications, complications requiring hospitalization, and histopathological results.

Upon reviewing the records, we found that tonsillectomy was performed for the following indications: obstruction, recurrent tonsillitis, suspicion of malignancy, chronic caseous tonsillitis, and PFAPA syndrome. A polysomnography test could not be performed on pediatric patients with obstruction, the most common indication, due to limited access to the test. However, a polysomnography test was conducted on adult patients before surgery. The Paradise criteria were used for surgical indications for recurrent tonsillitis (Table 1).

The pathological results of the tonsillectomy specimens were examined and classified as either benign or malignant. The complications observed post-tonsillectomy were classified according to the file records. Postoperative bleeding was categorized as primary or secondary based on the timing of occurrence. Additionally, bleeding complications were further categorized according to the need for reoperation.

Statistics

IBM SPSS Statistics 20 (Statistical Package for Social Sciences v.21, IBM, Chicago, IL) program was used to calculate statistical data. Mean, standard deviation, minimum, and maximum values are given in descriptive statistics for the data.

RESULTS

Of the 775 patients who underwent tonsillectomy, 459 (59.2%) were male and 316 (40.8%) were female. The mean age of male patients was 11.4 years, while the mean age of female patients was 11.8 years, resulting in an overall mean age of 11.6 years. The youngest patient who underwent tonsillectomy was 11 months old, while the oldest was 81 years old. 630 patients (81.3%) were under 18, with an mean age of 6.1

Table 2: Demographic Distributions of Patients Included in the Study

Demographic Distributions of Patients		
	Number of Patients / Percentage	**Mean Age(Years)**
Total	775	11.6
Male	459 / 59.2%	11.4
Female	316 / 40.8%	11.8
< 18 age	630 / 81.3%	6.1
>18 age	145 / 18.7%	34.6

Table 3: Surgical indications, complications and pathology results of the patients

		Results			
		< 18 age		>18 age	
		Number	%	Number	%
Indication	Obstruction	404	64.1	39	26.9
	Recurrent Tonsillitis	209	33.1	67	46.2
	Suspicion of Malignancy	11	1.7	32	22.1
	Peritonsillar Abscess	0	0	4	2.7
	Chronic Caseous Tonsillitis	0	0	3	2.1
	PFAPA	6	0.9	0	0
Complication	Bleeding	18	2.8	15	10.3
	Oral Intake Disorder	4	0.6	0	0
Histopathological Result	Benign	630	100	136	93.8
	Malign	0	0	9	6.2

years. The number of patients aged 18 years and older was 145 (18.7%), with an mean age of 34.6 years (Table 2).

Regarding the surgical indications for our patients, 404 (64.1%) of the 630 pediatric patients under 18 underwent surgery for obstruction, 209 (33.1%) for recurrent tonsillitis, 11 (1.7%) for suspected malignancy, and 6 (0.9%) for PFAPA syndrome. Among the 145 adult patients aged 18 and over, 67 (46.2%) underwent surgery for recurrent tonsillitis, 39 (26.9%) for obstruction, 32 (22.1%) for suspected malignancy, 4 (2.7%) for peritonsillar abscess, and 3 (2.1%) for chronic caseous tonsillitis (Table 3).

In terms of complication rates, 18 (2.8%) of our 630 pediatric patients under 18 required rehospitalization for bleeding, and 4 (0.6%) for difficulty in oral intake. Additionally, 15 (10.3%) of the 145 adult patients aged 18 and over required rehospitalization for bleeding (Table 3).

When examining the histopathological results, all 630 pediatric patients under 18 were reported as having benign pathology. Among the 145 adult patients aged 18 and over, 136 (93.8%) had benign pathology, while 9 (6.2%) had malignant pathology (Table 3).

DISCUSSION

The primary indication for tonsillectomy is to manage infectious complications caused by tonsillitis. With the introduction of oral antibiotics in the 1960s, tonsillectomy surgeries decreased, resulting in a shift in surgical indications over time (10). In 1993, Derkay observed a decrease of more than two fold in the rates of tonsillectomy ± adenoidectomy performed from 1977 to 1989 (11). Similarly, Rosenfeld et al., found that the rates of tonsillectomy ± adenoidectomy decreased from 1978 to 1986 and identified obstructive sleep disorder as the primary indication (12). In another study, 88.4% of patients who underwent tonsillectomy ± adenoidectomy did so for infection; however, by 2005, only 23.2% of these surgeries were performed for that reason (13). In our study, the most common surgical indications for tonsillectomy were obstruction and recurrent tonsillitis. Other indications included suspected malignancy, chronic caseous tonsillitis, and PFAPA syndrome.

The two most common indications for tonsillectomy ± adenoidectomy in both pediatric and adult patients are infection and obstructive sleep disorder. Although tonsillectomy ± adenoidectomy for suspected or confirmed neoplasm is rarely performed in children, it is the third most common indication in adults. In pediatric patients, obstruction has been the primary indication for several decades. In a study of pediatric patients, obstructive causes accounted for 68.7%, while infection constituted only 31.3% (14). In our study of 630 pediatric patients, the indications for tonsillectomy were as follows: obstructive causes in 404 (64.1%), chronic infection in 209 (33.1%), suspected malignancy in 11 (1.7%), and PFAPA syndrome in 6 (0.9%) (15). Our findings regarding pediatric patients were found to be consistent with this study.

In some cases, tonsillectomy is performed for diagnostic purposes due to suspected malignancy. In 1998, Beaty et al. defined conditions suggesting malignancy as "High-Risk Factors" in adult patients (15). These risk factors include cancer history, tonsil asymmetry, tonsillar hardness on palpation, visible lesions on the tonsil, accompanying neck lymphadenopathy, unexpected weight loss, and constitutional symptoms (fatigue, night sweats, fever, anorexia) (15). Erdağ et al. found in 2005 that these risk factors were also important for the pediatric population (16). A study examined tonsillectomy± adenotonsillectomy specimens and found malignancy in 0.087%. Among the 54 patients with malignancy, 48 (88%) exhibited features that raised suspicion of malignancy in the tonsil, while no suspicious features were observed in the remaining 6 patients. Those with such features represent true occult malignancy, constituting 0.011% of the total cases (17). When examining studies investigating malignancy rates in pediatric and adult patients separately, Garavello et al. examined the malignancy rates in pediatric and adult patients separately and found malignancy in only 2 (0.18%) (Burkitt's lymphoma) of the pediatric patients (18). In our study, 7 out of 630 pediatric patients (1.1%) underwent diagnostic surgery due to the presence of risk factors, and 4 (0.6%) underwent lymph node excision and tonsillectomy together because of long-term suspicious lymphadenopathy in the neck. Malignancy was not detected in any of the tonsillectomy or lymph node excision specimens obtained from pediatric patients.

Beaty et al. conducted a study in the adult population aged 18 and over in 1998, finding that malignancy was detected in 25 (5.25%) of 476 patients after tonsillectomy (15). Notably, malignancy was not found in any patient without risk factors. In our study, nine out of 145 patients (6.2%) were diagnosed with malignancy. All of our patients diagnosed with malignancy were among the 32 (28%) cases performed for diagnostic purposes. We did not detect any true occult malignancy in our study. Non-Hodgkin lymphoma was

identified in 7 out of the 9 patients (77.7%) diagnosed with malignancy. Of the two patients with other malignancies, one was reported as non-keratinizing squamous cell carcinoma, and the other was classified as atypical.

Another indication for tonsillectomy is a recurrent peritonsillar abscess. This condition is most commonly observed in adults. Treatment options for peritonsillar abscesses include antibiotics, analgesics, steroids, needle aspiration, incision and drainage, emergency tonsillectomy, and interval tonsillectomy (19). Despite the high incidence of peritonsillar abscess, there is no national or international consensus on management, and practices vary among clinics. In their meta-analysis, Mughal et al. recommended emergency tonsillectomy for three patient groups: those who are already candidates for tonsillectomy due to recurrent tonsillitis, children who cannot comply with other procedures, and cases with persistent collections that do not respond to needle aspiration and incision-drainage (20). In our study, four patients underwent interval tonsillectomy due to peritonsillar abscess, all of whom were adults. Emergency tonsillectomy was never performed due to peritonsillar abscess in our study.

Another rare indication for tonsillectomy is chronic caseous tonsillitis, characterized by the retention and/or discharge of cheese-like, semi-solid whitish crypt material. It is usually painless, with halitosis being the only symptom in approximately 78% of patients. Nonsurgical treatments for chronic caseous tonsillitis include irrigation, saline gargling, manual tonsil massage, gentle curettage, topical antiseptics, anti-inflammatories, and systemic antibiotics. Tonsillectomy may be considered for patients who do not benefit from these treatments (21). In our study, we performed tonsillectomy for chronic caseous tonsillitis in three patients.

PFAPA is an abbreviation for an idiopathic inflammatory syndrome characterized by periodic fever, adenitis, pharyngitis, and aphthous stomatitis, first described by Marshall in 1987. In PFAPA syndrome, there is recurrent high fever that occurs at regular intervals every 2-8 weeks. Onset usually occurs before the age of 6, with recovery typically taking place 3 to 5 years after onset. Although PFAPA is generally a self-limiting condition, it can impose a significant disease burden due to recurrent attacks. Oral steroids are effective in controlling symptoms but may shorten the intervals between attacks. Tonsillectomy has been found to be effective in providing remission in up to 98% of patients with PFAPA (21). In our clinic, 6 patients underwent tonsillectomy due to PFAPA, and it was observed that their quality of life improved in the postoperative period.

Although tonsillectomy is generally considered a safe surgical procedure, it can lead to serious complications such as bleeding. Bleeding after tonsillectomy is classified as primary if it occurs within the first 24 hours post-surgery, and secondary if it occurs later. In a study by Osborne et al., it was found that adults were 3.5 times more likely to undergo reoperation for bleeding control than children (22). In other study, bleeding after tonsillectomy was observed in 78 patients (3.6%). More than one bleeding episode was observed in 2 of 78 patients (2.6%) with bleeding (7). Primary bleeding was observed in only 5 patients (0.23%). Secondary bleeding was observed in 73 patients (3.4%). Bleeding control was performed in the operating room under general anesthesia in 28% of patients with bleeding. In our study, bleeding was observed in 18 of 630 pediatric patients (2.8%) and they were followed up in the ward. One of these 18 patients (5.5%) had two episodes on the 6th and 9th postoperative days. For bleeding control, four of 18 patients (22.2%) underwent surgery under general anesthesia. On average, bleeding occurred on postoperative days seven and 27. The earliest bleeding was on postoperative day four; the latest bleeding was on postoperative day 12.

In a study by Torres et al., postoperative bleeding was observed in 17 patients (5.23%) (8). It was observed that three of the 17 patients with bleeding (17.6%) had primary bleeding; 14 of them (82.35%) had secondary bleeding. Of the 17 patients who developed bleeding complications, 13 (76.47%) underwent bleeding control in the operating room under anesthesia. In our study, bleeding was observed in 15 of 145 adult patients (10.3%) and they were followed up in the ward. Of these 15 patients (13.3%), two patients had a bleeding episodes and one patient (6.6%) had three bleeding episodes. Of the 15 patients with bleeding (33.3%), 5 were taken to surgery under general anesthesia for bleeding control. On average, bleeding occurred on postoperative days 8-36. The earliest bleeding occurred on postoperative day three; the latest bleeding occurred on postoperative day 20.

Another serious complication after tonsillectomy is impaired oral intake. Postoperative pain can lead to difficulties in eating and dehydration. Dehydration is the most common complication resulting in hospitalization after bleeding. In a study conducted by Rohlfing et al., which examined 473 pediatric patients, complications such as nausea, vomiting, and dehydration developed in 6 patients (1.3%) (9). In our study, 4 of 630 pediatric patients (0.6%) required re-hospitalization due to impaired oral intake, and 1 of these patients (25%) needed two hospitalizations for the same reason.

In a study by Torres et al., three patients (0.92%) experienced difficulty swallowing and painful swallowing, while two patients (0.61%) required readmission due to fever (8). In our study, none of the 145 adult patients required readmission due to impaired oral intake.

Long-term complications that may arise after tonsillectomy include lung infections, velopharyngeal insufficiency, and nasopharyngeal stenosis. Lung infections are typically caused by atelectasis or aspiration of loose teeth, blood, or residual tissue (23). Velopharyngeal insufficiency is more likely to occur in patients with cleft palate or previously undiagnosed palatal abnormalities. Hypernasality usually resolves spontaneously after surgery; therefore, follow-up is required for up to eight weeks. If symptoms persist, speech therapy and conservative treatments are recommended. If there is no improvement within 6 to 12 months, surgical intervention may be indicated (24). Nasopharyngeal stenosis, a rare complication of adenotonsillectomy, occurs as fresh mucosal surfaces approach each other during the healing process (25). None of these long-term complications were observed in our study.

CONCLUSION

Tonsillectomy is one of the most frequently performed surgeries worldwide. With the intensive use of antibiotics, more care should be taken when selecting patients in order to achieve the expected decrease in the number of operations performed for chronic and/or recurrent infection indications. In addition, it is important for patients to be followed up by the clinician for a while before deciding to operate. As a result, we believe that it is extremely important to pay attention to the recommendations emphasized in the relevant guidelines and studies during tonsil surgery in order to prevent complications.

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REFERENCES

1. Lock C, Wilson J, Steen N, Eccles M, Brittain K, Carrie S, et al. Childhood tonsillectomy: who is referred and what treatment choices are made? Baseline findings from the North of England and Scotland Study of Tonsillectomy and Adenotonsillectomy in Children (NESSTAC). Arch Dis Child. 2010;95(3);203-208. doi: 10.1136/adc.2009.165530.
2. Cullen KA, Hall MJ, Golosinskiy A. Ambulatory surgery in the United States, 2006. Natl Health Stat Report. 2009;28(11):1-25.
3. Baugh RF, Archer SM, Mitchell RB, Rosenfeld RM, Amin R, Burns JJ, et al. Clinical practice guideline: tonsillectomy in children Otolaryngol Head Neck Surg. 2011;144(1):S1-S30. doi: 10.1177/0194599810389949.
4. Inuzuka Y, Mizutari K, Kamide D, Sato M, Shiotani A. Risk factors of post-tonsillectomy hemorrhage in adults Laryngoscope Investig Otolaryngol. 2020;5(6):1056-1062. DOI: 10.1002/lio2.488.
5. Darrow DH, Siemens C. Indications for tonsillectomy and adenoidectomy. Laryngoscope 2002;112(8 Pt 2 Suppl 100):6-10. doi: 10.1002/lary.5541121404.
6. Paradise JL, Bluestone CD, Bachman RZ, D K Colborn, B S Bernard, F H Taylor, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. N Engl J Med 1984;310(11):674-83. doi: 10.1056/NEJM198403153101102.
7. Alvo A, Hall A, Johnston J, Mahadevan M. Paediatric Posttonsillectomy Haemorrhage Rates in Auckland: A Retrospective Case Series. Int J Otolaryngol. 2019;6:4101034. doi: 10.1155/2019/4101034.
8. Torres BPG, García FDM, Orozco JW. Tonsillectomy in adults: Analysis of indications and complications. Auris Nasus Larynx. 2018:45(3);517-521. doi: 10.1016/j.anl.2017.08.012.
9. Rohlfing ML, Wistermayer PR, Bungo TM, Mims JW, Kirse DJ. Investigation of Postoperative Oral Fluid Intake as a Predictor of Postoperative Emergency Department Visits After Pediatric Tonsillectomy. JAMA Otolaryngol Head Neck Surg. 2016;142(4):357-363. doi: 10.1001/jamaoto.2015.3711.
10. Chen JW, Liao PW, Hsieh CJ , Chen CC, Chiou SJ. Factors associated with changing indications for adenotonsillectomy: A population-based longitudinal study. Plos One. 2018:13(5):e0193317.
11. Derkay CS. Pediatric otolaryngology procedures in the United States: 1977–1987. Int J Pediatr Otorhinolaryngol. 1993: ;25(1-3):1-12. doi: 10.1016/0165-5876(93)90004-m.
12. Rosenfeld RM, Green RP. Tonsillectomy and adenoidectomy: changing trends. The Ann Otolaryngol. 1990:99;187–91.
13. Erickson BK, Larson DR, Sauver JLS, Meverden RA, Orvidas LJ. Changes in incidence and indications of tonsillectomy and adenotonsillectomy, 1970-2005. Otolaryngol Head Neck Surg. 2009:140(6);894-901. doi: 10.1016/j.otohns.2009.01.044.
14. Ahmed AO, Aliyu I, Kolo ES. Indications for tonsillectomy and adenoidectomy Our experience. Niger J Clin Pract. 2014;17(1):90-94. doi: 10.4103/1119-3077.122855.
15. Beaty MM, Funk GF, Karnell LH, Graham SM, McCulloch TM, Hoffman HT, et al. Risk factors for malignancy in adult tonsils. Head Neck.1998;20(5):394-403. doi: 10.1002/(sici)1097-0347(199808)20:5<399::aid-hed7>3.0.co;2-t.
16. Erdag TK, Ecevit MC, Guneri EA, Dogan E, Ikiz AO, Sutay S. Pathologic evaluation of routine tonsillectomy and adenoidectomy specimens in the pediatric population: is it really necessary? Int J Pediatr Otorhinolaryngol. 2005;69(10):1321–1325. doi: 10.1016/j.ijporl.2005.05.005.
17. Randall DA, Martin PJ, Thompson LDR. Routine Histologic Examination is Unnecessary for Tonsillectomy or Adenoidectomy. Laryngoscope. 2007;117(9):1600-1604. doi: 10.1097/MLG.0b013e318093ee4e.
18. Garavello W, Romagnoli M, Sordo L, Spreafico R, Gaini RM. Incidence of Unexpected Malignancies in Routine Tonsillectomy Specimens in Children. Laryngoscope. 2004;114(6):1103-1105. doi: 10.1097/00005537-200406000-00027.
19. Tsikopoulos A, Fountarlis A, Tsikopoulos K, Dilmperis F, Garefis K, Tsikopoulos L, et al. Immediate or interval abscess tonsillectomy? A systematic review and meta-analysis. Eur Arch Otorhinolaryngol. 2015;279(5):2245-2257. doi: 10.1007/s00405-022-07294-x.
20. Mughal Z, Gupta KK, Yeo JJY, Metcalfe C, Weller M. Blood, Sweat, and Tonsils: Bleeding After Abscess Tonsillectomy for Quinsy-A Meta-Analysis. Laryngoscope. 2024;134(10):4186-4195. doi: 10.1002/lary.31449.
21. Ferguson M, Aydin M, Mickel J. Halitosis and the Tonsils: A Review of Management. Otolaryngol Head Neck Surg. 2014;151(4):567-574. doi: 10.1177/0194599814544881.
22. Osborne MS, Clark MPA. The surgical arrest of post-tonsillectomy haemorrhage: Hospital Episode Statistics 12 years on. Ann R Coll Surg Engl. 2018;100(5):406-408. doi: 10.1308/rcsann.2018.0034.
23. Rasmussen N. Complications of tonsillectomy and adenoidectomy. Otolaryngol Clin North Am. 1987;20(2):383–390.
24. Obiako MN. Speech defects as an unusual complication of adenotonsillectomy. Ear Nose Throat J. 1988;67(10):752–754.
25. McLaughlin KE, Jacobs IN, Todd NW, Gussack GS, Carlson G. Management of nasopharyngeal and oropharyngeal stenosis in children. Laryngoscope. 1997;107(10):1322–1331. doi: 10.1097/00005537-199710000-00006.

ORIGINAL ARTICLE

Perinatal Weight Gain and its Effect on Pregnancy and Neonatal Results

Perinatal Kilo Alımının Gebelik Süreci ve Yenidoğan Üzerine Etkileri

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ABSTRACT

Objective: *The aim of this study was to figure out the relationship between body mass index (BMI) of pregnant women's body weight and neonatal height, weight, and head circumference (anthropometric measures).*

Material and Method: *Between January 2019 and December 2021, the BMI of pregnant women who received care at participating centers in Afyonkarahisar and the antropometic records were retrospectively studied. In our study, we formed two groups one for BMI over 30 which basically we call the obese group and the other group with a BMI under 30 that we use as a healthy control group. The neonates in the two groups were compared anthropometrically.*

Results: *In this study 347 patients participated. We compared the birth weights of the newborns from each group. This comparison showed that the babies of obese group were significantly heavier than the nonobese, and it was statistically significant ($p< 0.001$). The size and head circumference of babies born to obese pregnant women and babies born to non-obese pregnant women were similar in each group ($p=0.735$).*

Conclusion: *Obesity is the epidemic of our time, severely affecting people from all parts of our society and future generations from the earliest years of life. As with all individuals, the family, which is considered the source of a healthy life, and the future members of this family should be kept away from this epidemic as much as possible. Our study has shown that obesity has a negative impact on both the mother and the child.*

Key Words: *Pregnancy, Obesity, Newborns*

ÖZET

Amaç: *Bu çalışmamızda gebelerin vücut ağırlığının boya oranının Vücut Kitle İndeksi (VKİ) ile yeni doğan bebeklerin boy,kilo ve baş çevresi ölçümleri (Antropometrik ölçümler) arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.*

Yöntem ve Gereç: *Ocak 2019 ile Aralık 2021 tarihleri arasında Afyonkarahisar ilinde katılımcı merkezlerde izlenen gebelerin VKİ'si ile aynı hastanede doğum yapan bebeklerinin boy, kilo ve baş çevresi ölçüm kayıtları geriye dönük olarak incelendi . Çalışmamızda Vücut Kitle İndeksi (VKİ) 30 ve üzeri olan gebeler obez gebeler ana grubu; Vücut Kitle İndeksi (VKİ) <30 olan hamile obez olmayan gebeler ise kontrol grubunu oluşturdu. Gruplardan dünyaya gelen yenidoğanlar antropometrik olarak kıyaslandı.*

Bulgular: *Planladığımız üzere çalışmaya dahil olmayı kabul eden 347 gebenin dosya kayıtları çalışmamızda kullanıldı. Obez gebeler ile obez olmayan gebelerden doğan yenidoğanların doğum ağırlıkları karşılaştırıldı. Bu karşılaştırmada obez gebelerin bebeklerinin obez olmayan gebelerin bebeklerine göre belirgin şekilde daha ağır olduğu ve istatisliksel olarak anlamlılık ifade ettiği görüldü ($p<0,001$). Obez gebelerin bebekleri ile obez olmayan gebelerin bebeklerinin boy ve baş çevresi her grupta benzer olarak değerlendirildi ($p=0,735$).*

Sonuç: *Obezite çağımızın salgını olarak öne çıkmakta ve toplumumuzun her kesiminden insanı gelecek nesilleri de hayatlarının başında dahi kötü yönde etkilemektedir. Çalışmamızda, gebelikte obezitenin, yenidoğanların doğum ağırlıkları üzerinde anlamlı bir etki yarattığı tespit edilmiştir.Tüm yaş gruplarını etkisi altına alan obezitenin anne ve çocuk sağlığı açısından önemi vurgulanmıştır.*

Anahtar Kelimeler: *Doğum, Obezite, Yenidoğan*

INTRODUCTION

According to World Health Organization criteria (WHO), obesity is body mass index (BMI) ≥30. Obesity is a health issue that affects life quality. Like in other developed countries reproductive age and obesity is increasing in our country. This obesity and aging mother dilemma may lead to serious short and longterm complications for pregnant women, mothers, and newborns (1). With non increasing body mass index in pregnancy possible complications due to obesity, as well as preterm and post term births, are significantly reduced. Possible complications in newborns are also significantly reduced by normal BMI (2). Nearly half of women in developed countries have problems with their weight.

Pregnancy wellbeing is crucial for both maternal and fetal health. Research has shown that fertility is closely linked to proper nutrition and lifestyle choices. In recent years, fertility clinics have increasingly emphasized lifestyle changes alongside addressing health issues related to infertility. While losing weight can be challenging for individuals with long-term unhealthy eating habits, the prospect of improving health

Tablo 1: Demographic Features

Sociodemographic	(n=347)	%
Age		
≤ 23 y.	119	34.4
24- 29 y.	111	31.8
≥ 30 y.	117	33.7
Education		
Elemantary or none	151	43.5
Secondary	60	17.2
High	110	31.7
Collage Degree	26	7.49
Occupation		
Working	34	10.0
Unemployed	313	90.0
Income		
High Class	113	32.5
Mid. Class	210	60.5
Low Class	24	6.91

Tablo 2: Weight gain in perinatal period

	Obese (n=52)	Obese %	Non-Obese (n=295)	Non-obese %	P value*
Weight gain <8kg	14	28.7	135	46.0	
Weight gain 8-15kg	27	51.0	78	26.2	0.703
Weight gain >8kg	12	21.3	83	27.9	
Pregnancy week					
Preg.w <39	21	40.4	91	30.9	0.615
Preg.w ≥39	31	59.6	204	69.1	

for both mother and child provides a powerful motivation. Maintaining a healthy weight during pregnancy, or at least preventing excessive weight gain, is vital to avoid additional health complications. The goal of this study is to examine the impact of maternal obesity on neonatal birth weight and its implications for both maternal and infant health.

MATERIALS AND METHODS

İn our current study the body mass index and neonatal anthropometric measures of 347 pregnant women who received care in our labor units were retrospectively analyzed. Two groups were formed by BMI of 347 pregnant women. The first group was the pregnant women BMI over 30 and the second was BMI below 30 and that was the control group. For both groups anthropometric measurements were compared. Premature neonates under 37 weeks (about 8 and a half months) of age were not included in our study groups for not to misguide the study with the prematurity complications. This study was conducted with the necessary approvals from the relevant ethics committee. Since the study is retrospective, patient data were analyzed while maintaining confidentiality and adhering to ethical principles.

This research contributes to the literature by examining the impact of maternal obesity on neonatal birth weight. Unlike previous studies, it analyzes a specific population in Turkey, assessing regional differences. Additionally, it provides valuable data that could inform healthcare policies regarding perinatal weight gain and birth outcomes.

In our study, factors that could influence weight gain during pregnancy—such as diabetes (DM), preeclampsia, hypertension (HT), smoking, and substance use—were excluded. Since these factors are known to affect birth weight, excluding such cases enhances the reliability of our results.

As the study was conducted retrospectively, individual consent from patients was not obtained. However, all patient data were anonymized to ensure confidentiality, and ethical approval was secured before conducting the study.

Data analysis made with the latest SPSS program. Data distribution was assessed with the Kolmogorov-Smirnov test. We preferred the Chi-square test for parametric data. The confidence interval of 95% and a significance level of 5% were evaluated.

RESULTS

Data from total of 347 patients were used for the study. Pregnant women in this study have a mean age of 27.50±5.08 (17-44) years. The age distribution of the groups was similar. Our demographic table 1 shows that 43.5% of participants had a primary school diploma or less. The same data highlights that the most of women were housewife's, and only half of them has a income financially (Table 1).

When it comes to weight gain during pregnancy no significance between the obese and non-obese groups (Table 2).

As expected, HbA1c levels are higher in obese pregnant women than in the control group (p<0,001). Total cholesterol and LDL levels are significantly lower in nonobese pregnant women than in obese pregnant women, but not statistically significant (Table 3).

The comparison of head circumference, body size, laboratory values, and mode of delivery was not statistically significant (Table 4).

DISCUSSION

The obesity in pregnant women in this study is 15.0%. In a similar study with a bigger scale over 1000 patients have 3% of obesity (3). Another study from our country with smaller scale have 28 % of obesity (4). Obesity of pregnancy is 18.5% in an european country like England in another study. In USA , the prevalence of obesity in pregnant women was 14% and 35% . From all these study results, the prevalence in the world is quite high numerically (5). When we superimpose these results, they show that obesity in pregnancy differs in many ways. In the guide for Obesity and Physical Activity by the Turkish health ministry, it is recommended at least 30 minutes of moderate exercise every day (6). Also ACOG supports mobility and exercise if there are no excuse. Just walking is a suitable form of exercise in pregnancy. Also, swimming, can be a good choice if possible (7). Many studies have highlighted the same statement that obese pregnant women are more likely to have a macrosomic newborn. According to a guide published after a 2009 IOM study, half of women

Table 3: Comparing the laboratory results

Laboratory Parameters	Obese(n=90)	Non obese (n=90)	P value*
Glucose (µmol/L)	83.88±11.12	84.51±12.87	0.727
HbA1C	4.92±0.39	4.27±0.33	<.001
Total Cholesterol	256.79±43.64	213.45±43.17	0.021
HDL	62.20±11.85	63.75±10.86	0.072
LDL	204.45±43.17	134.06±33.04	0.003
VLDL	52.44±18.58	45.47±14.49	0.078
Triglyceride	247.16±96.87	231.28±76.42	0.078
Hemoglobin	12.26±1.27	12.23±1.28	0.906
Platelets	234.59±61.72	225.64±64.93	0.374

*Independent T-Test**

Tablo 4: Comparing the neonate results

Newborn		Obese(n=52)	Non obese(n=295)	P- value*
Weight (Kg)		3425.64 ±510.47	3215.45 ±387.08	<.001
Head (cm)		35.72 ±1.76	34.46 ±2.16	0.736
Height (cm)		48.45±2.57	49.59 ±2.47	0.841
Hb (gr/dl)		11.2±2.35	11.6±2.45	0.541
Delivery	Vaginal	20 (40.2%)	193(65.7%)	0.195**
	Cesarean section	32 (59.7%)	102(34.2%)	
Gender	Girl	25 (48.0%)	145 (49.1%)	0.078**
	Boy	27 (51.9%)	150 (50.8%)	

**İndependet T-Test*
***Fisher exact test*

reported weight gain in the prenatal period, but only one in five achieved the correct weight (8). To ensure proper weight gain, weight gain charts should be used during pregnancy (9). In our study, the babies of the obese patients were heavier than the neonates of the nonobese patients. However, the results of head circumference and height measurements were not statistically significant. In another study in Türkiye the rate of LGA newborns was 22% in obese pregnant women and 7% in nonobese pregnant women (10). In a study conducted in US indicates that babies born to obese pregnant women had an increased risk of becoming obese (11). In a cohort study conducted in the United States, found that the newborns of obese pregnant women were macrosomic (12). According to a study in Austria, there is a positive relationship between pre-pregnancy BMI and newborn birth weight (3). A study conducted in Sweden indicates maternal weight gain was related to infant birth weight (14). Several cohort studies have found a correlation between birth weight of obese pregnant women and birth weight of newborns. Maternal obesity has been associated with abnormal fetal growth in the literature (15). Obese pregnant women may have births with IUGR and SGA (16). However, one of the most worrisome complications is fetal macrosomia. In overweight pregnant women, the risk of LGA in the newborn is increased three fold (17). There is a direct association between maternal obesity and fetal macrosomia. In our study, maternal obesity was not related to the size and head circumference of the baby. In the literature, a recent cohort study indicates that newborns of obese patients were on average 1.1 cm smaller than newborns of nonobese patients (18). Similar to other studies our study indicates that neonates of pregnant women with normal body weight were longer (mean 0.14 cm) than neonates of pregnant women but shows no significance statistically. According to the results of our study, maternal obesity does not affect the size and head circumference of the newborn (19).

CONCLUSION

It is obvious that a well-planned and adequately followed pregnancy leads to better results. The importance of proper nutrition and physical activity during these follow-ups is undeniable. We believe that this follow-up can be done at the highest level with a multidisciplinary approach involving the patient's primary care physician and an obstetrician and perinatologist who can act as a consultant if needed.

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REFERENCES

1. Feng N, Huang XK. Effect of pre-pregnancy body mass index and gestational weight gain on perinatal outcomes. Int J Clin Exp Med 2021;14.
2. Champion ML, Harper LM. Gestational Weight Gain: Update on Outcomes and Interventions. Curr Diab Rep 2020;20. https://doi.org/10.1007/s11892-020-1296-1.
3. Paredes-Díaz SE, Neglia-Cermeño CS, Vidal-Cabrera E del P, Lescano-Pereda LG, Meneses-La-Riva ME, Barrera MJ. Eating Habits, Nutritional Status in Pregnant Women and Weight of Newborns, La Libertad - Peru. Academic Journal of Interdisciplinary Studies 2023;12. https://doi.org/10.36941/ajis-2023-0036.
4. Cheng ZH, Wei YM, Li HT, Yu HZ, Liu JM, Zhou YB. Gestational Diabetes Mellitus as an Effect Modifier of the Association of Gestational Weight Gain with Perinatal Outcomes: A Prospective Cohort Study in China. Int J Environ Res Public Health 2022;19. https://doi.org/10.3390/ijerph19095615.
5. Xu MY, Guo YJ, Zhang LJ, Lu Q Bin. Effect of individualized weight management intervention on excessive gestational weight gain and perinatal outcomes: A randomized controlled trial. PeerJ 2022;10. https://doi.org/10.7717/peerj.13067.
6. Yurtcu E, Mutlu S, Ozkaya E. The Effects of Pre-Pregnancy Body Mass Index and Weight Gain During Pregnancy on Perinatal Outcomes: A Retrospective Cohort Study. Gynecology Obstetrics & Reproductive Medicine 2021. https://doi.org/10.21613/gorm.2021.1149.
7. Feghali MN, Catov JM, Zantow E, Mission J, Caritis SN, Scifres CM. Timing of gestational weight gain and adverse perinatal outcomes in overweight and obese women. Obstetrics and Gynecology 2019;133. https://doi.org/10.1097/AOG.0000000000003234.
8. Shay LA, Sangi-Haghpeykar H, Aagaard KM, Mastrobattista J. 682 Everything in moderation: impact of extremes of BMI & gestational weight gain on perinatal outcomes. Am J Obstet Gynecol 2021;224. https://doi.org/10.1016/j.ajog.2020.12.706.
9. Xu MY, Guo YJ, Zhang LJ, Lu Q Bin. Effect of individualized weight management intervention on excessive gestational weight gain and perinatal outcomes: A randomized controlled trial. PeerJ 2022;10. https://doi.org/10.7717/peerj.13067.
10. Hasan SMT, Khan MA, Ahmed T. Institute of medicine recommendations on the rate of gestational weight gain and perinatal outcomes in rural Bangladesh. Int J Environ Res Public Health 2021;18. https://doi.org/10.3390/ijerph18126519.
11. Hasan SMT, Ahmed SI, Khan MA, Sarker SA, Ahmed T. Achieving optimal gestational weight gain, birth weight, and perinatal outcomes among pregnant women at risk of hypertension: Protocol for a pilot randomized controlled trial. JMIR Res Protoc 2020;9. https://doi.org/10.2196/16676.
12. Delfino E, Peano L, Wetzl RG, Giannì ML, Netto R, Consales A, et al. Newborn Weight Loss as a Predictor of Persistence of Exclusive Breastfeeding up to 6 Months. Front Pediatr 2022;10. https://doi.org/10.3389/fped.2022.871595.
13. Chen CN, Chen HS, Hsu HC. Maternal prepregnancy body mass index, gestational weight gain, and risk of adverse perinatal outcomes in Taiwan: A population-based birth cohort study. Int J Environ Res Public Health 2020;17. https://doi.org/10.3390/ijerph17041221.
14. Almeida NB, de Menezes RCE, dos Santos Sobral K, Gomes JF, Longo-Silva G, da Silveira JAC. Pre- And perinatal factors associated with weight gain among preschool children enrolled at day care centers. Revista Paulista de Pediatria 2020;38. https://doi.org/10.1590/1984-0462/2020/38/2019060.
15. Koech WA, Lilly CL. Association of county perinatal resources and gestational weight gain in West Virginia, United States. BMC Pregnancy Childbirth 2019;19. https://doi.org/10.1186/s12884-019-2650-7.
16. Lin L hua, Weng Y lin, Lin Y ying, Huang X xian, Lin Y, Xiu X yan, et al. Examining the effects of second-and third-trimester gestational weight gain rates on the perinatal outcomes among Chinese twin pregnancies: a retrospective cohort study. BMC Pregnancy Childbirth 2022;22. https://doi.org/10.1186/s12884-022-04467-8.
17. Mosquera PS, Malta MB, de Araújo Damasceno AA, Neves PAR, Matijasevich A, Cardoso MA. Associations of Gestational Weight Gain with Perinatal Outcomes in Western Brazilian Amazon. Matern Child Health J 2022;26. https://doi.org/10.1007/s10995-022-03480-9.
18. Perumal N, Wang D, Darling AM, Wang M, Liu E, Fawzi W. Associations Between Gestational Weight Gain Adequacy and Perinatal Outcomes in Tanzania. Curr Dev Nutr 2021;5. https://doi.org/10.1093/cdn/nzab045_059.
19. Gonzalez-Ballano I, Saviron-Cornudella R, Esteban LM, Sanz G, Castán S. Pregestational body mass index, trimester-specific weight gain and total gestational weight gain: how do they influence perinatal outcomes? Journal of Maternal-Fetal and Neonatal Medicine 2021;34. https://doi.org/10.1080/14767058.2019.1628942.

ORIGINAL ARTICLE

Screening of Renal Cell Carcinoma Cases in Pathology Reports

Renal Hücreli Karsinom Vakalarının Patoloji Raporlarında Taranması

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ABSTRACT

Objective: *Renal cell carcinoma in the kidney accounts for 1-3% of all malignant tumors. Histologically, 80% of renal cell carcinomas are clear cell type. The Fuhrman grading system is related to the nucleus in renal cell carcinomas. Furthermore, it is a significant indicator in predicting prognosis. This study scanned the cases diagnosed with renal cell carcinoma between 2015 and 2022 from the hospital's digital environment from pathology reports and discussed the relationships between them together with the literature.*

Material and Method: *The hospital's digital environment had 318 renal cell carcinoma cases between January 2015 and January 2022. SPSS 15.0 for Windows program was used for statistical analysis. The ratios in independent groups were compared with the Chi-Square test. Statistical alpha significance level was accepted as p< 0.05.*

Results: *There were 318 cases of renal cell carcinoma, 213 were male, and 105 were female. 156 of the tumors were located on the left; whereas 155 were on the right side. The most common histological type was clear-type renal cell carcinoma, with 195 incidences (61.3%). Fuhrman grade 2 was the most common and the number was 137. Grading was performed in 190 of 195 clear cell renal cell carcinomas.*

Conclusion: *There were approximately twice as many cases in men as in women, with 213 men and 105 women. There was a statistically significant difference between Fuhrman grades in different histology types (p=0.002). Grade 1 was higher in clear papillary, grade 2 was higher in clear type and papillary renal cell carcinoma. According to histological subtypes, necrosis rates differed significantly (p=0.043).*

Key Words: *Renal cell carcinoma, Clear cell renal cell carcinoma, Prognosis*

ÖZET

Amaç: *Böbrekte görülen renal hücreli karsinom tüm malign tümörlerin % 1- 3'ünü teşkil eder. Renal hücreli karsinomların histolojik olarak %80' ini berrak hücreli tip oluşturmaktadır. Renal hücreli karsinomlarda nükleus ile alakalı olan Fuhrman derecelendirme sistemi, prognozu tahmin etmede önemli bir belirteçtir. Bu yazıda 2015- 2022 yılları arasındaki böbrek hücreli karsinom tanılı vakalar patoloji raporları üzerinden hastane dijital ortamında taranmış elde edilen veriler ve aralarındaki ilişkiler literatür eşliğinde tartışılmıştır.*

Gereç ve Yöntem: *Ocak 2015- ocak 2022 yılları arasındaki 318 renal hücreli karsinom vakası hastane dijital ortamında taranarak belirlendi. İstatistiksel analiz için SPSS 15.0 for Windows programı kullanıldı. Bağımsız gruplarda oranlar Ki Kare testi ile karşılaştırıldı. İstatistiksel alfa anlamlılık seviyesi p< 0,05 olarak kabul edildi.*

Bulgular: *213'ü erkek ve 105'i kadın olmak üzere 318 renal hücreli karsinom vakası vardı. Tümörlerin 156'sı sol; 155'i sağ tarafta yerleşmişti. Histolojik tiplerden en sık görüleni berrak tip böbrek hücreli karsinom olup sayısı 195 (% 61,3)'ti. En sık Fuhrman derece 2 görülmüş ve sayısı 137'ti. 195 berrak hücreli renal hücreli karsinomun 190'ında derece belirtilmişti.*

Sonuç: *213'ü erkek ve 105'i kadın olmak üzere erkeklerde kadınlardan yaklaşık iki kat daha fazla vaka görüldü. Histolojik tiplerde Fuhrman derecelerinde istatistiksel olarak anlamlı fark tespit edildi (p=0,002). Grade 1 berrak papiller tipte daha yüksek, grade 2 ise berrak tip ve papiller renal hücreli karsinomda daha yüksekti. Nekroz oranlarında histolojik alt tiplere göre istatistiksel olarak anlamlı fark tespit edildi (p=0,043).*

Anahtar Kelimeler: *Renal hücreli karsinom, Berrak hücreli renal hücreli karsinom, Prognoz*

INTRODUCTION

Renal cell carcinoma (RCC) is a fatal malignant tumor in urology. It accounts for 1-3% of all malignant tumors (1,2). Clear cell, papillary, and chromophobe RCCs comprise more than 90% of all RCCs (1). Although it is limited to the kidney in pathology reports, recurrence or distant metastasis can manifest in 30% of cases. Surgeons rely on pathology reports to predict tumor recurrence. In determining the prognosis, the Fuhrman rating has a predictive accuracy of 0.65. An increase in metastasis and a decrease in survival rate were present in patients with Fuhrman grade III or IV (3). In this research article, we wanted to present the data of 318 RCC cases diagnosed between January 2015 and January 2022 in the pathology department of Haseki Training and Research Hospital, in the light of the literature.

MATERIALS AND METHODS

Ethical permission has been granted by the Clinical Research Ethics Committee of Haseki Training and Research Hospital (Date: 06.04.2022; Decision No: 68-2022). RCC cases between January 2015 and January 2022 were determined by scanning in the hospital's digital environment. There were 318 cases of RCC, 213 males, and 105 females. The following information was scanned from the electronic system as predictors: Type of surgery (partial/ radical), age, gender, tumor location, tumor diameter, Fuhrman grade, perinephritic spread, renal sinus invasion, pathological tumor stage, presence of sarcomatoid differentiation, and the presence of necrosis.

SPSS 15.0 for Windows program was used for statistical analysis. In descriptive statistics; numbers and percentages for categorical variables, and mean, standard deviation,

minimum, maximum, and median for numerical variables. The ratios in independent groups were compared with the Chi-Square test. Statistical alpha significance level was accepted as $p< 0.05$.

RESULTS

The mean age was 59.1 years, and the median age was 60 years. Of the 318 patients, 207 (65%) were older than 55 years of age, of which 135 were male; 9 (2.8%) were younger than 35 years of age, of which five were male. 156 of the tumors were left; 155 were located on the right side, and the side was not specified in 7 partial nephrectomy cases. 101 males and 55 females had left-sided tumors, whereas 108 males and 47 females had right-sided tumors. While the largest diameter in tumor size was 22 cm, the smallest was 0.2 cm, and the median value was 4.5 cm, the mean and standard value was 5.58+/- 3.32. The most common histological type is the clear cell RCC (ccRCC). Its incidence is 195 (61.3%). Other RCC types were 51 (16%) papillary; 48 (15.1%) chromophobe; 7 (2.2%) clear papillary; 5 (1.6%) multiloculated cystic kidney cell carcinoma, respectively. Of the 10 patients with sarcomatoid differentiation, 7 were ccRCC; two were chromophobe and one was unclassified RCC 12 (3.7%). The grade of the nucleus was determined as the Fuhrman grade. The most common Fuhrman grade 2 was seen and the number was 137, while the number of the others was grade 3 and the number was 62, respectively; degree 1 and number 42; degree 4 and number 13. The stage information was present in 313 patients. 136 male and 71 female patients were in the T1 stage, and three male patients were in the T4 stage. Since the subcategory of pathological staging was available in limited cases, the general category was included in the article. There were no female patients in the T4 stage. The relationship between stage, age, and grade is in Table 1. Although grading is not recommended in chromophobe renal cell carcinoma (chRCC), grading was performed in 9 of 48 cases. Grade was specified in 190 of 195 CRCCs. There was a statistically significant difference in Fuhrman grades in histological types ($p=0.002$). Comparison of grade, age, histological type is summarized in Table 2. Grade 1 was higher in clear papillary RCC, grade 2 was higher in ccRCC, papillary RCC (PRCC), and multiloculated cystic RCC; grade 3 was higher in chRCC. The relationship between perirenal fatty tissue infiltration, renal sinus invasion, gerato fascia invasion, necrosis and histological subtypes is summarized in Table 3, and a statistically significant difference was found in necrosis rates in histological types ($p=0.043$). In our screening, four cases had more than one focus, and one had ccRCC in both kidneys.

DISCUSSION

Renal cell carcinoma constitutes 85% of the cancers in the kidney and 2-3% of all body cancers (4,5). Most RCCs are diagnosed in the early stages (6). The gold standard in treating kidney tumors is radical or partial nephrectomy (7). It has been

Table 1: The relationship between stage, age, and grade.

Stage		T1		T2		T3		T4		
		n	%	n	%	n	%	n	%	p-value
Sex	Male	136	65.7	32	76.2	39	63.9	3	100	0.368
	Female	71	34.3	10	23.8	22	36.1	0	0	
Age	<35	6	2.9	3	7.1	0	0.0	0	0.0	0.274
	35-55 years	64	30.9	17	40.5	19	31.1	1	33.3	
	>55 years	137	66.2	22	52.4	42	68.9	2	66.7	
Grade	I	38	23.3	0	0.0	4	8.0	0	0.0	<0.001
	II	93	57.1	18	52.9	22	44.0	1	50.0	
	III	29	17.8	15	44.1	15	30.0	1	50.0	
	IV	3	1.8	1	2.9	9	18.0	0	0.0	

Table 2: The relationship between grade, sex, age, histological type.

		Grade 1		Grade 2		Grade 3		Grade 4		
		n	%	n	%	n	%	n	%	p-value
Sex	Male	27	15.6	93	53.8	47	27.2	6	3.5	0.182
	Female	15	18.5	44	54.3	15	18.5	7	8.6	
Age	<35 years	1	16.7	3	50.0	2	33.3	0	0.0	0.855
	35-55 years	15	17.6	43	50.6	24	28.2	3	3.5	
	>55 years	26	16.0	91	55.8	36	22.1	10	6.1	
Histological type	Clear	30	15.8	109	57.4	44	23.2	7	3.7	0.002
	Chromophobe	1	11.1	2	22.2	4	44.4	2	22.2	
	Papillary	6	16.7	20	55.6	10	27.8	0	0.0	
	Clear papillary	4	57.1	2	28.6	1	14.3	0	0.0	
	Multiloculated cyst	0	0.0	2	66.7	1	33.3	0	0.0	

Table 3: The relationship between PRI, renal sinus invasion, gerato fascia invasion, necrosis and histological subtypes.

		PRI		Sinus invasion		Gerato fascia invasion		Necrosis	
		n	%	n	%	n	%	n	%
Histological type	**Clear**	22	11.4	29	14.9	1	0.5	56	30.9
	Chromophobe	5	10.4	2	4.2	0	0.0	7	15.6
	Papillary	5	9.8	4	8.0	0	0.0	13	27.7
	Clear papillary	0	0.0	0	0.0	0	0.0	2	28.6
	Multiloculated cyst	0	0.0	0	0.0	0	0.0	0	0.0
	p-value	0.084		0.052		1.000		0.043	

**PRI: Perirenal fatty tissue infiltration.*

approximately twice as common in males as in females in the literature, and the sex distribution is similar in our screening (5). In our study, 213 (66%) of 318 patients were male and 105 (34%) were female.

In the article of Uçar et al., 80% of RCCs were ccRCC, 10% were PRCC, and 5% were chRCC (8). Tumor rates in our patients were ccRCC in 195 of them (61.3%), PRCC in 51 (16%), and chRCC in 48 (15.1%), respectively.

In newly diagnosed RCC cases, the age range is mostly 60-79. Advanced age is associated with poor survival (9). It is reported in the literature that the risk for RCC increases between the ages of 50-70 (7). In our screening, there were 207 (65.1%) patients older than 55 years, and the mean age of all cases was 59.1 years. While there were 162 (51%) patients older than 60 years, the number of patients over 70 years was 58 (18%).

Nine patients were under 35 years of age, and there were no Fuhrman grade 4 and pathological stage 4 among them. Looking at Table 2, it is noteworthy that higher grades are seen in those older than 55 years of age. While the number of grade 2 cases between the ages of 35 and 55 is 43, 91 were in those over 55 years. While the number of grade 2 cases between the ages of 35 and 55 is 43, this is 91 cases in those older than 55 years. While the number of grade 4 patients between 35 and 55 is 3, it is 10 in those over 55 years. Andreiana et al. (10) screened 75 ccRCC cases; the rate of Fuhrman grade 2 was 42 (56%). Grade 2 incidence was more frequent in 190 ccRCC, and the ratio was similar 109 (57.4%) in our study.

The right and left sides were almost equal, although 7 cases were not reported, including partial (PN) and total nephrectomy (RN). Alanee et al. (11) reported that left RN was 51.01%, left PN was 50.46%, whereas right RN was 48.83% and PN was 49.36%.

TNM classification does not include capsular invasion and is based on the invasion of adipose tissue around the kidney. Turun et al. (3) reported in their retrospective study that RCC would progress significantly in patients with capsule invasion. Perinephric adipose tissue invasion (PRI) was present in 32 (11.6%) of our cases, of which 22 (11.4%) were ccRCC. Renal sinus invasion (RSI) manifested in 35 (11.9%) cases, of which 29 (14.9%) were ccRCC. In the literature, RSI has been reported to be more common than PRI invasion, and although there is no fibrous barrier between the renal sinus and parenchyma, there is a fibrous barrier between the perinephric adipose tissue and the parenchyma (12). As is known, tumor infiltration in both regions indicates that the universe is pT3a (13). In our screening, PRI and RSI were not present in patients younger than 35.

Rating systems related to the nucleus in RCC, such as the Fuhrman system, are considered a significant indicator in predicting prognosis and are compatible with ccRCC. The nuclear grade is not recommended in chRCC (14). In our scan, a directly proportional relationship between histological grade and pathological tumor stage was present (<0.001).

In a study based on the tumor size of 7 cm, the researchers found that Fuhrman grade and necrosis and renal vascular invasion were more likely to occur in cases where the tumor was large (15,16). Again, in this study, there was no difference between tumor sizes below and above 7 cm in RSI (15). In our cases, a direct correlation was present between tumor diameter and pathological tumor stage (<0.001). There was no relationship between diameter and age, and diameter and grade. There are 91 cases larger than 7 cm. 137 cases were smaller than 4 cm, while 37 cases were larger than 10 cm. The mean tumor diameter is 5.58. The median value is 4.5 cm.

In a retrospective study of 37 patients diagnosed with RCC with vascular invasion, vascular invasion was associated with high mortality in RCC (17). We had a case of lymphovascular invasion. The histological type of this case was in the ccRCC and pT3 stages and included adipose tissue invasion and necrosis around the kidney.

Tumor necrosis is one of the factors of interest in predicting prognosis. It is assumed to occur with chronic hypoxia. According to a meta-analysis, tumor necrosis had a weak association with cancer-specific survival, overall survival, recurrence-free survival, and progression-free survival (2). In our study, a statistically significant difference was present between necrosis and histological types (p=0.043). Necrosis was present in 83 cases, and 56 were ccRCC.

Sarcomatoid differentiation is not a separate histological subtype in RCC and is classified according to the epithelial component. In a meta-analysis, sarcomatoid differentiation showed a low recurrence-free, general, and progression-free survival (6). In our screening, 8 of the 10 cases with sarcomatous differentiation had necrosis; eight had stage pT3, and 5 of 7 cases, except for chromophobe and unclassified RCC, had Fuhrman grade 4. Sarcomatoid differentiation can indicate a poor prognosis considering the stage, grade, and necrosis.

As a result, the limited number of our cases, the pathological tumor stage and Fuhrman grade, were not mentioned in some reports; and the fact that we did not include the survival times of the patients in the screening were among the limitations of our study. Multicenter screening is likely to yield more meaningful results. The factors mentioned in our reports remain essential regarding the patient's prognosis.

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Ethics: This research is approved by the Clinical Research Ethics Committee of Haseki Training and Research Hospital (Date: 06.04.2022; Decision No: 68-2022).
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REFERENCES

1. Muglia VF, Prando A. Renal cell carcinoma: histological classification and correlation with imaging findings . Radiol Bras. 2015;48(3):166-174. doi:10.1590/0100-3984.2013.1927
2. Zhang L, Zha Z, Qu W, Zhao H, Yuan J, Feng Y, et al. Tumor necrosis as a prognostic variable for the clinical outcome in patients with renal cell carcinoma: A systematic review and meta-analysis. BMC Cancer. 2018;18(1). doi:10.1186/s12885-018-4773-z
3. Song T, Yin Y, Liao B, Zheng S, Wei Q. Capsular invasion in renal cell carcinoma: A meta-analysis. Urol Oncol. 2013;31(7):1321-1326. doi: 10.1016/j.urolonc.2011.12.019.
4. Zhao Y, Chen H, Xıe Y, Zhang C, Hou Y, Jın M. Clinicopathologic features and prognostic factors in patients with renal cell carcinoma with sarcomatoid differantiation. APMIS. 2020;128(5):378-386. doi:10.1111/apm.13035
5. Aron M, Nguyen MM, Stein RJ, Gill IS. Impact of Gender in Renal Cell Carcinoma: An Analysis of the SEER Database. Eur Urol. 2008;54(1):133-142. doi:10.1016/J.EURURO.2007.12.001
6. Zhi H, Feng M, Liu S, Na T, Zhang N, BiLiGe WE. Prognostic Significance of Sarcomatoid Differentiation in Patients With Metastatic Renal Cell Carcinoma: A Systematic Review and Meta-Analysis. Front Oncol. 2020;10. doi:10.3389/fonc.2020.591001
7. Devrim T. Böbrek Tümörü Vakalarının Retrospektif Olarak Değerlendirilmesi. Kırıkkale Üni Tıp Der. 2019;21(2):212-217. doi:10.24938/kutfd.552211
8. Uçar M, Soyupek S, Oksay T, Özorak A, Güzel A, Öztürk Sefa A, et al. Renal kitle nedeniyle radikal nefrektomi yapılan hastaların tümör karakteristiklerinin değerlendirilmesi; 18 yıllık sonuçlarımız. Med J SDU. 2019;26(3):288-94. doi:10.17343/sdutfd.460209
9. Sun M, Abdollah F, Bianchi M, Trinh Quoc-D, Jeldres C, Tian Z, et al. A Stage-for-Stage and Grade-for-Grade Analysis of Cancer-Specific Mortality Rates in Renal Cell Carcinoma According to Age: A Competing-Risks Regression Analysis. Eur Urol. 2011;60(6):1152-1159. doi:10.1016/J.EURURO.2011.07.064
10. Andreiana BC, Emilian Stepan A, Mărgăritescu C, Taisescu O, Osman A, Simionescu C. Original Paper Histopathological Prognostic Factors in Clear Cell Renal Cell Carcinoma. Curr Health Sci J. 2018;44(3). doi:10.12865/CHSJ.44.03.01
11. Alanee S, Nutt M, Moore A, Holland B, Dynda D, Wilber A et al. Partial nephrectomy for T2 renal masses: contemporary trends and oncologic efficacy. Int Urol Nephrol. 2015;47(6):945-950. doi:10.1007/s11255-015-0975-3
12. Ni D, Ma X, Li HZ, Y Gao, XT Li, Y Zhang, et al. Factors Associated with Postoperative Renal Sinus Invasion and Perinephric Fat Invasion in Renal Cell Cancer: Treatment Planning Implications. Oncotarget. 2017;15;9(11):10091-99. doi: 10.18632/oncotarget.23497
13. Swami U, Nussenzveig RH, Haaland B, Agarwal N. Revisiting AJCC TNM staging for renal cell carcinoma: quest for improvement. Ann Transl Med. 2019;7(S1):S18-S18. doi:10.21037/atm.2019.01.50
14. Cornejo KM, Dong F, Zhou AG, Wu CL, Young RH, Braaten K et al. Papillary renal cell carcinoma: correlation of tumor grade and histologic characteristics with clinical outcome. Hum Pathol. 2015;46(10):1411-1417. doi:10.1016/J.HUMPATH.2015.07.001
15. Chen L, Ma X, Li H, Gu L, Li X, Gao Yu, et al. Influence of tumor size on oncological outcomes of pathological T3aN0M0 renal cell carcinoma treated by radical nephrectomy. PLoS One. 2017;12(3). doi:10.1371/journal.pone.0173953
16. Pecoraro A, Deuker M, Rosiello G, Stolzenbach F, Luzzago S, Tian Z, et al. Comparison between small renal masses 0-2 cm vs. 2.1-4 cm in size: A population-based study. Urologic Oncology: Seminars and Original Investigations. 2021;39(4):239.e1-239.e7. doi:10.1016/J.UROLONC.2021.01.003
17. Rodríguez-Cabello MA, Laso-García I, Donis-Canet F, Gómez-Dos-Santos V, Varona-Crespo C, Burgos-Revilla FJ. Renal cell carcinoma with vascular invasion: Mortality and prognostic factors. Actas Urológicas Españolas (English Edition). 2017;41(2):132-138. doi:10.1016/J.ACUROE.2016.12.008

ORIGINAL ARTICLE

Nature or Nurture? Factors Influencing Newborn Weight

Doğa mı, Yetiştirme mi? Yenidoğan Kilosunu Etkileyen Faktörler

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ABSTRACT

Objective: *A pattern is emerging leading to a rise in birth weights and instances of macrosomia in numerous countries globally. Our study's objective is to contrast the average birth weights between 2016 and 2020. We aim to explore whether there exists a tendency toward increased mean birth weight and higher rates of macrosomia. Additionally, we seek to assess how neonatal gender, birth method, maternal age, and birth season impact newborn weight.*

Material and Method: *Retrospective analysis encompassed data from a combined 1,348 newborns in 2016 (n: 692) and 2020 (n=656), all born within the 37-40 weeks gestational range. A statistical analysis was conducted on data related to the birth weight of newborns, their gender, gestational duration, the age of the mothers, method of delivery, and the time of year they were born.*

Results: *The research findings indicated a significant increase in the occurrence of macrosomia (defined as birth weight ≥4000 g), rising from 4.8% in 2016 to 8.2% in 2020. In both years, there is a modest positive correlation between the age of the mother and the weight of the newborns. In 2020, a significant disparity in birth weight was noticed between infants delivered via cesarean section and those delivered through the natural birthing process. The study indicated that the season of birth did not have any impact on birth weight.*

Conclusion: *Macrosomia rates experienced an upsurge in 2016. Maternal age, gender of the newborn, and gestational age were examined as distinct risk factors contributing to macrosomia. The study noted that both maternal age and neonatal gender influenced newborn weight, whereas birth seasons had no impact on neonatal weight.*

Key Words: *Newborn, Birth weight, Macrosomia*

ÖZET

Amaç: *Dünya genelinde birçok ülkede doğum ağırlıklarının yükselmesi ve makrosomi vakalarının artışına işaret eden bir eğilim ortaya çıkıyor. Çalışmamızın amacı, 2016 ile 2020 arasındaki ortalama doğum ağırlıklarını karşılaştırmaktır. Ortalama doğum ağırlığında artış eğilimi ve makrosomi oranlarında artış olup olmadığını araştırmayı amaçlıyoruz. Ayrıca, yenidoğan cinsiyeti, doğum yöntemi, anne yaşı ve doğum mevsiminin, yenidoğan ağırlığına nasıl etki ettiğini değerlendirmeyi amaçlıyoruz.*

Gereç ve Yöntem: *Geriye dönük analiz, 2016 (n: 692) ve 2020 (n=656) yıllarında doğan toplam 1.348 yenidoğanın verilerini içeriyordu. Tüm yenidoğanlar, 37-40 hafta gebelik aralığında doğmuşlardır. Yenidoğanların doğum ağırlığı, cinsiyeti, gebelik süresi, anne yaşı, doğum yöntemi ve doğum mevsimiyle ilgili istatistiksel bir değerlendirme yapıldı..*

Bulgular: *Çalışma, makrosomi (doğum ağırlığı ≥4000 g) vakalarında belirgin bir artış ortaya koydu; bu oran 2016'da %4.8'den 2020'de %8.2'ye yükseldi. Her iki yılda da, anne yaşı ile yenidoğan ağırlığı arasında hafif bir pozitif ilişki tespit edilmiştir. 2020'de, sezaryen ile doğan bebekler ile normal doğum yapan bebekler arasında doğum ağırlığında dikkate değer bir artış gözlendi. Çalışma, doğum mevsiminin doğum ağırlığı üzerinde herhangi bir etkisi olmadığını gösterdi*

Sonuç: *Makrosomi oranları 2020 yılında bir yükseliş yaşadı. Çalışma, hem anne yaşının hem de yenidoğan cinsiyetinin yenidoğan ağırlığını etkilediğini, ancak doğum mevsiminin yenidoğan ağırlığı üzerinde herhangi bir etkisinin olmadığını belirtti. Anne yaşı, yenidoğanın cinsiyeti ve gebelik yaşı, makrosominin katkı sağlayan ayrı risk faktörleri olarak incelendi*

Anahtar Kelimeler: *Yenidoğan, Doğum ağırlığı, Makrozomi*

INTRODUCTION

Birth weight stands as a crucial metric that mirrors the conditions within the womb. Accumulating evidence indicates that infants born with birth weights significantly higher or lower than expected for their gestational age are associated with adverse perinatal outcomes and an increased risk of cardio-metabolic problems in their later lives (1).The most frequently utilized threshold is a weight exceeding 4500 g, although a weight exceeding 4000 g is also commonly employed (2). Macrosomia refers to surpassing a specific growth threshold, regardless of the gestational age. Furthermore, the frequency of macrosomia varies among distinct racial and ethnic groups, impacting approximately 6-10% of newborns (3). The occurrence of macrosomia, leading to detrimental effects on both the mother and newborn, has experienced a significant increase over the last decade. Macrosomia may result in difficulties such as shoulder dystocia, perinatal oxygen deprivation, brachial plexus injuries, congenital abnormalities, and a heightened frequency of admissions to intensive care units. For mothers, this scenario can also lead to postpartum hemorrhage, prolonged labor, tears in the perineal area, thromboembolic events, a higher probability of undergoing a cesarean section, and complications associated with anesthesia. Apart from

gestational diabetes mellitus, the primary factors increasing the likelihood of macrosomia in newborns include maternal obesity, increased weight gain during pregnancy, advanced maternal age, multiple pregnancies, post-term gestation, factors related to ethnicity and race, as well as the male gender of the fetus (4). Our study aims to compare the average birth weights between 2016 and 2020, and to examine whether there exists a rising pattern in the mean birth weight and rates of macrosomia during this timeframe. We evaluate the relationship between the gender of the newborn, the method of delivery, the age of the mother, and the season of birth in relation to the weight of the newborn. Previously, there has been no investigation into the influence of seasons on newborn weight and macrosomia rates, particularly within the central Anatolian region of Turkiye. In this context, our study will serve as an augmentation to the current corpus of literature.

MATERIALS AND METHODS

Study design

This research was conducted within the Obstetrics and Gynecology Department of Afyonkarahisar State Hospital, covering the periods from January 1st to December 31st in both 2016 and 2020. The research was granted ethical authorization by the Ethics Committee for Non-Interventional Research at Afyonkarahisar Health Sciences University Faculty of Medicine, as evidenced by Decision No: 196, issued on April 13, 2020, following 36 committee meetings. The study involved documenting the birth weights of newborns in grams, categorized by their gestational age. It conducted statistical analyses to compare the data from 2016 and 2020 in a retrospective inquiry. These measurements of newborn weights were conducted using a precise digital scale, with an accuracy level of 5 grams. The weight measurements were taken during the first hour after birth, prior to any feeding, and with the baby in an unclothed state. The research also included an examination of the newborn's gender, the age of the mother in years, the length of gestation in weeks, the method of delivery, and the specific season of birth for both the years 2016 and 2020.

Study Group

All birth records from the years 2016 and 2020 were meticulously reviewed. Retrospective data were gathered from newborns born to mothers aged between 18 and 40 years, with gestational ages falling within the range of 37 to 40 weeks. In the year 2016, there were a total of 1,681 births, while in 2020, the number rose to 1,839 births. Among these, 688 births from 2016 and 887 births from 2020 were considered for inclusion in the study. The study excluded patients with significant maternal illnesses that could potentially impact the health of the baby and measurements of neonatal birth weight. The research deliberately excluded various conditions, including diabetes mellitus, hypertension, congenital heart disease, chronic pulmonary diseases (such as COPD, cystic fibrosis, asthma) leading to maternal hypoxemia, hematological disorders like severe anemia, sickle cell anemia, and thalassemia, as well as maternal malnutrition due to conditions like Crohn's disease, ulcerative colitis, or gastric bypass surgery. Rheumatologic illnesses such as SLE and rheumatoid arthritis, infants born to mothers with TORCH group infections, and newborns with placental anomalies were also not part of the study. The research did not encompass cases involving multiple pregnancies, chromosomal abnormalities, or congenital anomalies in newborns. This study intentionally omitted multiple pregnancies due to the potential dangers they pose to both mothers and infants. These risks encompass preterm birth, low birth weight, preeclampsia, postpartum bleeding, restricted fetal growth, neonatal health issues, and a heightened rate of neonatal death.

Statistical analysis

Categorical variables were represented using counts and corresponding percentages (n%), whereas continuous variables were summarized by indicating the mean ± standard deviation (SD). For the comparison of year groups and categories of newborn weight, the Chi-square test was employed. In the years 2016 and 2020, separate analyses using Student's t-test were conducted to compare newborn weights across different gender and delivery method categories. One-way ANOVA was utilized to ascertain the presence of significant distinctions in mean newborn weight with regard to maternal age and season variables that included more than two categories. To assess the homogeneity of variances and conduct multiple comparisons among groups, Scheffe tests were applied. Logistic regression analysis was conducted to identify significant predictors of the macrosomia variable. In the preliminary phase, univariate analysis was employed to evaluate potential risk factors that could exert an influence on macrosomia. These risk factors included variables such as maternal age, gender, year of birth, gestational age, and season of birth. Subsequently, based on a significance criterion of $p < 0.25$, the variables of maternal age, gender, and gestational age were selected for inclusion in the multiple logistic regression analysis. A statistical significance level of 0.05 was utilized for all statistical tests. All analytical procedures were executed using Statistical Package for the Social Sciences software, version 26 (SPSS, Version 26.0).

RESULTS

In our study, we observed that the average weight of newborns in 2020 (3334.3±480.1) was significantly greater than that of newborns in 2016 (3253.7±3240.0) ($p=0.010$). In 2020, births tended to occur at a more advanced gestational week, and there existed a statistically significant distinction when compared to 2016. In 2020, we observed a median gestational age of 39 weeks, whereas in 2016, it stood at 38 weeks ($p<0.001$). However, when comparing newborn weights within the same gestational week, there were no statistically significant differences between 2016 and 2020 ($p>0.05$). Interestingly, both in 2016 and 2020, male newborns consistently displayed higher birth weights than their female counterparts ($p<0.001$). The mean maternal age was 28.7±5.2 for 2012 and 28.6±5.4 for 2016, with no statistically significant difference noted in the average maternal age between the two years ($p=0.762$). (Table 1)

What's intriguing is that in both 2016 and 2020, we observed a trend where newborn birth weight increased as maternal age advanced. There was a subtle positive correlation between maternal age and newborn weight in both 2016 and 2020 ($p<0.001$), with correlation coefficients of 0.156 and 0.152, respectively. When exploring the relationship between the gestational week at birth and newborn weight, we discovered a significant increase in newborn weight with each subsequent gestational week ($p<0.001$). For proper contextualization, it's of paramount importance to delineate the definitions pertaining to birth weight. Low birth weight is conventionally demarcated as a live birth weight below 2500 grams. Conversely, macrosomia is frequently defined by birth weights that surpass the 4000-gram mark, occasionally extending to 4500 grams. Birth weights within the range

Table 1: Comparison of Newborn Weight, Gestational Age, and Maternal Age in 2016 and 2020

Year	Average Newborn Weight (g)	Gestational Age (weeks)	Maternal Age (years)	Correlation between Maternal Age and Newborn Weight	Newborn Weight Comparison (p-value)	Male vs. Female Newborn Weight (p-value)
2016	3253.7±240.0	38	28.7±5.2	0.156 (p<0.001)	No significant difference (p>0.05)	Male > Female (p<0.001)
2020	3334.3±480.1	39	28.6±5.4	0.152 (p<0.001)	No significant difference (p>0.05)	Male > Female (p<0.001)

of 2500 to 4000 grams are considered within the norm. In our research, we specifically identified newborns with birth weights equal to or exceeding 4000 grams as infants falling under the macrosomia category. The incidence of newborns with low birth weight was 3.7%, while the rate of newborns with normal birth weight was 91.4%, and the occurrence of macrosomic births was 4.8% during the year 2016. The proportion of newborns with low birth weight was 4.3%, while the percentage of newborns with a normal birth weight was 87.6%. Additionally, the rate of macrosomic births stood at 8.1% in the year 2016. A significant statistical rise in the macrosomy rate was noted in 2020 (p=0.033). (Table 2)

Table 2: Distribution of Low, Normal, and Macrosomic Births in 2016 and 2020 with Statistical Significance

Year	Low Birth Weight (%)	Normal Birth Weight (%)	Macrosomic Births (%)	Statistical Significance (p-value)
2016	3.7	91.4	4.8	-
2020	4.3	87.6	8.1	0.033

During the year 2016, there were a total of 687 births. Among these, 362 births (52.7%) were carried out through caesarean section, while 323 births (47.1%) followed the normal vaginal delivery route. In the year 2016, there were a total of 885 births. Among these, 484 births (54.6%) were delivered via caesarean section, while 401 births (45.2%) followed the normal vaginal delivery route. In the year 2016, no statistically significant distinction in birth weight was observed between infants delivered via cesarean section and those born through the vaginal delivery route (p=0.212). However, in 2020, newborns born through cesarean section exhibited a statistically significant increase in birth weight compared to infants delivered vaginally (p=0.014). (Table 3)

Table 3: Comparison of Cesarean Section and Vaginal Delivery Rates in 2016 and 2020

Year	Total Births	Cesarean Section (%)	Vaginal Delivery (%)	Statistical Significance (p-value)
2016	687	52.7	47.1	0.212
2020	885	54.6	45.2	0.014

It is worth noting that the influence of seasons on newborn weight did not yield statistically significant findings in both years (p>0.05). Our research employed an extensive multiple logistic regression analysis, revealing several independent predictors of macrosomia. These included maternal age (odds ratio [OR]=1.09; 95% confidence interval [CI], 1.05-1.14), gender (OR=1.95; 95%CI, 1.28-2.97; P=0.002), year (OR=1.62; 95%CI, 1.05-2.49; P=0.030), the 39th gestational week (OR=2.61; 95%CI, 1.18-5.76; P=0.018), and the 40th gestational week (OR=2.92; 95%CI, 1.29-6.58; P=0.010).

DISCUSSION

In research carried out within the past decade in North America, Europe, Australia, and China, a trend of rising birth weights among newborns was noted (5). In our publication, we determined that the mean birth weight of infants delivered in 2020 was greater in comparison to those born in 2016. Furthermore, it was observed that births in 2020 took place at a later gestational week compared to 2016. We believe that this disparity in birth weight could potentially be attributed to this difference in gestational timing. Nonetheless, it is imperative to underline that there were no statistically significant fluctuations observed in neonatal weights when comparing the years 2016 and 2020 within the same gestational week. However, it is noteworthy that our analysis does illuminate an upsurge in the prevalence of macrosomia rates.To conduct a comprehensive exploration of potential risk factors associated with macrosomia, we judiciously employed logistic regression analysis. The discerned results unequivocally pinpoint maternal age, newborn gender, and gestational age as formidable risk factors for macrosomia (6). Of particular significance is the prominence of gestational age, emerging as the predominant determinant influencing birth weight in term singleton infants, thus aligning harmoniously with the empirical findings of our present study. A parallel investigation conducted in China, spearheaded by Yi and colleagues, lent credence to these assertions (7). Their findings converged with our own, elucidating that maternal age, pregnancy-related weight gain, and gestational age are integral factors conferring a heightened risk for macrosomia. Additionally, an expanding body of scientific inquiry substantiates the ascending trajectory in macrosomia rates. Certain studies posit that this surge may be intricately associated with an augmentation in maternal body mass index (BMI). Moreover, it is worth emphasizing that infants born with higher birth weights often embark on a developmental trajectory characterized by an amplified body mass index (BMI) throughout their subsequent life stages. This developmental course is intricately linked to an increased susceptibility to specific categories of malignancies. It is imperative to acknowledge that this

research lacks comprehensive data concerning maternal weight gain during pregnancy and maternal body mass index (BMI) (8). Consequently, the full extent of the impact of these factors on macrosomia remains beyond the scope of our investigation. Our observations underscore a noteworthy gender-based disparity, with female participants exhibiting lower birth weights in contrast to their male counterparts (9). Additionally, there exists a discernible trend suggesting lower birthweights within both the youngest and oldest maternal age groups. It is a widely accepted convention that the optimal age range for childbirth typically falls between 20 and 34 years (10). However, it is pertinent to note that the preterm birth rate increases significantly for offspring born to mothers aged under 17, as well as for pregnancies occurring after the age of 40. Furthermore, a surge is observed in admissions to neonatal intensive care units and an elevated incidence of fetal abnormalities in pregnancies beyond the age of 40. Pertinently, our research findings resonate with existing literature, which suggests that the risk of perinatal mortality surges to 2.7 times greater in pregnancies occurring after the age of 40. Additionally, it has been reported that maternal age exceeding 35 years triples the risk of fetal macrosomia (11). Within the confines of our study, we deliberately opted to include mothers whose ages fell within the range of 18 to 40 years. Notably, our findings unveiled a marked distinction in maternal age between newborns with macrosomia and those with typical birth weights, with the former group being characterized by a tendency towards relatively higher maternal ages. It is noteworthy that a study conducted in Israel posited a hypothesis suggesting a potential connection between heightened sunlight exposure during the final weeks of pregnancy and an accompanying increase in birth weight. However, our study, in contrast to these findings, conveys a different perspective. Our analysis revealed that seasonal variations did not exert any discernible impact on birth weight. This conclusion was derived from an examination of the average birth weight of newborns delivered in 2016 and 2020 across different seasons. It is crucial to underscore that our study was conducted in a region located in central Anatolia, Turkey, where abundant sunlight prevails consistently throughout all seasons. This unique environmental factor may have contributed to the absence of observable seasonal effects on birth weight within our study. In a broader context, it is imperative to acknowledge that the present study is not immune to certain limitations, the primary one being the inherent challenges associated with accessing digital data from the period before 2016. The retrospective nature of our study inherently imposes inherent limitations. Regrettably, pertinent information concerning factors that could potentially exert an influence on newborn weight and the incidence of macrosomia remained inaccessible from the digital database registry. These factors encompassed crucial elements such as the mother's body mass index, pregnancy-related weight gain, maternal marital status, educational background, the frequency of pregnancy check-ups, employment status, as well as behavioral habits including smoking, alcohol consumption, and substance use. In light of these inherent constraints, our data analysis brought to the fore a significant and noteworthy trend when comparing the year 2020 to 2016. This discernible trend revealed a marked increase in both newborn weights and the prevalence of macrosomia in the year 2020. Moreover, our observations suggest that neonatal weight is affected by both maternal age and the gender of the newborn, while there is no apparent correlation between neonatal weight and the changing seasons. These discoveries emphasize the significance of taking maternal age, newborn gender, and gestational age into account as notable risk factors for the development of macrosomia. We anticipate that the data gathered during our study will make a valuable contribution to the field of antenatal care within gynecology and obstetrics clinics, as well as to the broader realm of public health.

Conflict of Interest: No conflict of interest was declared by the authors
Ethics: This research is approved by the Ethics Committee for Non-Interventional Research at Afyonkarahisar Health Sciences University Faculty of Medicine (Date: April 13, 2020, Decision Number: 196).
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REFERENCES

1. Lin J, Wang C, Li S, Zhang J, Jin L, Tong M, et al. Periconceptional Folic Acid Supplementation and Newborn Birth Weights. Front Pediatr. 2022;10:844404. doi: 10.3389/fped.2022.844404.
2. Flaherman VJ, Robinson A, Creasman J, McCulloch CE, Paul IM, Pletcher MJ. Clinical Decision Support for Newborn Weight Loss: A Randomized Controlled Trial. Hosp Pediatr. 2022;12(6):e180-e184. doi: 10.1542/hpeds.2021-006470.
3. Paredes-Díaz SE, Neglia-Cermeño CS, Vidal-Cabrera E del P, Lescano-Pereda LG, Meneses-La-Riva ME, Barrera MJ. Eating Habits, Nutritional Status in Pregnant Women and Weight of Newborns, La Libertad - Peru. Academic Journal of Interdisciplinary Studies. 2023;12:126-136.
4. Feng N, Huang XK. Effect of pre-pregnancy body mass index and gestational weight gain on perinatal outcomes. Int J Clin Exp Med. 2021;14:2180-2188.
5. Xu MY, Guo YJ, Zhang LJ, Lu QB. Effect of individualized weight management intervention on excessive gestational weight gain and perinatal outcomes: a randomized controlled trial. PeerJ. 2022;10:e13067. doi: 10.7717/peerj.13067.
6. Hasan SMT, Khan MA, Ahmed T. Institute of Medicine Recommendations on the Rate of Gestational Weight Gain and Perinatal Outcomes in Rural Bangladesh. Int J Environ Res Public Health. 2021;18(12):6519. doi: 10.3390/ijerph18126519.
7. Chen CN, Chen HS, Hsu HC. Maternal Prepregnancy Body Mass Index, Gestational Weight Gain, and Risk of Adverse Perinatal Outcomes in Taiwan: A Population-Based Birth Cohort Study. Int J Environ Res Public Health. 2020;17(4):1221. doi: 10.3390/ijerph17041221.
8. Shay LA, Sangi-Haghpeykar H, Aagaard KM, Mastrobattista J. 682 Everything in moderation: impact of extremes of BMI & gestational weight gain on perinatal outcomes. Am J Obstet Gynecol. 2021;224:Suplement428.
9. Gonzalez-Ballano I, Saviron-Cornudella R, Esteban LM, Sanz G, Castán S. Pregestational body mass index, trimester-specific weight gain and total gestational weight gain: how do they influence perinatal outcomes?. J Matern Fetal Neonatal Med. 2021;34:1207-1214. doi:10.1080/14767058.2019.1628942
10. Koech WA, Lilly CL. Association of county perinatal resources and gestational weight gain in West Virginia, United States. BMC Pregnancy Childbirth. 2019;19:497. doi:10.1186/s12884-019-2650-7
11. Senbanjo OC, Akinlusi FM, Ottun TA. Early pregnancy body mass index, gestational weight gain and perinatal outcome in an obstetric population in Lagos, Nigeria. Pan Afr Med J. 2021;39:136. doi:10.11604/pamj.2021.39.136.25926

ORIGINAL ARTICLE

An Anatomy of a Fear: Clinical Outcomes of Measles-Mumps-Rubella Vaccination in Children with Egg Allergy

Bir Korkunun Anatomisi: Yumurta Alerjisi Olan Çocuklarda Kızamık-Kabakulak-Kızamıkçık Aşılamasının Klinik Sonuçları

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ABSTRACT

Objective: *This study aimed to evaluate the frequency and clinical characteristics of allergic reactions following Measles-Mumps-Rubella (MMR) vaccination in children with egg allergy. Our aim in selecting the MMR vaccine was to better understand vaccine-related allergic reactions in children with egg allergy and to assess its reliability.*

Material and Method: *A retrospective analysis was conducted on 202 patients diagnosed with egg allergy who received the MMR vaccine in our clinic between 2023 and 2024. Demographic, clinical, and laboratory data were reviewed. Patients' age, sex, concomitant allergic diseases, total IgE, specific IgE for milk, egg, and nuts, skin prick tests, and post-vaccination reactions were recorded.*

Results: *The median age of the patients was 12 months (range: 7-84 months), and 57.4% were male. Sensitization to cow's milk was detected in 29.2% of the patients, while 6.9% had nut allergen sensitivity. The most common clinical conditions were urticaria (43.1%) and atopic dermatitis (36.6%). Following vaccination, only four patients (2%) developed localized rash, and none had a history of anaphylaxis.*

Conclusion: *No severe systemic reactions were observed following MMR vaccination in children with egg allergy. Our findings support current guidelines, suggesting that MMR vaccination can be safely administered under standard conditions in children with egg allergy. In our study, 29.2% of patients with egg allergy had cow's milk allergy, and 6.9% had nut allergy, suggesting that food allergies are often seen together in childhood. Additionally, it is emphasized that the India-made MMR vaccines used in Turkey contain milk proteins, which may increase the risk of anaphylaxis in individuals with milk and egg allergies, highlighting the need for careful evaluation of the vaccine prospectus before vaccination in these children.*

Keywords: *Egg allergy, Measles-Mumps-Rubella vaccine, Allergic reaction, Anaphylaxis, Cow's milk allergy*

ÖZET

Amaç: *Bu çalışma, kızamık-kabakulak-kızamıkçık (KKK) aşısı sonrası yumurta alerjisi olan çocuklarda alerjik reaksiyonların sıklığını ve klinik özelliklerini değerlendirmeyi amaçlamaktadır. KKK aşısını seçme amacımız, özellikle yumurta alerjisi olan çocuklarda aşıya bağlı alerjik reaksiyonların daha iyi anlaşılması ve güvenilirliğinin değerlendirilmesidir.*

Gereç ve Yöntem: *2023-2024 yılları arasında kliniğimizde KKK aşısı yapılan ve yumurta alerjisi tanısı almış 202 hasta üzerinde retrospektif bir analiz gerçekleştirildi. Hastaların demografik, klinik ve laboratuvar verileri incelendi. Yaş, cinsiyet, eşlik eden alerjik hastalıklar, total IgE, süt, yumurta ve kuruyemişlere özgü IgE düzeyleri, deri prick testleri ve aşılama sonrası reaksiyonlar kaydedildi.*

Bulgular: *Hastaların medyan yaşı 12 ay (dağılım: 7-84 ay) olup, %57,4'ü erkekti. Hastaların %29,2'sinde inek sütü duyarlılığı, %6,9'unda ise kuruyemiş alerjeni duyarlılığı saptandı. En sık görülen klinik durumlar ürtiker (%43,1) ve atopik dermatit (%36,6) idi. Aşılama sonrasında yalnızca dört hastada (%2) lokal döküntü gelişti ve hiçbir hastada anafilaksi öyküsü bulunmadı.*

Sonuç: *Yumurta alerjisi olan çocuklarda KKK aşısı sonrası ciddi sistemik reaksiyon gözlenmedi. Bulgularımız, mevcut kılavuzları desteklemekte olup, yumurta alerjisi olan çocuklarda KKK aşısının standart koşullar altında güvenle uygulanabileceğini göstermektedir. Çalışmamızda, yumurta alerjisi olan hastaların %29,2'sinde inek sütü alerjisi, %6,9'unda kuruyemiş alerjisi görülmesi çocukluk çağında gıda alerjilerinin sıklıkla bir arada görüldüğünü düşündürmektedir. Ayrıca Türkiye'de kullanılan Hindistan menşeili KKK aşılarının süt proteinleri içerdiği ve bu durumun süt ve yumurta alerjisi olan bireylerde anafilaksi riskini artırabileceği, bu çocuklar aşılanmadan önce aşı prospektüslerinin titizlikle değerlendirilmesi gerektiği vurgulanmaktadır.*

Anahtar Kelimeler: *Yumurta alerjisi, Kızamık-Kabakulak-Kızamıkçık aşısı, Alerjik reaksiyon, Anafilaksi, İnek sütü alerjisi*

INTRODUCTION

Food allergies can be classified as IgE-mediated (urticaria, angioedema, anaphylaxis), non-IgE-mediated (food protein-induced enterocolitis, food protein-induced proctocolitis), and mixed-type (eosinophilic esophagitis, atopic dermatitis). IgE-mediated reactions typically have an acute onset and primarily affect the skin, gastrointestinal system, and respiratory system. In contrast, non-IgE-mediated food allergies manifest

as vomiting, abdominal pain, bloody stools, failure to thrive, and diarrhea (1,2). Over the years, the prevalence of food allergies has increased worldwide, with rates ranging from 1% to 10% in children globally, and approximately 8% in Western societies (3,4).

Egg allergy is one of the most common food allergies in childhood and can significantly impact the quality of life from an early age. Its prevalence ranges between 0.5% and 2.5% (5). In adults, it tends to decrease, with an estimated prevalence of around 0.1% (6). Egg allergy can cause symptoms such as urticaria, atopic dermatitis, cough, wheezing, vomiting, diarrhea, and even anaphylaxis (7). While most reactions are IgE-mediated, non-IgE and mixed-type reactions can also occur. The diagnosis of egg allergy is based on clinical history, skin prick tests, specific IgE tests, and oral food challenge tests (8). The allergic reaction is mediated by specific IgE antibodies against ovalbumin (Gal d 2) and/or ovomucoid (Gal d 1) found in egg white (9).

Vaccines such as measles-mumps-rubella (MMR), influenza, and yellow fever, which are produced using egg embryos, may contain trace amounts of egg protein. The MMR vaccine is produced in fibroblast cultures derived from chicken embryos and contains minimal amounts of egg protein (0.5–1 nanogram of ovalbumin per 0.5 mL dose) (10,11). However, several studies suggest that allergic reactions associated with these vaccines are primarily due to gelatin and neomycin rather than egg protein (12,13). Additionally, some vaccine brands may include milk protein in their manufacturing process, which necessitates careful evaluation of vaccine content in children with milk allergies.

The most recent guidelines from the European Academy of Allergy and Clinical Immunology (EAACI) state that MMR vaccines can be safely administered under standard conditions to children with egg allergy (14). Nevertheless, there are case reports of anaphylaxis occurring after MMR vaccination in egg-allergic patients (15). A study by Altaş et al. suggested that children with severe egg allergy may be evaluated in pediatric allergy clinics, but this should not lead to delays in the MMR vaccination schedule (16).

Given the conflicting findings in the literature regarding MMR vaccination in egg-allergic children, we aimed to present our clinical experience in this area. Our study seeks to provide a detailed analysis of allergic reactions and clinical features following MMR vaccination in children with egg allergy, thereby contributing to the existing body of knowledge.

MATERIALS AND METHODS

The study included a total of 202 patients aged 0-7 years who were diagnosed with egg allergy and received the MMR vaccine at our clinic between January 1, 2023, and December 31, 2024. Patients with primary or secondary immunodeficiency, those vaccinated during an acute infection, those receiving systemic steroids or immunosuppressive treatment, and those whose families did not provide consent for participation were excluded.

The demographic, clinical, and laboratory data of the retrospectively analyzed patients were evaluated. The parameters examined included age, sex, age at diagnosis, comorbid allergic diseases, and reactions following the MMR vaccine (Priorix, GlaxoSmithKline, Belgium). Laboratory assessments included eosinophil count and percentage, total IgE levels, and sensitization to milk, egg, and nut allergens (specific IgE levels and skin prick test results). Eosinophil counts were obtained from complete blood count parameters, while total IgE levels were measured using a nephelometric method with a Siemens Healthcare Diagnostics Products device (Marburg, Germany). Specific IgE levels were analyzed using the ImmunoCAP system (UniCAP; Uppsala, Sweden), with values ≥0.35 kIU/L considered positive. In the skin prick test, results were deemed positive if there was no wheal formation or dermographism in the negative control, and an induration of ≥3 mm was present (17,18). Patients with positive skin prick test and/or specific IgE results underwent oral egg provocation testing, and those with a positive result were considered to have egg allergy.

Ethics

This study was approved by the Ethics Committee of the University of Health Sciences Ümraniye Training and Research Hospital (Date: 12.12.2024, decision no: 419). The study was conducted in accordance with the principles of the Helsinki Declaration.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows 25.0. Normal distribution was assessed using visual (graphs) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests). Descriptive results were presented as medians, minimum and maximum values, numbers (n), and percentages (%). In all analyses, a statistical significance level of $p < 0.05$ was considered.

Table 1: Patients' Age, Gender, and Additional Food Allergy Data

Age (months), median (min-max)		12.0 (7.0-84.0)
		n (%)
Gender	Female	86 (42.6)
	Male	116 (57.4)
Milk allergen sensitivity		59 (29.2)
Nut allergen sensitivity		14 (6.9)

RESULTS

A total of 202 patients with egg allergen sensitivity were evaluated. The median age was 12.0 months (7.0–84.0). Of the patients, 57.4% (n=116) were male. Sensitization to milk allergens was observed in 29.2% (n=59) of the patients, while

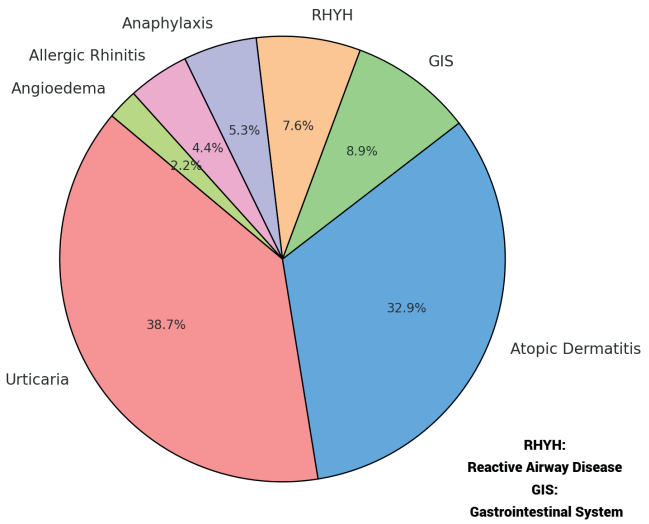

Figure 1: Distribution of Patients' Clinical Characteristics

Table 2: Patients' Laboratory Values

	Median	Minimum	Maximum
Absolute Eosinophil Count (cells/mm³)	380..0	0.0	3320.0
Eosinophil Percentage (%)	3.70	0.30	23.50
Total IgE (IU/mL)	58	0	5657
Specific IgE – Egg (kIU/L)	4.23	0.35	100.00
Specific IgE – Milk (kIU/L)	1.14	0.41	100.00
Skin Prick Test - Egg	5	3	11
Skin Prick Test - Milk	6	3	7

Table 3: Characteristics of Patients with Post-Vaccination Reactions

	Gender	Age (Month)	Reaction	History of Anaphylaxis	Eosinophil (cells/mm³)	Eosinophil (%)	Total IgE (IU/mL)	Egg spesific IgE (kIU/L)
1st Patient	Male	13.0	Local-Rash	No	260.0	2.80	2	0.85
2nd Patient	Female	12.0	Local-Rash	No	-	-	-	-
3rd Patient	Male	12.0	Local-Rash	No	390.0	4.20	87	0.81
4th Patient	Female	9.0	Local-Rash	No	650.0	7.70	151	0.40

6.9% (n=14) had nut allergen sensitivity (Table 1).

When assessing clinical conditions associated with egg allergy, 43.1% of patients had urticaria, and 36.6% had a history of atopic dermatitis. Angioedema was observed in five patients, and anaphylaxis occurred in twelve patients. Additionally, ten patients had concomitant allergic rhinitis (Figure 1).

The median absolute eosinophil count was 380.0 cells/mm³ (0–3320.0), and total IgE levels had a median of 58.0 IU/mL (0–5657.0). The median specific IgE level for egg was 4.23 kIU/L (0.35–100.0) (Table 2).

Following vaccination, reactions were observed in four patients, all of whom experienced localized rash. In two patients, the rash appeared 30 minutes after injection, in one patient after 15 minutes, and in another after 1 hour. None of the patients who developed post-vaccination reactions had a prior history of anaphylaxis (Table 3).

DISCUSSION

In Turkey, the national vaccination schedule recommends the administration of the Measles, Mumps, and Rubella (MMR) vaccine at 12 months of age. However, due to the presence of migrant children, this vaccine may also be administered at 9 months in certain cases. Some physicians exhibit hesitation in vaccinating children with egg allergy, leading to referrals to pediatric allergy centers for vaccine administration (19).

In our study, 202 patients with egg allergen sensitivity were evaluated. The median age was 12.0 months, and 57.4% (n=116) of the patients were male. Similarly, another study examined 130 patients and reported that 55.3% (n=72) were male, with a mean age of 13.7 months (20). The relatively high number of patients in our study enhances the reliability of statistical analyses. In both studies, the proportion of male patients was higher, aligning with literature findings that allergic diseases are more prevalent in male children. The fact that patients were vaccinated around 12 months of age indicates a high level of vaccine awareness in our clinic and appropriate guidance for families. This finding suggests adherence to the vaccination schedule in allergic children, without significant delays. In our clinic, families receive regular information to ensure timely vaccination at 12 months.

In our study, 29.2% (n=59) of the patients had concomitant cow's milk allergen sensitivity, while 6.9% (n=14) had nut allergen sensitivity. In the study by Keleş et al., 41.3% (n=33) of the patients had cow's milk allergy in addition to egg allergy, and 18.8% (n=15) had food allergies other than cow's milk. The most common concomitant allergies with egg allergy were milk, wheat, and nuts (19). Food allergies frequently coexist in childhood, and the immunological mechanisms in polyallergic individuals are believed to be more complex. Egg and milk proteins commonly cause allergies together due to their structural and immunological characteristics. The prevalence of cow's milk allergy was higher in the study by Keleş et al. (41.3%) compared to our study. This discrepancy may be attributed to variations in sample size, diagnostic methods, and regional differences in patient populations. The prevalence of allergens such as wheat and nuts is influenced by regional dietary habits and genetic predisposition. The frequency of food allergies varies across populations, which may account for differences in study results. Additionally, some series of measles and MMR vaccines used in Turkey may contain milk proteins, posing a risk of anaphylaxis in individuals allergic to cow's milk and egg. There is evidence suggesting that certain vaccines, such as the India-originated Tresivac, may cause severe reactions in patients with such allergies. Therefore, the composition and production conditions of each vaccine should be thoroughly examined, and package inserts should be carefully reviewed when vaccinating children with food allergies.

When evaluating comorbidities, 38.7% of our patients had urticaria, 32.9% had atopic dermatitis (AD), 7.6% had reversible airway disease, 8.9% had GIS, 4.4% had allergic rhinitis, and 5.3% had a history of anaphylaxis. The higher number of Reversible airway disease and GIS cases compared to anaphylaxis or rhinitis suggests a possible link to the patients' clinical profiles and the diversity of pathophysiological mechanisms in allergic reactions. In another study, it was reported that 79% (n=49) of egg-allergic patients had a history of atopic dermatitis, 12% (n=8) had urticaria, and 3.2% (n=2) had a history of anaphylaxis. These differences may be attributed to variability in patient populations, diagnostic criteria, and environmental factors.

However, to enhance the accuracy and generalizability of these results, further advanced studies with larger sample sizes and different populations are needed.

In our study, the median absolute eosinophil count was 380.0 cells/mm³ (0-3320.0), total IgE was 58.0 IU/mL (0-5657.0), and egg white-specific IgE median was 4.23 kIU/L (0.35-100.0). In Sayar's study, the mean egg white-specific IgE was 3.18 ± 6.3 kIU/L, while the mean total IgE and eosinophil count were 54.3 ± 78.1 IU/mL and 370.6 ± 218 cells/mm³, respectively (22). The eosinophil count, total IgE, and egg white-specific IgE levels observed in our study are comparable to those reported by Sayar et al. However, our study reported a higher median egg white-specific IgE level (4.23 kU/L). This difference may be due to variations in the severity of allergy, age distribution of patient groups, and methodological differences between studies. Larger sample-sized studies are essential for a detailed evaluation of the clinical correlations of these parameters.

Among the 202 patients we followed, four experienced post-vaccination reactions, all of which were localized rashes. In two patients, the rash appeared 30 minutes after injection, in one patient after 15 minutes, and in another after 1 hour. None of the patients who developed post-vaccination reactions had a prior history of anaphylaxis. In the study by Özdemir et al., macular rash was observed in only 1 (2.9%) of 36 vaccine doses administered to 18 patients (23). Similarly, in the study by Altaş et al., urticaria developed in only 1 out of 179 vaccinated patients, with no other adverse reactions observed (16). The fact that only four patients (1.98%) in our study developed localized rashes post-MMR vaccination, consistent with other studies, supports the overall safety of the vaccine in children with egg allergy. Additionally, the mild nature of the reactions and the absence of anaphylaxis in any patient indicate that the vaccine does not cause severe allergic side effects.

Our findings align with existing literature and confirm that the MMR vaccine is largely safe for patients with egg allergy. However, some MMR vaccines have been reported to contain trace amounts of milk protein. Although larger sample-sized and long-term follow-up studies are needed, the current data suggest that vaccination in allergic children is generally safe. Nonetheless, the composition of vaccines should be carefully reviewed, particularly in patients with milk allergy, and clinical observation should be recommended for potential reactions.

Limitations and Strengths: As a retrospective study, data deficiencies may be present. Since the evaluation of allergic reactions is based on patient records, mild reactions may have been underreported. The generalizability of the results is limited as the study was conducted at a single center. Additionally, due to the lack of long-term follow-up after vaccination, delayed reactions could not be assessed. Among the strengths of the study is the relatively large patient population.

Conflict of Interest: No conflict of interest was declared by the authors

Ethics: The Ethics Committee of the University of Health Sciences, Ümraniye Training and Research Hospital, approved the study (date: 12.12.2024, decision no: 419).

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REFERENCES

1. Burks AW, Tang M, Sicherer S, Wood R, Assa'ad A, Jones SM, et al. ICON: food allergy. J Allergy Clin Immunol. 2012;129(4):906-920.
2. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy. 2014;69(8):1008-1025.
3. Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunol. 2014;133(2):291-307.
4. Chafen JJS, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ, et al. Diagnosing and managing common food allergies: a systematic review. JAMA. 2010;303(18):1848-1856.
5. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. J Allergy Clin Immunol. 2007;120(3):638-646.
6. Tedner SG, Asarnoj A, Thulin H, Westman M, Konradsen JR, Nilsson C. Food allergy and hypersensitivity reactions in children and adults: A review. J Intern Med. 2022;291(3):283-302.
7. Magistà S, Albanesi M, Chaoul N, Di Bona D, Di Leo E, Nettis E, et al. Safety of measles, mumps, and rubella vaccine in egg allergy: in vivo and in vitro management. Clin Mol Allergy. 2020;18:1-5.
8. Urisu A, Kondo Y, Tsuge I. Hen's egg allergy. Chem Immunol Allergy. 2015;101:124-130.
9. Leech SC, Ewan PW, Skypala IJ, Brathwaite N, Erlewyn-Lajeunesse M, Heath S, et al. BSACI 2021 guideline for the management of egg allergy. Clin Exp Allergy. 2021;51(9):1262-1278.
10. Dreskin SC, Halsey NA, Kelso JM, Wood RA, Hummell DS, Edwards KM, et al. International Consensus (ICON): allergic reactions to vaccines. World Allergy Organ J. 2016;9:32.
11. Cerecedo Carballo I, Dieguez Pastor MC, Bartolomé Zavala B, Sánchez Cano M, de la Hoz Caballer B. Safety of measles-mumps-rubella vaccine (MMR) in patients allergic to eggs. Allergol Immunopathol (Madr). 2007;35(3):105-109.
12. Dumortier B, Nosbaum A, Ponvert C, Nicolas JF, Bérard F. Measles-mumps-rubella vaccination of an egg-allergic child sensitized to gelatin. Arch Pediatr. 2013;20(8):867-870.
13. Freitas DR, Moura E, Araújo G, Soárez PC, Fernandes EG, Monteiro AM, et al. Investigation of an outbreak of hypersensitivity-type reactions during the 2004 national measles-mumps-rubella vaccination campaign in Brazil. Vaccine. 2013;31(6):950-954.
14. Nilsson L, Brockow K, Alm J, Cardona V, Caubet JC, Gomes E, et al. Vaccination and allergy: EAACI position paper, practical aspects. Pediatr Allergy Immunol. 2017;28(7):628-640.
15. Yavuz ST, Şahiner UM, Sekerel BE, Tuncer A, Kalaycı O, Sackesen C. Anaphylactic reactions to measles-mumps-rubella vaccine in three children with allergies to hen's egg and cow's milk. Acta Paediatr. 2011;100(6):e94-e96.
16. Altaş U, Çetemen A, Altaş ZM, Akkelle E, Özkars MY, Doğru M. Experience of measles-mumps-rubella vaccine among children with egg allergy: Measles-mumps-rubella vaccine and egg allergy. The Injector. 2023;2(3):157-162.
17. Çiçek F, Köle MT. Evaluation of the impact of serum vitamin D levels on the Scoring Atopic Dermatitis Index in pediatric atopic dermatitis. Children. 2023;10(10):1522.
18. Buczyńska A, Grzybowska-Chlebowczyk U, Pawlicki K. IgE-dependent food sensitisation and its role in clinical and laboratory presentation of pediatric inflammatory bowel disease. Nutrients. 2023;15(8):1804.
19. Keleş Ş, Filiz S. Evaluation of reaction status following measles-mumps-rubella vaccination in children with egg allergy. Pamukkale Med J. 2020;13(3):687-693.
20. Ayçin GD. Prick test results and vaccine reactions before measles-mumps-rubella vaccination in children with egg allergy. Osmangazi Med J. 2020;42(4):378-383.
21. Çöğürlü MT, Simsek IE. How necessary is skin testing before measles-mumps-rubella vaccination in children with egg allergy? How safe is the vaccine? Kocaeli Med J. 2019;8(1):220-225.
22. Sayar EH. Experience of measles-mumps-rubella vaccination in infants with egg allergy. Acta Med Alanya. 2019;3(3):283-286.
23. Özdemir Ö, Ersavaş D. Measles, measles-mumps-rubella (MMR), and varicella vaccinations in children with egg allergy. J Acad Res Med. 2017;7(2):42-45.

ORIGINAL ARTICLE

Relationship Between TMPRSS6 Polymorphisms and Serum Iron Status in the Treatment of Iron Deficiency Anemia in Subclinical Hypothyroidism: A Pilot Study

Subklinik Hipotiroidizmde Demir Eksikliği Anemisinin Tedavisinde TMPRSS6 Polimorfizmleri ile Serum Demir Durumu Arasındaki İlişki: Pilot Çalışma

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ABSTRACT

Objective: *This study aims to investigate the impact of three SNPs (rs4820268, rs2235321, rs855791) in the TMPRSS6 gene on iron metabolism in patients with subclinical hypothyroidism and iron deficiency anemia (IDA), as well as to evaluate the effects of iron-only and iron-thyroxine combination treatments on individuals with heterozygous and mutant genotypes.*

Material and Method: *Ninety-five patients with subclinical hypothyroidism and IDA, alongside 30 healthy controls, participated in the study. Participants were grouped as follows: Control (N=30), Hypothyroidism (N=30), Hypothyroidism IDA (N=30), and Hypothyroidism IDA+Thyroxine (N=35). TMPRSS6 rs4820268 and rs855791 polymorphisms were analyzed using TaqMan SNP Genotyping Assays and qPCR, while rs2235321 was genotyped using Allele-Specific PCR (ASPCR). Complete blood count, iron levels, and total iron-binding capacity (TIBC) were measured with an automated analyzer, while ferritin levels were analyzed using immunoassay.*

Results: *No significant differences were found in the genotype and allele distributions of TMPRSS6 polymorphisms (rs4820268, rs2235321, rs855791) between patients and controls. For rs4820268 and rs855791 heterozygous and mutant genotypes, ferritin levels were lower in the Hypothyroidism and Hypothyroidism IDA groups compared to controls, while TIBC was higher in the Hypothyroidism group. Ferritin was elevated and TIBC decreased in the Hypothyroidism IDA+Thyroxine group compared to Hypothyroidism and Hypothyroidism IDA groups. In terms of the rs2235321 polymorphism, iron and ferritin levels were higher in the Hypothyroidism+IDA+Thyroxine group than in the other hypothyroidism groups, but TIBC was lower.*

Conclusion: *No significant variation was observed in the genotype and allele frequencies of TMPRSS6 polymorphisms between healthy individuals and those with hypothyroidism. Nevertheless, considering the relationship between hypothyroidism, iron metabolism, and treatment response, particularly in patients receiving combined therapy, treatment-related changes in TIBC and ferritin levels were observed.*

Keywords: *Subclinical Hypothyroidism, Iron Deficiency Anemia, TMPRSS6 Gene, SNP.*

ÖZET

Amaç: *Bu çalışma, TMPRSS6 genindeki üç tek nükleotid polimorfizminin (SNP) (rs4820268, rs2235321, rs855791) subklinik hipotiroidizm ve demir eksikliği anemisi (DEA) olan hastalarda demir metabolizması üzerindeki etkilerini incelemeyi ve heterozigot ve mutant genotiplere sahip bireylerde yalnızca demir ve demir-tiroksin kombinasyon tedavilerinin etkilerini değerlendirmeyi amaçlamaktadır.*

Gereç ve Yöntem: *Çalışmaya subklinik hipotiroidizm ve DEA tanılı 95 hasta ile 30 sağlıklı kontrol dahil edilmiştir. Katılımcılar şu gruplara ayrılmıştır: Kontrol (N=30), Hipotiroidizm (N=30), Hipotiroidizm+DEA (N=30) ve Hipotiroidizm+DEA+Tiroksin (N=35). TMPRSS6 rs4820268 ve rs855791 polimorfizmleri TaqMan SNP Genotipleme Analizleri ve qPCR ile, rs2235321 polimorfizmi ise Alel-Spesifik PCR (ASPCR) yöntemi ile genotiplendirilmiştir. Tam kan sayımı, demir seviyeleri ve total demir bağlama kapasitesi (TDBK) otomatik analizör ile ölçülürken, ferritin seviyeleri immünoassay yöntemi ile analiz edilmiştir.*

Bulgular: *TMPRSS6 polimorfizmlerinin (rs4820268, rs2235321, rs855791) genotip ve alel dağılımlarında hasta ve kontrol grupları arasında anlamlı bir fark saptanmamıştır. Rs4820268 ve rs855791 heterozigot ve mutant genotipleri açısından incelendiğinde, Hipotiroidizm ve Hipotiroidizm+DEA gruplarında ferritin seviyeleri kontrol grubuna göre daha düşük, TDBK ise Hipotiroidizm grubunda daha yüksek bulunmuştur. Hipotiroidizm+DEA+Tiroksin grubunda ise ferritin seviyeleri artarken, TDBK düşmüştür. rs2235321 polimorfizmi açısından, Hipotiroidizm+DEA+Tiroksin grubunda demir ve ferritin seviyeleri diğer hipotiroidi gruplarına göre daha yüksekti, ancak TDBK daha düşüktü.*

Sonuç: *TMPRSS6 polimorfizmlerinin genotip ve alel frekanslarında sağlıklı bireyler ile hipotiroidi hastaları arasında anlamlı bir farklılık gözlenmemiştir. Bununla birlikte, hipotiroidizm, demir metabolizması ve tedavi yanıtı arasındaki ilişki dikkate alındığında, özellikle kombine tedavi alan hastalarda TDBK ve ferritin seviyelerinde tedaviye bağlı değişiklikler gözlemlenmiştir.*

Anahtar Kelimeler: *Subklinik Hipotiroidizm, Demir Eksikliği Anemisi, TMPRSS6 Geni, SNP*

INTRODUCTION

Thyroid hormones play a crucial role in normal development, metabolic balance, and the physiological functions of body tissues. Among hormonal disorders, hypothyroidism, characterized by insufficient secretion of thyroid hormones, represents the largest category. Subclinical hypothyroidism is a thyroid disorder in which thyroid-stimulating hormone (TSH) levels are elevated above normal, while free thyroid hormone levels remain within the normal range in the blood (1-3).

Subclinical hypothyroidism, a common clinical issue, has a prevalence of 4–10% in the general population and exceeds 20% in women over 60 years of age (4). In addition, the evaluation and therapy of subclinical thyroid dysfunction is a controversial issue, and there are different practices in the therapy of patients with TSH values of 4.5-10 mIU/liter in consensus panels conducted in different years (2,5,6).

The prevalence of anemia is high in individuals with hypothyroidism. Therefore, it is crucial to identify the points where iron metabolism intersects with thyroid hormone action and signaling pathways. Several factors are involved in iron metabolism, and several rare genetic markers with a significant impact on this process have been identified. Genome-wide association studies have pinpointed several single nucleotide polymorphisms (SNPs) that contribute to erythropoiesis and have a lesser impact on iron metabolism (7-9). Research has suggested that SNPs in the transferrin (TF), human hemochromatosis (HFE), transferrin receptor 2 (TFR2), and transmembrane protease, serine 6 (TMPRSS6) genes are genetic risk factors influencing iron homeostasis. Matriptase-2, encoded by the TMPRSS6 gene, is a serine protease that inhibits hepcidin expression by cleaving membrane-bound hemojuvelin (10).

Hepcidin is a key regulator of human iron homeostasis, controlling both dietary iron absorption and iron release by macrophages (11). Several studies have identified multiple TMPRSS6 SNPs that are associated with iron-refractory iron deficiency anemia (IRIDA) and iron deficiency anemia (IDA), as well as low iron and blood indices. These SNPs were classified into synonymous, missense, intron, 5'-UTR, and intergenic variants. The most frequently reported TMPRSS6 SNPs, rs855791 and rs4820268, have been linked to poor iron status biomarkers and low blood indices. Other TMPRSS6 SNPs, such as rs2235321, rs2235324, rs5756504, rs5756506, and rs1421312, were also associated with iron deficiency biomarkers (12-18). Most of the studies on TMPRSS6 SNPs affecting biochemical parameters have been conducted in Caucasian populations, with fewer studies in Asian populations (13-17). Several studies have found specific SNPs in TMPRSS6 to be associated with iron and hematological parameters (8,19,20). Batar et al. suggested in their study that variations in TMPRSS6 may not be a risk factor for IDA. However, they found that TMPRSS6 polymorphisms were associated with increases in various iron-related hematological parameters (21). Our study aims to explore the impact of three SNPs (rs4820268, rs2235321, and rs855791) within the TMPRSS6 gene on patients with subclinical hypothyroidism. Additionally, we seek to assess how iron-only and combined iron and thyroxine treatments influence iron metabolism in individuals with heterozygous and mutant genotypes.

MATERIALS AND METHODS

Case selection

The study included 95 patients diagnosed with newly identified IDA and subclinical hypothyroidism, referred to the Internal Medicine outpatient clinic at Sakarya University Training and Research Hospital, along with 30 healthy individuals. Participants were divided into four groups based on complete blood count, iron levels, iron-binding capacity, ferritin, TSH, and free thyroxine (fT4) values: a Control group (N=30), a Hypothyroidism group of untreated subclinical hypothyroid patients (N=30), a Hypothyroidism IDA group of subclinical hypothyroid patients with IDA receiving iron treatment (80 mg ferrous sulfate) (N=30), and a Hypothyroidism IDA + Thyroxine group of subclinical hypothyroid patients with IDA receiving both iron and thyroxine treatment (80 mg ferrous sulfate and 25 µg levothyroxine) (N=35). All participants gave informed consent, and the study protocol was approved by the Ethics Committee of Sakarya University Medical Faculty (29.09.2016-E.12812).

Sample collection

Blood samples were collected after an overnight fast, using tubes containing ethylenediaminetetra-acetic acid (EDTA) and tubes without anticoagulants (Vacuette®, Z Trace Elements Serum Clot Activator; Greiner Bio-One GmbH, Austria). Whole blood in tubes without anticoagulants was allowed to clot and then centrifuged at 1500×g for 10 minutes to separate the serum. The samples were stored at -20 °C until further biochemical analysis. Complete blood count was performed using the Abbott Diagnostics Cell Dyn 3700 hematology analyzer (Abbott Diagnostics, IL, USA). Iron levels and total iron-binding capacity (TIBC) were measured using the Abbott Architect C16000 autoanalyzer (Abbott Diagnostics, IL, USA). TSH, fT4, and ferritin were analyzed using the Abbott ARCHITECT i2000SR immunoassay analyzer (Abbott Diagnostics, IL, USA).

DNA isolation and TMPRSS6 polymorphisms analysis

Genomic DNA was isolated from peripheral blood using a DNA extraction kit (Jena Bioscience GmbH, Jena, Germany) according to the manufacturer's instructions. The concentration and purity of the DNA samples were determined using a NanoDrop spectrophotometer, which measured the 260/280 nm optical density ratio. TaqMan® SNP Genotyping Assays (Applied Biosystems, Life Technologies, USA) and qPCR ProbesMaster (Jena Bioscience, Germany) were used to investigate the polymorphisms of rs4820268 and rs855791 related to the TMPRSS6 gene, as indicated in Table 1. According to the qPCR ProbesMaster protocol, each reaction was prepared as follows: 10 µL of qPCR Probes Master, 1 µL of PrimerProbMix, 7 µL of PCR-grade water, and 2 µL

Table 1: Context sequences of the investigated TMPRSS6 polymorphisms (rs4820268 and rs855791)

SNP ID	Context sequence [VIC/FAM]	
rs855791	GCGTGGCGTCACCTGGTAGCGATAG CCTCGCTGCACAGGTCCTGTGGGAT	[A/G]
rs4820268	CCTACCTTCCTGGCACTGCTCTTC TCGCTGCCGTTGAGACAATCAGGCT	[A/G]

Table 2: TMPRSS6 (rs2235321) genetic PCR mixture (final volume 25 µl)

	Stock solution in molarity	Working solution of molarity	Final molarity
PCR Buffer	10X	—	1X
Primers C, A, Common	100 µM	10 µM	0.4 µM
dNTPs	100 mM	2 mM	0.2 mM
Taq Polymerase	5U/µM	—	1 U
DNA	—	—	~50ng

Table 3: Bands formed after electrophoresis of TMPRSS6 (rs2235321) gene

Amplification PCR Product	Normal homozygous (GG)		Heterozygous (AG)		Mutant homozygous (AA)	
	C tube	A tube	C tube	A tube	C tube	A tube
TMPRSS6 (rs2235321) (122 bp)	—		—	—		—

of DNA on ice. PCR amplification was performed using a Bio-Rad CFX device (Bio-Rad Laboratories, Irvine, CA, USA) with Bio-Rad CFX Manager Software. Amplification was performed on a Bio-Rad CFX device with an initial denaturation at 95°C for 2 minutes, followed by 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. SNP genotypes were determined from fluorescence data using allelic discrimination plots and amplification curves.

Genotyping of the TMPRSS6 (rs2235321) polymorphism was conducted using Allele-Specific PCR (ASPCR), a sensitive and specific method for detecting single nucleotide changes. This technique relies on primers binding to the mutation site, with amplification occurring only if the mutation is present. PCR mixture information of rs2235321 is shown in Table 2. The primers used were: Common primer: 5'-ATCCTTTCTCCCTCCTCTCT-3', Primer C (normal allele): 5'-AGCGAGGTCTATCGCTTT-3', Primer A (mutant allele): 5'-AGCGAGGTCTATCGCTTC-3'. Each sample was tested in two PCR tubes: one with Primer C and the common primer, and the other with Primer A and the common primer. Genotypes were determined as follows: GG (normal homozygous): Amplification in C tube only, AA (mutant homozygous): Amplification in A tube only, AG (heterozygous): Amplification in both tubes. PCR conditions included an initial denaturation at 95°C for 5 minutes, followed by 45 cycles of 95°C for 30 seconds, 60°C for 1 minute, and 72°C for 30 seconds, with a final extension at 72°C for 5 minutes. The amplified products (122 bp) were separated on a 3% agarose gel, stained with ethidium bromide, and visualized under UV light for genotype determination. The bands formed after electrophoresis of the TMPRSS6 (rs2235321) gene are presented in Table 3.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics 21.0 software. The Hardy-Weinberg equilibrium was tested using Chi-square analysis. Genotype and allele frequencies were compared between the patient and control groups using Chi-square analysis. The odds ratio (OR) and 95% confidence intervals (CIs) were calculated to assess the effects of differences in allelic and genotype distributions. Comparisons of other parameters were made using the unpaired Student's t-test (for normally distributed variables) or the Mann-Whitney U test (for non-normally distributed variables). A P-value of < 0.05 was considered statistically significant.

RESULTS

The clinical characteristics are summarized in Table 4. Age and gender distributions were similar across all groups. Serum TSH levels were significantly higher in the Hypothyroidism and Hypothyroidism IDA groups compared to the control group ($P < 0.001$ for both). TSH levels were lower in the

Table 4: Comparison of some biochemical parameters between patients with subclinical hypothyroidism and control subjects

Parameters	Control (N=30)	Hypotyroidism (N=30)	Hypotyroidism IDA (N=30)	Hypotyroidism IDA+Thyroxyne (N=35)
TSH (mIU/L)	2.07±1.29	11.04±11.31a***	10.00±10.90b***	3.93± 1.77d**, e**
fT4 (pmol/L)	12.44±1.23	10.84±3.06	10.98±1.99	12.60± 1.95d*,e*
Erythrocyte (M/µL)	4.76±0.47	4.53±0.53a*	4.51±0.51	4.56±0.55d***,e*
Hct (%)	40.08±4.23	36.52±4.61	36.48±4.40	37.95±5.02
Hb (g/dL)	13.49±1.53	12.02±1.65a*	11.98±1.55b*	12.72±1.84
MCV (fL)	84.38±6.16	80.98±7.84	80.69±6.14	83.01±7.40
MCH (pg)	28.38±2.38	26.72±2.90	26.00±2.63b*	27.64±3.16
MCHC (g/dL)	33.62±0.59	32.89±1.09a*	32.45±1.03b**	32.82±1.47c***
RDW (%)	16.09±1.49	17.89±2.04	17.84±2.21b**	16.78±2.29c*
Iron (µg/dL)	79.10±35.08	58.82±29.19	54.47±20.73	80.43±32.22e*
TIBC (µg/dL)	304.80±102.60	383.50±77.54a***	351.60±93.38b***	282.10±58.83d**,e*
Ferritin (ng/mL)	43.07±39.96	11.01±8.51a***	13.81±7.11b***	34.71± 18.43d**,e**

*Data are presented as mean ± SD. IDA, Iron deficiency anemia, Hct, Hematocrit, Hb, Hemoglobin, MCV, Mean corpuscular volume, MCH, Mean corpuscular haemoglobin, MCHC, Mean corpuscular hemoglobin concentration, RDW, Red cell distribution width, TIBC, Total iron binding capacity, TSH, Thyroid stimulating hormone, fT4, Free thyroxine, aControl vs. Hypotyroidism, bControl vs. Hypotyroidism IDA, cControl vs. Hypotyroidism IDA+Thyroxyne, dHypotyroidism vs. Hypotyroidism IDA+Thyroxyne, eHypotyroidism IDA vs. Hypotyroidism IDA+Thyroxyne, *P<0.05, **P<0.01, ***P<0.001.*

Hypothyroidism IDA + Thyroxine group compared to both the Hypothyroidism and Hypothyroidism IDA groups ($P < 0.01$ for both). fT4 levels were elevated in the Hypothyroidism IDA + Thyroxine group compared to the Hypothyroidism and Hypothyroidism IDA groups ($P < 0.05$ for both). No significant differences in fT4 levels were found among the other groups ($P > 0.05$ for all) (Table 4).

When evaluating biochemical parameters, erythrocyte count, hemoglobin (Hb), mean corpuscular hemoglobin concentration (MCHC), and ferritin levels were lower, while TIBC was higher in the Hypothyroidism group compared to the Control group ($P < 0.05$, $P < 0.05$, $P < 0.05$, $P < 0.001$, and $P < 0.001$, respectively). In the Hypothyroidism IDA group, Hb, mean corpuscular hemoglobin (MCH), MCHC, and ferritin levels were lower, while red cell distribution width (RDW) and TIBC were higher compared to the control group ($P < 0.05$, $P < 0.05$, $P < 0.01$, $P < 0.001$, $P < 0.01$, and $P < 0.001$, respectively). In the Hypothyroidism IDA + Thyroxine group, MCHC was lower, and RDW was higher compared to the control group ($P < 0.001$ and $P < 0.05$, respectively). No significant differences were observed in other parameters ($P > 0.05$).

In the comparison between the Hypothyroidism and Hypothyroidism IDA+Thyroxine groups, erythrocyte count and ferritin were higher in the Hypothyroidism IDA+Thyroxine group, while TIBC was lower ($P < 0.001$, $P < 0.01$, and $P < 0.01$, respectively). In the comparison between the Hypothyroidism IDA and Hypothyroidism IDA+Thyroxine groups, erythrocyte count, iron, and ferritin were higher in the Hypothyroidism IDA+Thyroxine group, while TIBC was lower ($P < 0.05$, $P < 0.05$, $P < 0.01$, and $P < 0.05$, respectively). No significant differences were observed in other parameters ($P > 0.05$).

We investigated the polymorphisms located in the TMPRSS6 gene (rs4820268, rs2235321, and rs855791), and the genotype frequencies for both the patient and control groups are presented in Table 5. Statistical analysis of the allele frequencies and genotype distributions of the rs4820268, rs2235321, and rs855791 SNPs revealed no significant differences. To evaluate whether these gene polymorphisms (rs4820268, rs2235321, and rs855791) influenced iron, TIBC, and ferritin levels, these parameters were compared between the patient groups and the control group for homozygous mutant and heterozygous genotypes (Table 6).

Initially, iron, TIBC, and ferritin levels for the rs4820268 polymorphism were compared between homozygous mutant and heterozygous genotype carriers (Table 6). Ferritin levels were found to be lower in the Hypothyroidism and Hypothyroidism IDA groups compared to the Control group ($P < 0.01$ and $P < 0.05$, respectively). Ferritin levels were also lower in the Hypothyroidism group compared to the Hypothyroidism IDA + Thyroxine group ($P < 0.05$). Furthermore, TIBC levels were higher in the Hypothyroidism group compared to the Control group ($P < 0.05$), and lower in the Hypothyroidism IDA + Thyroxine group compared to both the Hypothyroidism and Hypothyroidism IDA groups ($P < 0.001$ and $P < 0.05$, respectively).

Next, the patient and control groups with homozygous mutant and heterozygous genotypes of the rs2235321 polymorphism were compared (Table 6). It was found that iron levels were higher in the Hypothyroidism IDA + Thyroxine group compared to the Hypothyroidism and Hypothyroidism IDA

Table 5: Distribution of genotype and allele frequencies of rs4820268, rs2235321 and rs855791 SNPs in healthy controls and subjects with subclinical hypothyroidism (untreated, treated with IDA or and IDA+Thyroxine)

Genotype	Control	Hypotyroidism n (%)	Hypotyroidism IDA n (%)	Hypotyroidism IDA+Thyroxyne n (%)
rs4820268 Genotypes				
GG	12 (41)	10 (42)	3 (16)	8 (27)
AG	12 (41)	11 (46)	11 (58)	15 (50)
AA	5 (18)	3 (12)	5 (26)	7 (23)
Allele frequency				
G	36 (62)	31 (65)	17 (45)	31 (52)
A	22 (38)	17 (35)	21 (55)	29 (48)
rs2235321 Genotypes				
AA	2 (10)	3 (14)	2 (11)	2 (6)
AG	13 (65)	18 (82)	15 (83)	29 (91)
GG	5 (25)	1 (4)	1 (6)	1 (3)
Allele frequency				
A	17 (43)	24 (55)	19 (53)	33 (52)
G	23 (57)	20 (45)	17 (47)	31 (48)
rs855791 Genotypes				
AA	10 (34)	10 (40)	1 (5)	5 (16)
AG	18 (62)	14 (56)	18 (90)	26 (81)
GG	1 (4)	1 (4)	1 (5)	1 (3)
Allele frequency				
A	38 (66)	34 (68)	20 (50)	36 (56)
G	20 (34)	16 (32)	20 (50)	28 (44)

Table 6: Effect of TMPRSS6 gene polymorphisms (rs4820268, rs2235321, and rs855791) on iron levels, TIBC, and ferritin in individuals with heterozygous and mutant genotypes

	Control AG+AA	Hypotyroidism AG+AA	Hypotyroidism IDA AG+AA	Hypotyroidism IDA+Thyroxyne AG+AA
rs4820268	**(n=17)**	**(n=14)**	**(n=14)**	**(n=22)**
Iron (µg/dL)	76.82±28.13	58.60±30.76	59.63±19.07	82.48±33.11
TIBC (µg/dL)	310.80±78.84	383.60±81.88a*	365.50±95.91	284.20±53.72c***,d*
Ferritin (ng/mL)	41.46±41.58	11.61±8.78a**	13.98±7.32b*	33.00±16.88c*
rs2235321	**(n=18)**	**(n=19)**	**(n=16)**	**(n=30)**
Iron (µg/dL)	76.65±26.60	49.44±11.02	55.80±21.61	83.04±31.54c**,d*
TIBC (µg/dL)	326.50±74.39	381.40±62.44	353.90±98.36	281.20±57.74c***,d**
Ferritin (ng/mL)	33.38±32.10	10.59±8.74a**	13.76±7.49b*	35.12±18.98c***,d**
rs855791	**(n=19)**	**(n=15)**	**(n=19)**	**(n=27)**
Iron (µg/dL)	78.60±35.30	58.82±29.19	54.47±20.73	83.14±33.94
TIBC (µg/dL)	319.30±89.68	384.00±79.64a*	351.60±93.38	279.60±60.65c***,d*
Ferritin (ng/mL)	41.14±40.21	10.98±8.74a**	13.81±7.11b*	35.01±18.68c*

*Data are presented as mean ± SD. IDA, Iron deficiency anemia, TIBC, Total iron binding capacity, aControl vs. Hypotyroidism, bControl vs. Hypotyroidism IDA, cHypotyroidism vs. Hypotyroidism IDA+Thyroxyne, dHypotyroidism IDA vs. Hypotyroidism IDA+Thyroxyne, *P<0.05, **P<0.01, ***P<0.001.*

groups ($P < 0.01$ and $P < 0.05$, respectively). TIBC levels were lower in the Hypothyroidism IDA + Thyroxine group compared to the Hypothyroidism and Hypothyroidism IDA groups ($P < 0.001$ and $P < 0.01$, respectively). Additionally, ferritin levels were lower in the Hypothyroidism and Hypothyroidism IDA groups compared to the Control group ($P < 0.01$ and $P < 0.05$, respectively), and higher in the Hypothyroidism IDA + Thyroxine group compared to both the Hypothyroidism and Hypothyroidism IDA groups ($P < 0.001$ and $P < 0.01$, respectively).

Finally, the iron, TIBC, and ferritin levels of homozygous mutant and heterozygous genotypes in the rs855791 polymorphism were compared (Table 6). Iron levels were found to be higher in the Hypothyroidism IDA + Thyroxine group compared to the Hypothyroidism IDA group ($P < 0.05$). TIBC levels were higher in the Hypothyroidism group compared to the Control group ($P < 0.05$), and lower in the Hypothyroidism IDA + Thyroxine group compared to both the Hypothyroidism and Hypothyroidism IDA groups ($P < 0.001$ and $P < 0.01$, respectively). Moreover, ferritin levels were lower in the Hypothyroidism and Hypothyroidism IDA groups compared to the Control group ($P < 0.001$ and $P < 0.01$, respectively), and higher in the Hypothyroidism IDA + Thyroxine group compared to both the Hypothyroidism and Hypothyroidism IDA groups ($P < 0.01$ for both).

DISCUSSION

In this study, the three most common SNPs (rs4820268, rs2235321, and rs855791) in the TMPRSS6 gene were investigated in patients with subclinical hypothyroidism and IDA, and the effects of iron-only or combined iron and thyroxine treatments on certain biochemical parameters were evaluated. Although no statistically significant differences were detected among the selected SNPs between the groups, notable changes in iron, TIBC, and ferritin levels were observed in association with the heterozygous and mutant variants of rs4820268, rs2235321, and rs855791 in the treatment of anemia in subclinical hypothyroidism. To the best of our knowledge, this is the first study to examine the status of rs4820268, rs2235321, and rs855791 SNPs in the TMPRSS6 gene in patients with subclinical hypothyroidism and IDA.

Thyroid hormone plays a vital role in metabolism regulation. Thyroid disorders due to iodine deficiency and IDA are major global health concerns. While IDA and thyroid hormone deficiency are treatable (22), subclinical hypothyroidism treatment remains debated (23). Studies suggest IDA treatment in subclinical hypothyroidism is more effective with thyroid hormone supplementation (3, 24), and genetic factors influence iron metabolism (25). TMPRSS6 variants are linked to serum iron levels and hematological parameters in various diseases and healthy individuals (19, 26-30). Genome-wide studies in European and Asian populations identified TMPRSS6 and TF gene variants affecting iron status. A 2009 study on European and South Asian individuals found rs855791 (V736A) as the most associated SNP, with the A allele linked to lower Hb levels via hepcidin regulation (8). In Australian individuals, rs855791 correlated with reduced transferrin saturation, serum iron, Hb levels, and mean corpuscular volume (MCV) in both adolescents and adults (19). Jallow et al. examined the effects of TMPRSS6 and TF SNPs on iron status in 1,316 healthy Gambians from the Keneba Biobank. TMPRSS6 SNPs (rs2235321, rs855791, rs4820268, rs2235324, rs2413450, rs5756506) and TF SNPs (rs3811647, rs1799852) were assessed for iron biomarkers, with some SNPs linked to ferritin, hepcidin, Hb, transferrin, unsaturated iron-binding capacity (UIBC), and transferrin saturation, though their contribution to population variance was minimal (29). Delbini et al. sequenced the TMPRSS6 gene in 16 IRIDA patients, identifying 27 polymorphisms. Eight SNPs and four haplotypes were significantly associated with IRIDA, including rs855791, rs2235320, rs4820268, rs11704654, and rs2543519. These nonsynonymous variants were linked to altered amino acid sequences, leading to dysregulated hepcidin expression and changes in MT-2 catalytic activity (20). Elmahdy et al. found rs855791 and rs4820268 significantly associated with reduced Hb, MCV, MCH, ferritin, and iron levels, along with increased TIBC in IDA and IRIDA patients (31). Another study analyzing multiple TMPRSS6 SNPs in IDA patients found no direct impact on IDA but noted their influence on iron metabolism parameters (21). In our study, no significant differences in TMPRSS6 polymorphisms (rs4820268, rs2235321,

rs855791) were observed between subclinical hypothyroidism and control groups. However, in patients, heterozygous and mutant variants were associated with decreased ferritin and increased TIBC levels.

Poggiali et al. studied the response to iron therapy in relation to TMPRSS6 polymorphisms and found significant differences in the frequencies of common TMPRSS6 polymorphisms, including V736A, SNP-120, SNP-113, F5F, P33P, K253E, S361S, Y418Y, D521D, D15accc, and Y739Y, between persistent IDA patients (with poor oral iron therapy response) and the control group. They also observed that heterozygous and homozygous rs855791 genotypes were associated with lower serum iron, transferrin saturation, Hb, and MCV levels in IDA patients (32). Shinta et al. investigated the effects of dietary iron on anemia and iron deficiency in young children. Data from 121 Indonesian children aged 6–17 months were analyzed. The minor alleles of TMPRSS6 rs855791 (A) and rs4820268 (G) were found to reduce serum ferritin levels by 4.50 g/L and 5.00 g/L, respectively. However, no significant association was observed between these SNPs and soluble transferrin receptor (sTfR) or hemoglobin (Hb) concentrations (13). In our study, no significant differences were found in rs4820268, rs2235321, and rs855791 SNPs between subclinical hypothyroid patients receiving iron therapy and healthy individuals. However, in the patient group, ferritin levels were lower in heterozygous and mutant variants of these SNPs compared to controls. In patients receiving both iron and thyroxine therapy, iron and ferritin levels increased, and TIBC decreased, compared to those receiving only iron therapy. These findings suggest that specific TMPRSS6 SNPs (rs4820268, rs2235321, and rs855791) may influence iron metabolism in subclinical hypothyroid patients undergoing combined therapy.

To the best of our knowledge, polymorphisms in the TMPRSS6 gene have not been studied in hypothyroidism, although they have been observed to contribute to iron deficiency and anemia in diseases such as celiac disease and diabetes. It is seen that the data obtained from these studies are also contradictory. A study on the rs855791 SNP and anemia in celiac disease found that the rs855791 variant was more prevalent in adults with celiac disease compared to a control group. However, no significant difference was observed between celiac patients with persistent IDA and those without IDA regarding the rs855791 polymorphism (33). Another study reported that the T allele of rs855791 was more frequent in celiac patients with persistent IDA and was associated with a lower response to oral iron supplementation (27). Liu et al. observed a trend toward a significant association between the T allele of rs855791 and an increased risk of gestational diabetes mellitus in pregnant Han Chinese women. They also found significant associations between rs855791 and rs4820268 SNPs with serum iron and transferrin saturation, suggesting a link between TMPRSS6 variants and gestational diabetes risk (34). Moremi et al. reported no significant difference in the frequency distributions of the TMPRSS6 c.2207C>T variant between multiple sclerosis patients and controls but found a significant difference in the risk of iron deficiency between homozygous T and C allele carriers, with lower ferritin levels in patients compared to controls (28). Similarly, Gan et al. found that both rs855791 (V736A) and rs4820268 (D521D) SNPs were significantly associated with ferritin, Hb levels, iron overload risk, and type 2 diabetes risk (26).

Several studies have shown that thyroid hormones stimulate red blood cell production (22-25). In hypothyroidism, erythrocyte lifespan is normal, but hypoproliferative erythropoiesis occurs. Various mechanisms are involved in the stimulation of erythropoiesis by thyroid hormones. One of these mechanisms is suggested to be related to erythropoietin, which increases metabolic rate and the resulting increase in oxygen demand. Although the data obtained are closely related to the improvement in iron variables, it has been suggested that stimulation of erythropoiesis by thyroid hormones is not the only mechanism, and that the effects of thyroid hormone on iron metabolism are quite complex. The TMPRSS6 gene, which encodes matriptase-2, plays a direct role in the regulation of dietary iron absorption and utilization. The TMPRSS6 SNP may be associated with an increased risk of iron-restricted erythropoiesis resulting from inadequate iron absorption from dietary sources. Although further functional studies are needed to elucidate the effect of TMPRSS6 polymorphisms on iron deficiency anemia developing in subclinical hypothyroidism, our findings suggest that combined homozygous and heterozygous genotypes in TMPRSS6 affect circulating iron, TIBC and ferritin levels. On the other hand, the distribution of genotypes of these polymorphisms is likely to be associated with various risk factors for the development of iron deficiency anemia. There were some limiting factors in our study. These limiting factors include the fact that our sample groups were collected from the same center and region at certain time intervals and the small number of patients in our groups in terms of follow-up.

CONCLUSIONS

In this study, hypothyroid patients receiving iron therapy were found to have lower ferritin and iron levels and higher TIBC levels compared to healthy individuals. In individuals receiving both iron and thyroid treatment, TIBC levels were found to decrease, while ferritin and iron levels increased. No significant differences were observed in the genotype and allele frequency distributions of TMPRSS6 rs4820268, rs2235321 and rs855791 between healthy and subclinical hypothyroid individuals. However, these polymorphisms affected treatment-related changes, especially in patients receiving combined therapy, where ferritin levels increased and TIBC decreased. These findings highlight the relationship between hypothyroidism, iron metabolism and response to treatment, but further studies in larger sample groups are needed to elucidate the underlying molecular mechanisms.

Conflict of Interest: No conflict of interest was declared by the authors

Ethics: The study protocol was approved by the Ethics Committee of the Medical Faculty at Sakarya University (29.09.2016-E.12812), and was conducted in accordance with the Declaration of Helsinki.

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REFERENCES

1. Yen PM. Physiological and molecular basis of thyroid hormone action. Physiological reviews 2001; 81: 1097-1142.
2. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. The journal of clinical endocrinology & metabolism 2005; 90: 581-585.
3. Cinemre H, Bilir C, Gokosmanoglu F, Bahcebasi T. Hematologic effects of levothyroxine in iron-deficient subclinical hypothyroid patients: a randomized, double-blind, controlled study. The Journal of Clinical Endocrinology & Metabolism 2009; 94: 151-156.
4. Mehmet E, Aybike K, Ganidagli S, Mustafa K. Characteristics of anemia in subclinical and overt hypothyroid patients. Endocrine journal 2012; 59: 213-220.
5. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. Jama 2004; 291: 228-238.
6. Cooper DS. Subclinical hypothyroidism. New England Journal of Medicine 2001; 345: 260-265.
7. Ganesh SK, Zakai NA, Van Rooij FJ, Soranzo N, Smith AV, Nalls MA, et al. Multiple loci influence erythrocyte phenotypes in the CHARGE Consortium. Nature genetics 2009; 41: 1191-1198.
8. Chambers JC, Zhang W, Li Y, Sehmi J, Wass MN, Zabaneh D, Hoggart C, Bayele H, McCarthy MI, Peltonen L. Genome-wide association study identifies variants in TMPRSS6 associated with hemoglobin levels. Nature genetics 2009; 41: 1170-1172.
9. Soranzo N, Spector TD, Mangino M, Kühnel B, Rendon A, Teumer A, et al. A genome-wide meta-analysis identifies 22 loci associated with eight hematological parameters in the HaemGen consortium. Nature genetics 2009; 41: 1182-1190.
10. Pelusi S, Girelli D, Rametta R, Campostrini N, Alfieri C, Traglia M, et al. The A736V TMPRSS6 polymorphism influences hepcidin and iron metabolism in chronic hemodialysis patients: TMPRSS6 and hepcidin in hemodialysis. BMC nephrology 2013; 14: 1-9.
11. Kato A, Tsuji T, Luo J, Sakao Y, Yasuda H, Hishida A. Association of prohepcidin and hepcidin-25 with erythropoietin response and ferritin in hemodialysis patients. American Journal of Nephrology 2007; 28: 115-121.
12. Mohd Atan FNE, Wan Mohd Saman WA, Kamsani YS, Khalid Z, Abdul Rahman A. TMPRSS6 gene polymorphisms associated with iron deficiency anaemia among global population. Egyptian Journal of Medical Human Genetics 2022; 23: 147.
13. Shinta D, Asmarinah, Adhiyanto C, Htet MK, Fahmida U. The association of TMPRSS6 gene polymorphism and iron intake with iron status among under-two-year-old children in Lombok, Indonesia. Nutrients 2019; 11: 878.
14. Bhatia P, Singh A, Hegde A, Jain R, Bansal D. Systematic evaluation of paediatric cohort with iron refractory iron deficiency anaemia (IRIDA) phenotype reveals multiple TMPRSS6 gene variations. British Journal of Haematology 2017; 177: 311-318.
15. Piao W, Wang L, Zhang T, Wang Z, Shangguan S, Sun J, Huo J. A single-nucleotide polymorphism in transferrin is associated with soluble transferrin receptor in Chinese adolescents. Asia Pacific Journal of Clinical Nutrition 2017; 26: 1170-1178.
16. Athiyarath R, Shaktivel K, Abraham V, Singh D, Bondu JD, Chapla A, et al. Association of genetic variants with response to iron supplements in pregnancy. Genes & Nutrition 2015; 10: 1-8.
17. Kamatani Y, Matsuda K, Okada Y, Kubo M, Hosono N, Daigo Y, et al. Genome-wide association study of hematological and biochemical traits in a Japanese population. Nature genetics 2010; 42: 210-215.
18. Seiki T, Naito M, Hishida A, Takagi S, Matsunaga T, Sasakabe T, et al Association of genetic polymorphisms with erythrocyte traits: verification of SNPs reported in a previous GWAS in a Japanese population. Gene 2018; 642: 172-177.
19. Benyamin B, Ferreira MA, Willemsen G, Gordon S, Middelberg RP, McEvoy BP, et al. Common variants in TMPRSS6 are associated with iron status and erythrocyte volume. Nature genetics 2009; 41: 1173-1175.
20. Delbini P, Vaja V, Graziadei G, Duca L, Nava I, Refaldi C, Cappellini MD. Genetic variability of TMPRSS6 and its association with iron deficiency anaemia. British journal of haematology 2010; 151: 281-284.
21. Batar B, Bavunoglu I, Hacioglu Y, Cengiz M, Mutlu T, Yavuzer S, et al. The role of TMPRSS6 gene variants in iron-related hematological parameters in Turkish patients with iron deficiency anemia. Gene 2018; 673: 201-205.
22. Garofalo V, Condorelli RA, Cannarella R, Aversa A, Calogero AE, La Vignera S. Relationship between Iron Deficiency and thyroid function: a systematic review and meta-analysis. Nutrients 2023; 15: 4790.
23. Fatourechi V. Subclinical hypothyroidism: an update for primary care physicians. Mayo Clinic Proceedings: Elsevier; 2009. p. 65-71.
24. Ravanbod M, Asadipooya K, Kalantarhormozi M, Nabipour I, Omrani GR. Treatment of iron-deficiency anemia in patients with subclinical hypothyroidism. The American journal of medicine 2013; 126: 420-424.
25. da Conceição RR, Giannocco G, Herai RH, Petroski LP, Pereira BG, de Oliveira KC, et al. Thyroid dysfunction alters gene expression of proteins related to iron homeostasis and metabolomics in male rats. Molecular and Cellular Endocrinology 2024; 579: 112086.
26. Gan W, Guan Y, Wu Q, An P, Zhu J, Lu L, et al. Association of TMPRSS6 polymorphisms with ferritin, hemoglobin, and type 2 diabetes risk in a Chinese Han population. The American journal of clinical nutrition 2012; 95: 626-632.
27. De Falco L, Tortora R, Imperatore N, Bruno M, Capasso M, Girelli D, et al. The role of TMPRSS6 and HFE variants in iron deficiency anemia in celiac disease. American journal of hematology 2018; 93: 383-393.
28. Moremi K, Van Rensburg S, Fisher LR, Davis W, Cronje FJ, Dashti JSM, et al. Association of an iron-related TMPRSS6 genetic variant c. 2207 C> T (rs855791) with functional iron deficiency and its effect on multiple sclerosis risk in the South African population. South African Journal of Psychiatry 2013;19(3): 120-121.
29. Jallow MW, Campino S, Prentice AM, Cerami C. Association of common TMPRSS6 and TF gene variants with hepcidin and iron status in healthy rural Gambians. Scientific reports 2021; 11: 8075.
30. Buerkli S, Pei S-N, Hsiao SC, Lee CT, Zeder C, Zimmermann MB, Moretti D. The TMPRSS6 variant (SNP rs855791) affects iron metabolism and oral iron absorption–a stable iron isotope study in Taiwanese women. haematologica 2020; 106: 2897.
31. Elmahdy M, Elhakeem H, Gaber F, Mourad F. TMPRSS6 gene polymorphism and serum hepcidin in iron deficiency anemia. The Egyptian Journal of Hospital Medicine 2018; 73: 7090-7103.
32. Poggiali E, Andreozzi F, Nava I, Consonni D, Graziadei G, Cappellini MD. The role of TMPRSS6 polymorphisms in iron deficiency anemia partially responsive to oral iron treatment. American Journal of Hematology 2015; 90: 306-309.
33. Elli L, Poggiali E, Tomba C, Andreozzi F, Nava I, Bardella MT, et al. Does TMPRSS6 RS855791 polymorphism contribute to iron deficiency in treated celiac disease? Official journal of the American College of Gastroenterology| ACG 2015; 110: 200-202.
34. Liu PJ, Yao A, Chen XY, Liu Y, Ma L, Hou YX. Associations of TMPRSS6 polymorphisms with gestational diabetes mellitus in Chinese Han pregnant women: a preliminary cohort study. Biological Trace Element Research 2021; 199: 473-481.

ORIGINAL ARTICLE

Comparison of BAR, BISAP and NEWS Scores in Predicting Mortality in Patients with Acute Pancreatitis

Akut Pankreatitli Hastalarda Mortaliteyi Tahmin Etmede BAR, BISAP ve NEWS Skorlarının Karşılaştırılması

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ABSTRACT

Objective: *Acute pancreatitis is a gastrointestinal emergency with a high mortality rate. Multiple biomarkers and scoring systems are used to predict mortality in acute pancreatitis. Traditional methods such as BISAPS (Bedside Index of Severity of Acute Pancreatitis Score) and NEWS (National Early Warning Score) contain too many parameters. To predict mortality in patients with acute pancreatitis who apply to the emergency department with the BUN/Albumin ratio (BAR).*

Material and Method: *Patients who were admitted to the emergency department between 01/01/2021 and 31/12/2022 and whose lipase value was more than three times the reference value were included in our study by retrospectively scanning hospital data.Patients were divided into two groups according to in-hospital mortality. BAR, BISAP and NEWS values of all patients were calculated and compared.*

Result: *In the ROC analysis performed to evaluate the mortality predictive power; AUC values of NEWS 0.637 (0.546-0.727), BISAPS 0.684 (0.589-0.779), BAR 0.748 (0.663-0.832) were obtained. In the logistic regression analysis; BAR was found to be the highest independent predictor of in-hospital mortality of acute pancreatitis. It was found that a 1 unit increase in BAR increased in-hospital mortality by 1,071 times.*

Conclusions: *BAR is more effective in predicting mortality than NEWS and BISAPS in patients with acute pancreatitis who present to the emergency department.*

Keywords: *Acute Pancreatitis, BAR, BISAPS, NEWS, Mortality*

ÖZET

Amaç: *Akut pankreatit, yüksek mortalite oranına sahip bir gastrointestinal acil durumdur. Akut pankreatitte mortaliteyi öngörmek için çeşitli biyobelirteçler ve skorlama sistemleri kullanılmaktadır. BISAPS (Bedside Index of Severity of Acute Pancreatitis Score) ve NEWS (National Early Warning Score) gibi geleneksel yöntemler çok fazla parametre içermektedir. Bu çalışmada, acil servise başvuran akut pankreatitli hastalarda BUN/Albümin oranı (BAR) ile mortalitenin öngörülmesi amaçlandı.*

Gereç ve Yöntem: *01/01/2021 ile 31/12/2022 tarihleri arasında acil servise başvuran ve lipaz değeri referans değerin üç katından fazla olan hastalar, hastane verileri retrospektif olarak taranarak çalışmaya dahil edildi. Hastalar, hastane içi mortaliteye göre iki gruba ayrıldı. Tüm hastaların BAR, BISAP ve NEWS değerleri hesaplanarak karşılaştırıldı.*

Bulgular: *Mortaliteyi öngörme gücünü değerlendirmek için yapılan ROC analizinde; AUC değerleri NEWS için 0,637 (0.546-0.727), BISAPS için 0,684 (0.589-0.779), BAR için 0,748 (0.663-0.832) olarak bulundu. Lojistik regresyon analizinde; BAR, akut pankreatitli hastalarda hastane içi mortalitenin en güçlü bağımsız belirleyicisi olarak bulundu. BAR'da 1 birimlik artışın hastane içi mortaliteyi 1,071 kat artırdığı tespit edildi.*

Sonuç: *Acil servise başvuran akut pankreatitli hastalarda, BAR skoru, NEWS ve BISAPS skorlarına göre mortaliteyi öngörmede daha etkilidir.*

Anahtar Kelimeler: *Akut Pankreatit, BAR, BISAPS, NEWS, Mortalite*

INTRODUCTION

In non-traumatic emergency department (ED) admissions, gastrointestinal (GI) system diseases are seen as the most common second system disease. Among GI system diseases, one of the most common reasons for admission is acute pancreatitis. Therefore, multiple scoring systems have been used to determine the prognosis in patients with acute pancreatitis (1-2). Biomarkers and scoring systems have been used to predict mortality in patients with acute pancreatitis due to the high mortality rate associated with the condition (3-4).

One of the scoring systems used to predict mortality early in acute pancreatitis is the Bedside Index of Severity in Acute Pancreatitis (BISAP) score (4). The BISAP scoring system contains fewer parameters compared to traditional pancreatitis scoring systems (Apache II, Ranson, and Balthazar) and is easier to use (5). BISAP is a newer scoring system compared to the old Ranson criteria. Data scoring is not required until 48 hours after patients are admitted to the hospital. The BISAP scoring system also includes consciousness status and Systemic Inflammatory Response Syndrome (SIRS) criteria. Evaluation with this scoring system may be challenging and may yield misleading results in patients with cognitive diseases like dementia, sequelae of previous illnesses, and

mental disorders.

The National Early Warning Score (NEWS) is a scoring system used in many clinical conditions to predict mortality (6). Its ability to predict mortality is attributed to being a scoring system based on vital parameters. Therefore, while it accurately predicts mortality in the geriatric population, it may not perform well in non-geriatric patient populations due to compensatory mechanisms (endocrine, cardiac, central). Recently, various parameters have been compared with NEWS in literature studies in various clinical conditions (7).

Blood urea nitrogen (BUN) is a type of nitrogen produced in protein metabolism and excreted by the kidneys (8). Blood urea nitrogen is associated with mortality linked to sepsis-related dehydration (9). Blood urea nitrogen and albumin reflect protein intake, protein catabolism, and fluid balance in patients. Both are also frequently used as prognostic markers (10). Increased fluid requirements and BUN elevation leading to acute kidney injury develop in acute pancreatitis due to increased fluid needs and inflammation (11-13). BUN values are also included in the calculation of BISAP scores and Ranson criteria.

The Blood Urea Nitrogen/Albumin Ratio (BAR) has gained a place as a prognostic marker in literature studies in various clinical conditions due to being a quickly accessible and easily calculable parameter (14)

In this study, we aimed to compare BAR with NEWS and BISAP scoring systems in predicting mortality in patients with acute pancreatitis presenting to the ED.

MATERIAL AND METHODS

This study received ethical approval from the Necmettin Erbakan University (Konya, Turkey) Faculty of Medicine Clinical Studies Ethics Committee on 7 June 2024, with decision number 2024/4997. Patients' medical data were accessed retrospectively through the hospital's electronic medical record system, following the approval of the institutional ethics committee. All data were anonymized to protect patient confidentiality. Patients who presented to the ED between 01/01/2021 and 31/12/2022 with a lipase value three times higher than the reference value were screened. Patients under eighteen years of age, trauma patients, those with missing laboratory parameters, those with missing vital signs, and those whose final diagnosis was not pancreatitis were excluded from the study (Figure 1). The parameters analyzed in the study were obtained from history taken in the ED, physical examination findings, laboratory, and imaging results. Patients who met at least two of the diagnostic criteria for acute pancreatitis (three times the reference value of amylase and/or lipase, typical abdominal pain of acute pancreatitis, and imaging findings) were considered to have acute pancreatitis and included in the study. Demographic data, vital signs (blood pressure, temperature, pulse rate, respiratory rate, oxygen saturation), consciousness status (AVPU score), laboratory findings (hemoglobin, leukocyte, neutrophil, lymphocyte, BUN, creatinine, amylase, lipase, albumin, CRP, lactate), presenting complaints, comorbidities, etiological causes, and hospital outcomes of the patients included in the study were recorded. BAR values and BISAP, NEWS scores were calculated from the obtained data.

RESULTS

A total of 934 patients were included in the study, and their medical records were reviewed. The median age of the patients was determined to be 59, and 507 (54.3%) were female. The most common complaint detected at admission was abdominal pain with 902 patients. The most common comorbidities were hypertension with 319 (34.2%), diabetes with 190 (20.3%), and coronary artery disease with 108 (11.6%) (Table 1 and Table 2). The median BAR value of the cases was found to be 3.62 (2.63-5.34). The median NEWS and BISAPS values of the cases were 1 (0-2) and 1 (0-1), respectively. The cases were divided into biliary (558 (59.7%)) and non-biliary (376 (40.3%)) etiological causes. Among non-biliary causes, mass (abscess, tumor) was the most common cause with a total of 51 patients. Of the patients, 791 were hospitalized, and 63 were admitted to the intensive care unit. As a hospital outcome, 796

Figure 1: Flowchart

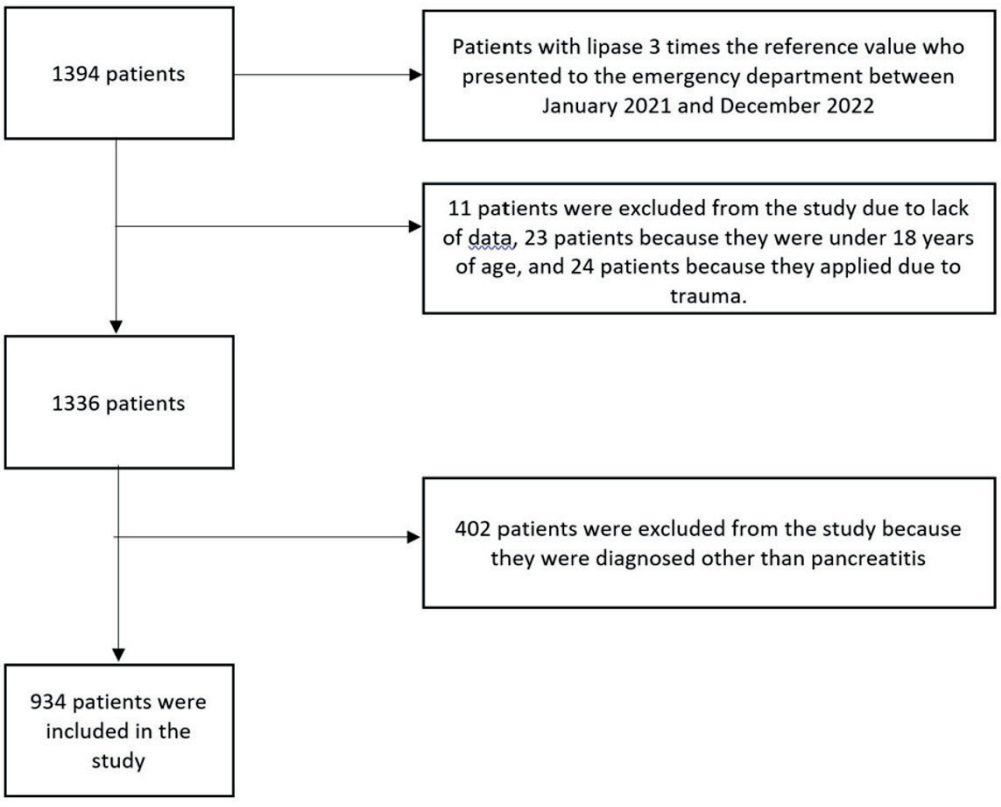

Table 1: Features of Participants and comparison of survivor and nonsurvior

		Total patients (n=934)	Non survivor (n=44)	Survivor (n=890)	p value
Age		59(43.75-72)	69(57.75-81.75)	57(42-71)	0.001*
NEWS		1(0-2)	1(0.25-4)	1(0-2)	<0.001*
BISAPS		1(0-1)	1.5(1-2.75)	1(0-1)	<0.001*
eGFR		86.54(62.58-107)	64.71(40.77-90.24)	86.33(65.08-107.83)	0.001*
BUN		15.3(11.23-20.74)	22.22(15.61-41.32)	14.77(10.98-20.23)	<0.001*
Albumine		4.15(3.75-4.4)	3.66(3.12-4.14)	4.16(3.8-4.41)	<0.001*
BAR		3.62(2.63-5.34)	6.34(4.52-10.96)	3.5(2.6-5.14)	<0.001*
Creatinine		0.84(0.7-1.1)	1.04(0.8-1.71)	0.85(0.7-1.09)	0.001*
Sodium		138(136-140)	137(132-139)	138(136-140)	0.013*
Potassium		4.3(3.98-4.6)	4.31(3.89-4.69)	4.26(3.96-4.58)	0.449*
Amilase		731(264-1709.5)	356(168.75-1385)	753(270.5-1715	0.014*
Lipase		1389.85(536.28-3182.25	670(372.88-2285.63)	1444(547.5-3201.35)	0.011*
CRP		11(3.4-38.15)	57.25(15.32-158.01)	10.44(3.2-33.54)	<0.001*
WBC		10.49(8.16-13.3)	11.57(7.98-18.61)	10.46(8.18-13.15)	0.088*
Neutrophil		8.1(5.76-10.91)	9.64(5.97-16.45)	8.04(5.71-10.81)	0.031*
Lymphocyte		1.32(0.88-1.83)	1(0.59-1.63)	1.33(0.9-1.86)	0.008*
NLR		6.01(3.38-11.41)	11.21(5.36-22.4)	5.87(3.36-10.96)	<0.001*
Hgb		13.41±2.03	13.19±2.89	13.42±1.98	0.617**
Hospital Stay Duration		5(3-8)	4(2.25-21)	5(3-8)	0.527*
Intensive Care Hospitalization Duration		0(0-0)	2(1-7)	0(0-0)	<0.001*
Sex	Male	427(45.7%)	26(59.1%)	401(45.1%)	0.068***
	Female	507(54.3%)	18(40.9%)	489(54.9%)	

**: Man whitney u test was used*
***: Student t test was used*
****: Chi square test was used*
NEWS: National Early Warning Score, BISAPS: Bedside Index of Severity of Acute Pancreatitis Score eGFR: Estimate Glomerular Filtration Rate, BUN: Blood Urea Nitrogen, BAR: BUN – Albumin Ration, CRP: C-reactive protein, Hgb: haemoglobin

(85.2%) of the patients were discharged (Table 3).

The cases were examined by dividing them into two groups according to in-hospital mortality status. The group with mortality comprised 44 patients, constituting 4.7% of the cases. The collected data between the two groups were compared. The median BAR, BISAPS, NEWS values of the cases with mortality were statistically significantly higher compared to those who survived (6.34 (4.52-10.96), 3.5 (2.6-5.14), p<0.001; 1.5 (1-2.75), 1 (0-1), p<0.001; 1 (0.25-4), 1 (0-2), p<0.001). The median NLR and CRP values were also statistically significantly higher in the mortality group compared to the other group (11.21 (5.36-22.4), 5.87 (3.36-10.96), p<0.001; 57.25 (15.32-158.01), 10.44 (3.2-33.54), p<0.001). Moreover, non-biliary causes in etiology and the occurrence of malignancies as comorbidities were more common in the mortality group and statistically significant (30 (68.2%), 346 (38.9%), p <0.001; 14 (31.8%), 57 (6.4%), p<0.001). Detailed characteristics of the compared data between the two groups are given in Table 1 and Table 2.

In ROC analysis conducted to evaluate the predictive power of mortality; AUC values of BAR 0.748 (0.663-0.832), BISAPS 0.684 (0.589-0.779), NEWS 0.637 (0.546-0.727), NLR 0.677 (0.583-0.771) were obtained (Table 4) (Figure 2).

In logistic regression analysis, BAR, NLR, and CRP were found to be independent predictors in predicting in-hospital mortality of acute pancreatitis. An increase of 1 unit in BAR, NLR, and CRP values was found to increase in-hospital

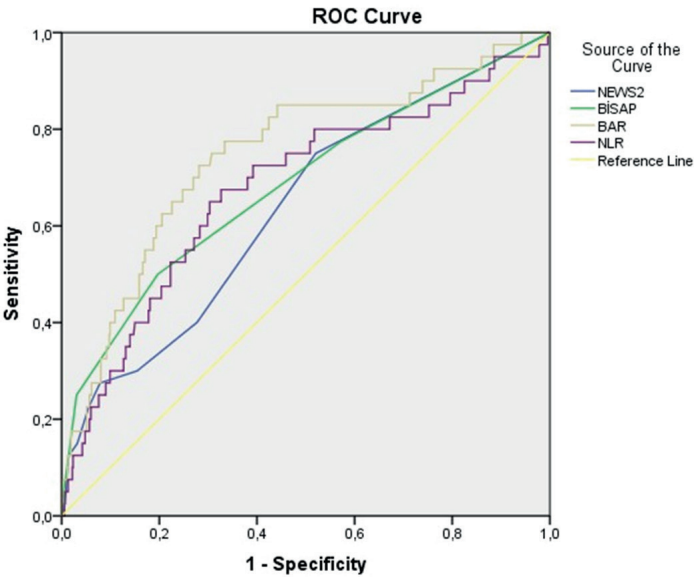

Figure 2: ROC Curve Analysis of Prognostic Scores for Mortality Prediction

Table 2: Comparative analysis of survivors and non-survivors with respect to initial clinical presentation and past medical history

		n(%)	n(%)	n(%)	p value
Abdominal pain		902(96.6)	43(97.7)	859(96.5)	0.999*
Nausea-vomiting		508(54.4)	20(45.5)	488(54.8)	0.223**
Back pain		352(37.7)	14(31.8)	338(38)	0.411**
Abdominal swelling		13(1.4)	2(4.5)	11(1.2)	0.122*
Other complaint		54(5.8)	10(22.7)	44(4.9)	<0.001*
Etiology	**Biliary**	558(59.7)	14(31.8)	544(61.1)	<0.001**
	Nonbiliary	376(40.3)	30(68.2)	346(38.9)	
Morbidity		635(68)	35(79.5)	600(67.4)	0.092**
Pancreatitis		129(13.8)	5(11.4)	124(13.9)	0.630**
Hyperlipidemia		59(6.3)	3(6.8)	56(6.3)	0.753*
Hypertension		319(34.2)	14(31.8)	305(34.3)	0.738**
Diabetes mellitus		190(20.3)	11(25)	179(20.1)	0.432**
Coronary artery disease		108(11.6)	5(11.4)	103(11.6)	0.966**
Congestive heart failure		38(4.1)	3(6.8)	35(3.9)	0.418*
Arrhythmia		29(3.1)	3(6.8)	26(2.9)	0.152*
Liver, pancreas and biliary tract malignancies		14(1.5)	4(9.1)	10(1.1)	0.003*
Malignancy		71(7.6)	14(31.8)	57(6.4)	<0.001*
Asthma-COPD		78(8.4)	5(11.4)	73(8.2)	0.405*
Chronic renal failure		56(6)	3(6.8)	53(6)	0.743*
Cerebrovascular disease		37(4)	2(4.5)	35(3.9)	0.692*
Thyroid		34(3.6)	2(4.5)	32(3.6)	0.672*
Gastrointestinal tract bleeding		1(0.1)	0(0)	1(0.1)	0.999*
Crohn's disease, ulcerative colitis, celiac		9(1)	0(0)	9(1)	0.999*
Rheumatological disease		30(3.2)	3(6.8)	27(3)	0.164*
Liver cirrhosis		5(0.5)	0(0)	5(0.6)	0.999*
Other comorbidity		36(3.9)	3(6.8)	33(3.7)	0.238*
Cholecystitis		1(0.1)	0(0)	1(0.1)	0.999*
Cholelithiasis, Choledocholithiasis		56(6)	1(2.3)	55(6.2)	0.511*
Cholecystectomy		130(13.9)	3(6.8)	127(14.3)	0.163**

**: Ficher exact test was used*
***: Chi square test was used*
COPD: Chronic obstructive pulmonary disease

Table 3: Patients' emergency outcomes, in-hospital outcomes, and in-hospital mortality

Emergency department outcome	Discharge	33(3.5%)
	Service Hospitalization	791(84.7%)
	Intensive Care Hospitalization	63(6.7%)
	Discharged voluntarily	43(4.6%
	Transfer to another hospital	4(0.4%)
Hospital outcome	Discharge	796(85.2%)
	Discharged voluntarily	84(9%)
	Transfer to another hospital	10(1.1%)
	Exitus	44(4.7%)
In-hospital mortality		44(4.7%)

mortality by 1.071, 1.022, and 1.006 times, respectively (Table 5).

DISCUSSION

Acute pancreatitis has a high mortality rate among GI emergencies and constitutes the majority of ED admissions. NEWS and BISAP scoring systems were used in the study on acute pancreatitis (15). Therefore, predicting mortality in patients with acute pancreatitis is important. Our study aims to demonstrate the predictive power of BAR in predicting mortality. To the best of our knowledge, our study is the first to evaluate mortality in acute pancreatitis using BAR in the literature.

BUN value is a frequently used biomarker to assess kidney function and is commonly used in clinical practice. The increase in BUN value in patients with acute pancreatitis is due to increased fluid needs associated with intravascular fluid loss, leading to acute kidney injury (14). Additionally, kidney damage occurs due to inflammatory release (16). Albumin regulates plasma osmotic pressure and constitutes the majority of plasma proteins (17). Albumin is also a negative

Table 4: AUC value of ROC Analysis

ROC Analysis	AUC	95% CI	p value
Age	0.667	0.583-0.750	<0.001
NEWS	0.637	0.546-0.727	0.004
BISAPS	0.684	0.589-0.779	<0.001
eGFR	0.626	0.527-0.726	0.007
BUN	0.695	0.602-0.789	<0.001
Albumin	0.709	0.615-0.803	<0.001
BAR	0.748	0.663-0.832	<0.001
Creatin	0.620	0.518-0.722	0.011
CRP	0.744	0.663-0.824	<0.001
Neutrophil	0.590	0.481-0.699	0.056
Lymphocyte	0.637	0.547-0.728	0.004
NLR	0.677	0.583-0.771	<0.001

NEWS: National Early Warning Score, BISAPS: Bedside Index of Severity of Acute Pancreatitis Score eGFR: Estimate Glomerular Filtration Rate, BUN: Blood Urea Nitrogen, BAR: BUN – Albumin Ration, CRP: C-reactive protein, NLR: Neutrophil Lymphocyte Ratio

acute-phase reactant. While serum albumin levels decrease during inflammatory processes, the transfer of albumin from the vascular compartment to the outside increases, and hypoalbuminemia deepens (18). Kang et al. found in a study that the BUN value is correlated with mortality in patients with acute pancreatitis (19) There are also studies showing that BAR is an independent prognostic factor in various diseases such as community-acquired pneumonia, ischemic stroke, and COVID-19 pneumonia (20-22). In a study on the use of BAR in predicting mortality in patients with early-stage sepsis admitted to the ED by Tianyong and colleagues, the AUC value of BAR was found to be 0.741 (23). We found the AUC value of BAR to be 0.748 in our study. When comparing the AUC values of NEWS, BISAPS, and BAR, we reached values of 0.637, 0.684, and 0.748, respectively. We observed that the BAR value was more effective in predicting in-hospital mortality compared to the BISAPS and NEWS scoring systems.

In our study, the NEWS value was found to be high in patients with acute pancreatitis who had a fatal course. In a study conducted by the PANC study group with 2580 patients, they found the NEWS value of all pancreatitis patients to be 1 (0-2) (24). Furthermore, in our study, the NEWS value was found to be high in patients with acute pancreatitis who had a fatal course. In a study by Tan JW and colleagues, the median NEWS value of patients with fatal pancreatitis was found to be 11 (0-18) (25). In our study, we found the median NEWS value in patients with fatal pancreatitis to be 1 (0-14).

In our study, the average age of patients with acute pancreatitis presenting to our ED was 59, and the female ratio was 54.3%. In a study aimed at preventing hospitalization of patients with acute pancreatitis, the average age was found to be 56, and the female ratio was 53.2% (26) Our study is consistent with the literature. The most common complaint was abdominal pain, and the most common comorbidity was hypertension at 34.2%. The most common etiology was biliary pathologies at 59.7%. The most common cause among non-biliary pathologies was a mass. In a study by Şenkal et al. on patients with acute pancreatitis, the most common etiology was biliary pathologies at 76%. Alcohol was the most common cause among non-biliary pathologies at 20% (27,28).

There are some limitations to our study. Our study was a single-center and retrospective study. Moreover, the number of patients with fatal outcomes in our study had a small sample size. Also, during the screening of patients in our study, patients with amylase and lipase values three times higher than the reference value were included; however, patients whose amylase and lipase values were not three times higher than the reference value but who had imaging and typical abdominal pain of acute pancreatitis were not included in the study. If these patients had been included in the study, the results could have varied. For these reasons, it is recommended to conduct multicenter studies with larger sample sizes.

CONCLUSION

In patients with acute pancreatitis presenting to the ED with a fatal course, NEWS, BISAPS, and BAR values were found to be statistically significantly higher compared to those who

Table 5: Logistic Regression Analysis Result

	Univariate			Multivariate			
Parameters	**Odds rate**	**95% CI**	**p value**	**Parameters**	**Odds rate**	**95% CI**	**p value**
Age	1.032	1.012-1.052	0.001*	Age	1.016	0.990-1.043	0.234
NEWS	1.374	1.223-1.544	<0.001*	NEWS	1.077	0.908-1.279	0.395
BISAPS	2.567	1.890-3.486	<0.001*	BISAPS	1.084	0.648-1.814	0.758
eGFR	0.995	0.987-1.003	0.251				
BUN	1.036	1.022-1.050	<0.001				
Albumin	0.228	0.134-0.387	<0.001				
BAR	1.124	1.073-1.177	<0.001*	BAR	1.071	1.016-1.129	0.011
Creatin	1.194	0.980-1.456	0.079				
CRP	1.009	1.006-1.013	<0.001*	CRP	1.006	1.002-1.010	0.001
Neutrophil	1.118	1.063-1.175	<0.001				
Lymphocyte	0.675	0.444-1.027	0.066				
NLR	1.036	1.017-1.055	<0.001*	NLR	1.022	0.977-1.048	0.013

**: Parameters included in multivariate analysis*

NEWS: National Early Warning Score, BISAPS: Bedside Index of Severity of Acute Pancreatitis Score eGFR: Estimate Glomerular Filtration Rate, BUN: Blood Urea Nitrogen, BAR: BUN – Albumin Ration, CRP: C-reactive protein, NLR: Neutrophil Lymphocyte Ratio

survived. The AUC value of BAR in predicting in-hospital mortality was found to be higher compared to the AUC values of NEWS and BISAPS.

BAR is more effective than NEWS and BISAPS in predicting mortality in patients with acute pancreatitis presenting to the ED.

This study highlights BAR as a stronger and more practical predictor of in-hospital mortality than NEWS and BISAP in patients with acute pancreatitis. Its ease of calculation and accessibility make it a promising tool for early risk assessment in emergency settings.

Conflict of Interest: No conflict of interest was declared by the authors

Ethics: Necmettin Erbakan University Meram Medical Faculty Pharmaceutical and Non-Medical Device Studies Ethical Committee by the decision number of 2024/4997

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Approval of final manuscript: All authors.

REFERENCES

1. Waller A, Long B, Koyfman A, Gottlieb M. Acute Pancreatitis: Updates for Emergency Clinicians. J Emerg Med. 2018;55(6):769-779. doi:10.1016/j.jemermed.2018.08.009
2. Venkatesh NR, Vijayakumar C, Balasubramaniyan G, Kandhasamy C, Sundaramurthi S, Sreenath GS, et al. Comparison of Different Scoring Systems in Predicting the Severity of Acute Pancreatitis: A Prospective Observational Study. Cureus. 12(2):e6943. doi:10.7759/cureus.6943
3. Pando E, Alberti P, Mata R, Gomez MJ, Vidal L, Cirera A, et al. Early changes in blood urea nitrogen (BUN) can predict mortality in acute pancreatitis: comparative study between BISAP score, APACHE-II, and other laboratory markers—a prospective observational study. Can J Gastroenterol Hepatol. 2021;2021.
4. Yucel A, Kilic AO, Kilinc SB. The role of the Inflammatory Biomarkers in the Early Production of the Severity of Paediatric Acute Pancreatitis. Selcuk Med J 2022;38(4): 186-193
5. Kumaravel A, Stevens T, Papachristou GI, Muddana V, Bhatt A, Lee PJ, et al. A model to predict the severity of acute pancreatitis based on serum level of amylase and body mass index. Clin Gastroenterol Hepatol. 2015;13(8):1496-1501.
6. Anudeep K, Kiliyanari A, Chandran I, Jose P, Mathew J. Prediction of Adverse Outcome and Mortality in Patients with Acute Pancreatitis Using BISAP Scoring System. Int J Life Sci Biotech Pharma Res. 2023;12(2).
7. Dundar ZD, Kocak S, Girisgin AS. Lactate and NEWS-L are fair predictors of mortality in critically ill geriatric emergency department patients. Am J Emerg Med. 2020;38(2):217-221.
8. Echevarria C, Steer J, Bourke SC. Comparison of early warning scores in patients with COPD exacerbation: DECAF and NEWS score. Thorax. Published online 2019:thoraxjnl-2019-213470.
9. Checchio LM, Como AJ. Electrolytes, BUN, creatinine: Who's at risk? Ann Emerg Med. 1986;15(3):363-366.
10. Aronson D, Mittleman MA, Burger AJ. Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure. Am J Med. 2004;116(7):466-473.
11. Küçükceran K, Ayrancı MK, Girişgin A, Koçak S, Dundar ZD. The role of the lactate/albumin ratio in predicting mortality in COVID-19 patients in the emergency department. Mevlana Tıp Bilim Derg. 2023;3(1):5-10.
12. He WH, Zhu Y, Zhu Y, Jin Q, Xu HR, Xion ZJ, et al. Comparison of multifactor scoring systems and single serum markers for the early prediction of the severity of acute pancreatitis. J Gastroenterol Hepatol. 2017;32(11):1895-1901.
13. Koutroumpakis E, Wu BU, Bakker OJ, Dudekula A, Singh VK, Besselink MG, et al. Admission hematocrit and rise in blood urea nitrogen at 24 h outperform other laboratory markers in predicting persistent organ failure and pancreatic necrosis in acute pancreatitis: a post hoc analysis of three large prospective databases. Off J Am Coll Gastroenterol ACG. 2015;110(12):1707-1716.
14. Kerner T, Vollmar B, Menger MD, Waldner H, Messmer K. Determinants of pancreatic microcirculation in acute pancreatitis in rats. J Surg Res. 1996;62(2):165-171.
15. Dundar ZD, Kucukceran K, Ayranci MK. Evaluation of The Predictive Power of Blood Urea Nitrogen/Albumin Ratio for in-Hospital Mortality in Critically III Patients. Selcuk Univ Med J. 2021;37(4):294-300. doi:10.30733/std.2021.01508
16. Lukens FJ, Ko D, Kröner PT, Salazar M, Raimondo M, Argueta PP. Modified Bedside Index for severity in acute pancreatitis (BISAP) score validation in the national inpatient sample database. Adv Med Sci. 2023;68(2):208-212.
17. Akcay A, Nguyen Q, Edelstein CL. Mediators of Inflammation in Acute Kidney Injury. Morand E, ed. Mediators Inflamm. 2010;2009:137072. doi:10.1155/2009/137072
18. Choi JW, Park JS, Lee CH. Genetically determined hypoalbuminemia as a risk factor for hypertension: instrumental variable analysis. Sci Rep. 2021;11(1):11290. doi:10.1038/s41598-021-89775-3
19. Don BR, Kaysen G. Poor Nutritional Status and Inflammation: Serum Albumin: Relationship to Inflammation and Nutrition. Semin Dial. 2004;17(6):432-437. doi:10.1111/j.0894-0959.2004.17603.x
20. Zou K, Huang S, Ren W, Xu H, Zhang W, Shi X, et al. Development and Validation of a Dynamic Nomogram for Predicting in-Hospital Mortality in Patients with Acute Pancreatitis: A Retrospective Cohort Study in the Intensive Care Unit. Int J Gen Med. Published online 2023:2541-2553.
21. Akyil FT, Yalcinsoy M, Hazar A, Cilli A, Celenk B, Kilic O, et al. Prognosis of hospitalized patients with community-acquired pneumonia. Pulmonology. 2018;24(3):164-169.
22. Bae SJ, Lee SH, Yun SJ, Kim K. Usefulness of the blood urea nitrogen-to-serum albumin ratio as a prognostic indicator of severity in acute ischemic stroke. Signa Vitae. 2021;17(4).
23. Okşul M, Bilge Ö, Taştan E, Işık F, İnci Ü, Akın H, et al. Evaluation of the effect of bun/albumin ratio on in-hospital mortality in hypertensive COVID-19 patients. Eur Rev Med Pharmacol Sci. 2023;27(5).
24. Han T, Cheng T, Liao Y, Tang S, Liu B, He Y, et al. Analysis of the value of the blood urea nitrogen to albumin ratio as a predictor of mortality in patients with sepsis. J Inflamm Res. Published online 2022:1227-1235.
25. PANC Study (Pancreatitis: A National Cohort Study): national cohort study examining the first 30 days from presentation of acute pancreatitis in the UK. BJS Open. 2023;7(3):zrad008.
26. Tan JW, Zhang XQ, Geng CM, Peng LL. Development of the National Early Warning Score-Calcium Model for predicting adverse outcomes in patients with acute pancreatitis. J Emerg Nurs. 2020;46(2):171-179.
27. Anderson K, Shah I, Yakah W, Cartelle AL, Zuberi SA, McHenry N, et al. Prospective evaluation of an emergency department protocol to prevent hospitalization in mild acute pancreatitis: Outcomes and predictors of discharge. Pancreatology. 2023;23(3):299-305.
28. Şenkal, N, Karahan L, Bardak AE, Konyaoğlu H, Teberik Kama E, İnci İ, et al. Akut Pankreatitte Ranson Skorunun Değerlendirilmesi: Acil Servise Başvuru Anında Değeri. İstanbul Tıp Fakültesi Derg. 2023;86(3):198-203. doi:10.26650/IUITFD.1272976

LETTER TO EDITOR

Commentary on Prognostic Scoring Systems for Septic Patients in the Emergency Department

Acil Serviste Sepsisli Hastaların Prognozuna Yönelik Skorlama Sistemleri Üzerine Yorumlar

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Dear Editor,

We read with great interest the article titled "Comparison of MEWS, qSOFA, and MEDS Scores in Predicting the Prognosis of Septic Patients in the Emergency Department," published in the November 2023 issue of your journal. The retrospective study by Arı et al. addresses a critical clinical question by comparing the prognostic value of various scoring systems in emergency department patients diagnosed with sepsis (1).

While we commend the authors for their meticulous work, we would like to offer several points that may contribute to the ongoing discussion:

Study Population Characteristics: The mean age of the included patients is relatively high (73.4 ± 14.6 years), which accurately reflects a high-risk elderly population in the context of sepsis. However, this demographic profile may limit the generalizability of the findings to younger populations or different healthcare settings. As highlighted in a recent meta-analysis, current data remain insufficient for pediatric and young adult populations, indicating a need for further studies focused on these groups (2).

Primary Endpoint – 28-Day Mortality: The selection of 28-day mortality as the primary outcome is both methodologically sound and consistent with the existing literature. Nevertheless, clarification on whether late mortality or hospital readmissions beyond this time frame were evaluated would provide deeper clinical insight.

Clinical Utility of Scoring Systems: The high sensitivity and negative predictive value of the MEDS score in predicting mortality are noteworthy. However, its relatively complex structure may reduce its practical utility in fast-paced emergency settings where rapid decision-making is essential (3). It may be beneficial for the authors to address this limitation.

Proposal for Score Modification: One component of the MEDS score is the presence of a lower respiratory tract infection (LRTI). Despite advancements in treatment, LRTIs remain a significant global health burden, particularly among elderly and immunocompromised individuals, contributing substantially to morbidity and mortality (4). In this context, the authors' suggestion to increase the weighting of LRTI within the MEDS score is notable. Prospective, multicenter studies are needed to assess the validity of such revisions, which could enhance the accuracy of risk stratification in septic patients and improve clinical decision-making.

Further Statistical Analysis: Although the AUC values derived from ROC analysis provide valuable information, conducting statistical comparisons of AUCs—such as using the DeLong test—would strengthen the methodological rigor and substantiate the superiority of the MEDS score over others.

In conclusion, this study offers a valuable comparative analysis for early risk stratification of septic patients in the emergency department. Future investigations supporting the proposed revisions to the MEDS score may further refine clinical decision-making processes.

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REFERENCES

1. Arı E, Demir ÖF, Arı M, Yıldırımer Çelik Y, Gülmez A. Acil Servisteki Sepsisli Hastaların Prognozunda MEWS, qSOFA ve MEDS Skorlarının Karşlaştırılması. Phnx Med J. 2023, 5(3):189-95.
2. Majidazar M, Hamidi F, Masoudi N, Vand-Rajabpour Z, Paknezhad SP. Comparing the Predictive Value of SOFA and SIRS for Mortality in the Early Hours of Hospitalization of Sepsis Patients: A Systematic Review and Meta-analysis. Arch Iran Med. 2024, 27(8):439-446.
3. Elbaih AH, Elsayed ZM, Ahmed RM, Abd-Elwahed SA. Sepsis patient evaluation emergency department (SPEED) score & mortality in emergency department sepsis (MEDS) score in predicting 28-day mortality of emergency sepsis patients. Chin J Traumatol. 2019, s. 22(6):316-322.
4. Moschopoulos CD, Kotanidou A, Tsiodras S, Fragkou PC. Editorial for Special Issue “Antimicrobial Treatment of Lower Respiratory Tract Infections”. Antibiotics (Basel). 2025, 14(3):232.