KASTAMONU MEDICAL JOURNAL

The Official Journal of
Medical Faculty of Kastamonu University

KASTAMONU MEDICAL JOURNAL 2021

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Volume : 5
Issue : 3
Year : 2025

e-ISSN: 2757-9336

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KASTAMONU MEDICAL JOURNAL

Original Article

DOI: 10.51271/KMJ-0200

Kastamonu Med J. 2025;5(3):145-149

Screening patients with metabolic syndrome for risk of obstructive sleep apnea: the syndrome Z

Hacı Ahmet Aydemir[1], Mustafa Bayraktar[2]

[1]Department of Family Medicine, Filiz Dolunay Family Health Center, Erzurum, Turkiye

[2]Department of Family Medicine, Faculty of Medicine, Atatürk University, Erzurum, Turkiye

Cite this article as: Aydemir HA, Bayraktar M. Screening patients with metabolic syndrome for risk of obstructive sleep apnea: the syndrome Z. *Kastamonu Med J.* 2025;5(3):145-149.

Received: 08.10.2024 ◆ **Accepted**: 15.01.2025 ◆ **Published**: 03.09.2025

ABSTRACT

Aims: Syndrome Z is defined as the coexistence of obstructive sleep apnea (OSA) and metabolic syndrome. As family medicine takes on the role of preventive medicine, syndrome Z is gaining importance in primary care. We aimed to determine the prevalence of syndrome Z in primary care by examining the risk of OSA in individuals with metabolic syndrome.

Methods: A cross-sectional study of patients diagnosed with metabolic syndrome according to NCEP-ATP III criteria was conducted at the family health center. Patients' anthropometric measurements (waist circumference, neck circumference, height, and weight) were recorded. OSA risk assessment scales included the Berlin and STOP-BANG questionnaires, which have been shown in studies to be more sensitive tests and were therefore selected for use in our study.

Results: Of 156 participants, 37.8% (n=59) were at high risk for OSA on both questionnaires. According to STOP-BANG, 57.4% of men and 31.6% of women were at high risk, which was statistically significant. No association was found between OSA and diabetes, hypertension, and dyslipidemia. However, in both questionnaires, obesity and high body-mass index significantly increased the risk of OSA. The area under the curve was 0.649 with a specificity of 80.6% using a cut-off of 34.5 kg/m² for BMI.

Conclusion: Obese individuals with metabolic syndrome should be assessed for syndrome Z in primary care settings and preventive services should be offered to those at risk.

Keywords: Metabolic syndrome, obstructive sleep apnea syndrome, primary care, screening, syndrome Z

INTRODUCTION

Background

Obstructive sleep apnea syndrome (OSAS) is a syndrome characterized by recurrent episodes of apnea and hypopnea during sleep that cause interrupted sleep and decreased oxygen saturation.[1] OSAS has been found to be an independent risk factor for the development of hypertension, atherosclerosis, cardiovascular morbidity, and all-cause mortality.[2] It has also been determined that OSAS and short-term sleep cause metabolic changes such as glucose intolerance and insulin resistance.[3] Therefore, early detection and management of OSAS is very important in terms of preventing the development of many chronic diseases.

Although it is accepted that the gold standard diagnosis of OSAS is polysomnography,[4] it is not possible to screen all risky individuals with polysomnography due to the limited number of sleep laboratories and trained personnel. Therefore, clinical and evidence-based questionnaires will be helpful for risk detection and screening of OSAS in non-sleep clinical settings, but not for the confirmation of diagnosis.[4] For this purpose, it has been evaluated that the Epworth Sleepiness Scale, the STOP-BANG questionnaire, the STOP questionnaire, the Berlin questionnaire and the Pittsburgh Sleep Quality Index can be used to determine the risk of OSAS, and among which the STOP-BANG and Berlin questionnaires were identified as having the uppermost sensitivity.[5] In a meta-analysis of 14 studies assessing the diagnostic accuracy of the surveys, it was determined that the Berlin and the STOP-BANG questionnaires were found to have higher sensitivity in the diagnosis of OSAS.[6]

Metabolic syndrome (MetS) is defined as a metabolic dysfunction in which the risk of developing diabetes and cardiovascular disease in the future increases two to five times.[7] National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III criteria are most commonly used for the diagnosis.[8] Accordingly, an increase in waist circumference, high blood pressure or receiving treatment for hypertension, high fasting blood sugar and triglyceride, and low level of high-density lipoprotein (HDL) cholesterol were the parameters for the diagnosis of MetS.[9]

OSAS and MetS are increasingly being associated, and the coexistence of OSAS and MetS is defined as syndrome Z.[10] Since the exact pathological basis has not yet been

Corresponding Author: Mustafa Bayraktar, mustafabayraktar@atauni.edu.tr

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determined, there are many publications in the literature to reveal the relationship between OSAS and MetS.[8,11-13] In a study, OSAS was found to be significantly associated with an increased risk of MetS.[12] The relationship between OSAS and systemic disease was investigated in another study and it was determined that the comorbidity of systemic diseases such as hypertension, diabetes mellitus and cardiovascular diseases increased with the severity of OSAS,[13] as in MetS. This reveals the necessity of screening and distinguishing people who have OSAS and MetS in order not to have a higher risk for developing systemic diseases.

Objective

The primary duty of family medicine is to provide preventive healthcare services and to identify the risks related to health in individuals through screening. In this context, it should be evaluated that family physicians should screen syndrome Z, the co-occurrence of OSAS in patients with MetS, to prevent the development of possible comorbidities. For this purpose, in this study, we investigated the risk of OSAS in people with MetS who applied to Family Health Centers through two different questionnaires.

METHODS

Ethical Approval

Ethical approval was obtained from the Atatürk University Faculty of Medicine Clinical Researches Ethics Committee (Date: 27.06.2019, Decision No: 09). Written informed consent was obtained from participants and the tenets of the Declaration of Helsinki were followed throughout the study.

Study Design and Setting

This study was designed as a cross-sectional descriptive study. The study was conducted between August 2019 and January 2020 at an educational family health center (FHC) in Erzurum, in the eastern part of Turkiye.

Participants

The study population consisted of patients over 20 years of age who enrolled in the FHC and were diagnosed with MetS according to NCEP-ATP III criteria. For the diagnosis of MetS according to NCEP-ATP III, the presence of three or more of the following five characteristics was accepted as MetS: 1. Waist circumference (>88 cm in females, >102 cm in males), 2. Elevated serum triglyceride level (≥150 mg/dl), 3. Decreased HDL cholesterol levels (<50 mg/dl in women, <40 mg/dl in men), 4. Elevated blood pressure (≥130/85 mmHg), 5. Elevated fasting glucose levels (≥100 mg/dl).[14]

The participants' age, sex, metabolic diseases, and anthropometric measurements (waist circumference, neck circumference, height, weight) were recorded. In terms of anthropometric measurements, the normal range of neck circumference was 43 cm in men and 38 cm in women, increased waist circumference was more than 88 cm in women and 102 cm in men, normal body-mass index (BMI) was less than 25 kg/m^2, while obesity was considered as BMI more than 30 kg/m^2 in both sexes.

Questionnaires

Among the scales used to determine the risk of OSAS, the Berlin and STOP-BANG questionnaires have been shown in studies to be more sensitive tests[5,6] and were therefore selected and used in our study.

The STOP-BANG questionnaire was developed by Ong et al.[15] in 2010, and its Turkish validity and reliability tests was conducted by Acar et al.[16] in 2013. According to the Turkish version, the sensitivity and specificity values were given as 93.2% and 97.2% when the apnea-hypopnea index (AHI) was >5; 92.3% and 96.6% when the AHI was >15; and 96.9% and 93.6% when the AHI was >30. The STOP-BANG questionnaire consists of eight questions, and patients are classified as low, medium, and high risk for OSAS. Those who answer yes to 0-2 out of eight questions are considered low-risk, those who answer yes to 3-4 of them are considered medium-risk, and those who answer yes to 5-8 of them are considered high-risk.

The Berlin questionnaire was developed by Netzer et al.,[17] and its Turkish version was conducted by Ulasli et al.[18] in 2014. According to the Turkish version, the sensitivity and specificity values of AHI scores of 5, 15, and 30 were defined as 73.1% and 44.5%, 76.4% and 39.5%, and 80.3% and 35.3%, respectively. The Berlin questionnaire consists of three categories and 10 questions in total. The first category consists of five questions, the second and the third categories consist of four and one questions, respectively. If two or more significant scores are obtained from these categories (category 1≥2 points, or category 2≥2 points, or category 3≥1 point) it reveals high risk for OSAS, if significant scores are not obtained, it means low risk.

Sample Size

The power analysis performed determined that the number of patients required for the study was 156, with a type 1 error of 0.05 and a confidence interval of 80%.

Statistical Analysis

SPSS 20 (IBM, NY, USA) was used for statistical analyses. Descriptive statistics were presented as frequencies and percentages for categorical data, and means and standard deviations for numerical data. The suitability of the numerical variables for normal distribution was examined using histogram graphs. One-way ANOVA, Fischer's exact, ROC analysis, and Chi-square tests were used as hypothesis tests. Statistical significance was set as $p<0.05$.

RESULTS

A total of 156 participants who met the MetS criteria were included in our study. The mean age was 61.7±10.5 years; neck circumference was 39.2±3.0 cm, waist circumference was found as 110.5±10.6 cm; and mean BMI was 33.4±5.3 kg/m^2 (**Table 1**). Of the 156 participants included, 95 (60.1%) were female and 61 (39.1%) were male. Among them, 126 (80.8%) people had diabetes mellitus, 148 (94.9%) had hypertension, 103 (66%) had dyslipidemia, and 118 (75.6%) had obesity. Considering the distribution of individuals according to BMI, six (3.8%) participants had normal weight, 32 (20.5%) were overweight, and 118 (75.6%) were obese.

Using the STOP-BANG questionnaire to assess the risk of OSAS, 65 (41.7%) subjects had a high risk of OSAS, 74 (47.4%) had a moderate risk of OSAS, and 17 (10.9%) had a low risk of OSAS. When the risk assessment of the individuals was made according to the Berlin Questionnaire, it was found that 94 (60.3%) people had a high risk of OSAS and 62 (39.7%) people had a low risk of OSAS (**Figure 1**).

Table 1. Anthropometric measurement data of the participants

	n	Min	Max	Mean	SD
Age	156	35	87	61.67	10.48
Height (m)	156	1.42	1.82	1.61	0.08
Weight (kg)	156	53.5	140.2	86.39	13.51
Neck circumference (cm)	156	32	52	39.20	3.00
Waist circumference (cm)	156	86	142	110.52	10.64
Body-mass index (kg/m²)	156	23.72	46.61	33.38	5.29

Min: Minimum, Max: Maximum, SD: Standard deviation

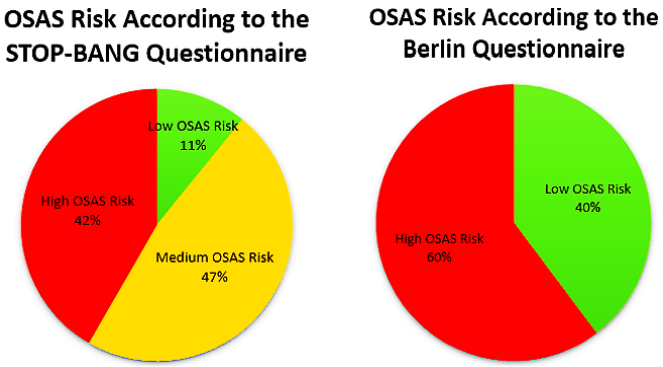

Figure 1. OSAS risk categories of individuals based on the STOP-BANG and Berlin questionnaires

OSAS: Obstructive sleep apnea syndrome

When comparing the OSAS risk status of individuals according to the STOP-BANG and Berlin questionnaires, 59 (37.8%) individuals were found to be at high risk of OSAS according to both questionnaires. However, 35 (22.4%) people who had a moderate risk of OSAS according to the STOP-BANG questionnaire were found to have a high risk of OSAS according to the Berlin questionnaire (Figure 2).

When the risk of OSAS was examined in terms of gender, 36 (59%) of the male participants were found to be at high risk, while 58 (61.1%) of the female participants were found to be at high risk according to the Berlin Questionnaire, but no statistically significant difference was found (p=0.80). On the other hand, 35 (57.4%) of the men were found to be at high risk according to the STOP-BANG questionnaire, while 30 (31.6%) of the women were found to be at high risk. Men were found to have a statistically higher risk than women (p=0.04) (Table 2).

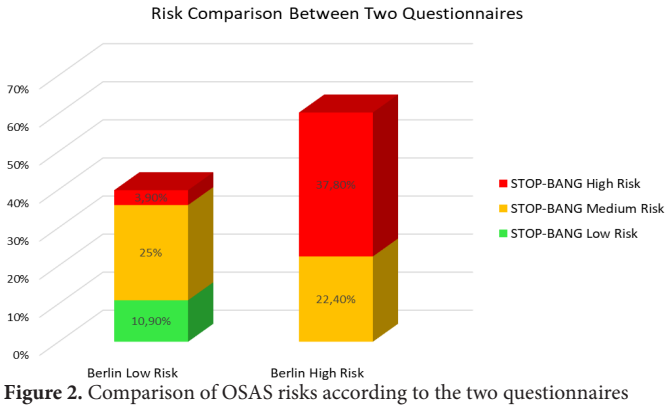

Figure 2. Comparison of OSAS risks according to the two questionnaires

OSAS: Obstructive sleep apnea syndrome

Neck and waist circumferences according to the Berlin scale were found to be higher in the high-risk group, but the difference between the groups was not statistically significant. On the other hand, both neck and waist circumferences were found to be higher in individuals at high risk for OSAS according to the STOP-BANG Scale, which was statistically significant (p<0.01) (Table 2).

When examining the MetS parameters (diabetes mellitus, hypertension, and dyslipidemia) and OSAS risk analysis according to the Berlin Questionnaire, no significant difference was observed in these three conditions (p=0.389, p=0.266, and p=0.746, respectively). Similarly, according to the STOP-BANG questionnaire, there were no statistically significant OSAS risks in the presence of diabetes mellitus, hypertension or dyslipidemia (p=0.579; p=0.264 and p=0.366, respectively). In contrast, the presence of obesity was found to significantly increase the risk of OSAS according to the Berlin Questionnaire (p=0.003). Similarly, the presence of obesity was associated with a significantly higher risk of OSAS according to the STOP-BANG questionnaire (p=0.001) (Table 3).

Table 2. OSAS risk comparison by gender, BMI, neck and waist circumferences of participants according to Berlin and STOP-BANG questionnaires

		Berlin Questionnaire			STOP-BANG Questionnaire			
		Low risk	High risk	p**	Low risk	Medium risk	High risk	p**
Gender (n, %)	Men	25 (41.0%)	36 (59.0%)	0.800	3 (4.9%)	23 (37.7%)	35 (57.4%)	0.04
	Women	37 (38.9%)	58 (61.1%)		14 (14.7%)	51 (53.7%)	30 (31.6%)	
BMI (kg/m²)*		31.7±4.7	34.5±5.4	0.001	29.3±3.5	32.7±4.7	35.2±5.6	<0.05
Neck circumference (cm)*		38.7±2.5	39.55±3.2	0.069	37.4±1.8	38.2±2.6	40.8±3.0	<0.01
Waist circumference (cm)*		108.6±9.1	111.8±11.4	0.054	104.4±8.9	108.7±9.7	114.3±10.9	<0.01

*Mean, standard deviation, **Chi-square test, BMI: Body-mass index

Table 3. OSAS risk comparisons according to the Berlin and STOP-BANG questionnaires in individuals with or without metabolic syndrome parameters

		Berlin Questionnaire			STOP-BANG Questionnaire			
	Total	Low risk	High risk	p*	Low risk	Medium risk	High risk	p*
Diabetes mellitus (n, %)	126 (80.8%)	48 (30.8%)	78 (50.0%)	0.389	13 (10.3%)	58 (46.0%)	55 (43.7%)	0.579
Hypertension (n, %)	148 (94.9%)	57 (36.5%)	91 (58.3%)	0.266	15 (9.6%)	70 (44.9%)	63 (40.4%)	0.264
Dyslipidemia (n, %)	103 (66.0%)	40 (25.6%)	63 (40.4%)	0.746	10 (6.4%)	53 (34.0%)	40 (25.6%)	0.366
Obesity (n, %)	118 (75.6%)	39 (25.0%)	79 (50.6%)	0.003	7 (4.5%)	56 (35.9%)	55 (35.3%)	0.001

*Chi-square test, OSAS: Obstructive sleep apnea syndrome

When the effect of BMI of the study participants was examined using the Berlin Questionnaire, the mean BMI of the high-risk participants was 34.5±5.4 kg/m^2, while the mean BMI of the low-risk participants was 31.7±4.7 kg/m^2. High BMI was found to significantly increase the risk of OSAS (p=0.001). According to the STOP-BANG questionnaire, the mean BMI of the high-risk participants was 35.2±5.6 kg/m^2, while the mean BMI of the low-risk participants was 29.3±3.5 kg/m^2. It was also observed that a high BMI significantly increased the risk of OSAS (p<0.05) (**Table 2**).

The BMI values of the participants with the Berlin questionnaire were statistically evaluated by ROC analysis, because the risk assessment of the Berlin questionnaire had two categories as low and high risk. The cut-off value for BMI was found to be 34.5 kg/m^2 (**Figure 3**). It was found that individuals with a BMI higher than this value had a statistically significant higher risk compared to the Berlin questionnaire. The area under the curve (AUC) was 0.649 and the sensitivity was 44.7% and the specificity was 80.6% for the BMI cut-off of 34.5 kg/m^2 (p=0.002).

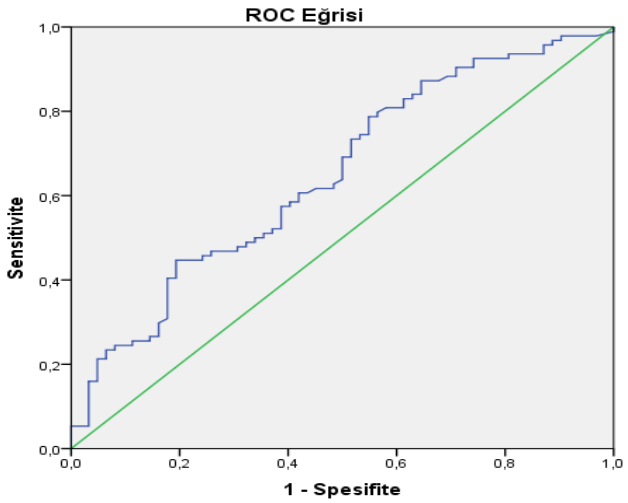

Figure 3. ROC analysis curve of the BMI and OSAS risk of the participants according to the Berlin questionnaire

ROC: Receiver operating characteristic, BMI: Body-mass index, OSAS: Obstructive sleep apnea syndrome

DISCUSSION

OSAS is very important in terms of metabolic diseases that it paves the way for, rather than being a sleep disorder on its own. According to a study, when individuals with and without OSAS were compared, it was observed that insulin resistance, obesity, and lipid profile were independent and strongly correlated with MetS in individuals with OSAS.[12] It was also revealed that OSAS is associated with metabolic diseases such as obesity, insulin resistance, type 2 DM, non-alcoholic fatty liver disease.[19] Patients with OSAS was found to have additional chronic diseases such as hypertension, diabetes mellitus, coronary artery disease, and chronic heart failure, and it was observed that the comorbidity of systemic diseases increased as the severity of OSAS increased.[13] In our study, it was found that, obesity and high BMI were significantly associated with the risk of OSAS in both Berlin and STOP-BANG questionnaires, in primary care patients.

A systematic review and meta-analysis investigated the possible association of resistant hypertension with OSAS and found a significantly increased risk of resistant hypertension in OSAS patients with or without risk factors.[20]

In studies investigating the association of OSAS and metabolic diseases, the association of OSAS and obesity is seen at a very high level. In a study, obese individuals were examined by the Epworth Sleepiness Scale, and it was observed that daytime sleepiness increased with increasing BMI.[21] Similarly, in our study, BMI was found to be statistically significantly higher in high-risk groups in both the Berlin and STOP-BANG questionnaires.

In our study, both in Berlin and STOP-BANG questionnaires, the BMI of the high-risk groups were found to be significantly higher (p≤0.01). On the other hand, no significant difference was found between neck and waist circumferences and the risk of OSAS according to the Berlin questionnaire (p>0.05). According to the STOP-BANG questionnaire, the neck and waist circumferences were found to be significantly higher in the high-risk group, therefore, a significant relationship was found between the BMI, waist and neck circumferences with the high OSAS risk group according to the STOP-BANG questionnaire.

It is known that the gold standard diagnostic method of OSAS is polysomnography. However, due to the lack of sufficient number of sleep laboratories in the world and in our country, and due to the long assessment durations, expensiveness, and special equipment requirements, alternative diagnostic methods have been searched and different cost-effective, out-of-hospital screening methods as a polysomnography alternative, have been used and recommended.[22] For this purpose, a study using BMI and neck circumference measurements, conducted on patients diagnosed with OSAS by polysomnography, and according to the results they obtained, it was determined that higher BMI and neck circumference values predicted and increased risk of severe OSAS in both genders.[23]

A study that examined the risk of OSAS in primary care using the Berlin Questionnaire found a high risk of OSAS of 27.4%.[24] Although this is lower than that found in our study, it is worth noting that diagnosis and screening for OSAS is important and necessary in primary care, which is the first point of contact individuals have with the healthcare system.

In our study, an investigation was conducted in patients with MetS using the Berlin and STOP-BANG questionnaires, whose validity and reliability studies were performed in order to determine OSAS risk and screening. As a strength of our study, these questionnaires were used for the first time in MetS patients for the assessment of OSAS risk and in the screening for risk of syndrome Z in primary care, as far as we know. Within the scope of preventive health services and periodic examinations, which are among the primary duties of family physicians, screening for OSAS in MetS patients with questionnaires should be recommended and performed. The Berlin or STOP-BANG questionnaires, which are simple, quick and reliable, should be offered by family physicians as part of regular screening in the future.

Limitations

This study is one of the few that has looked at syndrome Z in a primary care setting. However, it has some limitations. First, the relatively small sample size and the single-center design of the study may limit the generalizability of the results. Despite the proven high sensitivity and specificity of the Berlin and STOP-BANG questionnaires, the risk and diagnosis of OSAS

was not confirmed by follow-up polysomnography. As another limitation, this study was designed as a cross-sectional descriptive study, and at-risk patients were not followed for OSAS development.

CONCLUSION

In this study, screening for syndrome Z in primary care was investigated by assessing the risk of OSAS in patients with MetS who presented to primary care practices. The risk of OSAS was statistically higher with high BMI, waist and neck circumference in the STOP-BANG questionnaire and with high BMI in the Berlin questionnaire. In primary care, OSAS questionnaires should be used as a simple, applicable, and rapid method for screening OSAS risk in patients with MetS, especially in obese individuals.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Atatürk University Faculty of Medicine Clinical Researches Ethics Committee (Date: 27.06.2019, Decision No: 09).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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KASTAMONU MEDICAL JOURNAL

Original Article

DOI: 10.51271/KMJ-0201

Kastamonu Med J. 2025;5(3):150-156

Overlooked challenges after kidney transplantation: non-immunologic complications from a single-center experience

Betül Gülsüm Yavuz Veizi[1], Gizem Kumru[2], Şiyar Erdoğmuş[3], Acar Tüzüner[4], Kenan Keven[2]

[1]Department of Geriatrics, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, University of Health Sciences, Ankara, Turkiye

[2]Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Ankara University, Ankara, Turkiye

[3]Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Başkent University, Ankara, Turkiye

[4]Department of General Surgery, Faculty of Medicine, Ankara University, Ankara, Turkiye

Cite this article as: Yavuz Veizi BG, Kumru G, Erdoğmuş Ş, Tüzüner A, Keven K. Overlooked challenges after kidney transplantation: non-immunologic complications from a single-center experience. *Kastamonu Med J.* 2025;5(3):150-156.

Received: 14.12.2024 ◆ **Accepted**: 16.01.2025 ◆ **Published**: 03.09.2025

ABSTRACT

Aims: This study investigates non-immunologic complications in kidney transplant recipients, focusing on their incidence and risk factors.

Methods: A retrospective observational analysis was conducted on 416 adult patients who underwent kidney transplantation at a tertiary care hospital between 2002 and 2016. Demographic, clinical, and laboratory data, as well as post-transplant complications, were extracted from medical records. Statistical analysis was performed to evaluate risk factors associated with new-onset diabetes mellitus (NODAT), hypertension, dyslipidemia, hyperuricemia, and avascular necrosis.

Results: The most common complication was dyslipidemia (70.2%), followed by NODAT (24.8%), hypertension (19.7%), hyperuricemia (10.6%), and avascular necrosis (4.8%). Advanced age, higher BMI, elevated CRP, male gender, and CMV positivity were significantly associated with NODAT. Hypertension was linked to calcineurin inhibitor use, while dyslipidemia correlated with higher BMI and cyclosporine therapy. Hyperuricemia was significantly associated with lower GFR and male gender. Avascular necrosis was predominantly observed in glucocorticoid-treated patients. Effective management of these complications is critical to improving patient outcomes.

Conclusion: Metabolic complications are prevalent and have a significant impact on post-transplant survival. Regular follow-up and individualized management strategies are essential to address these risks and enhance long-term outcomes for kidney transplant recipients. Further multicenter prospective studies are recommended to validate these findings.

Keywords: Kidney transplantation, postoperative complications, non-immunologic complications, new-onset diabetes after transplantation, NODAT, metabolic diseases

INTRODUCTION

Kidney transplantation is the gold standard treatment for patients diagnosed with end-stage renal disease (ESRD).[1] This method significantly improves patients' quality of life and long-term survival rates compared to other renal replacement therapies. However, despite the success of kidney transplantation, patients experience various complications in the post-transplant period that can have a negative impact on survival rates and quality of life.[2] These complications include both immunologic and non-immunologic problems, both of which must be carefully managed during post-transplant care and treatment.[3]

Non-immunologic complications are among the most common and need to be treated in the post-transplant period. Cardiovascular disease, hypertension, dyslipidemia, new-onset diabetes mellitus (NODAT), hyperuricemia and metabolic bone disorders are common metabolic complications in this patient group.[3] Cardiovascular disease is a major cause of mortality after transplantation and plays a crucial role in the long-term prognosis of patients.[4,5] Therefore, early detection and effective treatment of these complications are crucial for improving patient survival and quality of life.

Immunosuppressive therapy regimens play a central role in the development of metabolic complications.[6] While these drugs are used to prevent allograft rejection, their metabolic side effects are significant and should not be overlooked.[7] Metabolic complications such as dyslipidemia, hypertension and NODAT are common in patients receiving immunosuppressive treatment.[8-10] These complications can impair renal function and significantly reduce patients' quality of life.[11-13] Therefore, the management of immunosuppressive therapy should be carefully planned to take into account the patient's individual risk factors.

Corresponding Author: Betül Gülsüm Yavuz Veizi, dr.bgyavuz@hotmail.com

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In this study, non-immunologic complications observed in kidney transplant patients in a tertiary care facility were investigated in detail. The aim of the study is to evaluate the incidence, etiologic factors and long-term impact of these complications on patient survival in the post-transplant period. The data obtained will also be used to provide recommendations for the management of post-transplant complications and contribute to the existing literature.

METHODS

Study Design and Patient Selection

Ethics committee approval for the study was obtained from the Ankara University Faculty of Medicine Clinical Researches Ethics Committee (Date: 14.03.2016, Decision No: 05-184-16). The study adhered to the Declaration of Helsinki throughout the research process.

This retrospective observational study was conducted by retrospectively reviewing the medical records of patients who had undergone kidney transplantation at Ankara University Faculty of Medicine, Department of Nephrology between January 2002 and January 2016. The study population consisted of adults (18 years and older) who were followed up for at least one year after transplantation. A total of 534 patient records were reviewed. However, patients under the age of 18 (n=54), foreign nationals (n=26) and patients with incomplete follow-up data (n=38) were excluded from the study. The final analysis included 416 patients.

Data Collection and Analysis

Demographic data [age, sex, body-mass index (BMI)], transplant-related data (date of transplant, type of transplant-living or deceased donor), primary renal disease, renal replacement therapy (hemodialysis or peritoneal dialysis) and duration before transplantation, age and sex of donor, HLA tissue compatibility and PRA positivity (panel reactive antibodies) were collected. In addition, data on post-transplant complications [such as new-onset diabetes mellitus (NODAT), hypertension, dyslipidemia, hyperuricemia, metabolic bone disorders and avascular necrosis] were also recorded in detail. In excluded patients, while identifying post-transplant metabolic complications, those with a history of hyperlipidemia before transplantation were excluded from the cohort screened for post-transplant hyperlipidemia; those with a history of hypertension were excluded from the cohort screened for post-transplant hypertension; and those with a history of diabetes were excluded from the cohort screened for post-transplant diabetes. Patients without these pre-existing conditions were evaluated for potential complications. These data were obtained from hospital records and regular clinical follow-up.

Definitions of Complications

New-onset diabetes mellitus: Diagnosed according to ADA (American Diabetes Association) criteria if the twice-measured fasting plasma glucose value was ≥126 mg/dl or the randomly measured plasma glucose value was ≥200 mg/dl in patients without a previous diagnosis of diabetes before transplantation.[14]

Hypertension: Defined as an average blood pressure of ≥140/90 mmHg measured twice in a sitting position after rest or the need for antihypertensive medication.[15]

Dyslipidemia: Defined as an LDL cholesterol level of ≥100 mg/dl or a non-HDL cholesterol level (total cholesterol-HDL) of ≥130 mg/dl.[16]

Hyperuricemia: Defined as a serum uric acid level of ≥7 mg/dl in men and ≥6 mg/dl in women.[17]

Metabolic bone disorders and avascular necrosis: Metabolic bone disorders were defined as decreased bone mineral density in the post-transplant period, and conditions such as osteoporosis and osteopenia were studied under this category.[18] Avascular necrosis was defined as damage to trabecular bone tissue and osteocytes without infection, confirmed by MRI.[19]

Statistical Analysis

The data analysis was carried out with the software "SPSS for Windows 22.0". Descriptive statistics were presented as mean±standard deviation, median, frequency and percentages. Categorical data were analyzed using Pearson's chi-square test and Fisher's Exact test. The normality of continuous data was assessed using visual (histograms, Q-Q plots) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). The Mann-Whitney U test was used for comparisons of non-normally distributed data. A p-value of <0.05 was considered statistically significant in all analyses, and appropriate parametric or non-parametric tests were applied depending on the normality of the data distribution.

RESULTS

Demographic and Clinical Characteristics

The study population comprised 416 individuals, with a mean age at transplantation of 37.80±12.01 years. The gender distribution revealed a predominance of males (62.0%) compared to females (38.0%). The mean BMI was 22.94±3.85 kg/m^2. Chronic renal failure was attributed to various etiologies, the most common being unknown causes (26.4%), followed by chronic glomerulonephritis (24.0%) and hypertensive nephropathy (11.5%). A smaller proportion of patients were diagnosed with diabetic nephropathy (9.9%) or amyloidosis (6.3%) (**Table 1**).

Renal replacement therapies predominantly involved hemodialysis (64.4%), with peritoneal dialysis (11.4%) and preemptive transplantation (18.3%) being less common. The mean duration of dialysis prior to transplantation was 43.01±51.22 months. Hospitalization duration post-transplantation averaged 16.20±12.15 days. Regarding donor characteristics, 57.3% of donors were female. Positive PRA rates were observed in 10.4% of patients for class-I and class-II antibodies, with 15.9% exhibiting both class-i and class-ii positivity (**Table 1**).

The first-month follow-up data for the 416 patients revealed a mean GFR of 73.18±23.07 ml/min. Proteinuria was observed in 31.0% of patients. The mean BMI was 23.04±3.55 kg/m^2, while the mean plasma glucose level was 97.6±40.5 mg/dl. Mean uric acid and LDL levels were 4.86±1.30 mg/dl and 119.5±42.1 mg/dl, respectively. Inflammatory markers indicated a mean CRP level of 7.01±22.89 mg/dl (**Table 2**).

Electrolyte levels were within expected ranges, with mean calcium and phosphorus levels recorded as 9.45±0.70 mg/dl and 2.90±0.97 mg/dl, respectively. The mean albumin level was 4.00±0.48 mg/dl. Regarding viral infections, 2.6% of

Table 1. Study population

Variables	Total n=416
Age at transplantation, mean±SD	37.80±12.01
Gender, n (%)	
Male	258 (62.0)
Female	158 (38.0)
BMI, kg/m², mean±SD	22.94±3.85
Diagnosis of chronic renal failure, n (%)	
Unknown	110 (26.4)
Chronic glomerulonephritis	100 (24.0)
Hypertensive nephropathy	48 (11.5)
Diabetic nephropathy	41 (9.9)
Other known causes	33 (7.9)
Amyloidosis	26 (6.3)
Vesicoureteral reflux nephropathy	20 (4.8)
Chronic pyelonephritis	14 (3.4)
Polycystic kidney disease	13 (3.1)
Systemic lupus erythematosus	7 (1.7)
Congenital kidney disease	4 (1.0)
Renal replacement therapy applied, n (%)	
Peritoneal dialysis	46 (11.4)
Hemodialysis	261 (64.4)
Preemptive	74 (18.3)
Hemodialysis+peritoneal dialysis	24 (5.9)
Duration of dialysis, months, mean±SD	43.01±51.22
Length of hospitalization, days, mean±SD	16.20±12.15
Donor gender, n (%)	
Male	156 (42.7)
Female	209 (57.3)
Positive PRA, n (%)	
Class-I	42 (10.4)
Class-II	42 (10.4)
Class I and II	66 (15.9)

SD: Standard deviation, BMI: Body-mass index

Table 2. Post-transplantation 1st-month follow-up data

Variables	Total (n=416)
GFR, ml/min, mean±SD	73.18±23.07
Proteinuria, n (%)	129 (31.0)
BMI, kg/m², mean±SD	23.04±3.55
Plasma glucose level, mg/dl, mean±SD	97.6±40.5
Uric acid, mg/dl, mean±SD	4.86±1.30
LDL, mg/dl, mean±SD	119.5±42.1
CRP, mg/dl, mean±SD	7.01±22.89
Calcium, mg/dl, mean±SD	9.45±0.70
Phosphorus, mg/dl, mean±SD	2.90±0.97
Albumin, mg/dl, mean±SD	4.00±0.48
Anti-HCV positive, n (%)	11 (2.6)
HCV RNA positive, n (%)	7 (18.4)
CMV positive, n (%)	42 (10.3)

GFR: Glomerular filtration rate; BMI: Body-mass index; LDL: Low density lipoprotein, CRP: C-reactive protein, HCV: Hepatitis C virus, CMV: Cytomegalovirus

patients tested positive for anti-HCV antibodies, with 18.4% of these having detectable HCV RNA. CMV positivity was documented in 10.3% of the cohort (Table 2).

Post-Transplant Complications

During the follow-up period, a range of complications was observed among the 416 patients. Dyslipidemia was the most common complication, affecting 70.2% of the cohort. Diabetes mellitus developed in 24.8% of patients, while hypertension was reported in 19.7%. Hyperuricemia was observed in 10.6% of the patients, and 4.8% experienced avascular necrosis.

New Onset Diabetes Mellitus

The distribution of 1st-month risk factors varied significantly between the non-NODAT group (n=313) and the NODAT group (n=103). Transplantation age ≥45 years was significantly more common in the NODAT group (44.1%) compared to the non-NODAT group (22.5%) (p=0.001). Similarly, a higher proportion of patients in the NODAT group had a BMI ≥25 kg/m² (35.6% vs. 22.8%, p=0.010). CRP levels were elevated in the NODAT group (8.83±26.47 mg/dl) compared to the non-NODAT group (6.44±21.66 mg/dl, p=0.030) (Table 3).

Table 3. Distribution of relevant 1 -month risk factors according to NODAT development

Variables	Non-NODAT group (n=313)	NODAT group (n=103)	p
Transplantation age ≥45 years, n (%)	69 (22.5)	45 (44.1)	0.001***
BMI ≥25 (kg/m²), n (%)	71 (22.8)	36 (35.6)	0.010***
HCV Positive, n (%)	7 (2.3)	4 (3.9)	0.477*
Donor gender, female, n (%)	156 (58.0)	53 (55.2)	0.636***
Recipient gender, male, n (%)	185 (59.1)	73 (70.9)	0.033***
CRP, mean±SD	6.44±21.66	8.83±26.47	0.030**
Acute rejection, n (%)	43 (13.7)	6 (5.8)	0.031***
Proteinuria, n (%)	200 (63.9)	71 (68.9)	0.352***
CMV infection, n (%)	62 (19.8)	36 (35.0)	0.002***

NODAT: New onset diabetes after transplantation, DM: Diabetes mellitus, BMI: Body-mass index, CRP: C-reactive protein, HCV: Hepatitis C virus, CMV: Cytomegalovirus, SD: Standard deviation, *Fisher's exact test, **Mann-Whitney U test, ***Chi-square test

Recipient gender also showed a significant association, with 70.9% of the NODAT group being male compared to 59.1% in the non-NODAT group (p=0.033). CMV infection rates were notably higher in the NODAT group (35.0%) than in the non-NODAT group (19.8%) (p=0.002). No statistically significant differences were observed for HCV positivity, donor gender, proteinuria, or acute rejection between the two groups (Table 3).

Hypertension

The distribution of 1st-month risk factors for post-transplantation hypertension (HT) showed no significant differences between the non-HT group (n=334) and the HT group (n=82) for most variables. The mean age at transplantation was similar between the groups (37.93±12.35 years in the non-HT group vs. 37.26±10.57 years in the HT group, p=0.846). Likewise, donor gender (female: 59.1% vs. 50.0%, p=0.157) and recipient gender (male: 62.3% vs. 61.0%, p=0.828) did not show statistically significant differences (Table 4).

Table 4. Distribution of relevant 1st-month risk factors according to post-transplantation HT development

Variables	Non-HT group (n=334)	HT group (n=82)	p
Age at transplantation, mean±SD	37.93±12.35	37.26±10.57	0.846**
Donor gender, female, n (%)	172 (59.1)	37 (50.0)	0.157***
Recipient gender, male, n (%)	208 (62.3)	50 (61.0)	0.828***
Proteinuria, mg/dl, mean±SD	219 (65.6)	52 (63.4)	0.714***
GFR, mean±SD	73.87±23.29	70.38±22.08	0.175**
Acute rejection, n (%)	35 (10.5)	14 (17.1)	0.097***
Erythrocytosis, n (%)	23 (6.9)	3 (3.7)	0.279***

HT: Hypertension, SD: Standard deviation, GFR: Glomerular filtration rate, *Fisher's exact test, **Mann-Whitney U test, ***Chi-square test

Table 5. Distribution of relevant 1st-month risk factors according to post-transplantation dyslipidemia development

Variables	Non-dislipidemia group (n=108)	Dislipidemia group (n=308)	p
Age at transplantation, mean±SD	37.75±12.53	37.82±11.85	0.852**
Donor gender, female, n (%)	52 (62.7)	157 (55.7)	0.259***
Recipient gender, male, n (%)	62 (57.4)	196 (63.6)	0.251***
Proteinuria, mg/dl, mean±SD	69 (63.9)	202 (65.6)	0.750***
GFR, mean±SD	71.87±22.64	73.62±23.23	0.387**
BMI ≥25 (kg/m^2), n (%)	18 (16.7)	89 (29.2)	0.011***

SD: Standard deviation, GFR: Glomerular filtration rate, BMI: Body-mass index, *Fisher's exact test, **Mann-Whitney U test, ***Chi-square test

The mean GFR was slightly lower in the HT group (70.38±22.08 ml/min) compared to the non-HT group (73.87±23.29 ml/min), but this difference was not significant (p=0.175). Proteinuria and erythrocytosis rates were comparable between groups, with no significant differences (p=0.714 and p=0.279, respectively). Although acute rejection was more frequent in the HT group (17.1%) than in the non-HT group (10.5%), the difference did not reach statistical significance (p=0.097) (Table 4).

Dyslipidemia

Dyslipidemia was observed in 70.2% of the study population (n=158). Of the patients with dyslipidemia, 65% had LDL cholesterol levels above 130 mg/dl and 30% had levels above 160 mg/dl. In addition, 55% of patients had non-HDL cholesterol levels (total cholesterol-HDL) above 150 mg/dl. The majority of patients who developed dyslipidemia (n=120) were treated with cyclosporine, and there was a significant association between LDL levels and cyclosporine use (p<0.01) (Table 5).

Hyperuricemia

Hyperuricemia developed in 10.6% of patients (n=44) after transplant. Of these patients, 81.8% were male and 18.2% were female (p=0.004). In addition, 31.8% of patients with hyperuricemia also had hypertension, which was significantly higher than in patients without hyperuricemia (p=0.033). The mean glomerular filtration rate (GFR) in patients with hyperuricemia was 59.76±24.45 ml/min, which was significantly lower than in patients without hyperuricemia (p<0.001) (Table 6).

Avascular Necrosis

Avascular necrosis was observed in 4.8% of patients (n=20). Among these, 80% were male, and 20% were female (p=0.089). No significant differences were found between patients with and without avascular necrosis regarding age, dialysis duration, donor type, or glomerular filtration rate (p>0.05). In addition, there was no significant difference in uric acid levels between patients with and without avascular necrosis (p=0.748) (Table 7).

Table 6. Distribution of relevant 1st-month risk factors according to post-transplantation hyperuricemia development

Variables	Non-hyperuricemia group (n=313)	Hyperuricemia group (n=103)	p
Age at transplantation, mean±SD	37.54±12.05	40.01±11.59	0.171**
BMI ≥25 (kg/m^2), n (%)	92 (24.9)	15 (34.1)	0.190***
Recipient gender, male, n (%)	222 (59.7)	36 (81.8)	0.004***
Proteinuria, mg/dl, mean±SD	243 (65.3)	28 (63.6)	0.824***
GFR, mean±SD	74.72±22.43	59.76±24.45	<0.001**

SD: Standard deviation, BMI: Body-mass index, GFR: Glomerular filtration rate, *Fisher's exact test, **Mann-Whitney U test, ***Chi-square test

Table 7. Distribution of relevant 1st-month risk factors according to post-transplantation avascular necrosis development

Variables	Non-avascular necrosis group (n=396)	Avascular necrosis group (n=82)	p
Age at transplantation, mean±SD	37.58±11.97	41.14±12.33	0.116**
Recipient gender, male, n (%)	242 (61.1)	16 (80.0)	0.089***
GFR, mean±SD	73.17±23.15	73.45±22.52	0.683**
Uric acid, mean±SD	4.87±1.29	4.80±1.41	0.748**
Calcium, mean±SD	9.44±0.70	9.75±0.66	0.063**
Phosphorus, mean±SD	2.91±0.99	2.68±0.63	0.387**
Albumin, mean±SD	4.00±0.48	4.02±0.40	0.984**
Osteoporosis, n (%)	37 (57.8)	3 (42.9)	0.691*
Acute rejection, n (%)	46 (11.6)	3 (15.0)	0.718*

SD: Standard deviation, GFR: Glomerular filtration rate, *Fisher's exact test, **Mann-Whitney U test, ***Chi-square test

DISCUSSION

In this study, metabolic complications in the post-transplant period were analyzed in detail. Our results emphasize the prevalence of these complications and make an important contribution to existing literature. Our study is particularly noteworthy as it defines the common complications observed in the post-transplant period and provides insights regarding their management.

The etiological distribution of end-stage renal disease patients in this study differs somewhat from the general patterns of end-stage renal disease in our country. This may be due to the fact that we specifically examined patients who underwent transplantation, as well as the tendency for these patients to receive transplants predominantly from living donors.[20] This could be one of the significant differences in the etiological distribution of end-stage renal disease within the study population. On the other hand, the fact that the study was conducted in a tertiary center, which is a major transplant center, may have contributed to the identification of a more diverse range of end-stage renal disease diagnoses.

Our study found that approximately a quarter of patients developed NODAT after kidney transplantation, which aligns with the reported rates of 15-30% in the literature.[12,21,22] Advanced age (≥45 years), higher BMI ≥25 kg/m^2, elevated CRP levels, male gender, and CMV infection were identified as significant risk factors for NODAT development. The higher prevalence of NODAT in patients aged ≥45 years can be attributed to decreased pancreatic reserves and increased metabolic dysfunction exacerbated by immunosuppressive therapy in older individuals.[22-25] Similarly, the association of higher BMI with NODAT underscores the role of heightened insulin resistance in this group.[26] The elevated CRP levels observed in the NODAT group support the detrimental effects of systemic inflammation on pancreatic beta-cell function.[27] Moreover, the significant relationship between male gender and NODAT may reflect sex-specific hormonal differences influencing insulin sensitivity. Additionally, the markedly higher incidence of CMV infection in NODAT patients suggests that CMV may act as a trigger for diabetes through direct pancreatic cell damage and systemic inflammation.[28,29] The significant association between corticosteroid use and NODAT aligns with existing literature, as high-dose corticosteroids are known to elevate the risk of hyperglycemia and diabetes.[30,31] Immunosuppressive therapies, particularly corticosteroids and calcineurin inhibitors, are well-documented contributors to NODAT.[30,31] On the other hand, variables such as HCV positivity, donor gender, proteinuria, and acute rejection did not show a significant relationship with early NODAT development, indicating their limited role in this period. These findings highlight the multifactorial nature of NODAT and the critical importance of individualized monitoring and preventive strategies in the post-transplant period. Controlling modifiable risk factors such as advanced age, obesity, inflammation, and CMV infection, along with careful management of immunosuppressive regimens, is essential to reduce the risk of NODAT and improve outcomes in kidney transplant recipients.

Hypertension is one of the most common complications after kidney transplantation, with a reported prevalence ranging from 15% to 80% in the literature.[15,32] In this study, the prevalence of hypertension was found to be 19.7%, which is relatively low compared to some reports. This may reflect the effective use of immunosuppressive therapy and antihypertensive treatment in our study population. Apart from post-transplantation complications, some of the patients followed may have had age-related hypertension and dyslipidemia. For this reason, the frequency of hypertension in this group is higher than the expected incidence of hypertension. Hypertension management is critical for maintaining long-term graft survival and protecting patient health.[15,33] Regular blood pressure monitoring and the implementation of appropriate antihypertensive therapies are essential for ensuring the overall health of transplant recipients. This study also examined the first-month risk factors associated with post-transplant hypertension and found no statistically significant differences between the HT and non-HT groups for most variables. The similarity in age, donor, and recipient gender suggests that these factors do not play a significant role in the early development of post-transplant HT.[34] Likewise, slight differences in GFR values between the groups were not significant, indicating that renal function changes in the early post-transplant period may not independently contribute to HT risk.[35] Proteinuria and erythrocytosis, often associated with hypertension in transplant recipients, were observed at similar rates in both groups, supporting their limited role in the early onset of HT.[36] Interestingly, while the acute rejection rate was slightly higher in the HT group, this difference did not reach statistical significance. This suggests that rejection episodes may influence HT risk over the long term or in combination with other factors.[36] The role of calcineurin inhibitors, particularly cyclosporine and tacrolimus, in increasing vascular resistance and blood pressure is consistent with the literature.[37] These findings underline the multifactorial nature of post-transplant hypertension, with no single variable emerging as a dominant risk factor in the first month after transplantation. Effective antihypertensive therapy and tailored monitoring strategies remain pivotal in mitigating hypertension-related risks and improving patient outcomes.

The dyslipidemia rate of 70.2% observed in this study highlights the frequent disturbance of lipid metabolism in the post-transplant period. This prevalence is consistent with literature findings, which report dyslipidemia rates ranging from 59% to 69% after transplantation.[10,38,39] Dyslipidemia is a critical risk factor for cardiovascular disease and may negatively impact graft survival, emphasizing the need for its effective management.[10] This study further analyzed first-month risk factors for post-transplant dyslipidemia and identified a significant association with higher BMI, while other variables, such as age at transplantation, donor gender, and recipient gender, showed no statistically significant differences. This finding aligns with prior research indicating that dyslipidemia in transplant recipients is more influenced by metabolic and immunological factors rather than demographic characteristics.[40] The significantly higher prevalence of BMI ≥25 kg/m^2 in the dyslipidemia group underscores obesity as a modifiable risk factor. Elevated BMI is known to impair lipid metabolism by promoting insulin resistance and altering adipokine levels, exacerbating dyslipidemia.[40] In contrast, variables such as GFR and proteinuria, which were comparable between the groups, suggest a limited role of early renal function variations in the development of dyslipidemia.[41] Additionally, the association

between cyclosporine use and dyslipidemia supports its known adverse effects on lipid metabolism, further reinforcing the role of immunosuppressive therapy in the pathophysiology of dyslipidemia.[38,39] These findings underscore the importance of addressing modifiable risk factors, such as obesity, and implementing regular lipid profile monitoring alongside necessary pharmacologic interventions. Tailored management strategies are essential for mitigating the cardiovascular and graft-related risks associated with dyslipidemia in transplant recipients.

Hyperuricemia was observed in 10.6% of patients, a rate consistent with the 10% to 50% prevalence reported in the literature.[42-44] It was also found that the rate of hyperuricemia was higher in patients receiving calcineurin inhibitors. These drugs are known to increase serum uric acid levels by increasing renal tubular urate reabsorption.[43] As hyperuricemia can impair graft function and increase the risk of cardiovascular complications, early diagnosis and treatment of this condition is crucial.[44,45] Control of serum uric acid levels may reduce the risk of complications in these patients.

Metabolic bone disorders, particularly osteopenia and osteoporosis, were found in 20% of the study population, while avascular necrosis was observed in 4.8%. This rate of avascular necrosis is consistent with the 3 to 5% reported in the literature.[46,47] Glucocorticoid use is a known risk factor for avascular necrosis, and all patients with avascular necrosis in this study had a history of glucocorticoid use.[47] Glucocorticoid use can increase bone resorption and lead to a decrease in bone mineral density.[46,47] Regular monitoring of bone health and the use of measures such as vitamin D, calcium supplements and bisphosphonates are recommended to prevent these complications.

Limitations

One of the strengths of this study is that it includes a large patient population and analyzes data collected over a long follow-up period. This comprehensive data set increases the generalizability of the results and lends greater reliability to the study's findings. In addition, the detailed investigation of metabolic complications in the post-transplant period helps to identify important strategies that can be applied in clinical practice. However, the study has some limitations. Since it is a retrospective design, it is difficult to establish clear cause-effect relationships. In addition, the fact that complete follow-up data were not available for some patients limits the certainty of the results. An additional limitation is the fact that we did not possess pre-transplantation data regarding blood biochemical and microbiological parameters, which limited our ability to perform a comparative analysis. Strengthening the relationship between all post-transplant non-immunological complications and their potential risk factors with multivariate regression analysis would have been more appropriate. However, this aspect was not evaluated as it falls outside the scope of the study hypothesis. Evaluating certain post-transplant non-immunological complications, such as examining the relationship with post-transplant-controlled creatinine levels in cases like hyperuricemia, could have provided more sensitive results. However, the study aimed to analyze the relationship with values from the first month. This approach may have led to some relationships being overestimated or underestimated. Furthermore, the fact that the study was conducted at a single center limits the generalizability of the results to other populations. It is therefore recommended that the results be validated in other centers and supported by larger prospective studies.

CONCLUSION

The results of this study show that metabolic complications are common after kidney transplantation and that these complications can significantly affect patient survival. Early diagnosis and effective management of complications such as NODAT, hypertension, dyslipidemia, hyperuricemia and metabolic bone disorders can improve graft survival and overall patient health. Based on these findings, regular follow-up of transplant patients and the use of individualized treatment approaches are critical. Future research may provide opportunities to develop more innovative strategies to prevent and treat these complications.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara University Faculty of Medicine Clinical Researches Ethics Committee (Date: 14.03.2016, Decision No: 05-184-16).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

Disclosure

The authors of this manuscript declare that they have no conflicts of interest with regard to this study and its results.

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KASTAMONU MEDICAL JOURNAL

Original Article

DOI: 10.51271/KMJ-0202

Kastamonu Med J. 2025;5(3):157-161

Evaluation of the incidence and risk factors of acute renal injury according to the pRIFLE criteria in children with ventricular septal defect (VSD) and atrioventricular septal defect (AVSD) after cardiovascular interference

Arzu Aras[1], Zehra Esra Önal[2], Mustafa Orhan Bulut[3], Hatice Öztürk[4], Mehmet Dedemoğlu[5], Nurgül Yurtseven[6], Numan Ali Aydemir[3], Çağatay Nuhoğlu[2]

[1]Department of Pediatric Gastroenterology, Antalya Training and Research Hospital, Antalya, Turkiye
[2]Department of Pediatrics, Haydarpaşa Training and Research Hospital, İstanbul, Turkiye
[3]Department of Pediatric Cardiology, İzmir Training and Research Hospital, İzmir, Turkiye
[4]Department of Pediatrics, Çorlu State Hospital, Tekirdağ, Turkiye
[5]Department of Pediatric Cardiovaskular Surgery, Ümraniye Training and Research Hospital, İstanbul, Turkiye
[6]Department of Anesthesiology and Reanimation, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Turkiye

Cite this article as: Aras A, Önal ZE, Bulut MO, et al. Evaluation of the incidence and risk factors of acute renal injury according to the pRIFLE criteria in children with ventricular septal defect (VSD) and atrioventricular septal defect (AVSD) after cardiovascular interference. *Kastamonu Med J.* 2025;5(3):157-161.

Received: 13.11.2024 ◆ **Accepted**: 22.01.2025 ◆ **Published**: 03.09.2025

ABSTRACT

Aims: We aimed to determine the incidence and risk factors of acute kidney injury (AKI) according to pRIFLE (risk, injury, failure, loss, endstage) criteria and to evaluate its effect on prognosis in patients followed up in intensive care unit after interventions for heart disease.

Methods: The study included 84 patients who underwent surgery for VSD and AVSD between January 2016 and September 2016 in the Pediatric Cardiovascular Surgery Clinic of Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital. Patients were prospectively analyzed. Primary disease, demographic data, duration of intensive care and hospital stay, duration of follow-up on ventilator, urine output, vital signs, intraoperative data, primary and secondary problems, and renal function tests were recorded.

Results: Among the patients, 35 were male, 49 were female, 30 were diagnosed with AVSD and 54 with VSD. pRIFLE classification revealed AKI in 19 patients. When the AKI (+) and non-AKI (+) groups were compared, no significant difference was found between the duration of cardiopulmonary bypass (CPB) in the AKI (+) group, while hypothermia levels were significantly lower (p=0.003). Mortality and length of hospital stay were significantly higher in the AKI (+) group.

Conclusion: AKI is a serious complication in pediatric cardiac surgery patients. The presence and extent of damage is closely related to morbidity and mortality. The use of an inexpensive, easily applicable method such as pRIFLE criteria is recommended for the detection and grading of AKI.

Keywords: Acute kidney injury, pRIFLE criteria, congenital heart disease

INTRODUCTION

Pediatric cardiac surgery became successfully feasible with the introduction of the heart-lung machine discovered by Gibbon in 1953. The majority of these operations, which are performed as palliative and complete correction operations, require cardiopulmonary bypass support.

Acute kidney injury (AKI) describes damage to the kidneys that starts at the cellular level and can progress from transient dysfunction to permanent dysfunction. Depending on the primary cause, it may be partially or completely reversible. Acute renal failure (ARF) describes the inability of the kidneys to maintain fluid and electrolyte hemostasis.

In pediatric cardiac surgery patients, AKI may occur in the perioperative period due to many causes. In particular, approximately 30% of patients undergoing surgery with cardiopulmonary bypass (CPB) develop severe AKI. CPB initiates the inflammatory response, increases antidiuretic hormone (ADH) release and capillary membrane permeability and leads to renal damage by decreased renal perfusion

Corresponding Author: Arzu Aras, drarzum@hotmail.com

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pressure, activation of proinflammatory mediators and direct nephrotoxic effect.[1,2] In pediatric patients who have undergone cardiac surgery, volume depletion, inadequate fluid support, inadequate cardiac pump function and use of nephrotoxic drugs also contribute to AKI.

CPB duration is also important in the development of AKI.[3] As the duration of CPB increases, the risk of coagulopathy increases and more blood product transfusion support causes severe hypoperfusion and increases the frequency of AKI. Delay in the diagnosis of AKI increases morbidity and mortality, which can be reversed with early diagnosis of AKI.

RIFLE, pRIFLE and AKIN classifications have been developed to determine the severity of AKI. The common feature of these classifications is that they are cheap, simple, easily applicable and provide standardization in determining the degree of acute kidney injury.

METHODS

The study was carried out with the permission of the Haydarpaşa Numune Training and Research Hospital Clinical Researches Ethics Committee (Date: 09.05.2016, Decision No: HNEAH-KAEK 2016/KK/50). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients hospitalized in the Pediatric Cardiovascular Intensive Care Unit of Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital between January 2016 and September 2016 were prospectively analyzed. Eighty-four patients operated for VSD and AVSD were included in the study. Patients with incomplete investigations and patients older than 15 years were excluded.

Primary disease, demographic data, duration of intensive care unit and hospital stay, duration of follow-up on ventilator, duration of operation and intraoperative body temperature, urine output, vital signs, primary and secondary problems, preop-perop and postop renal function tests were recorded.

Preoperative, intraoperative and postoperative glomerular filtration rate (GFR) values of the patients were calculated according to Schwartz formula with the collected data. To diagnose AKI, the class of the patients was determined by evaluation with pRIFLE classification.

Since our patients had congenital heart disease, were receiving preoperative or postoperative diuretic, vasopressor and inotrope support due to their existing pathologies and these treatments had effects on urine output, GFR parameter was used in all patients to determine AKI. Preop, perop and postop t-GFR values of the patients were calculated by Schwartz formula and evaluated according to the t-GFR parameter in pRIFLE classification.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) programme was used for statistical analyses. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used to evaluate the study data. Friedman Test was used for intra-group comparisons of measurements that did not show normal distribution and Wilcoxon Signed Ranks test was used for the evaluation of pairwise comparisons. Fisher's exact test and Yates' continuity correction test (Chi-square with Yates' correction) were used for comparison of qualitative data. Significance was evaluated at $p<0.01$ and $p<0.05$ levels.

RESULTS

Our study was performed with a total of 84 patients, 41.7% (n=35) male and 58.3% (n=49) female, who were followed up after VSD/AVSD operation. The mean age was 2.00±3.48 years.

AVSD was present in 35.7% (n=30), VSD in 64.3% (n=54) and 28.6% (n=24) had a family history of heart disease. Eight of the patients were in the neonatal period and 7 of them had Down syndrome. Cardiac murmurs of 3-4/6 intensity were detected in 97% (n=82) of the patients and all were diagnosed by electrocardiographic examination. Cross-clamp times of the patients operated by CPB access were 74.51±32.83 minutes (min) and total perfusion times were 102.90±44.68 min. Body temperature was 31.43±1.34 C erythrocyte suspension (ES) transfusion was required in 92.9% (n=78) of the cases. Mechanical ventilation (MV) duration was 6.33±10.48 min, intensive care unit (ICU) duration was 9.18±12.06 min, and hospital stay was 20.72±21.29 days. Postoperative cardiac arrest was observed in 6% (n=5) and AV block in 3.6% (n=3) of cases. There was no operative mortality in our patients. Postoperative inotropic support was required in 81% (n=68) of cases and MV support was required again after postoperative extubation in 17.9% (n=15). Renal replacement therapy (RRT) was administered during ICU follow-up in 6% (n=5) of cases. While 95.2% (n=80) of the patients were discharged with cure, 4.8% (n=4) of them died (**Table 1, Figure 1**).

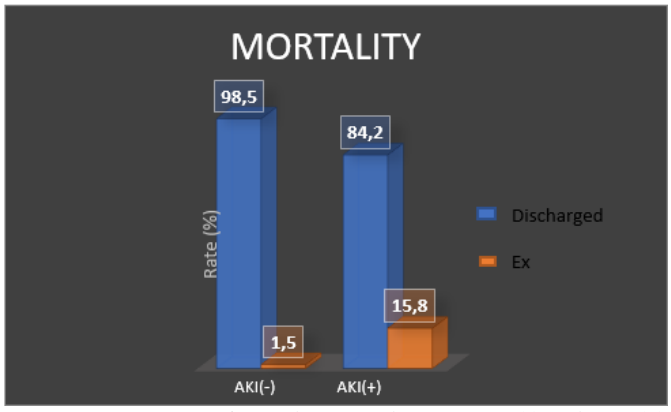

Figure 1. Comparison of mortality status between AKI (-) and AKI (+) groups

AKI: Acute kidney injury

There was no statistically significant difference between the groups when age, gender distribution, primary disease and presence of heart disease in the family were analyzed ($p>0.05$).

While Preop CrCl [creatinine clearance (ml/min)] measurements did not show significant difference between the groups ($p=0.168$; $p>0.05$), the fact that the Perop CrCl measurements of the AKI (+) group were lower than the AKI (-) group was found to be close to significance ($p=0.064$; $p>0.05$). It was found significant that the postop CrCl measurements of the AKI (+) group were lower than the AKI (-) group ($p=0.005$; $p<0.01$).

The change in preop, perop and postop CrCl measurements of the AKI (+) group was found to be significant ($p=0.001$; $p<0.01$). While the decrease of 7.96±11.44 in perop CrCl measurements was found to be significant ($p=0.001$; $p<0.01$),

Table 1. Demographic characteristics of the patients, intraoperative and postoperative results

		Min-max (median)	Mean±SD			n	(%)
Distribution of preoperative characteristics	Age (years)	0.08-15.00 (0.58)	2.00±3.48	Sex	Male	35	41.7
					Female	49	58.3
				Primary disease	AVSD	30	35.7
					VSD	54	64.3
				Family history of heart disease		24	28.6
Distribution of surgery data	Cross-clamp time (min)	25-162 (63.5)	74.51±32.83	ES replacement		78	92.9
	CPB time (min)	40-276 (90.5)	102.90±44.68				
	Body temperature (C)	28-34 (32)	31.43±1.34				
Distribution of postoperative characteristics	MV duration (days)	1-54 (2)	6.33±10.48	Cardiac arrest		5	6.0
				Re-intubation		15	17.9
	ICU time (days)	1-60 (3.5)	9.18±12.06	AV blk		3	3.6
				Inotr. support		68	81.0
				RRT		5	6.0
	Length of hospital stay (days)	5-150 (14.5)	20.72±21.29	Mortality	Discharged	80	95.2
					Ex	4	4.8

Min: Minimum, Max: Maximum, SD: Standard deviation, AVSD: Atrioventricular septal defect, VSD: Ventricular septal defect, CPB: Cardiopulmonary bypass, MV: Mechanical ventilation, ES: Erythrocyte suspension, ICU: Intensive care unit, AV: Atrio ventricular, RRT: Renal replacement therapy, Ex: Excitus

the change in postop CrCl measurements was not significant (p=0.291; p>0.05). The increase of 10.14±13.42 in postop CrCl measurements compared to Preop was found to be significant (p=0.001; p<0.01). The change in preop, perop and postop CrCl measurements of AKI (-) group was found to be significant (p=0.001; p<0.01). While the decrease of 31.04±13.55 in perop CrCl measurements compared to preop (p=0.001) and the decrease of 27.60±20.62 in postop CrCl measurements compared to preop (p=0.001) were found significant (p<0.01); the change in postop CrCl measurements compared to Perop was not found significant (p=0.546; p>0.05) (Figure 2).

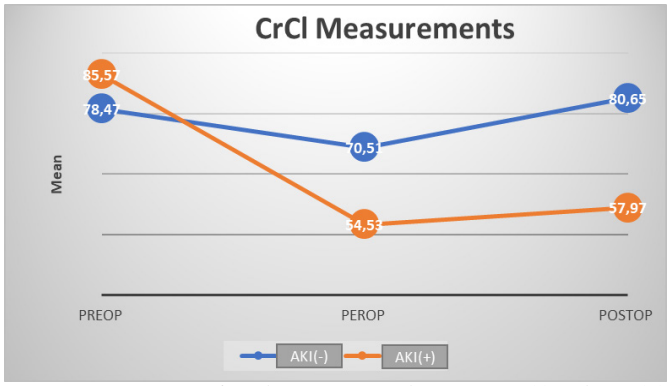

Figure 2. Comparison of CrCl measurements between AKI (-) and AKI (+) groups

CrCl: Creatinine clearance, AKI: Acute kidney injury

It was found significant that the change in perop CrCl (p=0.001) and postop CrCl (p=0.001) measurements of AKI (+) cases compared to preop was higher than the AKI (-) group (p<0.01). The change in postop CrCl measurements of the patients compared to preop did not differ significantly according to the groups (p=0.111; p>0.05) (Table 2).

Cross-clamp and CPB durations and the presence of ES transfusion were not significantly different between the groups (p>0.05), whereas the body temperatures of the AKI (+) group were significantly lower than the AKI (-) group (p=0.003; p<0.01) (Table 3).

Table 2. Comparison of CrCl measurements of AKI (-) and AKI (+) groups

		AKI (-) (n=65)	AKI (+) (n=19)	[a]p
Preop. CrCl	Min-max (median)	31-163 (70)	53-140 (81)	0.168
	Mean±SD	78.47±28.15	85.57±22.58	
Perop. CrCl	Min-max (median)	30-130 (61)	25-88 (57)	0.064
	Mean±SD	70.51±25.37	54.53±16.91	
Postop. CrCl	Min-max (median)	31.5-165 (70)	24-106 (48)	0.005**
	Mean±SD	80.65±32.86	57.97±23.26	
	[d]p	0.001**	0.001**	
Preop.-Perop. difference	Min-max (median)	-48-15 (-8)	-65-(-12) (-32)	0.001**
	Mean±SD	-7.96±11.44	-31.04±13.55	
	[c]p	0.001**	0.001**	
Preop.-Postop. difference	Min-max (median)	-34-44 (0)	-71-5 (-27)	0.001**
	Mean±SD	2.18±14.10	-27.60±20.62	
	[c]p	0.291	0.001**	
Perop.-Postop. difference	Min-max (median)	-21-52 (10)	-24-38 (1)	0.111
	Mean±SD	10.14±13.42	3.44±19.65	
	[c]p	0.001**	0.546	

CrCl: Creatinine clearance, AKI: Acute kidney injury, Preop.: Preoperative, Perop.: Peroperative, Postop.: Postoperative, Min: Minimum, Max: Maximum, SD: Standard deviation, Mann-Whitney U test, Friedman test, Wilcoxon signed ranks test, **p<0.01

Table 3. Comparison of operative data of AKI (-) and AKI (+) groups

		AKI (-) (n=65)	AKI (+) (n=19)	p
Cross-clamp time (min)	Min-max (median)	25-154 (62)	37-162 (67)	[a]0.556
	Mean±SD	73.49±32.06	78±36.01	
CPB duration (min)	Min-max (median)	40-276 (86)	56-238 (94)	[a]0.490
	Mean±SD	100.71±42.58	110.42±51.78	
Body temperature (C)	Min-max (median)	28-34 (32)	28-32 (32)	[a]0.003**
	Mean±SD	31.66±1.09	30.63±1.77	
Number of ES transfusions (%)		60 (92.3)	18 (94.7)	[c]1.000

AKI: Acute kidney injury, Min: Minimum, Max: Maximum, SD: Standard deviation, CPB: Cardiopulmonary bypass, ES: Erythrocyte suspension, Mann-Whitney U test, Fisher's exact test, **p<0.01

MV, ICU durations and the presence of cardiac arrest were not significantly different between the groups (p>0.05). The duration of hospitalization in the AKI (+) group was significantly higher than the AKI (-) group (p=0.004; p<0.01). Reintubation, AV block and inotropic support status were not significantly different between the groups (p>0.05). RRT rate (21.1%) of AKI (+) group was significantly higher than AKI (-) group (p=0.009; p<0.01). The mortality rate in the AKI (+) group was significantly higher than that in the AKI (-) group (p=0.035; p<0.05) (**Table 4**).

DISCUSSION

AKI describes a broad process that can progress from reversible loss of renal function to permanent kidney damage. There are many definitions and the RIFLE and pRIFLE classifications are used for standardization.

The pRIFLE classification provides the definition and classification of AKI in the pediatric group. In the past, the diagnosis of AKI was made by an increase in serum creatinine level, but nowadays this classification can also be used to grade the damage. Catching and treating AKI at a reversible stage significantly reduces the morbidity and mortality of the patient.

AKI is a serious complication after cardiac surgery. Decreased intraoperative renal blood flow, development of postoperative low flow syndrome and decreased autoregulation are the main reasons for AKI, and cyanosis, young age, cardiac volume changes and the presence of a single ventricle also contribute to decreased renal function.[4-6] Intraoperative CPB is also closely associated with morbidity and mortality.

In our study group, AKI was detected in 22% (n=19) patients with the pRIFLE classification, whereas this rate was 51% in the study by Scott I. Aydın et al.[7] using the same classification. The exclusion of patients with complicated surgeries other than VSD and AVSD in our study group and the fact that the proportion of patients with a mean age of <1 month was 4.7% (n=4) in our study, whereas it was 62.2% in their study constitute the main reason. The immaturity of the renal tubules in the neonatal group, inflammation caused by CPB and inadequate response to ischemic reperfusion damage increase the likelihood of renal damage in this group.

Although there was no statistical difference in the mean age of the patients between our patient groups who developed AKI and those who did not develop AKI, the most common age distribution in the AKI (+) group was around 1 year of age. In similar studies by Toth[8] and Zappitelli et al.,[9] the rate of AKI development was found to be higher in patients aged 1 year and younger.

Sami Kallel et al.[10] found a significant effect of CPB duration and degree of hypothermia on the development of AKI. In our study, no significant difference was found between CPB durations, whereas body temperature was found to be significantly lower in the AKI (+) group. The fact that VSD correction operations were performed in a shorter period of time and renal perfusion was sufficient caused the CPB duration to be insignificant in that group. Hypothermia increases the risk of AKI independent of the type of congenital heart disease.

Ricc et al.[11] found that the length of stay in MV and ICU was longer in patients with AKI (+) than in patients with AKI (-). Similar results were found in our study and no statistically significant difference was found. The duration of hospitalization in the AKI (+) group was found to be significantly higher.

In terms of postoperative complications, 17.8% (n=15) of our patients needed reintubation and 5.9% (n=5) developed cardiac arrest during postoperative follow-up. Stanimir et al.[12] observed that 28.4% of pediatric patients who underwent cardiac surgery needed postoperative reintubation and attributed this to diaphragmatic paralysis due to phrenic nerve injury during the operation. The fact that our patient group did not undergo a complex surgery caused this rate to be low. Joan Fernando et al.[13] reported a 6.5% rate of cardiac arrest after cardiac surgery, which is consistent with our study.

The incidence of heart block after pediatric cardiac surgery has been reported between 1-3% and has been associated with surgery close to the AV node.[14] In our study, AV block was observed with a rate of 4.6% (n=3), which is higher compared to other studies because surgery was performed close to the AV node.

In our study group, 6% (n=5) patients needed RRT. In the study by Zaccaria et al.[15] 8.1% RRT was performed, which supports our study.

Table 4. Comparison of postoperative characteristics of AKI (-) and AKI (+) groups

		AKI (-) (n=65)	AKI (+) (n=19)	p
MV duration (days)	Min-max (median)	1-25 (2)	1-54 (3)	[a]0.091
	Mean±SD	4.31±5.58	13.26±18.18	
ICU duration (days)	Min-max (median)	1-36 (3)	1-60 (5)	[a]0.106
	Mean±SD	7.11±8.18	16.26±19.09	
Duration of hospital stay (days)	Min-max (median)	5-81 (12)	7-150 (27)	[a]0.004**
	Mean±SD	16.18±12.52	36.26±34.70	
Cardiac arrest; n (%)		2 (3.1)	3 (15.8)	[c]0.074
Reintubation; n (%)		9 (13.8)	6 (31.6)	[c]0.094
AV block; n (%)		3 (4.6)	0 (0)	[c]1.000
Inotrope support; n (%)		51 (78.5)	17 (89.5)	[c]0.506
RRT; n (%)		1 (1.5)	4 (21.1)	[c]0.009**
Mortality; n (%)	Discharged	64 (98.5)	16 (84.2)	[c]0.035*
	Ex	1 (1.5)	3 (15.8)	

AKI: Acute kidney injury, MV: Mechanical ventilation, ICU: Intensive care unit, AV: Atrio ventricular, RRT: Renal replacement therapy, Ex: Excitus, Mann-Whitney U test, Fisher's exact test, **p<0.01, *p<0.05

Many studies have reported that patients with AKI, especially those undergoing pediatric cardiac surgery and hospitalized in the pediatric intensive care unit, have 3-4 times higher mortality.[16] In our study, total mortality was found to be 4.8% (n=4), 1.5% (n=1) of which was in the AKI (-) group and 15.8% (n=3) in the AKI (+) group, which is consistent with the literature.

Limitations

The most important limitations of our study include the lack of more congenital heart disease types and the lack of larger series. Prospective studies with larger series are needed for more definite results.

CONCLUSION

AKI is closely associated with morbidity and mortality and is more related to the degree of damage. Patients detected in early stages can be prevented from progression to AKI with appropriate treatments. Therefore, it is important to determine the degree of damage.[17] It is recommended to use an inexpensive, easily applicable method such as pRIFLE in the evaluation and grading of AKI, especially in patients undergoing pediatric cardiac surgery.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Haydarpaşa Numune Training and Research Hospital Clinical Researches Ethics Committee (Date: 09.05.2016, Decision No: HNEAH-KAEK 2016/KK/50).

Informed Consent

All parents signed an explicit and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

Acknowledgments

I would like to thank Mustafa Aldağ for his help in obtaining the patient data.

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KASTAMONU MEDICAL JOURNAL

Original Article

DOI: 10.51271/KMJ-0203

Kastamonu Med J. 2025;5(3):162-165

Evaluation of the antimicrobial activity of *Castanea sativa* against imipenem-resistant non-fermentative bacteria

Ülkü Zeynep Üreyen Esertaş[1], İnci Durukan[2], Enis Fuat Tüfekci[3], Saliha Ekşi[2], Ali Osman Kılıç[2]

[1]Department of Medical Microbiology, Faculty of Medicine, Ağrı İbrahim Çeçen University, Ağrı, Turkiye
[2]Department of Medical Microbiology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkiye
[3]Department of Medical Microbiology, Faculty of Medicine, Kastamonu University, Kastamonu, Turkiye

Cite this article as: Üreyen Esertaş ÜZ, Durukan İ, Tüfekci EF, Ekşi S, Kılıç AO. Evaluation of the antimicrobial activity of *Castanea sativa* against imipenem-resistant non-fermentative bacteria. *Kastamonu Med J.* 2025;5(3):162-165.

Received: 27.08.2024 ◆ **Accepted**: 03.02.2025 ◆ **Published**: 03.09.2025

ABSTRACT

Aims: Carbapenems, particularly imipenem, are a class of antibiotics commonly used for treating infections caused by antibiotic-resistant gram-negative bacteria. However, the increasing prevalence of imipenem-resistant bacterial strains underscores the necessity of discovering alternative therapeutic options. The current study assessed the ethanol (EtOH) extract of *Castanea sativa (C. sativa)* Mill. flowers for its antimicrobial activity and potential as an adjuvant in antibiotic therapy against imipenem-resistant clinical strains of *Acinetobacter baumannii (A. baumannii)* and *Pseudomonas aeruginosa (P. aeruginosa)*.

Methods: A total of 40 non-duplicate clinical strains of *P. aeruginosa* (n=21) and *A. baumannii* (n=19), belonging to non-fermentative gram-negative bacteria, were included in the study. The antimicrobial activity of the extract and its potential to potentiate imipenem were evaluated using the disk diffusion method.

Results: The inhibition zone diameters for the extract alone ranged from 7 mm to 10 mm for *P. aeruginosa* strains and from 11 mm to 14 mm for *A. baumannii* strains. When combined with imipenem, these diameters increased slightly, ranging from 8 mm to 11 mm and 11 mm to 15 mm for *P. aeruginosa* and *A. baumannii* strains, respectively.

Conclusion: The findings suggest that the EtOH extract of *C. sativa* flowers possesses antimicrobial activity against imipenem-resistant *P. aeruginosa* and *A. baumannii* strains, albeit with a minimal imipenem-potentiating effect. Further studies are required to explore the full potential of this extract in combating resistant bacterial infections.

Keywords: *Acinetobacter baumannii*, *Castanea sativa* Mill., carbepenems, drug potentiation, *Pseudomonas aeruginosa*

INTRODUCTION

The escalating threat of antibiotic-resistant bacteria is one of the most pressing challenges in modern medicine.[1] In particular, multidrug-resistant (MDR) pathogens, such as *Acinetobacter baumannii (A. baumannii)* and *Pseudomonas aeruginosa (P. aeruginosa)*, are of particular concern.[2] *A. baumannii* and *P. aeruginosa* are clinically significant non-fermentative gram-negative bacteria frequently implicated in nosocomial infections. Their high prevalence in healthcare settings is attributed to their remarkable ability to colonize hospital environments, as well as their intrinsic and acquired resistance mechanisms against a broad spectrum of antibiotics, including those routinely employed in clinical settings.[3,4]

Carbapenems, including imipenem and meropenem, are broad-spectrum β-lactam antibiotics used to treat infections caused by antibiotic-resistant gram-negative and gram-positive bacteria.[5] However, the alarming global rise in carbapenem-resistant isolates, including *A. baumannii* and *P. aeruginosa*, underscores the pressing need for alternative antimicrobial strategies.[3,6] In this context, plant-derived natural products have attracted significant interest as potential sources of bioactive compounds with antimicrobial properties.[7]

Castanea sativa (C. sativa) Mill. (sweet chestnut), belonging to the *Fagaceae* family, has been traditionally utilized in ethnomedicine for diverse therapeutic applications, particularly in treating various ailments. Notably, its flowers are commonly used in teas and beverages, attributed to their purported health benefits.[9] Numerous studies have investigated the antimicrobial properties of *C. sativa* extracts against various microorganisms.[10-13] Nevertheless, research specifically evaluating its imipenem-potentiating activity and effectiveness against carbapenem-resistant clinical strains remains relatively limited. Addressing this gap, the present study aimed to evaluate the ethanol (EtOH) extract of *C. sativa* flowers for its antimicrobial activity and potential as an adjuvant in antibiotic therapy against imipenem-resistant clinical strains of *A. baumannii* and *P. aeruginosa*.

METHODS

Ethics

This study did not require ethical approval as it did not involve any human subjects or animal experiments. All procedures were carried out in accordance with the ethical rules and the principles.

Corresponding Author: Ülkü Zeynep Üreyen Esertaş, uzesertas@agri.edu.tr

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Preparation of Plant Extracts

The flowers of *C. sativa* were collected from the İkizdere district of Rize Province, Turkiye, in July 2021. The extraction was performed using the maceration method.[10] Briefly, 20 g of freshly collected and dried flower parts were finely ground in a mortar, transferred to a flask, and then extracted with 70% EtOH at a ratio of 1:10 (w/v). The mixture was stirred at room temperature using a magnetic stirrer for 24 to 48 hours. Subsequently, the extracts were filtered through filter paper, and the solvent was evaporated under reduced pressure using a rotary evaporator at 40°C. The extract was then dissolved in pure dimethyl sulfoxide (DMSO) at a concentration of 10 mg/ml and stored at -20°C.

Isolates and Antibiotic Susceptibility Test

Forty carbapenem-resistant *P. aeruginosa* (n=21) and *A. baumannii (n=19)* strains, isolated from various clinical samples submitted to the Microbiology Laboratory of Kastamonu Training and Research Hospital between April 2018 and June 2021, were included in the study. Duplicate strains isolated from the same patient were excluded. The identification of the isolates was carried out using the VITEK 2 Compact automated system (BioMérieux, France), along with conventional microbiological methods, including colony morphology, gram staining, oxidase testing, and pigment production. Additionally, the identification of *A. baumannii* strains was verified through the amplification of the *bla*OXA-51-like gene region. Imipenem susceptibility of the isolates was determined and evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines using the VITEK 2 Compact automated system.[14] The strains were named with KPA (Kastamonu *P. aeruginosa*) and KA (Kastamonu *A. baumannii*) codes and isolate numbers. The strains were stored in nutrient broth and Mueller-Hinton broth containing 20% glycerol (v/v) at -80°C until further use.

Disk Diffusion Method

The antimicrobial activity of the extract was assessed using the disk diffusion method, following EUCAST recommendations.[15] In brief, the inoculum was prepared from fresh cultures of the strains to a density of 0.5 McFarland (~1.0×10^8 CFU/ml) and subsequently seeded onto the surface of Mueller-Hinton agar (MHA). Three imipenem disks (10 µg/disk, Oxoid, UK) were then placed onto the medium as standard antibiotics, along with two blank disks. To investigate both the antimicrobial activity of the extract and its potential imipenem-potentiating activity, an imipenem disk, and a blank disk were each impregnated with 10 µL of a 10 mg/ml extract stock solution, resulting in a final concentration of 100 µg of extract per disk. For comparison, an imipenem disk and a blank disk were each impregnated with 10 µL of pure DMSO as a negative control, as DMSO was used as the solvent for the plant extract. The remaining imipenem disk was used to confirm imipenem resistance. The cultures were incubated at 37°C for 24 hours, and the diameters of the inhibition zones (IZ) around the disks were measured using a ruler (in millimeters) at the end of the incubation period. The imipenem-potentiating activity of the extract was categorized into three classes: indifferent/no potentiation (ΔIZ<4 mm), low potentiation/additive effect (4≤ΔIZ<6 mm), and potentiation effect (ΔIZ≥6 mm), based on the inhibition of growth of the strains ($\Delta IZ=IZ_{imipenem+extract}-IZ_{extract}$).[16]

Statistical Analysis

The data were assessed for normality using the Wilks-Shapiro test. The results were analyzed using the Mann-Whitney U test with SPSS version 23 (IBM Inc., Armonk, NY, USA) for Windows. Tha data were presented as the median and the interquartile range [Me (Q25-Q75)] and a p-value of less than 0.05 was considered statistically significant.

RESULTS

It was determined that the 40 strains included in the study were isolated from respiratory secretions (n=21, 52.5%), blood (n=11, 27.5%), urine (n=5, 12.5%), and wound cultures (n=3, 7.5%). No inhibition zone diameter was observed for DMSO and imipenem disks. The median inhibition zone diameter for the extract against *P. aeruginosa* strains was 9 mm (IQR: 9 mm, range: 7-10 mm), while for the extract-imipenem combination, it was 10 mm (IQR: 9-11 mm, range: 8-11 mm). Similarly, for *A. baumannii* strains, the median inhibition zone diameter was 13 mm (IQR: 13-14 mm, range: 11-14 mm) with the extract and 14 mm (IQR: 14 mm, range: 11-15 mm) for the extract-imipenem combination (**Figure 1**). As determined by comparing the inhibition zone diameters, *A. baumannii* strains were significantly more susceptible to the extract than *P. aeruginosa* strains ($p<0.05$). The imipenem-potentiating activity of the extract was categorized as "no potentiation" for all strains, with the difference in inhibition zone diameters (ΔIZ) being less than 4 mm. The results are summarized in the **Table**. Furthermore, a representative result from the disk diffusion test is shown in the **Figure 2**.

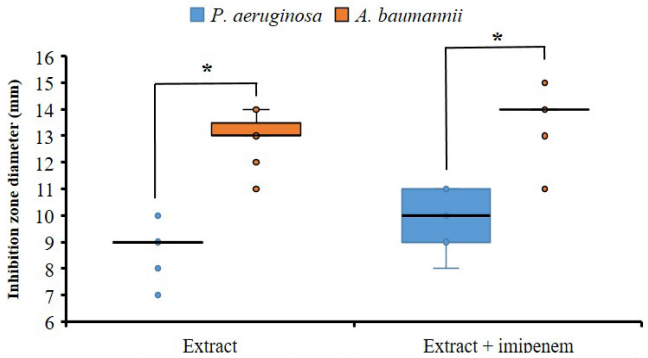

Figure 1. Boxplots displaying the inhibition zone diameters (mm) for *Pseudomonas aeruginosa* and *Acinetobacter baumannii* strains treated with extract and its combination with imipenem. Median values are shown as horizontal lines within the boxes, which represent the interquartile range. Whiskers indicate data range, and dots outside the whiskers represent outliers. Statistically significant differences are marked with asterisks (*)

Figure 2. Representative image of antibacterial activity of the tested agents against imipenem-resistant strains (1: Extract, 2: Extract+imipenem, 3: DMSO, 4: Imipenem, 5: DMSO+imipenem)

DMSO: Dimethyl sulfoxide

Table. Antibacterial zone diameters for tested agents

Strain	Extract (mm)	Extract+imipenem (mm)	ΔIZ (mm)
KPA-1	9	11	2
KPA-2	10	10	0
KPA-3	10	11	1
KPA-4	9	11	2
KPA-7	9	9	0
KPA-9	9	11	2
KPA-10	9	9	0
KPA-12	9	9	0
KPA-15	9	10	1
KPA-16	9	10	1
KPA-17	9	10	1
KPA-18	9	11	2
KPA-19	8	8	0
KPA-20	9	11	2
KPA-21	9	9	0
KPA-28	10	11	1
KPA-37	8	9	1
KPA-43	10	10	0
KPA-51	9	11	2
KPA-54	7	9	2
KPA-67	9	11	2
KA-1	14	15	1
KA-2	12	13	1
KA-3	13	14	1
KA-4	13	14	1
KA-5	13	14	1
KA-6	13	14	1
KA-7	14	15	1
KA-8	13	14	1
KA-9	14	15	1
KA-10	14	15	1
KA-11	13	14	1
KA-12	13	14	1
KA-19	13	14	1
KA-20	12	13	1
KA-28	13	14	1
KA-34	13	14	1
KA-35	14	14	0
KA-40	11	11	0
KA-49	13	14	1

KPA: *Pseudomonas aeruginosa*, **KA:** *Acinetobacter baumannii*, **ΔIZ: Change in inhibition zone diameter**

DISCUSSION

The increasing prevalence of antibiotic resistance, particularly to carbapenems, among common nosocomial pathogens such as *P. aeruginosa* and *A. baumannii* poses a significant threat to public health.[17] This rising resistance underscores the urgent need to identify or develop novel antibacterial agents or compounds that can enhance the effectiveness of carbapenems in combating resistant pathogens. In this regard, natural products, particularly those derived from plants and their bioactive compounds, are expected to provide a viable solution to this challenge.[18]

This study evaluated the antimicrobial efficacy of EtOH extracts from *C. sativa* flowers against imipenem-resistant *P. aeruginosa* and *A. baumannii* strains. The antimicrobial activity of various parts of *C. sativa* has been reported in numerous studies. For example, Živković et al.[19] investigated the effects of shell and catkin extracts, whereas Üreyen Esertas et al.[20] focused on extracts from the flower parts. Similarly, Rodrigues et al.[21] evaluated aqueous extracts from burs and leaves, along with hydroalcoholic extracts from shells. Agarwal et al.[22] examined extracts from tree bark, and Genovese et al.[12] highlighted the antimicrobial properties of extracts from the pellicle.

Consequently, the extract exhibited inhibition zones ranging from 7 mm to 10 mm for *P. aeruginosa* strains and 11 mm to 14 mm for *A. baumannii* strains, with considerable antibacterial activity against both pathogens in this study. Moreover, the extract showed significantly larger inhibition zones against *A. baumannii* strains than *P. aeruginosa*, suggesting potentially inherent differences in susceptibility mechanisms between these species. These differences may stem from variations in outer membrane properties, such as permeability or differential efflux pump activity between these species, which could influence their susceptibility to the extract.[23]

The findings underscore the therapeutic potential of the *C. sativa* flower extract as a novel approach to combating drug-resistant pathogens. Its antimicrobial properties may be attributed to phenolic compounds, such as trigalloyl-hexahydroxydiphenoyl-glucoside and pentagalloyl-glucoside, previously identified as major components of *C. sativa* flower extracts.[24,25] Since phytochemicals are known to exhibit antimicrobial activity through mechanisms such as inhibition of bacterial cell-wall biosynthesis, disruption of cell membranes, inhibition of bacterial protein biosynthesis, DNA replication and repair, and interference with metabolic pathways, it is likely that the bioactive compounds in the extract exert antimicrobial effects through similar mechanisms.[26] Although the specific bioactive components responsible for these effects were not investigated in this study, the findings suggest potential applications of *C. sativa* flower extract in developing advanced antimicrobial solutions, including topical formulations or combination therapies to combat multidrug-resistant infections.

In addition to examining the antimicrobial activity, the potential potentiating effect of the extract on imipenem was also assessed in this study. When combined with imipenem, the extract resulted in a slight increase in the inhibition zones compared to when used alone. For *P. aeruginosa* strains, the inhibition zones increased from a range of 7-10 mm to 8-11 mm. Similarly, for *A. baumannii*, the zones expanded from 11-14 mm to 11-15 mm. Although the potentiation of imipenem was relatively modest, these findings highlight the potential for further optimization through precise combination ratios or the identification of synergistic bioactive compounds. Existing literature suggests that plant-derived bioactive compounds, mainly phenolic compounds, may potentiate antibiotic efficacy by inhibiting efflux pumps, a mechanism that enhances drug retention within bacterial cells and counteracts resistance mechanisms.[26,27] However, further in-depth studies are required to fully elucidate the specific mechanisms by which the extract potentiates imipenem's effectiveness.

Limitations

Despite the promising results observed with the extract in the disk diffusion assay, its limitations-especially the inability to assess the activity of nonpolar compounds due to poor diffusion in agar-necessitate further research employing more advanced methodologies such as checkerboard assays or time-kill curves. These additional studies will help elucidate how *C. sativa* extracts can enhance the effectiveness of carbapenems, especially against multidrug-resistant strains.

CONCLUSION

The results of this study demonstrate that the EtOH extract of *C. sativa* flowers exhibits antibacterial activity against imipenem-resistant clinical non-fermentative bacterial strains, underscoring its potential as a promising candidate for the development of novel antibacterial agents. Future synergy testing will be pivotal in confirming the therapeutic potential of combining *C. sativa* extract with carbapenems. Moreover, isolating and characterizing the bioactive compounds responsible for these effects could facilitate the development of novel antimicrobial formulations.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study did not require ethical approval as it did not involve any human subjects or animal experiments.

Informed Consent

Because the study has no study with human participants, no written informed consent form was obtained.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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KASTAMONU MEDICAL JOURNAL

Original Article

DOI: 10.51271/KMJ-0204

Kastamonu Med J. 2025;5(3):166-171

The protective effect of Chrysin against glutamate-induced oxidative stress and inflammation in SH-SY5Y cells

Adem Ahlatcı[1], Yener Yazğan[2], Kenan Yıldızhan[3]

[1]Department of Health Technicianship, Vocational School of Health Services, Van Yüzüncü Yıl University, Van, Turkiye
[2]Department of Biophysics, Faculty of Medicine, Kastamonu University, Kastamonu, Turkiye
[3]Department of Biophysics, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkiye

Cite this article as: Ahlatcı A, Yazğan Y, Yıldızhan K. The protective effect of Chrysin against glutamate-induced oxidative stress and inflammation in SH-SY5Y cells. *Kastamonu Med J.* 2025;5(3):166-171.

Received: 29.11.2024 ◆ **Accepted**: 05.03.2025 ◆ **Published**: 03.09.2025

ABSTRACT

Aims: Chrysin is a flavonoid with economic value and medicinal effects commonly found in propolis, honey, and blue passion flowers. It has many pharmacological properties such as anticancer, antitumor, antioxidant, neurotrophic, and antidepressant. Glutamate plays an important role in brain functions; however, its high concentration in the central nervous system causes neurotoxic effects. This study aimed to investigate the effect of Chrysin on glutamate-induced cytotoxicity in SH-SY5Y neuroblastoma cells.

Methods: This study was conducted in 4 groups; control, Chrysin (50 μM), glutamate (10 mM), and glutamate+Chrysin. cell viability, total oxidant status (TOS), total antioxidant status (TAS), tumor necrosis factor alfa (TNF-α), and interleukin 1 β (IL-1β) levels in the cells were determined by ELISA kit.

Results: It is shown that glutamate application caused cytotoxicity in SH-SY5Y neuroblastoma cells and increased TOS, TNF-α, and IL-1β levels. However, in SH-SY5Y cells treated with Chrysin before glutamate incubation, TOS, TNF-α, and IL-1β levels decreased compared to the glutamate group, while TAS and cell viability levels increased.

Conclusion: Chrysin's antioxidant properties played a protective role in SH-SY5Y cells against glutamate-induced increased oxidative stress and inflammation.

Keywords: Anti-inflammatory, Chrysin, glutamate, oxidative stress, SH-SY5Y cells

INTRODUCTION

Chrysin is a 15-carbon skeleton polyphenolic molecule belonging to the flavone class.[1] Propolis, honey, and passion fruit (passiflora spp.) are the most significant natural sources. The oral bioavailability of Chrysin is low. It is rapidly excreted with faeces. Sulfate form in plasma can be detected. It has very low bioavailability as it is a substance with very low solubility, poorly absorbed, and rapidly metabolized.[2] Unlike other flavonoids, Chrysin has a chemical structure with hydroxyl groups (5,7-dihydroxy) on the A ring and no adducts on the B ring. The absence of oxygenation in the B and C rings is linked to the biological actions of Chrysin. The chemical structures of certain flavones determine their antioxidant action. Chrysin's antioxidant action is intimately linked to the carbonyl group on C-4 and the double bond between C-2 and C-3.[3] Chrysin is effective against obesity and cardiovascular diseases. It has many properties such as antiallergic, hepatoprotective, neuroprotective, anticancer, antidiabetic, antibacterial, antihypertensive, vasodilator, anxiolytic, antiviral, antiestrogenic, antiaging, anticonvulsant, antioxidant and anti-inflammatory effects. It increases mesenchymal stem cell proliferation.[4-6]

Glutamate is a neuroessential dicarboxylic amino acid found almost everywhere in the nervous system and involved in neuron cell metabolism. The studies conducted in the 1950s proved to be responsible for neuronal excitation in mammalian spinal cord cells; subsequent studies have shown that it functions as a neurotransmitter in the thalamus, hippocampus, cerebral cortex, primary sensory nucleus, and reticular formation. It is accepted that glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS) and is responsible for 1/3 of the excitatory synapses.[7] Glutamate is stored in synaptic vesicles, similar to other neurotransmitters. After passing into the synaptic gap, it is taken back by glial cells and converted to glutamine. Glutamine is transferred to neurons through carriers using active transport, where it is converted back to glutamate by glutaminase and stored in vesicles. In addition, glutamate can also be taken back by pre-post neurons. The cell is highly regulated in the release and reuptake of glutamates.[8] As a result of neurons' excessive activation, the calcium ion (Ca^{2+}) ratio inside the cell increases. For this situation to occur, both ionotropic and metabotropic glutamate

Corresponding Author: Yener Yazğan, yener8275@hotmail.com

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receptors are needed. As a result of glutamate binding, the ionotropic NMDA receptor causes Ca^{2+} to enter the cell from the extracellular space. Since this situation causes the Ca^{2+} balance within the cell to deteriorate, cell death is triggered through mitochondrial membrane depolarization, caspase activation, and the formation of free radicals. The formation of free radicals is effective in excitotoxic cell death.[9]

Although glutamate plays an important role in brain functions, its high concentration in the CNS causes the neurotoxic effect of glutamate. The positive effects of phenolic components on neurotoxic effects are known. However, the effect of Chrysin, one of the important phenolic components, on glutamate excitotoxicity has not yet been fully determined. This study aimed to examine the effect of Chrysin on glutamate excitotoxicity in the SH-SY5Y neuroblastoma cell line.

METHODS

Ethics

The current study does not involve research conducted with human subjects or participants. Commercially purchased cell lines are not subject to ethics committee approval. All procedures were carried out in accordance with the ethical rules and the principles.

Cell Culture and Experimental Groups

SH-SY5Y cells are one of the most commonly used cell lines in neurotoxicity studies and were obtained from ATTC (American Type Culture Collection).[10] Cells were grown in Dulbecco's modified eagle medium (DMEM) cell culture medium containing 10% fetal bovine serum (FBS) and 1% antibiotics (penicillin/streptomycin) in 75 cm^2 flasks at 37°C in a CO_2 incubator. For 24 hours, the cells were seeded in 75 cm^2 cell culture flasks. Glutamate and Chrysin were obtained from Sigma-Aldrich (St. Louis, MO, USA).

The study was conducted in 4 groups;

- **Control group:** No treatment was applied to this group,
- **Chrysin group:** 50 µM Chrysin was added and incubated for 24 hours.[11]
- **Glutamate group:** 10 mM glutamate was added and incubated for 24 hours.[12]
- **Glutamate+Chrysin group:** The SH-SY5Y cells were treated with Chrysin 50 µM 1 h prior to glutamate exposure and incubated for 24 hours.

Cell Viability Assay

The SH-SY5Y system, which was planted in a vial, was removed with trypsin EDTA after reaching sufficient stability. It was counted under an inverted microscope. The calculated cells were planted in 96-well plates with $7x10^3$ cells in each well. The CCK-8 (Abbkine, Cat#KTA1020) test, which gives color through mitochondrial enzymes, was used to evaluate cell viability after glutamate toxicity of Chrysin. Cell viability was measured at 450 nm using commercial ELISA kits on the BioTek ELx808™ instrument, following the instructions in the kit procedure. Experiments were repeated three times to determine the cell viability rate in the groups.

Measurement of Biochemical Parameters in SH-SY5Y Cells by ELISA Kits

Before starting the study, they were placed in separate sterile tubes for each group. The tubes were centrifuged at 1000 rpm for 20 minutes according to the kit procedure. After removal of the supernatants, cell pellets were suspended in PBS at a concentration of approximately 1x 10^6 cell/ml cells at pH: 7,4. Cells were lysed to separate them from elements resulting from repeated freeze-thaw cycles. The Bradford protein determination method was developed by taking advantage of the fact that the Coomassie Brilliant Blue G-250 dye molecule creates the blue colour of different intensities in protein solutions at different concentrations in the presence of protein and in an acidic environment.[13] Total antioxidant status (TAS), total oxidant status (TOS), tumor necrosis factor alfa (TNF-α), and interleukin 1 β (IL-1β) levels in the supernatants of SH-SY5Y cells were determined by ELISA kits (Bioassay Technology Lab. China). Measurements were made using ELISA kits BioTek ELx808™ device by the kit procedures.

Statistical Analysis

All data were presented as mean±standard deviation (SD). For statistical evaluation, one-way ANOVA (analysis of variance) was performed using the SPSS software for normally distributed data. The post-hoc Tukey test was conducted for all data that showed statistically significant differences. The results were expressed as mean±standard deviation (mean±SD). All probability test results were considered significantly different at $p<0.05$.

RESULTS

Effect of Chrysin on SH-SY5Y Cell Viability

In this study, the effect of Chrysin against glutamate toxicity was used to investigate cell viability in the study groups. For this purpose, the CCK-8 cell viability kit was employed. To examine the growth inhibitory effect of Chrysin, the anti-proliferative efficacy of Chrysin on SH-SY5Y cells was first assessed (**Figure 1**). It was observed that cell viability decreased significantly in the glutamate group compared to the control and Chrysin groups ($p<0.05$). It was observed that the cell viability level increased significantly in the cells in the glutamate+Chrysin group compared to the glutamate group ($p<0.05$).

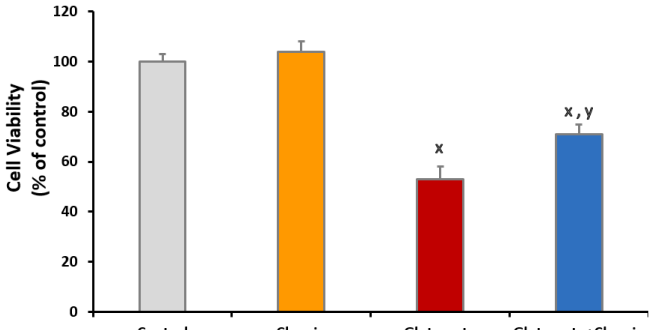

Figure 1. Effect of Chrysin on cell viability after glutamate-induced excitotoxicity in the SH-SY5Y cells. $^{x}p<0.05$ as compared to control and Chrysin groups, $^{y}p<0.05$ compared to glutamate group

Effect of Chrysin on TAS and TOS Lvels in SH-SY5Y Cells

Colourimetric TAS and TOS measurement commercial kits were used to evaluate the effects of Chrysin on oxidative stress after excitotoxicity caused by glutamate in cell lysates. According to TAS results, the application of 10 mM glutamate to SH-SY5Y cells showed a decrease in TAS level compared to the control and Chrysin groups ($p<0.05$; **Figure 2**). It was observed that the TAS level increased significantly in the cells

in the glutamate+Chrysin group compared to the glutamate group.

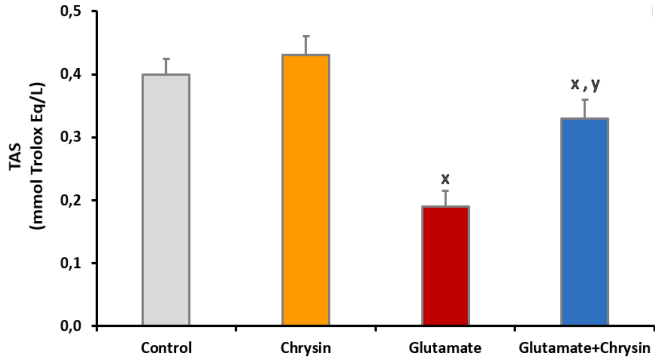

Figure 2. Effect of Chrysin on TAS level in SH-SY5Y cells after glutamate-induced cytotoxicity. $^{x}p<0.05$ as compared to control and Chrysin groups, $^{y}p<0.05$ compared to glutamate group

TAS: Total antioxidant status

According to TOS results, the application of 10 mM glutamate to SH-SY5Y cells significantly increased the TOS level compared to the control and Chrysin groups ($p<0.05$; **Figure 3**). There was no statistical difference between the control and Chrysin groups. It was observed that the TAS level increased in the cells in the glutamate+Chrysin group compared to the glutamate group, and the TOS level decreased significantly ($p<0.05$).

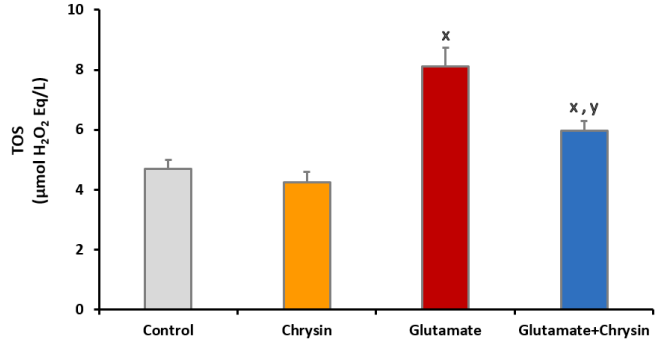

Figure 3. Effect of Chrysin on TOS level in SH-SY5Y cells after glutamate-induced cytotoxicity. $^{x}p<0.05$ as compared to control and Chrysin groups, $^{y}p<0.05$ compared to glutamate group

TOS: Total oxidant status

Effect of Chrysin on TNF-α and IL-1β Levels in SH-SY5Y Cells

TNF-α ELISA commercial kit was used to measure TNF-α values in Chrysin-applied and non-applied groups in SH-SY5Y cells in which glutamate excitotoxicity was induced. ELISA test results showed that TNF-α levels in the glutamate group increased statistically significantly compared to the control and Chrysin groups ($p<0.05$; **Figure 4**). On the other hand, a significant decrease in TNF-α levels was detected in the group given Chrysin together with glutamate compared to the glutamate group ($p<0.05$).

IL-1β ELISA commercial kit was used to evaluate the effect of Chrysin on IL-1β levels in SH-SY5Y cells with glutamate excitotoxicity. The test data obtained as a result of the application showed that IL-1β levels in the glutamate group increased significantly compared to the control and Chrysin groups ($p<0.05$; **Figure 5**). A significant decrease in IL-1β level was detected in cells treated with Chrysin along with glutamate compared to the glutamate group ($p<0.05$).

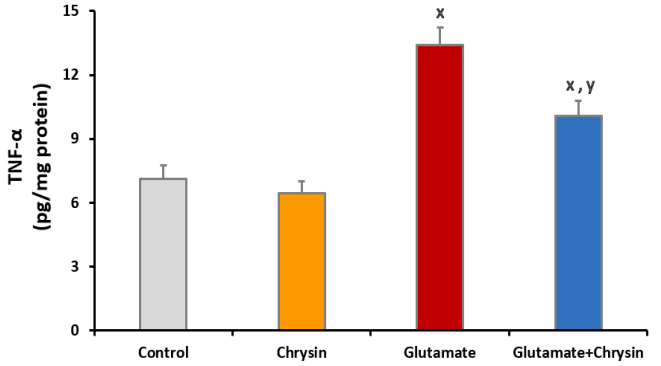

Figure 4. Effect of Chrysin on TNF-α level in SH-SY5Y cells after glutamate-induced cytotoxicity. $^{x}p<0.05$ as compared to control and Chrysin groups, $^{y}p<0.05$ compared to glutamate group

TNF-α: Tumor necrosis factor alfa

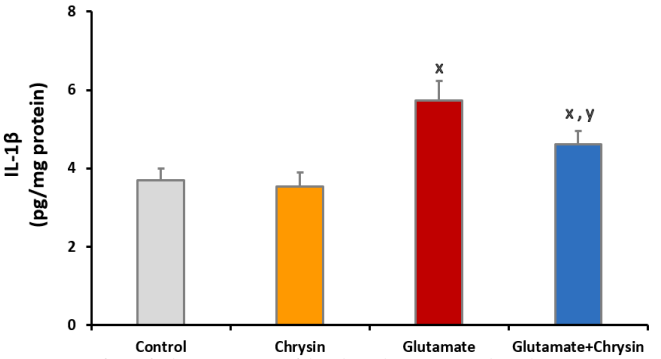

Figure 5. Effect of Chrysin on IL-1β level in glutamate-induced cytotoxicity in SH-SY5Y cells. $^{x}p<0.05$ as compared to control and Chrysin groups, $^{y}p<0.05$ compared to glutamate group

IL-1β: Interleukin 1 β

DISCUSSION

Glutamate has important functions as a major excitatory neurotransmitter in the mammalian brain.[14] However, excessive release of glutamate results in excitotoxicity. Excitotoxicity is an important factor in a variety of pathologies, from ischemic brain injury to neurodegenerations associated with many acute and chronic diseases.[15] Many studies have been conducted to understand the pathogenesis of these diseases. The basic mechanism is excitotoxicity caused by excessive glutamate stimulation. Various studies have been conducted to prevent pathologies caused by glutamate-induced excitotoxicity.[15-17] Although many substances with anti-inflammatory, antioxidant, and antiproliferative properties have been used in studies to prevent excitotoxicity through various mechanisms, no study has been found in the literature on the effect of Chrysin on glutamate excitotoxicity. Studies have shown that Chrysin exhibits a wide range of bioactivities, such as antitumor, antiulcer, antimicrobial, and antiproliferative effects on cancer cells.[18] One of the anticancer, antiulcerative and antiproliferative effects of Chrysin is to protect the cell from apoptosis by reducing oxidative stress. In our study, the effect of Chrysin pre-treatment against glutamate-dependent toxicity induced in vitro was examined.

It was demonstrated that cyclophosphamide caused cell toxicity in SH-SY5Y cells and that antioxidant treatments suppressed cell death in a study assessing the potential therapeutic effects of ferulic acid, quercetin, Chrysin, and caffeic acid against cyclophosphamide-induced toxicity in SH-SY5Y neuronal cells. By lowering lipid peroxidation levels,

downregulating the expression of Bax, cytochrome c, and Cas-3, and upregulating the expression of the anti-apoptotic gene Bcl-2, Chrysin protected SH-SY5Y cells.[19] In another study on Chrysin, it was shown that Chrysin suppressed diclofenac-induced apoptosis and oxidative damage in HT-29 cells and reduced cell death. Diclofenac-induced cell death caused an increase in ROS, malondialdehyde levels, and lactate dehydrogenase release, while it led to a decrease in total antioxidant and catalase activity. It was reported that pretreatment with Chrysin reversed these effects. Additionally, the expression levels of p53, Cas-3, Cas-8, Bax, and cytochrome c increased in the diclofenac-treated group but decreased following treatment with Chrysin.[20] In our study, it was determined that pretreatment with Chrysin increased cell viability and reduced cell death against glutamate-induced cytotoxicity in SH-SY5Y neuroblastoma cells (Figure 1). In line with the literature, our study results showed that high-dose glutamate exposure reduces cell viability by triggering intracellular oxidative stress-induced cascade pathways, whereas Chrysin' prevents this damage mechanism thanks to its antioxidant properties.

In a study on glutamate excitotoxicity in SH-SY5Y neuroblastoma cells, it was shown that TAS levels decreased while TOS levels increased.[21] In another study on glutamate excitotoxicity using primary rat cortical neurons, it was found that glutamate reduced TAS levels and increased TOS levels.[22] Similarly, in our study, TAS levels decreased, whereas TOS levels increased in the glutamate group (**Figure 2, 3**). In our study, Chrysin increased cell viability and TAS levels and decreased TOS levels by showing antioxidant properties in SH-SY5Y cells. In this context, we can also say that Chrysin has a protective effect against glutamate-induced neurotoxicity.

In neuroinflammatory diseases, the neuronal system and functions in the CNS are disrupted. Neuroinflammation is a protective mechanism aimed at repairing damaged glial cells and neuronal cells in the CNS. Unlike other cells, once neurons are damaged or degenerate, they cannot be repaired or regenerated in the CNS. Neuroinflammation is an important protective response for the brain, but excessive inflammatory responses are dangerous and can hinder neuronal regeneration. Microglia and astrocytes are influenced and altered by peripheral inflammatory conditions, thereby affecting neuroinflammation and neurodegeneration.[23]

A proinflammatory cytokine, TNF-α plays crucial roles in the central nervous system's homeostatic and pathological processes. Significant amounts of TNF-α are released by microglia under pathological conditions; this production is an essential component of the neuroinflammatory response associated with a number of neurological diseases. Furthermore, TNF-α can increase glutamate-induced cytotoxicity in two complementary ways: first, by indirectly blocking astrocyte glutamate transport processes; and second, by simultaneously decreasing the number of inhibitory GABA receptors and quickly increasing the surface expression of Ca^{2+}-permeable AMPA and NMDA receptors in neurons. Thus, the overall impact of TNF-α is to increase the synaptic excitatory/inhibitory ratio by shifting the balance between excitation and inhibition.[24]

There is a strong relationship between oxidative stress and cytokines, especially TNF-α.[25] Increased TNF-α level leads to oxidative stress. Previous studies have shown the existence of a parallel relationship between TNF-α and the reduction of oxidative stress during the healing process.[26] Therefore, we examined the relationship between the reduction of oxidative stress mediated by Chrysin and TNF-α. Proinflammatory cytokines are both key mediators and key mediators of neuroinflammation, and they have an important role in responding to neuronal damage.[27-29] Strong evidence indicates that proinflammatory cytokines stimulated by glutamate are involved in the progression and pathophysiology of neuronal diseases.[30] We observed that TNF-α expression significantly increased after glutamate application to SH-SY5Y cells and that Chrysin application prevented these neuroinflammatory events. In this context, Chrysin exhibits antioxidant and anti-inflammatory properties. We can also say that they have a protective effect against glutamate-induced neurotoxicity.

The first studies showing that TNF-α can potentiate excitotoxicity were conducted in human neuron cultures.[31] In a study investigating the effects of Chrysin against hepatotoxicity induced by high-dose paracetamol, it was observed that paracetamol increased lipid peroxidation and liver enzyme activities in rats while reducing antioxidant enzyme activities. Paracetamol also triggered an inflammatory response by raising the levels of TNF-α and IL-1β.[32] In a study on Chrysin, known as Chinese propolis, its effects against tunicamycin-induced neuronal cell death were evaluated in SH-SY5Y cells. Chrysin inhibited tunicamycin-induced cell death, caspase-3 activation, and its effects on mitochondria in a concentration-dependent manner.[33] In a study aimed at investigating the potential protective effects of Chrysin on oxidative status and the histological changes in liver and kidney tissues induced by carbon tetrachloride (CCl4) in rats, it was observed that CCl4 increased the levels of MDA, serum TNF-α, AST, ALT, urea, and creatinine, and the addition of Chrysin reversed these results.[34] In another study, he protective properties of Chrysin against cyclophosphamide-induced cardiotoxicity in rats were investigated. The results showed that cyclophosphamide significantly increased cardiac MDA, TNF-α, IL-1β, and IL-6 levels. And also, cardiac antioxidant enzyme activities such as superoxide dismutase (SOD) and catalase (CAT), as well as glutathione (GSH) levels, were suppressed. Treatment with Chrysin significantly restored these altered biochemical and antioxidant properties. Consequently, these findings suggest that Chrysin offers cardioprotective potential against cyclophosphamide-induced cardiotoxicity, which may be attributed to its antioxidant and anti-inflammatory properties.[35] In our study, Chrysin exhibited a protective effect in SH-SY5Y neuroblastoma cells by reducing the levels of TNF-α and interleukin-1β inflammation markers, which increased as a result of glutamate excitotoxicity (**Figure 4, 5**).

CONCLUSION

As a result, this study concluded that Chrysin increased the proliferation of SH-SY5Y neuroblastoma cells. The research findings indicate that an appropriate dose of Chrysin enhances cellular resistance to glutamate-induced cytotoxicity in these cells. We propose that glutamate's harmful effects are mediated through the activation of oxidative stress pathways. Consequently, it is suggested that Chrysin at the right dosage may offer protection against glutamate toxicity in central nervous system disorders and serve as a valuable therapeutic

agent for conditions associated with neuronal damage. Also, it was found in the study that Chrysin affects the SH-SY5Y cells. Nonetheless, additional in vitro and in vivo studies are required to explore the potential mechanisms by which Chrysin exerts its effects on glutamate toxicity.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethics committee approval is not required for cell culture studies.

Informed Consent

Because the study has no study with human and human participants, no written informed consent form was obtained.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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KASTAMONU MEDICAL JOURNAL

Original Article

DOI: 10.51271/KMJ-0205

Kastamonu Med J. 2025;5(3):172-176

Can the percentage of immature granulocytes predict mortality of octogenarian patients in intensive care?

Berkay Küçük, Metin Yarıcı, Eda Macit Aydın, Gül Meral Kocabeyoğlu, Mehmet Murat Sayın

Department of Intensive Care, Ankara Etlik City Hospital, Ankara, Turkiye

Cite this article as: Küçük B, Yarıcı M, Macit Aydın E, Kocabeyoğlu GM, Sayın MM. Can the percentage of immature granulocytes predict mortality of octogenarian patients in intensive care? *Kastamonu Med J.* 2025;5(3):172-176.

Received: 07.02.2025 ◆ **Accepted**: 19.03.2025 ◆ **Published**: 03.09.2025

ABSTRACT

Aims: This study aimed to investigate the effectiveness of immature granulocyte count and the percentage of immature granulocytes in predicting mortality in patients aged 80 years and older (octogenarians) in intensive care units.

Methods: This retrospective study included 333 patients aged 80 years and older who were followed up in the intensive care unit. Demographic data, laboratory values, clinical outcomes, and mortality status were recorded. The data were evaluated in two groups: survivors and deaths. Differences between the groups were statistically analyzed and compared.

Results: While the Glasgow Coma Scale (GCS) was lower in the mortality group, the acute physiology and chronic health evaluation II (APACHE II) and sequential organ function assessment (SOFA) scores were higher than in the survivors ($p<0.001$ for all). C reactive protein (CRP), neutrophil-to-lymphocyte ratio, and lactate values were significant markers for mortality prediction. No significant difference was found for immature granulocyte count and percentage when the groups were compared. APACHE II and SOFA scores had the highest discriminatory power in predicting mortality, with the area under the curve =0.74.

Conclusion: In octogenarian patients followed up in the intensive care unit, we found that the number and percentage of immature granulocytes was not an effective biomarker for predicting mortality despite its cheap and easy use. In the future, more comprehensive studies may show the importance of immature granulocytes.

Keywords: Octogenarian, immature granulocyte, mortality, intensive care

INTRODUCTION

In the medical literature, old age is analyzed under different categories. Although individuals between 80 and 89 are defined as octogenarians, this age group has been admitted to intensive care units more frequently due to modern medical innovations, improved surgical and anesthesia practices, and increased life expectancy.[1] However, intensive care follow-up of octogenarian patients has unique challenges due to age-related physiologic changes and the multiplicity of comorbid diseases.[2] While the risk of infection increases due to the immune system weakness that develops due to aging, the healing process is more complex, and aggressive treatment is required.[3]

Long-term survival rates in octogenarians are generally low, and intensive care mortality rates are significantly higher than in younger age groups.[4] Multiple comorbid conditions, low functional capacity before intensive care, the need for advanced supportive therapies such as mechanical ventilation and hemodialysis, and high indicators in mortality-related scoring systems are associated with mortality.[5]

There is still no definitive laboratory parameter or scoring system to indicate the severity of the disease and predict the prognosis in intensive care unit patients. However, some biomarkers are being investigated and used to predict morbidity and mortality in octogenarian patients.[6-9]

Immature granulocytes (IGs) are immature cells that pass into the peripheral blood due to stimulation of the bone marrow for various reasons and indicate bone marrow activation. They are elevated mainly due to severe infections, inflammation, sepsis, malignancies, hypoxic conditions, or bone marrow involvement.[10] Increased IG levels in patients followed up in intensive care can indicate the catabolism process in the body and disease severity and can be used as a biomarker that can predict mortality.[11] This may guide in determining patients' follow-up and treatment strategies in the intensive care unit.

In this retrospective study, we aimed to investigate the role of IG number and percentage in predicting the mortality of octogenarian patients in the intensive care unit.

METHODS

Ethics

The study was conducted retrospectively after ethics committee approval was obtained from Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee

Corresponding Author: Berkay Küçük, berkaykck@hotmail.com

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(Date: 08.05.2024, Decision No: AEŞH-BADEK2024-413). All procedures were carried out according to the ethical rules and principles of the Declaration of Helsinki.

Study Population and Protocol

The data of this retrospective study were obtained from patients aged ≥80 who were followed up in the intensive care units of Ankara Etlik City Hospital between May 01, 2023, and May 01, 2024. Patients who stayed in the intensive care unit for less than 48 hours, patients younger than 80, and patients with missing medical data records were excluded.

Data Collection

Age, gender, comorbidities, diagnosis and diagnosis groups, laboratory values, intensive care unit stay duration, total length of hospitalization, disease outcome (live-ex), and GCS were obtained from the hospital information management system and patient observation forms. The need for invasive mechanical ventilation in the intensive care unit, vasopressor requirement, development of acute kidney injury, and whether renal replacement therapy was administered were recorded. Arterial blood gas, hemogram, and biochemical parameters were evaluated based on samples taken on admission to the intensive care unit. IG count and percentage were recorded at the time of admission, on the day of discharge from the intensive care unit, and 24 and 48 hours before discharge. Neutrophil count, lymphocyte count, neutrophil/lymphocyte ratio, platelet count, white blood cell count, hemoglobin, creatinine, procalcitonin, CRP, and lactate values were obtained from the hospital information management system. APACHE II and SOFA scores calculated within the first 24 hours of admission were recorded. Patients were categorized into two groups: those who lived (survivors) and those who died (mortality group). The primary outcome of the study was intensive care unit mortality.

Statistical Analysis

The Kolmogorov-Smirnov test was used to assess the normality of continuous variables. Continuous variables were presented as mean±standard deviation (SD) and were analyzed with the Mann-Whitney U test. Categorical variables were expressed as frequency (n) and percentage (%) and analyzed using the Chi-square test. Receiver operating characteristic (ROC) curves were employed to determine the optimal cut-off values for continuous variables that showed significant differences in paired comparisons. Metrics such as the area under the curve (AUC), sensitivity, specificity, negative likelihood ratio, and positive likelihood ratio were calculated. A two-sided p-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA), and Python version 3.11.6, with the libraries "statsmodels,""scikit-learn,""matplotlib," and "seaborn."

RESULTS

A total of 333 octogenarian patients were included in the study. The median age of the patients included in the study was 84 (interquartile range (IQR): 80-98) years; 40.24% were male. Respiratory diseases accounted for 34.83%, sepsis 21.32%, and neurologic diseases 11.41% of the patients. 149 (44.74%) of the patients died (**Table 1**).

Table 1. The demographic and clinical characteristics of the patients

	n (%)
Gender	
Male	134 (40.24)
Female	199 (59.76)
Diagnosis groups	
Respiratory	116 (34.83)
Sepsis	71 (21.32)
Neurological	38 (11.41)
Postoperative	29 (8.71)
Cardiovascular	26 (7.81)
Renal-metabolic	19 (5.71)
Gastrointestinal	16 (4.8)
Trauma	12 (3.6)
Oncologic	4 (1.2)
Hematologic	2 (0.6)
Patient outcome	
Surviving	184 (55.26)
Exitus	149 (44.74)
Invasive mechanical ventilation requirement	160 (48.05)
Requirement for vasopressors in ICU	200 (60.06)
Acute kidney injury	170 (51.05)
Requirement for dialysis and/ or CRRT	83 (24.92)

ICU: Intensive care unit, CRRT: Continuous renal replacement therapy

The median values for APACHE II, SOFA, and GCS were 22 (IQR: 4-47), 6 (IQR: 1-14), and 13 (IQR: 3-15), respectively. The median values for intensive care unit length of stay and total hospitalization were 8 (IQR: 3-114) days and 18 (IQR: 3-258) days, respectively.

Of 184 patients in the surviving group, 63 (34.23%) were male, and the median age was 84 (IQR: 80-97) years. The median length of intensive care unit stay and total hospitalization were 6 (IQR: 3-96) days and 17 (IQR: 4-258) days, respectively. Of the 149 patients in the mortality group, 71 (47.65%) were male, and the median age was 85 years (IQR: 80-98). The median length of intensive care unit stay and total hospitalization were 12 (IQR: 3-114) days and 18 (IQR: 3-114) days, respectively.

While the GCS was lower in the mortality group, APACHE II and SOFA scores were higher in the mortality group compared to the survivors ($p<0.001$ for all). In laboratory results, neutrophil-to-lymphocyte ratio, lactate, and CRP values were higher in the mortality group ($p<0.001$, $p<0.001$, $p=0.014$, respectively). When the groups were compared for IG%, although the IG% values measured at discharge and 24 hours before discharge were higher in the mortality group, there was no statistically significant difference between the two groups. In addition, there was no significant difference in the IG% values measured at admission and 48 hours before discharge (**Table 2**).

When the ROC curve analyses were analyzed, the AUC value was 0.560, the cut-off value was 0.6, the sensitivity value was 0.68, and the specificity value was 0.5 in the prediction of IG % mortality 48 hours before discharge. The highest AUC values in the analyses were APACHE II and SOFA scores. The AUC value for both values was 0.740. Cut-off values were 21 and 7, respectively (**Table 3, Figure**).

Table 2. Clinical and laboratory findings of the whole study group and subgroups

	Total (n=333) study group	Survival group (n=184)	Mortality grup (n=149)	p-value
Age, years	84 (80-98)	84 (80-97)	85 (80-98)	0.13
Gender (male)	134 (40.24%)	63 (34.23%)	71 (47.65%)	0.26
Length of intensive care unit stay (days)	8 (3-114)	6 (3-96)	12 (3-114)	**<0.001**
Length of hospital stay (days)	18 (3-258)	17 (4-258)	18 (3-114)	0.63
Glasgow Coma Scale score	13 (3-15)	14 (5-15)	12 (3-15)	**<0.001**
APACHE II score	22 (4-47)	18 (4-40)	25 (5-47)	**<0.001**
SOFA score	6 (1-14)	5 (1-14)	8 (1-13)	**<0.001**
Creatinine mg/dl	1.32 (0.39-7.95)	1.265 (0.4-7.95)	1.36 (0.39-5.63)	0.143
CRP mg/L	83.8 (0.42-438.34)	65.35 (0.42-367.12)	105.62 (0.74-438.34)	**0.014**
Procalcitonin ng/ml	0.38 (0.02-100)	0.265 (0.02-100)	0.66 (0.02-100)	3.994
WBC $\times10^3$/uL	12.28 (2.06-38.53)	11.515 (2.06-31.49)	13.01 (3.6-38.53)	0.149
Hemoglobin ×g/dl	10.5 (4-17.4)	10.7 (4-17.4)	10.4 (4.3-15.9)	0.72
Thrombocytes $\times10^3$/uL	222 (11-660)	228 (16-660)	217 (11-651)	0.09
Neutrophil- lymphocyte ratio	11.75 (0.85-157.47)	10.735 (0.85-128.5)	14.06 (1.23-157.47)	**<0.001**
Lactate mmol/L	2.04 (0.67-14.76)	1.9 (0.78-14.76)	2.33 (0.67-8.75)	**<0.001**
IG admission $\times10^3$/uL	0.08 (0.01-1.99)	0.07 (0.01-1.04)	0.08 (0.01-1.99)	0.08
IG% admission	0.7 (0.1-86.2)	0.7 (0.1-13.2)	0.7 (0.1-86.2)	0.2
IG 48 hours before $\times10^3$/uL	0.07 (0.01-1.96)	0.06 (0.01-1.24)	0.07 (0.01-1.96)	0.6
IG% 48 hours before	0.7 (0.1-10.7)	0.7 (0.1-6.2)	0.7 (0.1-10.7)	0.15
IG 24 hours before $\times10^3$/uL	0.06 (0.01-1.9)	0.06 (0.01-1.26)	0.07 (0.01-1.9)	0.88
IG% 24 hours before	0.7 (0.1-11.6)	0.7 (0.1-8.4)	0.8 (0.1-11.6)	0.29
IG at discharge $\times10^3$/uL	0.08 (0.01-6.25)	0.06 (0.01-1.27)	0.1 (0.01-6.25)	0.52
IG% at discharge	0.8 (0.1-25.5)	0.7 (0.1-6)	0.9 (0.2-25.5)	0.5

Bold values are significant, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Function Assessment, WBC: White blood cell, CRP: C-reactive protein, IG: Immature granulocyte

Table 3. Results of ROC curve analyses

	AUC	p-value	Cut-off value	Sensitivity	Specifity	PLR	NLR
Glasgow coma scale score	0.73	<0.001	12	0.56	0.81	0.64	0.76
APACHE II score	0.74	<0.001	21	0.68	0.67	0.55	0.78
SOFA score	0.74	<0.001	7	0.62	0.76	0.68	0.71
IG admission $\times10^3$/uL	0.4	0.08	0.04	0.54	0.9	0.31	0.54
IG% admission	0.52	0.2	0.45	0.46	0.6	0.48	0.58
IG 48 hours before $\times10^3$/uL	0.54	0.6	0.04	0.69	0.33	0.46	0.57
IG% 48 hours before	0.56	0.15	0.6	0.68	0.5	0.45	0.72
IG 24 hours before $\times10^3$/uL	0.48	0.88	0.04	0.65	0.33	0.44	0.54
IG% 24 hours before	0.54	0.29	0.43	0.88	0.24	0.41	0.77
IG at discharge $\times10^3$/uL	0.48	0.52	0.06	0.84	0.33	0.43	0.78
IG% at discharge	0.48	0.5	0.44	0.84	0.29	0.41	0.75

ROC: Receiver operating characteristic, AUC: Area under curve, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Function Assessment, IG: Immature granulocyte

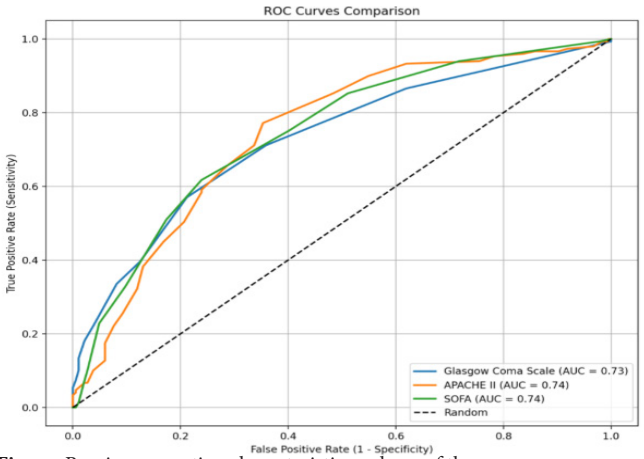

Figure. Receiver operating characteristic analyses of the scores

DISCUSSION

The elderly population is constantly increasing worldwide due to the development of modern medical techniques, increased quality of life, and improved medical diagnosis and treatment possibilities.[12] The aging of the population has also increased the incidence of acute and chronic diseases, malignancies, organ failures, and infections in these patients.[13] Therefore, many treatments that were previously not recommended or not applicable to the elderly group have started to be applied, and the intensive care needs of patients have increased during the follow-up and treatment process.[14,15]

Patients aged 80 years and older, defined as octogenarians, are a group that should be followed carefully because of their cognitive and physical capacities and comorbid diseases.[16]

Follow-up and treatment of these patients in the intensive care unit is both more difficult and associated with worse outcomes compared to the younger patient group.[17,18] In a multicenter study of patients with septic and septic shock, Bruno et al.[19] found higher mortality rates in patients over 80 years of age compared to the group aged 65-79 years. In intensive care units, predicting which patients are at risk for critical illness or mortality remains uncertain. Although there is currently no optimal biomarker to determine this, studies are ongoing worldwide.

IG is a biomarker that shows bone marrow activation and increases in conditions such as infection, inflammation, hypoxia, and sepsis. One of the reasons why it has attracted attention in recent years is that it can be easily detected during routine complete blood count and does not create an additional cost.[10] Today, many scoring systems such as APACHE II, Nutrition risk in the critically ill (NUTRIC) score, and SOFA score, and many parameters such as CRP, procalcitonin, neutrophil-lymphocyte ratio, and lactate continue to be used to evaluate the prognosis of diseases.[6-9] In the literature, many publications are investigating IG in terms of predicting the severity and prognosis of diseases such as pneumonia, appendicitis, pancreatitis, epilepsy, especially infection and sepsis.[20-24]

In a retrospective study of 438 cases in which appendectomy was performed, Unal found that the number of IGs and the percentage of IGs were significant in diagnosing acute appendicitis and had a more substantial value than classical parameters in predicting complicated appendicitis. The AUC value for predicting complicated appendicitis was 0.979, considerably higher than values such as neutrophil-lymphocyte ratio and white blood cell count.[21] Karakulak et al.[22] analyzed pancreatitis cases in a retrospective study, which included 218 cases. This study found that complicated pancreatitis and in-hospital mortality were associated with an increase in IG%. While the cut-off value of 1.1 and the AUC value of 0.698 were associated with disease severity, they reported that when the cut-off value exceeded 1.8, the AUC value was 0.708, and in-hospital mortality increased.

Akay Çizmecioğlu et al.,[23] in a study of 80 geriatric pneumonia cases, showed that although IG was effective in showing disease severity, it was low effective in showing mortality. For mortality, they determined p=0.561 and AUC value of 0.628 in all patients; when they excluded oncologic patients from the analysis, they expressed p=0.570 and AUC value of 0.732. The small number of patients in the study and the fact that the patient group included oncologic cases may be a factor in the emergence of these data. It has been stated that oncologic data affect the study's results, and the fact that the patient groups were different and no specific patient group in our study may have been decisive in our results. In the study by Bildirici et al.[24] evaluating the distinction between epilepsy and psychogenic non-epileptic seizures, the number of IGs was not found to be effective in differentiating the two conditions. Similarly, the study by Yaşar et al.[25] found that IG had no prognostic value in detecting idiopathic sudden sensorineural hearing loss. Sengul et al.[26] also found that IG count and IG% did not help determine Helicobacter pylori density and severity of inflammation.

Su et al.[27] evaluated the ability of IG to distinguish between simple and complicated diverticula of the right colon as strong in their study of 289 patients. They found a high AUC value of 0.93 and argued that surgeons could positively guide diverticulum treatment management medically and surgically.

When we compared our study with other studies, we may have obtained different results due to patient characteristics, comorbidities, presence or absence of a septic picture, malignancies, and hospital and intensive care unit admission duration. Although the IG values at discharge and 24 hours before discharge were high, we could not detect a statistically significant difference. However, it was valuable that we recorded the IG values at admission to the intensive care unit, discharge, 24 and 48 hours before discharge. In other studies, only a single IG data was evaluated. This made daily follow-up of IG values and correlation with other infection and inflammation parameters important. In systematic reviews and meta-analyses, it has been reported that IG is a strong predictor of mortality, especially in infection and sepsis.[28] IG is a valuable parameter in the early diagnosis of sepsis, exclusion of sepsis, monitoring response to treatment, and prediction of multiple organ failure. Its short half-life, ability to be obtained by routine blood count, reproducibility, and lack of additional cost make it easy to use.[10,11] There is no definite cut-off value and evaluation time for IG. Its elevation can be detected at admission to the emergency department, admission to the intensive care unit, preoperative period, postoperative period, discharge time, and any time during periodic monitoring. This can be answered by where the patient is in the picture of infection, inflammation, or sepsis. The stage of the disease and the presence or absence of complications in the postoperative period may affect the IG. In the literature, there are almost no studies on the efficacy of IG and its prognosis prediction in octogenarian patients followed up in the intensive care unit. In addition, although the number of patients in our study was high and sufficient compared to other studies, the mixed population, the presence of diagnoses in different groups, and the presence of malignant conditions may have created a heterogeneous environment regarding IG. It is possible to obtain significant results in an isolated patient group. IG, inexpensive, easy to look at, and reproducible, can be used safely in intensive care for octogenarian patients like other parameters.

Limitations

Since this was a retrospective and single-center study, the efficacy of IG should be confirmed by other studies. Secondary infection, sepsis, septic shock, and malignancy were not taken into consideration in the follow-up of IG. In addition, patients with different diagnostic groups followed up in the intensive care unit were analyzed together. IG was examined at the time of admission, at the time of discharge, and at 24 and 48 hours before discharge, while other markers were evaluated only at the time of admission.

CONCLUSION

In octogenarian patients followed up in the intensive care unit, IG, which is safe in terms of cost and ease of use, was not found to be an effective biomarker in predicting mortality. We think that regular follow-up instead of a single measurement and looking at the upward-downward trend will have an important place in patient follow-up and treatment. We believe that comprehensive studies in more specific and homogeneous patient groups will be enlightening and guiding.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee (Date: 08.05.2024, Decision No: AEŞH-BADEK2024-413).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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KASTAMONU MEDICAL JOURNAL

Original Article

DOI: 10.51271/KMJ-0206

Kastamonu Med J. 2025;5(3):177-181

Identification of laryngeal mask airway failure in pediatric patients: a pilot study

Hatice Selçuk Kuşderci, Özgür Kömürcü, Sevda Akdeniz, Durmuş Mehmet Sezgin, Mustafa Süren

Department of Anesthesiology and Reanimation, Faculty of Medicine, Samsun University, Samsun, Turkiye

Cite this article as: Selçuk Kuşderci H, Kömürcü Ö, Akdeniz S, Sezgin DM, Süren M. Identification of laryngeal mask airway failure in pediatric patients: a pilot study. *Kastamonu Med J.* 2025;5(3):177-181.

Received: 25.01.2025 • **Accepted**: 07.04.2025 • **Published**: 03.09.2025

ABSTRACT

Aims: The study was conducted to identify predictors of laryngeal mask airway (LMA) placement failure in pediatric patients and to investigate the relationship between LMA placement failure and postoperative airway complications.

Methods: This study was designed as a prospective observational trial including 66 ASA I patients aged 2-12 years who were scheduled for elective surgery. The patients were divided into two groups based on the placement of the LMA: group S (successful placement of LMA at first attempt) and group non-S (non-successful placement of LMA at first attempt). The relationship between LMA placement failure with airway leakage, peak airway pressure, peripheral oxygen saturation, and expiratory CO_2 measurements was evaluated.

Results: Airway leakage and peak airway pressure was significantly higher in group non-S when compared to group S [(median-IQR) (ml); 10 (4) vs. 5 (5); p<0.001] and [(median-IQR) (cm-H_2O); 14 (3.5) vs.13 (2); p=0.038], respectively. Patients in group non-S exhibited a higher incidence of postoperative respiratory complications when compared to group S (72.4% vs 27.6%; p<0.001).

Conclusion: Airway leak and peak airway pressure can serve as determinants of LMA failure in pediatric patients.

Keywords: Laryngeal mask airway, pediatric surgery, airway management, anesthesia

INTRODUCTION

Laryngeal mask airway (LMA) is a supraglottic airway device that is inserted into the pharynx for the purpose of ventilation. One significant benefit of LMA is that it is simpler to insert than an endotracheal tube during general anesthesia.[1] It has gained popularity as it can be inserted more rapidly when compared to endotracheal intubation, particularly by healthcare personnel with limited experience.[2] Furthermore, the utilization of a laryngeal mask has a lower incidence of complications, including postoperative cough, laryngospasm, soft tissue trauma, and sore throat, in comparison to tracheal intubation, as well as fewer hemodynamic changes.[1]

In comparison to endotracheal intubation, LMA applications present a variety of hazards, including a higher risk of gastric insufflation, a lower level of airway protection, and a higher incidence of hypoxemia.[3] Various studies have focused on lowering these risks.[2,4] Identification of risk factors for LMA failure could help anesthesiologist with evaluation of airway conditions and improvement of patient management.[5,6] Nevertheless, although objective data such as air leak, high airway pressure, inadequate lung ventilation, and single lung ventilation can be used to detect inappropriate or failed endotracheal intubation, no objective criteria is available for the detection of LMA misplacement.[7-9]

The aim of this study was to determine objective predictors for LMA placement failure in pediatric patients following anesthesia induction and to examine the correlation between LMA placement failure and postoperative airway complications.

METHODS

Ethics

This single-center, prospective, observational study was approved by Samsun University Clinical Researches Ethics Committee (Date: 23.08.2023, Decision No: 2023/15/13) and registered with clinicaltrials.gov (NCT06337006). The study was conducted between 15/09/2023 and 15/07/2024 in a tertiary women's health and pediatric hospital. Written informed consent was obtained from all parents of patients before enrollment. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Study Populations

The study included patients between the ages of 2 and 12 who were scheduled for elective out-patient surgery (hernia repair, circumcision, orthopedic corrections etc.), who had an American Society of Anesthesiologists (ASA) physical

Corresponding Author: Özgür Kömürcü, zgrkom@gmail.com

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status score of 1, and where an anesthesiologist planned to use a LMA for upper airway support during surgery. The study excluded patients who were at risk of gastroesophageal reflux and gastric aspiration, had a known airway malformation, hyperthyroidism, goiter, or known airway mass, had a surgery >1 hour, or were considered to have a difficult airway prior to anesthesia.

Anesthesia with LMA Insertion

A pre-anesthesia check was performed before surgery and all children fasted in accordance with protocol.[10] Upon arrival in the operating room, the patient was connected to a multichannel monitor that displayed heart rate, peripheral oxygen saturation (SpO_2), and noninvasive blood pressure (systolic, diastolic, and mean arterial pressure). Before the induction of anesthesia, vital parameters were recorded. The institute's protocol was followed when administering standard anesthesia to all children.

In the operating room prior to induction, children were preoxygenated with 100% oxygen at 6 L/min for 3 minutes with a face mask and the head held in a neutral position. Anesthesia induction was administered to children with intravenous (IV) access using propofol 2-3 mg/kg and fentanyl 1 µg/kg. Children lacking IV access underwent induction with inhaled sevoflurane. The value of basal End tidal CO_2 ($EtCO_2$) (mmHg) was recorded during mask ventilation. Adequate depth of anesthesia was determined to be achieved when the jaw was fully relaxed and the eyelash reflex was dissipated. Rocuronium 0.2 mg/kg IV was administered for muscle relaxation after the mask ventilation was confirmed to be adequate.

The capsule of the classic LMA (Intavent Direct, Maidenhead, UK) was evenly coated with 1-2 ml of lidocaine gel. The manufacturer's recommendation was followed in selecting the appropriate size of the LMA (2 for 10-20 kg and 1.5 for 5-10 kg). An experienced anesthesiologist positioned the fully deflated LMA with the patient's head in a neutral position. The patient's mouth was then opened, and the device was advanced along the hard palate while the patient was held parallel to the torso. The manufacturer's instructions were followed to ensure that the cuff of the device was adequately inflated. The following criteria were used to determine successful LMA placement: equal chest movement on inspiration, square wave capnograph, no gastric insufflation or air leak by sound and adequate tidal volume. If all criteria were met, LMA placement was accepted as a success (group S), and if one or more criteria failed, patients were deemed to have unsuccessful LMA placement (group non-S). The mechanical ventilator is equipped with an adjustable pressure limiting (APL) valve that operates at 25 cm-H_20, a tidal volume (VT) of 8 ml/kg, and a fresh gas flow (FGF) of 3 L/min. The inspiration-expiration ratio was 1/2. The arithmetic average of the VT, expiratory VT, airway peak pressure, SpO_2, and $EtCO_2$ measurements was recorded by an additional experienced anesthesiologist in three respiratory cycles following the initial placement of the LMA. Airway loss (ΔVT) was determined by subtracting the adjusted VT from the expiratory VT. SpO_2 and $EtCO_2$ measurements, airway leak volume, and airway peak pressure were identified as potential predictors of LMA placement failure. Postoperative airway complications were identified and documented as cough attack, bleeding, sore throat, soft tissue trauma, and laryngospasm-bronchospasm.

Outcomes

The primary outcome was the identification of the determinants for LMA placement failure, while the secondary outcome was the determination of the relationship between LMA placement failure and postoperative airway complications.

Statistical Analysis

Using a 95% confidence level (1-α), a test power of 95% (1-β), and an effect size of d=1.016, the sample size, calculated using G*power, was determined to be a minimum of 22 cases for each group and a total of at least 44 cases.[11] To account for potential data loss, the authors intended to conduct the trial with a minimum of 25 patients in each group. Statistical analyses were conducted using SPSS version 26 (IBM Corporation, Armonk, NY, USA.) Data normality was tested using the Kolmogorov-Smirnov test and the Shapiro-Wilk test for groups with sample sizes below 30. Quantitative data were presented as mean [±standard deviation (SD)] or median [interquartile range (IQR)] and frequency (percentage) for categorical data. Quantitative variables were compared using the student T test or Mann-Whitney U test. Categorical data were compared using the Chi-square ($\chi 2$) or Fisher's exact test. In LMA placement failure, ROC analysis was used to calculate the sensitivity and specificity for the difference between adjusted tidal volume and measured inspiratory tidal volume, airway peak pressure, peripheral oxygen saturation, and expiratory CO_2. $p<0.05$ was used as statistical significance in all tests.

RESULTS

The study was completed with 66 patients. The flow chart of the study is shown in **Figure 1**. LMA placement failure was seen in 35.6% of patients. Patients' demographic and clinical data are shown in **Table**. Body weight (kg) [(median-IQR); 15 (9.7) vs. 22 (13); p=0.007] and body-mass index (BMI, kg/m^2) [(median-IQR); 14.2 (3.9) vs. 16.8 (4.3); p=0.013] were found to be lower in group non-S when compared to group S. ΔVT measured to assess airway leak [(median-IQR) (ml); 10 (4) vs. 5 (5); p<0.001] and airway peak pressure [(median-IQR) (cm-H_2O); 14 (3.5) vs.13 (2); p=0.038] was found to be significantly higher in group non-S. SpO_2 was similar between groups before anesthesia induction and after LMA placement (p>0.05). $EtCO_2$ was similar between two groups before induction. However, $EtCO_2$ was higher in group non-S when compared to group S after LMA placement [(median-IQR); 39 (3) vs. 37 (2); p=0.001]. However, $EtCO_2$ was within normal physiological rates in both groups after LMA placement. The variables that predict the failure of LMA placement by group are illustrated in **Figure 2**.

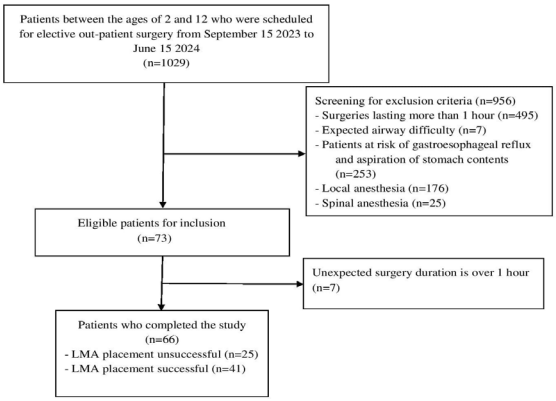

Figure 1. Flowchart of the study

Table. Patient demographic and clinical characteristics

	All patients	Group S (n=41)	Group non-S (n=25)	p
Demographics				
Age (year) (median-IQR)	4 (4)	4.5 (4.75)	2.5 (3.25)	0.064
Gender (male) (n, %)	60 (90.9)	36 (60)	24 (40)	0.261
Body weight (kg) (median-IQR)	18 (11)	22 (13)	15 (9.7)	0.007
Body-mass index (kg/m^2) (median-IQR)	15.9 (4.6)	16.8 (4.3)	14.2 (3.9)	0.013
Surgical procedure				0.012
Abdominal surgery (n, %)	23 (34.8)	19 (82.6)	4 (17.4)	
Genitourinary surgery (n, %)	43 (65.2)	22 (51.2)	21 (48.8)	
Before anesthesia induction				
Heart rate (minute/beat) (median-IQR)	120 (24.2)	118 (26)	131 (21.5)	0.003
SpO_2 (%) (median-IQR)	100 (1)	100 (1)	100 (1)	0.540
$EtCO_2$ (mmHg) (median-IQR)	36 (2)	36 (2)	36 (2.5)	0.661
Systolic artery pressure (mmHg) (mean±SD)	105.9±11.9	107.8±10.6	102.8±13.4	0.099
Diastolic artery pressure (mmHg) (mean±SD)	57.6±18.2	55.4±14.5	61.2±12.7	0.060
Mean artery pressure (mmHg) (mean±SD)	73.7±10.5	72.8±10.6	75.1±12.1	0.410
After LMA attempt				
Heart rate (min/beat) (median-IQR)	111 (33.7)	104 (16)	123 (25)	0.001
SpO_2 (%) (median-IQR)	100 (1)	100 (1)	100 (0)	0.435
$EtCO_2$ (mmHg) (median-IQR)	38 (3)	37 (2)	39 (3)	0.001
Systolic artery pressure (mmHg) (mean±SD)	96.1±9.4	96.7±9	96±10.3	0.978
Diastolic artery pressure (mmHg) (mean±SD)	49.8±8.8	48.3±9.5	52.1±9	0.098
Mean artery pressure (mmHg) (mean±SD)	65.2±9.5	64.3±7.9	66.7±8.8	0.245
Mechanical ventilation				
Adjusted VT (ml) (median-IQR)	150 (82.5)	170 (100)	120 (70)	0.026
Expiratory VT (ml) (median-IQR)	140 (100)	170 (100)	90 (67.5)	<0.001
ΔVT (ml) (median-IQR)	8 (20)	5 (5)	10 (4)	<0.001
Peak airway pressure (cm-H_2O) (median-IQR)	13 (3)	13 (2)	14 (3.5)	0.038
Postoperative complication				
Cough (n, %)	7 (10.6)	2 (28.6)	5 (71.4)	0.221
Minimal bleeding (n, %)	6 (9.1)	1 (16.7)	5 (83.3)	0.082
Sore throat (n, %)	4 (6.1)	3 (75)	1 (25)	0.297
Tissue trauma (n, %)	3 (4.5)	1 (33.3)	2 (66.6)	0.552
Cough and minimal bleeding (n, %)	9 (13.6)	1 (11.1)	8 (89.1)	0.010

IQR: Interquartile range, SpO_2: Peripheral oxygen saturation, $EtCO_2$: End-tidal CO_2, CO_2: Carbon dioxide, SD: Standard deviation, LMA: Laryngeal mask airway, VT: Volume tidal, ΔVT: Adjusted VT-expiratory VT

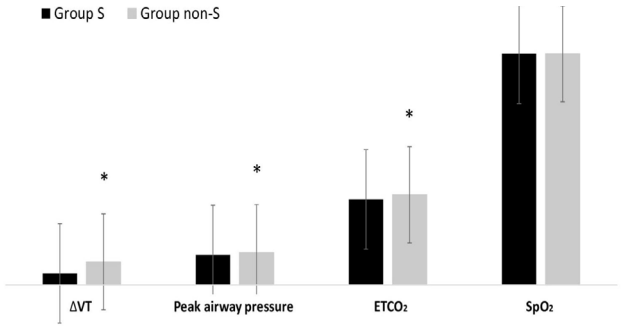

Figure 2. The variables that predict the failure of LMA placement by groups. $EtCO_2$, End-tidal CO_2; SpO_2, Peripheral oxygen saturation; ΔVT, adjusted VT-expiratory VT

LMA: Laryngeal mask airway, $EtCO_2$: End-tidal CO_2, CO_2: Carbon dioxide, SpO_2: Peripheral oxygen saturation, ΔVT: Adjusted VT-expiratory VT, VT: Volume tidal

Following the establishment of the ROC curve for ΔVT and peak airway pressure (**Figure 3**), the cutoff values for predicting the failure of LMA placement were determined to be 7 ml and 13.5 cm-H_2O, respectively. The sensitivities and specificities for ΔVT were 80% and 65% (AUC, 0.790; 95% CI, 0.682-0.898; p<0.001) and for airway peak pressure were 60% and 61% (AUC, 0.651; 95% CI, 516-787; p=0.040), respectively.

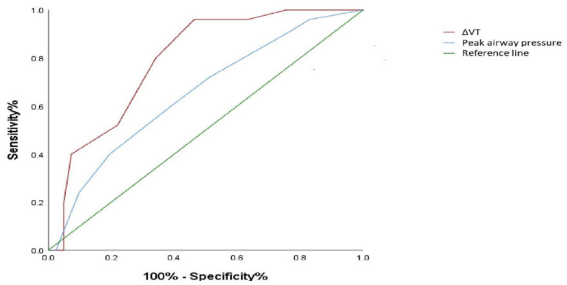

Figure 3. Receiver operating curve for changes in ΔVT and peak airway pressure on the risk of developing failure of LMA placement. It is a plot of the true positive rate (sensitivity) versus the false positive rate (1-specificity) at various thresholds of ΔVT and peak airway pressure. The area under the curve is a measure of the diagnostic accuracy for changes in ΔVT and peak airway pressure of predicting failure of LMA placement

ΔVT: Adjusted VT-expiratory VT, VT: Volume tidal, LMA: Laryngeal mask airway

The prevalence of all defined postoperative respiratory complications, except for sore throat (group non-S vs group S; 25 vs 75%; p=0.297), was higher in group non-S when compared to group S (72.4% vs 27.6%; p<0.001).

DISCUSSION

As SpO_2 did not significantly change between before anesthesia induction and after LMA placement, and as $EtCO_2$ remained within normal physiological ranges despite a statistically significant increase between before anesthesia induction and after LMA placement, we conclude that SpO_2 and $EtCO_2$ cannot be determining factors of LMA placement failure in children. We observed that ΔVT and peak airway pressure were significantly higher in group non-S when compared to group S. Therefore, ΔVT and peak airway pressure could be used as determining factors of LMA placement failure.

In order to prevent potential hypoxia and hypercarbia, it is essential to provide optimal respiratory support during general anesthesia.[12,13] LMA safeguards patients from hypoxia during surgical procedures that are conducted under general anesthesia or sedation. Khatavkar et al.[14] demonstrated that LMA facilitated stable O_2 saturation in children during fiberoptic bronchoscopy under sedation, in contrast to nasal airway-assisted bronchoscopy. In addition, it has been reported that the LMA is more effective in preventing hypoxia in pediatric patients compared to tracheal intubation.[1,15] It is generally emphasized that the successful prevention of hypoxia is achieved through the proper application of LMA. Nevertheless, the criteria for effectively applying LMA are not clearly defined. In their study examining the efficacy of LMA placement in children, Asida et al.[16] defined SpO_2 ≤92% as unsuccessful LMA placement. However, the cutoff value of SpO_2 or any other oxygenation parameter has not been determined. In this pilot study, we selected SpO_2 change as one of the predictors for LMA placement failure. Due to the immaturity of respiratory control in children, the high flow resistance of the airways, rapid airway collapse, low gas exchange surface of the lungs, faster oxygen desaturation, and the potential for bradycardia and cardiac arrest as a result of very short-term hypoxia, our study was conducted over three respiratory cycles. In the study population, there was no significant change in SpO_2 levels, and it was determined that SpO_2 levels were an inappropriate predictor for the study group. Similarly, we believe that the $EtCO_2$ change, which we maintained within normal limits for ethical and safety reasons, cannot be a predictor for LMA placement, despite the fact that $EtCO_2$ increased statistically significantly compared to the beginning of the study, as hypercarbia that may transpire following anesthesia induction can lead to severe complications, particularly in children.[17]

The authors of a study that examined the perioperative risk factors of first-attempt LMA placement failure in 461 adult patients undergoing general anesthesia defined LMA placement failure as a severe air leak (>20% VT) or high airway pressure (peak pressure >25 cm-H_2O).[18] Again, in a study that compared two distinct supraglottic airways (SGA) in adult patients, excessive placement of the supraglottic airway device was defined as a minimum expiratory tidal volume of 6 ml/kg during controlled ventilation without oropharyngeal leak or gastric insufflation, and a peak airway pressure of less than 17 cm-H_2O.[19] The optimal peak airway pressure for successful LMA placement in children is unclear. Gursoy et al.[20] determined that the airway leak pressure in pediatric patients was 17 mbar following the appropriate placement of the LMA. Another study compared two different appropriately placed SGAs in pediatric patients and determined that the LMA airway pressure should be 15.3±3.4 cmH_2O to attain the desired VT.[21] While mean airway pressure for SGA's can change according to study population, SGA size, cuff pressure and fresh gas flow used during measurements,[22] the cutoff value for LMA placement failure in our study was established as the peak airway pressure exceeding 13 cm-H_2O after the LMA cuff was inflated to the manufacturer's recommended size and volume. The airway leak pressure was not assessed in the study, as the detection of an airway leak through listening after the initial LMA application was deemed an unsuccessful LMA application. A cutoff of 7 ml was established for airway loss volume in our study population.

Failure to position the LMA on the initial attempt resulted in additional airway attempts. Consequently, patients with failed LMA placement on the first attempt had an increase in postoperative airway problems due to potential upper airway injury. None of these complications, however, resulted in any severe complications.

After LMA placement, adequate sealing allows effective positive pressure ventilation without leakage. Prevents gastric air insufflation. Guarantees adequate ventilation. Increased airway pressures are also associated with increased airway and lung injury in patients with LMA placement.[23] There was no statistically significant difference in postoperative airway complications of airway leakage or airway pressures between the groups with and without successful LMA placement. This may be due to the limitation of the study to 3 respiratory cycles to prevent possible hypoxia and hypercarbia.

Limitations

The study has several limitations. Initially, the variables we identified as predictors, and our results may have been influenced by the definition of the groups based on observational data. Secondly, the examination findings were used to assess the difficulty of airway access in children. Nevertheless, the child's complete orientation is necessary to evaluate other challenging airway markers, such as Mallampati. This may have restricted by the age distribution of the study group. Thirdly, fiberoptic imaging has been recommended in recent studies to ensure the successful placement of LMAs. We refrained from employing a fiberoptic imaging technique in our patients because it had the potential to influence the data we intended to measure. Lastly, the study method was designed to include three respiratory cycles, as the study population would experience severe complications as a result of uncontrolled fluctuations in SpO_2 and $EtCO_2$ levels. Consequently, the authors-maintained control over the variations in SpO_2 and $EtCO_2$. This may have restricted the potential of these two parameters to determine.

CONCLUSION

Objective data are needed to evaluate the safety and clinical performance of the produced supraglottic airway devices. The study showed that airway leakage and peak airway pressure can be used for LMA placement success in children. However, although statistically significant, the specificity and sensitivity of these two parameters are low. Therefore, we think that studies planned with large populations can help increase the safety and clinical.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Samsun University Clinical Researches Ethics Committee (Date: 23.08.2023, Decision No: 2023/15/13).

Informed Consent

Written informed consent was obtained from all parents of patients before enrollment.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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KASTAMONU MEDICAL JOURNAL

Original Article

DOI: 10.51271/KMJ-0207

Kastamonu Med J. 2025;5(3):182-187

Comparison of PI-RADS categories, prostate volume and prostate specific antigen parameters among prostate biopsy results

Mustafa Koyun[1], İsmail Taşkent[2], Bünyamin Ece[2]

[1]Department of Radiology, Kastamonu Training and Research Hospital, Kastamonu, Turkiye
[2]Department of Radiology, Faculty of Medicine, Kastamonu University, Kastamonu, Turkiye

Cite this article as: Koyun M, Taşkent İ, Ece B. Comparison of PI-RADS categories, prostate volume and prostate specific antigen parameters among prostate biopsy results. *Kastamonu Med J.* 2025;5(3):182-187.

Received: 14.02.2025 ◆ **Accepted**: 14.04.2025 ◆ **Published**: 03.09.2025

ABSTRACT

Aims: The aim of this study was to compare PI-RADS (Prostate Imaging-Reporting and Data System) categories, prostate volume, and prostate-specific antigen (PSA) parameters among prostate biopsy results.

Methods: A total of 367 patients who underwent multiparametric magnetic resonance imaging (mpMRI) between July 2021 and February 2023 were retrospectively analyzed. Age, total PSA (tPSA), free PSA (fPSA), tPSA/fPSA ratio, PSA density (PSAD, tPSA/prostate volume), and PI-RADS categories were recorded for each patient. 199 patients were excluded from the study due to insufficient data, and the study was conducted with the remaining 168 patients. The mpMRI were performed using a 1.5 T MRI scanner. PI-RADS categories 1, 2, and 3 obtained from mpMRI were classified as PI-RADS≤3, while PI-RADS categories 4 and 5 were classified as PI-RADS>3. Prostate biopsy was performed as a 12-core biopsy under transrectal ultrasonography (TRUS) guidance. Independent samples T test, Mann-Whitney U test and Chi-square test were used to compare the data of histopathologically benign and malignant groups. A p-value <0.05 was considered statistically significant.

Results: Of the 168 patients included in the study, 105 (62.5%) were benign and 63 (37.5%) were malignant based on histopathological results. Statistically significant differences were found between malignant/benign groups in mean age (69.9/67.0 years, p=0.002), prostate volume (62.5/93.9 ml, p<0.001), fPSA/tPSA ratio (0.13/0.20, p=0.048), and PSAD (0.25/0.14 ng/ml^2, p=0.003); while no significant differences were found in tPSA (13.9/11.5 ng/ml, p=0.419) and fPSA (1.63/1.68 ng/ml, p=0.922) values. A statistically significant difference was found between PI-RADS results of malignant/benign cases (p<0.001). Of the cases classified as PI-RADS>3 according to PI-RADS, 44 (26.2%) cases were histopathologically benign, while 21 (12.5%) cases classified as PI-RADS≤3 according to PI-RADS were histopathologically malignant. In the remaining 103 (61.3%) cases, PI-RADS and histopathology results were concordant.

Conclusion: Our study demonstrated that while tPSA and fPSA alone were insufficient for detecting prostate malignancy, fPSA/tPSA ratio and PSAD showed significant association with histopathologically confirmed malignancy. An inverse relationship was observed between prostate volume and malignancy risk. Substantial discordance (38.7%) was detected between PI-RADS categories and histopathological results, which may be attributed to the limitations of TRUS-guided 12-core prostate biopsy. Evidence suggests that MRI/TRUS fusion biopsy could improve concordance between imaging findings and histopathological results. In clinical practice, the combined evaluation of PSA parameters, prostate volume measurements, and mpMRI data offers more accurate prediction of prostate cancer compared to individual parameters alone.

Keywords: Multiparametric magnetic resonance imaging, prostate carcinoma, Prostate Imaging Reporting and Data System, prostate-specific antigen, prostate volume, transrectal ultrasonography

INTRODUCTION

Prostate carcinoma (PCa) is one of the most prevalent malignant neoplasms in the male population, and its global incidence is progressively increasing.[1] Global epidemiological data indicate that PCa is diagnosed in approximately one million men annually, resulting in approximately 300,000 mortality cases; in mortality rankings, PCa is documented as the second major etiological factor for cancer-related deaths in the male population, following lung carcinoma.[2]

PCa presents a broad and heterogeneous disease spectrum ranging from low-grade and clinically insignificant tumors to metastatic diseases carrying high morbidity and mortality risks. This diversity and marked differences in prognosis have necessitated risk stratification approaches in the management of PCa.[3] Classification systems based on biochemical, clinical, and histopathological data, such as the National Comprehensive Cancer Network (NCCN) guidelines and D'Amico risk scale, are frequently preferred in urology and are effectively used in the management of this patient group.

In the diagnostic approach to PCa, when elevation in serum prostate-specific antigen (PSA) levels or pathological findings in digital rectal examination (DRE) are detected, a standardized systematic 12-core biopsy protocol is performed

Corresponding Author: Mustafa Koyun, dr.mustafakoyun@gmail.com

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under transrectal ultrasonography (TRUS) guidance.[1] Although PSA is used as a PCa screening test due to its high sensitivity, it has low specificity as it can also increase in benign conditions such as prostatitis, prostate biopsy, seminal vesicle manipulation, ejaculation, and prostate massage.[4,5] Furthermore, serum PSA levels within the normal reference range do not definitively exclude the presence of PCa.[5] Although PSA-based PCa screening has contributed to a reduction in disease-specific mortality, it has resulted in an approximately 70-80% increase in the frequency of prostate biopsies.[6] Furthermore, PSA-based screening results in the detection of clinically insignificant PCa cases, potentially leading to unnecessary therapeutic interventions[7,8] PSA-derived parameters such as free PSA/total PSA (fPSA/tPSA) ratio, PSA velocity (change in PSA/time elapsed), and PSA density (PSAD, tPSA/prostate volume) have been developed to increase the specificity of PSA, aiming to both improve PCa detection rates and prevent unnecessary biopsies.[9] Among these additional parameters, PSAD is reported to potentially enhance the diagnostic efficiency of serum PSA alone by improving specificity while maintaining sensitivity.[7] Although PSAD has been routinely implemented in clinical practice, discussions continue on various aspects, such as which PSAD threshold value should be preferred.[9] The limitations of PSA parameters in PCa diagnosis necessitate the utilization of imaging modalities.

Magnetic resonance imaging (MRI) is considered the most successful imaging modality for detection, localization, and evaluation of local invasion of PCa.[7] Multiparametric MRI (mpMRI), which combines T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and T1-weighted dynamic contrast enhancement (DCE) imaging, has recently become a standard imaging modality in PCa diagnosis.[10] While mpMRI increases the detection of clinically significant cancer, it reduces the diagnosis rate of clinically insignificant cancers.[11] The data from the PROMIS study revealed that invasive biopsy procedures could be avoided in 27% of men with elevated serum PSA levels who had not yet undergone biopsy, due to the absence of suspicious lesions on mpMRI.[12] In 2012, the European Society of Urogenital Radiology established the Prostate Imaging-Reporting and Data System (PI-RADS) to standardize prostate mpMRI evaluation. This system facilitated the implementation of standardized terminology between clinicians and radiologists, established structured reporting criteria, and enabled systematic risk stratification for clinically significant cancer. Based on contemporary literature data and clinical experience, the PI-RADS v2.1 consensus guideline, representing an optimized version of the PI-RADS system, was published and implemented in 2019.[13] Although the role of mpMRI in prostate cancer diagnosis and treatment is increasingly expanding, the generalizability and reliability of results from studies conducted at different centers should be meticulously evaluated before widespread adoption of this imaging modality in routine clinical practice.

This study aimed to evaluate the relationship between histopathological results of prostate biopsies and various parameters including PI-RADS categories, prostate volume, and PSA measurements.

METHODS

Ethics

This retrospective study was conducted in accordance with ethical guidelines and received approval from the Kastamonu University Clinical Researches Ethics Committee (Date: 08.03.2023, Decision No: 2023-KAEK-28). As the study was retrospective, obtaining written informed consent from the patients was not required. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection

Our study was conducted retrospectively on patients who underwent prostate mpMRI at our center between July 2021 and February 2023. The inclusion criteria for patients were defined as: having undergone prostate mpMRI prior to biopsy, completion of TRUS-guided 12-core prostate biopsy, availability of parameters such as tPSA, fPSA, fPSA/tPSA ratio, and PSAD in the hospital information management system, and MRI images being artifact-free to allow unrestricted evaluation. In this context, 367 patients were examined, and 199 patients were excluded due to reasons such as missing histopathology results, incomplete PSA parameters, and artifacts in mpMRI images. The study was conducted on the remaining 168 patients.

Demographic Data and PSA Parameters

Patients' age and PSA parameters (tPSA, fPSA, fPSA/tPSA ratio, and PSAD) were identified and recorded through the hospital information management system. Care was taken to ensure that the dates of obtaining PSA parameters preceded the biopsy dates. This was to prevent potential PSA elevations resulting from biopsy procedures from influencing the results.

Imaging Protocol and PIRADS Assessment

All prostate mpMRI examinations were conducted using a 1.5 tesla MRI scanner (Signa Explorer-GE Medical Systems, Milwaukee, Wisconsin, USA). The mpMRI protocol incorporated T2WI, DWI, and T1W DCE sequences. Image interpretation was performed independently by two radiologists with 8 and 10 years of experience utilizing PI-RADS v2.1 criteria, with final categories determined by consensus.[13] For analytical purposes, PI-RADS categories were dichotomized, with categories 1, 2, and 3 classified as PI-RADS≤3 and categories 4 and 5 as PI-RADS>3 (**Figure 1, 2**). Prostate gland dimensions were measured on axial and sagittal T2WI sequences, and volumetric calculations were performed using the ellipsoid formula (width×height×length×0.523).

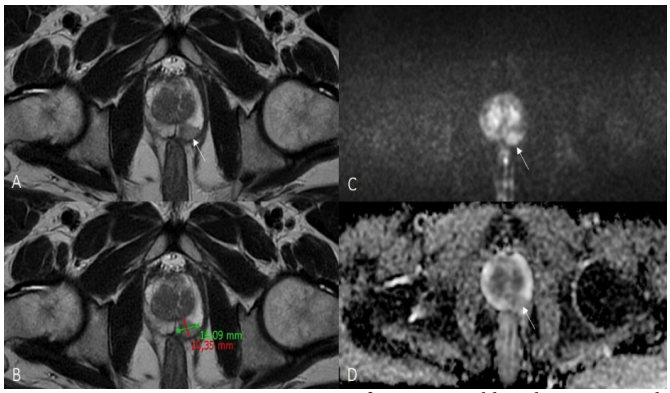

Figure 1. Magnetic resonance images of a 62-year-old male patient with histopathologically confirmed prostate adenocarcinoma. Axial T2-weighted images (A and B) demonstrated an oval-shaped, hypointense lesion measuring 14×10 mm in the left peripheral zone (arrow). The lesion exhibited hyperintense signal characteristics on diffusion-weighted imaging (C) and corresponding hypointensity on apparent diffusion coefficient image (D), consistent with restricted diffusion (arrow). Based on these imaging features, the lesion was classified as Prostate Imaging-Reporting and Data System category 4, indicating a high probability of clinically significant cancer

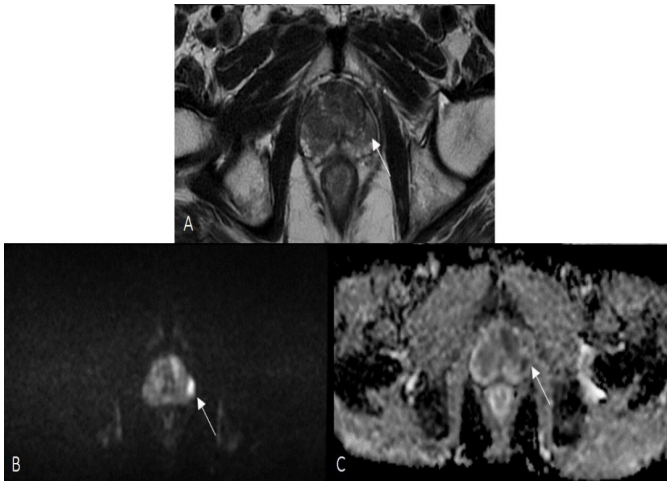

Figure 2. Magnetic resonance images of a 69-year-old male patient with histopathologically confirmed prostate adenocarcinoma. Axial T2-weighted image (A) demonstrated an oval-shaped, hypointense lesion in the left peripheral zone (arrow). The lesion exhibited hyperintense signal characteristics on diffusion-weighted imaging (B) and corresponding hypointensity on apparent diffusion coefficient (C), consistent with restricted diffusion (arrow). This lesion was categorized as Prostate Imaging-Reporting and Data System category 4

Prostate Biopsy Procedure

All patients underwent TRUS-guided systematic 12-core prostate biopsy procedure. This is due to the lack of MRI/TRUS fusion biopsy equipment in our center and the widespread use of TRUS-guided biopsy in routine clinical practice.

Histopathological Evaluation

Histopathological results were classified into two groups as benign and malignant. Patients with pathology results reported as malignant (such as prostate adenocarcinoma) and premalignant (such as prostatic intraepithelial neoplasia, atypical small acinar proliferation) were included in the malignant group; patients reported as benign (such as prostatic hyperplasia, acute/chronic prostatitis) were included in the benign group.

Statistical Analysis

Data analyses were performed using IBM SPSS 23 software (IBM Corporation, Armonk, NY, USA). The normality of data distribution was assessed using the Kolmogorov-Smirnov test. For continuous variables with normal distribution, parametric tests (independent samples t-test) were used, while for variables not normally distributed, non-parametric tests (Mann-Whitney U test) were applied. Data were presented as mean±standard deviation (SD). Categorical variables were expressed as frequencies and percentages. The association between PI-RADS and histopathological results was evaluated using Chi-square test. Statistical significance was defined as $p<0.05$ for all analyses.

RESULTS

Of the 168 patients included in the study, 105 (62.5%) were reported as benign, while 63 (37.5%) were reported as malignant. The mean age was 67±5.8 years in the benign group and 69.9±5.9 years in the malignant group, with a statistically significant difference between them (p=0.002) (**Table 1**). The mean prostate gland volume in the benign group was calculated as 93.9±42.8 ml, which was statistically higher than the mean volume of the malignant group (62.5±32.4 ml) ($p<0.001$). The fPSA/tPSA ratio was higher in the benign group compared to the malignant group, with the difference being statistically significant (p=0.048) (**Table 1, Figure 3**). PSAD was found to be higher in the malignant group compared to the benign group, with a statistically significant difference (p=0.003) (**Table 1, Figure 3**). No significant difference was found between the two groups in terms of tPSA and fPSA parameters ($p>0.05$) (**Table 1**).

Table 1. Comparison of obtained data between histopathologically benign and malignant groups

	Benign (n=105)	Malign (n=63)	p-value
Histopathology, n (%)	105 (62.5)	63 (37.5)	
Age, years, mean±SD	67±5.8	69.9±5.9	0.002
Prostate volume, ml, mean±SD	93.9±42.8	62.5±32.4	<0.001
fPSA/tPSA ratio, mean±SD	0.2±0.11	0.13±0.07	0.048
PSAD, ng/ml^2, mean±SD	0.14±0.16	0.25±0.44	0.003
tPSA, ng/ml, mean±SD	11.5±9.9	13.9±21.7	0.419
fPSA, ng/ml, mean±SD	1.68±1.35	1.63±1.70	0.922

SD: Standard deviation, fPSA: Free prostate-specific antigen, tPSA: Total prostate-specific antigen, PSAD: PSA density

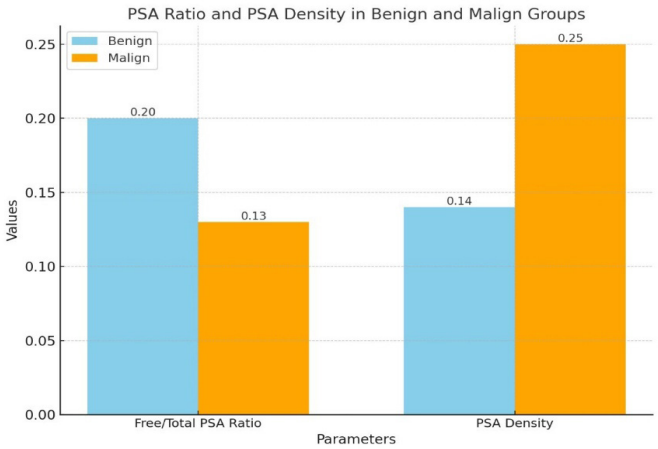

Figure 3. Comparison of fPSA/tPSA ratio and PSAD between histopathologically benign and malignant groups. The fPSA/tPSA ratio demonstrated higher values in the benign group, whereas PSAD values were significantly elevated in the malignant group

fPSA: Free prostate-specific antigen, tPSA: Total prostate-specific antigen, PSAD: PSA density

Statistical analysis revealed a highly significant difference in the comparison of PI-RADS categories with histopathological results ($p<0.001$). Of cases classified as PI-RADS>3 by PI-RADS, 44 (26.2%) were histopathologically benign (18 prostatitis, 26 benign prostatic tissue), while 21 cases (12.5%) classified as PI-RADS≤3 by PI-RADS were histopathologically malignant (8 high-grade prostatic intraepithelial neoplasia, 13 adenocarcinoma) (**Table 2**). Concordance between PI-RADS and histopathological findings was observed in the remaining 103 cases (61.3%).

Table 2. Comparison of PI-RADS and histopathologically benign and malignant groups

	PI-RADS≤3 n (%)	PI-RADS>3 n (%)	Total n (%)	p-value
Histopathology-benign	61 (36.3)	44 (26.2)	105 (62.5)	<0.001
Histopathology-malign	21 (12.5)	42 (25)	63 (37.5)	
Total	82 (48.8)	86 (51.2)	168 (100)	

PI-RADS: Prostate Imaging-Reporting and Data System

DISCUSSION

According to the 2024 cancer statistics, PCa remains the most prevalent malignancy among males.[14] The diagnostic algorithm for PCa encompasses DRE, PSA parameters, advanced imaging modalities such as mpMRI, and histopathological evaluation through biopsy. In the present study, we evaluated the correlation between prostate biopsy results and their relationship with PI-RADS categories, prostate volume, and PSA parameters.

In our study, PI-RADS categories and histopathology results were concordant in 103 (61.3%) cases. However, of the 86 cases evaluated as PI-RADS>3 according to PI-RADS, 44 (26.2%) were histopathologically benign, while of the 82 cases evaluated as PI-RADS≤3 according to PI-RADS, 21 (12.5%) were reported as histopathologically malignant. Recent meta-analysis studies have revealed that the probability of detecting prostate cancer in lesions categorized as low-risk, such as PI-RADS 1 and 2 categories, is approximately 4%, which demonstrates that mpMRI provides a very high negative predictive value in these risk groups.[15-17] However, even in lesions classified as high-risk in the PI-RADS 5 category, the positive predictive value of mpMRI varies between 69% and 75%.[18] Another meta-analysis study examining the diagnostic value of prostate mpMRI technique revealed that this imaging method has a sensitivity of 77% and specificity of 88% in detecting PCa.[19] Despite mpMRI's reliability in detecting clinically significant prostate cancer (csPCa), research indicates that up to 60% of patients with a PI-RADS score ≥3 still yield negative results on subsequent biopsies.[20] Tonkaz et al.[5] reported that mpMRI did not achieve a positive predictive value high enough to replace systematic biopsy. The discordance between PI-RADS categories and histopathological results demonstrates the need to develop patient-specific management strategies. Accordingly, in cases where lesions with PI-RADS>3 category result in benign histopathology, clinicians should evaluate whether sampling errors occurred during systematic biopsy Follow-up strategies for these patients may include PSA monitoring, repeat mpMRI after 6-12 months, or consideration of MRI/TRUS fusion biopsy when available.[3] In cases categorized as PI-RADS≤3, especially PI-RADS 3 "equivocal" cases, clinicians should maintain a higher index of suspicion when other risk factors are present (elevated PSAD, lower fPSA/tPSA ratio, positive DRE, or family history).

Another finding was that histopathologically benign cases had larger prostate gland volumes compared to malignant cases (93.9 ml/62.5 ml, p<0.001). Some studies in the literature have reported that PCa detection rates decrease as prostate gland volume increases.[21-23] The probable reason for this is shown to be the lower probability of sampling malignant foci with biopsy in larger prostates. However, there are also studies indicating that PCa detection rates increase with increasing prostate gland volume.[24] These varying results suggest that the relationship between prostate volume and PCa is complex, and other factors such as PSA levels should be considered when evaluating this relationship. The results obtained in our study support an inverse relationship between prostate volume and PCa.

PSA is a frequently used parameter in PCa screening, with 4.0 ng/ml used as the cut-off value. In our study, no statistically significant difference was found between malignant and benign groups in terms of tPSA and fPSA values (tPSA: 13.9/11.5 ng/ml, p=0.419; fPSA: 1.63/1.68 ng/ml, p=0.922). These results demonstrate that, consistent with the literature, the PSA test is not specific to prostate cancer and will not provide a definitive result in diagnosis.[5,25]

In our study, the fPSA/tPSA ratio was found to be higher in histopathologically benign cases compared to malignant ones (0.20/0.13, p=0.048). A low fPSA/tPSA ratio is known to be a significant marker for malignancy. This finding is consistent with literature data emphasizing the importance of fPSA/tPSA ratio in PCa diagnosis.[26,27]

Although there are differences in the literature regarding the cut-off value of PSAD in predicting clinically significant prostate cancer (csPCa), the value of 0.15 ng/ml^2 is widely accepted.[20,28,29] When this value is used, csPCa can be predicted with 74% sensitivity and 61% specificity.[28] In our study, consistent with literature data, PSAD values were higher in malignant cases compared to benign ones (0.25/0.14 ng/ml^2, p=0.003).[9,30] Elevated PSAD values indicate increased PSA production per unit volume of prostatic tissue, which is interpreted as suggestive of malignancy. Although both parameters play crucial roles in PCa prediction, PSAD is considered a more reliable marker than PSA alone, particularly in patients with PSA values ranging from 4-10 ng/ml, owing to its incorporation of volumetric parameters.[31] The diagnostic value of PSAD becomes even more significant when evaluated in conjunction with mpMRI findings. Studies conducted by Hansen et al.[32] and Rico et al.[33] examined the diagnostic value of mpMRI in PCa detection. These studies utilized different threshold values for PSAD-Hansen's team used below 0.20, while Rico's team based their analysis on 0.15 and below. Both studies demonstrated that using these PSAD threshold values in patients with negative or indeterminate MRI results positively influenced the diagnostic capability of mpMRI. In particular, improvements were shown in the test's sensitivity and negative predictive value. However, consensus has not yet been reached regarding the optimal PSAD threshold value to be used for achieving a higher predictive value in predicting malignancy.

Limitations

Our study has several limitations. Primarily, its retrospective design and reflection of single-center experience represent significant limitations. Additionally, the performance of prostate biopsies under TRUS guidance with 12-core systematic sampling rather than MRI/TRUS fusion biopsy may have led to discrepancies in histopathological verification, particularly for lesions detected on mpMRI. The relatively small number of patients included in the study (n=168) and the exclusion of 199 patients from the initial 367 due to insufficient data limit the generalizability of results. Furthermore, potential interobserver variations among radiologists in prostate mpMRI evaluation and PI-RADS category assignment constitute another limitation of our study.

CONCLUSION

As a result, our study findings demonstrated that while mpMRI has an important role in PCa diagnosis, it is not sufficient alone. An inverse relationship was detected between prostate volume and PCa, and fPSA/tPSA ratio and PSAD were confirmed to be valuable parameters in PCa diagnosis. The 38.7% discordance rate observed in our study between PI-

RADS categories and histopathological results highlights the limitations of traditional biopsy methods. MRI/TRUS fusion biopsy technique has the potential to reduce this discordance by enabling more accurate sampling of suspicious lesions and detecting clinically significant cancers at a higher rate.[34] A more comprehensive approach integrating PSA parameters, prostate volume assessments, and mpMRI findings provides superior diagnostic accuracy for prostate cancer detection in routine clinical settings than relying on any single metric alone.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kastamonu University Clinical Researches Ethics Committee (Date: 08.03.2023, Decision No: 2023-KAEK-28).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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KASTAMONU MEDICAL JOURNAL

Original Article

DOI: 10.51271/KMJ-0208

Kastamonu Med J. 2025;5(3):188-193

Computed tomography assisted transthoracic needle aspiration biopsy: 5 years experience*

Gül Erdal Dönmez, Selahattin Öztaş, Dilek Ernam

Department of Pulmonology, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkiye

Cite this article as: Erdal Dönmez G, Öztaş S, Ernam D. Computed tomography assisted transthoracic needle aspiration biopsy: 5 years experience. *Kastamonu Med J.* 2025;5(3):188-193.

Received: 12.03.2025 ◆ **Accepted**: 07.05.2025 ◆ **Published**: 03.09.2025

ABSTRACT

Aims: Transthoracic needle aspiration biopsy (TTNAB) is used to diagnose thoracic lesions and has a wide range of indications and few contraindications. The aims of this study were to assess the diagnostic value and complication rate of computed tomography-guided TTNAB for malignant diseases, to identify factors that influence diagnostic value and complication rate, and to compare our practices to those described in the literature.

Methods: A retrospective, observational, and cross-sectional study was designed to investigate the complication incidence and diagnostic value of the TTNAB. In Our study, 208 patients who underwent computed tomography-guided transthoracic needle aspiration biopsy at our hospital by pulmonologists between July 2007 and February 2013 were analyzed. In addition to descriptive statistical methods the Pearson Chi-square test was used to compare quantitative data when evaluating the study's data. The significance level of the results was accepted as $p<0.05$ with a 95% confidence interval.

Results: The ages of the patients ranged from 33 to 88 years and the 179 of them were male. The procedure's outcomes and rates of complications were documented. To evaluate the diagnostic value, we analyzed the clinical and radiologic follow-up results of 136 patients whose data were available. The rate of malignant diagnoses was 72.1%, while the rate of benign diagnoses was 4.4%. For malignant lung tumors, the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of the procedure were calculated to be 80%, 93%, 99%, 37%, and 82%, respectively. The only observed complication was pneumothorax, which occurred in 8 of 208 patients (3.8%). Diagnostic value and complication rate were unaffected by lesion size and needle thickness.

Conclusion: According to the findings of this study, computed tomography-guided TTNAB procedures in the diagnosis of malignant thoracic lesions have good diagnostic accuracy and low complication rates, which is consistent with litreture.

Keywords: Tomography, needle, biopsy, sensitivity, lung neoplasms

*Presented as an oral presentation at the IV. International Science and Innovation Congress-INSI 2023.

INTRODUCTION

Transthoracic needle aspiration biopsy (TTNAB) is a well-described and reliable procedure for diagnosing thoracic lesions.[1,2] TTNAB is commonly used to diagnose lung nodules and masses, mediastinal lesions and hilar lesions, chest wall invasion, infiltration, and consolidations.

TTNAB has 64-100% sensitivity for malignant disorders.[1,3-6] 12-68% specificity for benign diseases.[7-9] The most common procedure-related complication is pneumothorax, which occurs 8-64%.[10-13] Hemoptysis, hemorrhage, systemic air embolism, inlet line tumor cell growth, empyema, lung torsion, and pericardial tamponade are rare complications.[14,15]

It is essential to diagnose malignant disease with a minimally invasive method, such as TTNAB, in patients who cannot be evaluated further due to general condition disturbance, advanced age, or additional disease. In addition, the use of TTNAB for the diagnosis of benign tumors can prevent unnecessary surgical procedures. There is an extensive amount of literature that investigates the various aspects that impact the diagnostic efficacy of the TTNAB procedure. The objective of this study is to evaluate the complication incidence and diagnostic value of the TTNAB procedure performed by pulmonologists for the diagnosis of malignant diseases and also to examine the factors that may affect these parameters.

METHODS

Study Design

A retrospective, observational, and cross-sectional study was designed to investigate the complication incidence and diagnostic value of the TTNAB. CT-guided TTNAB patients at our hospital from July 2007 to February 2013 were retrospectively analyzed. According to the institutional protocol at the time, all biopsies had been performed under the supervision of two pulmonologists and informed consent had been obtained from all patients prior to the procedure. This

Corresponding Author: Gül Erdal Dönmez, gulerdal84yahoo.com

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study was approved by the Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital Scientific Researches Ethics Committee (Date: 27.02.2025, Decision No: 2024-44). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Evaluation of Diagnostic Value

To determine diagnostic value, the outcomes of patient samples were classified as malignant, benign, or non-diagnostic. Malignant aspiration samples contained malignant or atypical cells that were highly suggestive of cancer. Pathological symptoms of benign diseases like tuberculosis and pneumonia were seen as benign consequences. Non-diagnostic biopsies were those in which enough tissue was extracted but only inflammatory cells were found in the cytology and benign disease could not be determined.

The results of the biopsy were compared to clinical follow-up, therapy response, and other diagnostic procedures. Patients with less than a year of follow-up or who were lost to follow-up were excluded from the analysis. Only 136 patients' follow-up data were available. 136 patient records were used to determine the number of patients diagnosed with true positive, false positive, true negative, and false negative. The flowchart for the study is shown in **Figure**.

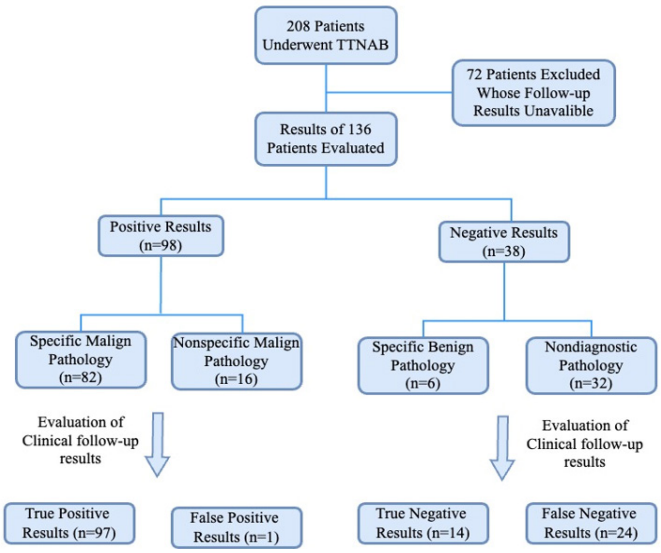

Figure. Flowchart of the study

To determine how lesion size affects diagnostic value, patients were divided into two groups. Lesions under 3 cm were in group one, whereas those 3 cm and over were in group two. The groups' sensitivity and diagnostic accuracy were assessed. Three groups (18-gauge, 20 gauge, and 22 gauge) were created based on needle thickness and tested for sensitivity and diagnostic accuracy.

Evaluation of Complications

We documented pneumothorax and other complications in patients on whom we performed biopsies. In the monitoring room, patients were observed after the procedure. One hour later, all patients had a control chest radiograph. Patients at high risk of pneumothorax had a second chest radiograph four hours later. To investigate the effect of lesion size on pneumothorax development, two groups were created based on lesion size. The large tumor group contained lesions measuring at least 3 centimeters in diameter, whereas the small tumor group contained lesions measuring less than 3 cm. The frequency of pneumothorax was determined and compared in groups with small and large tumors. Similarly, three groups were formed depending on the size of the biopsy needle: 18-, 20-, and 22-gauge, and pneumothorax rates were compared between these groups.

Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows 17.0 was utilized for statistical analysis. Continuous variables were written based on their distribution. The mean and standard deviation were utilized to summarize data with a normal distribution. Those with non-normal distributions were represented by median and interquartile ratios (25%-75%). Using the Shapiro Wilk Test, the normality of distributions was analyzed. The dichotomous values were calculated as a number and a percentage value (%). In addition to descriptive statistical methods the Pearson Chi-square test was used to compare quantitative data when evaluating the study's data. The significance level of the results was accepted as $p<0.05$ with a 95% confidence interval.

RESULTS

CT-guided TTNAB was performed on 208 patients (86% male) from July 2007 to February 2013. The sample population has a median age of 62, ranging from 88 to 33. Seventy-two (34.6%) of 208 TTNAB patients were excluded due to lack of follow-up data. **Table 1** provides a detailed review of patient demographics, needle size distribution, lesion size, pathological findings, and complications in the TTNAB.

Table 1. TTIAB patient demographics, lesion size and needle size distribution, and complications

Age, median (25%-75%)	62 (53-69)
Male, n (%)	117 (86)
Lesion size, n (%)	
<3 cm	13 (10)
≥3 cm	123 (90)
Needle size, n (%)	
18-gauge	20 (15)
20-gauge	74 (54)
22-gauge	42 (31)
TTIAB pathology, n (%)	
Malign	98 (72)
Benign	6 (4)
Nondiagnostic	32 (24)
Malign pathological results of TTIAB, n (%)	
Non-small cell lung carcinoma	47 (49)
Squamous cell carcinoma	17 (17)
Adenocarcinoma	14 (14)
Small cell carcinoma	4 (4)
Nonspecific malignant cells	16 (16)
Benign pathological results of TTIAB, n (%)	
Tuberculosis granuloma	3 (50%)
Pneumonia	3 (50%)
Complications, n (%)	
Pneumothorax	8 (3.8)

TTIAB: Transthoracic needle aspiration biopsy

Although adequate material was obtained by aspiration, 32 (23.5%) of the biopsies were categorized as non-diagnostic. Because the pathology comprised of only inflammatory cells and these findings were insufficient for a definitive diagnosis of benign disease. After follow-up, 24 (75%) of these 32 patients had definite malignant disease identified by surgery, bronchoscopy, lymph node biopsy, or endobronchial ultrasound, and 8 (25%) had benign disease. **Table 2** shows 32 patients' final diagnosis. **Table 3** shows TTİAB's sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy.

Table 2. Final diagnoses of non-diagnostic TTNAB

Final diagnoses	Diagnostic method	Total, n (%)
Malign		24
Adenocarcinoma	Surgery, lymph node biopsy	8 (33)
Squamous cell carcinoma	Surgery, bronchoscopy, endobronchial ultrasonography	7 (30)
Non-small cell lung cancer	Bronchoscopy, endobronchial ultrasonography, lymph node biopsy	3 (13)
Atypical carcinoid	Surgery	1 (4)
Large cell carcinoma	Surgery	1 (4)
Hodgkin lymphoma	Surgery	1 (4)
Mesothelioma	Surgery	1 (4)
Thymic carcinoma	Surgery	1 (4)
Solitary fibrous tumor	Surgery	1 (4)
Benign		8
Pneumonia	Surgery	3 (38)
Tuberculosis granuloma	Surgery	2 (25)
Granulomatous inflammation	Surgery, lymph node biopsy	2 (25)
Organized pneumonia	Surgery	1 (12)

TTIAB: Transthoracic needle aspiration biopsy

Table 3. Diagnostic value of transthoracic needle aspiration biopsy

	%	95% confidence interval upper-lower limit
Sensitivity	80	0.73-0.88
Specificity	93	0.80-1
Positive diagnostic value	99	0.97-1.00
Negative diagnostic value	37	0.21-0.53
Overall accuracy	82	0.75-0.89

To determine the factors influencing the diagnostic value, we calculated sensitivity and accuracy based on the size of the lesion and the thickness of the needle used in TTİAB procedure. **Table 4** presents a summary of the results.

Table 4. Diagnostic value of the TTIAB procedure according to lesion and needle size

Lesion size	Sensitivity (%)	Accuracy (%)
*<3cm	75	84.6
**≥3cm	80.5	81.3
Needle size		
18-gauge	77.8	80
20-gauge	87.5	87.8
22-gauge	69.2	71.4

*: Small tumor group, **: Large tumor group, TTIAB: Transthoracic needle aspiration biopsy

Between July 2007 and February 2013, 8 of the 208 patients who underwent TTNAB showed pneumothorax. One patient required a chest tube. The calculated rate of complications was 3.8%. The effect of lesion size and needle thickness on the rate of complications was analyzed in 136 patients for whom follow-up information was available. Lesions were divided into two groups: those measuring less than 3 centimeters and those measuring 3 cm or more. There was no statistically significant difference between the groups' incidence of complications. To examine the effect of needle thickness on pneumothorax rate, biopsy needles were divided into three groups according to gauge size (18-20-22). There was no difference in pneumothorax rate between the groups. Results are summarized in **Table 5**.

Table 5. Comparison of complication rates according to lesion and needle size

		Complication		p
		Yes, n (%)	No, n (%)	
Lesion size	<3cm	2 (15%)	11 (85%)	0.060
	≥3cm	6 (5%)	117 (95%)	
Needle size	18-gauge	0	32 (100%)	0.464
	20-gauge	5 (5%)	101 (95%)	
	22-gauge	3 (4%)	67 (96%)	

DISCUSSION

TTNAB is unusually complicated and safe procedure. Therefore, it is often used to diagnose thoracic lesions. It is less expensive and easier than thoracotomy and open lung biopsy.[16,17] CT-guided transthoracic needle aspiration biopsies for malignant lung tumors had 80% sensitivity and 82% accuracy in our investigation. The scientific literature reports that TTNAB's sensitivity for malignant illnesses ranges from 64 to 100%, but is usually 80-97%.[1,3-6] Diagnostic accuracy exceeds 97%.[18] Zhuang et al.[6] found 96.3% sensitivity and 96.1% diagnostic accuracy in 102 CT-guided TTNAB patients. Wallace et al.[11] demonstrated 82% sensitivity and 88% diagnostic accuracy using CT-guided TTNAB on 61 sub-1 cm lesions. Transthoracic sampling cannot always diagnose benign lesions. Solak et al.[4] found 34% of 102 USG-guided TTNAB cases benign. This rate is 31%, per McSweeney et al.[19] After the study's follow-up, 13 patients were diagnosed with benign illness, however TTNAB only identified six of them.

The results of our TTNAB are consistent with the findings reported in the literature for both malignant and benign diagnoses. The absence of a cytopathologist during TTNAB may have decreased sensitivity and diagnostic accuracy by raising our inappropriate sampling rate. Other studies show that pathologists improve diagnosis accuracy.[3,20-22] The non-diagnostic rate for TTNAB ranged from 5.5% to 29% in various studies.[23-26] Our study had 23.5%. Malignant diagnosis in the follow-up of non-diagnostic TTNAB results was 100% in one research, but it normally ranges from 33 to 73%.[19,23-26] Our 32 patients had non-diagnostic TTNAB results. 24 had malignant disease throughout follow-up, while 8 had benign disease. False-negative cases were calculated at 17.7%. According to a study, false-negative cases should be around 10%.[21] False negatives often come from insufficient sampling. Inflammation, fibrosis, and tumor necrosis around a malignant nodule may prevent adequate sampling.[4]

One of the elements influencing TTNAB's diagnostic value is the size of the lesion. There is inconsistency in the terminology used to define large tumor groups and small tumor groups in studies investigating this topic. To provide a consistent approach, the investigation border was set at 3 cm, considering the definition of a solitary pulmonary nodule in our study. While sensitivity is higher in the group with large tumors, the overall accuracy rate is greater in the group with small tumors. This could be due to the lower false-negative rate observed in the group with the largest tumors. Various studies in the literature present different results regarding the relationship between lesion size and the diagnostic value of TTNAB.[6,11,25,27] Furthermore, these studies differ in terms of the imaging methodologies and needle diameters used. This could also alter the diagnostic value.

Another factor influencing the diagnostic value of TTNAB is the size of the biopsy needle. A study compared 18 gauge (n=324) and 19 gauge (n=527) coaxial systems to investigate the effect of needle size on the diagnostic value of TTNAB.[12] In the 18-gauge group, both sensitivity and diagnostic accuracy were 96%, whereas in the 19-gauge group, sensitivity was 89% and diagnostic accuracy was 92%. The authors state that these ratios are comparable. In our analysis, we compared 18-, 20-, and 22-gauge single aspiration needles. The 20-gauge group's calculated sensitivity and diagnostic accuracy were greater than those of the other groups. Due to the heterogeneity of the groups in terms of the type and extent of lesions treated by the procedure, it is difficult to interpret this result.

Pneumothorax remains the most prevalent complication associated with TTNAB.[15,28-31] According to various studies, the incidence of pneumothorax ranges from 8% to 64%, and the proportion of pneumothorax cases requiring a chest tube ranges from 3.3% to 15%.[32,33] In our investigation, eight out of 208 patients who underwent TTNAB developed pneumothorax. 3.8% was the calculated pneumothorax rate. Only one patient (0.4%) required a tube thoracostomy to manage pneumothorax.

Similar to our findings, Salepci et al.[3] observed 3.5% pneumothorax. This study used computed tomography (CT) immediately after the surgery to evaluate all individuals for pneumothorax, but chest radiography was performed only 5 to 6 hours later in high-risk cases. In our study, all patients who underwent CT evaluation following the procedure also received a chest radiograph one hour later. Patients with a high probability of pneumothorax were the only ones who received repeat chest radiographs four hours later. Consequently, it is possible that some patients were not evaluated for late-onset pneumothorax. Our pneumothorax rate is lower than the literature's, consistent with Salepci et al. study. Age, gender, lesion distance from the pleural surface, emphysema, smoking history, sampling method (aspiration needle, cutting needle), number of passages through the pleura, operator experience, and patient compliance all affect pneumothorax risk. Many research have addressed these variables in the literature.[12,30,34]

Lesion size and needle thickness in pneumothorax were one of our objectives. We divided needles into three groups to determine how needle thickness affected pneumothorax rate. Pneumothorax rates were not significantly different across 18-, 20-, and 22-gauge groups.

In 846 patients, Geraghty et al.[12] found that the 19-gauge needle group had a 50% lower pneumothorax rate than the 18-gauge group. Age, gender, lesion size, and cutting system did not affect the this statistically significant outcome.In 102 patients, Zuanq et al.[6] reported no statistically significant difference in pneumothorax rates between 18-gauge and 20-gauge aspiration needles. Shaukat et al.[35] observed no difference in pneumothorax incidence with 18-, 20-, and 22-gauge aspiration needles in a trial like ours.

Studies have also examined lesion size as a factor influencing the pneumothorax rate. Laurent et al.[31] found 15% pneumothorax in 67 patients with 2 cm lesions and 16% in 135 individuals with >2 cm lesions. There was no statistically significant difference in pneumothorax incidence between groups. Yeow et al.[34] observed a statistically significant association between lesion size and pneumothorax rate, showing that decreased lesion size increased pneumothorax rate. The same study found that experience can lower pneumothorax risk up to a 2 cm critical lesion while performing a routine biopsy. In this investigation, the pneumothorax rate in the 2 cm lesion group was independent of operation experience, however it reduced as procedure experience increases. The effect of lesion size on pneumothorax rate is uncertain, however our study demonstrated no statistically significant difference between groups with lesion diameters less than 3 cm and higher than 3 cm. Since the same team performed all study activities, we believe our findings are independent of practitioner experience.

Paranchymal hemorrhage is the second most common TTNAB complication.[36] No TTNAB procedures in our sample had hemorrhage or rare complications like systemic air embolism, tumor cell spread along the entry line, empyema, lung torsion, or pericardial tamponade.

Recent studies continue to affirm the diagnostic efficacy and safety profile of CT-guided TTNAB. For instance, a 2023 study reported a diagnostic accuracy exceeding 90% for TTNAB in peripheral lung lesions, highlighting its reliability in clinical practice. Moreover, the incidence of pneumothorax, the most common complication associated with TTNAB, has been reported to range between 9% and 54%, with an average around 20%. These findings underscore the importance of meticulous technique and patient selection to minimize complications. Our study's results align with these recent findings, reinforcing the role of CT-guided TTNAB as a valuable diagnostic tool in thoracic oncology.[37,38]

Limitations

However, it is essential to recognize the limitations of our investigation. Due to the retrospective character of the study, there may be missing data. Second, the extent of the group of patients with small tumors was minuscule. Although we examined the effect of lesion size and needle thickness on the complication rate and diagnostic value, we did not take into account other variables, including age, gender, distance of the lesion from the pleural surface, sampling procedure, number of pleural passages, and patient compliance. These variables may also play an important role, but they were excluded from our analysis. As detailed in the discussion section, two further significant limitations of our study are the absence of a cytopathologist during the TTIAB procedure and the failure to evaluate the patients in terms of late pneumothorax. TTNAB without a cytopathologist may increase improper sampling and lower sensitivity and diagnostic accuracy.

Failure to evaluate late pneumothorax may have biased the complication rate.

CONCLUSION

This study demonstrates that CT-guided TTNAB can diagnose lung tumors, especially malignant ones, quickly and accurately. Lesion and needle size did not affect TTNAB complications. Our research demonstrated that TTNAB is a safe procedure and that its diagnostic efficacy is consistent with the literature. Further research is needed to better understand the impact of lesion size, imaging techniques, and needle sizes on the diagnostic value of TTNAB.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital Scientific Researches Ethics Committee (Date: 27.02.2025, Decision No: 2024-44).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

Acknowledgments

This study was prepared based on the medical specialization thesis titled "Bilgisayarlı tomografi altında transtorasik igne aspirasyon biopsisinin tanısal değeri, komplikasyonları ve bunları etkileyen faktörler", which we completed in 2013 under the supervision of Associate Professor Dilek Ermam.

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KASTAMONU MEDICAL JOURNAL

Original Article

DOI: 10.51271/KMJ-0209

Kastamonu Med J. 2025;5(3):194-197

Incidental brain MRI findings in intensive care unit patients: a retrospective analysis

Hakan Gökalp Taş[1], Necip Gökhan Taş[2], Sonay Aydın[3]

[1]Department of Anesthesiology and Reanimation, Faculty of Medicine, Erzincan Binali Yıldırım University, Erzincan, Turkiye

[2]Department of Experimental Animals Application and Research Center, Faculty of Medicine, Erzincan Binali Yıldırım University, Erzincan, Turkiye

[3]Department of Radiology, Faculty of Medicine, Erzincan Binali Yıldırım University, Erzincan, Turkiye

Cite this article as: Taş HG, Taş NG, Aydın S. Incidental brain MRI findings in intensive care unit patients: a retrospective analysis. *Kastamonu Med J.* 2025;5(3):194-197.

Received: 23.03.2025 ◆ **Accepted**: 07.05.2025 ◆ **Published**: 03.09.2025

ABSTRACT

Aims: Magnetic resonance imaging (MRI) frequently shows unexpected results unrelated to the presumed pathology. The aim of this study is to look into the frequency and type of incidental brain MRI findings in ICU patients.

Methods: The Anesthesiology and Reanimation Intensive Care Unit at Erzincan Mengücek Gazi Training and Research Hospital was the setting for the retrospective observational study. A total of 5,145 ICU patients admitted between 2021 and 2023 were screened using the hospital information management system, eliminating those without a brain MRI. Incidental findings in brain MRI data were documented and divided into five categories: vascular (aneurysms, cavernomas, and other vascular structures), neoplastic (meningioma, pituitary mass, glioma, and other tumors), Chiari malformation, pineal cyst, and arachnoid cyst.

Results: 1317 (25.6%) participants who received brain MRI were included in the study. Incidental MRI findings were detected in 366 patients (27.8%). The most common incidental discoveries were vascular anomalies (9.79%, primarily aneurysms and cavernomas), neoplastic lesions (8.81%, primarily meningiomas and pituitary masses), arachnoid cysts (2.89%), nonspecific plaques (2.81%), pineal cysts (2.66%), and Chiari malformations (0.84%). A large majority of these patients had clinically important findings that demanded additional clinical follow-up or evaluation; nevertheless, none required emergency surgical intervention. Patients with incidental findings had a mean age of 70.92±18.42 years (range 18-98).

Conclusion: In conclusion, incidental MRI results are common in critically ill patients and have significant clinical consequences. Enhanced clinician awareness and consistent management practices are critical for improving patient care, reducing unnecessary interventions, and optimizing results. Future prospective studies are required to create tailored guidelines for this population.

Keywords: Magnetic resonance imaging, incidental findings, critical care, brain diseases

INTRODUCTION

Magnetic resonance imaging (MRI) is becoming more common in clinical practice as technology advances and is widely used due to its greater capacity to visualize anatomical structures and disease processes. This broad use has resulted in increasing discovery of incidental findings unrelated to the initially suspected disease or anomaly.[1,2] Incidental findings detected using MRI cover an extensive range of asymptomatic disorders, including neoplastic masses and vascular abnormalities such as arteriovenous malformations, aneurysms, and other less common vascular anomalies.[3,4] Previous research has found differing incidence rates of incidental observations in different populations, emphasizing their clinical significance. Specifically, incidental discoveries in MRI have been observed at rates between 2.7% and 18% in general populations, including healthy young adults, the elderly, and pediatric patients.[5-7] Despite the extensive literature on incidental MRI results, little is known about the occurrence, nature, and clinical importance of incidental brain MRI findings in critically ill patients admitted to intensive care units (ICUs). Addressing this gap is vital because critically ill patients frequently undergo MRI for a variety of therapeutic causes, which may result in the discovery of incidental diseases that affect clinical care. Clarifying the occurrence and clinical significance of these incidental discoveries might help enhance diagnostic strategies and clinical management protocols, ultimately improving patient outcomes in critical care settings.

The objectives of this study are to determine the frequency and nature of incidental MRI findings and to evaluate their clinical relevance in terms of management and prognosis in ICU patients. The study's findings are intended to give useful clinical insights, guide future clinical decision-making processes, and improve healthcare policies on the management of incidental MRI findings in critically ill populations.

Corresponding Author: Necip Gökhan Taş, necip.tas@erzincan.edu.tr

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METHODS

Study Desing

This retrospective observational study was carried out at Erzincan Mengücek Gazi Training and Research Hospital's Anesthesiology and Reanimation Intensive Care Unit, in accordance with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines. The study was approved by the Erzincan Binali Yıldırım University Non-interventional Scientific Researches Ethics Committee (Date: 01.08.2024, Decision No: 2024-10/10). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Since this was a retrospective study, routine general consent obtained from ICU patients upon hospital admission was used. All adult patients ages 18 to 100 who were admitted to the intensive care unit for any reason between January 2021 and December 2023 were included in the analysis. Patients who did not get a brain MRI scan for any reason were eliminated.

Data Collection

The study included all patients with an anesthesia intensive care unit admission code recorded in the hospital information management system within the given dates. The faculty of our hospital's Department of Radiology examined and reported on MRI reports. Two radiologists with over ten years of experience independently reviewed the reports, and disagreements were resolved through consensus. Incidental findings in MRI reports were recorded and classified into five categories, as described by Sunny et al.,[4] vascular (aneurysm, cavernoma, other vascular lesions), neoplastic (meningioma, pituitary mass, glioma, other neoplastic masses), Chiari malformation, pineal cyst, and arachnoid cyst.

Bias Reduction Measures

To reduce bias, all ICU patients who received MRI scans during the specified time frame were included. Furthermore, the study time was purposely extended to increase the number of patients and limit the possibility of bias.

Statistical Analysis

Statistical analyses were carried out using IBM SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). The normality of continuous data distribution was determined using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Continuous data with normal distribution were summarized using mean±standard deviation (SD), while continuous variables with non-normal distribution were reported as median with minimum and maximum range. Categorical variables were summarized using frequency and percentages. The frequencies and percentages of incidental MRI findings were calculated, and the results were shown using bar graphs generated in Python using the Matplotlib tool. Since this was a retrospective study with a fixed sample size, no a priori power analysis was performed.

RESULTS

This study involved a total of 5145 patients admitted to the Anesthesiology and Reanimation Intensive Care Unit between 2021 and 2023. 1317 patients had brain MRI scans. Among the patients who had MRI scans, 866 (65.8%) were men and 451 (34.2%) were women. The patients' mean age was 70.92±18.42 years (range 18-98 years).

Incidental findings were found in a variety of categories (**Table, Figure**). The most common incidental finding was classified as "other" vascular abnormalities (3.49%), followed by aneurysms (3.26%) and meningiomas (3.11%). Other common incidental findings included cavernomas (3.04%), arachnoid cysts (2.89%), nonspecific plaques (2.81%), pineal cysts (2.66%), pituitary masses (2.96%), gliomas (1.37%), and other neoplastic masses (1.37%). Chiari malformation was the least often observed incidental finding, appearing in only 0.84% of individuals. **Table** shows the detailed frequencies and percentages of incidental findings.

Table. Frequency and percentage of incidental MRI findings

Incidental finding category	Number of patients	Percentage (%)
Other vascular anomalies	46	3.49
Aneurysm	43	3.26
Meningioma	41	3.11
Cavernoma	40	3.04
Pituitary mass	39	3.96
Arachnoid cyst	38	2.89
Nonspecific plaque	37	2.81
Pineal cyst	35	2.66
Glioma	18	1.37
Other neoplastic masses	18	1.37
Chiari malformation	11	0.84

MRI: Magnetic resonance imaging

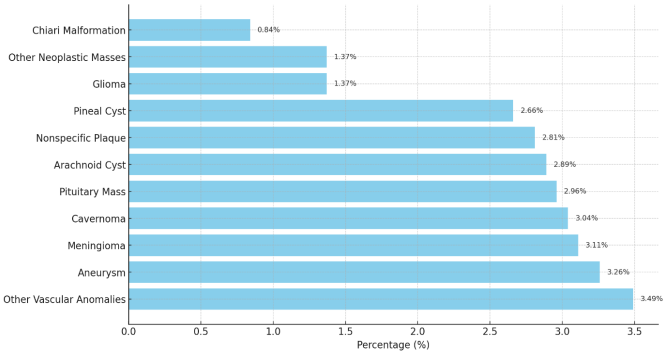

Figure. Bar graph showing the percentage distribution of incidental MRI findings

MRI: Magnetic resonance imaging

DISCUSSION

This study demonstrated a considerable prevalence of incidental findings on brain MRI in critically ill ICU patients, providing valuable insights into an underrepresented population in the literature. Our findings are consistent with earlier research, indicating a high frequency of incidental finds across multiple populations, but with some variation in prevalence rates.

The finding that vascular anomalies, notably aneurysms and cavernomas, are among the most prevalent incidental findings supports previous research. Vernooij et al.[3] reported cerebral aneurysms as major incidental findings in the general population, underlining their clinical relevance and the potential for severe outcomes if undiagnosed or mistreated. Similarly, Weber and Knopf[1] highlighted vascular abnormalities as notable incidental discoveries among healthy

young males, demonstrating that these results are not isolated to the old or symptomatic populations.

Meningiomas and pituitary tumors were also common in the group we studied. Previous investigations back up these findings, establishing meningiomas as prevalent benign brain tumors typically met incidentally in elderly persons.[2,5] Pineal and arachnoid cysts, which we discovered at rather high frequency, have repeatedly been reported as common incidental findings across diverse age groups.[7,8]

The relatively high prevalence of nonspecific white matter lesions or plaques observed in our study echoes findings from broad population-based studies, indicating an increasing trend in incidental detection of these lesions, possibly associated with vascular risk factors prevalent in ICU populations.[9,10]

In contrast to our findings, pediatric studies, such as Dangouloff-Ros et al.,[6] show that incidental findings in young people typically differ in prevalence and clinical significance compared to adult populations, with intracranial cysts and developmental anomalies like Chiari malformations being more common. These discrepancies highlight the importance of age-appropriate interpretation and management recommendations. Additional investigations reinforce the clinical importance of incidental MRI findings across diverse demographics, emphasizing their potential impact on healthcare management, costs, and other consequences.[11-13]

Our study showed a higher rate (27.8%) of incidental findings compared to previous studies (2.7%-18%). This may be since of the older average age, expanded predominance of comorbidities, and basic ailment status of ICU patients, which may incline them to such discoveries.

This study focuses on incidental MRI findings in critically ill ICU patients, a cohort that has not been substantially explored previously. ICU patients may have many concomitant diseases, complicating the management of incidental findings. Such findings may have an impact on treatment decisions, length of hospital stay, and prognosis. As a result, developing a defined management approach for incidental findings in critically ill patients is vital.

Limitations

The limitations of this investigation must be noted. Its retrospective, single-center approach may induce selection bias and reduce generalizability. The lack of prospective data gathering could have resulted in missing or incomplete information. Furthermore, even when experienced radiologists are involved, inconsistency in MRI interpretation may influence outcomes. As a result, our findings should be taken with caution when applied to other patient demographics or therapeutic contexts.

Nevertheless, our study offers some advantages. It comprises a high number of severely ill ICU patients, which improves the accuracy of prevalence estimations. Furthermore, all MRI evaluations were consistently done by highly experienced radiologists, resulting in good diagnostic accuracy and little inter-observer variability. Furthermore, the broad inclusion criteria, which included all adult ICU patients having MRI, increased the representativeness of our findings.

Our findings have substantial therapeutic implications for the management of ICU patients, emphasising the importance of structured follow-up and treatment plans for incidental findings. Future research should concentrate on prospective, multicenter studies to properly control for potential biases and validate these findings across multiple therapeutic settings. Additional research could look into the effects of certain incidental findings on long-term patient outcomes and healthcare resource consumption.

Due to the retrospective nature of this investigation and the limitations of the available data, no subgroup analyses were undertaken. Future prospective studies could look into specific subgroups based on demographic or clinical variables to provide more precise insights.

CONCLUSION

As a result, incidental MRI findings among intensive care unit patients are frequent and significant from a clinical standpoint. Patient outcomes may be enhanced by acknowledging and appropriately managing these results. Prospective investigations and the creation of uniform techniques are required.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Erzincan Binali Yıldırım University Non-interventional Scientific Researches Ethics Committee (Date: 01.08.2024, Decision No: 2024-10/10).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

Acknowledgments

The authors thanks all the physicians contributed to work.

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KASTAMONU MEDICAL JOURNAL

Original Article

DOI: 10.51271/KMJ-0210

Kastamonu Med J. 2025;5(3):198-202

From summer heat to winter cold: ICU admissions and survival patterns across seasons

Payam Rahimi[1], Nuri Burkay Soylu[2], Zafer Çukurova[1]

[1]Department of Anesthesiology and Reanimation, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Turkiye

[2]Department of Anaesthesiology and Reanimation, Çanakkale Mehmet Akif Ersoy State Hospital, Çanakkale, Turkiye

Cite this article as: Rahimi P, Soylu NB, Çukurova Z. From summer heat to winter cold: ICU admissions and survival patterns across seasons. *Kastamonu Med J.* 2025;5(3):198-202.

Received: 20.02.2025 ◆ **Accepted**: 27.05.2025 ◆ **Published**: 03.09.2025

ABSTRACT

Aims: Seasonal variations may influence intensive care unit (ICU) admissions, survival, and mortality rates due to climate-related illnesses, trauma, and infectious diseases. Understanding these patterns is crucial for optimizing healthcare resources and improving patient outcomes. This study investigates the impact of seasonal changes on ICU admissions, survival rates, and mortality patterns. Additionally, it evaluates how these seasonal effects interact with different age groups.

Methods: This retrospective observational study analyzed 18.046 ICU admissions at Bakırköy Dr. Sadi Konuk Training and Research Hospital from 2008 to 2024. Patients were categorized by season (Spring, Summer, Autumn, Winter) based on admission dates. Age groups were also assessed to determine variations in admission patterns and outcomes. Descriptive statistics, ANOVA, and chi-square tests were used for analysis.

Results: Seasonal fluctuations in ICU admissions were observed but were not statistically significant (p=0.42). However, specific age groups displayed notable seasonal trends. Younger patients (0-20 and 21-40) had increased ICU admissions in summer, while older patients (61-80 and 81+) were more frequently admitted in winter. Mortality rates were highest in winter, particularly among elderly patients (p=0.048). Survival rates were slightly higher in autumn, but no significant seasonal difference was found overall (p=0.074).

Conclusion: While total ICU admissions did not demonstrate a strong seasonal influence, age-specific trends were evident. Increased trauma-related ICU admissions in summer and higher elderly mortality rates in winter highlight the need for targeted healthcare strategies, such as preventive countermeasures against trauma in summer and enhanced respiratory care in winter. Future studies should consider broader geographical comparisons to refine these findings.

Keywords: Season, ICU admission, mortality

INTRODUCTION

Intensive care units (ICUs) play a critical role in the medical care of critically ill patients, operating 24/7. The variability in the intensity of these units throughout the year, including changes in morbidity and mortality rates, variations in patient admissions, or differences in length of stay, has long captured attention.[1] Understanding whether seasonal factors influence ICU admissions and clinical outcomes is crucial for analyzing the burden on the healthcare system and assessing whether patients are affected by these cycles. Identifying such variations, if they exist, is critical for planning healthcare resources accordingly.[2,3]

The impact of seasonal changes on ICUs can be assessed from various perspectives. First, environmental conditions may influence patient admission rates. For instance, respiratory infections, flu outbreaks, and cold-weather-related cardiovascular problems may lead to increased ICU admissions during winter. In summer, trauma-related admissions, heatwave-induced illnesses, and accidents stemming from water sports may affect ICU utilization. These seasonal effects not only impact admission rates but may also manifest in patient outcomes, such as increased mortality rates from respiratory infections in winter or varying rates of trauma-related deaths in summer.[4]

Another significant factor affecting ICU outcomes is the seasonal changes specific to age groups. Different age groups have varying healthcare needs and physiological responses to seasonal changes. For example, younger age groups are at higher risk of trauma during summer, while older patients are more vulnerable to respiratory infections and cold-weather-related complications in winter. These differences in ICU admissions and outcomes must be considered when planning healthcare services.[5]

This study aims to investigate the impact of seasonal changes on ICU admissions, mortality, and survival rates. Seasonal admission rates, mortality rates, and survival rates across the four seasons were analyzed, and the interaction of these

Corresponding Author: Nuri Burkay Soylu, drburkaysoylu@gmail.com

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variables with age groups was evaluated. The findings provide significant insights for more effective healthcare planning and efficient use of resources. Understanding the effects of seasonal changes on ICUs contributes to shaping future healthcare strategies, fostering a more resilient and proactive healthcare system.

METHODS

This research adopts a retrospective observational study design and examines a database of 18,046 patients admitted to pediatric and adult ICUs at Bakırköy Dr. Sadi Konuk Training and Research Hospital, beginning from patients admitted in 2008, after the ethics committee approval was received from Bakırköy Dr. Sadi Konuk Training and Research Hospital Non-interventional Scientific Researches Ethics Committee (Date: 05.02.2025, Decision No: 2025-03-02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study aims to explore the seasonal distributions of ICU-admitted patients, the variations in admission rates by age groups, and the potential effects of these variables on survival and mortality rates.

Data were retrieved from the hospital's information management system, Metavision QlinIcu (IMDSoft, TPG Finance, USA), covering all patients admitted to ICUs between 2008 and 2024. The study included patients who stayed in the ICU for at least 24 hours, with separate groups for adults (18 years and older) and children (0-17 years). However, during analysis, age categories were further refined (0-20, 21-40, 41-60, 61-80, and 81+) to account for differences between pediatric and adult groups.

Collected data included demographic information, admission date, ICU stay duration, discharge dates, survival or mortality status, age, gender, season-reflecting admission dates, and additional medical parameters (e.g., diagnosis codes, comorbidities). Each patient was categorized by season based on the admission date (Spring: March-May, Summer: June-August, Autumn: September-November, Winter: December-February).

During data cleaning, patients with incomplete or inconsistent records were excluded from the study. For example, cases where seasonal information was unclear or admission dates were missing were removed. Additionally, patients who stayed in the ICU for less than 24 hours or were admitted for routine postoperative monitoring were excluded. Based on these criteria, a total of 18,046 patients with sufficient and consistent data were included in the analysis.

The findings revealed the potential effects of seasonal distribution and age categories on ICU admissions, survival, and mortality rates. During interpretation, auxiliary variables such as admission pathways (outpatient clinic, emergency service), comorbidities, and diagnostic protocols were also considered. Consequently, this material and method approach enabled a statistical understanding of seasonal and age-based variations in 18,046 ICU patients admitted since 2008.

Statistical Analysis

For data analysis, descriptive statistics (mean, standard deviation, percentages) summarized the data. To evaluate significant differences between groups, one-way ANOVA tests were applied to survival and mortality rates, with a significance level set at $p<0.05$. The interaction between age groups and seasons was examined using the chi-square test, and post-hoc analyses (e.g., standardized residuals) were used to identify which age groups were over or underrepresented in specific seasons. All statistical analyses were performed using SPSS (v26.0, IBM, USA).

RESULTS

Seasonal Distribution of Total ICU Admissions

Throughout the years analyzed (2008-2024), total ICU admissions were categorized into four seasons: Winter, Spring, Summer, and Autumn. The numerical data and comparisons are summarized in **Table 1, and 2**. Note that comparisons were conducted using Winter as the reference season; a significance level of 0.05 was applied. The p-values in the table are illustrative examples reflecting multiple comparisons in the database.

Table 1. Seasonal distribution of total ICU admissions (n=18.046)

Season	ICU admission (n)
Spring	4619
Summer	4535
Autumn	4630
Winter	4261

ICU: Intensive care unit

Table 2. Seasonal comparisons. Reference season has been Winter as it has the lowest admission rate

Season	p-value (comparison with Winter)
Spring	0.1
Summer	0.18
Autumn	0.08

The table highlights that Autumn had the highest number of ICU admissions (4,630), while Winter had the lowest (4,261). However, the presented p-values (e.g., Winter vs. Autumn: $p=0.08$) indicate that differences between seasons were not statistically significant ($p=0.42$). Although seasonal fluctuations were observed, the overall impact of seasons on ICU admissions does not have a strong statistical basis.

The general seasonal distribution does not support the expected hypothesis of "highest admissions in Winter," as Winter admissions were relatively low. The higher number of admissions in Autumn might be associated with post-holiday stress, seasonal transitions, and increased respiratory illnesses, which will be discussed in the next section.

Seasonal Survival and Mortality Rates

The survival and mortality rates of ICU-admitted patients were compared across seasons. These data are presented in **Table 3**.

Table 3. Seasonal survival rates

Season	Survival rate (%)
Winter	76.7
Spring	76.1
Summer	77.8
Autumn	78.3

ANOVA: $F=2.31$; $p=0.074$. No significant difference. Statistical significance threshold $p<0.05$, ANOVA: Analysis of variance

Autumn stood out with the highest survival rate (78.3%). Although Spring had the lowest survival rate (76.1%), it was not significantly different from Winter (76.7%; p>0.05). The pairwise comparisons showed no statistically significant differences among the seasons (p<0.05).

The seasonal distribution of survival and mortality rates was not statistically significant (p=0.074). In other words, the observed minor differences were not strong enough to establish a statistically meaningful relationship. However, the relative advantage in Autumn may be linked to variations in seasonal disease prevalence or organizational factors in hospital care processes.

Seasonal ICU Admissions by Age Groups

The study analyzed the seasonal frequency of admissions among five age groups (0-20, 21-40, 41-60, 61-80, and 81+ years). A chi-square test was conducted to assess statistical significance, and the results are presented in Table 4 using standardized residuals.

Table 4. Seasonal ICU admissions by age groups

Age group	Winter (Z-Resid.)	Spring (Z-Resid.)	Summer (Z-Resid.)	Autumn (Z-Resid.)
0-20	-2.12	-0.20	+2.64	-0.32
21-40	-2.88	-1.95	+3.60	+1.23
41-60	+0.12	+0.05	-0.10	-0.07
61-80	+1.35	+0.85	-1.93	+0.27
81+	+1.21	+0.33	-0.17	-1.37

Standardized residuals, p<0.001, ICU: Intensive care unit

The positive residuals indicate higher-than-expected admission rates, while negative residuals indicate otherwise.

- **0-20 age group:** The +2.64 value in Summer shows a significantly higher admission rate in this season (p<0.05).
- **21-40 age group:** The +3.60 value in Summer indicates a substantial increase in admissions for this group (p<0.05).
- **61-80 age group:** A mild increase in Winter (+1.35) and a notable decrease in Summer (-1.93) were observed.
- **81+ age group:** Admissions in Winter were slightly higher (+1.21), while admissions in Autumn were lower (-1.37).

These findings indicate that younger age groups tend to have higher ICU admissions during summer, while older age groups show higher admissions during winter. The chi-square test confirmed the statistical significance of this relationship (p<0.001)

Seasonal Survival and Mortality Rates by Age Groups

Although the overall survival rates did not show significant seasonal differences, specific age groups displayed noteworthy variations. Table 5 outlines the survival and mortality rates for age groups (0-20, 21-40, 61-80, and 81+) across Winter, Spring, Summer, and Autumn, including pairwise comparisons.

The 0-20 age group showed a significant difference between Winter and Summer (p=0.02), with higher survival rates in Summer.

In the 61-80 age group, survival rates in Summer and Autumn were significantly higher compared to Winter (p=0.03, p=0.04).

Table 5. Seasonal survival rates by age groups

Age group	Season	Survival (%)
0-20	Winter	82.1
	Spring	81.5
	Summer	84.2
	Autumn	83.7
21-40	Winter	79.3
	Spring	78.9
	Summer	80.5
	Autumn	80.8
61-80	Winter	72.5
	Spring	71.9
	Summer	74.0
	Autumn	73.8
81+	Winter	70.2
	Spring	69.7
	Summer	70.5
	Autumn	71.0

For the 81+ age group, Winter displayed higher mortality rates, although significance hovered near the threshold (p=0.05-0.07).

DISCUSSION

The findings reveal that seasons generally do not have a statistically significant impact on ICU admissions, but when examined specifically by age groups, young people are more likely to be admitted to the ICU in summer, while older people are more likely to be admitted in winter, and this affects survival rates. Our findings also suggest that seasonal ICU outcomes may be more favorable for younger age groups during Summer due to less severe conditions, while Winter presents a higher risk for older age groups due to severe illnesses and complications.[6,7]

One of the most striking findings of our study is the lack of statistically significant difference in total ICU admissions across seasons (p=0.42). Although the highest number of admissions (4,630) was observed in Autumn and the lowest (4,261) in Winter, this fluctuation is not statistically significant. This result contradicts the expectation of increased ICU admissions in winter due to increased respiratory infections and cardiovascular events.[8,9] There are studies in the literature showing an increase in hospitalizations and ICU admissions during winter.[10,11] We could speculate possible reasons why our study did not meet this expectation. Firstly, Istanbul's temperate climate, with less exposure to extreme cold and snowfall in winter, may limit the impact on ICU admissions in winter. Secondly, the socioeconomic status of the region where the hospital is located and the level of access to healthcare services may be relevant.[8] A third possibility is that increased influenza vaccination campaigns and public health measures in recent years may have reduced winter ICU admissions due to respiratory infections.

The high number of ICU admissions in autumn in our study may be related to the factors such as post-holiday stress, seasonal transitions, and an increase in some respiratory diseases. During this period, the rate of spread of respiratory infections among children may increase with the opening of

schools, which may indirectly increase the risk of infection in adults as well. In addition, increased stress from work and daily life in individuals returning from summer vacation may weaken the immune system and increase susceptibility to diseases.[12]

In terms of survival and mortality rates, our study shows no statistically significant difference between seasons (p=0.074). Although Autumn stands out with the highest survival rate (78.3), this difference is not statistically significant. This finding suggests that seasonal effects are not a strong determinant of mortality in ICU patients. However, analyses by age group reveal that seasonal effects are more pronounced in certain age groups. It should be noted that Villavicencio et al.[4] also reported a spike that happened in November in their study, which coincides with our findings regarding Autumn.

One of the most important findings of our study is that the relationship between age groups and seasons being statistically significant. The increase in ICU admissions among young people in summer can be attributed to traumatic injuries, drowning incidents, and accidents related to recreational activities, which are more common in this age group.[13,14] In particular, the significant increase observed in the 0-20 age group in summer may be a result of children and adolescents participating more in outdoor activities and water sports during the summer months. Similarly, the significant increase observed in the 21-40 age group in summer may be explained by the fact that individuals in this age group participate more in outdoor activities and travel as part of their work and social lives. But further studies specifically focusing on causality and results are needed.

The increase in ICU admissions in winter in older age groups be explained by the negative effects of cold weather and respiratory infections on the elderly. Elderly patients are more vulnerable to complications in winter due to decreased physiological reserves and weakened immune systems. In particular, the increase observed in the 61-80 age group in winter may be the most related. In addition, the negative effects of cold weather on the cardiovascular system may also increase ICU admissions in the elderly during winter.[8]

When seasonal survival and mortality rates are examined by age groups, the survival rate in the 0-20 age group is significantly higher in summer compared to winter, while the mortality rate in the 61-80 age group is significantly increased in winter. These findings suggest that the causes of ICU admission in younger age groups may be more treatable and less fatal in summer, while the causes of ICU admission in older age groups may be more serious and fatal in winter.

Limitations

The strengths of our study are its coverage of a wide time period (2008-2024) and a large patient population (18,046), inclusion of both pediatric and adult ICUs, and detailed analyses by age group. However, our study also has some limitations. Firstly, as our study is a retrospective observational study, it is not possible to establish a cause-and-effect relationship. Secondly, as our study includes data from a single center, results can't be valid for other centers. Thirdly, factors such as socioeconomic status, underlying diseases, and indications for ICU admission, which may affect the impact of seasons on ICU admissions and survival rates, were not examined in detail. Additionally, our hospital is located right next to a very busy main road in İstanbul, Turkiye. Therefore, amount of trauma cases admitted to our hospital is very high. This may negatively affect the seasonal patient number-profile fluctuation pattern. Although it is a busy center, an intensive care nurse in our center never cares for more than 2 patients. In addition, while every branch doctor provides 7/24 consultant physician services in our hospital, a specialist physician and an assistant physician are constantly on duty in our intensive care units, and continuous consultation services are also provided by the department responsible faculty members. All of these may affect the results of our hospital to be different, by even being more optimistic than other institutions.

CONCLUSION

This study reveals that the impact of seasonal variability on ICU admissions varies across age groups. The findings highlight the importance of considering age-specific seasonal risk profiles in healthcare planning and resource allocation. In particular, expanding trauma prevention programs for young people in summer and influenza vaccination and respiratory infection prevention programs for the elderly in winter may contribute to reducing the seasonal burden on ICUs. In future studies, it would be beneficial to conduct larger-scale studies covering different geographical regions and different healthcare systems to more comprehensively evaluate the effects of seasons on ICU admissions and survival rates and to examine the factors affecting these effects in detail.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Bakırköy Dr. Sadi Konuk Training and Research Hospital Non-interventional Scientific Researches Ethics Committee (Date: 05.02.2025, Decision No: 2025-03-02).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

Acknowledgements

This research was conducted independently, without any financial support, sponsorship, or affiliations with any institutions or organizations. All findings, interpretations, and conclusions are solely those of the authors and do not reflect any institutional or external influence.

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KASTAMONU MEDICAL JOURNAL

Original Article

DOI: 10.51271/KMJ-0211

Kastamonu Med J. 2025;5(3):203-207

Improvement of image quality and dose reduction with SEMAR and AIDR 3D in paranasal sinus CT

Şeyma Nur Altınok[1], Adem Karaman[2], Gökhan Polat[3], Elshad İsmayılov[2], Muhammed Halid Yener[2], Recep Sade[2], Fatih Alper[2]

[1]Department of Radiology, Amasya Sabuncuoğlu Şerefeddin Training and Research Hospital, Amasya, Turkiye
[2]Department of Radiology, Faculty of Medicine, Atatürk University, Erzurum, Turkiye
[3]Department of Radiology, Faculty of Medicine, Kütahya Health Sciences University, Kütahya, Turkiye

Cite this article as: Altınok ŞN, Karaman A, Polat G, et al. Improvement of image quality and dose reduction with SEMAR and AIDR 3D in paranasal sinus CT. *Kastamonu Med J.* 2025;5(3):203-207.

Received: 21.12.2024 ◆ **Accepted**: 07.07.2025 ◆ **Published**: 03.09.2025

ABSTRACT

Aims: Computed tomography (CT) is a frequently used and useful technique although it causes radiation exposure. In some situations, metal artefacts can reduce the diagnostic value of imaging. Our study aims to investigate the CT parameters for paranasal sinus imaging with less artefact and lower radiation dose at diagnostic limits, by applying single energy metal artifact reduction+adaptive iterative dose reduction (SEMAR+AIDR 3D) techniques together.

Methods: A head-neck equivalent phantom was used to create a setup containing tissue-like densities and metal artefact at the paranasal sinus level. Then CT scans were performed with different tube voltage and current values when SEMAR+AIDR 3D techniques were off and on. Effective doses were calculated for each CT scan. Signal-to-noise ratio and contrast-to-noise ratio values were calculated for objective evaluation and image quality was assessed subjectively by two different observers blindly.

Results: After tecniques, significant improvments were observed both objective and subjective values ($p<0.05$ and $p<0.0001$ respectively). 16 low-dose scans were diagnostically adequate for both observers, SEMAR+AIDR 3D was present in 15 of the 16. The lowest effective dose (0.0145 mSv) was acquired with SEMAR+AIDR 3D at 100 kVp and 3 mAs parameters.

Conclusion: Image quality can be improved by using SEMAR+AIDR 3D in paranasal sinus CT, it is possible to obtain reasonable quality CT scans at head radiography effective dose values.

Keywords: AIDR 3D, CT, paranasal sinus imaging, radiation dose reduction, SEMAR

INTRODUCTION

Computed tomography (CT) is useful for detecting anatomy and pathology in the paranasal sinuses and surrounding tissues.[1,2] However, a limitation of paranasal CT images is the radiation dose received. Iterative reconstruction (IR), one of the applications developed to obtain images with lower radiation dose while preserving image quality, is offered by manufacturers in compatible devices to reduce radiation dose in CT. With IR, a comparison is made using the first image obtained on CT or a model, and the final image is reached through repeated reconstructions.[3] The aim is to obtain images with lower radiation dose but similar quality to standard shots, with acceptable noise and blur levels.[3] One of the IR applications is the AIDR 3D (adaptive iterative dose reduction) uses first images produced with filtered back projection (FBP), which is the standard reconstruction algorithm in CT, and reaches final images.[4]

In paranasal sinus CT scans, there can be limitations due to the presence of metallic surgical materials and other high-density foreign objects such as malposed dental implants in the imaged area which may cause artefacts and hinder evaluation.[5] This can affect the quality of the diagnosis, requiring repeat imaging and exposing the patient to more radiation. To address this issue, metal artefact reduction (MAR) applications have been developed to minimize artefacts caused by high-density objects such as metal in CT scans.[6] One of these applications is SEMAR (single energy metal artifact reduction), which aims to identify the position of high-density objects in the image and reduce the artefacts.

IR applications are commonly used in CT imaging today and they provide advantages in dose reduction, also they show a greater improvement in image quality when used together with MAR techniques in images with metal artefacts.[7] Studies have shown that using IR techniques in paranasal sinus CT scans can lead to a significant reduction in radiation dose.[8-10] However, it has not been evaluated how combining IR and MAR techniques can specifically reduce radiation in this region when metal artefacts are present. In such cases, we aimed to investigate how to acquire images with lower radiation doses while maintaining image quality in different scan parameters using SEMAR+AIDR 3D.

Corresponding Author: Şeyma Nur Altınok, seymanuraltinok1@gmail.com

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METHODS

This study was approved by the Atatürk University Faculty of Medicine Clinical Researches Ethics Committee (Date: 30.09.2021, Decision No:30). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was performed with an adult head-neck region equivalent phantom. (ATOM® 701-B, Computerized Imaging Reference System Inc Norfolk, VA/ABD). Different holes in the paranasal sinuses region were filled in soft tissue, fat, mucosa and metal density materials. In the study, a platinum-containing peripheral coil was used to create the metal density and artefact. To provide other tissue equivalent densities, chicken meat, oil and water were used, respectively. Before placement in the phantom, the materials were tested with our routine paranasal sinus CT protocol to verify the appropriateness of their density values. These materials were used in dimensions that matched the available compartment size of the phantom.

CT acquisitions were performed using a Multidetector CT scanner (Aquilion ONE, Canon Health Systems, Otawara/Japan). CT images were acquired using the following parameters: helical mode; four different tube voltages (80, 100, 120 and 135 kV); six different tube currents (3, 7, 14, 32, 64, and 129 mAs); 9 cm scan length, 1 mm slice thickness. Considering the parameter ranges frequently used in dose studies in the literature, the initial and final kVp and mAs values supported by the scanner were identified and utilized in this study. This approach was adopted to ensure comparability with clinical practice and to maintain consistency with previously published findings. Using the settings above a total of 48 CT scans were performed before and after SEMAR+AIDR 3D techniques.

Image Analysis

Attenuations of CT images [expressed as the mean number of Hounsfield units (HU)] and their standard deviations (SD) were measured by placing at least 10 mm² region of interest (ROI) in similar locations for soft tissue, fat, mucosa, and air (**Figure 1**). Then using HU and SD values, Signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) were calculated for objective evaluation. The formulas used to calculate SNR and CNR are as follows:

$$SNR = \frac{\text{average signal intensity of the selected area } (SI_{ROI})}{\text{signal standard deviation of the selected area } (SD_{ROI})} \quad [11]$$

$$CNR = \frac{\text{average signal intensity difference of selected areas } (\Delta(SI_{ROIa}, SI_{ROIb}))}{\sqrt{(\text{the sum of squares of signal standard deviations of selected areas})}\left(\sqrt{(SD_{ROIa})^2+(SD_{ROIb})^2}\right)} \quad [11]$$

Radiation Dose

For each CT scan, the effective dose (ED) was calculated using the equation:

ED = CTDIvol (CT scan data) x 9 cm (scan length) x ED/DLP conversion factor (0.0023 for the head region[12]).

Subjective Evaluation

Two radiologists evaluated the images independently and blindly, without knowledge of the image acquisition features and each other's scores. A scoring table (**Table 1**) was prepared using the European Guidelines on Quality Criteria for Computed Tomography[12] and images were assigned scores ranging from 1 to 5 based on their anatomical details, noise level, and artefacts. 5 point was the highest score for evaluations. The average scores given by the radiologists were calculated for each CT scan. Images receiving an average score of three or more from both observers were categorised as diagnostically sufficient (**Figure 2**).

Table 1. Subjective Evaluation Scoring Scale

Categories/ scores	Noise	Artefacts	Anatomic details
5	No or minimal	No or minimal artefacts	Clear, sharp edges
4	Mild	Less artefacts	Clear, but slight artefact
3	Moderate/ acceptable	Acceptable artefacts, diognosis is possible	Anatomic structures can be vizualized
2	Heavy	Considerable artefacts make diagnosis difficult	Anatomic structures can not be visualized clearly
1	Severe/ unacceptable	Not diagnostic	Unable to identify

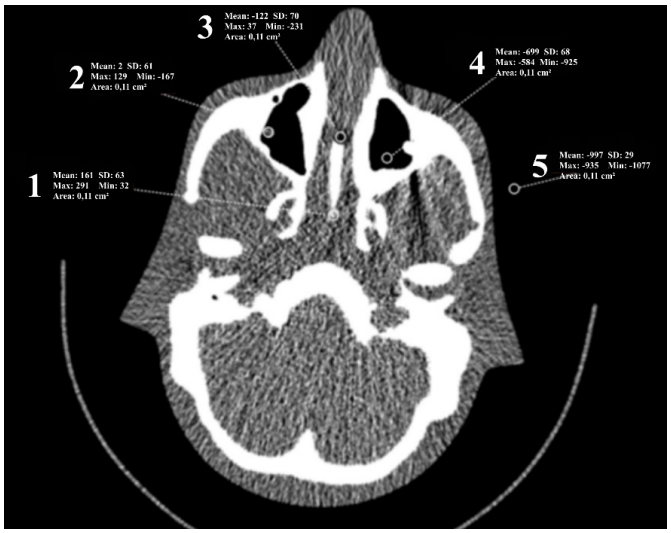

Figure 1. Example of measurements; soft tissue (1), mucosa (2), fat (3), paranasal air (4) and external air (5), respectively

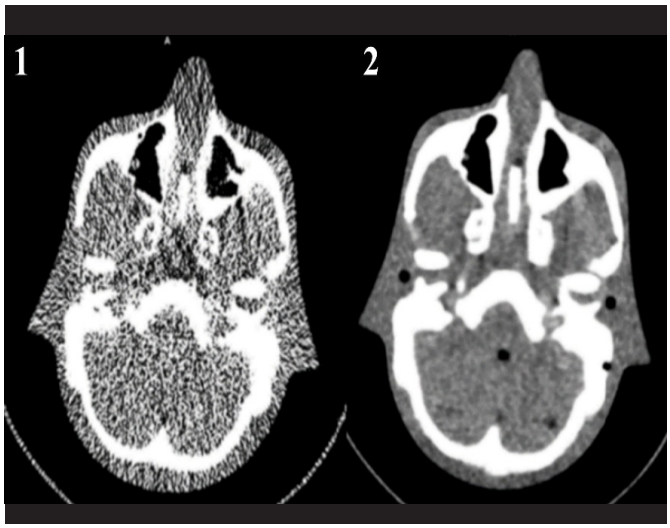

Figure 2. Left-sided (1) image had the worst subjective score (80 kVp/3 mAs/ without SEMAR+AIDR 3D). The right-sided (2) image had the lowest ED in the acceptable subjective scores (100 kVp/3 mAs/with SEMAR+AIDR 3D)

SEMAR+AIDR 3D: Single energy metal artifact reduction+adaptive iterative dose reduction, ED: Effective dose

Statistical Analysis

Data analyses were performed using SPSS (IBM, Armonk, NY, USA) software version 23. Both analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) and visual (histogram) methods were used to examine whether the data conformed to normal distribution. Descriptive statistics were presented as mean±standard deviation (mean±SD) for normally distributed variables, and median and interquartile range (IQR) for non-normally distributed variables. To determine the impact of SEMAR and AIDR 3D on the SNR and CNR values, a paired T test for normally distributed variables and the Wilcoxon test for non-normally distributed variables were used. For subjective scoring statistics, the Wilcoxon and McNemar tests were used. The presence and level of interobserver agreement were investigated using the Kappa test. p=0.05 was used to determine statistical significance.

RESULTS

SNR and CNR Values

After applying SEMAR and AIDR 3D, all SNR and CNR changes were statistically significant (p=0.034 for mucosa SNR, p<0.0001 for all other regions' SNR and CNR). The soft tissue showed the most significant improvement in SNR (mean±SD 2.36±1.78 when the SEMAR+AIDR 3D were off, 6.28±2.64 when they were on), while the paranasal air showed the most significant improvement in CNR (median value 2.429 when the SEMAR+AIDR 3D were off, 7.7487 when they were on).

Radiation Dose

There were 24 different EDs for a total of 48 scans performed before and after SEMAR+AIDR 3D. The range of ED in all scans was between 0.0083 mSv and 1.1861 mSv. Compared to the ED (0.3726 mSv) calculated for the same scan length in paranasal sinus CT routinely used in our institution, 38 of the 48 scans had lower radiation doses. Observers found adequate diagnostic quality in 16 out of the 38 low-dose scans. SEMAR+AIDR 3D was present in 15 of the 16 scans. The scan with the lowest ED (0.0145 mSv) found suitable for evaluation was performed with SEMAR+AIDR 3D at 100 kVp and 3 mAs parameters (Table 2).

Table 2. Parameters of images with adequate diagnostic quality and lower ED

kVp/mAs	SEMAR+AIDR 3D	ED (mSv)
80/32	+	0.0725
80/64	+	0.1449
80/129	+	0.2919
100/3	+	0.0145
100/7	+	0.0290
100/14	+	0.0600
100/32	+	0.1346
100/64*	-/+	0.2712
120/3	+	0.0228
120/7	+	0.0455
120/14	+	0.0932
120/32	+	0.2111
135/7	+	0.0600
135/14	+	0.1221
135/32	+	0.2795

*: Observers found the image diagnostically sufficient with/without SEMAR+AIDR 3D in these parameters, SEMAR+AIDR 3D: Single energy metal artifact reduction+adaptive iterative dose reduction, ED: Effective dose

Subjective Evaluation

After SEMAR+AIDR 3D, there was a significant improvement in the median subjective score from 2.5 to 3.67 (p<0.0001). Before SEMAR+AIDR 3D, observers rated only 6 of 24 CT scans as adequate, of which only one was low-dose. After SEMAR+AIDR 3D, 20 of 24 CT scans were found suitable, of which 15 were low-dose. Interobserver agreement for subjective scoring was good (p<0.0001, Kappa=0.61).

The dot plots showed a positive correlation between subjective and objective data for all region subgroups (Figure 3).

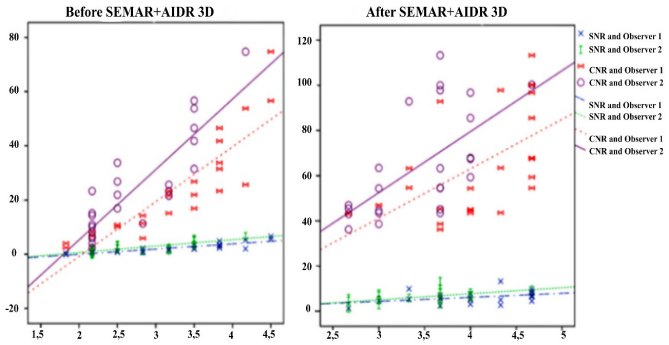

Figure 3. Correlation graph for soft tissue subgroup data

DISCUSSION

When evaluating the three areas examined in the current study (image noise, subjective image quality, and radiation dose reduction), images with the same acquisition parameters and dose values showed better diagnostic performance after applying SEMAR+AIDR 3D. Although 19 of the 24 acquisition presets had lower doses than our institutional dose, after the techniques there were significant improvements in all SNR and CNR values and subjective scores, in line with the aim of dose and artefact reduction. It is desirable to reduce both artefacts and radiation dose in imaging, but this may result in the loss of the high-acuity images to which the eye is accustomed and a decrease in diagnostic quality. Parallelly, even after applying SEMAR+AIDR 3D, 4 of 19 low-dose scans still weren't diagnostic sufficiency for observers. X-Ray exposure due to CT causes damage to DNA with direct and indirect effects and causes an increase in the risk of some cancers.[13,14] According to AAPM's report, the dose value of dental radiography is <0.1 mSv, while the dose value of CT for the head area is 1-2 mSv.[15] The ED for the adult head radiograph ranges between 0.107 and 0.022 mSv.[16] Even though a CT scan contains at least 10-20 times more radiation dose compared to radiography, it is diagnostically superior to radiographs.[17,18] In our study, when SEMAR+AIDR 3D was applied, diagnostic adequacy could be achieved in low-dose paranasal CT scans. The lowest ED we found was within the dose range specified for standard radiographs (0.0145 mSv). Thus, we achieved to combine the diagnostic superiority of CT with the low doses of radiographs, as the ALARA (as low as reasonably achievable) principle.

Studies conducted with IR techniques attempt to provide diagnostic image quality while reducing ED. Some studies in adult cadavers or real patients have shown that ED can be reduced to 0.08-0.11 mSv for the paranasal sinus region with various IR applications,[8-10] and some more recent studies on the pediatric population have shown that dose reduction with IR applications can reach 0.008-0.05 mSv[19,20] The ED

we obtained (0.0145 mSv) was lower compared to the results of adult studies. Our study shares similarities with others in terms of anatomical localization and the use of IR, but differs in that it was conducted using a phantom, includes metal artefacts, and employs the IR technique supported by the MAR technique. It is stated that the use of MAR and IR together is superior to their use alone in terms of image quality.[7] One study has shown that in addition to reducing metal artefacts, image quality can be preserved in low-dose CT using the combination of iMAR+ADMIRE.[21] Similar to this, in our study, SEMAR+AIDR 3D was used in 15 of the 16 low-dose scans that the observers found sufficient. There wasn't only AIDR 3D group in our study, but the dose value we reached was lower compared to containing only IR studies. SEMAR, which we used additional here, was likely to contribute. Another IR study with SAFIRE in this region found that while the low radiation dose was sufficient in real patients, the same dose was insufficient in the phantom.[22] Considering studies together, the scanning parameters we achieved in the phantom and found lower ED can also be sufficient in real patient studies. It is not yet clear whether our protocol is sufficient for real-patient CT scans, but we hope that our results may guide real patients undergoing CT scans. In the next step, it will be appropriate to validate our findings in an actual patient study. We predict that similar results can be obtained in other devices but some studies suggest that not all manufacturers' techniques are equally effective.[23]

Limitations

The most important one is there were no real patients. We were able to perform many different scans using phantom without worrying about radiation exposure, but we may not be aware of the obstacles in real scanning. So, it is needed to investigate the parameters we found in our study on real patients. Another limitation is that we examined the techniques we used from only one manufacturer (Canon). Therefore, it may not be possible to talk about a clear result at this point.

CONCLUSION

Developments in CT show that image quality will improve with much lower radiation exposure than known. In paranasal sinus CT, it is possible to perform images with sufficient quality at lower radiation doses with SEMAR+AIDR 3D techniques. Thus, detecting pathologies that may be overlooked due to artefacts will be easier. Imaging scenarios for real patients can be constructed using the data from our study.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Atatürk University Faculty of Medicine Clinical Researches Ethics Committee (Date: 30.09.2021, Decision No:30).

Informed Consent

As no biological material from humans or animals was used in the study, informed consent was not required.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

This study was supported by Atatürk University the Coordination Unit of Scientific Research Projects. Project code: TTU-2021-9902.

Author Contributions

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

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author.

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KASTAMONU MEDICAL JOURNAL

Case Report

DOI: 10.51271/KMJ-0212

Kastamonu Med J. 2025;5(3):208-213

Catatonia and associated psychopathologies in adolescence: case series and a brief review

Makbule Esen Öksüzoğlu[1], Burcu Ersöz Alan[2]

[1]Department of Child and Adolescent Psychiatry, Faculty of Medicine, Kastamonu University, Kastamonu, Turkiye

[2]Department of Child and Adolescent Psychiatry, Faculty of Medicine, Hacettepe University, Ankara, Turkiye

Cite this article as: Esen Öksüzoğlu M, Ersöz Alan B. Catatonia and associated psychopathologies in adolescence: case series and a brief review. *Kastamonu Med J.* 2025;5(3):208-213.

Received: 12.11.2024 ◆ **Accepted**: 16.12.2024 ◆ **Published**: 03.09.2025

ABSTRACT

Catatonia is a severe motor dysregulation syndrome observed in both psychiatric and medical conditions, with potentially fatal outcomes if untreated. This report presents three adolescent cases diagnosed with catatonia; each associated with distinct psychiatric pathologies. Despite varying symptoms, including negativism, mutism, echolalia, and rigidity, all cases responded to benzodiazepine treatment, with one requiring electroconvulsive therapy due to malignant catatonia. This brief review discusses the diagnostic challenges, treatment approaches, and importance of early intervention in catatonia. The comparison of symptoms across cases highlights the role of differential diagnosis in optimizing treatment outcomes for pediatric catatonia.

Keywords: Catatonia, adolescents, benzodiazepines, electroconvulsive therapy, differential diagnosis

INTRODUCTION

Catatonia is a motor dysregulation syndrome rather than a diagnosis and may have psychiatric, neurological, autoimmune or toxic etiologies.[1] The incidence in psychiatry clinics among adults varied from 6 to 38%,[2] while it has been reported between 0.6-17.7% in child and adolescent psychiatry clinics.[3,4] Although rare, morbidity and mortality are high in children and adolescents.[5,6]

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5),[7] the diagnostic criteria for catatonia require at least three of the following twelve symptoms: stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerism, stereotypy, agitation, grimacing, echolalia, and echopraxia. However, these criteria have been critiqued for redundancy, and the absence of time criteria poses challenges, particularly in pediatric populations. Common signs of catatonia in all cases are posturing, waxy flexibility, staring, negativism, withdrawal and social withdrawal. Catalepsy is considered an advanced degree of posturing,[8] while some authors consider it under the heading of waxy flexibility. Posturing and waxy flexibility were observed in all cases, so catalepsy could be considered an indirect positive symptom. This is why the DSM-5 criteria are criticized for repetition. More than 40 symptoms associated with catatonia have been described in literature. In children and adolescents, withdrawal, refusal to eat or drink, and social withdrawal are often prominent symptoms that demand special attention. The absence of time criteria in DSM-5 is also considered as a limitation.

Excitation, agitation, talkativeness, and disorganization, when observed alongside catatonic symptoms, are collectively referred to as excited catatonia (also known as delirious mania or Bell's mania).[9] Although excited catatonia and delirious mania are often considered part of the same spectrum, the term excited catatonia is more appropriate when catatonic symptoms predominate, as delirious symptoms tend to be more severe in cases classified as delirious mania. One of the most severe complications of catatonia is malignant catatonia, which has been frequently reported in undiagnosed or untreated cases.[6] Malignant catatonia is characterized by autonomic and thermoregulatory dysfunctions, with clinical manifestations including fluctuations in blood pressure and heart rate, diaphoresis, high fever, laboratory abnormalities, and a general deterioration of the patient's condition. If left untreated, the mortality rate for malignant catatonia ranges from 10% to 20%, with respiratory failure being the most common cause of death.[10,11] Another less common subtype, periodic catatonia, is defined by the rapid onset of repetitive hypokinetic and hyperkinetic episodes lasting 4 to 10 days.[12] These episodes can recur over weeks or even years. Some cases of periodic catatonia exhibit a familial pattern with autosomal dominant inheritance, linked to abnormalities on chromosome 15q15, which are associated with syndromes such as Prader-Willi and Angelman.[13]

Bush Francis Catatonia Rating Scale,[8] Modified Rogers Scale, Northoff Catatonia Rating Scale, Brauning Catatonia Evaluation Scale and Kanner Scale are used frequently.[14]

Corresponding Author: Makbule Esen Öksüzoğlu, esenmakbule@gmail.com

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The Bush Francis Catatonia Rating Scale (BFCRS), which is the gold standard in studies and is used widely, consists of 23 items (30 findings) and was developed based on the definitions in DSM and international statistical classification of diseases (ICD) classifications, as well as Kahlbaum, Krapelin. Pediatric Catatonic Rating Scale (PCRS) was developed as a modified version of the BFCRS for children and adolescents.[15] In addition to the 17-item of the BFCRS, six symptoms were added based on the analysis of 463 catatonic cases and the review of descriptions of pediatric catatonia: (1) Withdrawal was divided into refusal to eat/drink and social withdrawal to facilitate differentiation with other pediatric psychiatric disorders such as eating disorders or autism spectrum disorders (ASD) (2) Incontinence, a symptom of general psychomotor regression, highly reported in children with catatonia[16-18] (3) Automatic compulsive movements were proposed instead of automatic obedience and were considered a presentation of psychomotor automatism (4) Schizophasia and acrocyanosis were added as an indication of malignant catatonia in youths in addition to autonomic abnormality, and (5) grimacing was combined with mannerism (**Table 1**).

Dysfunction in multiple neurotransmitter systems has been implicated in the pathophysiology of catatonia. The glutamatergic system, mediated by N-methyl-D-aspartate (NMDA) receptors, plays a critical role, as evidenced by the induction of catatonia-like symptoms in healthy individuals following the administration of ketamine, an NMDA receptor antagonist.[19] Similarly, the presence of catatonic symptoms in anti-NMDA receptor encephalitis and the therapeutic efficacy of amantadine, an NMDA receptor agonist, further underscore the involvement of NMDA receptor dysregulation in catatonia.[20] The GABAergic system is equally significant, with high doses of benzodiazepines, which act on the benzodiazepine-sensitive GABA-A receptor complex, demonstrating robust efficacy in alleviating catatonic

Table 1. Comparison of catatonia symptoms in evaluation

	DSM-5	BFCRS	PCRS
Motor symptoms			
Catalepsy (passive induction of a posture held against gravity)	+	+	+
Posturing (maintaining constant posture)	+	+	+
Stereotypy (repetitive, abnormally frequent, non-goal directed movements)	+	+	+
Stupor/immobility (no psychomotor activity or decreased)	+	+	+
Agitation (not influenced by external stimuli)	+		
Mannerism (odd, purposeful movements)	+	+	+
Waxy flexibility (allows repositioning)	+	+	+
Grimacing (maintenance of odd facial expressions)	+	+	
Echopraxia (mimicking movements)	+	+	+
Negativism (resistant to instructions)	+	+	+
Staring (fixed gaze, decreased blinking)		+	+
Grasp reflex (automatic closure of palm when touched)		+	
Rigidity (rigid position despite efforts to be moved)		+	+
Impulsivity (suddenly engages in inappropriate behavior without provocation)		+	
Automatic obedience (exaggerated cooperation)		+	
Mitgehen (arm rising with light pressure, “anglepoise lamp”)		+	
Gegenhalten (resistance to passive movements)		+	
Ambitendency (indecisive hesitant movement)		+	
Perseveration (repeating same topic or movement)		+	
Automatic compulsive movements (involuntary muscle activity exhibited in posture, attitudes, mimic or gesture due to inhibition or forced motoraction			+
Excitement (extreme hyperactivity)		+	+
Other symptoms			
Mutism (verbally unresponsive or very little response)	+	+	+
Echolalia (mimicking speech)	+	+	+
Verbigeration (repetition of nonsensical phrases)		+	+
Withdrawal (refusal to eat/drink)			+
Social withdrawal (refusal to make eye contact)			+
Schizophasia (scrambled speech)			+
Acrocyanosis (cyanosis of the extremities)			+
Autonomic abnormality (change in temperature, BP, pulse, laboratory findings and diaphoresis)			+
Incontinence (nocturnal enuresis, daytime urinary incontinence, fecal incontinence)			+
Combativeness (belligerence, aggression)		+	

DSM-5: Diagnostic and Statistical Manual of Mental Disorders-5, BRCRS: Bush Francis Catatonia Rating Scale, PCRS: Pediatric Catatonic Rating Scale, BP: Blood pressure

symptoms. This response highlights potential changes in GABA-A receptor function as a key mechanism. Although alterations in GABAergic and glutamatergic activity likely contribute to various catatonic phenotypes, the relative involvement of these systems may vary across different types of catatonias. The role of the dopaminergic system, while less well-defined, warrants further investigation to fully elucidate its contribution to catatonia.[21]

Here three adolescents with catatonia will be presented and clinical presentation, differential diagnosis and management of catatonia will be reviewed. The catatonia symptoms of cases were compared in **Table 2**. The informed consents were received from the cases and their families for this report.

Table 2. Comparison of catatoni symptoms between cases

	Case 1	Case 2	Case 3
Catatonic symptoms			
Catalepsy			
Posturing	+	+	+
Stereotypy			
Stupor/immobility	+	+	
Agitation			+
Mannerism			
Waxy flexibility	+	+	+
Grimacing	+		
Echopraxia			+
Negativism	+	+	+
Staring	+	+	+
Grasp reflex	+		
Rigidity	+		
Impulsivity			+
Automatic obedience	+		
Mitgehen			
Gegenhalten			
Ambitendency	+		+
Perseveration			+
Automatic compulsive movements			
Excitement			+
Mutism	+	+	
Echolalia	+		+
Verbigeration			+
Withdrawal	+	+	+
Social withdrawal	+	+	+
Schizophasia			+
Acrocyanosis			
Autonomic abnormality	+		
Incontinence	+		
Combativeness			+
Other symptoms			
Psychotic symptoms	+	+	+
Disorganization in speech and behavior	+		+
Depressed mood	+	+	
Emotional lability			+

CASE PRESENTATIONS

Case 1

A 17-year-old male with a history of bipolar affective disorder (BAD) for 11 months, Specific Learning Disorder, and attention deficit hyperactivity disorder (ADHD) since the age of eight, was brought to the emergency department by his family due to a progressive decline in sleep, movement, speech, and daily functioning over the past week. The family described an abrupt onset of symptoms, beginning with episodes of lying motionless on the sofa for extended periods, followed by standing motionlessly in front of the refrigerator for hours and refusing to eat or drink for three consecutive days.

The patient had been receiving olanzapine for BAD; however, it had been switched to aripiprazole (5 mg/day) three weeks prior due to metabolic side effects. He had no family history of psychiatric disorders. On examination, the patient was uncooperative, mute, slow in movements, and exhibited rigidity. He refused to sit, stood with a dull expression, stared at a fixed point, avoided eye contact, and did not follow commands. He displayed negativism, resisting passive movement of his extremities.

Clinical findings included subfebrile fever, tachycardia, hypertension, and excessive sweating. Laboratory results revealed impaired liver function tests, leukocytosis, and elevated creatine kinase (CK) levels, although imaging (brain MRI), EEG, lumbar puncture, blood cultures, and toxicology were unremarkable. Due to the severity of his condition, diazepam (10 mg, intramuscular) was administered, but minimal improvement was observed after two days of treatment. Oral lorazepam (2 mg/day) was initiated, leading to slight improvement, including eating, drinking, and answering simple questions.

The patient was diagnosed with Malignant Catatonia related to mood disorder and admitted to an inpatient psychiatry clinic. Despite increasing lorazepam to 10 mg/day, symptoms persisted, including echolalia, ambivalence, and agitation. Bilateral electroconvulsive therapy (ECT) was initiated, with treatments administered twice weekly. After eight weeks, his symptoms significantly improved, and his BFCRS (Bush Francis Catatonia Rating Scale) score reduced from 29/69 to 16/69 within one week of ECT initiation and further to 3/69 after three weeks.

During treatment, his mood and motor symptoms improved; however, persistent grandiose and persecutory delusions with disorganized speech and behavior became evident. Treatment with valproic acid (1000 mg/day) and clozapine (300 mg/day) was initiated alongside ongoing ECT. While mood symptoms resolved, psychotic symptoms persisted, leading to a diagnosis of schizoaffective disorder. The patient was discharged on mood stabilizers and antipsychotics for outpatient follow-up. Despite poor insight and persistent psychotic symptoms during six months of follow-up, he managed daily activities effectively.

Case 2

A 16-year-old female with no prior medical or psychiatric history presented to the emergency department with confusion, weakness, and fainting. The family reported a 13 kg weight loss over two months, insomnia, a lack of self-care,

and excessive fear for her family's safety. The patient refused to allow her father to go to work or her sister to bathe. Upon examination, she was agitated, mute, and immobile, with no evaluable orientation or thought content. Findings included negativism, mutism, irritability, and avoidance of eye contact.

Initial assessments revealed electrolyte imbalances, hypoglycemia, and ketoacidosis. Fluid therapy was initiated, and imaging (brain MRI), EEG, and urine toxicology tests were normal. A diagnosis of catatonia related to psychiatric pathology was established, and lorazepam (2 mg/day) was administered. Although this improved her ability to provide brief responses, she continued refusing food and required hospitalization with nasogastric feeding.

Further history revealed an episode one year prior involving disinhibition, agitation, and hallucinations, treated briefly with olanzapine before being discontinued without follow-up. Subsequently, she exhibited withdrawal, repetitive questioning, restlessness, and emotional outbursts. Her family noted increasing social isolation over the two months preceding hospitalization.

During inpatient care, the patient gained 3 kg over two weeks and showed decreased motor hypoactivity but continued mutism. She was discharged on olanzapine (15 mg/day) and lorazepam (2 mg/day), with lorazepam gradually discontinued during follow-up. Olanzapine was increased to 20 mg/day, leading to improvements in sleep, eating, and self-care, though short answers, affective bluntness, and persecutory delusions persisted.

Her clinical history suggested catatonia secondary to schizoaffective disorder. While she could not return to school, psychotic symptoms were manageable with ongoing follow-up.

Case 3

A 15-year-old female, previously healthy, presented to the emergency department with bizarre behavior, pressured speech, and insomnia. The insomnia began 20 days earlier, with her sleeping only 2.5 hours per night. After three days, she developed crying episodes and fears that others doubted her abilities. She expressed irrational fears, such as aversion to certain letters ("A" and "E") and concern about bread being infected with a virus.

The patient was agitated, talkative, and fearful during examination, with disorganized speech and persecutory delusions. Neurological findings included echolalia, ambivalence, excitation, and waxy flexibility. Despite disorganized thought processes, her orientation was intact. A family history of schizophrenia was noted in a distant relative.

Vital signs and laboratory evaluations, including imaging (brain MRI), EEG, lumbar puncture (negative for encephalitis autoantibodies), and urine toxicology, were unremarkable. After oral lorazepam (1 mg), the patient began eating, drinking, and calming down. Lorazepam was increased to 4 mg/day, leading to resolution of catatonia symptoms within two weeks.

She was diagnosed with catatonia related to mood disorder and discharged on olanzapine (15 mg/day) and lithium (900 mg/day). During outpatient follow-up, no mood or catatonia symptoms were observed after four weeks.

DISCUSSION

The diagnosis of catatonia in each case was based on DSM-5 criteria and the BFCRS. Approximately 20% of catatonia cases in children and adolescents are associated with underlying medical conditions.[22] During the evaluation, medical pathologies such as infectious, neurological, and metabolic diseases must be thoroughly investigated. Common associated conditions include genetic disorders (e.g., Prader-Willi syndrome, Down syndrome, Huntington disease), neurological conditions (e.g., seizures, trauma), infectious diseases (e.g., viral encephalitis), toxic states (e.g., Ecstasy-induced), and autoimmune disorders.[22,23] Effective prognosis and significant improvement in catatonia can be achieved when specific etiological treatment is combined with catatonia treatment.[22,24,25] The Causality Assessment Score (CAUS) can assist in distinguishing autoimmune from non-autoimmune cases.[25]

Autoimmune disorders such as anti-NMDA receptor encephalitis,[26] systemic lupus erythematosus (SLE),[27] Hashimoto encephalopathy (HE),[28] and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) or pediatric acute-onset neuropsychiatric syndrome (PANS)[29,30] often present with acute-onset severe psychiatric symptoms, including catatonia. Diagnosis in these cases relies on identifying antibody levels in cerebrospinal fluid and evaluating neurological findings such as atypical EEG patterns and cranial MRI results.

When catatonia occurs without any underlying organic disease, a detailed psychiatric examination and long-term follow-up are essential. In adults, mood disorders, schizophrenia, posttraumatic stress disorder, and eating disorders are the most commonly associated psychiatric conditions, whereas in children and adolescents, schizophrenia spectrum disorders, ASD, Down syndrome, mood disorders, and obsessive-compulsive disorders are more prevalent.[2] Catatonia is more common in males within pediatric populations, likely due to the higher prevalence of schizophrenia spectrum disorders in this demographic, as opposed to the higher prevalence of mood disorders in adult females.[31-33] Differential diagnosis in children with ASD and developmental disorders can be particularly challenging since overlapping symptoms such as stereotypies and echolalia may mask catatonic features.[34] A prevalence of catatonia in ASD has been reported at 17%, with four core symptoms aiding in differential diagnosis:[35] 1. Increasing psychomotor and verbal slowness, 2. Difficulties in initiating and completing actions, 3. Increased reliance on physical or verbal prompts, 4. Increased passivity and apparent lack of motivation.

In the present cases, underlying medical and psychiatric conditions were carefully evaluated. Case 1 involved BAD and a family history of mood disorders in Case 2 suggested a psychiatric etiology for catatonia. In Case 3, the absence of prior psychiatric symptoms supported a diagnosis of acute-onset catatonia with manic/mixed mood symptoms. Regardless of the underlying cause, benzodiazepines and ECT remain the cornerstone of catatonia treatment.[2]

In Case 1, significant weight gain (20 kg over five months) during olanzapine treatment for BAD required a switch to aripiprazole. The slower titration and reduced mood-stabilizing effects of aripiprazole compared to olanzapine may have contributed to psychotic depressive symptoms and catatonia.

The absence of improvement with benzodiazepines and the clinical presentation of malignant catatonia necessitated ECT, which resulted in marked improvement.[36] The decrease in BFCRS scores and clinical symptoms highlights the utility of BFCRS for tracking symptom recovery in children.

In Case 2, severe refusal to eat and drink resulted in electrolyte imbalances, dehydration, and ketoacidosis, posing life-threatening risks. Benzodiazepines such as lorazepam produced a rapid response,[37] but nasogastric feeding was essential to prevent refeeding syndrome. This highlights the importance of timely fluid and nutritional support in catatonia management.[38]

In Case 3, primary symptoms such as disorganized speech and behavior, affective lability, and excitation were associated with manic/mixed episodes. Treating only mood and psychotic symptoms without addressing catatonia could have worsened the condition. This case underscores the importance of detailed psychiatric evaluation and targeted treatment for excited catatonia, as excessive motor activity in excited catatonia may increase the risk of progression to malignant catatonia. Fortunately, malignant catatonia was not observed in this case.

Antipsychotics during the acute phase of catatonia are not recommended due to the risk of malignant catatonia and deterioration of catatonic symptoms. Some reports suggest limited benefits of second-generation antipsychotics like aripiprazole[39,40] and quetiapine[41] during acute catatonia treatment. However, the lack of repeated assessment and concurrent benzodiazepine administration in these studies limits the ability to determine the true efficacy of these drugs. Antipsychotics should be introduced cautiously after the resolution of catatonic symptoms to manage underlying psychiatric disorders. Given the higher sensitivity of children to neuroleptic-induced motor symptoms,[42] these drugs must be used sparingly in pediatric cases. In Case 1, antipsychotics were introduced after the stabilization of catatonia to address persistent psychotic symptoms. Despite the addition of mood stabilizers and antipsychotics, psychotic symptoms such as disorganized behavior, derailments in thought processes, and grandiose and persecutory delusions persisted. This highlights the importance of long-term follow-up in cases where initial diagnoses may shift, as demonstrated by the reclassification of this case to a schizophrenia spectrum disorder.[43]

The findings in these cases emphasize the need for individualized treatment plans, combining benzodiazepines, supportive care, and cautious use of antipsychotics to manage catatonia and its underlying causes effectively.

CONCLUSION

This study is subject to several limitations. The small sample size of only three cases restricts the generalizability of the findings, and larger case series or cohort studies would provide more robust evidence. Additionally, the absence of a control group or randomized comparisons limits the ability to draw definitive conclusions about the effectiveness of treatment methods. Limited information on long-term functionality and psychiatric recovery, particularly regarding the persistence of psychotic symptoms in Case 1, further highlights the need for extended follow-up studies. Catatonia, a complex syndrome associated with various medical and psychiatric conditions, requires a thorough differential diagnosis in children and adolescents. Timely recognition and treatment of medical etiologies are crucial for improving prognosis. While benzodiazepines are the primary treatment option, ECT remains highly effective for refractory cases. However, untreated catatonia carries a significant risk of progression to malignant catatonia, which is associated with a high mortality rate. A multidisciplinary approach, including medical management, supportive care, and psychiatric follow-up, is essential for successful treatment. The lack of randomized controlled studies in pediatric populations remains a critical limitation that warrants further research.

ETHICAL DECLARATIONS

Informed Consent

All parents signed an explicit and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

Acknowledgements

The authors convey their gratitude to all of the youths and parents who consented to share their medical record. Furthermore, they thank the paediatric nurses, medics and doctors for their important help with treatment management.

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KASTAMONU MEDICAL JOURNAL

Erratum

DOI: 10.51271/KMJ-0213

Kastamonu Med J. 2025;5(3):214

Erratum to "Effects of phantom shocks on anxiety levels, coping skills and sleep quality in patients with implantable cardioverter/defibrillators" [Kastamonu Medical Journal 5 2 111 116]

Gözde Yontar[1], Neriman Aras[2]

[1]Department of Psychiatry, Samsun Training and Research Hospital, Samsun, Turkiye
[2]Department of Psychiatry, Samsun Mental Health and Disorders Hospital, Samsun, Turkiye

Cite this article as: Yontar G, Aras N. Erratum to "Effects of phantom shocks on anxiety levels, coping skills and sleep quality in patients with implantable cardioverter/defibrillators". *Kastamonu Med J.* 2025;5(3):214.

Received: 17.07.2025 ◆ **Accepted**: 29.07.2025 ◆ **Published**: 03.09.2025

Dear Editor,

We are writing to address an error identified in our recently published article titled "Effects of phantom shocks on anxiety levels, coping skills, and sleep quality in patients with implantable cardioverter/defibrillators" (doi:10.51271/KMJ-0194).

Upon careful review, we have discovered that two references-listed as numbers 19 and 20 in the bibliography-were inadvertently incorrect. While the citations within the main text of the manuscript correctly referred to the intended sources, the corresponding entries in the reference list mistakenly cited unrelated articles.

The corrected references should read as follows:

19. Elenizi K, Alharthi R. Incidence, risk factors and predictors of phantom shocks in patients with implantable cardioverter defibrillators: state-of-the-art review. *Arrhythm Electrophysiol Rev.* 2024;13:e18. doi:10.15420/aer.2024.25

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We sincerely apologize for this unintentional oversight and any confusion it may have caused to readers. Please let us know if any further documentation or procedural steps are required to facilitate the correction.

We remain committed to upholding the highest standards of scholarly accuracy and integrity in the publication process.

Thank you for your understanding and attention to this matter.

Sincerely,

Gözde Yontar

Corresponding Author: Gözde Yontar, gozdeyontar@gmail.com

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