ACTA MEDICA

Volume 56 • Issue 3 • 2025

formerly

Hacettepe Medical Journal

from the seniors to the students

ACTA MEDICA

formerly Hacettepe Medical Journal

www.actamedica.org

Vol 56 • Issue 3 • 2025

online ISSN: 2147-9488

ACTA MEDICA

online ISSN: 2147-9488

www.actamedica.org

Cilt 56, Sayı 3, 2025

Hacettepe Üniversitesi Tıp Fakültesi adına sahibi
Hakan Göker

Sorumlu Yazı İşleri Müdürü
Gözde Yazıcı

Yayının Türü
Yaygın Süreli Yayının

Yayının Şekli
Üç aylık İngilizce

Baş Editör
Gözde Yazıcı
Sevinç Sarınç

Editöryal İletişim
Hacettepe Üniversitesi
Tıp Fakültesi Dekanlığı
06100 Sıhhiye - Ankara
E-posta: editor@actamedica.org

Yayıncı
Hacettepe Üniversitesi
Tıp Fakültesi Dekanlığı
06100 Sıhhiye - Ankara
Telefon: 0 312 305 10 80
Belgeç (faks): 0 312 310 05 80
E-posta: tipmaster@hacettepe.edu.tr

Yayıncılık Hizmetleri
Akdema Bilişim ve Yayıncılık
Telefon: 0 533 166 80 80
E-posta: bilgi@akdema.com
Web: www.akdema.com

ACTA MEDICA

online ISSN: 2147-9488

www.actamedica.org

Vol 56, Issue 3, 2025

Owner on behalf of the Hacettepe Medical School
Hakan Göker

Administrator
Gözde Yazıcı

Publication Type
Peer-reviewed journal

Publication Frequency and Language
Quarterly, English

Editor-in-Chief
Gözde Yazıcı
Sevinç Sarınç

Editorial Office
Hacettepe University
Hacettepe Medical School
06100 Sıhhiye - Ankara
E-mail: editor@actamedica.org

Publisher
Hacettepe University
Hacettepe Medical School
06100 Sıhhiye - Ankara
Phone: +90 312 305 10 80
Fax: 0 312 310 05 80
E-mail: tipmaster@hacettepe.edu.tr

Publishing Services
Akdema Informatics and Publishing
Phone: +90 533 166 80 80
E-mail: bilgi@akdema.com
Web: www.akdema.com

ACTA MEDICA

formerly Hacettepe Medical Journal

Volume 56; Issue 3; 2025

CONTENTS

ORIGINAL ARTICLES

CASE REPORTS

online ISSN: 2147-9488

acta medica

ORIGINAL ARTICLE

Impact of generative artificial intelligence tools on the academic performance of Iraqi medical students in cross-sectional study

Zainab Abdul Ameer Jaafar[1]
ORCID: 0000-0002-8367-3731

Rania H. Al-Taie[1]
ORCID: 0009-0005-2259-0499

Ammar Sameer Mohammed Raoof[2]
ORCID: 0000-0009-2226-2670

Abdallah M. Mujbel[1]
ORCID: 0000-0008-1284-4207

Mohammed S. Al-Sandooq[1]
ORCID: 0000-0009-5470-0401

Mustafa Abdulameer[1]
ORCID: 0000-0001-4193-0402

Abdulrahman Y. Ghaffoori[1]
ORCID: 0009-0009-4285-5676

Fatima Mohamed[1]
ORCID: 0000-0003-0254-5135

[1]Department of Obstetrics and Gynecology, College of Medicine, Al-Mustansiriya University, Baghdad, Iraq

[2]Al-Karama Teaching Hospital, Baghdad, Iraq

Corresponding Author: Rania H. Al-Taie
E-mail: raniahussain03@gmail.com

Received: 27 January 2025, Accepted: 20 June 2025, Published online: 30 September 2025

ABSTRACT

Background: Artificial intelligence (AI) has emerged as a transformative tool in medical education, offering significant potential to enhance student learning and engagement. However, its integration also raises challenges, including over-reliance, ethical concerns, and variability in accuracy.

Objective: This study aims to assess the impact of AI tools on the academic performance, knowledge, attitudes, and practices of medical students in Baghdad, Iraq.

Methods: A cross-sectional survey was conducted among 1,340 undergraduate medical students in Baghdad in 2024. The primary measurement tool was a structured, self-administered questionnaire designed to assess multiple domains. These included demographic characteristics, students' knowledge of artificial intelligence, attitudes toward its application in medical education, and the academic impact of AI tool usage. Knowledge was evaluated through binary-response items, while attitudes were measured using a Likert-scale format to capture perspectives on AI's utility, ethical implications, and future role in medicine. Data were analyzed using SPSS version 25.0, employing frequency tables and chi-square tests to determine associations between variables.

Results: The majority of participants (56.9%) expressed positive attitudes toward AI, and 47% demonstrated adequate knowledge of its applications. Significant associations were observed between AI usage and improvements in subject understanding ($\chi^2 = 15.165$, $p < .001$) and grades ($\chi^2 = 24.808$, $p < .001$). ChatGPT was the most frequently used AI tool (80.8%), followed by Canva (21.3%). Participants highlighted AI's ease of use (85% agreed or strongly agreed) and time-saving benefits (82.8% agreed or strongly agreed), though concerns about reliability and critical thinking persisted.

Conclusion: AI tools have positively influenced the academic outcomes of Iraqi medical students, particularly in subject understanding and grades. However, ensuring ethical and balanced integration of AI into curricula is essential to maximize its potential while addressing limitations.

Keywords: academic performance, artificial intelligence, ChatGPT, cross-sectional study, Iraq, medical education.

INTRODUCTION

Artificial intelligence (AI) plays a key role in higher education and has great implications for the day-to-day and academic lives of students [1]. AI in medical school has numerous benefits that have the potential to transform this learning process. For starters, AI-based technologies have the ability to enhance students' engagement and retention of information through customization of learning. For instance, AI-based writing software gives automatic feedback in grammar, punctuation, and style. This tool greatly enhanced the students' writing quality. Other examples include AI-based adaptive learning platforms, which enable the creation of personally tailored educational content for learners, and automated evaluation systems that streamline assessment processes [2,3]. Preliminary studies have shown that AI tools like ChatGPT can generate valid knowledge in specific disciplines for medical students. Nevertheless, their standardization, reliability, and integrity are yet to be rigorously tested. Moreover, AI simulates the clinical environment, improving critical thinking skills and decision-making [4,5]. These findings indicate that AI has the potential to greatly enhance the educational experience for medical students. With all these benefits, however, there are challenges which face AI upon integration in the area of medical education. For example, it can be limiting as overreliance may hinder independent critical thinking and problem-solving. Accuracy differs for content produced, and so it could further result in real misinformation. Other key concerns related to AI concern ethical matters involving data privacy and potential biases within algorithms. These challenges clearly indicate that what needs to be done with regard to AI in the medical curriculum includes cautious assessment and responsible integration to make it only complementary, not compromising, in the educational process [1,5].

This present study analyze the influence of AI tools on medical students' academic performance, knowledge, attitudes, and practices. It compares groups of students who use AI-based toolkits with the group that applies traditional assessment methods. It also ascertains attitudes towards AI, particularly in relation to its perceived reliability, competence, ease of use, and time efficiency, constructs aligned with the Technology Acceptance Model and goes on to proffer recommendations for optimum usage in the medical education sphere.

METHOD

Study design and population

This investigation employs a cross-sectional survey design to evaluate the academic performance of medical students in 2024, in regards to AI. Undergraduate medical students who were enrolled in these institutions comprised the target population. The Department of Obstetrics and Gynecology at Mustansiriyah University and College of Medicine supervised the study.

Measurements

The questionnaire from this study is designed in such a manner to comprehensively assess the adoption and perception of AI among medical students. The instrument is divided into several key sections. The demographic section is the first part, including items on age, gender, and year of study. Although this section does not have a scored outcome for the learner, it provides a critical contextualization of the responses. The second areas are those that test knowledge about artificial intelligence. This begins with the assessment of whether the respondents have any prior knowledge of AI basics and proceeds to the different generations of AI that they do know. Scoring is based on binary Yes/No-type answers. Every correct identification or acknowledgement adds up to a knowledge score, which shows familiarity with AI. It further goes on to explore the integration of AI into medical education by asking if the respondents have been taught about AI during their undergraduate studies, and what their understanding is regarding data requirements for AI, more specifically labeled data. Added to this is assessing students' understanding of the barriers that exist toward applying artificial intelligence in medical education. These questions are scored both for the degree of formal education in AI that the students have received and for their level of consciousness with the challenges in AI implementation. The assessment of the attitude toward AI is, therefore, critical to understanding

students' perception and attitude toward the role of AI in medical education. This scale has a set of statements rated by the respondents on a five-point Likert scale, ranging from "Strongly Disagree" to "Strongly Agree." The statements query students' beliefs about the necessity of AI education, the potential impact of AI in the medical field and its ethical implications, and what that really means for the future of AI in clinical practice. These responses are summed to provide an overall attitude score, where high scores indicate a more positive or receptive attitude toward AI in relation to the medical field.

The last section is Academic Performance, which seeks to establish the direct effect of AI tool usage on students' results or academic outcomes. This section opens with the main purposes that students use AI tools for. In addition, this section shall aspire to explore any perceived disadvantages of AI. Students are asked to rate the effect of AI tools on their understanding of specific subjects and report any changes in grade after using AI. This section is scored with variables such as the degree of grade improvement and the factors that motivate AI usage, rated on a Likert scale.

Instrument validity and reliability

The questionnaire used in this study was developed based on prior literature and expert consultation in medical education (Supplementary 1). Content validity was ensured through review by a panel of three academic experts in medical education who evaluated the questionnaire for clarity, relevance, and comprehensiveness. To assess reliability, a pilot test was conducted with 10 students from one medical college not included in the final sample.

Data collection procedure

Data were collected through a self-administered online questionnaire using Google Forms between June 2024 to August 2024. The survey link was distributed via official university communication platforms and student WhatsApp groups. Participation was voluntary, and informed consent was obtained at the beginning of the form.

Statistical analysis

The data was analyzed using SPSS version 25.0. We employed frequency tables to visualize the frequencies of the variables.

Ethical approval

This study was reviewed and approved by the Ethics Committee of Mustansiriyah University, College of Medicine. Prior to participation, all students were presented with an online informed consent form embedded at the beginning of the survey. The participant's anonymity and autonomy were prioritized in this observational study. The participant was unable to be identified as the study did not include any names or emails. The privacy of each participant was adequately protected during the course of the investigation. The investigation was conducted in strict adherence to the principles of the Declaration of Helsinki. Before completing the survey, all participants provided informed consent.

RESULTS

The final sample consisted of 1,340 undergraduate medical students from various medical colleges across Iraq, with one incomplete response excluded. The mean age of participants was 21.9 years (SD = 24.1). The gender distribution showed a slightly higher proportion of females (57.9%) compared to males (42.1%). Participants were drawn from more than 30 institutions, with the largest group from Mustansiriyah University (23.6%), followed by the University of Anbar College of Medicine (12.2%) and Baghdad University (5.9%). Regarding academic year, most students were in their 4th year (21.6%), 2nd year (20.1%), or 6th year (20.4%), indicating broad representation across all stages of undergraduate training.

Knowledge scores

The analysis revealed that 53.0% of participants exhibited inadequate knowledge of AI, while 47.0% demonstrated adequate knowledge. Gender-based comparisons showed no significant difference in knowledge scores ($\chi^2 = 2.195$, $p = .138$), with similar distributions of adequate and inadequate knowledge among males and females (Table 1). Significant variations in knowledge levels were observed across universities ($\chi^2 = 61.063$, $p = .001$). Students' knowledge varied significantly across academic years ($\chi^2 = 15.982$, $p = .007$). Higher academic years were associated with increased adequate knowledge scores, particularly among 4th-year students (21.8%) and 6th-year students (20.5%) (Table 2).

Table 1. Gender and knowledge score categories

			Knowledge score categories		Total
			Inadequate knowledge	Adequate knowledge	
Gender	Male	Count	286	279	565
		% of Total	21.3%	20.8%	42.2%
	Female	Count	424	351	775
		% of Total	31.6%	26.2%	57.8%
Total		Count	710	630	1340
		% of Total	53.0%	47.0%	100.0%

Table 2. Knowledge score distribution across academic years

			Knowledge score categories		Total
			Inadequate knowledge	Adequate knowledge	
Academic year	1st year	Count	14	11	25
		% of Total	1.0%	0.8%	1.9%
	2nd year	Count	119	149	268
		% of Total	8.9%	11.1%	20.0%
	3rd year	Count	117	114	231
		% of Total	8.7%	8.5%	17.2%
	4th year	Count	158	134	292
		% of Total	11.8%	10.0%	21.8%
	5th year	Count	153	96	249
		% of Total	11.4%	7.2%	18.6%
	6th year	Count	149	126	275
		% of Total	11.1%	9.4%	20.5%
Total		Count	710	630	1340
		% of Total	53.0%	47.0%	100.0%

Attitudes toward AI

The majority of participants (56.9%) expressed a positive attitude toward AI, with 40.7% remaining neutral and only 2.4% holding negative attitudes. A significant proportion believed AI would revolutionize education (74.3%), though only 7.2% strongly agreed that AI would replace human teachers in the foreseeable future (Figure 1).

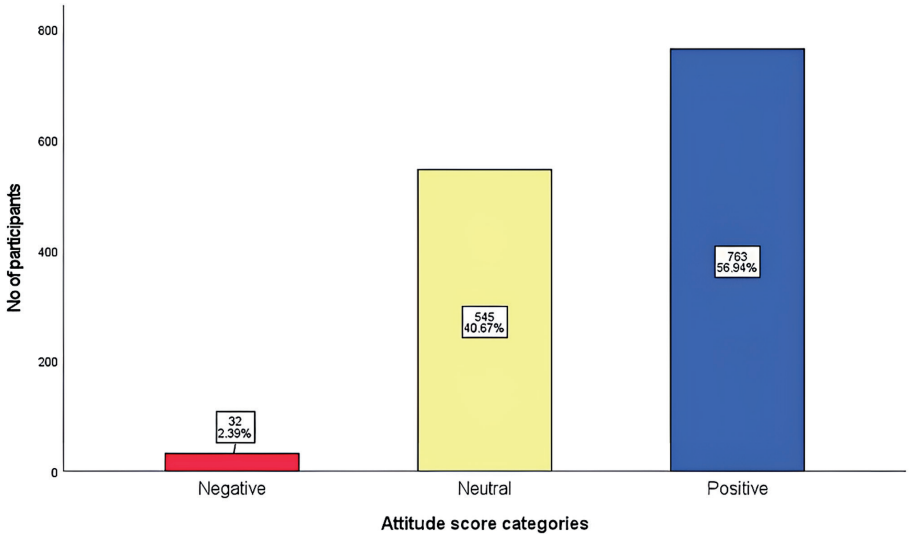


Figure 1. Distribution of participants' attitudes toward AI in medical education

Table 3. Distribution of AI utilization across medical subjects among study participants

		Frequency	Percent
Anatomy	Yes	464	34.6
	No	876	65.4
Physiology	Yes	471	35.1
	No	869	64.9
Biochemistry	Yes	393	29.3
	No	947	70.7
Pharmacology	Yes	343	25.6
	No	997	74.4
Pathology	Yes	334	24.9
	No	1006	75.1
Microbiology	Yes	246	18.4
	No	1094	81.6
Internal medicine	Yes	393	29.3
	No	947	70.7
Surgery	Yes	290	21.6
	No	1050	78.4
Paediatric	Yes	156	11.6
	No	1184	88.4
Obstetrics and gynaecology	Yes	178	13.3
	No	1162	86.7
	Total	1340	100.0

AI usage varied by subject, with the highest reported impacts in anatomy (34.6%), physiology (35.1%), and biochemistry (29.3%). Significant relationships were observed between AI usage and improved knowledge in anatomy ($\chi^2 = 15.165$, $p = .000$), physiology ($\chi^2 = 5.028$, $p = .025$), and biochemistry ($\chi^2 = 7.143$, $p = .008$) (Table 3).

The frequency of AI usage varied, with 33.4% using it sometimes for exam preparation, 24.0% often, and 11.2% all the time. For research purposes, 26.4% often used AI, and 18.4% reported consistent usage (Figure 2).

AI was rated positively for ease of use ($\chi^2 = 18.152$, $p = .001$) and time preservation ($\chi^2 = 8.573$, $p = .073$). While most participants believed AI tools were reliable (36.3% agreed or strongly agreed), 18.1% highlighted issues with accuracy, and 29.9% identified errors needing further verification (Figure 3).

Participants' perceptions of AI tools were evaluated across four dimensions: reliability, competence, ease of use, and time preservation. Regarding reliability, 36.3% of participants either agreed or strongly agreed that AI tools are reliable, whereas 45% remained neutral, and 18.7% expressed disagreement. In terms of competence, 60.2% of participants believed AI tools to be competent, with 17.2% strongly agreeing and 43% agreeing, while 32.9% held a neutral stance. Ease of use emerged as the most positively rated dimension, with 85% of participants agreeing or strongly agreeing that AI tools are easy to use, and 47.2% expressing strong agreement. Similarly, time preservation was highly rated, with 82.8% of participants agreeing or strongly agreeing that AI tools save time, including 47.9% strongly agreeing. These findings indicate that participants generally view AI tools favorably, particularly for their ease of use and efficiency in saving time, though there is a notable proportion of neutrality in reliability and competence evaluations (Table 4).

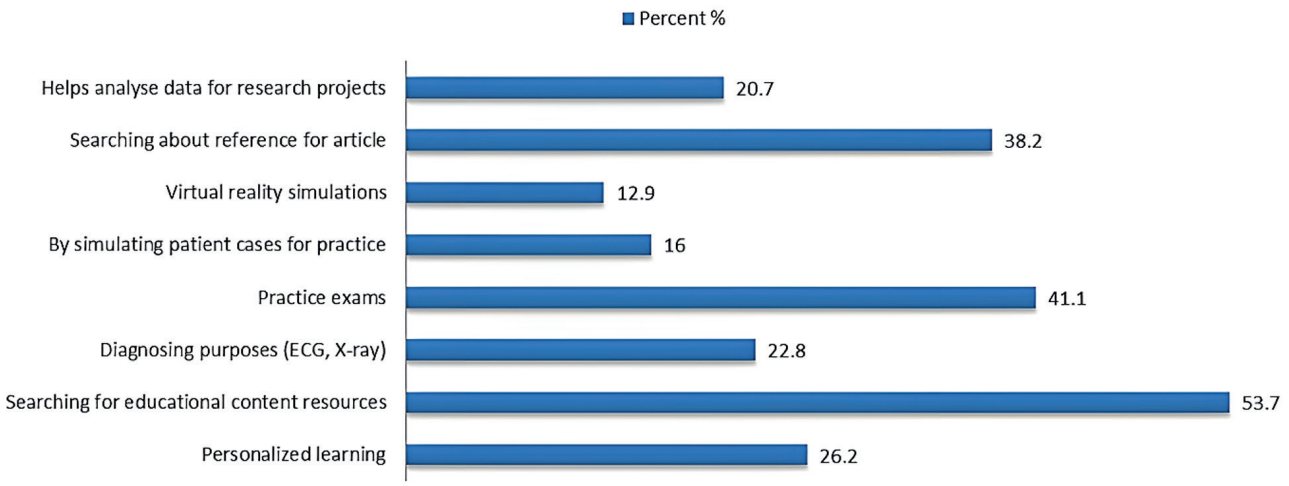


Figure 2. Percentage of AI usage across various academic and clinical applications

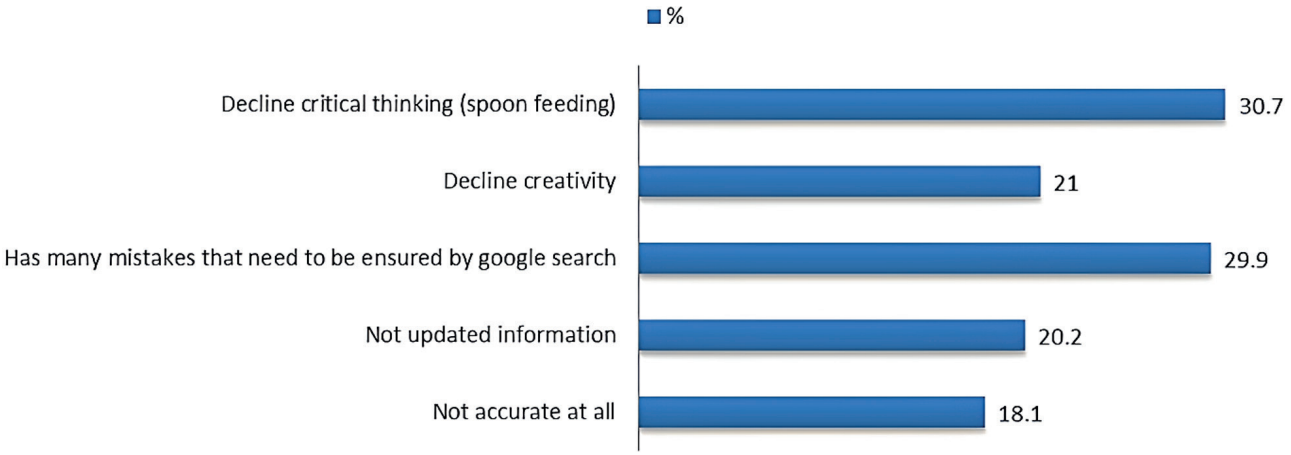


Figure 3. Perceived limitations and concerns of AI usage in academic applications

Table 4. Participants' perceptions of AI tools across key dimensions

		Frequency	Percent
Reliable	Strongly Agree	142	10.6
	Agree	344	25.7
	Neutral	603	45.0
	Disagree	217	16.2
	Strongly disagree	34	2.5
Competent	Strongly Agree	230	17.2
	Agree	576	43.0
	Neutral	441	32.9
	Disagree	74	5.5
	Strongly disagree	19	1.4
Easy to use	Strongly Agree	632	47.2
	Agree	506	37.8
	Neutral	165	12.3
	Disagree	27	2.0
	Strongly disagree	10	.7
Preserve time	Strongly Agree	642	47.9
	Agree	468	34.9
	Neutral	195	14.6
	Disagree	25	1.9
	Strongly disagree	10	0.7
	Total	1340	100.0

Impact of AI tools on academic performance

AI tools had a measurable impact on understanding course subjects, with 39.9% reporting moderate improvement, 24.7% significant improvement, and 5.1% dramatic improvement. A smaller fraction (9.2%) reported no impact. Changes in academic grades were also noted, with 28.3% observing improvement and 8.5% experiencing a decline (χ^2 = 17.254, p = .000). The degree of grade improvement varied, with 28.4% reporting moderate improvement, 7.8% significant improvement, and 2.3% dramatic improvement (χ^2 = 24.808, p = .000) (Table 5). These findings highlight a generally positive impact of AI tools on students' academic outcomes, with variability in the degree of perceived benefits (Table 6, Table 7).

The table highlights the frequency and percentage of participants using various AI tools. ChatGPT was the most commonly used tool, with 80.8% of participants reporting usage. Canva was utilized by 21.3% of participants, while Copilot (11.0%) and Gemini (13.0%) had lower adoption rates. Additionally, 14.7% of participants reported not using any of these tools (Table 8). These findings reflect a strong preference for ChatGPT among participants, with limited use of other AI platforms.

DISCUSSION

The advent of AI in medical education presents a transformative potential, as reflected in this study of Iraqi medical students. Our findings align with and expand upon prior global research, underscoring the nuanced role AI plays in modern medical education.

Our study also showed that more than half of the participants had poor knowledge about AI, though AI is gaining much importance in healthcare and education. This reflects the general trend, as was also pointed out by Al-Qerem et al. [6] and Allam et al. [5], where foundational AI knowledge among medical students is often limited. While this knowledge gap points to an urgent need for structured AI education in medical curricula, the challenges lie in ensuring that such training is accessible, context-

Table 5. The impact of AI tools on understanding of the learning subjects

			Knowledge score categories	
			Inadequate knowledge	Adequate knowledge
Rate the impact of AI tools on your understanding of the subjects you used them for	No impact	Count	86	37
		% of Total	6.4%	2.8%
	Slight improvement	Count	146	138
		% of Total	10.9%	10.3%
	Moderate improvement	Count	279	255
		% of Total	20.8%	19.0%
	Significant improvement	Count	160	171
		% of Total	11.9%	12.8%
	Dramatic improvement	Count	39	29
		% of Total	2.9%	2.2%
Total		Count	710	630
		% of Total	53.0%	47.0%

Table 6. Impact of AI tools on participants' understanding and academic performance

		Frequency	Percent
Rate the impact of AI tools on your understanding of the subjects you used them for	No impact	123	9.2
	Slight improvement	284	21.2
	Moderate improvement	534	39.9
	Significant improvement	331	24.7
	Dramatic improvement	68	5.1
Have you seen changes in your grades in that specific lecture	Improved	379	28.3
	Neutral	847	63.2
	Declined	114	8.5
If your grades have changed, how much was the change?	No impact	448	33.4
	Slight improvement	376	28.1
	Moderate improvement	381	28.4
	Significant improvement	104	7.8
	Dramatic improvement	31	2.3
	Total	1340	100.0

specific, and inclusive of both technical and ethical dimensions. Interestingly, gender-based analysis in our study showed no significant differences in AI knowledge levels, contrasting with some regional findings, such as those reported by Al-Qerem et al. [6], where a slight male predominance in AI knowledge and use was noted. These regional differences may stem from variations in cultural attitudes, exposure to technology, or educational opportunities, emphasizing the need for a tailored approach to integrating AI education in diverse contexts.

The largely optimistic attitudes of participants in the present research are promising, with a vast majority aware of the potential of AI to revolutionize the educational system. Such results agree with the results provided by Jackson et al. [7] and Civaner et al. [8], when students were also optimistic that AI will play a useful role in enhancing efficiencies and reducing errors in medicine. The participants, however, remain skeptical about the possibility of AI replacing the jobs of human doctors, with 37.6% of participants indicating fear of replacement at the workplace. This tallies with the findings of Kansal et al. [9], and Swed et al. [10], where the majority did not agree with the statement that AI will take over human expertise. Ethical implications related to AI confidentiality breaches, loss of patient trust, and dehumanization of care were huge concerns among our respondents. Most of the participants were wary of AI, expressing apprehension that AI may exert an adverse influence on the physician-patient relationship. Evidence of such results can

Table 7. Association between AI tool usage and academic outcomes: understanding, grades, and magnitude of change

Category	Negative	Neutral	Positive	Total
Impact of AI Tools				
No Impact	8 (0.6%)	57 (4.3%)	58 (4.3%)	123 (9.2%)
Slight Improvement	9 (0.7%)	126 (9.4%)	149 (11.1%)	284 (21.2%)
Moderate Improvement	12 (0.9%)	232 (17.3%)	290 (21.6%)	534 (39.9%)
Significant Improvement	2 (0.1%)	109 (8.1%)	220 (16.4%)	331 (24.7%)
Dramatic Improvement	1 (0.1%)	21 (1.6%)	46 (3.4%)	68 (5.1%)
Change in Grades				
Improved	6 (0.4%)	109 (8.1%)	264 (19.7%)	379 (28.3%)
Neutral	17 (1.3%)	385 (28.7%)	445 (33.2%)	847 (63.2%)
Declined	9 (0.7%)	51 (3.8%)	54 (4.0%)	114 (8.5%)
Magnitude of Change				
No Impact	18 (1.3%)	224 (16.7%)	206 (15.4%)	448 (33.4%)
Slight Improvement	4 (0.3%)	145 (10.8%)	227 (16.9%)	376 (28.1%)
Moderate Improvement	5 (0.4%)	132 (9.9%)	244 (18.2%)	381 (28.4%)
Significant Improvement	2 (0.1%)	31 (2.3%)	71 (5.3%)	104 (7.8%)
Dramatic Improvement	3 (0.2%)	13 (1.0%)	15 (1.1%)	31 (2.3%)
Total	32 (2.4%)	545 (40.7%)	763 (56.9%)	1340 (100.0%)

Table 8. Frequency and percentage of AI tool usage among participants

		Frequency	Percent
ChatGPT	Yes	1083	80.8
	No	257	19.2
Copilot	Yes	148	11.0
	No	1192	89.0
Canva	Yes	285	21.3
	No	1055	78.7
Gemini	Yes	174	13.0
	No	1166	87.0
None of them	Yes	197	14.7
	No	1143	85.3
	Total	1340	100.0

be represented in Jackson et al. [7] and Civaner et al. [8]. These concerns underscore the importance of embedding ethical training within AI-related education to equip future professionals with the skills needed to navigate these challenges responsibly.

A high number of participants also noted improvements in the understanding of course content with the help of AI tools, most notably in anatomy and physiology. This corroborates Stogiannos et al.' [11] results, who noted AI's ability to improve comprehension of key concepts in medicine via adaptive learning tools and virtual simulation. However, the use of AI for more complex clinical applications, such as patient simulations and diagnostic training, remains underutilized, pointing to an opportunity for future innovation. Interesting to note here that these uses turned out to be skewed toward more practical and accessible areas, like grammar checking and basic research support, as seen in Al-Qerem et al. [6]. In other words, this would mean that while AI related to advanced clinical and judgment areas is talked about, its practical application may turn out to be far from reality, either because it has not been adequately trained in the field or the access route to such an advanced tool is obscure. This gap could be minimized, for example, by subjecting students to AI-powered clinical scenarios and decision-support systems. Despite its benefits, AI's integration into education raises important concerns. In our study, 30.7% of participants believed over-reliance on AI could inhibit critical thinking, a sentiment mirrored by Jackson et al. [7] and Sarwar et al. [12]. This highlights the delicate balance required in leveraging AI as an aid rather than a replacement for traditional learning methods. AI should augment rather than undermine the

development of problem-solving skills, creativity, and clinical judgment. This cross-sectional design precludes the possibility of determining causality or evaluating the longitudinal effects. Furthermore, the fact that the data comes from self-reported responses predisposes it to biases, including social desirability or overestimation of the benefits of AI. Future studies should overcome such limitations by using longitudinal designs and, via the use of survey triangulation.

The findings of this study highlight the urgent need to integrate AI into medical curricula—not only as a technical tool but as a subject of ethical and clinical significance. As emphasized by Knopp et al. [13], ethical oversight and responsible adoption are essential as AI reshapes medical education. Structured training should include hands-on, interdisciplinary approaches, supported by Fatima et al. [14], who advocate for AI-driven, project-based learning to build real-world skills. Access disparities must also be addressed. Muhammad and Orji [15] stress that democratizing AI tools is vital to ensure equitable educational outcomes, particularly in under-resourced settings. Furthermore, Lu et al. [16] argue that AI ethics, including data privacy, algorithmic bias, and patient autonomy, must become a core part of medical training to prepare students for complex decision-making in digital healthcare.

A recent study by Murad [17] offers valuable initial insights into the perceptions of Iraqi medical students toward artificial intelligence, highlighting strong interest in AI and a recognized need for educational integration. Building on this foundational work, our study expands the scope by incorporating a larger, more diverse national sample and examining not only attitudes but also knowledge, usage patterns, and self-reported academic impact. To our knowledge, this makes the present study among the first comprehensive, multi-institutional analyses of AI in undergraduate medical education in Iraq, offering practical insights to inform curricular reform and policy.

Limitations

This study has several limitations. First, its cross-sectional design prevents causal inferences about the long-term impact of AI tools on academic performance. Second, the reliance on self-reported data introduces potential biases, including social desirability and recall bias. Lastly, the measurement tool, while piloted and expert-reviewed, may not fully capture the nuanced competencies and ethical reasoning required for effective AI integration in clinical practice.

CONCLUSION

This research has justified the significant impact of AI tools on students' academic performances and their perception at medical schools in Baghdad, Iraq. In fact, AI tools, particularly ChatGPT, are considered to be taken into great account in developing understanding in medical subjects and academic grades considerably. While most of the participants had presented a positive approach toward AI, a large number had also raised certain challenges like over reliability, ethics, and un reliability. Future research should explore longitudinal impacts of AI integration, focus on its role in clinical training, and evaluate methods to mitigate its limitations. By fostering a thoughtful, ethical, and inclusive approach to AI in education, medical institutions can unlock its full potential to enhance learning outcomes and prepare students for the evolving demands of the healthcare field.

Author contribution

Study conception and design: ZAAJ and RHA-T; data collection: AMM, MSS, MA, AY Gh, FM, and RHA-T; analysis and interpretation of results: ASMR; draft manuscript preparation: AMM, MSS, MA, AY Gh, FM, and RHA-T. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ethics Committee of Mustansiriyah University, College of Medicine.

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Chen L, Chen P, Lin Z. Artificial intelligence in education: A review. IEEE Access 2020;8:75264-75278. https://doi.org/10.1109/ACCESS.2020.2988510

[2] Temsah O, Khan SA, Chaiah Y, et al. Overview of early ChatGPT's presence in medical literature: Insights from a hybrid literature review by ChatGPT and human experts. Cureus 2023;15(4):e37281. https://doi.org/10.7759/cureus.37281

[3] Lee J, Wu AS, Li D, Kulasegaram KM. Artificial intelligence in undergraduate medical education: A scoping review. Acad Med 2021;96(11S):S62-S70. https://doi.org/10.1097/ACM.0000000000004291

[4] Allam AH, Eltewacy NK, Alabdallat YJ, et al. Knowledge, attitude, and perception of Arab medical students towards artificial intelligence in medicine and radiology: A multi-national cross-sectional study. Eur Radiol 2024;34(7):1-14. https://doi.org/10.1007/s00330-023-10509-2

[5] Alam F, Lim MA, Zulkipli IN. Integrating AI in medical education: Embracing ethical usage and critical understanding. Front Med (Lausanne) 2023;10:1279707. https://doi.org/10.3389/fmed.2023.1279707

[6] Al-Qerem W, Eberhardt J, Jarab A, et al. Exploring knowledge, attitudes, and practices towards artificial intelligence among health professions' students in Jordan. BMC Med Inform Decis Mak 2023;23(1):288. https://doi.org/10.1186/s12911-023-02403-0

[7] Jackson P, Ponath Sukumaran G, Babu C, et al. Artificial intelligence in medical education-perception among medical students. BMC Med Educ 2024;24(1):804. https://doi.org/10.1186/s12909-024-05760-0

[8] Civaner MM, Uncu Y, Bulut F, Chalil EG, Tatli A. Artificial intelligence in medical education: A cross-sectional needs assessment. BMC Med Educ 2022;22(1):772. https://doi.org/10.1186/s12909-022-03852-3

[9] Kansal R, Bawa A, Bansal A, et al. Differences in knowledge and perspectives on the usage of artificial intelligence among doctors and medical students of a developing country: A cross-sectional study. Cureus 2022;14(1):e21434. https://doi.org/10.7759/cureus.21434

[10] Swed S, Alibrahim H, Elkalagi NKH, et al. Knowledge, attitude, and practice of artificial intelligence among doctors and medical students in Syria: A cross-sectional online survey. Front Artif Intell 2022;5:1011524. https://doi.org/10.3389/frai.2022.1011524

[11] Stogiannos N, O'Regan T, Scurr E, et al. Lessons on AI implementation from senior clinical practitioners: An exploratory qualitative study in medical imaging and radiotherapy in the UK. J Med Imaging Radiat Sci 2025;56(1):101797. https://doi.org/10.1016/j.jmir.2024.101797

[12] Sarwar S, Dent A, Faust K, et al. Physician perspectives on integration of artificial intelligence into diagnostic pathology. NPJ Digit Med 2019;2:28. https://doi.org/10.1038/s41746-019-0106-0

[13] Knopp MI, Warm EJ, Weber D, et al. AI-enabled medical education: Threads of change, promising futures, and risky realities across four potential future worlds. JMIR Med Educ 2023;9:e50373. https://doi.org/10.2196/50373

[14] Fatima SS, Sheikh NA, Osama A. Authentic assessment in medical education: Exploring AI integration and student-as-partners collaboration. Postgrad Med J 2024;100(1190):959-967. https://doi.org/10.1093/postmj/qgae088

[15] Muhammad F, Orji CM. Revolutionizing education in the digital era: The role of AI in promoting inclusivity, equality, and ethical innovation. The American Journal of Social Science and Education Innovations 2024;6(9):151-157. https://doi.org/10.37547/tajssei/Volume06Issue09-16

[16] Lu H, Alhaskawi A, Dong Y, et al. Patient autonomy in medical education: Navigating ethical challenges in the age of artificial intelligence. Inquiry 2024;61:469580241266364. https://doi.org/10.1177/00469580241266364

[17] Murad H. Artificial intellegence in the future of Iraqi healthcare system. Journal of Informatics, Network, and Computer Science 2024;7(1):1-8. https://doi.org/10.21070/joincs.v7i1.1635

Supplementary 1. Questionnaire on AI Use in Medical Education

Section 1: Demographics

1. Age:

[Open response]

2. Gender:

☐ Male

☐ Female

3. University: (Select one)

Baghdad University

Al-Kindy College, University of Baghdad

Mustansiriyah University

Nahrain University

Iraqia University

Ibn Sina University

University of Fallujah College of Medicine

University of Anbar College of Medicine

University of Tikrit College of Medicine

University of Babylon College of Medicine

University of Babylon College of Medicine Hammurabi

University of Karbala College of Medicine

University of Kufa College of Medicine

Jabir ibn Hayyan University College of Medicine

University of Mosul College of Medicine

University of Nineveh College of Medicine

University of Kirkuk College of Medicine

University of Wasit College of Medicine

University of Maysan College of Medicine

University of ThiQar College of Medicine

University of Sumer College of Medicine

University of Muthanna College of Medicine

University of Qadisiya College of Medicine

University of Basra College of Medicine

Al-Zahraa College of Medicine, University of Basra

University of Diyala College of Medicine

University of Sulaymaniyah College of Medicine

University of Warith Al-Anbiyaa College of Medicine

University of Ameer College of Medicine

University of Al-Ain College of Medicine

University of Hawler College of Medicine

University of Dohuk Faculty of Medicine

4. Academic Year:

☐ 1st Year

☐ 2nd Year

☐ 3rd Year

☐ 4th Year

☐ 5th Year

☐ 6th Year

Section 2: Knowledge Assessment

5. Do you have a solid knowledge of the basics of AI?

☐ Yes

☐ No

6. Do you know what type of generation of AI (Rule-based, ML, DL, RL)?

☐ Yes

☐ No

7. Do you know any application of AI in your field of interest (e.g., medicine)?

☐ Yes

☐ No

Section 3: AI Usage and Exposure

8. Which AI tools do you use most frequently in your academic activities? (Select all that apply)

☐ ChatGPT

☐ Copilot

☐ Canva

☐ Gemini

☐ None of the above

9. Have you attended any online/offline courses regarding AI?

☐ Yes

☐ No

10. Name the AI program you use most frequently:

[Open response]

11. Have you ever been taught about AI in your undergraduate studies?

☐ Yes

☐ No

12. AI requires a lot of labeled data to learn.

☐ Yes

☐ No

13. I understand the barriers to applying AI in medicine.

☐ Yes

☐ No

Section 4: Attitude Assessment

14. Healthcare students should learn the basics of AI.

15. AI will be a highly required tool in my field.

16. Ethical implications of AI must be understood by all students.

17. AI will revolutionize the educational system.

18. Human teachers will be replaced in the foreseeable future.

19. I'm excited about upcoming changes in education due to AI.

20. AI should be part of the training system in medical fields.

21. Clinical AI will be more accurate than physicians.

22. Some specialties are more prone to be replaced by AI.

23. AI could increase errors in diagnosis.

Response options for all above:

☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

Section 5: Frequency of AI Use

24. How frequently do you use AI to prepare for exams?

25. …for homework/assignments?

26. …for research?

27. …for idea generation and brainstorming?

28. …for personal choices/career guidance?

29. …for spelling and grammar checking?

30. …for personality development or other skills?

Response options for all above:

☐ All the time ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

Section 6: Academic Performance and AI Perception

31. For what purposes do you use AI in your studies? (Select all that apply)

☐ Personalized learning

☐ Searching for content

☐ Diagnosing (ECG, X-ray)

☐ Practice exams

☐ Simulating patient cases

☐ Virtual reality

☐ Searching for references

☐ Analyzing data

☐ Standardizing guidelines

☐ Other: [Open field]

32. What are the disadvantages of AI in your studies? (Select all that apply)

☐ Inaccurate information

☐ Not updated

☐ Requires validation

☐ Reduces creativity

☐ Reduces critical thinking

33. Impact of AI on understanding subjects used for:

☐ No impact ☐ Slight ☐ Moderate ☐ Significant ☐ Dramatic

34. For which subjects have you used AI? (Select all that apply)

☐ Anatomy ☐ Physiology ☐ Biochemistry ☐ Pharmacology

☐ Pathology ☐ Microbiology ☐ Internal Medicine

☐ Surgery ☐ Pediatrics ☐ Obstetrics/Gynecology

☐ I did not use AI at all

35. Have you seen changes in your grades in these lectures?

☐ Improved ☐ Neutral ☐ Declined

36. If grades changed, how much?

☐ No impact ☐ Slight ☐ Moderate ☐ Significant ☐ Dramatic

37. In your opinion, what makes you use AI?

Rate the following:

• Reliable

• Competent

• Easy to use

• Time-saving

Response options:

☐ Strongly Disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly Agree

acta medica

ORIGINAL ARTICLE

In silico prediction of rhabdomyolysis-inducing drugs utilizing a supervised machine learning model

Feyza Kelleci Çelik[1]
ORCID: 0000-0003-4874-6648

ABSTRACT

Objective: Rhabdomyolysis is a life-threatening syndrome characterized by the release of myocyte components into the bloodstream and can be induced by pharmaceutical agents. Although quantitative structure-activity relationship (QSAR) models are widely used for assessing adverse drug reactions, studies in computational toxicology focusing on rare and serious side effects, such as rhabdomyolysis, are still relatively limited. Due to this gap, this study aims to build an *in silico* QSAR model for early prediction of drugs at risk of rhabdomyolysis.

Materials and Methods: A binary dataset was developed by gathering 187 pharmaceutical compounds from the Drug-Induced Rhabdomyolysis Atlas (DIRA), and classification models were developed in the research. Machine learning (ML) algorithms, such as Instance-Based Learning with k-Nearest Neighbors (IBk), Simple Logistic (SL), and BayesNet (BN), were employed. Additionally, post-hoc model explanations and importance rankings of molecular descriptors were provided using Permutation Feature Importance (PFI).

Result: The performances of the ML classifiers ranged from 82.00% to 85.33% in the training set and from 75.67% to 81.08% in the test set. The highest success rate for the test set was achieved by the IBk model, with a rate of 81.08%. The most significant feature in the post-hoc IBk model explanation using PFI was highlighted as the JGI6 descriptor. The descriptor class with the most identifiers was the Electrotopological State Atom Type (E-State) Descriptors.

Conclusion: The physicochemical properties presented in this study regarding rhabdomyolysis and the developed models are anticipated to serve as effective tools for assessing the risk of rhabdomyolysis in drug molecules.

Keywords: machine learning, pharmaceutical toxicology, QSAR, rhabdomyolysis

[1]Karamanoğlu Mehmetbey University, Vocational School of Health Services, Karaman, Türkiye

Corresponding Author: Feyza Kelleci Çelik
E-mail: feyza-kelleci@hotmail.com

Received: 26 April 2025, Accepted: 7 July 2025,
Published online: 30 September 2025

INTRODUCTION

Rhabdomyolysis is a clinical syndrome characterized by the release of intracellular elements, including myoglobin, electrolytes, aldolase, and creatine kinase (CK), into the bloodstream as a result of acute or subacute damage to striated muscle [1,2]. Without prompt and aggressive interventions [3], fatal complications may occur, including acute renal failure [4], cardiac arrhythmia, intravascular coagulation [2], and acute muscle necrosis. Additionally, clinical signs such as limb weakness, myalgias, fever, leukocytosis, dark urine, and myoglobinuria may also develop [5]. The factors causing rhabdomyolysis are categorized into two main groups: hereditary and acquired. The acquired causes are further divided into traumatic and non-traumatic types. The most prevalent non-traumatic factors include the use of pharmaceuticals. Approximately 150 pharmaceutical compounds have been identified as causes of rhabdomyolysis [1], including various pharmacological groups such as psychoactive drugs [6], selective serotonin reuptake inhibitors [7], statins [8], antihistamines, and antidepressants [9]. In this regard, the Drug-Induced Rhabdomyolysis Atlas (DIRA), a web-based application, was developed to ensure safe drug use without causing rhabdomyolysis. The DIRA presents a classification framework based on drug labeling information provided by the Food and Drug Administration (FDA). This framework classifies drugs into four classes based on their risk of causing rhabdomyolysis (DIR) [8].

Currently, quantitative structure-activity relationship (QSAR), a computational method used in drug development, serves as an essential tool for evaluating potential drug side effects. These computational models can predict possible toxicity profiles by analyzing the structural features of compounds. Based on machine learning (ML) algorithms, QSAR models analyze the information obtained from the input dataset and provide faster, ethical, and cost-effective results compared to traditional laboratory tests [10,11].

Despite the numerous [ITALIC]in silico[/ITALIC] studies in the literature concerning the toxic effects of pharmaceuticals, predictive models assessing the rhabdomyolysis risk remain relatively limited [12-14]. This study focused on predicting rare but life-threatening DIR risk using QSAR models. The dataset was collected from the DIRA, which contains 187 active pharmaceutical ingredients presented by Wen et al. to support developing new methodologies for addressing the rhabdomyolysis side effect [8]. The present study focused on the potential of pharmaceuticals to induce rhabdomyolysis rather than assessing varying degrees of risk. For this purpose, drugs with varying hazard levels in DIRA were grouped together, whereas safe drugs with no rhabdomyolysis risk were classified separately. Thus, the drug status was evaluated as binary: "induces rhabdomyolysis" or "does not induce rhabdomyolysis". In the current study, classification-based QSAR models were created as binary, and the Permutation Feature Importance (PFI) method was employed to improve the model's explainability and prioritize the descriptors. These models enable the early identification of rhabdomyolysis risk for a molecule with an unclear side effect profile during the initial phases of drug development. Furthermore, the prioritized descriptors guide which physicochemical properties need to be modified. Thus, optimizing molecular descriptors may prevent or reduce the risk of rhabdomyolysis. These QSAR models can enhance the management of side effect profiles for pharmaceuticals, resulting in safer and more sustainable drug development.

MATERIALS AND METHODS

Data collection, curation, and preparation

The dataset comprised 187 orally or parenterally administered pharmaceuticals for human use, split into two groups: DIR-positive (n=147) and DIR-negative (n=40) (Table S1). All individual molecules were collected from the FDA-based DIRA website [8]. The molecular characteristics were gathered from two-dimensional structure data files (2D-SDFs) [15]. Then, the open-source PaDEL tool was used to generate the descriptors. The software currently calculates 1444 2D physicochemical properties of the molecules [16].

Data curation and preparation are crucial processes for converting raw data into a suitable format for modeling. The steps include cleaning, instance reduction, attribute selection, data transformation, and data partitioning [17]. This research utilized

Python 3.9.5 [18] and WEKA 3.9.5 [19] to prepare the raw data. WEKA 3.9.5 is an open source software package used for data mining and machine learning applications [19]. Raw 2D-SDFs were initially analyzed, and then corrupted data was removed. Noisy and duplicate data were removed.

The attribute selection process finds the optimal descriptor set with the highest correlation with the specific target variable [20]. This study utilized the CfsSubsetEval-Best First method in WEKA 3.9.5 [19] to select a relevant subset of features for model construction.

To mitigate the impact of large values on smaller ones, the data are scaled using a suitable scaling method during the data transformation step. We employed the popular Min-Max scaling approach [16]. After scaling the data, the analysis set was randomly divided into training (80%, n=150) and test sets (20%, n=37) (Table 1).

Table 1. Composition of the training and test sets

	Dataset (n=187)	
	Training set (80%, n=150)	**Test set (20%, n=37)**
DIR-positive	120	27
DIR-negative	30	10

n: number of molecules; DIR: drug-induced rhabdomyolysis

Development and validation of the models

The three ML algorithms—Instance-Based Learning with k-Nearest Neighbors (IBk) [21], Simple Logistic (SL) [22], and BayesNet (BN) [23]—were employed to construct binary-QSAR models based on the selected optimal identifiers. IBk is grounded in instance-based classification, relying on k-nearest neighbour methods for prediction. Instead of constructing a general model, it retains all training instances and classifies new inputs based on the majority class among the k nearest examples, determined by a distance metric [21]. SL is a classification algorithm that builds logistic regression models using the LogitBoost technique. It incrementally adds base learners to minimize logistic loss, resulting in a probabilistic model suitable for both binary and multi-class problems [22]. BN employs a directed acyclic graph to represent a probabilistic model, illustrating the relationships between random variables and their conditional dependencies. Its fundamental mathematical foundation is based on Bayes' theorem [23].

The k-fold cross-validation technique is used for validating the training set. This technique divides the data set into k equal parts, using each part as a validation set while the remaining parts are used to train the model. Repeating the process k times measures the model's generalization ability and reduces the risk of overfitting [24]. The 10-fold cross-validation method was employed in the study. Additionally, an independent test set was used for external validation to assess the model's performance.

This research employed the Topliss ratio, as recommended by the OECD, for validation in drug modeling studies. The ratio is key in assessing the model's reliability [24]. For a model to be considered validated under this criterion, the Topliss ratio must exceed 5 [25].

The model's performance was evaluated using the true positive (TP), true negative (TN), false positive (FP), and false negative (FN) components of the confusion matrix. Performance metrics, including accuracy (ACC), specificity (SP), sensitivity (SE), F-score, and Matthews correlation coefficient (MCC), were computed using the confusion matrix elements. The metrics were calculated using equations (1) through (5), as shown below.

Accuracy (ACC)

$$ACC = \frac{TP + TN}{TP + TN + FP + FN}. \quad (1)$$

Specificity (SP)

$$SP = \frac{TN}{TN + FP}. \quad (2)$$

Sensitivity (SE)

$$SE = \frac{TP}{TP + FN}. \quad (3)$$

F-score

$$F - score = \frac{2\,x\,TP}{2\,x\,TP + FP + FN}. \quad (4)$$

Matthews correlation coefficient (MCC)

$$MCC = \frac{TP\,x\,TN - FP\,x\,FN}{\sqrt{(TP + FP)(TP + FN)(TN + FP)(TN + FN)}}. \quad (5)$$

The Organisation for Economic Co-operation and Development (OECD) has established a framework of rules to ensure the applicability of models to different chemical structures. In this context, defining an applicability domain (AD) is essential. This domain sets the boundaries for the structures

to which the model can provide accurate and reliable predictions. The Tanimoto index [26] and chemical space analysis [24] were employed to establish a well-defined AD in this research. The Tanimoto index measures chemical diversity, with values ranging from 0 to 1. An index closes to 0 indicates a high degree of diversity, while one close to 1 indicates a high degree of similarity [26]. The chemical space analysis shows the distribution of the test and training sets in chemical space [24].

Post-Hoc explainability of the models

The OECD guidance on QSAR models encourages improving model explainability to increase reliability [24]. The PFI analysis from the model-agnostic methods is widely employed to explain decisions made by black-box models. The PFI method quantifies the effect of each feature on the predictive accuracy. To understand the effect on the model's performance, the values of a specific feature are randomly mixed, and the change in the accuracy is measured. This analysis enhances the clarity of the complex estimation processes [27].

RESULTS

Selected molecular descriptors

1444 2D descriptors were calculated by the open-source PaDEL tool [16]. After this process, the best 24 2D descriptors were selected using the CfsSubsetEval filter+BestFirst search method. Consequently, we created prediction models utilizing the 24 optimal descriptors (Table 2) to enhance modeling success.

Table 2. The selected molecular descriptors

No	Descriptor	Description	Descriptor Class
1.	JGI6	Mean topological charge index of order 6	Topological Charge Descriptor
2.	GGI7	Topological charge index of order 7	
3.	maxsOH	Maximum atom-type E-State: -OH	Electrotopological State Atom Type (E-State) Descriptor
4.	hmin	Minimum H E-State	
5.	minHBint10	Minimum E-State descriptors of strength for potential Hydrogen Bonds of path length 10	
6.	minHBint5	Minimum E-State descriptors of strength for potential Hydrogen Bonds of path length 5	
7.	DELS	Sum of all atoms intrinsic state differences	
8.	maxHCsats	Maximum atom-type H E-State: H bonded to B, Si, P, Ge, As, Se, Sn or Pb	
9.	naaS	Count of atom-type E-State: aSa	
10.	MATS4s	Moran autocorrelation - lag 4 / weighted by I-state	Autocorrelation Descriptor
11.	MATS2c	Moran autocorrelation - lag 2 / weighted by charges	
12.	ATSC8p	Centered Broto-Moreau autocorrelation - lag 8 / weighted by polarizabilities	
13.	MIC3	Modified information content index (neighborhood symmetry of 3-order)	Information Content Descriptor
14.	MIC2	Modified information content index (neighborhood symmetry of 2-order)	
15.	VE3_D	Logarithmic coefficient sum of the last eigenvector from detour matrix	Detour Matrix Descriptor
16.	VE3_Dt	Logarithmic coefficient sum of the last eigenvector from detour matrix	
17.	VE2_Dzp	Average coefficient sum of the last eigenvector from Barysz matrix / weighted by polarizabilities	Barysz Matrix Descriptor
18.	VE3_DzZ	Logarithmic coefficient sum of the last eigenvector from Barysz matrix / weighted by atomic number	
19.	VC-3	Valence cluster, order 3	Chi Cluster Descriptor
20.	SCH-5	Simple chain, order 5	Chi Chain Descriptor
21.	nF9Ring	Number of 9-membered fused rings	Ring Count Descriptor
22.	nAtomLAC	Number of atoms in the longest aliphatic chain	Longest Aliphatic Chain Descriptor
23.	WTPT-5	Sum of path lengths starting from nitrogens	Weighted Path Descriptor
24.	SpMin7_Bhm	Smallest absolute eigenvalue of Burden modified matrix - n 7 / weighted by relative mass	Burden Modified Eigenvalues Descriptor

Table 3. Performance measurements of the classifiers

	IBk		SL		BN	
	Training	**Test**	**Training**	**Test**	**Training**	**Test**
ACC %	84.00	81.08	85.33	78.38	82.00	75.67
SP	0.833	0.806	0.844	0.773	0.855	0.732
SE	0.840	0.811	0.853	0.784	0.820	0.757
F-score	0.936	0.808	0.847	0.776	0.831	0.727
MCC	0.476	0.506	0.509	0.420	0.531	0.293

IBk: Instance-Based Learning with k-Nearest Neighbors; SL: Simple logistic; BN: BayesNet; ACC: Accuracy; SP: Specificity; SE: Sensitivity; MCC: Matthews correlation coefficient.

Evaluation of the model performance

In the current study, the IBk [21], SL [22], and BN [23] algorithms were used to construct QSAR models due to their highest performance. The ACC, SP, SE, F-score, and MCC metrics were computed for each algorithm. The internal and external validation outcomes were analyzed to assess the performance (Table 3).

The classifiers' performances were recorded with values ranging from 82.00% to 85.33% in the training set and from 75.67% to 81.08% in the test set. The model has been trained using the training dataset, and the observed performance reflects its capability and consistent learning from the training data. In this study, the 10-fold cross-validation technique was preferred for internal validation. The k-fold cross-validation assesses training performance by dividing the data into several subgroups. The approach guarantees strong predictive performance and versatility across different chemical domains for the model [28]. The test set is a dataset that is excluded from the training process, serving to evaluate the model's ability to generalize. The model's final performance evaluation is conducted on the test set. In the current model, the IBk algorithm demonstrated the highest success rate on the test set (81.08%), along with all other evaluated metrics. The values of 0.806 and 0.811 for SP and SE, respectively, indicate the model's high capability for true negative and true positive rates. The results from the internal and external validation processes demonstrated the IBk model's high generalization capability and reliability. Specifically, the ACC rates for the training and test sets indicated that the IBk model achieved consistent success, with rates of 84.00% and 81.08%, respectively. This consistency enhances the model's ability to prevent overfitting and adapt to new real-world data. The findings indicate that the IBk model effectively distinguishes between DIR-positive and DIR-negative compounds, demonstrating its robust predictive capabilities.

Calculating the Topliss ratio is crucial in validating the QSAR model [24]. The proposed models met the validity criteria, achieving a Topliss ratio of 7.8, based on 187 compounds and 24 descriptors. Based on this result, overfitting appears to be prevented.

We performed analyses of the Tanimoto similarity index [26] and chemical space distribution [24] to establish a reliable AD area for ensuring model robustness. The average Tanimoto scores for the training and test datasets were recorded as 0.3739 and 0.4070, respectively. These scores indicate chemical diversity and AD compatibility within the datasets. Molecular weight (MW) and Ghose-Crippen LogKow (ALogP) values were utilized to analyze the distribution of chemical space (Figure 1). The MW values of the molecules ranged from 131.0946 to 2637.0983 g/mol, while their ALogP values were from -26.7021 to 3.8871. This visualization confirmed that the test set components were adequately included in the chemical domain of the training set.

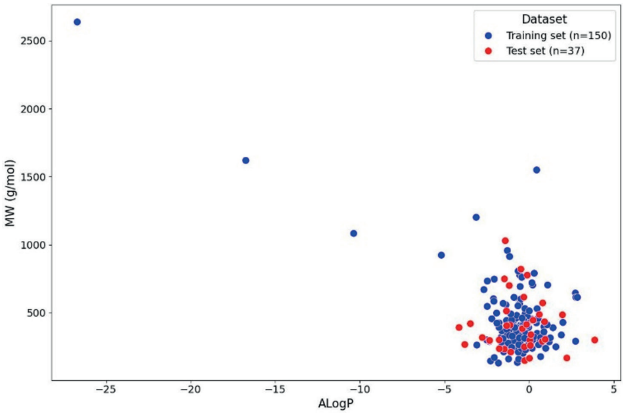


Figure 1. Distribution analysis in chemical space

(n: number of molecules; MW: Molecular Weight; AlogP: Ghose-Crippen LogKow)

These techniques enhanced the current model's validity and clarified AD's boundaries. The IBk model shows promise in producing robust and reliable predictions across various chemical domains. These findings support the selection of the IBk algorithm to ensure inter-class consistency.

Explanation of the top-performing model

The top-performing IBk model was explained using PFI analysis (Figure 2). The graph's vertical axis (Y-axis) lists the features utilized by the model, arranged from bottom to top according to increasing relative importance—features positioned higher have a greater effect on the model's predictions. The horizontal axis (X-axis) indicates the importance score attributed to each feature within the model. This score is computed by assessing the decrease in model accuracy when the values of a particular feature are randomly permuted. Variables with higher values along the X-axis strongly influence the model's decisions. Variables near zero minimally affect model predictions. This analysis highlights the features exerting the greatest influence on predictions [27].

The most significant descriptor for the IBk model is JGI6, followed by maxsOH, MATS4s, and nAtomLAC. Next, MATS2c, MIC3, and MIC2 show equal influence. After these, VC-3 and SpMin7_Bhm yield similar effects. Following this are VE3_D and maxHCsats, which also exhibit comparable impacts. Then, WTPT-5 and SCH-5 rank similarly in their effects. Next is hmin, followed by minHBint10. Additionally, minHBint5, DELS, and VE2_Dzp share equal importance, trailing behind nF9Ring. Following these are naaS, VE3_Dt, and VE3_DzZ, which indicate equal impact. Lastly, GGI7 and ATSC8p are noted as having a negligible effect.

DISCUSSION

The majority of the descriptors in the model belong to the Electrotopological State Atom Type (E-State) Feature class (maxsOH, maxHCsats, hmin, minHBint10, minHBint5, DELS, and naaS). The E-state index encodes both electronic and topological information at the atomic and sub-molecular levels [29]. This class plays a crucial role in identifying functional regions of molecules with potential pharmacophore or toxicophore properties. The capability to evaluate electronic structures and topological properties via a comprehensive approach has established E-state indices as a crucial instrument for QSAR analyses [30]. Our model's descriptors mainly consist of E-state indices consistent with the chemoinformatics literature. This model contains three descriptors from the Autocorrelation Descriptor class [31]: MATS4s, MATS2c, ATSC8p. Some drugs known to cause rhabdomyolysis have been reported to trigger this condition through direct toxicity to skeletal muscle, by increasing intracellular free ionized calcium levels, and by decreasing serum coenzyme Q levels

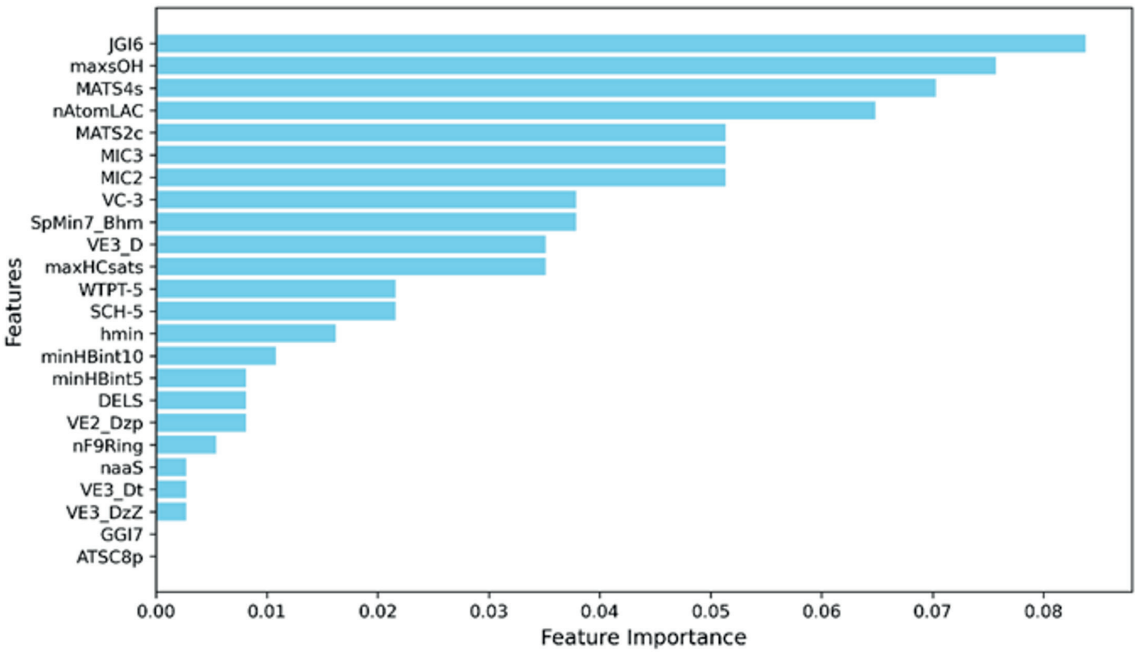


Figure 2. The contribution of molecular descriptors to the top-performing model

[9]. In a QSAR model for predicting the activity of 3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, various descriptors from the E-State, Autocorrelation, Topological Charge, Detour Matrix, and Barysz Matrix Descriptor classes were utilized, similar to our study. These characteristics significantly impacted the model's estimating capacity [32]. Additionally, a study aimed at identifying newly synthesized HMG-CoA reductase inhibitors through [ITALIC]in silico[/ITALIC] methods employed chemical similarity analysis and QSAR model integration, with Autocorrelation descriptors serving as a significant component [33]. Our QSAR model also included descriptors from Topological Charge (JGI6 and GGI7), Information Content (MIC3 and MIC2), Detour Matrix (VE3_D and VE3_Dt), and Barysz Matrix (VE2_Dzp and VE3_DzZ). Given that rhabdomyolysis is a serious side effect of statins, using these descriptor classes in our study is significant. In the model of statin activity created by Ancuceanu et al. [32], the JGI5 descriptor from the Topological Charge index was used. Higher HMG-CoA reductase inhibitory activity was linked to higher JGI5 levels. The sixth-order derivative, JGI6, was the strongest descriptor in the current model. JGI6 tends to rise as the molecular structure becomes more complicated, with more ring systems, branching, and more heteroatoms [32]. Based on the chemoinformatic literature and current findings, it can be suggested that a higher JGI6 value may increase the risk of drug-induced rhabdomyolysis.

The current model includes one descriptor for each class in the Chi Cluster Descriptor (VC-3), Chi Chain Descriptor (SCH-5), Longest Aliphatic Chain Descriptor (nAtomLAC), Burden Modified Eigenvalues Descriptor (SpMin7_Bhm), Weighted Path Descriptor (WTPT-5), and Ring Count Descriptor (nF9Ring). Rajathei et al. developed a 2D-QSAR model by correlating the structural features of a series of atorvastatin analogs identified as HMG-CoA reductase inhibitors with their biological activities [33]. One of the significant descriptors in the HMG-CoA reductase inhibitors model was SCH-7, a Chi Chain Descriptor family member. The SCH-x descriptors of the Kier and Hall molecular connectivity indices [34] are the x-th degree chain (or ring) type versions, describing the x-th degree of connectivity of non-hydrogen atoms in molecules. According to a study by Rajathei et al., the inhibitory action of SCH-7 may be attributed to its higher degree of connectivity, resulting from its increasing positive value [33]. Similarly, the 5th-level derivative of this descriptor, SCH-5, emerged as a significant predictor in the current DIR model. The current model suggests that the susceptibility of medications to rhabdomyolysis may increase as the SCH-5 value increases. Another significant descriptor highlighted in the aforementioned study is the VE3_Dt descriptor derived from the Detour Matrix index [33], which is also included in our model. Furthermore, the present model employed VE3_D, while the HMG-CoA reductase inhibitors model used VE1_D and VE2_D [33].

The PIF analysis revealed that GGI7 and ATSC8p have the lowest impact on the current model prediction. After removing these features and rebuilding the model, a slight decrease in performance was observed. This implies that these features may interact with other variables as they are not entirely independent. In the presence of interrelated variables, assessing feature combinations yields more reliable insights than analyzing individual predictors [35]. The descriptors presented in this study are suggested as potential toxicophore structures responsible for a molecule's rhabdomyolysis risk. Before modifying drugs at the molecular level to reduce the risk of rhabdomyolysis, an assessment should consider the descriptors supported by other studies and the importance ranking determined by the PIF analysis (Figure 2) to ensure the decision-making process is well-founded.

Prior molecular modifications aimed at minimizing DIR, a comprehensive assessment should be conducted based on the importance hierarchy determined through PIF analysis (Figure 2) and descriptors validated by previous studies to ensure a robust and evidence-based decision-making framework.

Strengths and limitations of the model

DIR is a potentially fatal idiosyncratic adverse drug reaction. Diagnosing DIR in clinics can often be challenging due to the limited availability of methods. Current methods, particularly monitoring CK levels and testing for myoglobinuria in urine, are inadequate for the early and definitive detection of DIR [36]. Various commonly prescribed medications, such as antidepressants (e.g., promazine, trifluoperazine), lipid-lowering medications

(e.g., clofibrate, lovastatin), and antihistamines (e.g., doxylamine, diphenhydramine), have the potential to trigger rhabdomyolysis. As more newly synthesized drugs are introduced into clinical use, the risk of rhabdomyolysis associated with these drugs is expected to increase [9]. Thus, accurately identifying the DIR risk before marketing is crucial. Utilizing [ITALIC]in silico[/ITALIC] analysis is recommended as the quickest and most economical approach in the initial phase [23].

The limited number of DIR cases and the inclusion of drugs without conclusive safety evidence regarding rhabdomyolysis risk in the 'safe' group limit the accuracy and reliability of several DIR models available in the literature. To address this gap in the literature, a 2D-QSAR model was developed in this study to predict the pharmaceutical-related risk of rhabdomyolysis using DIRA data. In this context, models were developed utilizing the IBk, SL, and BN algorithms with data categorized as DIR-positive and DIR-negative. The IBk model, noted for its strong predictive performance, was analyzed in detail. The binary IBk model achieved an accuracy of 81.08% on the test set. In the multiclass DIR QSAR model developed by Zhou et al., a success rate of 73.00% was recorded using the Random Forest (RF) algorithm. Although assessing various levels of rhabdomyolysis risk in the RF model is considered an advantage, it requires improvements to increase its success rate [13].

In the current study, collecting data from a single source increased homogeneity and positively contributed to data consistency and model accuracy. However, depending on a single source dataset can present challenges in creating comprehensive datasets. Conversely, the accuracy of both the positive and negative groups in the present dataset is supported by the literature. In this respect, compared to other models that accept medications without rhabdomyolysis data as negative, it offers a more reliable dataset. For example, Cui et al. developed a binary DIR prediction model using 163 drug molecules associated with rhabdomyolysis risk and 1341 drug molecules with no reported rhabdomyolysis risk. In the study, the RF algorithm achieved the highest success rate of 79.28% [12]. Besides, the binary rhabdomyolysis QSAR model developed using the Support Vector Machine (SVM) algorithm, based on a dataset of similar size to the current study, achieves an accuracy rate of 84.50%. Although the study demonstrated a higher performance than the 81.08% ACC rate obtained in our study, a direct comparison is not appropriate due to dataset differences. The SVM model's dataset includes various ingredients, pharmaceuticals, and chemicals [9]. The diversity in the dataset is a crucial factor directly affecting the model's generalization capacity. Concentrating exclusively on pharmaceutical compounds has both advantages and limitations. Utilizing only pharmaceutical-grade ingredients ensured consistency in the dataset, enhancing the model's sensitivity to a specific chemical group and contributing to safer drug development processes. Additionally, the presented model explanations provide new insights into minimizing or preventing potential drug side effects. In this context, the present model excludes non-pharmaceutical substances. Furthermore, as in traditional QSAR modeling, salts and inorganic compounds have been excluded from the scope of analysis. Restructuring the algorithms used in the model requires high expertise; however, the availability of the datasets simplifies the process of creating the model.

In conclusion, the QSAR models developed in the present study can support DIR assessment during drug development and the early stages of preclinical research. Integrating QSAR-based approaches into drug safety management offers an ethically sustainable alternative, enhancing both economic efficiency and time effectiveness. Alongside the strong predictive performance demonstrated by the DIR model, this study aims to contribute to safer drug development by providing structural insights. The study anticipates that the presented physicochemical properties and the developed DIR models will serve as significant guides and effective analytical tools for assessing DIR-related risks.

Author contribution

Study conception and design: FKÇ; data collection: FKÇ; analysis and interpretation of results: FKÇ; draft manuscript preparation: FKÇ. The author reviewed the results and approved the final version of the manuscript.

Ethical approval

For this study, which was conducted entirely using *in silico* methods, ethics committee approval was not required as no human participants, animals, or identifiable personal data were involved.

Funding

The author declare that the study received no funding.

Conflict of interest

The author declare that there is no conflict of interest.

REFERENCES

[1] Waldman W, Kabata PM, Dines AM, et al. Rhabdomyolysis related to acute recreational drug toxicity-A Euro-DEN study. PLoS One 2021;16(3):e0246297. https://doi.org/10.1371/journal.pone.0246297

[2] Baeza-Trinidad R. Rhabdomyolysis: A syndrome to be considered. Med Clin (Barc) 2022;158(6):277-283. https://doi.org/10.1016/j.medcli.2021.09.025

[3] Hohenegger M. Drug induced rhabdomyolysis. Curr Opin Pharmacol 2012;12(3):335-339. https://doi.org/10.1016/j.coph.2012.04.002

[4] Morin AG, Somme D, Corvol A. Rhabdomyolysis in older adults: Outcomes and prognostic factors. BMC Geriatr 2024;24(1):46. https://doi.org/10.1186/s12877-023-04620-8

[5] Nance JR, Mammen AL. Diagnostic evaluation of rhabdomyolysis. Muscle Nerve 2015;51(6):793-810. https://doi.org/10.1002/mus.24606

[6] Amanollahi A, Babeveynezhad T, Sedighi M, et al. Incidence of rhabdomyolysis occurrence in psychoactive substances intoxication: A systematic review and meta-analysis. Sci Rep 2023;13(1):17693. https://doi.org/10.1038/s41598-023-45031-4

[7] Wang Y, Lin Y, Lin Q, Liang H, Cai W, Jiang D. Exploring the association between selective serotonin reuptake inhibitors and rhabdomyolysis risk based on the FDA pharmacovigilance database. Sci Rep 2023;13(1):12257. https://doi.org/10.1038/s41598-023-39482-y

[8] Wen Z, Liang Y, Hao Y, et al. Drug-Induced Rhabdomyolysis Atlas (DIRA) for idiosyncratic adverse drug reaction management. Drug Discov Today 2019;24(1):9-15. https://doi.org/10.1016/j.drudis.2018.06.006

[9] Hu X, Yan A. In silico prediction of rhabdomyolysis of compounds by self-organizing map and support vector machine. Toxicol in Vitro 2011;25(8):2017-2024. https://doi.org/10.1016/j.tiv.2011.08.002

[10] Chang Y, Hawkins BA, Du JJ, Groundwater PW, Hibbs DE, Lai F. A guide to in silico drug design. Pharmaceutics 2022;15(1):49. https://doi.org/10.3390/pharmaceutics15010049

[11] Kelleci Çelik F, Yılmaz Sarıaltın S. An explainable prediction model for drug-induced interstitial pneumonitis. J Res Pharm 2025;29(1):322-334. https://doi.org/10.12991/jrespharm.1644357

[12] Cui X, Liu J, Zhang J, Wu Q, Li X. In silico prediction of drug-induced rhabdomyolysis with machine-learning models and structural alerts. J Appl Toxicol 2019;39(8):1224-1232. https://doi.org/10.1002/jat.3808

[13] Zhou Y, Li S, Zhao Y, et al. Quantitative Structure-Activity Relationship (QSAR) model for the severity prediction of drug-induced rhabdomyolysis by using random forest. Chem Res Toxicol 2021;34(2):514-521. https://doi.org/10.1021/acs.chemrestox.0c00347

[14] Poorsarvi Tehrani P, Malek H. Early detection of rhabdomyolysis-induced acute kidney injury through machine learning approaches. Arch Acad Emerg Med 2021;9(1):e29. https://doi.org/10.22037/aaem.v9i1.1059

[15] Kim S, Chen J, Cheng T, et al. PubChem 2023 update. Nucleic Acids Res 2023;51(D1):D1373-D1380. https://doi.org/10.1093/nar/gkac956

[16] Yap CW. PaDEL-descriptor: An open source software to calculate molecular descriptors and fingerprints. J Comput Chem 2011;32(7):1466-1474. https://doi.org/10.1002/jcc.21707

[17] Fan C, Chen M, Wang X, Wang J, Huang B. A review on data preprocessing techniques toward efficient and reliable knowledge discovery from building operational data. Front Energy Res 2021;9:652801. https://doi.org/10.3389/fenrg.2021.652801

[18] Python 3.9.5. Software. Available at: https://www.python.org/ (Accessed on August 20, 2024).

[19] Frank E, Hall MA, Witten IH. The WEKA workbench. Online appendix for "Data mining: Practical machine learning tools and techniques". 4th ed. Burlington, MA, USA: Morgan Kaufmann; 2016.

[20] Iranzad R, Liu X. A review of random forest-based feature selection methods for data science education and applications. Int J Data Sci Anal 2024;20:197–211. https://doi.org/10.1007/s41060-024-00509-w

[21] Aha D, Kibler D, Albert MK. Instance-based learning algorithms. Mach Learn 1991;6:37-66. https://doi.org/10.1007/BF00153759

[22] Sumner M, Frank E, Hall M. Speeding up logistic model tree induction. In: Jorge AM, Torgo L, Brazdil P, Camacho R, Gama J, editors. Knowledge Discovery in Databases: PKDD 2005. Berlin, Heidelberg: Springer; 2005: 675-683. https://doi.org/10.1007/11564126_72

[23] Hogg RV, Tanis EA. Probability and statistical inference. Macmillan: New York; 1977: 993.

[24] Organisation for Economic Co-operation and Development (OECD). Guidance Document on the Validation of (Quantitative) Structure-Activity Relationship [(Q)Sar] Models. In: OECD Series on Testing and Assessment. Paris: OECD Publishing; 2017: 1-154. https://doi.org/10.1787/20777876

[25] Cherkasov A, Muratov EN, Fourches D, et al. QSAR modeling: Where have you been? Where are you going to? J Med Chem 2014;57(12):4977-5010. https://doi.org/10.1021/jm4004285

[26] Vogt M, Bajorath J. Modeling tanimoto similarity value distributions and predicting search results. Mol Inform 2017;36(7):10.1002/minf.201600131. https://doi.org/10.1002/minf.201600131

[27] Kaneko H. Cross-validated permutation feature importance considering correlation between features. Anal Sci Adv 2022;3(9-10):278-287. https://doi.org/10.1002/ansa.202200018

[28] Héberger K. Selection of optimal validation methods for quantitative structure-activity relationships and applicability domain. SAR QSAR Environ Res 2023;34(5):415-434. https://doi.org/10.1080/1062936X.2023.2214871

[29] Hall LH, Kier LB. Electrotopological state indices for atom types: A novel combination of electronic, topological, and valence state information. J Chem Inf Comput Sci 1995;35:1039-1045. https://doi.org/10.1021/ci00028a014

[30] Roy K, Mitra I. Electrotopological state atom (E-state) index in drug design, QSAR, property prediction and toxicity assessment. Curr Comput Aided Drug Des 2012;8(2):135-158. https://doi.org/10.2174/157340912800492366

[31] Todeschini R, Consonni V. Molecular descriptors for chemoinformatics. Weinheim: Wiley VCH; 2009. https://doi.org/10.1002/9783527628766

[32] Ancuceanu R, Popovici PC, Drăgănescu D, Busnatu Ș, Lascu BE, Dinu M. QSAR regression models for predicting HMG-CoA reductase inhibition. Pharmaceuticals (Basel) 2024;17(11):1448. https://doi.org/10.3390/ph17111448

[33] Rajathei DM, Parthasarathy S, Selvaraj S. Combined QSAR model and chemical similarity search for novel HMGCoA reductase inhibitors for coronary heart disease. Curr Comput Aided Drug Des 2020;16(4):473-485. https://doi.org/10.2174/1573409915666190904114247

[34] Kier LB, Hall LH. Molecular connectivity in chemistry and drug research. New York: Academic Press; 1976.

[35] Naik AK, Kuppili V. Dynamic relevance and interdependent feature selection for continuous data. Expert Systems with Applications 2022;191:116302. https://doi.org/10.1016/j.eswa.2021.116302

[36] Keltz E, Khan FY, Mann G. Rhabdomyolysis. The role of diagnostic and prognostic factors. Muscles Ligaments Tendons J 2014;3(4):303-312.

acta medica

ORIGINAL ARTICLE

Linking eveningness to depression and anxiety: the mediating role of impulsivity and resilience

İpek Özönder Ünal[1]
ORCID: 0000-0003-3509-0061

Miray Pirinççi Aytaç[2]
ORCID: 0000-0002-3076-7670

Derya Adalı Aker[3]
ORCID: 0000-0003-1362-2880

Tonguç Demir Berkol[4]
ORCID: 0000-0003-4341-6826

[1]Department of Psychiatry, Tuzla State Hospital, Istanbul, Türkiye

[2]Department of Psychiatry, Sancaktepe Şehit Prof. Dr. İlhan Varank Training And Research Hospital, Sancaktepe, Istanbul, Türkiye

[3]Department of Psychiatry, Medipol University, Istanbul, Türkiye

[4]Department of Psychiatry, Bakirkoy Research and Training Hospital for Psychiatry, Istanbul, Türkiye

Corresponding Author: İpek Özönder Ünal
E-mail: ipekozonder@gmail.com

Received: 6 May 2025, Accepted: 27 July 2025,
Published online: 30 September 2025

ABSTRACT

Objective: This study investigated the interrelationships between chronotype, impulsivity, resilience, and affective symptomatology in individuals with Major Depressive Disorder (MDD) in remission. Specifically, it examined whether impulsivity and resilience mediate the association between eveningness and depressive and anxiety symptoms, and whether sleep quality moderates these pathways.

Materials and Methods: This cross-sectional study was conducted between February and April 2025 at Istanbul Tuzla State Hospital, Türkiye, and included 203 patients diagnosed with MDD in remission. Participants were assessed using validated psychometric instruments, including the Morningness-Eveningness Questionnaire (MEQ), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Psychological Resilience Scale (PRS-33), Barratt Impulsiveness Scale (BIS-11), and the Pittsburgh Sleep Quality Index (PSQI). Analyses were conducted using SPSS 22.0, including correlations, multiple linear regression, and PROCESS-based mediation and moderation models.

Results: Eveningness was significantly associated with increased severity of both depressive and anxiety symptoms. Non-planning and attentional impulsivity partially mediated the relationship between eveningness and depressive symptoms. Resilience also partially mediated the link between eveningness and depression, indicating a protective psychological buffer. Sleep quality moderated the chronotype–depression association, such that poor sleep exacerbated depressive symptoms in evening types, but it did not moderate the chronotype–anxiety link.

Conclusion: Chronotype influences mental health outcomes through intricate cognitive-affective pathways. Evening-type individuals are more vulnerable to affective symptoms due to heightened impulsivity and reduced resilience. These findings emphasize the need for multidimensional interventions that address not only circadian misalignment but also impulsivity regulation and resilience enhancement to improve psychological outcomes in mood disorder populations.

Keywords: anxiety, chronotype, depression, impulsivity, resilience

INTRODUCTION

Major depressive disorder (MDD) remains one of the most significant global health burdens, necessitating a comprehensive understanding of its multifaceted etiology [1]. While genetic predispositions, environmental stressors, and neurobiological mechanisms are well-established contributors emerging research underscores the critical influence of individual differences in neurobiological rhythms and psychological traits—particularly chronotype, impulsivity, and resilience—on vulnerability to MDD and overall psychological well-being [2].

Chronotype, defined as an individual's biological preference for activity and alertness in the morning or evening, has gained attention as a chronobiological factor linked to emotional and psychiatric outcomes. A growing body of research suggests that eveningness is associated with greater susceptibility to depression, anxiety, and impulsivity, likely due to circadian misalignment and sleep disruptions [3,4]. In contrast, morningness has been linked to increased psychological resilience and reduced vulnerability to mood disturbances [5,6]. Importantly, chronotype effects extend beyond this dichotomy, as circadian rhythm amplitude and stability also play a vital role in coping mechanisms, affective regulation, and mental health outcomes [7].

Psychological resilience—the capacity to adapt to and recover from adversity—acts as a protective buffer against psychiatric disorders, including depression and anxiety [8]. Resilient individuals tend to regulate emotions more effectively and cope better with stress, maintaining psychological well-being despite life challenges. Recent studies suggest that resilience may mediate the impact of chronotype on psychopathology, potentially mitigating the negative consequences of eveningness [6,9,10]

Impulsivity, characterized by difficulties in self-regulation, delayed gratification, and increased risk-taking, is another psychological trait closely associated with mood disorders. Individuals with an evening chronotype tend to exhibit higher levels of impulsivity, which can exacerbate emotional dysregulation, increase susceptibility to depression and anxiety, and promote maladaptive behaviors [4,11]. Additionally, personality traits such as neuroticism and low conscientiousness may moderate the chronotype–impulsivity–depression pathway, further emphasizing the need to consider trait-level individual differences [12].

Anxiety symptoms frequently co-occur with depressive disorders, and comorbidity rates are particularly high among individuals diagnosed with MDD. Research indicates that nearly half of patients with MDD also meet criteria for an anxiety disorder, a co-occurrence that significantly increases illness severity, functional impairment, and the risk of poor treatment outcomes [13].

Despite extensive evidence linking chronotype, impulsivity, and resilience to mental health, inconsistencies persist regarding their direct and indirect effects. Some studies challenge the assumption that eveningness is inherently maladaptive, suggesting its impact may be context-dependent and shaped by environmental, cognitive, and social factors [14]. Moreover, the stability of chronotype in clinical populations and the potential for therapeutic circadian interventions remain topics of ongoing investigation. Other contributing factors, such as cognitive rumination, emotional dysregulation [3], and genetic variations (e.g., PER3 gene [15]), may further mediate these complex interactions.

While previous research has established links between chronotype and mood disorders [3,4], the current study aims to make several unique and important contributions. Specifically, we focus on individuals with Major Depressive Disorder (MDD) in remission—a clinically relevant yet relatively understudied population in circadian rhythm research. Investigating this group is crucial, as remitted patients often continue to experience residual cognitive and emotional vulnerabilities [3], including poor sleep and diminished resilience, which can predict relapse. Studying MDD in remission therefore offers a strategic opportunity to identify underlying risk pathways that persist beyond symptom resolution. To our knowledge, this is the first study to simultaneously examine both impulsivity and resilience as key mediating

factors in the relationship between chronotype and affective symptoms (both depressive and anxiety) in a remitted MDD patient group. Most prior research has typically focused on either a single mediator [4] or broader associations between chronotype and mood symptomatology [5], or has examined bipolar populations [11]. Our integrated approach incorporates both mediation and moderation analyses, enabling a more nuanced understanding of how sleep quality interacts with chronobiological preference and cognitive-affective traits. This framework may help uncover distinct and potentially overlapping pathways linking eveningness to depressive and anxiety symptoms, thereby offering novel insights for the development of more tailored and targeted interventions for individuals with mood disorders.

MATERIALS AND METHODS

Study population and sample

This study was conducted on a clinical sample of patients diagnosed with Major Depressive Disorder (MDD) based on the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The diagnosis of MDD was confirmed using the Structured Clinical Interview for DSM-5 Disorders (SCID-5), a gold-standard diagnostic tool for psychiatric assessment. Participants were recruited from the outpatient psychiatry clinics of Istanbul Tuzla State Hospital. A total of 203 patients who met the eligibility criteria and provided written informed consent were included in the study. Data collection was conducted between February 2025 and April 2025.

At the time of assessment, all participants were in remission, defined by the absence of active depressive symptoms based on clinical evaluation and SCID-5 criteria. However, we acknowledge that residual symptoms—particularly sleep disturbances—may persist during remission, as noted in previous research [16].

Inclusion and exclusion criteria

To ensure a homogeneous sample, this study implemented a set of strict inclusion and exclusion criteria. Participants were eligible for inclusion if they were between the ages of 18 and 65 years, literate, and capable of independently completing self-report questionnaires. Additionally, all participants had a confirmed diagnosis of Major Depressive Disorder (MDD), which was established using the Structured Clinical Interview for DSM-5 Disorders (SCID-5). At the time of assessment, participants were required to be in remission, as determined by clinical psychiatric evaluation, ensuring the absence of active depressive symptoms. Furthermore, only individuals who were receiving routine follow-up care at the outpatient clinic were considered for inclusion. Prior to their participation, all individuals provided written informed consent after receiving comprehensive information about the study, including its objectives, procedures, and their rights as participants.

To eliminate potential confounding factors and maintain the validity of the findings, several exclusion criteria were applied. Patients who were currently experiencing an active major depressive episode at the time of assessment were excluded, as were those with a history of intellectual disability (IQ < 70), dementia, or other neurocognitive disorders that could impair their ability to comprehend or complete the study assessments. Furthermore, individuals with severe and potentially confounding psychiatric disorders were excluded. These encompassed psychotic disorders such as schizophrenia, schizoaffective disorder, and delusional disorder; bipolar and related disorders including bipolar I disorder, bipolar II disorder, and cyclothymic disorder, due to the distinct affective and circadian rhythm profiles characteristic of these conditions; and severe personality disorders—such as borderline or antisocial personality disorder—when, in the judgment of the evaluating psychiatrist, these were likely to significantly compromise the accuracy of self-report measures or introduce marked emotional instability beyond the scope of MDD.

To further minimize the influence of undiagnosed psychiatric comorbidity, all participants underwent the SCID-5, and only individuals with a primary diagnosis of MDD in remission and no comorbid psychiatric disorders at the diagnostic level were included. Consequently, no subgroup reanalysis for psychiatric comorbidity was required.

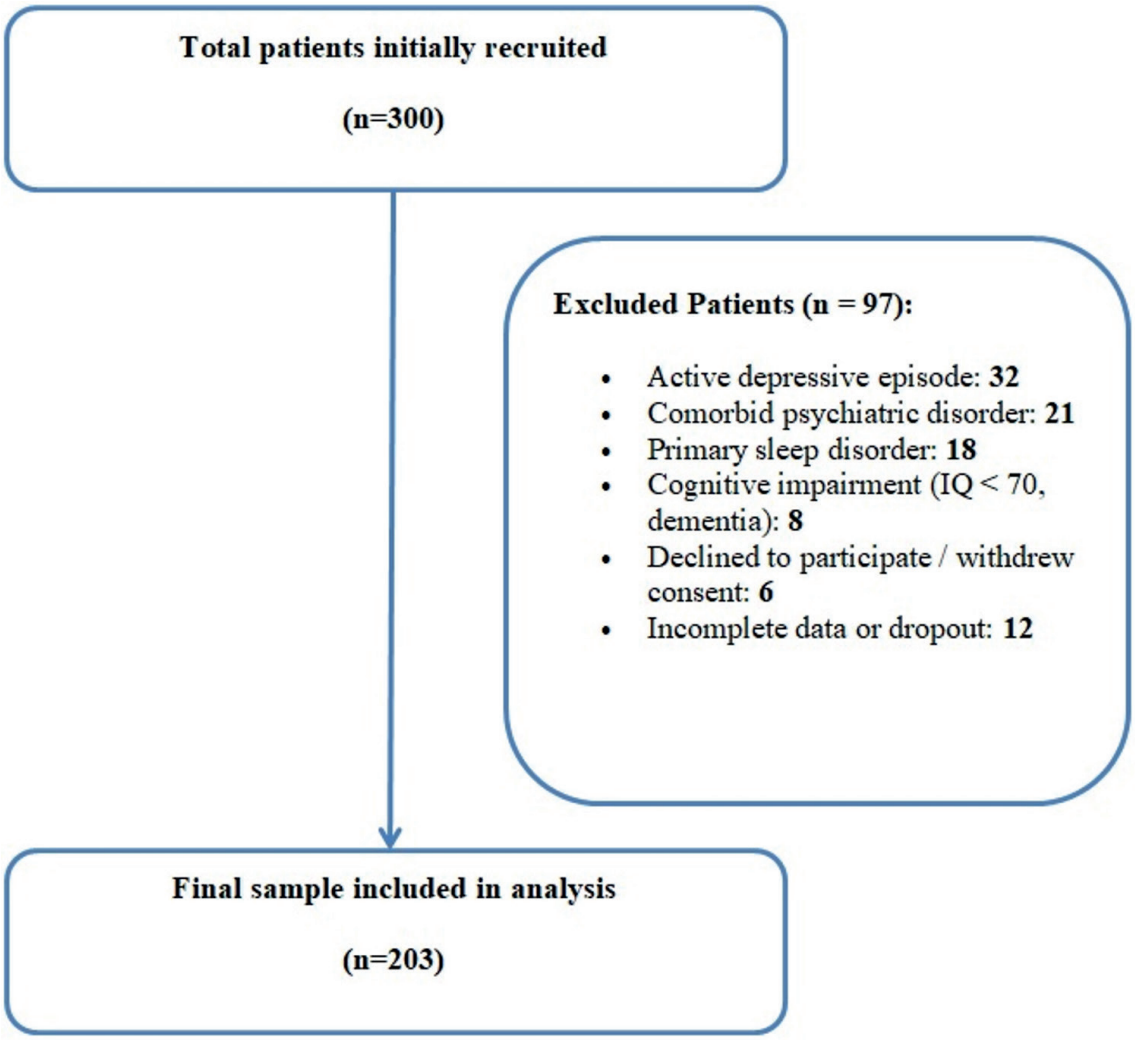


Figure 1. Flowchart of participant recruitment and exclusion criteria

In addition, individuals with primary sleep disorders—including insomnia, obstructive sleep apnea, or restless legs syndrome—diagnosed independently of depressive symptoms, were excluded, as these conditions could independently influence key psychological variables such as mood, sleep quality, and impulsivity. Lastly, participants who were unable or unwilling to provide informed consent were not included in the study (see Figure 1).

Measures

A combination of structured clinical interviews and validated psychometric instruments was employed to assess the key psychological constructs relevant to the study.

Sociodemographic and clinical characteristics—including age, gender, education, marital status, illness onset, duration, psychiatric history, suicide attempts, family psychiatric history, and substance use—were collected via a structured researcher-developed questionnaire. To assess depressive and anxiety symptoms, participants completed the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI), both widely validated self-report measures that assess symptom severity [17,18]. Psychological resilience was measured using the Psychological Resilience Scale for Adults (PRS-33), which evaluates resilience across six dimensions [19].

Chronotype was assessed using the Morningness-Eveningness Questionnaire (MEQ), a validated measure that classifies individuals into morning, evening, or intermediate types based on their sleep-wake preferences [20]. Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI), a self-report instrument assessing subjective sleep quality over the past month [21]. To

measure impulsivity, the study utilized the Barratt Impulsiveness Scale - Short Form (BIS-11-SF), which assesses impulsivity across attentional, motor, and non-planning dimensions [22].

All psychometric instruments used in this study have been adapted into Turkish, with their validity and reliability confirmed through prior research [23-27].

Procedure

Participants who met the eligibility criteria were invited to participate in the study. After obtaining written informed consent, they completed self-report questionnaires under the supervision of trained research staff. The assessments were conducted in a standardized and structured manner to ensure consistency and minimize potential biases.

Clinical and demographic data were gathered through structured interviews and supplemented with a review of hospital medical records. The SCID-5 interview was conducted by trained psychiatrists to confirm the diagnosis of MDD. The absence of active depressive symptoms was clinically evaluated, ensuring that all participants were in remission.

Statistical analysis

An a priori power analysis was performed using GPower (version 3.1.9.7) to estimate the minimum sample size needed for detecting a moderate effect size ($f^2 = 0.08$) in a multiple linear regression model with six predictors, including chronotype, sleep quality, impulsivity subscales, and resilience. With an alpha level of 0.05 and desired power of 0.80, the required sample size was calculated to be 160 participants. The final sample of 203 exceeded this threshold, ensuring adequate statistical power to detect hypothesized effects.

The Kolmogorov–Smirnov test was applied to evaluate the normality of data distributions for all continuous variables. Descriptive statistics, including mean ± standard deviation (SD) for normally distributed variables and median (minimum–maximum) for non-normally distributed variables, were used to summarize continuous demographic and clinical characteristics. Categorical variables were summarized using frequencies and percentages (n, %). Pearson's correlation coefficients were calculated to assess bivariate relationships among key study variables, including chronotype, sleep quality, impulsivity, resilience, and affective symptoms. To examine the predictive power of chronotype, impulsivity, and resilience on depressive and anxiety symptoms, multiple linear regression analyses were performed. To test indirect and conditional effects, mediation and moderation analyses were conducted using the PROCESS macro for SPSS (Model 4 and Model 1, respectively; Hayes, 2018). Mediation models assessed whether impulsivity (non-planning and attentional) or resilience served as mediators in the relationship between chronotype and affective symptoms. Moderation models explored whether sleep quality (PSQI) or impulsivity dimensions moderated the effect of chronotype on depression or anxiety outcomes. All analyses were performed using IBM SPSS Statistics (Version 22.0; IBM Corp., Armonk, NY, USA). Statistical tests were two-tailed, and significance was set at $p < 0.05$.

Ethical considerations

This study was approved by the Istanbul Medipol University Noninterventional Clinical Research Ethics Committee (Protocol No: E-10840098-202.3.02-1257; Date: 13.02.2025) and conducted in accordance with the Declaration of Helsinki (2013). Written informed consent was obtained from all participants. Confidentiality and anonymity were ensured through coded data and secure storage procedures.

RESULTS

Table 1 provides a comprehensive overview of the sociodemographic and clinical characteristics of the patient sample, offering insights into the composition and clinical profiles of the study participants. The sample consisted of 203 patients, with a mean age of 39.01 ± 10.13 years, representing a broad adult age range. A majority of participants were female (64.5%), and more than half were unmarried (53.7%), a factor often associated with increased psychological vulnerability in clinical populations. Further details are summarized in Table 1.

Table 1. Sociodemographic and clinical characteristics of patients

	n (%) mean ± SD median (min-max)
Gender	
Female	131 (64.5)
Male	72 (35.5)
Age	39.01 ± 10.13
Education (Years)	9.97 ± 2.69
Marital Status	
Single/Divorced/Widowed	109 (53.7)
Married	94 (46.3)
Work Status	
Employed	99 (48.8)
Not Working	51 (25.1)
Retired	37 (18.2)
Student	16 (7.9)
Smoking Status	
Smoker	112 (55.2)
Non-Smoker	91 (44.8)
Age of Disease Onset	31(13-62)
Illness Duration (Years)	6 (1-20)
History of Suicide Attempt	
Yes	14 (6.9)
No	189 (93.1)
Other Medical Comorbidities	
Yes	118 (58.1)
No	85(41.9)
Family History of Psychiatric Disorder	
Yes	65 (32.0)
No	138 (68.0)

Values presented as mean ± SD (standard deviation), median (min-max) and n (%).

Participants had a mean MEQ (chronotype) score of 43.46 ± 11.97, indicating a tendency toward eveningness. Average scores were 7.89 ± 2.19 on the BAI and 5.13 ± 1.15 on the BDI. The total PRS-33 averaged 114.45 ± 10.56, with subscale means as follows: Self-Perception (18.93 ± 4.39), Future Orientation (13.22 ± 3.99), Structured Style (13.96 ± 2.90), Social Competence (22.15 ± 5.43), Family Cohesion (20.11 ± 4.50), and Social Resources (26.08 ± 4.74). Sleep quality, measured by the PSQI, had a mean score of 7.54 ± 2.67. Impulsivity subscales of the BIS-11 yielded mean scores of 25.85 ± 4.16 for Non-Planning, 21.70 ± 5.64 for Motor, and 23.02 ± 5.09 for Attentional impulsivity.

Chronotype (MEQ) showed significant negative correlations with anxiety (BAI), depression (BDI), and all impulsivity subscales, while positively correlating with resilience (PRS-33). Poor sleep quality (PSQI) was positively associated with depressive symptoms but unrelated to anxiety or impulsivity. Resilience was negatively related to both depression and impulsivity. For detailed correlation coefficients and significance values, see Table 2.

Prior to conducting the multiple linear regression, a series of univariate linear regression analyses were performed to assess the individual predictive capacity of each independent variable on depressive symptoms, as measured by the BDI. The results indicated that chronotype, assessed by the MEQ, significantly predicted depressive symptoms ($\beta = -0.207$, $p = 0.003$). Sleep quality, measured by the PSQI, was also a significant predictor ($\beta = 0.289$, $p < 0.001$). All three subdimensions of the BIS-11 were significantly associated with depressive symptoms: Non-Planning Impulsivity ($\beta = 0.239$, $p = 0.001$), Motor Impulsivity ($\beta = 0.144$, $p = 0.040$), and Attentional Impulsivity ($\beta = 0.165$, $p = 0.019$). In terms of resilience, the total score of the PRS-33 was negatively associated with depressive symptoms ($\beta = -0.228$, $p = 0.001$), along with the following subdimensions: Self-Perception ($\beta = -0.176$, $p = 0.012$), Future Orientation ($\beta = -0.165$, $p = 0.019$), and Family Cohesion ($\beta = -0.144$, $p = 0.040$). Conversely, the subdimensions Structured Style ($\beta = -0.001$, $p = 0.984$), Social Competence ($\beta = -0.037$, $p = 0.599$), and Social Resources ($\beta = -0.020$, $p = 0.776$) did not significantly predict depressive symptomatology (Table 3).

A multiple linear regression analysis was conducted to examine the predictive capacity of MEQ, PSQI, BIS-11-NP, BIS-11-M, BIS-11-A, and PRS-33 on depressive symptoms, as measured by the BDI. The overall model was statistically significant, $F(6, 196) = 8.544$, $p < 0.001$, explaining 20.7% of the variance in BDI scores ($R^2 = 0.207$, Adjusted $R^2 = 0.183$). Among the predictors, PSQI ($\beta = 0.322$, $p < 0.001$), BIS-11-NP ($\beta = 0.208$, $p = 0.003$), and PRS-33 ($\beta = -0.148$, $p = 0.031$) were significant predictors of depressive symptoms. In contrast, MEQ ($\beta = -0.009$, $p = 0.904$), BIS-11-M ($\beta = 0.051$, $p = 0.441$), and BIS-11-A ($\beta = 0.133$, $p = 0.046$) did not significantly contribute to the model (Table 3).

Table 2. Correlation matrix of chronotype, impulsivity, resilience, and psychological symptoms

		MEQ	BAI	BDI	BIS-11-NP	BIS-11-M	BIS-11-A	PRS-33
MEQ	r	1.000	-0.241	-0.207	-0.259	-0.147	-0.147	0.311
	p	-	0.001**	0.003**	<0.001**	0.037*	0.037*	<0.001**
PSQI	r	-0.224	0.039	0.289	-0.117	0.059	-.0104	-0.004
	p	0.001	0.585	<0.001	0.098	0.407	0.138	0.953
BAI	r	-0.241	1.000	0.079	0.024	-0.094	0.230	-0.052
	p	0.001**		0.264	0.737	0.183	0.001**	0.459
BDI	r	-0.207	0.079	1.000	0.239	0.144	0.165	-0.226
	p	0.003**	0.264		0.001**	0.040*	0.019*	0.001**
BIS-11-NP	r	-0.259	0.024	0.239	1.000	0.171	0.164	-0.244
	p	<0.001**	0.737	0.001**	-	0.015*	0.020*	<0.001**
BIS-11-M	r	-0.147	-0.094	0.144	0.171	1.000	0.185	-0.089
	p	0.037*	0.183	0.040*	0.015*		0.008**	0.207
BIS-11-A	r	-0.147	0.230	0.165	0.164	0.185	1.000	-0.138
	p	0.037*	0.001**	0.019*	0.020*	0.008**	-	0.049*
PRS-33	r	0.311	-0.052	-0.226	-0.244	-0.089	-0.138	1.000
	p	<0.001**	0.459	0.001**	<0.001**	0.207	0.050*	

MEQ: Morningness-Eveningness Questionnaire, PSQI: Pittsburgh Sleep Quality Index, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, BIS-11-NP: Barratt Impulsiveness Scale-11 - Non-Planning Impulsivity, BIS-11-M: Barratt Impulsiveness Scale-11 - Motor Impulsivity, BIS-11-A: Barratt Impulsiveness Scale-11 - Attentional Impulsivity, PRS-33: Psychological Resilience Scale for Adults, r indicates Pearson correlation coefficient, ** p< 0.01, *p<0.05.

Table 3. Univariate and multivariable regression analyses of factors associated with depressive symptoms among patients

	Unstandardized Coefficients		Standardized Coefficients	CI		t	p
	B	Std. Error	β	Lower	Upper		
Univariate Analysis							
MEQ	-0.020	0.007	-0.207	-0.033	-0.007	-3.005	0.003
PSQI	0.125	0.029	0.289	0.067	0.182	4.288	<0.001
BIS-11-NP	0.066	0.019	0.239	0.029	0.103	3.491	0.001
BIS-11-M	0.029	0.014	0.144	0.001	0.057	2.067	0.040
BIS-11-A	0.037	0.016	0.165	0.006	0.068	2.366	0.019
PRS-33	-0.025	0.007	-0.226	-0.039	-0.010	-3.282	0.001
PRS-33-PS	-0.046	0.018	-0.176	-0.082	-0.010	-2.531	0.012
PRS-33-FO	-0.048	0.020	-0.165	-0.087	-0.008	-2.374	.0019
PRS-33-SS	-0.001	0.028	-0.001	-0.056	0.055	-0.021	0.984
PRS-33-SC	-0.008	0.015	-0.037	-0.037	0.022	-0.527	0.599
PRS-33-FC	-0.037	0.018	-0.144	-0.072	-0.002	-2.070	0.040
PRS-33-SR	-0.005	0.017	-0.020	-0.039	0.029	-0.284	0.776
Multivariate Analysis							
MEQ	-0.001	0.007	-0.009	-0.014	0.013	-0.120	0.904
PSQI	0.139	0.029	0.322	0.082	0.196	4.8	<0.001
BIS-11-NP	0.057	0.019	0.208	0.020	0.095	3.019	0.003
BIS-11-M	0.010	0.013	0.051	-0.016	0.037	0.773	0.441
BIS-11-A	0.030	0.015	0.133	0.001	0.060	2.008	0.046
PRS-33	-0.016	0.007	-0.148	-0.031	-0.001	-2.167	0.031

MEQ = Morningness-Eveningness Questionnaire; PSQI = Pittsburgh Sleep Quality Index; BIS-11-NP = Barratt Impulsiveness Scale-11 – Non-Planning Impulsivity; BIS-11-M = Barratt Impulsiveness Scale-11 – Motor Impulsivity; BIS-11-A = Barratt Impulsiveness Scale-11 – Attentional Impulsivity; PRS-33 = Psychological Resilience Scale for Adults – Total Score; PRS-33-PS = Self-Perception subscale; PRS-33-FO = Future Orientation subscale; PRS-33-SS = Structured Style subscale; PRS-33-SC = Social Competence subscale; PRS-33-FC = Family Cohesion subscale; PRS-33-SR = Social Resources subscale. Unstandardized coefficients (B), standard errors, standardized coefficients (β), confidence intervals (CI: lower and upper bounds), t-values, and p-values are reported for each predictor.

Table 4. Univariate and multivariable regression analyses of factors associated with anxiety symptoms among patients

	Unstandardized Coefficients		Standardized Coefficients	CI		t	p
	B	Std. Error	β	Lower	Upper		
Univariate Analysis							
MEQ	-0.044	0.013	-0.241	-0.069	-0.019	-3.524	0.001
PSQI	0.032	0.058	0.039	-0.082	0.146	0.546	0.585
PRS-33	-0.011	0.015	-0.052	-0.040	0.018	-0.742	0.459
PRS-33-PS	0.027	0.035	0.054	-0.042	0.096	0.764	0.446
PRS-33-FO	0.018	0.039	0.032	-0.058	0.094	0.460	0.646
PRS-33-SS	-0.055	0.053	-0.073	-0.160	0.049	-1.042	0.299
PRS-33-SC	-0.024	0.028	-0.059	-0.080	0.032	-0.832	0.406
PRS-33-FC	-0.043	0.034	-0.089	-0.111	0.024	-1.264	0.208
PRS-33-SR	0.001	0.033	0.003	-0.063	0.066	0.039	0.969
BIS-11-NP	0.012	0.037	0.024	-0.061	0.086	0.336	0.737
BIS-11-M	-0.036	0.027	-0.094	-0.090	0.017	-0.337	0.183
BIS-11-A	0.099	0.029	0.230	0.041	0.157	3.351	0.001
Multivariate analysis							
MEQ	-0.039	0.012	-0.212	-0.063	-0.014	-3.122	0.002
BIS-11-A	0.085	0.029	0.199	0.028	0.143	2.929	0.004

MEQ = Morningness-Eveningness Questionnaire; PSQI = Pittsburgh Sleep Quality Index; BIS-11-NP = Barratt Impulsiveness Scale-11 – Non-Planning Impulsivity; BIS-11-M = Barratt Impulsiveness Scale-11 – Motor Impulsivity; BIS-11-A = Barratt Impulsiveness Scale-11 – Attentional Impulsivity; PRS-33 = Psychological Resilience Scale for Adults – Total Score; PRS-33-PS = Self-Perception subscale; PRS-33-FO = Future Orientation subscale; PRS-33-SS = Structured Style subscale; PRS-33-SC = Social Competence subscale; PRS-33-FC = Family Cohesion subscale; PRS-33-SR = Social Resources subscale. Unstandardized coefficients (B), standard errors, standardized coefficients (β), confidence intervals (CI: lower and upper bounds), t-values, and p-values are reported for each predictor.

Prior to conducting the multivariable analysis, a series of univariate linear regression analyses were performed to evaluate the individual predictive capacity of each variable on anxiety symptoms, as measured by the BAI. The results indicated that MEQ (β = –0.241, $p = 0.001$) and BIS-11-A (β = 0.230, $p = 0.001$) were significant predictors of anxiety symptoms. In contrast, PSQI (β = 0.039, $p = 0.585$), PRS-33 (β = –0.052, $p = 0.459$), PRS-33-PS (β = 0.054, $p = 0.446$), PRS-33-FO (β = 0.032, $p = 0.646$), PRS-33-SS (β = –0.073, $p = 0.299$), PRS-33-SC (β = –0.059, $p = 0.406$), PRS-33-FC (β = –0.089, $p = 0.208$), PRS-33-SR (β = 0.003, $p = 0.969$), BIS-11-NP (β = 0.024, $p = 0.737$), and BIS-11-M (β = –0.094, $p = 0.183$) did not significantly predict anxiety symptoms (Table 4).

A multiple linear regression analysis was then conducted to examine the combined predictive capacity of MEQ and BIS-11-A on anxiety symptoms. The overall model was statistically significant, $F(2, 200) = 10.733$, $p < 0.001$, explaining 9.7% of the variance in BAI scores ($R^2 = 0.097$, Adjusted $R^2 = 0.088$). Both MEQ (β = –0.212, $p = 0.002$) and BIS-11-A (β = 0.199, $p = 0.004$) remained significant predictors in the multivariable model, highlighting their unique and additive contributions to anxiety symptomatology (Table 4).

The moderation analysis demonstrated that the interaction between chronotype (MEQ) and sleep quality (PSQI) significantly predicted depressive symptoms (BDI) (β = –0.006, $p = 0.025$), suggesting that the impact of chronotype on depression is contingent upon sleep quality. The overall model was statistically significant, $F(3, 199) = 9.706$, $p < 0.001$, explaining 12.8% of the variance in depressive symptoms ($R^2 = 0.128$). Probing the interaction revealed that MEQ scores were not significantly associated with BDI scores at low (–1 SD) levels of sleep disturbance (β = 0.005, $p = 0.639$) or at average levels (β = –0.010, $p = 0.146$). However, at high levels of sleep disturbance (+1 SD), lower MEQ scores (i.e., eveningness) were significantly associated with increased depressive symptoms (β = –0.025, $p = 0.002$).

In contrast, sleep quality did not significantly moderate the relationship between chronotype and anxiety symptoms (BAI), as the interaction term (MEQ × PSQI) was non-significant (β = 0.003, $p = 0.610$).

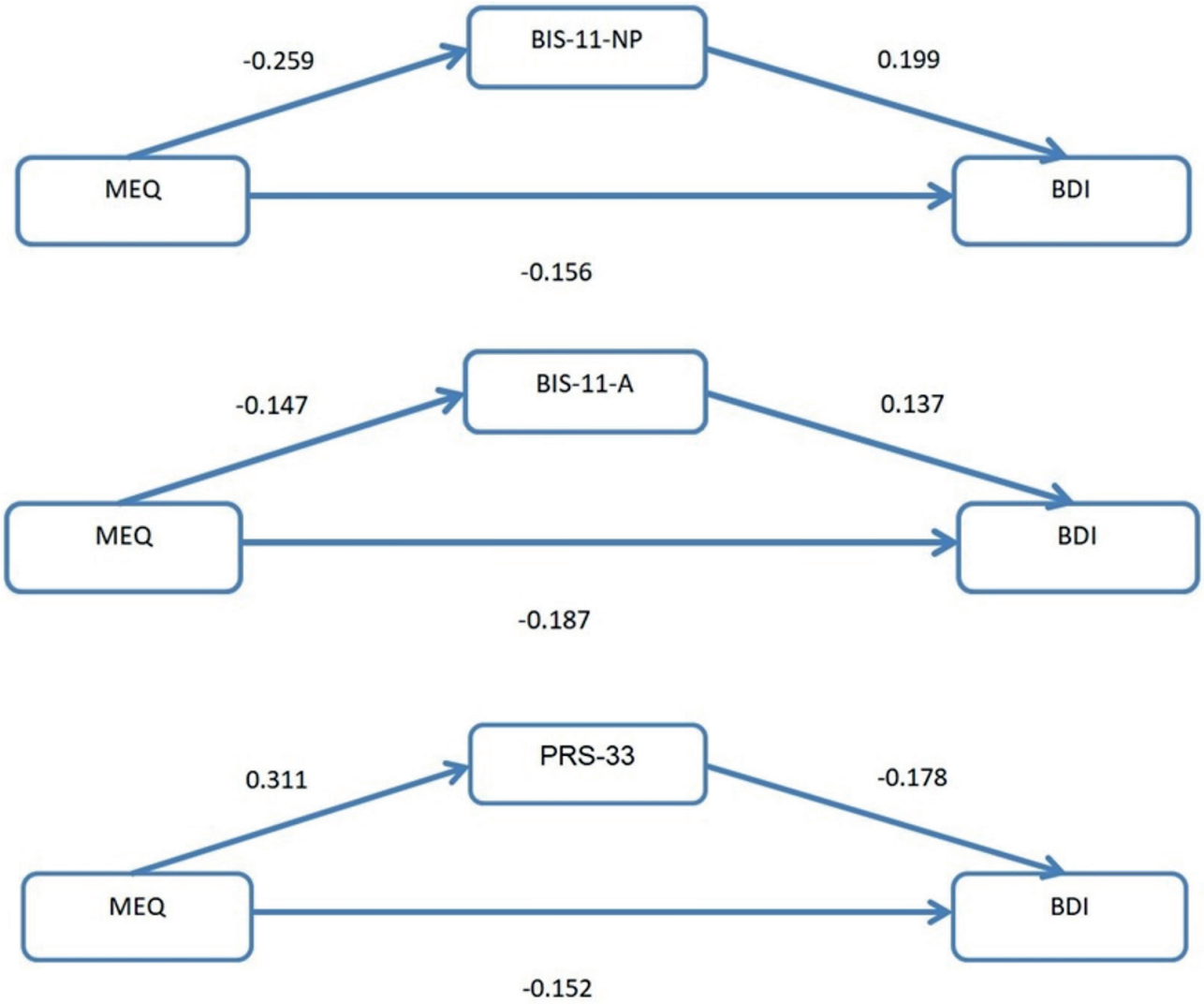


Figure 2. Structural model illustrating the hypothesized pathways linking chronotype (MEQ) to depressive symptoms (BDI), with psychological resilience (PRS-33) and impulsivity—non-planning (BIS-11-NP) and attentional (BIS-11-A)—as mediators. Values represent standardized coefficients.

The mediation analysis revealed that non-planning impulsivity (BIS-11-NP) partially mediated the relationship between chronotype (MEQ) and depressive symptoms (BDI). Lower MEQ scores (indicating eveningness) were significantly associated with higher levels of BIS-11-NP (β = –0.090, $p < 0.001$), which in turn predicted greater BDI scores (β = 0.055, $p = 0.005$). The indirect effect of MEQ on BDI through BIS-11-NP was statistically significant (β = –0.005, 95% CI [–0.011, –0.001]), confirming a mediation effect. Although the direct path from MEQ to BDI remained significant (β = –0.015, $p = 0.027$), the presence of this partial mediation suggests that non-planning impulsivity is a key psychological mechanism linking circadian misalignment to depressive symptomatology (Figure 2, Supplementary Table 1).

The mediation analysis revealed that attentional impulsivity (BIS-11-A) partially mediated the relationship between chronotype (MEQ) and depressive symptoms (BDI). Lower MEQ scores (indicating eveningness) were significantly associated with higher BIS-11-A scores (β = –0.062, $p = 0.037$), which in turn predicted increased BDI scores (β = 0.031, $p = 0.049$). The indirect effect of MEQ on BDI through BIS-11-A was marginally significant (β = –0.002, 95% CI [–0.005, -0.001]), suggesting a subtle mediation effect. Despite this, the direct path from MEQ to BDI remained significant (β = –0.018, $p = 0.007$), indicating that attentional impulsivity contributes to, but does not fully explain, the association between eveningness and Depression (Figure 2, Supplementary Table 2).

The mediation analysis demonstrated that psychological resilience (PRS-33) partially mediated the relationship between chronotype (MEQ) and depressive symptoms (BDI). Chronotype significantly predicted resilience (β = 0.274, p < .001), with morningness associated with higher resilience levels. In turn, resilience significantly predicted depressive symptoms (β = -0.019, p = .014), indicating that higher resilience was linked to lower depression severity. The indirect effect of chronotype on depressive symptoms through resilience was significant (β = -0.005, 95% CI [-0.011, -0.001]), suggesting that part of the protective effect of morningness on depression operates through enhanced resilience. However, the direct effect of chronotype on depressive symptoms remained significant (β = -0.015, p = 0.035), indicating that while resilience explains part of this relationship, other mechanisms may also contribute (Figure 2, Supplementary Table 3).

The mediation analysis demonstrated that attentional impulsivity (BIS-11-A) partially mediated the relationship between chronotype (MEQ) and anxiety symptoms (BAI). Chronotype significantly predicted BIS-11-A scores (β = –0.062, *p* = .037), with eveningness associated with higher levels of attentional impulsivity. In turn, greater BIS-11-A scores significantly predicted elevated BAI scores (β = 0.085, *p* = .004), indicating that individuals with higher impulsivity experienced more severe anxiety symptoms.

The indirect effect of chronotype on anxiety symptoms through attentional impulsivity was significant (β = -0.005, 95% CI [-0.014, -0.001]), suggesting that attentional impulsivity plays a role in the pathway linking chronotype to anxiety. However, the direct effect of chronotype on anxiety remained significant (β = -0.039, p = .002), indicating that while impulsivity explains part of this relationship, other mechanisms may also contribute (Figure 3, Supplementary Table 4).

DISCUSSION

The present study aimed to investigate the complex relationships between chronotype, impulsivity, resilience, depression, anxiety, and psychological well-being. Our findings suggest that chronotype—particularly eveningness—is linked to increased depressive symptoms and anxiety. This relationship appears to be mediated by impulsivity and moderated by both sleep quality and resilience. These results align with existing literature emphasizing the adverse psychological consequences of evening chronotype and underscore the importance of individual differences in circadian preference as a determinant of mental health outcomes.

Our findings reinforce the growing consensus that evening chronotype is significantly associated with elevated depressive symptoms, consistent with previous literature [3,4]. This association may be driven by circadian misalignment, which disrupts synchronization between endogenous rhythms and external social demands, compromising emotional regulation [28]. The circadian desynchrony hypothesis suggests that such misalignment may compromise neurobiological systems involved in affective regulation, thus increasing susceptibility to depressive symptoms.

In contrast to earlier studies that broadly link eveningness to depression and anxiety [3,4], our findings delineate specific cognitive-affective mechanisms—namely non-planning and attentional impulsivity, as well as psychological resilience—that mediate this association. Importantly, while much of the existing literature

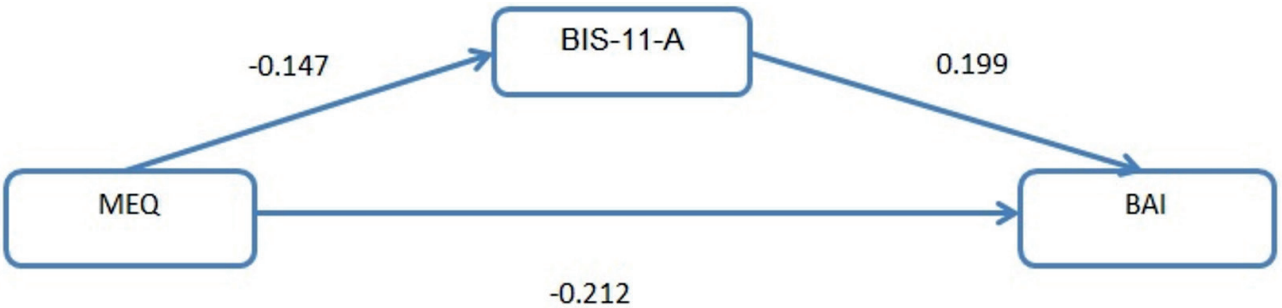


Figure 3. Structural model illustrating the hypothesized pathway linking chronotype (MEQ) to anxiety symptoms (BAI), with attentional impulsivity (BIS-11-A) as a mediator. Values represent standardized coefficients.

has focused on non-clinical populations or individuals with active depressive symptoms, our study uniquely examines individuals with MDD in remission, a group in whom underlying cognitive and emotional vulnerabilities may persist despite clinical improvement. For example, Tafoya et al. and Chung et al. investigated resilience in relation to chronotype in student or mixed samples, but did not assess impulsivity or employ mediation modeling [5,6]. Similarly, Hasler et al. linked eveningness to impulsivity traits but did not evaluate mood outcomes in a clinical context [4]. Our study builds on and integrates these findings, identifying distinct psychological pathways through which eveningness confers ongoing affective risk—even in the absence of active depressive episodes.

Importantly, our results extend this framework by showing that impulsivity—particularly non-planning and attentional dimensions—partially mediates this association. Individuals with an evening chronotype exhibited greater difficulties in future-oriented thinking and attentional control, both of which were linked to more severe depressive symptoms. These findings align with Hasler et al. and Gorgol et al., who argue that impulsivity may act as a key cognitive-affective pathway through which circadian preference influences mood [4,12]. In our study, non-planning impulsivity emerged as a robust mediator, suggesting that limited capacity for prospective thinking and goal-setting may exacerbate depressive risk in evening-type individuals.

Furthermore, we found that sleep quality moderated the link between chronotype and depression, such that the association was stronger among individuals with poor sleep. This interaction highlights the amplifying effect of sleep disturbances on the maladaptive impact of eveningness, reinforcing prior research that poor sleep may synergistically interact with biological predispositions to undermine psychological health [11]. Notably, eveningness was not associated with depression in individuals reporting good sleep, indicating a potential protective effect of sleep quality.

Although all participants were considered in symptomatic remission based on SCID-5 and clinical evaluation, PSQI scores varied considerably, indicating a range of subjective sleep quality. This finding aligns with prior research suggesting that sleep disturbances often persist even in remitted individuals and may continue to affect psychological well-being [16]. In our study, poor sleep quality remained a significant predictor of depressive symptoms, reinforcing the need to assess and address sleep problems even after mood symptoms have resolved. These results highlight that residual sleep disturbances may represent an ongoing vulnerability factor, with implications for relapse risk and functional recovery.

Taken together, these findings suggest that targeting impulsivity and sleep hygiene, rather than attempting to shift chronotype directly, may be a more feasible and effective approach in mitigating depressive risk. Interventions focusing on cognitive control (e.g., executive function training) and structured behavioral routines could support more adaptive functioning within an individual's chronotype constraints. This resonates with the growing movement toward personalized chronotherapeutic approaches, which aim to align therapeutic strategies with circadian and cognitive-affective profiles.

Our study found that attentional impulsivity significantly mediated the relationship between eveningness and anxiety symptoms, underscoring impulsivity as a key cognitive-affective pathway in the circadian–anxiety link (Supplementary Table 4). Specifically, individuals with an evening chronotype reported elevated levels of attentional impulsivity, which in turn predicted greater anxiety severity. This finding is consistent with prior research suggesting that cognitive dysregulation—particularly poor inhibitory control and attentional instability—may heighten emotional reactivity in evening types [4,11].

Interestingly, while a significant direct association between eveningness and anxiety was observed, sleep quality did not moderate this relationship. This contrasts with our findings in the depression model and suggests that anxiety symptoms in evening chronotypes may emerge independently of sleep disturbance, potentially through alternative pathways such as trait-level impulsivity, emotional dysregulation, or heightened cognitive reactivity. This further supports the notion that additional unmeasured moderators or neurobiological factors may be involved.

These results reinforce the idea that circadian typology not only affects physiological rhythms but also shapes the temporal structure of affective and cognitive processes. Evening-type individuals may exhibit heightened vulnerability to anxiety due to greater sensitivity to internal and external stressors, mediated by impulsive responding and reduced attentional control.

Our findings also build upon the work of Weiss et al., who demonstrated that sleep quality and genetic polymorphisms (e.g., PER3) mediate the chronotype–depression relationship, but not necessarily the chronotype–anxiety link [15]. In line with this, we found that while disrupted sleep may contribute to elevated anxiety, it does not appear to function as a moderator in this pathway. This divergence implies that depression may be more tightly coupled with physiological circadian disruptions, whereas anxiety may be more influenced by cognitive vulnerabilities associated with eveningness.

Collectively, these findings position attentional impulsivity as a promising intervention target for evening-type individuals at elevated risk for anxiety. Therapeutic strategies that enhance attentional control, emotional regulation, and executive function may reduce affective risk, especially in populations with pronounced eveningness and cognitive instability.

Our findings demonstrate that psychological resilience (PRS-33) partially mediates the relationship between chronotype and depressive symptoms, with morning-type individuals exhibiting significantly higher resilience, which in turn predicted lower depression severity (Supplementary Table 3). This supports the conceptualization of resilience as a critical psychological buffer—a protective factor that attenuates the maladaptive emotional consequences of eveningness. Resilient individuals may possess greater emotional regulation, stress tolerance, and adaptive coping capacities, making them less susceptible to mood disturbances, particularly within the context of circadian misalignment.

Importantly, while resilience significantly mediated the chronotype–depression relationship, it did not significantly predict anxiety symptoms. This divergence suggests that internal protective mechanisms such as resilience may differentially influence mood and anxiety domains, pointing to potentially distinct pathways of emotional regulation and vulnerability. Future research is warranted to explore these domain-specific resilience effects, including the possibility that trait-based resilience may be more tightly coupled to affective regulation in depression than in anxiety.

Our results are consistent with prior studies emphasizing the mediating role of resilience between circadian typology and mental health outcomes. Tafoya et al. and Chung et al. similarly found that morningness was associated with greater resilience, which helped mitigate depressive symptoms, particularly in clinical and student populations with disrupted sleep patterns [5,6]. Moreover, Jeon et al. observed that resilience buffered the adverse effects of circadian rhythm disturbances on subjective well-being [10], while Di Milia and Folkard highlighted the importance of circadian amplitude and stability in promoting coping and emotional endurance [7].

Taken together, these findings support the notion that resilience is a dynamic system—one that offers protection against both internal vulnerabilities (e.g., impulsivity) and external challenges (e.g., poor sleep quality). This reinforces the value of interventions aimed at enhancing resilience, particularly in evening-type individuals, who may be more susceptible to circadian misalignment and related affective disturbances.

From a translational perspective, stabilizing daily routines and promoting circadian regularity may simultaneously strengthen both biological and psychological resilience. Such synergy could enhance emotional stability, reduce depressive vulnerability, and contribute to long-term mental health improvement in chronotype-sensitive populations.

The present study contributes to a growing body of research linking eveningness with heightened psychological vulnerability, primarily through the mediating effects of impulsivity and reduced resilience. Evening-type individuals were more likely to exhibit elevated levels of both non-planning and attentional impulsivity, which in turn predicted increased symptoms of depression and anxiety. These findings support earlier assertions that impulsivity and circadian disruption frequently

co-occur, interacting to compound affective risk [11,12].

Moreover, the results revealed a nuanced divergence in how sleep quality interacts with affective outcomes: while poor sleep quality amplified depressive symptoms in evening chronotypes, it did not significantly influence anxiety symptoms. This pattern suggests that distinct pathways underlie the relationships between chronotype, sleep, and various mood domains. Specifically, attentional impulsivity emerged as a critical pathway linking circadian misalignment to depressive symptoms (Supplementary Table 2), highlighting the need to further investigate additional mediators such as cognitive biases, emotion regulation strategies, and neurobiological vulnerabilities.

Our findings reinforce the idea that chronotype exerts both direct and indirect effects on mood, with its impact mediated through cognitive-affective mechanisms, including impulsivity and resilience. In particular, eveningness may represent a broader psychobiological disposition characterized by reduced emotional regulation, diminished future orientation, and disrupted behavioral rhythms. From a real-world perspective, these insights can inform practical screening and intervention strategies in outpatient psychiatry and primary care settings. For instance, brief self-report measures of chronotype, impulsivity, and sleep quality can be incorporated into routine follow-ups for patients with remitted depression. This could allow clinicians to proactively identify residual cognitive-affective vulnerabilities and intervene before full relapse occurs.

Additionally, this study supports a multifactorial model of psychological well-being, one that integrates chronobiological factors, cognitive control, and trait-level psychological resilience. This aligns with findings by Kim et al., who demonstrated that eveningness, in combination with poor sleep quality, was associated with lower resilience and elevated depressive symptoms [9]. These associations underscore that chronotype is not merely a behavioral preference, but a dynamic factor shaping cognitive, emotional, and physiological processes. Implementing structured daily routines, psychoeducation on chronobiological rhythms, and targeted cognitive interventions may be feasible in outpatient practice and community mental health programs. These strategies are particularly relevant for working adults or students with evening chronotypes, whose schedules often clash with social norms, increasing stress and vulnerability.

A more comprehensive perspective on chronotype must therefore move beyond simple classifications of morningness or eveningness, and instead consider the regularity, flexibility, and stability of circadian rhythms. Such an approach allows for a deeper understanding of how biological timing systems interact with psychological traits to affect mental health —and how they can be modified in real-world therapeutic contexts.

Collectively, these findings call for multidimensional treatment approaches that target biological rhythms, impulsivity regulation, and resilience enhancement. Integrating cognitive-behavioral, chronotherapeutic, and lifestyle-based interventions may offer more effective strategies for improving mental health outcomes in individuals with evening chronotypes and affective vulnerabilities.

Clinical implications

A key strength of this study lies in the selection of a remitted MDD population. While many studies examine active depressive states, our focus on remission provides insights into underlying trait vulnerabilities—such as impulsivity and circadian misalignment—that may remain unaddressed despite clinical improvement. This has practical implications: identifying at-risk individuals during remission allows for preventive, resilience-building, and chronotherapeutic interventions aimed at reducing long-term recurrence risk.

The current findings offer meaningful implications for clinical practice, particularly in the personalized treatment of mood disorders. The demonstrated links between evening chronotype, impulsivity, and resilience highlight key intervention targets that extend beyond traditional symptom-focused approaches.

First, enhancing psychological resilience in evening-type individuals may serve as a protective buffer against depressive symptomatology. Interventions designed to cultivate resilience—such as stress management training, mindfulness-based therapy, and emotion regulation strategies—could

empower individuals to better cope with the psychological challenges associated with circadian misalignment.

Second, the role of impulsivity as a mediator of both depression and anxiety underscores the value of cognitive-behavioral interventions aimed at improving emotional foresight, inhibitory control, and decision-making. Targeting non-planning and attentional impulsivity may reduce affective vulnerability by strengthening executive function and reducing maladaptive reactivity.

Third, the findings support the implementation of chronotherapeutic strategies that promote circadian alignment. Interventions such as sleep hygiene education, light therapy, social rhythm therapy, and structured daily routines may help optimize functioning within an individual's natural circadian profile. These strategies may be particularly effective for evening-type individuals, who often experience greater circadian misalignment and mood instability.

Taken together, these results advocate for multimodal treatment approaches that simultaneously address biological rhythm regulation, cognitive-affective vulnerabilities, and protective psychological traits. By integrating chronotype-informed care with evidence-based psychological techniques, clinicians may improve emotional outcomes and reduce relapse risk in individuals with mood disorders.

Limitations and future directions

While this study provides important insights into the interplay between chronotype, impulsivity, resilience, and mood outcomes, several limitations warrant consideration.

First, the cross-sectional design precludes any inference of causal relationships among the observed variables. Although theoretical and empirical evidence supports directional pathways, longitudinal and prospective studies are essential to clarify the temporal dynamics and potential bidirectional influences between chronotype, impulsivity, and mood symptomatology.

Second, the sample consisted exclusively of individuals with Major Depressive Disorder (MDD) in remission, which may limit the generalizability of the findings to patients experiencing acute depressive episodes. Future studies should include diverse clinical populations, including those with active symptoms or comorbid disorders, to evaluate whether these associations remain robust under different affective states.

Third, although the study examined key mediators and moderators such as impulsivity, sleep quality, and resilience, other cognitive-affective factors—notably rumination, emotional dysregulation, and cognitive reactivity—were not directly assessed. These constructs have been previously implicated in the chronotype–mood relationship and should be systematically incorporated into future models [3].

Lastly, the reliance on self-report measures may introduce bias related to subjective reporting, particularly for constructs like sleep quality and impulsivity. Integrating objective measures and multi-informant approaches could provide a more comprehensive understanding of the mechanisms underlying circadian and affective vulnerability.

Future investigations should prioritize integrated, multidimensional frameworks encompassing biological, cognitive, affective, and behavioral domains to elucidate chronotype–mental health associations. Such work will be instrumental in advancing personalized chronotherapeutic and cognitive interventions for individuals at elevated risk of mood dysregulation.

CONCLUSION

This study underscores the complex interplay between chronotype, impulsivity, resilience, and affective symptomatology in individuals with Major Depressive Disorder. Eveningness was associated with increased depressive and anxiety symptoms, a relationship partially mediated by elevated impulsivity—particularly in the non-planning and attentional domains. Conversely, resilience emerged as a protective factor, mitigating the adverse effects of eveningness on depressive symptoms.

These findings highlight the need for targeted, multidimensional interventions that extend beyond circadian realignment alone. Clinical strategies should focus on enhancing self-regulation capacities, promoting psychological resilience,

and accommodating individual chronobiological profiles to optimize mental health outcomes. Future research integrating biological, cognitive, and behavioral frameworks will be critical to advancing personalized care for mood disorders.

Author contribution

Study conception and design: İÖÜ, MPA, DAA and TDB; data collection: İÖÜ; analysis and interpretation of results: İÖÜ, MPA, DAA and TDB; draft manuscript preparation: İÖÜ and MPA. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Istanbul Medipol University Noninterventional Clinical Research Ethics Committee (Protocol no. E-10840098-202.3.02-1257/13.02.2025).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] World Health Organization (WHO). Depression and other common mental disorders: Global health estimates. Geneva: WHO; 2017.

[2] Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron 2002;34(1):13-25. https://doi.org/10.1016/s0896-6273(02)00653-0

[3] Antypa N, Verkuil B, Molendijk M, Schoevers R, Penninx BWJH, Van Der Does W. Associations between chronotypes and psychological vulnerability factors of depression. Chronobiol Int 2017;34(8):1125-35. https://doi.org/10.1080/07420528.2017.1345932

[4] Hasler BP, Wallace ML, Graves JL, Molina BSG, Pedersen SL. Circadian preference is associated with multiple domains of trait and state level impulsivity. Chronobiol Int 2022;39(6):792-804. https://doi.org/10.1080/07420528.2022.2035392

[5] Chung JK, Choi KS, Kang HG, Jung HY, Joo EJ. The relationship between morningness-eveningness and resilience in mood disorder patients. Compr Psychiatry 2018;87:72-8. https://doi.org/10.1016/j.comppsych.2018.09.003

[6] Tafoya SA, Aldrete-Cortez V, Ortiz S, Fouilloux C, Flores F, Monterrosas AM. Resilience, sleep quality and morningness as mediators of vulnerability to depression in medical students with sleep pattern alterations. Chronobiol Int 2019;36(3):381-91. https://doi.org/10.1080/07420528.2018.1552290

[7] Di Milia L, Folkard S. More than morningness: The effect of circadian rhythm amplitude and stability on resilience, coping, and sleep duration. Front Psychol 2021;12:782349. https://doi.org/10.3389/fpsyg.2021.782349

[8] Bonanno GA. Loss, trauma, and human resilience: Have we underestimated the human capacity to thrive after extremely aversive events? Am Psychol 2004;59(1):20-8. https://doi.org/10.1037/0003-066X.59.1.20

[9] Kim J, Kim BJ, Lee CS, et al. Association between chronotype, sleep quality, resilience as well as anxiety among medical students. Sleep Medicine and Psychophysiology 2022;29(1):21-8.

[10] Jeon HJ, Bang YR, Park HY, Kim SA, Yoon IY. Differential effects of circadian typology on sleep-related symptoms, physical fatigue and psychological well-being in relation to resilience. Chronobiol Int 2017;34(6):677-86. https://doi.org/10.1080/07420528.2017.1309425

[11] Palagini L, Miniati M, Marazziti D, Massa L, Grassi L, Geoffroy PA. Circadian rhythm alterations may be related to impaired resilience, emotional dysregulation and to the severity of mood features in bipolar I and II disorders. Clin Neuropsychiatry 2022;19(3):174-86. https://doi.org/10.36131/cnfioritieditore20220306

[12] Gorgol J, Waleriańczyk W, Stolarski M. The moderating role of personality traits in the relationship between chronotype and depressive symptoms. Chronobiol Int 2022;39(1):106-16. https://doi.org/10.1080/07420528.2021.1979995

[13] Berkol TD, Özönder Ünal I. Exploring the clinical characteristics and etiological factors of comorbid major depressive disorder and social anxiety disorder. Biomol Biomed 2023;23(6):1136-45. https://doi.org/10.17305/bb.2023.9690

[14] Müller MJ, Cabanel N, Olschinski C, Jochim D, Kundermann B. Chronotypes in patients with nonseasonal depressive disorder: Distribution, stability and association with clinical variables. Chronobiol Int 2015;32(10):1343-51. https://doi.org/10.3109/07420528.2015.1091353

[15] Weiss C, Woods K, Filipowicz A, Ingram KK. Sleep quality, sleep structure, and PER3 genotype mediate chronotype effects on depressive symptoms in young adults. Front Psychol 2020;11:2028. https://doi.org/10.3389/fpsyg.2020.02028

[16] Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. Dialogues Clin Neurosci 2008;10(3):329-36. https://doi.org/10.31887/DCNS.2008.10.3/dnutt

[17] Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. J Consult Clin Psychol 1988;56(6):893-7. https://doi.org/10.1037//0022-006x.56.6.893

[18] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71. https://doi.org/10.1001/archpsyc.1961.01710120031004

[19] Friborg O, Hjemdal O, Rosenvinge JH, Martinussen M. A new rating scale for adult resilience: What are the central protective resources behind healthy adjustment? Int J Methods Psychiatr Res 2003;12(2):65-76. https://doi.org/10.1002/mpr.143

[20] Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 1976;4(2):97-110.

[21] Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. Psychiatry Res 1989;28(2):193-213. https://doi.org/10.1016/0165-1781(89)90047-4

[22] Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. J Clin Psychol 1995;51(6):768-74. https://doi.org/10.1002/1097-4679(199511)51:6<768::aid-jclp2270510607>3.0.co;2-1

[23] Hisli N. Beck Depresyon Envanterinin üniversite öğrencileri için geçerliği, güvenirliği. Psikoloji Dergisi 1989;7(23):3-13.

[24] Ulusoy M, Sahin NH, Erkmen H. Turkish version of the Beck Anxiety Inventory: Psychometric properties. Journal of Cognitive Psychotherapy 1998;12(2):163-72.

[25] Basım N, Çetin F. Yetişkinler için Psikolojik Dayanıklılık Ölçeği'nin güvenirlik ve geçerlik çalışması. Türk Psikiyatri Dergisi 2011;22(2):104-14.

[26] Punduk Z, Gür H, Ercan I. Sabahçil Akşamcil Anketi Türkçe uyarlamasinda güvenilirlik çalişmasi. Türk Psikiyatri Dergisi 2005;16(1):40-5.

[27] Güleç H, Tamam L, Turhan M, Karakuş G, Zengin M, Stanford MS. Psychometric properties of the Turkish version of the Barratt Impulsiveness Scale-11. Klinik Psikofarmakoloji Bulteni 2008;18(4):251-8.

[28] Walker WH, Walton JC, DeVries AC, Nelson RJ. Circadian rhythm disruption and mental health. Transl Psychiatry 2020;10(1):28. https://doi.org/10.1038/s41398-020-0694-0

Supplementary Table 1. Mediation Analysis of Non-Planning Impulsivity (BIS-11-NP) in the Relationship Between Chronotype (MEQ) and Depressive Symptoms (BDI)

Components	Effect	Standardized Error	Standardized Coefficient	t	Lower	Upper	p
MEQ-> BIS-11-NP	-0.090	0.024	-0.259	-3.797	-0.137	-0.043	<0.001
BIS-11-NP->BDI	0.055	0.019	0.199	2.831	0.017	0.093	0.005
Indirect Effect							
MEQ-> BIS-11-NP->BDI	-0.005	0.003			-0.011	-0.001	
Direct Effect							
MEQ->BDI	-0.015	0.007	-0.156	-2.221	-0.028	-0.002	0.027
Total Effect							
MEQ->BDI	-0.020	0.007	-0.207	-3.005	-0.033	-0.007	0.003

This table presents the mediation analysis examining the indirect effect of non-planning impulsivity (BIS-11-NP) in the relationship between chronotype (MEQ) and depressive symptoms (BDI). MEQ refers to the Morningness-Eveningness Questionnaire, BIS-11-NP to the Non-Planning subscale of the Barratt Impulsiveness Scale-11, and BDI to the Beck Depression Inventory. Reported values include unstandardized coefficients (Effect), standard errors (SE), standardized coefficients (Beta), t-values, 95% confidence intervals (CI: Lower and Upper bounds), and p-values.

Supplementary Table 2. Mediation Analysis of Attentional Impulsivity (BIS-11-A) in the Relationship Between Chronotype (MEQ) and Depressive Symptoms (BDI)

Components	Effect	Standardized Error	Standardized Coefficient	t	Lower	Upper	p
MEQ-> BIS-11-A	-0.062	0.030	-0.147	-2.101	-0.121	-0.004	0.037
BIS-11-A->BDI	0.031	0.016	0.137	1.980	0.001	0.062	0.049
Indirect Effect							
MEQ-> BIS-11-A->BDI	-0.002	0.001			-0.005	-0.001	
Direct Effect							
MEQ->BDI	-0.018	0.007	-0.187	-2.704	-0.031	-0.005	0.007
Total Effect							
MEQ->BDI	-0.020	0.007	-0.207	-3.005	-0.033	-0.007	0.003

This table presents the mediation analysis exploring the indirect role of attentional impulsivity (BIS-11-A) in the association between chronotype (MEQ) and depressive symptoms (BDI). MEQ indicates the Morningness-Eveningness Questionnaire; BIS-11-A refers to the Attentional Impulsivity subscale of the Barratt Impulsiveness Scale-11; and BDI denotes the Beck Depression Inventory. The table reports unstandardized coefficients (Effect), standard errors (SE), standardized coefficients (Beta), t-values, and 95% confidence intervals (CI: Lower and Upper bounds), along with corresponding p-values.

Supplementary Table 3. Mediation Analysis of Psychological Resilience (PRS-33) in the Relationship Between Chronotype (MEQ) and Depressive Symptoms (BDI)

Components	Effect	Standardized Error	Standardized Coefficient	t	Lower	Upper	p
MEQ-> PRS-33	0.274	0.059	0.311	4.638	0.158	0.391	<0.001
PRS-33 ->BDI	-0.019	0.008	-0.178	-2.488	-0.035	-0.004	0.014
Indirect Effect							
MEQ-> PRS-33 ->BDI	-0.005	0.003	-0.055		-0.011	-0.001	
Direct Effect							
MEQ->BDI	-0.015	0.007	-0.152	-2.119	-0.028	-0.001	0.035
Total Effect							
MEQ->BDI	-0.020	0.007	-0.207	-3.005	-0.033	-0.007	0.003

This table presents the mediation analysis assessing the indirect role of psychological resilience (PRS-33) in the relationship between chronotype (MEQ) and depressive symptoms (BDI). MEQ stands for the Morningness-Eveningness Questionnaire, PRS-33 represents the total score of the Psychological Resilience Scale for Adults, and BDI denotes the Beck Depression Inventory. The table reports unstandardized coefficients (Effect), standard errors, standardized coefficients (Beta), t-values, and 95% confidence intervals (Lower and Upper bounds), along with p-values.

Supplementary Table 4. Mediation Analysis of Attentional Impulsivity (BIS-11-A) in the Relationship Between Chronotype (MEQ) and Anxiety Symptoms (BAI)

Components	Effect	Standardized Error	Standardized Coefficient	t	Lower	Upper	p
MEQ-> BIS-11-A	-0.062	0.030	-0.147	-2.101	-0.121	-0.004	0.037
BIS-11-A->BAI	0.085	0.029	0.199	2.929	0.028	0.143	0.004
Indirect Effect							
MEQ-> BIS-11-A->BAI	-0.005	0.004	-0.029		-0.014	-0.001	
Direct Effect							
MEQ->BAI	-0.039	0.012	-0.212	-3.122	-0.063	-0.014	0.002
Total Effect							
MEQ->BAI	-0.044	0.013	-0.241	-3.524	-0.069	-0.019	0.001

This table displays the mediation analysis evaluating the role of attentional impulsivity (BIS-11-A) in the relationship between chronotype (MEQ) and anxiety symptoms (BAI). MEQ refers to the Morningness-Eveningness Questionnaire, BIS-11-A denotes the attentional subscale of the Barratt Impulsiveness Scale, and BAI is the Beck Anxiety Inventory. The table includes unstandardized coefficients (Effect), standard errors, standardized coefficients (Beta), t-values, and 95% confidence intervals (Lower and Upper bounds), with associated p-values.

acta medica

ORIGINAL ARTICLE

Treatment outcomes of postoperative abdominal bleeding after oncologic surgery: a retrospective comparative study of surgical and interventional radiologic treatments

Hilmi Anıl Dinçer[1]
ORCID: 0000-0002-3889-9395

Nezih Akkapulu[1]
ORCID: 0000-0001-7392-961X

Sara Koçi[1]
ORCID: 0009-0005-1427-9385

Doğukan Doğu[2]
ORCID: 0000-0002-1892-9358

Sermet Terzi[1]
ORCID: 0000-0003-3726-6526

Sinan Efe Yazıcı[1]
ORCID: 0009-0001-1803-0633

Ömer Cennet[1]
ORCID: 0000-0002-7430-1610

Ferdi Çay[3]
ORCID: 0000-0001-9589-7495

Fatma Gonca Eldem[3]
ORCID: 0000-0002-9887-4018

Ahmet Bülent Doğrul[1]
ORCID: 0000-0001-9837-0787

[1]Hacettepe University Faculty of Medicine, Department of General Surgery, Ankara, Türkiye

[2]Sincan Training and Research Hospital, Department of General Surgery, Ankara, Türkiye

[3]Hacettepe University Faculty of Medicine, Department of Radiology, Ankara, Türkiye

Corresponding Author: Hilmi Anıl Dinçer
E-mail: hilmianil.dincer@hacettepe.edu.tr

Received: 25 May 2025, Accepted: 26 July 2025,
Published online: 30 September 2025

ABSTRACT

Objective: Postoperative abdominal bleeding (POB) is a rare but life-threatening complication after abdominal oncologic surgery. POB can increase mortality by up to sixfold. Surgical treatment (ST) is generally preferred for early bleeding, while interventional radiologic treatment (IRT) is often favored for late bleeding; however, the literature remains inconclusive. This study aimed to compare the outcomes of ST and IRT in patients who developed POB after abdominal surgery for malignancy.

Methods: Patients who underwent abdominal surgery for malignancy between January 1, 2014, and December 31, 2024, were retrospectively reviewed. Bleeding occurring within 24 hours postoperatively was defined as early, while bleeding after 24 hours was considered late. Demographic data, clinical characteristics, treatment modalities, and outcomes were analyzed.

Results: Of 2,266 patients, 35 (1.54%) developed POB and were included. Seventeen (48.57%) had early bleeding, and 18 (51.43%) had late bleeding. ST was performed in 18 patients (51.43%), and IRT in 17 (48.57%). Median time from surgery to bleeding was significantly shorter in the ST group (1 vs. 14 days, $p<0.001$). The ST group also had lower median red blood cell transfusion requirements (6 vs. 25 units, $p<0.001$) and shorter hospital stays (15.5 vs. 33 days, $p=0.008$). Among four late-bleeding patients treated surgically, three (75%) died. Rebleeding occurred in three IRT patients (17.65%), two of whom had bleeding from pancreaticojejunal anastomosis. Overall mortality was 31.4%, with no significant difference between groups ($p=0.54$).

Conclusion: POB after malignant abdominal surgery is a serious condition. ST for early bleeding and IRT for late bleeding offer comparable success and mortality rates. However, IRT is associated with higher rate of rebleeding in cases of pancreaticojejunal anastomotic hemorrhage, while ST for late bleeding carries a high mortality risk. Major abdominal surgeries should be performed in centers equipped for IRT, and treatment decisions should be made within a multidisciplinary framework.

Keywords: intra-abdominal bleeding, interventional radiology, embolization, bleeding control, malignant abdominal surgery

INTRODUCTION

Despite advancements in surgical techniques and the standardization of operative procedures, postoperative bleeding remains a major cause of mortality following abdominal surgery. Postoperative intra-abdominal bleeding (POB) occurs in approximately 0.4% to 10% of abdominal procedures, with the majority of cases associated with pancreatic surgery [1,2]. Bleeding following pancreatoduodenectomy (PD) occurs in approximately 3% to 10% of cases and is associated with mortality rates as high as 50% in affected patients [3-5]. POB has been reported in 1% to 8% of cases following liver surgery, while its incidence after gastric surgery ranges from 1.3% to 3.8% [6-9].

The most widely accepted classification for POB is the postpancreatectomy hemorrhage (PPH) definition established by the International Study Group of Pancreatic Surgery (ISGPS) [10]. Bleeding occurring within the first 24 hours after surgery is categorized as early bleeding, while bleeding that occurs after 24 hours is defined as late bleeding. Based on this classification, various management algorithms have been proposed for the treatment of PPH [11]. Surgical treatment (ST) is generally recommended for early bleeding, while interventional radiologic treatment (IRT) is preferred for late bleeding. However, these recommendations remain controversial, and there is no universally accepted approach for managing POB following surgeries of other abdominal organs.

The aim of this study is to evaluate the characteristics and treatment outcomes of patients who developed POB after undergoing abdominal surgery for malignancy at our institution, a high-volume center specialized in oncologic surgery.

PATIENTS AND METHODS

Study design and patient selection

Patient data were retrospectively obtained from the hospital information system. Among 2,266 patients who underwent abdominal surgery for malignancy at our institution between January 1, 2014, and December 31, 2024, a total of 35 patients who received either surgical treatment (ST) or interventional radiologic treatment (IRT) for postoperative intra-abdominal bleeding (POB) were included in the study. The inclusion criteria were as follows: all adult patients who underwent laparoscopic or open surgery for malignancies of the pancreas, liver, biliary tract, stomach, colon, small intestine, or retroperitoneum and were subsequently treated with ST or IRT for POB. The exclusion criteria were as follows: patients under the age of 18; those who underwent abdominal surgery for non-malignant conditions; patients managed conservatively without surgical or interventional treatment following bleeding; and those who underwent surgery involving the kidneys or gynecologic organs. The process of patient selection is illustrated in Figure 1 as a flowchart.

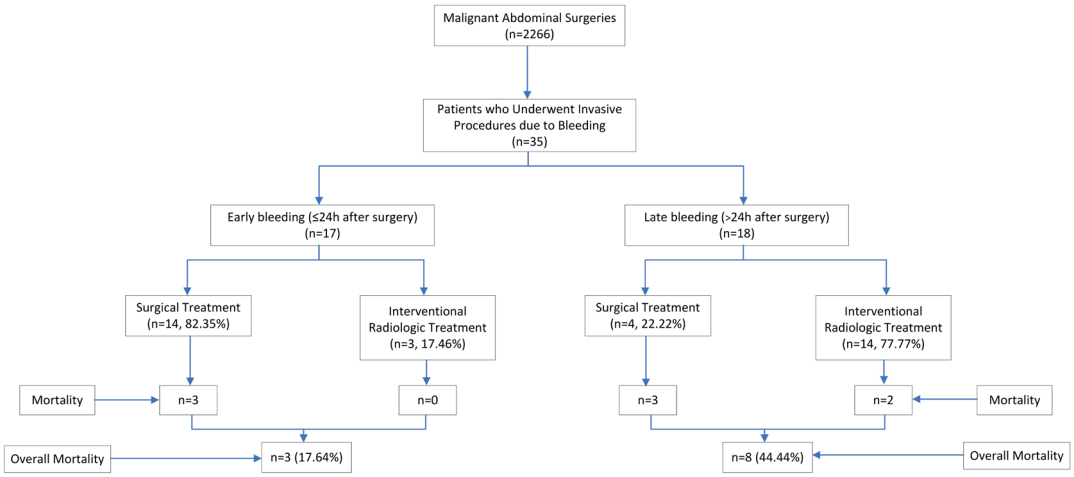


Figure 1. Flowchart

Ethical Approval: The study was approved by the Hacettepe University, Health Sciences Research Ethics Committee (Protocol no. 2025/05-48/18.02.2025). Written informed consent was obtained from all patients prior to treatment.

Demographic, clinical, and laboratory features

Data collected included patient age, sex, preoperative diagnosis, Charlson Comorbidity Index (CCI), type of index surgery, postoperative complications, Clavien–Dindo classification (C–D score), bleeding-related variables, characteristics of the surgical or interventional radiologic treatment performed for bleeding, and the outcomes of these interventions.

Definitions and classifications

In the postoperative period, the presence of hemorrhagic output from surgical drains or nasogastric tubes, as well as the development of hematemesis, melena, hematochezia, accompanying tachycardia, hypotension, oliguria, altered mental status, or a drop in hemoglobin levels, were clinically considered indicative of bleeding (Figure 2).

Figure 2. Appearance of hemorrhagic fluid coming from abdominal drain

Based on the ISGPS definition of PPH, bleeding occurring within 24 hours after abdominal surgery was defined as early bleeding, while bleeding after 24 hours was classified as late bleeding [10]. According to the same guideline, bleeding into the lumen of an intestinal organ was defined as intraluminal bleeding, while bleeding into the abdominal cavity was classified as extraluminal bleeding.

In line with the postoperative pancreatic fistula definition by the same study group, pancreatic fistulas were categorized as Grade A, B, or C, with Grade B and C fistulas considered clinically significant [12].

Rebleeding was defined as the occurrence of recurrent active bleeding after the initial hemostatic intervention had been performed.

Bleeding control procedures

Surgery

All surgical procedures were performed under general anesthesia with endotracheal intubation. The abdomen was accessed through reopening of the previous abdominal incision. After peritoneal lavage, the celiac trunk (CA), common hepatic artery (CHA), gastroduodenal artery (GDA), right hepatic artery (RHA), left hepatic artery (LHA), left gastric artery (LGA), splenic artery (SA), superior mesenteric artery (SMA), the surgical field, anastomotic sites, retroperitoneum, and diaphragmatic surfaces were systematically inspected for bleeding. Hemostasis was achieved, and after confirming the absence of active bleeding, the abdomen was closed with the placement of negative pressure closed-system silicone drains.

Interventional radiologic treatment

For interventional radiologic procedures, vascular access was obtained via the femoral or brachial artery using the Seldinger technique. A microcatheter was advanced in a superselective manner into branches of the CA, SMA, or abdominal aorta. Based on the location of the bleeding, mechanical or liquid embolic agents were used to achieve hemostasis following catheterization. Control angiographic images were obtained to confirm the absence of contrast extravasation (Figure 3).

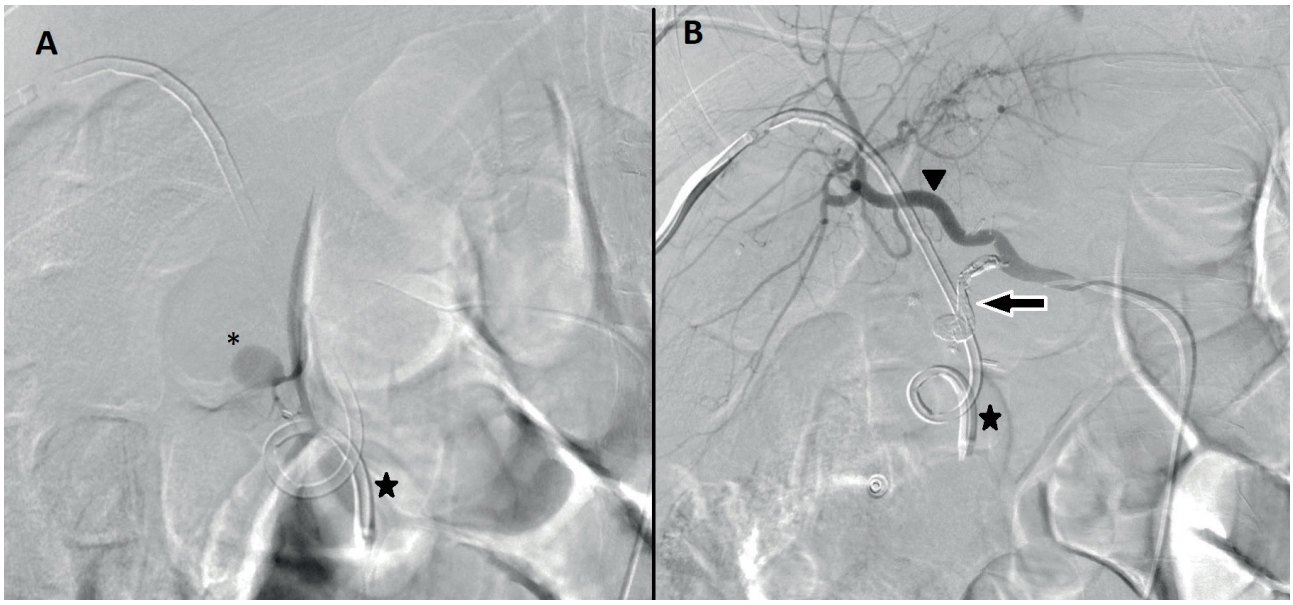


Figure 3. Interventional radiologic treatment. A 67-year-old male patient underwent an open subtotal gastrectomy with D2 lymphadenectomy for gastric adenocarcinoma. During his hospital stay, he was being managed for a postoperative duodenal stump leak with antibiotics and a drainage catheter. On postoperative day 28, the patient developed hemodynamic instability. Laboratory tests revealed a hemoglobin level of 5.5 g/dL. After initial resuscitation, imaging demonstrated active bleeding from a gastroduodenal artery pseudoaneurysm. The patient was successfully treated with coil embolization. A. Fluoroscopic image obtained during active bleeding. The asterisk indicates a pseudoaneurysm in the gastroduodenal artery; the black star indicates the drainage catheter. B. Fluoroscopic image after successful bleeding control with coil embolization. The black-and-white arrow indicates the embolized gastroduodenal artery; the black arrowhead indicates the proper hepatic artery; the black star indicates the drainage catheter.

Statistical analysis

Categorical variables were summarized as frequencies and percentages, while non-normally distributed continuous variables were presented as medians with corresponding minimum and maximum values. The Mann–Whitney U test was used to compare non-normally distributed continuous variables. The Pearson chi-square test or Fisher's exact test was applied for the analysis of categorical and ordinal variables, as appropriate. A two-tailed p-value of <0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Among 2,266 patients who underwent intra-abdominal surgery for malignancy during the study period, 35 patients (1.54%) who required treatment for postoperative bleeding were included in the study. Of these, 23 patients (65.7%) were male. ST was performed in 18 patients (51.43%), while IRT was applied in 17 patients (48.57%). When the demographic characteristics of the patients were analyzed, no statistically significant differences were observed between the groups in terms of age, CCI, ASA score, use of antithrombotic medications, or receipt of neoadjuvant therapy. In the ST group, bleeding occurred following pancreatic surgery in nine patients, colorectal surgery in five, resection of intra-abdominal masses in three, and liver surgery in one patient. In the IRT group, bleeding occurred after pancreatic surgery in nine patients, gastric surgery in six, and colorectal surgery in two. Demographic data and primary malignancy etiologies are summarized in Table 1.

When patients were evaluated based on the timing of bleeding, 17 (48.57%) experienced early bleeding, while 18 (51.43%) had late bleeding. Among early bleeding cases, 14 patients (82.35%) were treated with ST, whereas 14 patients (77.77%) with late bleeding received IRT. The mortality rate

Table 1. Patient characteristics and demographic data

	Surgical management (n=18)	Interventional radiologic management (n=17)	p-value
Gender (m/f)	9/9	14/3	0.07
Age, median (min-max)	63 (44-78)	56 (22-70)	0.07
Charlson Comorbidity Index, median (min-max)	4 (2-10)	4 (2-7)	0.36
ASA score, median (min-max)	2 (1-3)	2 (1-3)	0.22
Use of antithrombotic drug (n)	2/18	1/17	0.52
Etiology of primary malignancy, (n)			
Pancreas	9	9	
Ductal adenocarcinoma	8	6	
Neuroendocrine tumor	0	3	
Metastasis (Renal cell carcinoma)	1	0	
Stomach	0	6	
Adenocarcinoma	0	6	
Colon and rectum	5	2	
Adenocarcinoma	4	2	
Gastrointestinal stromal tumor	1	0	
Intraabdominal mass	3	0	
Leiomyosarcoma	1	0	
Carcinosarcoma	1	0	
Liposarcoma	1	0	
Liver	1	0	
Malign mesenchymal tumor	1	0	
Neoadjuvan treatment			
Chemotherapy, n (%)	5 (27.78)	6 (35.29)	0.63
Radiotherapy, n (%)	2 (11.11)	0	0.48

ASA: American Society of Anesthesiologists.

was 17.64% in the early bleeding group and 44.44% in the late bleeding group; however, this difference was not statistically significant (p=0.14).

When perioperative characteristics were examined, 28 patients (80%) had extraluminal bleeding, while 7 patients (20%) had intraluminal bleeding. In the ST group, extraluminal bleeding was observed in 15 patients and intraluminal bleeding in 3 patients. In the IRT group, 13 patients had extraluminal and 4 had intraluminal bleeding (p=0.10). Regarding the source of bleeding, no hemorrhagic drainage was detected in 18 patients (51.43%), whereas 10 patients (28.57%) showed blood in their abdominal drainage tubes. In the evaluation of the bleeding site, all patients in the IRT group (100%) underwent computed tomography angiography (CTA), while only one patient (5.55%) in the ST group, who experienced bleeding on postoperative day 9, underwent CTA. The median time from the index operation to the onset of bleeding was significantly shorter in the ST group compared to the IRT group (1 vs. 14 days, respectively; p<0.001). Similarly, the median red blood cell transfusion (RBC) requirement after bleeding diagnosis was significantly lower in the ST group than in the IRT group (6 vs. 25 units, respectively; p<0.001). Length of hospital stay was significantly shorter in the ST group (median 15.5 vs. 33 days, respectively; p=0.008). However, there were no statistically significant differences between the groups regarding ICU admission, number of lymph nodes removed, or in-hospital mortality. Likewise, when comparing early postoperative complications between groups, no statistically significant differences were found in rates of pancreatic fistula, biliary leakage, anastomotic leakage, sepsis, or intra-abdominal abscess (p=0.26, 0.73, 0.23, 0.60, and 0.07, respectively). C-D scores were also similar between the groups (p=0.83). The results are presented in Table 2.

Table 2. Perioperative characteristics of patients

	Surgical treatment (n=18)	Interventional radiologic treatment (n=17)	p-value
Type of Initial Surgery (n)			
Hepatectomy	1	0	
Segmentectomy (Segment 4)	1	0	
Pancreatic surgery	9	9	
Pancreaticoduodenectomy	8	8	
Laparoscopic distal pancreatectomy	1	0	
Enucleation	0	1	
Gastric surgery	0	6	
Subtotal gastrectomy	0	2	
Total gastrectomy	0	3	
Laparoscopic total gastrectomy	0	1	
Colorectal surgery	5	2	
Low anterior resection	2	0	
Right hemicolectomy	1	1	
Left hemicolectomy	1	0	
Total abdominal colectomy	1	0	
Total abdominal colectomy-HIPEC	0	1	
Intraabdominal tumor excision	3	0	
Postoperative early complications, n/total (%)			
Sepsis	3/18 (16.67)	1/17 (5.88)	0.60
Pancreatic fistula	4/9 (44.44)	2/10 (20)	0.26
Biliary leakage	1/9 (11.11)	1/8 (12.5)	0.73
Anastomotic leakage	1/13 (7.69)	4/16 (25)	0.23
Intraabdominal abscess	3/18 (16.67)	8/17 (47.05)	0.07
Claviden dindo classification, median (min-max)	4 (3-5)	4 (3-5)	0.83
Site of blood (n)			0.10
Extraluminal	15	13	
Dissection area	6	0	
Anastomosis	1	2	
Vascular	7	11	
Pancreatic duct	1	0	
Intraluminal	3	4	
Anastomosis	2	3	
Aortoenteric fistula	0	1	
Stress ulcer	1	0	
Source of bleeding (n)			0.06
Bleeding abdominal drainage tube	7	3	
Hematemesis	1	6	
None	10	8	
RBC transfusion*, unite, median (min-max)	6 (1-30)	25 (4-56)	<0.001
Time interval between index operation to hemorrhage, day, median (min-max)	1 (0-9)	14 (1-36)	<0.001
Number of Lymph node, median (min-max)	12 (0-31)	10 (0-33)	0.59
Length of Hospital stay, day, median (min-max)	15.5 (6-83)	33 (9-202)	0.008
ICU stay, day, median (min-max)	8.5 (0-32)	9 (0-80)	0.50
In-hospital mortality, n (%)	6 (33.33)	5 (29.41)	0.54

RBC: red blood cell; HIPEC: Hyperthermic Intraperitoneal Chemotherapy; ICU: Intensive care unit.

*The amount of transfusion after diagnosis of bleeding.

Table 3. Bleeding sites and treatment characteristics in patients who underwent interventional radiologic treatment

Patient Number	Source of hemorrhage	Endovascular treatment method
1	Left superior vesical artery	Glue
2	Aortoenteric fistula	Endovascular graft
3	Celiac artery	Glue
4	Segment 2-3 artery	Coil+Glue
5	Gastroduodenal artery	Coil
6	Gastroduodenal artery	Coil
7	Right external iliac artery	Endovascular graft
8	Gastrojejunostomy anastomosis line	Glue
9	Hepatic artery	Glue
10	Splenic artery	Coil
11	Pancreaticojejunostomy anastomosis line	Coil
12	Replaced right hepatic artery	Coil
13	Gastroduodenal artery	Coil
14	Gastroduodenal artery	Coil
15	Pancreaticojejunostomy anastomosis line	Glue
16	Gastroduodenal artery	Coil
17	Pancreaticojejunostomy anastomosis line	Coil

Table 4. Perioperative characteristics of patients who developed rebleeding

Patient	Initial management following bleeding	Interval between the initial and secondary procedures (day)	Secondary procedure	Location	Dead/Alive
1	Glue embolization	1	Relaparotomy	P-J anastomosis	Alive
2	Coil embolization	2	Relaparotomy	GDA	Alive
3	Coil embolization	9	Relaparotomy	P-J anastomosis	Alive

P-J: pancreaticojejunostomy; GDA: gastroduodenal artery.

When patients were analyzed according to the source of bleeding, it was found that in the ST group, eight patients had bleeding from the surgical site, three from the anastomotic line, two from behind the superior mesenteric vein, two from mesenteric vessels, one from the gastroduodenal artery (GDA), one from the gonadal vein, and one from the portal vein. The bleeding sites and treatment modalities in the IRT group are presented in Table 3.

Rebleeding occurred in three patients (17.65%) who underwent IRT for bleeding. All of these patients subsequently underwent surgical intervention to achieve bleeding control. No IRT-related mortality was observed in any of the patients. Perioperative characteristics of the patients are summarized in Table 4.

Despite treatment, in-hospital mortality occurred in 11 patients (31.4%). Six of these patients were in the ST group, and five were in the IRT group. Among these cases, the median survival time following bleeding control was 6 days. The final cause of death was identified as intra-abdominal sepsis in five patients, multiorgan failure secondary to hypovolemic shock in four patients, and pneumonia in two patients. Data on patients who experienced post-treatment mortality are presented in Table 5.

Table 5. Characteristics of patients who died following bleeding

Patient number	Index operation	Interval between index operation and death (day)	Bleeding source	Final treatment	Cause of death
1	Whipple operation	3	Dissection area	Relaparotomy	Pneumonia
2	Whipple operation	0	Uncinate process	Relaparotomy	Hipovolemic shock
3	Intraabdominal tumor resection	9	Gastroduodenal artery	Relaparotomy	Intraabdominal Sepsis
4	Left hemicolectomy	2	Retroperitoneal plane	Relaparotomy	Hipovolemic shock
5	Right hemicolectomy	0	Superior mesenteric artery	Relaparotomy	Hipovolemic shock
6	Laparoscopic distal pancreatectomy	1	Left adrenal gland	Relaparotomy	Hipovolemic shock
7	Total gastrectomy	36	Aortoenteric fistule	Graft	Intraabdominal Sepsis
8	Subtotal gastrectomy	28	Coeliac artery	Glue embolization	Intraabdominal Sepsis
9	Laparoscopic total gastrectomy	6	Gastroduodenal artery	Coil embolization	Pneumonia
10	Whipple operation	14	Pancreaticojejunostomy	Coil embolization	Intraabdominal Sepsis
11	Total gastrectomy, splenectomy, distal pancreatectomy	10	Gastroduodenal artery	Coil embolization	Intraabdominal Sepsis

DISCUSSION

Postoperative bleeding requiring treatment was observed in 1.54% of patients who underwent intra-abdominal surgery for malignancy. Among these, 48.57% were classified as early bleeding and 51.42% as late bleeding. Although not statistically significant, mortality was clinically higher in patients with late bleeding compared to those with early bleeding (17.65% vs. 44.44%, respectively; p=0.14). The overall mortality rate among patients with postoperative bleeding was 31.42%. ST was more commonly employed in early bleeding cases, whereas IRT was more frequently used for late bleeding. Notably, among patients who underwent ST for late bleeding, the mortality rate was 75%. Patients treated with ST had a lower requirement for RBC transfusion and a shorter length of hospital stay. IRT achieved a 100% technical success rate, with a 17.65% incidence of rebleeding and an 82.35% clinical success rate. Both treatment modalities yielded comparable morbidity and mortality outcomes. However, in cases of bleeding originating from pancreaticojejunostomy (P–J) anastomoses, rebleeding occurred in 66.66% of patients following IRT.

Advancements in oncology and innovations in neoadjuvant therapies have enabled surgical intervention for tumors that were previously considered locally advanced, unresectable, or inoperable. In parallel, progress in surgical techniques has led to more frequent performance of vascular resections. As a result, the incidence of POB has increased compared to previous years [13-16]. Although POB is most commonly observed after pancreatic surgery, it can occur following any type of abdominal operation. In cases of bleeding after pancreatic procedures, mortality rates can reach up to 50%, and the risk of death is reported to be up to six times higher in patients who experience bleeding compared to those who do not [4,17].

The most widely accepted definition of POB is the PPH classification proposed by the ISGPS [10]. This classification can also be applied to bleeding that occurs following intra-abdominal surgery for malignancy [18]. Bleeding within the first 24 hours after surgery is defined as early bleeding, while bleeding that occurs thereafter is classified as late bleeding. Early bleeding is often associated with inadequate intraoperative hemostasis or bleeding masked by vasoconstriction that goes undetected at the end of the procedure. In

contrast, late bleeding is considered the result of a more complex postoperative process and has been shown to be associated with complications such as intra-abdominal abscesses, anastomotic leakage, biliary leakage, and pancreatic fistulas [19-22]. Additionally, during peritumoral lymph node dissection, the adventitial layer of the vessels may be removed, leaving the vessels unprotected and more susceptible to injury [15]. Intra-abdominal fluid collections can erode the weakened vascular wall, leading to the development of pseudoaneurysms or sudden hemorrhage. In our study, early bleeding occurred in 17 patients (48.57%), while late bleeding was observed in 18 patients (51.42%). All pancreatic and gastric surgeries in the cohort involved lymph node dissection around the CA and CHA. Despite this, there was no statistically significant difference in early postoperative complications between the early and late bleeding groups—an observation that differs from what has been commonly reported in the literature.

Surgical treatment is generally the recommended approach for managing early bleeding [18,19]. In the past, ST was also the initial recommendation for managing late bleeding. Although relaparotomy may be considered effective not only for controlling bleeding but also for evaluating the abdominal cavity and addressing other potential complications, postoperative mortality rates of 32.3% to 37% have been reported following relaparotomy [23,24]. Due to its less invasive nature, high success rates, and rapid recovery outcomes compared to ST, IRT has increasingly become the first-line option, particularly in the management of late postoperative bleeding [24,25]. Some authors argue that hemodynamic stability is a prerequisite for performing IRT [26]. However, in a study investigating which type of emergency intervention should be performed, univariate analysis did not identify any significant predictors [27]. In our study, 14 (82.35%) of the 17 patients with early bleeding were treated with ST, while 14 (77.77%) of the 18 patients with late bleeding underwent IRT. Among the four late bleeding patients who received ST, the mortality rate was 75%. These findings are consistent with the literature, which recommends ST for early bleeding and IRT for late bleeding.

In studies examining the outcomes of IRT in the literature, technical success rates have been reported to range between 82% and 100%, rebleeding rates between 7% and 30%, hepatic complications between 12% and 63%, and mortality rates between 7% and 54% [28,29]. In a study evaluating 24 patients who developed POB after gastrectomy and were treated with IRT, the reported outcomes included a technical success rate of 100%, 30-day mortality of 12%, persistent bleeding in 4.16% of cases, rebleeding in 4.16%, and a clinical failure rate of 21% [30]. In contrast, a meta-analysis evaluating 163 cases found no significant differences between IRT and ST in terms of hemostasis, complication rates, or mortality [31]. Due to factors such as the limited number of cases and the emergency nature of the condition, there are no randomized controlled trials directly comparing IRT and ST. In a recent study by Habib et al., it was emphasized that endoscopic treatment of intraluminal bleeding is often unsuccessful due to massive hemorrhage and hemodynamic instability, which may delay the initiation of IRT [24]. The study also highlighted that IRT can achieve high success rates even in cases of intraluminal bleeding. In our study, none of the patients received endoscopic treatment. All six patients who developed POB after gastric surgery were treated with IRT. The technical success rate of IRT was 100%. Rebleeding occurred in 3 patients (17.64%) following IRT, resulting in a clinical failure rate of 17.64% and a clinical success rate of 82.36%. No IRT-related complications or organ failure were observed. Upon analysis of the three rebleeding cases, one was found to originate from the gastroduodenal artery (GDA), while the remaining two originated from the P–J anastomosis. Among the patients treated with IRT, three had P–J anastomotic bleeding, and two of these (66.66%) experienced rebleeding. Based on these findings, surgical treatment may be a more appropriate approach for patients with P–J anastomotic bleeding.

Despite literature suggesting surgical intervention in patients with postoperative complications, 14 of the patients (82.35%) in our study who underwent IRT had postoperative complications. Furthermore, there was no statistically significant difference between the IRT and ST groups in terms of postoperative complication rates (Table 2). Unlike previous reports, our findings demonstrate comparable success rates between

the two treatment modalities, even in the presence of complications. Among the 14 patients who underwent ST for early bleeding, complications developed in 6 patients (42.85%) during follow-up, and mortality occurred in 3 patients (21.42%). These results highlight the critical importance of achieving meticulous hemostasis during the initial surgical procedure.

In angiographic treatment, polyvinyl alcohol, glue, or coils are commonly used as embolic agents. When the bleeding vessel can be directly accessed, coils are preferred; for embolization of distal branches that cannot be directly catheterized, glue is typically used [28]. In previous studies, the most commonly reported bleeding vessels include the GDA, CA, CHA, LHA, RHA, SA, SMA, and LGA [32,33]. The risk of hepatic infarction following complete embolization of the CHA has been reported to be as high as 30% [34]. Selective embolization in GDA bleeding aims to preserve hepatic blood flow; however, although technically challenging, it carries a high risk of rebleeding [33]. Therefore, graft placement techniques have been developed to minimize both ischemic complications and the risk of rebleeding. Successful application of this method requires that the bleeding artery be anatomically suitable for graft placement [35]. However, graft-related complications such as infection and thrombosis have been reported. Additionally, antiplatelet therapy is typically recommended following graft placement, but in patients with POB, the necessity of antiplatelet use after treatment remains a matter of debate due to the increased risk of recurrent bleeding [36]. In our study, coil embolization was the most frequently used technique in IRT; however, no cases of organ dysfunction or procedure-related mortality were observed. Additionally, in line with the literature, the most commonly treated bleeding sources were the GDA, branches of the HA, and P–J anastomotic sites.

In our study, among patients who developed mortality, four had undergone pancreatic surgery, four had gastric surgery, two had colorectal surgery, and one had intra-abdominal tumor resection. The mortality rate was 29.41% among patients treated with IRT and 33.33% among those treated with ST. When evaluated according to the timing of bleeding, mortality was 17.65% in the early bleeding group and 44.44% in the late bleeding group. Although this difference was not statistically significant, it was considered clinically relevant. The overall mortality rate was 31.42%, which is consistent with previous literature. The similar mortality rates between ST and IRT suggest that both treatment modalities offer comparable success in managing POB. However, in clinical practice, a higher mortality risk should be anticipated in patients presenting with late bleeding.

In this study, comparison of perioperative characteristics between the two treatment groups revealed that the median RBC transfusion requirement was significantly lower in the ST group (6 vs. 25 units, respectively; $p<0.001$). Regarding the time interval between the index operation and the onset of hemorrhage, the median duration was 1 day in the ST group and 25 days in the IRT group ($p<0.001$). When comparing the length of hospital stay, it was significantly shorter in the ST group (median 15.5 vs. 33 days, respectively; $p=0.008$). These findings suggest that early bleeding is more frequently managed with ST, requires fewer RBC transfusions, and results in shorter hospitalization. The observed differences may be attributed to the fact that patients treated with IRT often had ongoing postoperative, surgery-specific complications, which necessitated prolonged hospitalization and additional blood product support even before the onset of bleeding.

One study reported that CT angiography was diagnostic in only 45% of cases, suggesting that it should not be routinely performed in all patients [24]. In our study, CT angiography was performed in only one patient (5.55%) in the ST group, and this was a late bleeding case on postoperative day nine. In contrast, all patients in the IRT group underwent CT angiography. Based on these findings, it can be concluded that in cases of early bleeding, treatment can often be planned without the need for pre-intervention imaging.

Our study has several limitations. The retrospective design, the use of data from a single center, and the relatively small sample size were among the primary limitations. Additionally, the lack of accessible data regarding sentinel bleeding—an important indicator for the early detection of severe hemorrhage in POB patients—was another major limitation. Moreover, factors such as the type of energy devices used during surgery, variations in perioperative patient management, and the

use of minimally invasive techniques are potential variables that may have influenced the study outcomes.

CONCLUSION

Postoperative bleeding following intra-abdominal surgery for malignancy is a life-threatening complication. As in pancreatic surgery, ST for early bleeding and IRT for late bleeding appear to offer acceptable success rates in surgeries involving other abdominal organs as well. However, in cases of bleeding from P–J anastomoses, ST should be prioritized as the first-line treatment. Additionally, in early bleeding, pre-intervention imaging may not be necessary. In conclusion, major abdominal oncologic surgeries should be performed in tertiary centers where IRT is readily available. In the event of POB, treatment decisions should be made on a case-by-case basis through a multidisciplinary approach involving both general surgeons and interventional radiologists.

Author contribution

Study conception and design: HAD, NA, OC, DD, FC, FGE and ABD; data collection: HAD, NA, SK, DD, ST, SEY, OC, FC, FCE and ABD; analysis and interpretation of results: HAD, NA, SK, DD, ST, SEY, OC, FC, FCE and ABD; draft manuscript preparation: HAD, NA, SK, DD, ST, SEY, OC, FC, FCE and ABD. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University, Health Sciences Research Ethics Committee (Protocol no. 2025/05-48/18.02.2025).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Tanizawa Y, Bando E, Kawamura T, Tokunaga M, Ono H, Terashima M. Early postoperative anastomotic hemorrhage after gastrectomy for gastric cancer. Gastric Cancer 2010;13(1):50-7. https://doi.org/10.1007/s10120-009-0535-6

[2] Martínez-Serrano MA, Parés D, Pera M, et al. Management of lower gastrointestinal bleeding after colorectal resection and stapled anastomosis. Tech Coloproctol 2009;13(1):49-53. https://doi.org/10.1007/s10151-009-0458-6

[3] Yekebas EF, Wolfram L, Cataldegirmen G, et al. Postpancreatectomy hemorrhage: diagnosis and treatment: an analysis in 1669 consecutive pancreatic resections. Ann Surg 2007;246(2):269-80. https://doi.org/10.1097/01.sla.0000262953.77735.db

[4] Wei HK, Wang SE, Shyr YM, et al. Risk factors for post-pancreaticoduodenectomy bleeding and finding an innovative approach to treatment. Dig Surg 2009;26(4):297-305. https://doi.org/10.1159/000228245

[5] Turrini O, Moutardier V, Guiramand J, et al. Hemorrhage after duodenopancreatectomy: impact of neoadjuvant radiochemotherapy and experience with sentinel bleeding. World J Surg 2005;29(2):212-6. https://doi.org/10.1007/s00268-004-7557-3

[6] Cho JY, Suh KS, Kwon CH, et al. Outcome of donors with a remnant liver volume of less than 35% after right hepatectomy. Liver Transpl 2006;12(2):201-6. https://doi.org/10.1002/lt.20592

[7] Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. Ann Surg 2006;243(3):373-9. https://doi.org/10.1097/01.sla.0000201483.95911.08

[8] Kim MC, Kim W, Kim HH, et al. Risk factors associated with complication following laparoscopy-assisted gastrectomy for gastric cancer: a large-scale korean multicenter study. Ann Surg Oncol 2008;15(10):2692-700. https://doi.org/10.1245/s10434-008-0075-z

[9] Jeong O, Park YK, Ryu SY, Kim DY, Kim HK, Jeong MR. Predisposing factors and management of postoperative bleeding after radical gastrectomy for gastric carcinoma. Surg Today 2011;41(3):363-8. https://doi.org/10.1007/s00595-010-4284-2

[10] Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007;142(1):20-5. https://doi.org/10.1016/j.surg.2007.02.001

[11] Gao F, Li J, Quan S, et al. Risk factors and treatment for hemorrhage after pancreaticoduodenectomy: a case series of 423 patients. Biomed Res Int 2016;2016:2815693. https://doi.org/10.1155/2016/2815693

[12] Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery 2017;161(3):584-591. https://doi.org/10.1016/j.surg.2016.11.014

[13] Miccio JA, Talcott WJ, Patel T, et al. Margin negative resection and pathologic downstaging with multiagent chemotherapy with or without radiotherapy in patients with localized pancreas cancer: a national cancer database analysis. Clin Transl Radiat Oncol 2020;27:15-23. https://doi.org/10.1016/j.ctro.2020.12.003

[14] De Simoni O, Scarpa M, Tonello M, et al. Oligometastatic pancreatic cancer to the liver in the era of neoadjuvant chemotherapy: which role for conversion surgery? A systematic review and meta-analysis. Cancers (Basel) 2020;12(11):3402. https://doi.org/10.3390/cancers12113402

[15] Habib JR, Kinny-Köster B, van Oosten F, et al. Periadventitial dissection of the superior mesenteric artery for locally advanced pancreatic cancer: surgical planning with the "halo sign" and "string sign". Surgery 2021;169(5):1026-1031. https://doi.org/10.1016/j.surg.2020.08.031

[16] Kinny-Köster B, Habib JR, Javed AA, et al. Technical progress in robotic pancreatoduodenectomy: TRIANGLE and periadventitial dissection for retropancreatic nerve plexus resection. Langenbecks Arch Surg 2021;406(7):2527-34. https://doi.org/10.1007/s00423-021-02261-2

[17] Kasumova GG, Eskander MF, Kent TS, et al. Hemorrhage after pancreaticoduodenectomy: does timing matter? HPB (Oxford) 2016;18(10):861-9. https://doi.org/10.1016/j.hpb.2016.07.001

[18] Yang J, Zhang XH, Huang YH, et al. Diagnosis and treatment of abdominal arterial bleeding after radical gastrectomy: a retrospective analysis of 1875 consecutive resections for gastric cancer. J Gastrointest Surg 2016;20(3):510-20. https://doi.org/10.1007/s11605-015-3049-z

[19] Farvacque G, Guilbaud T, Loundou AD, et al. Delayed post-pancreatectomy hemorrhage and bleeding recurrence after percutaneous endovascular treatment: risk factors from a bi-centric study of 307 consecutive patients. Langenbecks Arch Surg 2021;406(6):1893-902. https://doi.org/10.1007/s00423-021-02146-4

[20] Chen JF, Xu SF, Zhao W, et al. Diagnostic and therapeutic strategies to manage post-pancreaticoduodenectomy hemorrhage. World J Surg 2015;39(2):509-15. https://doi.org/10.1007/s00268-014-2809-3

[21] Pang T, Wu Z, Zeng H, Zhang X, Hu M, Cao L. Analysis of the risk factors for secondary hemorrhage after abdominal surgery. Front Surg 2023;10:1091162. https://doi.org/10.3389/fsurg.2023.1091162

[22] Lu JW, Ding HF, Wu XN, et al. Intra-abdominal hemorrhage following 739 consecutive pancreaticoduodenectomy: risk factors and treatments. J Gastroenterol Hepatol 2019;34(6):1100-7. https://doi.org/10.1111/jgh.14560

[23] Floortje van Oosten A, Smits FJ, van den Heuvel DAF, van Santvoort HC, Molenaar IQ. Diagnosis and management of postpancreatectomy hemorrhage: a systematic review and meta-analysis. HPB (Oxford) 2019;21(8):953-61. https://doi.org/10.1016/j.hpb.2019.02.011

[24] Habib JR, Gao S, Young AJ, et al. Incidence and contemporary management of delayed bleeding following pancreaticoduodenectomy. World J Surg 2022;46(5):1161-71. https://doi.org/10.1007/s00268-022-06451-x

[25] Bruder L, Schawe L, Gebauer B, et al. Evaluation of open surgical and endovascular treatment options for visceral artery erosions after pancreatitis and pancreatic surgery. Curr Oncol 2022;29(4):2472-82. https://doi.org/10.3390/curroncol29040201

[26] Roulin D, Cerantola Y, Demartines N, Schäfer M. Systematic review of delayed postoperative hemorrhage after pancreatic resection. J Gastrointest Surg 2011;15(6):1055-62. https://doi.org/10.1007/s11605-011-1427-8

[27] Jilesen APJ, Tol JAMG, Busch ORC, et al. Emergency management in patients with late hemorrhage after pancreatoduodenectomy for a periampullary tumor. World J Surg 2014;38(9):2438-47. https://doi.org/10.1007/s00268-014-2593-0

[28] Biondetti P, Fumarola EM, Ierardi AM, Carrafiello G. Bleeding complications after pancreatic surgery: interventional radiology management. Gland Surg 2019;8(2):150-63. https://doi.org/10.21037/gs.2019.01.06

[29] Kim J, Kim JK, Yoon W, et al. Transarterial embolization for postoperative hemorrhage after abdominal surgery. J Gastrointest Surg 2005;9(3):393-9. https://doi.org/10.1016/j.gassur.2004.07.015

[30] Han K, Ahmed BM, Kim MD, et al. Clinical outcome of transarterial embolization for postgastrectomy arterial bleeding. Gastric Cancer 2017;20(5):887-94. https://doi.org/10.1007/s10120-017-0700-2

[31] Limongelli P, Khorsandi SE, Pai M, et al. Management of delayed postoperative hemorrhage after pancreaticoduodenectomy: a meta-analysis. Arch Surg 2008;143(10):1001-7; discussion 1007. https://doi.org/10.1001/archsurg.143.10.1001

[32] Gwon DI, Ko GY, Sung KB, Shin JH, Kim JH, Yoon HK. Endovascular management of extrahepatic artery hemorrhage after pancreatobiliary surgery: clinical features and outcomes of transcatheter arterial embolization and stent-graft placement. AJR Am J Roentgenol 2011;196(5):W627-34. https://doi.org/10.2214/AJR.10.5148

[33] Hur S, Yoon CJ, Kang SG, et al. Transcatheter arterial embolization of gastroduodenal artery stump pseudoaneurysms after pancreaticoduodenectomy: safety and efficacy of two embolization techniques. J Vasc Interv Radiol 2011;22(3):294-301. https://doi.org/10.1016/j.jvir.2010.11.020

[34] Miura F, Asano T, Amano H, et al. Management of postoperative arterial hemorrhage after pancreato-biliary surgery according to the site of bleeding: re-laparotomy or interventional radiology. J Hepatobiliary Pancreat Surg 2009;16(1):56-63. https://doi.org/10.1007/s00534-008-0012-3

[35] Stoupis C, Ludwig K, Inderbitzin D, Do DD, Triller J. Stent grafting of acute hepatic artery bleeding following pancreatic head resection. Eur Radiol 2007;17(2):401-8. https://doi.org/10.1007/s00330-006-0359-2

[36] Hassold N, Wolfschmidt F, Dierks A, Klein I, Bley T, Kickuth R. Effectiveness and outcome of endovascular therapy for late-onset postpancreatectomy hemorrhage using covered stents and embolization. J Vasc Surg 2016;64(5):1373-83. https://doi.org/10.1016/j.jvs.2016.05.071

acta medica

ORIGINAL ARTICLE

Neuropsychological response to ventriculoperitoneal shunting in idiopatic normal pressure hydrocephalus: early gains and the importance of baseline cognition

Ezgi Yetim[1]
ORCID: 0000-0002-1132-3660

Amin Charehsaz[2]
ORCID: 0009-0001-4430-9996

Efecan Çekiç[2]
ORCID: 0000-0003-2203-5944

Ayşe Akyay[1]
ORCID: 0009-0002-6255-6277

Ahmet İlkay Işıkay[2]
ORCID: 0000-0001-7790-4735

Gül Yalçın Çakmaklı[1,3]
ORCID: 0000-0001-8545-7939

Rahşan Göçmen[4]
ORCID: 0000-0002-0223-9336

Bülent Elibol[1]
ORCID: 0000-0001-5015-0152

[1]Department of Neurology, Hacettepe University Faculty of Medicine, Ankara, Türkiye

[2]Department of Neurosurgery, Hacettepe University Faculty of Medicine, Ankara, Türkiye

[3]Institute of Neurological Sciences and Psychiatry Laboratory, Hacettepe University Faculty of Medicine, Ankara, Türkiye

[4]Department of Radiology, Hacettepe University Faculty of Medicine, Ankara, Türkiye

Corresponding Author: Ezgi Yetim
E-mail: ezgiyetim@hacettepe.edu.tr

Received: 26 May 2025, Accepted: 18 July 2025,
Published online: 30 September 2025

ABSTRACT

Objective: Idiopathic normal pressure hydrocephalus (iNPH) is a reversible cause of cognitive impairment in older adults, characterized by gait disturbance, urinary incontinence, and cognitive decline. While ventriculoperitoneal (VP) shunt surgery can improve the classical triad, its cognitive and emotional effects remain under characterized.

In this study we aim to investigate neuropsychiatric outcomes following VP shunt surgery in iNPH patients and to identify predictors of postoperative cognitive improvement.

Material and Methods: This retrospective single-center study included 55 patients with iNPH who underwent VP shunt surgery between 2020 and 2024. Neuropsychological testing was conducted preoperatively and at a median of 11 months postoperatively, evaluating global cognition, memory, attention, executive and visuospatial functions, and mood. Pre- and postoperative performances were compared, and multivariate regression models were used to determine independent predictors of cognitive gain.

Results: Significant postoperative improvements were observed in MMSE (median 24.0 to 27.0, $p < 0.001$), memory scores (ERCT: 40.0 to 45.0, $p < 0.001$), attention/executive functions and depression severity (BDI: 12.0 to 9.0, $p < 0.001$). Stratified regression analysis showed that patients in the lowest baseline MMSE and ERCT tertile experienced the greatest improvement shortly after surgery, with longer follow-up associated with diminishing gains (MMSE: $\beta = -0.76$, $p < 0.001$, ERCT: $\beta = -0.76$, $p < 0.001$).

Conclusion: Cognitive improvement after VP shunt surgery in iNPH is strongly influenced by baseline cognitive status and the timing of follow-up. Patients with lower preoperative scores benefit the most when evaluated in the early postoperative phase. These findings emphasize the need for timely intervention and tailored neuropsychological monitoring to optimize outcomes.

Keywords: idiopathic normal pressure hydrocephalus, ventriculoperitoneal shunt, cognitive impairment, neuropsychological testing

INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) is a neurological disorder predominantly affecting older adults, characterized by the classic triad of gait disturbance, urinary incontinence, and cognitive decline [1-3]. Its prevalence increases with age, reaching 1.4%–3.8% in individuals over 80 years according to Japanese data, and up to 8.9% in certain Western populations [4,5]. Ventriculoperitoneal (VP) shunt surgery remains the standard treatment, often leading to marked clinical improvement [6]. The pathophysiology of iNPH involves ventriculomegaly and disturbances in cerebrospinal fluid (CSF) dynamics, which may exert pressure on frontal-subcortical circuits. These alterations can result in various cognitive and neuropsychiatric symptoms, particularly apathy, executive dysfunction, and attentional deficits [7,8]. Although motor improvement is well-documented following shunting, the extent and pattern of cognitive recovery remain less predictable.

Growing evidence highlights the utility of comprehensive neuropsychological assessments not only in evaluating treatment response but also in differentiating iNPH from neurodegenerative dementias such as Alzheimer's disease [9,10]. Cognitive symptoms in iNPH often follow a subcortical pattern and may co-occur with neuropsychiatric disturbances such as depression and apathy, both of which are linked to poorer functional outcomes if left unaddressed [11,12]. Recent studies have shown that shunt surgery can lead to cognitive gains, particularly in executive and attention domains [13]. However, the trajectory of these improvements, their sustainability over time, and their relationship to baseline cognitive status remain underexplored. Despite increasing interest in cognitive outcomes, existing evidence is limited and lack of stratified analyses. Therefore, this study aims to evaluate neuropsychiatric outcomes after VP shunt surgery and to identify the factors that shape the trajectory of postoperative cognitive improvement.

METHODS

This study was approved by the Local Institutional Review Board (Approval Decision Number: 2023/01-30, Research Number: GO 22/1064, Date: January 24, 2023).

A total of 55 patients who underwent ventriculoperitoneal (VP) shunt surgery between January 2020 and December 2024 were included in this single-center study. iNPH was determined based on clinical and radiological criteria. Individuals aged 60 years and older, who underwent VP shunt surgery and were evaluated with the NPT battery before and after the procedure, have been included. Patients with secondary causes of hydrocephalus and secondary normal pressure hydrocephalus, as well as those not assessed by neuropsychological testing (NPT) battery both preoperatively and postoperatively, have been excluded from the study.

A comprehensive NPT battery was administered to evaluate cognitive performances prior to and on average 11 months following shunt surgery. The NPT battery included Mini-Mental State Examination (MMSE) [14,15], enhanced cued recall test (ERCT) [16], trail-making tests A and B [17,18], Stroop test [19,20], clock drawing test [21,22], and Beck Depression Inventory (BDI) [23,24]. Within the NPT battery, executive functions were not assessed via a single scale but were instead operationalized through a composite rating approach. Specifically, qualitative severity ratings (Severe, Moderate, Mild, Normal) were assigned based on the synthesis of performance across tests tapping into executive domains. This rating was established by the consensus of two raters (neurologist and clinical neuropsychologist) who independently reviewed the test performance and clinical interview notes, and resolved discrepancies through discussion. The same method was applied at follow-up using the equivalent battery.

Statistical analysis

Categorical variables are expressed as n (%) and continuous variables as mean ± standard deviation (SD) or median (interquartile range). Group-wise comparisons were performed by chi-square test for categorical variables and Student's t-test or Whitney U test for continuous variables depending on the normality of the distribution. The Wilcoxon signed-rank test was used to compare the numeric observations between pre- and postoperative in the cohort. Finally, linear regression models were constructed to determine independent factors related to the cognitive improvement. Age, sex, education and symptom duration were introduced into the models as independent variables. To evaluate whether the relationship between follow-up duration and cognitive improvement was moderated by baseline performance, we performed stratified analyses for the MMSE and the ERCT. Baseline scores were divided into tertiles to define three subgroups (low, medium, and high performance). Within each tertile, we examined the association between follow-up duration (in months) and change scores (postoperative – preoperative) using linear regression models. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed by using R version 4.4.2 (R Core Team, 2024).

RESULTS

A total of 55 patients (43.6% female, the median age: 71 years [IQR]: 67–75) who underwent VP shunt surgery for iNPH were included. NPT battery was performed preoperatively and at a median follow-up of 11(IQR: 8–14) months. Statistically significant postoperative improvements were observed across multiple cognitive domains.

The MMSE score improved from a median of 24.0 [20.0–27.0] to 27.0 [25.0–29.0] ($p < 0.001$), indicating an overall enhancement in global cognition. Depression severity, as measured by the BDI, significantly decreased from 12.0 [7.0–20.7] to 9.0 [4.0–13.0] ($p < 0.001$). Memory scores derived from ERCT also improved significantly from 40.0 [31.2–45.0] to 45.0 [42.0–48.0] ($p < 0.001$) (Figure 1). A negative correlation was found between memory score change and follow-up duration (Spearman's $\rho = -0.592$, $p < 0.0001$), indicating that memory gains were more prominent in the early postoperative period. A multiple linear regression analysis was conducted to determine independent predictors of memory and global cognitive improvement (post–pre difference). The model included baseline scores, follow-up duration, age, and sex. Among all predictors, only baseline memory score was found to be statistically significant ($\beta = -0.76$, $p < 0.001$).

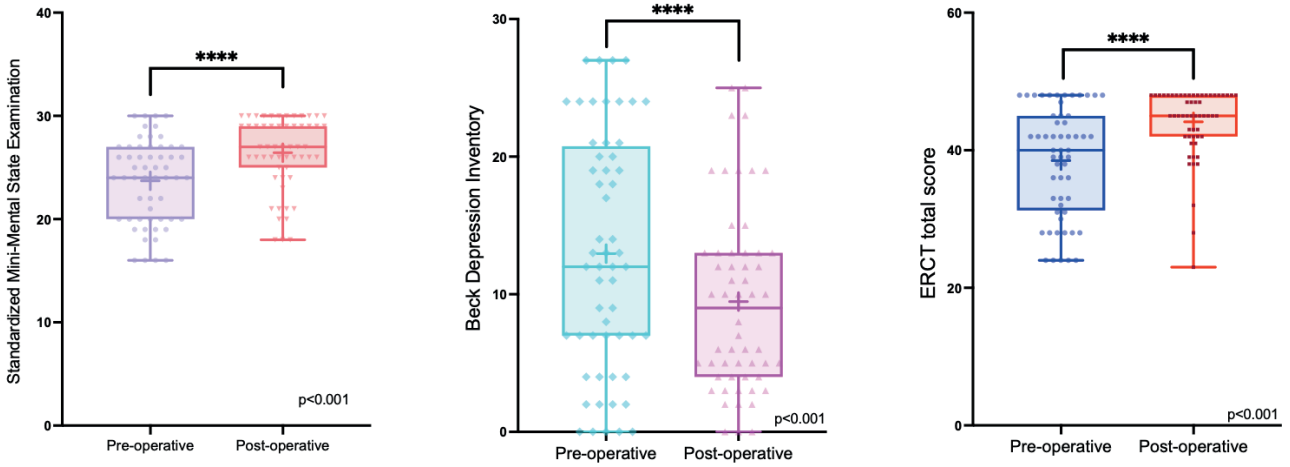


Figure 1. Changes in global cognition, depressive symptoms, and memory performance before and after VP shunt surgery in patients with iNPH.

Boxplots depict significant postoperative improvements in (A) Mini-Mental State Examination (MMSE), (B) Beck Depression Inventory (BDI), and (C) Enhanced Cued Recall Test (ERCT) total scores. All comparisons reached statistical significance at $p < 0.001$ (Wilcoxon signed-rank test).

Table 1. Multiple linear regression predicting memory improvement

	β¹	Std. error	t value	p-value	β²	95% CI (Lower–Upper)
Intercept	32.15	7.04	4.57	<0.001		17.99 – 46.30
Preoperative ERCT score	–0.76	0.10	–7.86	<0.001	–0.75	–0.95 – –0.57
Follow-up (Months)	–0.08	0.08	–1.13	0.265	–0.11	–0.24 – 0.07
Age	0.05	0.08	0.66	0.515	0,06	–0.11 – 0.21
Sex	0.41	1.43	0.29	0.775	0,03	–2.47 – 3.30

Residual standard error: 5.12 on 48 degrees of freedom; multiple R-squared: 0.638, adjusted R-squared: 0.608; β¹: Unstandardized regression coefficient; Std. error: Standard error; β²: Standardized regression coefficient.

Table 2. Multiple linear regression predicting global cognitive improvement

	β¹	Std. error	t value	p-value	β²	95% CI (Lower–Upper)
Intercept	10.92	3.62	3.01	<0.05		3.61 – 18.23
Preoperative MMSE score	–0.33	0.10	–3.32	<0.05	–0.52	–0.53 – –0.13
Follow-up (Months)	–0.08	0.04	–1.82	0.075	–0.24	–0.17 – 0.01
Age	0.03	0.04	0.80	0.426	0,09	–0.05 – 0.12
Sex	0.31	0.76	–0.41	0.685	–0.04	–1.85 – 1.23

Residual standard error: 2.76 on 48 degrees of freedom; multiple R-squared: 0.276, adjusted R-squared: 0.216; β¹: Unstandardized regression coefficient; Std. error: Standard error; β²: Standardized regression coefficient

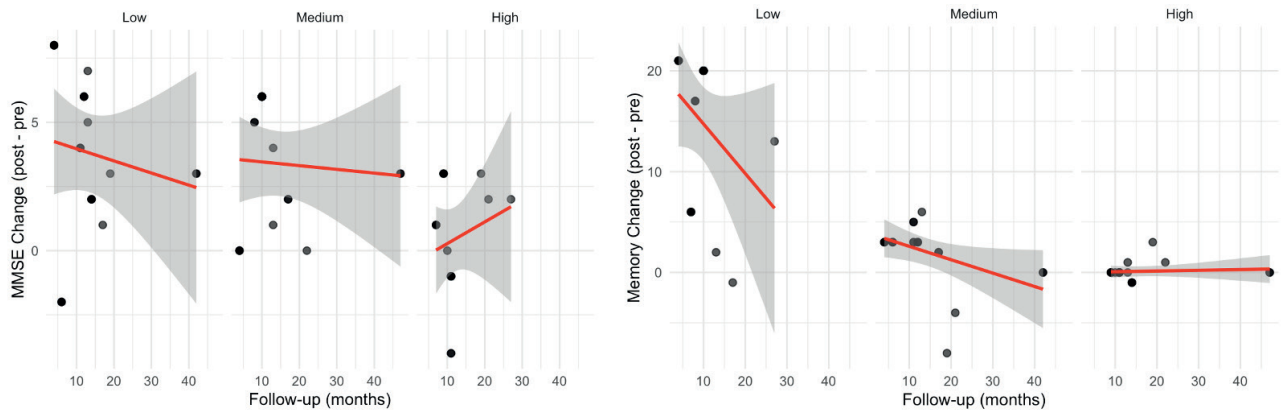


Figure 2. Change in MMSE and ERCT by follow-up duration stratified by baseline scores

The plot displays the relationship between follow-up duration and postoperative cognitive changes, stratified by baseline level (low, medium, high tertiles). Patients with lower baseline scores showed greater improvements when evaluated earlier, while those with higher baseline scores demonstrated minimal or slightly positive trends.

Also, multivariate analysis for MMSE similarly revealed pre-op MMSE score as the only significant predictor for postoperative improvement of global cognition (β = –0.33, $p < 0.05$) (Table 1 and Table 2).

To further explore the relationship between timing of assessment and cognitive outcomes, follow-up duration was analyzed in subgroups stratified by baseline MMSE and ERCT performance (low, medium, high tertiles). As shown in Figure 2, patients with low baseline scores exhibited a clear negative relationship between follow-up time and cognitive improvement, suggesting early postoperative gains were more pronounced in this subgroup. In contrast, patients with higher baseline scores showed minimal or slightly positive trends.

Pre- and postoperative ordinal ratings of executive function (Severe, Moderate, Mild, Normal) revealed categorical improvements. As depicted in Figure 3, most patients with moderate baseline dysfunction improved postoperatively. Specifically, 11 of 18 patients with moderate or severe executive dysfunction (61.1%) transitioned to a milder category: 6 to normal and 5 to mild. No patient showed deterioration.

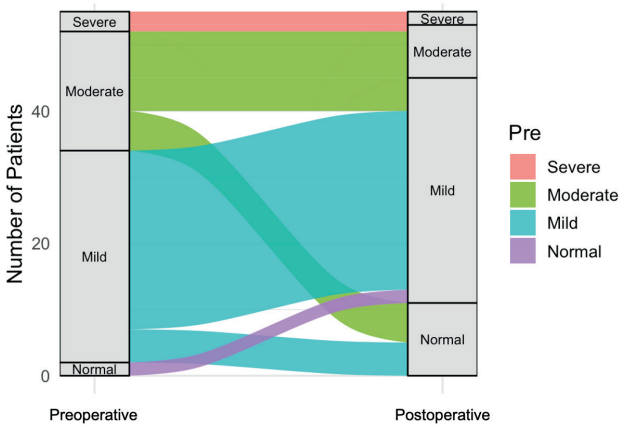


Figure 3. Transitions in executive function severity levels before and after surgery

The alluvial diagram illustrates individual-level changes in executive function severity from baseline (Preoperative) to follow-up (Postoperative). Categories include Severe, Moderate, Mild, and Normal. Flows between levels represent the number of patients who transitioned between categories. Improvements are indicated by flows moving from left to right toward less severe categories (e.g., Moderate to Mild or Normal). The majority of patients initially categorized as Moderate demonstrated clinical improvement postoperatively.

DISCUSSION

This study demonstrates that ventriculoperitoneal (VP) shunt surgery in patients with idiopathic normal pressure hydrocephalus (iNPH) is associated with significant improvements in global cognition, memory, executive functioning, and depressive symptoms. More importantly, cognitive benefits were more profound in patients with lower pre-op scores and earlier postoperative phases.

Our findings on the cognitive and emotional improvements following VP shunt surgery align with previous research, which suggests that iNPH patients often experience a range of neuropsychiatric symptoms, including mood disturbances, disinhibition, and cognitive deficits [25,26]. A recent study highlighted that therapeutic lumbar tapping or VP shunt surgery could lead to significant improvements in neuropsychiatric symptoms in a patient with normal pressure hydrocephalus [27]. Similar to previous studies, we observed marked improvements in overall cognitive status, memory, attention, and depression postoperative. These consistent results reinforce the efficacy of shunt surgery in addressing neuropsychiatric symptoms associated with iNPH [28,29].

Among the cognitive domains assessed, memory and MMSE scores showed the most robust improvements postoperatively. Importantly, our stratified regression analyses revealed that cognitive benefits were more pronounced in patients with lower baseline performance, highlighting the potential of reversibility of cognitive impairment and that even these patients may respond effectively to intervention. These findings support prior work suggesting that early-stage cognitive dysfunction may be more reversible following shunting, whereas more preserved baseline functioning may leave less room for observable gains. These improvements may be attributed to the relief of ventricular enlargement and subsequent normalization of CSF dynamics, which likely reduces periventricular white matter compression and restores functional connectivity within frontal-subcortical circuits. These circuits—particularly involving the dorsolateral prefrontal cortex, caudate nucleus, and anterior cingulate—are critical for executive function, working memory, and attention. Restored perfusion and synaptic efficiency in these regions may underlie the observed cognitive gains following VP shunt surgery [30].

However, our study diverges from some previous research regarding visuospatial abilities. Many studies reported improvements in all cognitive domains, especially processing speed, memory and attention have showed more robust improvement compared to visuospatial skills [31-35]. In the current study, visuospatial skills evaluated by clock drawing test did not improve significantly following the surgery. This discrepancy might be attributed to differences in patient populations, the test used to evaluate this domain, or the duration of follow-up periods.

The negative association between follow-up duration and cognitive improvement, particularly in memory scores, indicates that cognitive gains were most evident in earlier postoperative phases. This time-sensitive pattern may reflect the dynamic neurophysiological changes following VP shunting, including gradual improvements in cerebral perfusion, especially in frontal-subcortical regions implicated in attention and memory [36,37]. Our stratified regression models further reinforce the observation that patients with low baseline MMSE or ERCT scores demonstrated stronger improvements with earlier follow-up. Previous studies have also reported that significant improvements in MMSE and memory score are often observed within

the few weeks after surgery, but these gains may decline over longer follow-up periods [38,39]. This emphasizes that neurodegeneration is still a progressive process even after shunt surgery in iNPH. Although cognitive gains may attenuate over time, many patients retain a level of function above baseline for at least two years [39]. Therefore, even though the benefits may be time-limited, early intervention and monitoring remain critical components of effective iNPH management.

Preoperative neuropsychological performance is a key consideration in predicting outcomes after shunt surgery for iNPH. However, the association between preoperative cognitive scores and postoperative improvement is complex, with studies showing mixed results regarding their predictive value. Some studies found that neither baseline symptoms nor NPT scores could reliably forecast postoperative improvement [38,40]. There is substantial variability in individual outcomes: some patients with severe preoperative deficits show marked improvement, while others do not, and vice versa for those with milder deficits [38,41]. A notable exception is that a dominant complaint of memory problems at baseline may be associated with a lower likelihood of improvement [40]. In the current study, multivariate analyses identified baseline cognitive scores as the only significant independent predictor of cognitive change for both memory and global cognition. Although follow-up duration showed a negative correlation with cognitive improvement in univariate analysis, this relationship did not remain significant in the multivariate models. This suggests that the observed time-dependent gain may be confounded by baseline performance, highlighting the dominant role of preoperative cognitive reserve in determining postoperative recovery and underscores the importance of the time of surgical intervention.

Limitations

Our study has several limitations that warrant consideration. First, the relatively small sample size may limit the statistical power and reduce the generalizability of the findings to broader iNPH populations. Second, the retrospective study design inherently carries risks of selection bias and limits the ability to establish causal relationships. Third, the median follow-up duration of 11 months may not be sufficient to capture long-term cognitive trajectories and the single-center nature of the study may introduce center-specific procedural or population biases. Finally, the potential presence of co-existing neurodegenerative pathologies in patients diagnosed with iNPH. Although iNPH may present with overlapping features of other neurodegenerative dementias, we did not systematically apply biomarker-based, imaging, or clinical exclusion criteria—such as CSF biomarkers, amyloid or tau PET imaging, or expert structural MRI review—to rule out mixed pathologies. The absence of such assessments may represent a potential confounding factor, particularly in interpreting cognitive and emotional outcomes. Future research should aim to address these limitations by employing prospective, multicenter designs with larger cohorts and extended follow-up durations to enhance external validity.

CONCLUSION

Our findings suggest that cognitive improvements following VP shunt surgery in patients with iNPH are most pronounced in the early postoperative period. Baseline cognitive status emerged as the strongest independent predictor of postoperative outcomes, highlighting the importance of preoperative neuropsychological evaluation in clinical decision-making. These results contribute to the growing evidence base on cognitive trajectories in iNPH and emphasize the need for individualized, stage-sensitive management strategies. Integrating early neuropsychological screening into clinical protocols may facilitate timely referral and better long-term outcomes.

Author contribution

Study conception and design: EY, AC, and EÇ; data collection: AC, EÇ, AA, RG and İl; analysis and interpretation of results: EY, GYÇ, İl and BE; draft manuscript preparation: EY, AC and EÇ. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Ethical Commision of Health Sciences (Protocol no. GO 22/1064, 24 Jan 2025).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Ishida T, Murayama T, Kobayashi S. Current research of idiopathic normal pressure hydrocephalus: pathogenesis, diagnosis and treatment. World J Clin Cases 2023;11(16):3706-13. https://doi.org/10.12998/wjcc.v11.i16.3706

[2] Pedro MKF, Silva JFCD, Rocha SFBD, et al. Salomón Hakim: the man behind normal pressure hydrocephalus. Arq Neuropsiquiatr 2019;77(10):746-8. https://doi.org/10.1590/0004-282X20190096

[3] Hakim S, Adams RD. The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure. Observations on cerebrospinal fluid hydrodynamics. J Neurol Sci 1965;2(4):307-27. https://doi.org/10.1016/0022-510x(65)90016-x

[4] Iseki C, Takahashi Y, Wada M, Kawanami T, Adachi M, Kato T. Incidence of idiopathic normal pressure hydrocephalus (iNPH): a 10-year follow-up study of a rural community in Japan. J Neurol Sci 2014;339(1-2):108-12. https://doi.org/10.1016/j.jns.2014.01.033

[5] Andersson J, Rosell M, Kockum K, Lilja-Lund O, Söderström L, Laurell K. Prevalence of idiopathic normal pressure hydrocephalus: a prospective, population-based study. PLoS One 2019;14(5):e0217705. https://doi.org/10.1371/journal.pone.0217705

[6] Courville E, Rumalla K, Kazim SF, et al. Risk Analysis Index as a preoperative frailty tool for elective ventriculoperitoneal shunt surgery for idiopathic normal pressure hydrocephalus. J Neurosurg 2023;140(4):1110-6. https://doi.org/10.3171/2023.7.JNS23767

[7] Chatziioannidis S, Charatsidou I, Nikolaidis N, Garyfallos G, Giouzepas I. Psychotic symptoms in normal pressure hydrocephalus. Psychiatriki 2013;24(3):217-24.

[8] Oliveira MF, Oliveira JRM, Rotta JM, Pinto FCG. Psychiatric symptoms are present in most of the patients with idiopathic normal pressure hydrocephalus. Arq Neuropsiquiatr 2014;72(6):435-8. https://doi.org/10.1590/0004-282x20140047

[9] Kubo Y, Kazui H, Yoshida T, et al. Validation of grading scale for evaluating symptoms of idiopathic normal-pressure hydrocephalus. Dement Geriatr Cogn Disord 2008;25(1):37-45. https://doi.org/10.1159/000111149

[10] Sindorio C, Abbritti RV, Raffa G, et al. Neuropsychological assessment in the differential diagnosis of idiopathic normal pressure hydrocephalus. An important tool for the maintenance and restoration of neuronal and neuropsychological functions. Acta Neurochir Suppl 2017;124:283-8. https://doi.org/10.1007/978-3-319-39546-3_41

[11] Kito Y, Kazui H, Kubo Y, et al. Neuropsychiatric symptoms in patients with idiopathic normal pressure hydrocephalus. Behav Neurol 2009;21(3):165-74. https://doi.org/10.3233/BEN-2009-0233

[12] Peterson KA, Housden CR, Killikelly C, et al. Apathy, ventriculomegaly and neurocognitive improvement following shunt surgery in normal pressure hydrocephalus. Br J Neurosurg 2016;30(1):38-42. https://doi.org/10.3109/02688697.2015.1029429

[13] Saito M, Nishio Y, Kanno S, et al. Cognitive profile of idiopathic normal pressure hydrocephalus. Dement Geriatr Cogn Dis Extra 2011;1(1):202-11. https://doi.org/10.1159/000328924

[14] Güngen C, Ertan T, Eker E, Yaşar R, Engin, F. Standardize Mini Mental Testinin Türk toplumunda hafif demans tanısında geçerlik ve güvenilirliği. Turk Psikiyatri Derg 2002;13:273-81.

[15] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-98. https://doi.org/10.1016/0022-3956(75)90026-6

[16] Saka E, Mihci E, Topcuoglu MA, Balkan S. Enhanced cued recall has a high utility as a screening test in the diagnosis of Alzheimer's disease and mild cognitive impairment in Turkish people. Arch Clin Neuropsychol 2006;21(7):745-51. https://doi.org/10.1016/j.acn.2006.08.007

[17] Türkeş N, Can H, Kurt M, Elmastaş-Dikeç B. İz Sürme Testinin 20-49 yaş aralığında Türkiye için norm belirleme çalışması. Turk Psikiyatri Derg 2015;26(3):189-96.

[18] Reitan RM. Validity of the Trail Making test as an indicator of organic brain damage. Percept Motor Skills 1958;8(3):271-6. https://doi.org/10.2466/pms.1958.8.3.271

[19] Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18(6):643-62. https://doi.org/10.1037/h0054651

[20] Karakaş S, Erdoğan E, Sak L, et al. Stroop Test TBAG form: standardisation for Turkish culture, reliability and validity. Turkish J Clin Psy 1999;2(2):75-88.

[21] Mendez MF, Ala T, Underwood KL. Development of scoring criteria for the clock drawing task in Alzheimer's disease. J Am Geriatr Soc 1992;40(11):1095-9. https://doi.org/10.1111/j.1532-5415.1992.tb01796.x

[22] Hazan E, Frankenburg F, Brenkel M, Shulman K. The test of time: a history of clock drawing. Int J Geriatr Psychiatry 2018;33(1):e22-30. https://doi.org/10.1002/gps.4731

[23] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71. https://doi.org/10.1001/archpsyc.1961.01710120031004

[24] Hisli N. Beck Depresyon Envanterinin üniversite öğrencileri için geçerliği, güvenirliği. Psikoloji Dergisi 1989;7(23):3-13.

[25] Onder H, Akkurt I. Dramatic improvement of impulsive aggressive behaviour following shunt surgery in a patient with idiopathic normal pressure hydrocephalus. Neurol Sci 2017;38(10):1889-91. https://doi.org/10.1007/s10072-017-3015-5

[26] Tünel M, Çakmak S, Tamam L, Demir T. A case of simultaneous mania and idiopathic normal pressure hydrocephalus: etiology or comorbidity? Turk Psikiyatri Derg 2019;30(4):290-4.

[27] Padma K, Chandini, A SS, T SA, S RB. Neuropsychiatric manifestations in patient with normal pressure hydrocephalus improved with therapeutic lumbar tapping. Int J Res Med Sci 2019;7(5):1979-81. https://doi.org/10.18203/2320-6012.ijrms20191714

[28] Pujari S, Kharkar S, Metellus P, Shuck J, Williams MA, Rigamonti D. Normal pressure hydrocephalus: long-term outcome after shunt surgery. J Neurol Neurosurg Psychiatry 2008;79(11):1282-6. https://doi.org/10.1136/jnnp.2007.123620

[29] Kazui H, Miyajima M, Mori E, Ishikawa M, SINPHONI-2 Investigators. Lumboperitoneal shunt surgery for idiopathic normal pressure hydrocephalus (SINPHONI-2): an open-label randomised trial. Lancet Neurol 2015;14(6):585-94. https://doi.org/10.1016/S1474-4422(15)00046-0

[30] Xiao H, Hu F, Ding J, Ye Z. Cognitive impairment in idiopathic normal pressure hydrocephalus. Neurosci Bull 2022;38(9):1085-96. https://doi.org/10.1007/s12264-022-00873-2

[31] Behrens A, Elgh E, Leijon G, Kristensen B, Eklund A, Malm J. The Computerized General Neuropsychological INPH Test revealed improvement in idiopathic normal pressure hydrocephalus after shunt surgery. J Neurosurg 2019;132(3):733-40. https://doi.org/10.3171/2018.10.JNS18701

[32] Duinkerke A, Williams MA, Rigamonti D, Hillis AE. Cognitive recovery in idiopathic normal pressure hydrocephalus after shunt. Cogn Behav Neurol 2004;17(3):179-84. https://doi.org/10.1097/01.wnn.0000124916.16017.6a

[33] Hülser M, Spielmann H, Oertel J, Sippl C. Motor skills, cognitive impairment, and quality of life in normal pressure hydrocephalus: early effects of shunt placement. Acta Neurochir (Wien) 2022;164(7):1765-75. https://doi.org/10.1007/s00701-022-05149-2

[34] Peterson KA, Savulich G, Jackson D, Killikelly C, Pickard JD, Sahakian BJ. The effect of shunt surgery on neuropsychological performance in normal pressure hydrocephalus: a systematic review and meta-analysis. J Neurol 2016;263(8):1669-77. https://doi.org/10.1007/s00415-016-8097-0

[35] Raftopoulos C, Deleval J, Chaskis C, et al. Cognitive recovery in idiopathic normal pressure hydrocephalus: a prospective study. Neurosurgery 1994;35(3):397-404; discussion 404-5. https://doi.org/10.1227/00006123-199409000-00006

[36] Tullberg M, Hellström P, Piechnik SK, Starmark JE, Wikkelsö C. Impaired wakefulness is associated with reduced anterior cingulate CBF in patients with normal pressure hydrocephalus. Acta Neurol Scand 2004;110(5):322-30. https://doi.org/10.1111/j.1600-0404.2004.00325.x

[37] Kanemoto H, Kazui H, Suehiro T, et al. Apathy and right caudate perfusion in idiopathic normal pressure hydrocephalus: a case-control study. Int J Geriatr Psychiatry 2019;34(3):453-62. https://doi.org/10.1002/gps.5038

[38] Liu JT, Su PH. The efficacy and limitation of lumboperitoneal shunt in normal pressure hydrocephalus. Clin Neurol Neurosurg 2020;193:105748. https://doi.org/10.1016/j.clineuro.2020.105748

[39] Kambara A, Kajimoto Y, Yagi R, et al. Long-term prognosis of cognitive function in patients with idiopathic normal pressure hydrocephalus after shunt surgery. Front Aging Neurosci 2021;12:617150. https://doi.org/10.3389/fnagi.2020.617150

[40] Andrén K, Wikkelsø C, Laurell K, Kollén L, Hellström P, Tullberg M. Symptoms and signs did not predict outcome after surgery: a prospective study of 143 patients with idiopathic normal pressure hydrocephalus. J Neurol 2024;271(6):3215-26. https://doi.org/10.1007/s00415-024-12248-w

[41] Wallin M, Tullberg M, Wikkelsö C, Hellström P. Neuropsychological effects of shunting in iNPH - determining major and minor responses. Fluids Barriers CNS 2015;12:O53. https://doi.org/10.1186/2045-8118-12-S1-O53

acta medica

ORIGINAL ARTICLE

The lactate dehydrogenase-to-albumin ratio is a prognostic biomarker in extensive-stage small-cell lung cancer

Feride Yılmaz[1]
ORCID: 0000-0001-5848-3381

Serkan Yaşar[2]
ORCID: 0000-0002-1465-4131

Ömer Denizhan Tatar[3]
ORCID: 0000-0002-1860-7965

Hasan Çağrı Yıldırım[4]
ORCID: 0000-0003-3060-377X

Deniz Can Güven[5]
ORCID: 0000-0002-6924-9467

Hakan Taban[6]
ORCID: 0000-0002-2004-7741

Zafer Arık[5]
ORCID: 0000-0002-0598-389X

Mustafa Erman[5]
ORCID: 0000-0001-5884-4669

[1]Samsun Education and Research Hospital, Department of Medical Oncology, Samsun, Türkiye

[2]Abdurrahman Yurtaslan Oncology Education and Research Hospital, Department of Medical Oncology, Ankara, Türkiye

[3]Turkeli State Hospital, Department of Internal Medicine, Sinop, Türkiye

[4]Ege University, Faculty of Medicine, Department of Medical Oncology, İzmir, Türkiye

[5]Hacettepe University Cancer Institute, Department of Medical Oncology, Ankara, Türkiye

[6]Medicalpark Ankara Hospital, Department of Medical Oncology, Ankara, Türkiye

Corresponding Author: Feride Yılmaz
E-mail: doktorferide@gmail.com

Received: 30 June 2025, Accepted: 10 August 2025, Published online: 30 September 2025

ABSTRACT

Background: The lactate dehydrogenase-to-albumin ratio (LAR) is a promising prognostic marker in various malignancies. However, its clinical relevance in extensive-disease small-cell lung cancer (ED-SCLC) remains unclear.

Methods: We analyzed a total of 221 patients diagnosed with ED-SCLC between January 2008 and December 2021. Patients without treatment response data (n=8), those who did not receive systemic therapy (n=37), and those who lacked baseline LDH values (n=48) were excluded. The LAR was calculated by dividing baseline serum LDH (U/L) by albumin (g/L) and, using ROC analysis, the optimal cut-off level was determined to be 5.71 (sensitivity: 81.5%, specificity: 77.8%). Kaplan–Meier and Cox regression analyses were used to evaluate both progression-free (PFS) and overall survival (OS).

Results: A total of 128 patients diagnosed with ED-SCLC were included in our analysis. Patients with an LAR ≥5.71 had significantly shorter median OS (8.1 vs. 20.2 months, p<0.001) and PFS (5.9 vs. 9.4 months, p=0.003) compared to those with an LAR <5.71. In multivariate analysis, a high LAR was an independent predictor of a shorter OS (HR: 3.60; 95% CI: 1.35–9.60; p=0.010) and had a strong association with a shorter PFS (HR: 2.61; 95% CI: 0.95–7.14; p=0.063).

Conclusion: The LAR is a simple, cost-effective, and independent prognostic biomarker in patients with ED-SCLC. It could assist in risk stratification and guide treatment decisions in clinical practice.

Keywords: lactate dehydrogenase, albumin, LAR, small-cell lung cancer, prognosis, survival, biomarker

INTRODUCTION

Small-cell lung cancer (SCLC) is an aggressive neuroendocrine tumor and has a poorer prognosis than non-small cell lung cancer (NSCLC) [1,2]. Unfortunately, two-thirds of patients are diagnosed with Extensive-disease SCLC (ED-SCLC) at the time of diagnosis and this is associated with a median overall survival (OS) of less than one year despite systemic therapy [3]. While immune checkpoint inhibitors have modestly improved outcomes in some patients [4], identifying reliable and inexpensive prognostic biomarkers is an unmet critical need in clinical practice.

Serum lactate dehydrogenase (LDH) is a marker of tumor burden and has been shown to correlate with adverse outcomes in SCLC [5]. Albumin reflects both nutritional and inflammatory status as well and hypoalbuminemia has been linked to poor survival in several malignancies [6]. Lactate dehydrogenase-albumin ratio (LAR) is created by the combination of these two biomarkers. Several studies have demonstrated that an elevated LAR is significantly associated with worse prognosis in gastrointestinal cancers [7-12], oral cancers [13], bladder [14], breast cancers [15] and hematological malignancies [16].

Despite its growing application, data on LAR in the context of SCLC are extremely limited. Although some studies have explored LDH or albumin separately or in composite prognostic models [5,6], no prior research has directly evaluated LAR as a unified biomarker in an ED-SCLC population receiving systemic chemotherapy.

The objective of this research was to determine if pretreatment LAR could predict outcomes in patients with ED-SCLC. We hypothesize that a higher LAR might point to both aggressive tumor behavior and tumor-related inflammatory response and support more informed treatment choices.

MATERIALS AND METHODS

Patients and data collection

This retrospective study included 128 patients diagnosed with extensive-disease ED-SCLC between January 2008 and December 2021 at our University Cancer Institute. The study inclusion criteria were as follows: a pathologically confirmed SCLC diagnosis, clinical-stage ED-SCLC, and having received at least 2 cycles of chemotherapy after diagnosis. Patients without available treatment response data, those who did not receive chemotherapy, and those with missing baseline LDH values were excluded from the analysis (Figure 1). Demographic data, comorbidities, Eastern Oncology Cooperative Group (ECOG) performance status, metastatic sites, treatment modalities, and baseline laboratory parameters were collected from medical records. Tumor response was evaluated using computed tomography (CT), with Response Evaluation Criteria in Solid Tumors criteria version 1.1 every three cycles until treatment discontinuation or disease progression. Progression-free survival (PFS) referred to the time from the initiation of first-line therapy to either documented disease progression or death. OS was measured from the time the start of first-line treatment to either death or the last known follow-up.

This retrospective observational study was approved by the Hacettepe University Ethics Committee (Protocol no: GO 22/1119, Date: 01.11.2022).

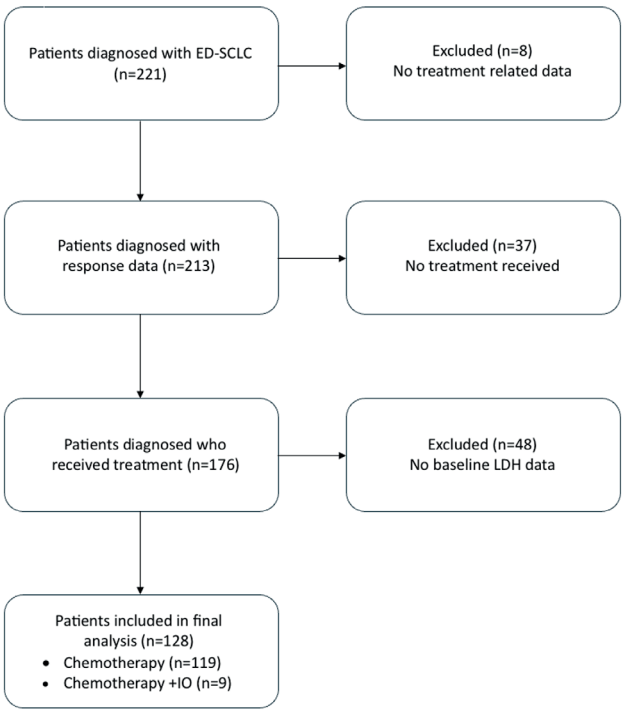


Figure 1. Flow chart of patient selection in ED-SCLC cohort.

ED-SCLC: extensive-disease small-cell lung cancer; IO: immunotherapy.

LAR and baseline laboratory parameters

Serum LDH and albumin levels were measured at the central biochemistry laboratory of our university hospital. LDH was measured using an enzymatic spectrophotometric method based on IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) standards. Albumin was measured using the bromocresol green method. Both tests were performed on routinely used automated analyzers. The LAR was calculated by dividing pretreatment serum LDH (U/L) by serum albumin (g/L). Baseline reference values were as follows: LDH = 240 U/L, albumin = 35-55 g/dL, and sodium = 135–145 mmol/L. Anemia was considered present if hemoglobin levels dropped below 13.5 g/dL in men or 12.0 g/dL in women.

Statistical analysis

Continuous variables are summarized as medians and interquartile ranges (IQRs), while categorical variables are mentioned as counts and percentages. Group comparisons for continuous variables based on LAR stratification were conducted using the Mann–Whitney U test for two groups and the Kruskal–Wallis H test for multiple groups. Categorical variables were compared using Fisher's exact test.

We used OS as the endpoint to calculate the LAR cut-off value and performed receiver operating characteristic (ROC) curve analysis. We calculated sensitivity and specificity using the area under the curve (AUC).

We conducted a bootstrapping analysis with 1000 resamples for validating the stability of the derived cut-off. In each repetition, a new sample was generated by using random sampling with replacement and the AUC was calculated again. Additionally, the mean AUC and 95% confidence interval were reported to evaluate the robustness of the model. The bootstrapping validation analysis was performed by using RStudio (version 2024.03.1+402) with the "pROC" package (version 1.18.5).

Furthermore, we assessed multicollinearity among LAR, LDH, and albumin using variance inflation factor (VIF) analysis. We calculated VIF values based on a linear regression model including these variables. A VIF value greater than 5 was considered indicative of significant collinearity. The VIF analysis was performed using RStudio (version 2024.03.1+402) with the "car" package.

Survival outcomes, including OS and PFS, were estimated using the Kaplan–Meier method. Differences between survival curves were evaluated via the log-rank test. The Cox proportional hazards regression model was employed for uni- and multivariate analyses to verify the independent predictive value of the pretreatment LAR in OS and PFS. Variables that showed a p-value below 0.10 in the univariate analyses were used for inclusion in the multivariate Cox regression models. Results are presented as hazard ratios (HRs) along with 95% confidence intervals (CIs). A two-sided p-value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were conducted using SPSS software, version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

A total of 128 patients diagnosed with ED-SCLC were included in the final analysis. We excluded patients with missing LDH, outcome, or treatment data. These missing values were not imputed, as they were considered clinically meaningful and non-random (Figure 1). The median age was 64 years (IQR: 58–69), and the majority were male (90.6%). Almost 73% of patients had an ECOG performance status of <2. In addition, approximately 70% (n=89) of patients had at least one comorbidity. One hundred and nineteen received platinum-etoposide-based chemotherapy, and nine patients (7%) received platinum-etoposide combined with immunotherapy as first-line treatment. No statistically significant differences were observed between the two groups regarding age, sex, ECOG performance status, metastatic involvement (including adrenal metastases, p=0.38), or administration of prophylactic cranial irradiation (PCI). The baseline characteristics of patients stratified by LAR levels are shown in Table 1.

Table 1. Baseline characteristics stratified by lactate dehydrogenase-to-albumin ratio (LAR) cut-off

Characteristic	Total N=128 (%100)	LAR<5.71 N=29 (22.7%)	LAR≥5.71 N=99 (77.3%)	p value
Age median (IQR), years	64 (58, 69)			
Age groups (years)				0.10
<65	70 (54.7)	12 (17.1%)	58 (82.9%)	
≥65	58 (45.3)	17 (29.3%)	41 (70.7%)	
Gender				0.21
Female	12 (9.4)	1 (8.3%)	11 (91.7%)	
Male	116 (90.6)	28 (24.1%)	88 (75.9%)	
Comorbidity				0.59
No	39 (30.5)	10 (25.6%)	29 (74.4%)	
Yes	89 (69.5)	19 (21.3%)	70 (78.7%)	
Cardiac Diseases	34 (26.6)	3 (8.8%)	31 (91.2%)	
Diabetes	24 (18.7)	7 (29.2%)	17 (70.8%)	
Hypertension	58 (45.3)	12 (20.7%)	46 (79.3%)	
Second Malignancy	13 (10.2)	7 (53.8%)	6 (46.2%)	
COPD	14 (10.9)	4 (30.8%)	9 (69.2%)	
ECOG				0.97
<2	93 (72.7)	21 (22.6%)	72 (77.4%)	
≥2	35 (27.3)	8 (22.9%)	27 (77.1%)	
Liver metastasis				0.13
Yes	46 (35.9)	7 (15.2%)	39 (84.8%)	
No	82 (64.1)	22 (26.8%)	60 (73.2%)	
Adrenal metastasis				0.38
Yes	25 (19.5)	4 (16.0%)	21 (84.0%)	
No	103 (80.5)	25 (24.3%)	78 (75.7%)	
Brain metastasis				0.43
Yes	14 (10.9)	2 (14.3%)	12 (85.7%)	
No	114 (89.1)	27 (23.7%)	87 (76.3%)	
Bone metastasis				0.41
Yes	66 (51.6)	13 (19.7%)	53 (80.3%)	
No	62 (48.4)	16 (25.8%)	46 (74.2%)	
1st-line chemotherapy				0.67
Cisplatin/etoposide	82 (64.2)	19 (23.2%)	63 (76.8%)	
Carboplatin/etoposide	39 (30.5)	10 (25.6%)	29 (74.4%)	
Oral etoposide	2 (1.5)	0 (0%)	2 (100%)	
Weekly carboplatin	2 (1.5)	0 (0%)	2 (100%)	
Carboplatin after cisplatin/etoposide	3 (2.3)	0 (0%)	3 (100%)	
Immunotherapy				**0.015**
Yes	9 (7)	5 (55.6%)	4 (44.4%)	
No	119 (93)	24 (20.2%)	95 (79.8%)	
PCI				0.20
Yes	21 (16.4)	7 (33.3%)	14 (66.7%)	
No	107 (83.6)	22 (20.6%)	85 (79.4%)	
Hemoglobin (g/dL)				0.85
Low	46 (35.9)	10 (21.7%)	36 (78.3%)	
Normal	82 (64.1)	19 (23.2%)	63 (76.8%)	
Na (mmol/L)				0.49
Low	28 (21.9)	5 (17.9%)	23 (82.1%)	
Normal	100 (78.1)	24 (24.0%)	76 (76.0%)	
LDH (U/L)				**<0.001**
Low	34	28 (82.4%)	6 (17.6%)	
High	94	1 (1.1%)	93 (98.9%)	
Albumin (g/L)				**0.017**
Low	24 (18.7)	1 (4.2%)	23 (95.8%)	
Normal	104 (81.3)	28 (26.9%)	76 (73.1%)	

LAR: lactate dehydrogenase-to-albumin ratio; IQR: interquartile range; COPD: chronic obstructive pulmonary disease; ECOG: Eastern Cooperative Oncology Group; PCI: prophylactic cranial irradiation; LDH: lactate dehydrogenase; Na: sodium.

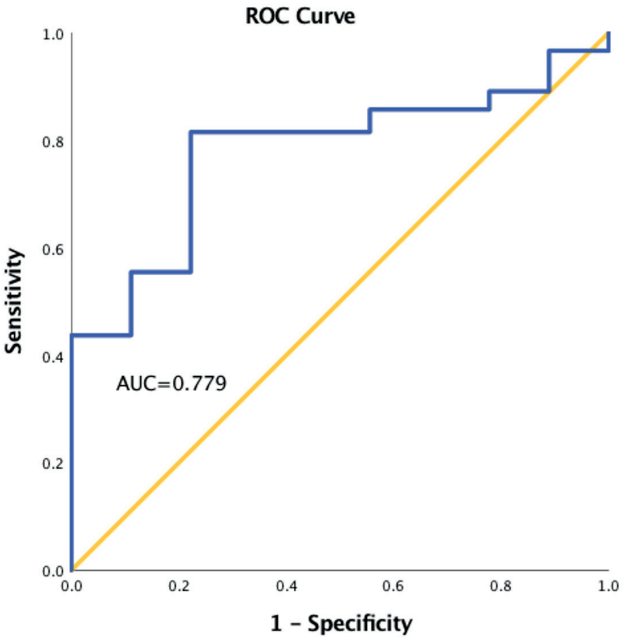


Figure 2. Receiver operating characteristic (ROC) curve of the lactate dehydrogenase-to-albumin ratio (LAR) for predicting overall survival. The area under the curve (AUC) was 0.779, indicating good discriminatory performance.

LAR cut-off value determination

The ROC analysis identified an optimal LAR threshold of 5.71 for predicting OS, with an AUC of 0.779. This cut-off provided a sensitivity of 81.5% and specificity of 77.8% for distinguishing between favorable and unfavorable survival outcomes (Figure 2).

We validated the stability of the cut-off value using the bootstrapping analysis. The mean AUC was 0.775 and the 95% CI ranged from 0.647 to 0.889. These results confirmed that the internal consistency of the LAR threshold (Supplementary Figure 1).

Survival outcomes

At the time of analysis, 123 patients (96.1%) had experienced progression, and 119 patients (92.9%) had died. A total of nine patients were censored in the survival analysis: two were lost to follow-up, and seven were alive at last follow-up. The median PFS in the low LAR group (<5.71) was 9.4 months (95% CI: 7.3–11.5), compared to 5.9 months (95% CI: 4.9–6.8) in the high LAR group (p=0.003) (Figure 3). The median OS was 20.2 months (95% CI: 11.7–28.7) in the low LAR group, markedly higher than the 8.1 months (95% CI: 6.9–9.3) in the high LAR group (p<0.001) (Figure 4). Furthermore, a low albumin level was associated with poor OS (5.6 months (95% CI, 2.96–8.24) vs. 10.4 months (95% CI, 7.85–12.94), p<0.001) and patients with high LDH values were found to have a shorter OS (15 (95% CI, 11.98–18.02) vs 8.3 (95% CI, 6.92–9.68) months, p=0.001).

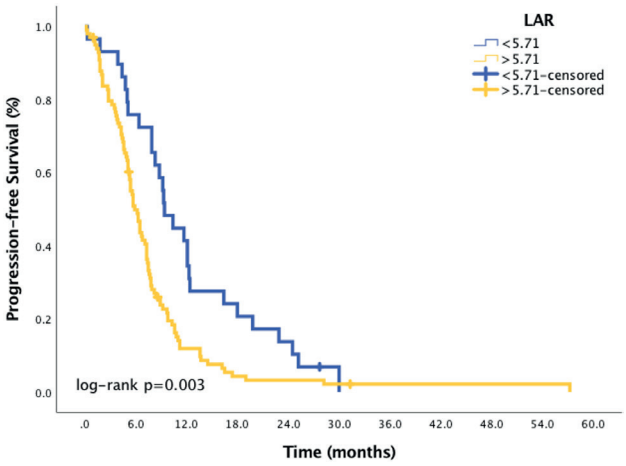


Figure 3. Kaplan–Meier curve for progression-free survival (PFS) stratified by lactate dehydrogenase-to-albumin ratio (LAR).

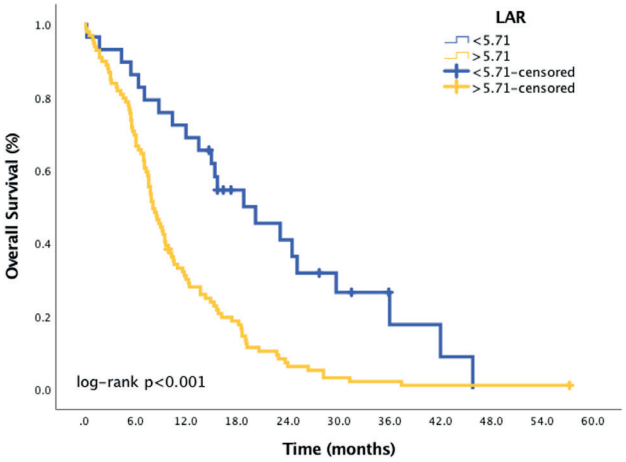


Figure 4. Kaplan–Meier curve for overall survival (OS) stratified by lactate dehydrogenase-to-albumin ratio (LAR).

Cox regression analysis

In univariate Cox regression analysis (Table 2), a high LAR was significantly associated with a shorter PFS (HR: 1.89; 95% CI: 1.23–2.90; p=0.004) and OS (HR: 3.36; 95% CI: 2.01–5.63; p<0.001); however, it did not remain significant in multivariate model for PFS (p=0.13). Other factors associated with a shorter PFS included liver (HR: 2.21; p<0.001) and brain metastases (HR: 2.24; p=0.007), low albumin (HR: 1.99; p=0.004), and an absence of PCI (HR: 0.39; p<0.001). Notably, liver (HR: 3.10; p<0.001) and brain metastases (HR: 3.80; p<0.001), elevated LDH

Table 2. Univariate and multivariate cox regression analysis for progression-free survival

Characteristics	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	p value	Hazard Ratio (95% CI)	p value
Age groups (years)				
<65	Reference			
≥65	1.05 (0.73-1.50)	0.79		
Gender				
Female	Reference			
Male	1.45 (0.77-2.73)	0.25		
Comorbidity				
Yes	1.08 (0.73-1.60)	0.69		
No	Reference			
ECOG				
0-1	Reference			
≥2	1.19 (0.79-1.79)	0.40		
Liver metastasis				
Yes	2.21 (1.49-3.26)	**<0.001**	1.53 (0.98-2.39)	0.06
No	Reference			
Adrenal metastasis				
Yes	0.88 (0.56-1.38)	0.57		
No	Reference			
Brain metastasis				
Yes	2.24 (1.25-4.01)	**0.007**	1.69 (0.89-3.17)	0.10
No	Reference			
Bone metastasis				
Yes	1.06 (0.74-1.5)	0.73		
No	Reference			
Immunotherapy				
Yes	1.22 (0.59-2.51)	0.59		
No	Reference			
PCI				
Yes	0.39 (0.24-0.66)	**<0.001**	0.47 (0.28-0.80)	**0.005**
No	Reference			
Hemoglobin				
Low	1.03 (0.71-1.49)	0.89		
Normal	Reference			
Na				
Low	1.25 (0.81-1.93)	0.20		
Normal	Reference			
LDH				
Normal	Reference			
High	1.67 (1.11-2.50)	**0.014**	0.76 (0.31-1.87)	0.55
Albumin				
Low	1.99 (1.25-3.16)	**0.004**	1.39 (0.82-2.38)	0.22
Normal	Reference			
LAR				
<5.71	Reference			
≥5.71	1.89 (1.23-2.92)	**0.004**	2.11 (0.81-5.50)	0.13

LAR: lactate dehydrogenase-to-albumin ratio; ECOG: Eastern Cooperative Oncology Group; PCI: prophylactic cranial irradiation; LDH: lactate dehydrogenase.

Table 3. Univariate and multivariate cox regression analysis for overall survival

Characteristics	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	p value	Hazard Ratio (95% CI)	p value
Age groups (years)				
<65	Reference			
≥65	0.99 (0.69-1.43)	0.97		
Gender				
Female	Reference			
Male	1.67 (0.88-3.17)	0.11		
Comorbidity				
Yes	1.17 (0.78-1.74)	0.44		
No	Reference			
ECOG				
0-1	Reference			
≥2	1.38 (0.91-2.09)	0.13		
Liver metastasis				
Yes	3.1 (2.03-4.78)	**<0.001**	1.93 (1.20-3.11)	**0.007**
No	Reference			
Adrenal metastasis				
Yes	0.90 (0.57-1.43)	0.67		
No	Reference			
Brain metastasis				
Yes	3.80 (2.07-6.99)	**<0.001**	2.84 (1.48-5.48)	**0.002**
No	Reference			
Bone metastasis				
Yes	1.35 (0.93-1.94)	0.11		
No	Reference			
Immunotherapy				
Yes	0.81 (0.35-1.83)	0.61		
No	Reference			
PCI				
Yes	0.34 (0.19-0.58)	**<0.001**	0.41 (0.23-0.73)	**0.002**
No	Reference			
Hemoglobin				
Low	0.93 (0.64-1.36)	0.72		
Normal	Reference			
Na				
Low	1.19 (0.78-1.84)	0.42		
Normal	Reference			
LDH				
Normal	Reference			
High	2.03 (1.31-3.14)	**0.001**	0.63 (0.28-1.42)	0.27
Albumin				
Low	2.47 (1.55-3.92)	**<0.001**	1.66 (0.99-2.79)	0.056
Normal	Reference			
LAR				
<5.71	Reference			
≥5.71	3.36 (1.38-8.14)	**<0.001**	3.2 (1.31-7.81)	**0.011**

LAR: lactate dehydrogenase-to-albumin ratio; ECOG: Eastern Cooperative Oncology Group; PCI: prophylactic cranial irradiation; LDH: lactate dehydrogenase.

(HR: 2.03; p=0.001), low albumin (HR: 2.47; p<0.001), and an absence of PCI (HR: 0.34; p<0.001) were also significant predictors for OS (Table 3). No significant association was found between sodium levels and either OS or PFS in both univariate and multivariate analyses (p=0.42 and p=0.20, respectively).

A high LAR remained an independent prognostic factor for OS (HR: 3.36; 95% CI: 1.38–8.14; p=0.007), along with liver and brain metastases, low albumin, and a lack of PCI in multivariate Cox analysis (Table 3). It's worth mentioning that the LAR did not reach statistical significance in the adjusted model (p=0.135), but liver and adrenal metastases and an absence of PCI remained significant for PFS (Table 2).

DISCUSSION

SCLC is a highly invasive malignancy with rapid growth, early spread and high recurrence rates. It represents approximately 13–15% of all lung cancers and is usually diagnosed at an extended stage of disease [17]. ED-SCLC treatment has recently been improved with the addition of first-line immune checkpoint inhibitors (ICIs) [18]. Despite improved treatment options, most patients still face a poor prognosis [19], and this makes it important to find simple, affordable biomarkers that can guide treatment decisions. Several inflammatory and nutritional biomarkers, such as the prognostic nutritional index and systemic immune–inflammation, have shown prognostic significance in SCLC treated with both chemotherapy and immunotherapy [6,13].

LDH levels often increase due to changes in tumor metabolism. Even when oxygen is present, cancer cells prefer glycolysis to produce energy which is known as the Warburg effect. This metabolic shift promotes lactate production and supports rapid tumor growth. LDH elevation may also reflect tumor-related necrosis and hypoxia. Therefore, serum LDH can act as an indirect indicator of tumor burden and aggressive biological behavior [20]. It has been associated with tumor burden, hypoxia, and poor outcomes in various malignancies, including SCLC [21]. In addition, Zhou et al. found a 1.92-fold increased risk of death in patients with abnormally elevated baseline LDH values compared to patients with normal LDH values [5]. Also, elevated LDH levels have been consistently associated with poor prognosis in SCLC patients in previous studies [22,23]. These findings align with our results and reinforce the clinical relevance of LDH as a readily accessible biomarker in the management of extensive-stage SCLC.

Albumin is an important biomarker that reflects systemic inflammation, nutritional status, and overall physiological reserve [24-26]. Low albumin levels, often reflecting malnutrition, have been associated with unfavorable outcomes in individuals with cancer [27]. Many studies have linked hypoalbuminemia to adverse outcomes in many conditions, including cardiovascular, surgical, and infectious diseases [28-31]. Similar to these studies, we observed that lower albumin levels were clearly associated with shorter OS in ED-SCLC [32].

As mentioned above, LAR combines tumor-related (LDH) and host-related (albumin) features in a single metric. This integration may better capture the interplay between tumor aggressiveness and the patient's systemic condition. In our study, LAR remained independently associated with survival, even after adjusting for LDH and albumin separately. These results suggest that LAR may offer more comprehensive prognostic value than either marker alone. Our results are also compatible with previous studies in other malignancies such as hepatocellular carcinoma [7], Hodgkin's lymphoma [33], nasopharyngeal carcinoma [34], and esophageal squamous cell carcinoma [35]. These findings underline the broad applicability of the LAR as a prognostic indicator.

Although CRP values were not available in our study cohort, inflammation-based prognostic tools such as the Glasgow Prognostic Score (GPS) may still be relevant. GPS incorporates serum CRP and albumin levels and reflects both nutritional and inflammatory status. Previous studies have shown that GPS has prognostic value in patients with extensive-stage small-cell lung cancer [36]. Including GPS or similar CRP-based indices alongside LAR in future studies could help provide a more comprehensive evaluation of systemic inflammation and survival outcomes.

In order to assess the robustness of the LAR cut-off value, we performed a bootstrapping analysis with 1000 iterations. The consistent AUC values

observed across samples indicate strong internal validity. Nonetheless, external validation remains essential to confirm generalizability.

The LAR cut-off value varies among studies, and values of, for example, 5.5 [7], 4.04 [37] and 3.8 [14] have been suggested. Differences in tumor type, sample size, geographical region and laboratory equipment may explain this variation. In our cohort, an LAR cut-off of 5.71 effectively distinguished patients with significantly different survival outcomes. While the LAR was independently associated with OS, it did not reach statistical significance for PFS (p=0.13). This may be due to the modest sample size or potential confounding factors. Therefore, conclusions regarding the predictive role of LAR for PFS should be interpreted cautiously and confirmed in larger cohorts.

LDH and albumin values, which showed a significant difference in survival in univariate analysis (p=0.014 and 0.004 for PFS; p=0.001 and <0.001 for OS, respectively), did not show this difference in multivariate analysis (p=0.55 and 0.22 for PFS; p=0.27 and 0.056 for OS, respectively). For this reason, we assessed multicollinearity using VIF analysis. Clearly, LAR and LDH showed very high VIF values (89.0 and 85.4, respectively) which reflecting strong collinearity due to the mathematical relationship between the variables. This likely explains why LDH lost statistical significance in multivariate analysis when LAR was included. Albumin showed a moderate VIF (2.98), suggesting acceptable collinearity. Eventually, these results support the idea that LAR captures the combined prognostic effect of LDH and albumin more effectively than when they are analyzed separately.

Multivariate Cox analysis further identified liver and brain metastases, low albumin, and an absence of PCI as independent predictors of OS. A high LAR remained significant after adjusting for these variables (HR: 3.36; 95% CI: 1.38–8.14; p=0.007). For PFS, liver and adrenal metastases were significantly associated with worse outcomes. These results emphasize the negative prognostic impact of visceral metastases [38,39]. Furthermore, an absence of PCI emerged as an independent adverse prognostic factor for both OS and PFS, in our study. This finding correlates with previous research indicating that PCI can reduce the occurrence of brain metastases in ED-SCLC while also enhancing disease management. According to recent meta-analyses PCI had significant reductions in brain metastasis risk and prolonged PFS, even when compared to MRI-based surveillance strategies [40,41]. Moreover, Chen et al. and Yılmaz et al. reported improved clinical outcomes in patients who received PCI following a good response to initial therapy [42,43].

In our cohort, hyponatremia was not significantly associated with survival outcomes. Although hyponatremia has been reported as a poor prognostic factor in SCLC in previous studies [44-46], its lack of significance in our analysis may be related to the limited number of patients with low sodium levels.

This study has several limitations. First, it is a retrospective, single-center analysis, which may affect the generalizability of the results and may introduce institutional bias related to patient management and data recording practices. Second, we excluded patients without baseline LDH or albumin values and those not receiving systemic therapy to ensure data completeness and consistency in prognostic analysis. We acknowledge that this may have introduced selection bias, possibly favoring patients with better overall performance status and more complete records. Third, although a minority of patients (n=9) received immunotherapy, this group was too small for subgroup analysis, and it had limited the applicability of our findings to current treatment standards. Additionally, the optimal LAR cut-off value may vary depending on population characteristics, laboratory methods, and therapeutic context. Therefore, albeit bootstrap analysis supported the internal consistency of our findings, our results require validation in larger, prospective cohorts.

In conclusion, pretreatment LAR can be used in clinical practice as an accessible, simple and promising prognostic tool in ED-SCLC and can reflect tumor burden and systemic status. Since LDH and albumin levels are routinely used in our daily oncology practice, clinicians can easily calculate LAR at the time of diagnosis. High LAR values may help to identify patients with a poor prognosis. These patients might benefit from closer follow-up, early supportive care, or more intensive treatment when appropriate. However, we should

also know that further prospective studies are needed to confirm its clinical usefulness, especially in the immunotherapy era.

Author contribution

Study conception and design: FY, SY, ÖDT, HÇY, DCG, HT, ZA and ME; data collection: FY, SY, ÖDT, HÇY, DCG, HT, ZA and ME; analysis and interpretation of results: FY, SY, HÇY, HT and ME; draft manuscript preparation: FY, SY, ÖDT, HÇY, DCG, HT, ZA and ME. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Ethics Committee (Protocol no: GO 22/1119, Date: 01.11.2022).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Kalemkerian GP, Akerley W, Bogner P, et al. Small cell lung cancer. J Natl Compr Canc Netw 2013;11(1):78-98. https://doi.org/10.6004/jnccn.2013.0011

[2] Xie D, Marks R, Zhang M, et al. Nomograms predict overall survival for patients with small-cell lung cancer incorporating pretreatment peripheral blood markers. J Thorac Oncol 2015;10(8):1213-20. https://doi.org/10.1097/JTO.0000000000000585

[3] Megyesfalvi Z, Gay CM, Popper H, et al. Clinical insights into small cell lung cancer: tumor heterogeneity, diagnosis, therapy, and future directions. CA Cancer J Clin 2023;73(6):620-52. https://doi.org/10.3322/caac.21785

[4] Wang S, Li Y, Liu Z, et al. Efficacy and safety of first-line immune checkpoint inhibitors combined with chemotherapy for extensive-stage small cell lung cancer: a network meta-analysis. Lung Cancer 2023;178:47-56. https://doi.org/10.1016/j.lungcan.2023.02.003

[5] Zhou L, Xie Z, Shao Z, et al. Modeling the relationship between baseline lactate dehydrogenase and prognosis in patients with extensive-disease small cell lung cancer: a retrospective cohort study. J Thorac Dis 2018;10(2):1043-9. https://doi.org/10.21037/jtd.2018.02.16

[6] Wu Y, Yang J, Qiao X, et al. Use of the prognostic nutrition index as a predictive biomarker in small-cell lung cancer patients undergoing immune checkpoint inhibitor treatment in the Chinese alpine region. Front Oncol 2023;13:1041140. https://doi.org/10.3389/fonc.2023.1041140

[7] Gan W, Zhang MX, Wang JX, et al. Prognostic impact of lactic dehydrogenase to albumin ratio in hepatocellular carcinoma patients with Child-Pugh I who underwent curative resection: a prognostic nomogram study. Cancer Manag Res 2018;10:5383-94. https://doi.org/10.2147/CMAR.S176317

[8] Gao S, Wu M, Chen Y, et al. Lactic dehydrogenase to albumin ratio in prediction of unresectable pancreatic cancer with intervention chemotherapy. Future Oncol 2018;14(14):1377-86. https://doi.org/10.2217/fon-2017-0556

[9] Bilge H, Başol Ö, Demir B, Oğuz A. The prognostic significance of serum lactate dehydrogenase to albumin ratio in pancreatic ductal adenocarcinoma. Acta Med 2023;54(2):109-15. https://doi.org/10.32552/2023.ActaMedica.819

[10] Aday U, Tatlı F, Akpulat FV, et al. Prognostic significance of pretreatment serum lactate dehydrogenase-to-albumin ratio in gastric cancer. Contemp Oncol (Pozn) 2020;24(3):145-9. https://doi.org/10.5114/wo.2020.100219

[11] Aday U, Böyük A, Akkoç H. The prognostic significance of serum lactate dehydrogenase-to-albumin ratio in colorectal cancer. Ann Surg Treat Res 2020;99(3):161-70. https://doi.org/10.4174/astr.2020.99.3.161

[12] Hu Y, Zhou Y, Cao Y, et al. Nomograms based on lactate dehydrogenase to albumin ratio for predicting survival in colorectal cancer. Int J Med Sci 2022;19(6):1003-12. https://doi.org/10.7150/ijms.71971

[13] Wang X, Ji X. Effect of preoperative serum lactate dehydrogenase-to-albumin ratio on the survival of oral cancer: a retrospective study. J Inflamm Res 2024;17:5129-38. https://doi.org/10.2147/JIR.S472041

[14] Xu H, Lin T, Ai J, et al. Utilizing the lactate dehydrogenase-to-albumin ratio for survival prediction in patients with bladder cancer after radical cystectomy. J Inflamm Res 2023;16:1733-44. https://doi.org/10.2147/JIR.S384338

[15] He J, Tong L, Wu P, Wu Y, Shi W, Chen L. Prognostic significance of preoperative lactate dehydrogenase to albumin ratio in breast cancer: a retrospective study. Int J Gen Med 2023;16:507-14. https://doi.org/10.2147/IJGM.S396871

[16] Wu W, Miao L, Zhao L, et al. Prognostic value of lactate dehydrogenase, serum albumin and the lactate dehydrogenase/albumin ratio in patients with diffuse large B-cell lymphoma. Hematology 2024;29(1):2293514. https://doi.org/10.1080/16078454.2023.2293514

[17] Wang Q, Gümüş ZH, Colarossi C, et al. SCLC: epidemiology, risk factors, genetic susceptibility, molecular pathology, screening, and early detection. J Thorac Oncol 2023;18(1):31-46. https://doi.org/10.1016/j.jtho.2022.10.002

[18] Belluomini L, Calvetti L, Inno A, et al. SCLC treatment in the immuno-oncology era: current evidence and unmet needs. Front Oncol 2022;12:840783. https://doi.org/10.3389/fonc.2022.840783

[19] Caliman E, Fancelli S, Petroni G, et al. Challenges in the treatment of small cell lung cancer in the era of immunotherapy and molecular classification. Lung Cancer 2023;175:88-100. https://doi.org/10.1016/j.lungcan.2022.11.014

[20] Farhana A, Lappin SL. Biochemistry, lactate dehydrogenase. Treasure Island (FL): StatPearls Publishing. 2023. Available at: https://www.ncbi.nlm.nih.gov/sites/books/NBK557536/ (Accessed on August 1, 2025).

[21] He M, Chi X, Shi X, et al. Value of pretreatment serum lactate dehydrogenase as a prognostic and predictive factor for small-cell lung cancer patients treated with first-line platinum-containing chemotherapy. Thorac Cancer 2021;12(23):3101-9. https://doi.org/10.1111/1759-7714.13581

[22] Hermes A, Gatzemeier U, Waschki B, Reck M. Lactate dehydrogenase as prognostic factor in limited and extensive disease stage small cell lung cancer - a retrospective single institution analysis. Respir Med 2010;104(12):1937-42. https://doi.org/10.1016/j.rmed.2010.07.013

[23] Li X, Tong L, Wang S, et al. Integration of clinical and blood parameters in risk prognostication for patients receiving immunochemotherapy for extensive stage small cell lung cancer: real-world data from two centers. BMC Med 2024;22(1):381. https://doi.org/10.1186/s12916-024-03612-8

[24] Egbert RC, Bouck TT, Gupte NN, et al. Hypoalbuminemia and obesity in orthopaedic trauma patients: body mass index a significant predictor of surgical site complications. Sci Rep 2020;10(1):1953. https://doi.org/10.1038/s41598-020-58987-4

[25] de Tymowski C, Pallado S, Anstey J, et al. Early hypoalbuminemia is associated with 28-day mortality in severely burned patients: a retrospective cohort study. Burns 2020;46(3):630-8. https://doi.org/10.1016/j.burns.2019.09.013

[26] Yin M, Si L, Qin W, et al. Predictive value of serum albumin level for the prognosis of severe sepsis without exogenous human albumin administration: a prospective cohort study. J Intensive Care Med 2018;33(12):687-94. https://doi.org/10.1177/0885066616685300

[27] Bullock AF, Greenley SL, McKenzie GAG, Paton LW, Johnson MJ. Relationship between markers of malnutrition and clinical outcomes in older adults with cancer: systematic review, narrative synthesis and meta-analysis. Eur J Clin Nutr 2020;74(11):1519-35. https://doi.org/10.1038/s41430-020-0629-0

[28] Berbel-Franco D, Lopez-Delgado JC, Putzu A, et al. The influence of postoperative albumin levels on the outcome of cardiac surgery. J Cardiothorac Surg 2020;15(1):78. https://doi.org/10.1186/s13019-020-01133-y

[29] Hardt J, Pilz L, Magdeburg J, Kienle P, Post S, Magdeburg R. Preoperative hypoalbuminemia is an independent risk factor for increased high-grade morbidity after elective rectal cancer resection. Int J Colorectal Dis 2017;32(10):1439-46. https://doi.org/10.1007/s00384-017-2884-7

[30] Sullivan SA, Van Le L, Liberty AL, Soper JT, Barber EL. Association between hypoalbuminemia and surgical site infection in vulvar cancers. Gynecol Oncol 2016;142(3):435-9. https://doi.org/10.1016/j.ygyno.2016.06.021

[31] Santos A, Jorgenson MR, Osman F, et al. Hypoalbuminemia is a risk factor for invasive fungal infections and poor outcomes in infected kidney transplant recipients. Clin Transplant 2023;37(10):e15052. https://doi.org/10.1111/ctr.15052

[32] Tang Q, Li X, Sun CR. Predictive value of serum albumin levels on cancer survival: a prospective cohort study. Front Oncol 2024;14:1323192. https://doi.org/10.3389/fonc.2024.1323192

[33] Reyes-Pérez EN, Flores-Cuevas LM, Martínez-Mier G, et. al. Predictive value of the lactate dehydrogenase-to-albumin ratio (LAR) in classical Hodgkin's lymphoma. Ann Blood 2023;8:32. https://doi.org/10.21037/aob-23-24

[34] Zhao R, Liang Z, Chen K, Zhu X. Nomogram based on inflammatory biomarkers and nutritional indicators for predicting overall survival in locoregionally advanced nasopharyngeal carcinoma. J Inflamm Res 2022;15:2971-81. https://doi.org/10.2147/JIR.S366299

[35] Feng JF, Wang L, Yang X, Jiang YH. Prognostic value of lactate dehydrogenase to albumin ratio (LAR) in patients with resectable esophageal squamous cell carcinoma. Cancer Manag Res 2019;11:7243-51. https://doi.org/10.2147/CMAR.S208320

[36] Igawa S, Yamamoto H, Yamada K, et al. The Glasgow Prognostic Score predicts survival outcomes in patients with extensive-stage small cell lung cancer. Oncology 2023;101(11):695-704. https://doi.org/10.1159/000532087

[37] Peng RR, Liang ZG, Chen KH, Li L, Qu S, Zhu XD. Nomogram based on Lactate Dehydrogenase-to-Albumin Ratio (LAR) and Platelet-to-Lymphocyte Ratio (PLR) for predicting survival in nasopharyngeal carcinoma. J Inflamm Res 2021;14:4019-33. https://doi.org/10.2147/JIR.S322475

[38] Ren Y, Dai C, Zheng H, et al. Prognostic effect of liver metastasis in lung cancer patients with distant metastasis. Oncotarget 2016;7(33):53245-53. https://doi.org/10.18632/oncotarget.10644

[39] Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. Nat Rev Dis Primers 2021;7(1):3. https://doi.org/10.1038/s41572-020-00235-0

[40] Gaebe K, Erickson AW, Li AY, et al. Re-examining prophylactic cranial irradiation in small cell lung cancer: a systematic review and meta-analysis. EClinicalMedicine 2024;67:102396. https://doi.org/10.1016/j.eclinm.2023.102396

[41] Wang Z, Chen L, Sun L, et al. Prophylactic cranial irradiation for extensive stage small cell lung cancer: a meta-analysis of randomized controlled trials. Front Oncol 2023;13:1086290. https://doi.org/10.3389/fonc.2023.1086290

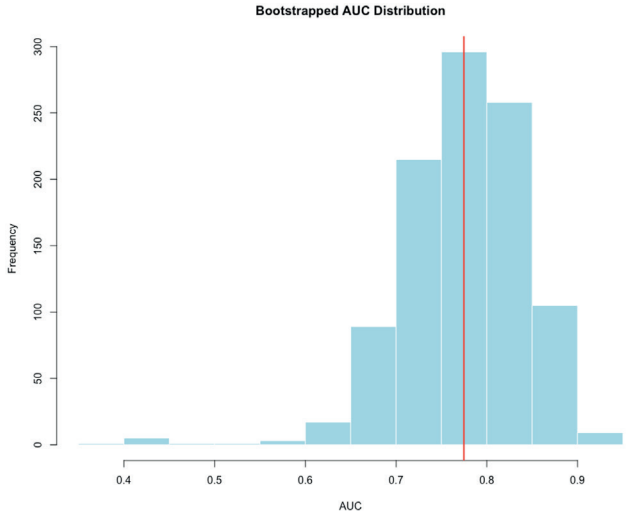
[42] Chen Y, Wang Y, Ren F, et al. Prophylactic cranial irradiation (PCI) versus active surveillance in patients with limited-stage small cell lung cancer: a retrospective, multicentre study. Respir Res 2022;23(1):274. https://doi.org/10.1186/s12931-022-02196-2

[43] Yılmaz F, Yaşar S, Tatar ÖD, et al. Bi-weekly irinotecan is an effective and convenient regimen in the treatment of relapsed or refractory small cell lung cancer. BMC Cancer 2024;24(1):1218. https://doi.org/10.1186/s12885-024-12935-x

[44] Cerny T, Blair V, Anderson H, Bramwell V, Thatcher N. Pretreatment prognostic factors and scoring system in 407 small-cell lung cancer patients. Int J Cancer 1987;39(2):146-9. https://doi.org/10.1002/ijc.2910390204

[45] Osterlind K, Andersen PK. Prognostic factors in small cell lung cancer: multivariate model based on 778 patients treated with chemotherapy with or without irradiation. Cancer Res 1986;46(8):4189-94.

[46] Hansen O, Sørensen P, Hansen KH. The occurrence of hyponatremia in SCLC and the influence on prognosis: a retrospective study of 453 patients treated in a single institution in a 10-year period. Lung Cancer 2010;68(1):111-4. https://doi.org/10.1016/j.lungcan.2009.05.015



Supplementary Figure 1. Bootstrapped distribution of AUC values for the LAR cut-off.

The histogram illustrates the distribution of AUC values obtained from 1000 bootstrap iterations. The red vertical line indicates the mean AUC. This analysis was conducted to assess the internal validity and robustness of the LAR cut-off in predicting overall survival. AUC: area under curve; LAR: lactate dehydrogenase-albumin ratio.

acta medica

ORIGINAL ARTICLE

Predictors of secondary traumatic stress: traumatic experience, psychiatric symptoms and gender vs. mindfulness and mortality awareness

Zehra Sena Giray[1]
ORCID: 0000-0003-3597-8490

Talat Demirsöz[2]
ORCID: 0000-0002-3786-1272

[1]Private Boylam Psychiatric Hospital, Ankara, Türkiye

[2]Hacettepe University Faculty of Medicine, Department of Psychiatry, Ankara, Türkiye

Corresponding Author: Zehra Sena Giray
E-mail: akdogusena@gmail.com

Received: 5 July 2025, Accepted: 27 August 2025, Published online: 30 September 2025

ABSTRACT

Objective: The present study mainly aimed to examine the relationship between mindfulness, mortality awareness, and the emergence of secondary traumatic stress (STS) symptoms in young adults who had been indirectly exposed to social media content related to the 6 February 2023 Kahramanmaraş earthquakes.

Materials and Methods: Data were collected online between June 2023 and May 2024 from 96 participants aged 18–26 (83% female). Exclusion criteria included direct exposure to the earthquake, residing in the affected provinces, bereavement of close relatives, or engagement in rescue operations. Measures included the Brief Symptom Scale-25, Multidimensional Mortality Awareness Measure, Secondary Traumatic Stress Scale for Social Media Users, and the Five Facet Mindfulness Questionnaire-Short Form. Hierarchical Regression Analysis was used to investigate predictive roles of mindfulness and mortality awareness for secondary traumatic stress symptoms, controlling the effects of gender, past traumatic experience, and the effect of general psychiatric symptomatology.

Results: Gender, psychiatric symptoms, and past trauma history significantly predicted STS, accounting for 30% of the variance. Being female, having more psychiatric symptoms, and a history of trauma were associated with higher STS levels. Adding mindfulness and mortality awareness increased the explained variance to 46%. Specifically, mortality fearfulness and mortality legacy positively predicted STS symptoms, suggesting that fear of death and the need to leave a legacy may heighten vulnerability. Conversely, the mindfulness sub-dimension of nonjudging inner experience negatively predicted STS, indicating a protective role. Independent-samples t tests indicated that STS scores were higher among participants with a past trauma history than those without (M=52.00 vs 43.30), t(94)=2.58, p=.011, and among females versus males (M=47.24 vs 36.20), t(93)=2.80, p=.006.

Conclusion: Controlling for established predictors (female gender, psychiatric symptomatology, and past trauma), mortality fearfulness and mortality legacy remained positive predictors of STS, whereas nonjudging of inner experience remained a negative predictor. This pattern suggests that mortality awareness and mindfulness facets contribute unique variance to STS beyond core risk factors.

Keywords: secondary traumatic stress, mindfulness, mortality awareness

INTRODUCTION

According to the American Psychiatric Association (APA), the term "trauma" is defined as an actual or threatening encounter with death, serious injury or sexual assault [1]. In accordance with this, the emphasis is placed on exposure rather than exclusively on firsthand victimization. These events, may have been either directly or indirectly experienced by the individual. Post-traumatic stress disorder (PTSD) is characterised by the involuntary resurgence of traumatic memories, distress when reminded of the event, and avoidance of related triggers. It can also involve negative alterations in cognition and mood related to the event. The condition may also manifest as symptoms of arousal and reactivity [1]. In this clinical context, trauma-related symptom constellations are predominantly discussed within the framework of PTSD.

The notion of STS which was first theorised by Ludick and Figley in 2017, can be defined as the risk of secondary traumatisation that occurs because of indirect exposure to the traumatic experiences of others [2]. In both direct and indirect exposure to traumatic experiences, the symptoms that develop in individuals are remarkably similar [3]. Like PTSD, STS includes intrusive thoughts, avoidance, hyperarousal, disturbing emotions, sleep problems, and interpersonal difficulties [4]. Although the existence of secondary trauma in professional groups that assist trauma victims is widely accepted, there is a paucity of research examining whether STS can occur in ordinary people exposing to trauma on the internet, television or social media [5]. While STS shares several common risk factors with PTSD—including female gender, high levels of psychological distress, and insufficient social support—it also differs in symptom severity, phenomenology, and etiology. Unlike PTSD, STS emerges from indirect exposure, such as repeatedly hearing about or witnessing others' trauma. The symptoms are usually less severe, but they can still be clinically important [6,7]. Moreover, the risk of STS is especially high in groups who are regularly exposed to others' suffering with strong empathy (such as healthcare providers, therapists, and humanitarian workers) and in situations of repeated indirect exposure, including media coverage of disasters [8,9]. These distinctions underline the importance of examining both shared and unique pathways to stress responses in the aftermath of collective trauma. On 6 February 2023, two earthquakes occurred in Turkey measuring 7.7 and 7.6 on the Richter scale, respectively, at 4:17 and 13:24. These seismic events affected a total of 11 provinces. Afterwards, it was estimated that approximately 13 million individuals were impacted, with a reported 46,000 fatalities [10,11]. Turkey is a disaster-prone country frequently exposed to large-scale events such as earthquakes, mining accidents, and industrial catastrophes, which increases collective vulnerability to secondary traumatization. Epidemiological studies show that PTSD prevalence rates after earthquakes in Turkey have been considerably high; for example, it is found that elevated PTSD symptoms among adults following the 2011 Van-Erciş earthquake [12]. These findings indicate that large-scale disasters in Turkey have left a lasting psychological impact on adults. In addition, it is reported that 74.4% of participants felt unprepared and anxious [13]. These findings underscore how inadequate preparedness amplifies psychological distress. Moreover, media coverage in Turkey often presents disaster-related events with repetitive, graphic, and emotionally charged content. International evidence suggests that such media exposure can amplify stress and secondary traumatization [14,15]. These structural and sociocultural factors likely contribute to elevated levels of STS within the Turkish society.

It is thought that even individuals who were not directly exposed to the earthquake may have been subjected to recurrent exposure to media portrayals regarding the earthquake in the following days of the disaster. In this context, the present study aims to investigate the secondary traumatic effects in individuals who have experienced the earthquake indirectly through the media.

The extant literature on trauma indicates that mindfulness and acceptance-based practices can improve the psychological adjustment of traumatized individuals and reduce the risk of developing PTSD symptoms [16]. Accordingly, it is important to specify what is meant by mindfulness in this context.

Mindfulness can be defined as the act of attending to the present moment nonjudgementally [17]. The term mindfulness is defined as the non-judgmental and non-reactive observation of the ongoing flow of internal and external stimuli including unwanted emotions and cognitions as they arise [18]. Practices of mindfulness-based stress reduction are thought to have a positive effect on emotional well-being [19]. Alongside the utilisation of mindfulness practices for the general public, there is also literature concerning their use for individuals who are indirectly exposed to trauma. For instance, Setti and Argentero's study in 2014 revealed a negative correlation between mindfulness and vicarious traumatization in a sample of firefighters [20]. Accordingly, it is thought that elevated levels of mindfulness appear to offer a safeguard against the occurrence of vicarious traumatization among firefighters. In a similar vein, a study conducted with lawyers reported that mindfulness was a negative predictor of STS [21]. In light of the accumulated research findings, it is hypothesized that the concept of mindfulness may be an important factor within the context of this study.

In addition to the concept of mindfulness, the concept of mortality awareness was introduced to deepen the issue because rescue activities received prolonged media coverage in the short period after earthquake. Thus, it is thought that people who follow these news through media channels have been exposed to the concept of death for a prolonged time. One of the significant theories associated with the notion of mortality awareness is the Terror Management Theory. In accordance with Terror Management Theory, the awareness of mortality and the inevitability of death can exert a significant influence on thoughts, feelings and behaviours [22,23]. In this context, it is estimated that a considerable number of individuals have been exposed to the destruction especially through the utilization of social media platforms. Within the scope of this study, the concept of mortality awareness consists of sub-dimensions such as mortality fearfulness, mortality legacy, mortality acceptance, mortality disempowerment and mortality disengagement [24]. Mortality legacy, in this context, is defined as the act of creating a legacy to ensure survival beyond death. The concept of mortality fearfulness is understood to reflect the anxiety associated with the impossibility of escaping death. Mortality acceptance, on the other hand, is defined as the acknowledgement that death is an inevitable part of life, as opposed to a rejection of death. Mortality disempowerment is explained as the perception that the individual perceives themselves as insignificant and that all is meaningless in the face of death. Mortality disengagement, in this regard, refers to the act of not thinking about death, which is indicative of an individual ignoring the reality of death and focusing on the present moment.

In addition to the aforementioned factors, there are other factors that are hypothesised to be related to STS. Psychiatric symptomatology and gender are accepted to be significant predictors of stress following exposure to traumatic experiences, whether direct or indirect. [25-27]. Another salient factor associated with traumatic stress is the existence of past traumatic experiences [26-29]. A body of research has demonstrated an association between repetitive traumatic experiences and alterations in brain function, as evidenced even by neuroimaging studies. These alterations manifest as increased activity in the amygdala, reduced volume in the hippocampus, and impaired prefrontal cortex function [30].

In order to provide a coherent theoretical foundation, the present study draws on two complementary perspectives: stress and coping framework [31] and contemporary resilience models [32,33]. The former conceptualizes stress as occurring when perceived demands exceed available resources, with outcomes shaped by individuals' threat appraisals and coping strategies. The latter emphasizes the protective factors that enable individuals to adapt positively in the face of adversity. These models enable us to identify both the risk and protective factors associated with STS.

More specifically, the stress and coping framework highlights the role of risk appraisal in shaping stress responses in the context of stress and coping framework. Within this framework, disaster-related media exposure can be considered a type of stressor that heightens vulnerability through threat/risk appraisal processes. In particular, in the aftermath of large-scale disasters, there is a demonstrable

correlation between repeated exposure to graphic media content and the sustaining of mortality salience. This, in turn, has been shown to be associated with heightened acute stress and symptoms of PTSD-like conditions in the general population [9,34]. This exposure also maintains the cognitive accessibility of the inevitability of death and, consequently, may therefore create a psychological vulnerability of risk for STS. This framework is thought to be align with Terror Management Theory (TMT). TMT explains that when people are more aware of death, they often react defensively and this can make them more vulnerable to stress. For example, they may strongly defend their cultural values, show prejudice toward out-groups, or seek higher self-esteem as a way to manage their anxiety [35]. Therefore, mortality awareness is thought to represent a theoretically grounded risk factor for STS in the stress and coping framework [9,34].

The resilience perspective on the other hand emphasizes the protective coping resources that foster positive adaptation in the face of adversity. Within this framework, mindfulness can be conceptualized as a protective factor that mitigates vulnerability to stress responses subsequent to indirect trauma exposure. Empirical studies demonstrate that mindfulness may foster acceptance, emotion regulation, and adaptive coping, thereby enhancing resilience and reducing vulnerability to STS [36-38]. In this sense, mindfulness operates as a protective predictor in elucidating the construct of STS after disaster-related media exposure.

By situating mortality awareness within the stress–coping/TMT framework as a risk factor and mindfulness within resilience models as a protective factor, the present study seeks to offer a broad account of predictors of STS following the indirect disaster exposure. Examining both risk and protective predictors within the stress–resilience framework allows for a more comprehensive understanding of why some individuals develop STS following indirect disaster exposure, whereas others remain more resilient.

Considering the huge magnitude of the disaster, the main aim of this present study is to investigate the relationship between mindfulness and mortality awareness in individuals who were not personally exposed to the earthquake, and the subsequent emergence of STS symptoms. The present examination is exploratory in nature.

MATERIALS AND METHODS

Participants

The present study was conducted with the approval of the Hacettepe University Health Sciences Research Ethics Committee (GO 23/344). Online data collection was conducted over the period from 23/06/2023 to 14/05/2024. Participants were recruited via social media and completed the scales after their consent being obtained online. The study's sample is comprised of 96 individuals ranging in age from 18 to 26. In accordance with the validity and reliability study of the Secondary Traumatic Stress Scale for Social Media Users (STSS-SM) employed in the research, which was conducted with young adults, the present study included only participants from this age group. The mean age of the subjects was 23.09 years (SD = 2.23). Upon analysis of the gender distribution of the sample, it was observed that 83.3% (n=80) of the subjects were female and 15.6% (n=15) were male. (see Table 1) One participant did not wish to specify gender. The inclusion criteria were determined as being between the ages of 18 and 26. The exclusion criteria included a history of head trauma resulting in lifelong impairment, bereavement of a close relative (mother, father, spouse, child, sibling, partner, relative, or close friend) during the 6 February 2023 Kahramanmaraş earthquakes, being a resident in one of the 11 provinces at the time of earthquake, and engagement in volunteer aid activities in one of the 11 affected provinces. In accordance with these exclusion criteria, 75 participants were excluded from the study and thanked for their interest.

Table 1. Demographic characteristics of the sample

	Mean	**SD.**
Age	23.09	2.23
	N	**Percentage (%)**
Gender		
Female	80	83.3
Male	15	15.6
Do Not Want to Specify	1	

Instruments

Demographic information form

A demographic information form was utilized to obtain descriptive information regarding the participants' age, gender, current psychiatric diagnosis, history of head trauma, current psychiatric medication use, city of residence at the time of the 6 February 2023 Kahramanmaraş earthquakes, loss of relatives in the 6 February 2023 Kahramanmaraş earthquakes, and past traumatic experiences. Participants were asked to select from a list of traumatic life events if they had experienced similar events.

Brief Symptom Inventory-25

The Brief Symptom Scale-25 was developed by Blais et al. in 2015 to measure general psychiatric symptomatology [39]. The Cronbach's alpha internal consistency reliability coefficient of both the original scale and that of Turkish adaptation of the scale was found to be 0.92. Turkish adaptation of the scale was conducted by Gülüm and Soygüt in 2017 [40]. It is a 7-point Likert-type scale (1=not at all, 7=extremely) and consists of 25 items.

Multidimensional Mortality Awareness Measure

The Multidimensional Mortality Awareness Measure was developed by Levasseur et al. in 2015 [41]. The original scale consists of 36 items and has 5 sub-dimensions. It is a 7-point Likert-type scale (1=strongly disagree, 7=strongly agree). The Cronbach's alpha internal consistency reliability coefficient of the original scale is between 0.59 and 0.87. The scale was adapted into Turkish by Bulut et al. in 2017 [24]. The Turkish adaptation consists of 30 items and 5 sub-dimensions (mortality fearfulness, mortality legacy, mortality acceptance, mortality disempowerment and mortality disengagement) and is a 5-point Likert-type scale (1=strongly disagree, 5=strongly agree). The Cronbach's a internal consistency reliability coefficient of the Turkish adaptation was found to be 0.79 and the split-half reliability coefficient was found to be 0.74.

Secondary Traumatic Stress Scale for Social Media Users (STSS-SM)

The Secondary Traumatic Stress Scale for Social Media Users (SM-STSS) was developed by Mancini in 2019 to assess the symptoms that may arise in relation to traumatic experiences indirectly exposed through social media [42]. The Cronbach's alpha internal consistency reliability coefficient of the original scale is 0.92. The Turkish adaptation of the scale was conducted by Balcı Çelik and Altınışık in 2021 [43]. The scale consists of 17 items and is scored on a 5-point Likert-type scale (1=Never, 5=Very Often). The Turkish adaptation of the scale consists of a single factor and Cronbach's alpha internal consistency reliability coefficient is 0.95.

Five Facet Mindfulness Questionnaire (FFMQ)-Short Form

Five Facet Mindfulness Questionnaire (FFMQ)-Short Form is a 20-item version of the 39-item and 5-factor scale developed by Baer et al. in 2006 to measure people's mindfulness levels and shortened by Tran et al. in 2013 [44,45]. The Turkish adaptation of the scale was conducted by Ayalp and Hisli Şahin in 2018 [46]. It is a 5-point Likert-type scale (1=Never, 5=Always). The scale has 5 sub-dimensions: observing, describing, acting with awareness, nonjudging of inner experience, nonreactivity to inner experience. Cronbach's α internal consistency reliability coefficient is between 0.69 and 0.85. The Cronbach's α internal consistency reliability coefficient of the total score of the scale is .71.

Statistical analysis

The analysis was conducted using IBM SPSS 26.0. Prior to analysis, outliers were identified skewness and kurtosis values pointed out a normal distribution [47]. Pearson Correlation Coefficient Analysis was conducted to examine the relationships between the variables. An independent sample t-test was conducted to compare participants' STS scores. The present study employed Hierarchical Regression Analysis to investigate the hypothesis that mindfulness and mortality awareness would predict STS symptoms, controlling the effects of gender, past traumatic experience and the effect of general psychiatric symptomatology.

RESULTS

The mean, standard deviation, minimum and maximum values of the participants' scores from the scales are presented in Table 2.

Table 2. Descriptive statistics regarding participants' scores on the scales

Variable	Mean	SD	Range
BSI	74.77	27.35	25-132
STS	45.39	14.47	19-80
M-Legacy	33.42	9.39	11-49
M-Fearfulness	41.06	15.59	12-75
M-Acceptance	27.39	3.41	16-33
M-Disempowerment	8.31	3.78	3-21
M-Disengagement	15.02	4.77	4-26
FFMQ-Observing	15.23	3.25	5-20
FFMQ-Describing	14.20	3.70	6-20
FFMQ-Acting with awareness	10.90	3.96	4-20
FFMQ-Nonjudging of inner experience	12.66	4.04	4-20
FFMQ-Nonreactivity to inner experience	12.27	3.35	4-20

SD: Standard Deviation, SD: Standard Deviation, BSI: Brief Symptom Inventory Total Score, STS: Secondary Traumatic Stress Scale for Social Media Users Total Score, M-: Multidimensional Mortality Awareness Measure sub-dimensions, FFMQ-: Five Facet Mindfulness Questionnaire (FFMQ)-Short Form sub-dimensions.

Table 3. Comparison of STSS-SM scores according to various variables

		N	Mean	SD.	Std. Error Mean.	t	p
Past Trauma History	Yes	23	52.00	13.32	1.67	2.58	.011
	No	73	43.30	14.27	2.78		
Gender	Female	80	47.24	14.00	1.57	2.80	.006
	Male	15	36.20	14.03	3.62		

N: Number of Participants, SD: Standard Deviation, Std. Error Mean.: Standard Error Mean, STSS-SM: Secondary Traumatic Stress Scale Score for Social Media Users, t: independent samples t test, F: One-way analysis of variance (ANOVA), p: significance value.

The findings of the independent samples t-test demonstrated that the STS scores of the participants with (mean=52.00, SD=13.32) and without a history of past traumatic history (mean=43.30, SD=14.27) statistically significantly differed (t(94)=2.58, p=.011). Furthermore, the analyses indicated that the STS levels of female (Mean = 47.24, SD = 14.00) and male (Mean = 36.20, SD = 14.03) participants statistically significantly differed (t (93)=2.80, p=.006) (see Table 3).

The correlational analyses indicated that STS was positively associated with psychiatric symptomatology and legacy and fearfulness subscales of MA suggesting that greater psychological distress and heightened death-related concerns are linked to higher levels of STS. Conversely, describing, nonjudging of inner experience, acting with awareness subscales of mindfulness facets of showed negative correlations with STS, indicating that a mindfulness practices may buffer against STS. In addition, gender was significantly correlated with STS, meaning that being female was associated with higher levels of stress. These results demonstrate that the key study variables are meaningfully interrelated at the bivariate level (see Table 4).

In the hierarchical regression analysis, STS level was included as the dependent variable, with gender, general psychiatric symptomatology, the presence of past traumatic history, the mindfulness and mortality awareness sub-dimensions included in the analysis as predictor variables. The subdimensions of mortality awareness and mindfulness, which showed a statistically significant correlation with the dependent variable, were included in the hierarchical regression analysis as predictor variables. In the first step of the analysis, gender, general psychiatric symptomatology, and the presence of past traumatic history were included as predictors. In the second step, the analysis incorporated the mindfulness and mortality awareness sub-dimensions. The results of the Hierarchical Regression Analysis demonstrate that gender, general psychiatric symptomatology and the presence of past traumatic experiences collectively accounted for 30% of the variance, and were statistically significant ($R2$= .30, F(3,92)=13.16, p< .001). The association between being female

Table 4. Results of correlational analyses

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. STS	—	.46**	-.28**	.26**	.21*	.37**	**-.07**	**.10**	**-.08**	**.16**	**-.19***	**-.33****	**-.24***	**-.17**
2. BSI		—	-.06	.14	.13	.25**	**-.05**	**.36****	**-.09**	**.01**	**-.32****	**-.37****	**-.47****	**-.18**
3. Gender			—	-.18*	.07	.06	**.09**	**.15**	**.07**	**-.13**	**.19***	**.08**	**.30****	**.24****
4. PTH				—	-.01	-.12	**.07**	**.05**	**.06**	**.14**	**.03**	**.04**	**-.18***	**-.06**
5. M-L					—	.08	**.35****	**-.19***	**.11**	**.14**	**.10**	**.11**	**.23***	**-.00**
6. M-F						—	**.17**	**.10**	**-.31****	**-.01**	**-.05**	**-.15**	**-.08**	**-.11**
7. M-A							—	**-.02**	**.24***	**.02**	**.29****	**.07**	**.12**	**.09**
8. M-DISEMP								—	**.05**	**.09**	**.10**	**.11**	**.05**	**.09**
9. M-DISENG									—	**.15**	**.16**	**.15**	**.18**	**.24***
10. F-OBS										—	**.10**	**-.15**	**-.12**	**-.11**
11. F-DES											—	**.07**	**.12**	**.09**
12. F-NONJ												—	**.12**	**.09**
13. F-ACTWA													—	**.09**
14. F-NONR														—

N=96. *p<.05, **p<.01. BSI: Brief Symptom Inventory Total Score, STS: Secondary Traumatic Stress Scale Total Score, PTH: Past Traumatic History, M-: Multidimensional Mortality Awareness Measure sub-dimensions (Legacy, Fearfulness, Acceptance, Disempowerment, Disengagement), FFMQ-: Five Facet Mindfulness Questionnaire sub-dimensions (Observing, Describing, Nonjudging of Inner Experience, Acting with Awareness, Nonreactivity to Inner Experience).

and higher levels of STS was found to be statistically significant (β =-0.23, p=.012). The general psychiatric symptomatology (β =0.43, p<.001) were found to be positive predictor of STS symptoms. In the subsequent phase, the analysis encompassed the sub-dimensions of mindfulness and mortality awareness. The statistically significant contribution of these variables to the initial model was 16% (*R(2) (change)* =.16, *F(change)* (4,88)=6.60, p<.001). The total variance explained at the conclusion of the second model was 46% *(R(2)* =.46, *F*(7,88)=10.78, p<.001). In the context of the present study, the presence of a history of traumatic experiences (β =0.24, p=.005) and sub-dimensions of mortality awareness such as mortality legacy (β=*0*.17, p=.044) and mortality fearfulness (β=*0*.31, p<.001) were found to positively predict STS symptoms. Conversely, nonjudging of inner experience (β=*-0*.23, p=.013) from the sub-dimensions of mindfulness was found to negatively predict STS symptoms (see Table 5).

Table 5. Results of hierarchical regression analysis conducted on the prediction of secondary traumatic stress symptoms

	Dependent Variable	**Predictor Variable**	**β**	**t**	**p**	**Tolerance**	**R**	**R^2**	**F**
Model 1	Secondary Traumatic Stress	Gender	-0.23	-2.57	**.012***	.965			
		Psychiatric Symptomatology	0.43	4.83	**.000****	.980	.548	.300	13.16
		Past Trauma History	0.16	1.75	.083	.950			
Model 2	Secondary Traumatic Stress	Gender	-0.26	-3.13	**.002***	.877			
		Psychiatric Symptomatology	0.28	2.80	**.006***	.637			
		Past Trauma History	0.24	2.87	**.005***	.906			
		Mortality Legacy	0.17	2.05	**.044***	.867	.679	.462	10.78
		Mortality Fearfulnes	0.31	3.72	**.000****	.905			
		Nonjudging of inner experience	-0.23	-2.53	**.013***	.769			
		Acting with awareness	0.09	0.91	.365	.580			

Note: * p<.05; ** p<.001.

DISCUSSION

Exposure to traumatic content through the media has been demonstrate to pose a risk for developing STS, thus emerging as a significant public health concern. The findings of the study reveal that both past traumatic experience, current psychiatric symptoms and gender, as well as mindfulness and mortality awareness are significant predictors of STS.

The present study provides further support to the findings in the literature [26,28,29]. by demonstrating that a history of traumatic experiences is a significant predictor of STS. On the other hand, another outcome of this study is that being female is a risk factor for STS. This finding regarding gender is consistent with the results reported in the existing literature [26]. As asserted by Bangasser and Wicks in 2017, research has indicated that the hypothalamic-pituitary-adrenal (HPA) axis, a regulatory system for the stress response, would exhibit greater dysregulation in women compared to men in response to traumatic events [48]. This biological difference has the potential to cause heightened sensitivity to stress in women, both emotionally and physiologically [48]. As demonstrated in the research by Bangasser and Valentino in 2014, hormonal fluctuations, particularly those associated with estrogen and oxytocin, have the potential to amplify the intensity of women's stress responses to traumatic stimuli [49]. In addition to these biological factors, research has demonstrated that women exhibit higher levels of empathy compared to men [50]. This higher empathic tendency in women compared to men may be a contributing factor to heightened emotional responses to traumatic experiences and the exacerbation of STS symptoms. Furthermore, the predominance of psychiatric symptomatology as a risk factor for STS symptoms is consistent with the findings of previous studies [27].

The study yielded additional findings, though contrary to expectations, these were less robust than the initial set of findings. It is found that nonjudging of inner experience, a component of mindfulness, functions as a negative predictor for the development of STS. The " nonjudging of inner experience " sub-dimension of mindfulness suggests that mindfulness may play a protective role against STS as a variable having the potential to increase emotion regulation capacity. This finding is consistent with the findings of researchers who have demonstrated that mindfulness-based interventions have a positive effect on emotional well-being [17-19]. Mindfulness has been shown to facilitate the development of an acceptance-based approach to traumatic thoughts, thereby reducing the impact of ruminative thought patterns [51]. In addition, when intrusive thoughts inevitably arise, mindfulness can increase the ability to tolerate related emotional arousal by facilitating the processing of distressing emotions [52]. The findings of the study indicate that certain sub-dimensions of mortality awareness, namely "mortality fearfulness" and "mortality legacy", predict STS. Therefore, these sub-dimensions can be regarded as risk factors for STS. When evaluated within the framework of TMT [22,23], the awareness of inevitability of death may increase the level of (death) anxiety in individuals. In this way, it can be assumed that fear of death intensifies STS reactions following exposure to traumatic material by excessively depleting the individual's cognitive and emotional resources.

On the other hand, when examined the findings of the present study, the necessity to establish a mortality legacy has been observed to emerge within the context of the individual's pursuit of continuity subsequent to death is found to be a risk factor for STS symptoms. The mortality legacy dimension is associated with the desire to create a legacy to ensure survival after death, as well as the endeavour to leave a lasting impression after death. However, given the age range of the participants in this study, it can be assumed that this dimension has not yet been fully developed. This incompleteness has the potential to act as a significant source of stress for the individual. Besides, this finding may also be related to the magnitude of the earthquake. In the face of the substantial destruction, it is thought that individuals may have sought to leave a record, yet found themselves powerless in doing so. Therefore, this increased risk of STS due to mortality legacy may be attributable to the aforementioned feelings of helplessness.

Upon comprehensive consideration of all the findings, it is imperative to identify individuals who are predisposed to STS within the context

of factors such as gender, the presence of past traumatic experiences, and the extent of psychiatric symptoms. The implementation of enhanced monitoring strategies for these individuals during the post-disaster phase has the potential to prevent the chronicity of the problem. The findings of this study also demonstrate that practices aimed at cultivating mindfulness in individuals function as a preventative and curative resource not only for those who have been directly exposed to trauma, but also for individuals who have been *indirectly* exposed to traumatic content. Besides, it is acknowledged that mortality awareness may serve a significant role in elucidating psychological responses to trauma experienced indirectly. Therefore, findings postulated that integrated practices of mindfulness and mortality awareness within the intervention programs are assumed to have a preventive role in terms of secondary traumatization, especially in individuals who follow media intensively after disasters.

The present research provides important findings within limitations. Firstly, the majority of the sample consists of women (83.3%) and young adults who are university students or graduates. This particular sample structure has the effect of limiting the generalizability of the findings to different age groups, socioeconomic levels or occupational groups. In 1995, Porst and von Briel posit that, in addition to personal and situational factors, women are more likely to respond to surveys due to altruism as cited in Becker' study [53]. Therefore, the higher number of female participants in this study is consistent with this finding. Secondly, the cross-sectional nature of this study does not permit the establishment of causal relationships between variables. The causal relationships between predictive variables and STS symptoms can be explained by conducting longitudinal studies in future research. Utilization of self-report data is another limitation for the study including confinements to the boundaries of social desirability.

Recommendations for future research

As previously stated, this study makes a significant contribution to the existing literature by demonstrating a relationship between STS symptoms and an individual's level of mindfulness. The development of short-term, group and/or online mindfulness-based psychoeducation programs would be a valuable for individuals who have been exposed to traumatic content through the media, particularly in the aftermath of traumatic events that have a societal impact. It is thought that these programs can assist in improving emotion regulation skills, reducing avoidant coping strategies, and enhancing the psychological resilience of the individuals. Alongside these programs, mental health professionals can prepare psychoeducational programmes for mass media as part of public health initiatives. Furthermore, TMT-based approaches or existential-based interventions would be incorporated into these psychoeducation programs to focus on awareness of mortality of the target groups. In order to mitigate the psychological impact on individuals, public service announcements informing the public about media use during disasters and about awareness of exposure to traumatic content, and mental health-based social media campaigns, can be prepared. To sum up, the presence of past traumatic experiences and the female sex are identified as risk factors for STS. The creation of preventative psychological support systems for these groups is recommended.

Author contribution

Study conception and design: ZSG, TD; data collection: ZSG, TD; analysis and interpretation of results: ZSG, TD; draft manuscript preparation: ZSG, TD. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Health Sciences Research Ethics Committee (Protocol no. GO 23/344/18.04.2023).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Amerikan Psikiyatri Birliği. Ruhsal örselenme (travma) ve tetikleyici etkenle (stresörle) ilişkili bozukluklar. In: Köroğlu E, translator. DSM-5-TR tanı ölçütleri başvuru el kitabı. 5th ed. Ankara: Esenkal Yayıncılık; 2022: 145-160.

[2] Ludick M, Figley CR. Toward a mechanism for secondary trauma induction and reduction: reimagining a theory of secondary traumatic stress. Traumatology 2017;23(1):112. https://doi.org/10.1037/trm0000096

[3] Figley CR. Compassion fatigue as secondary traumatic stress disorder: an overview. In: Figley CR, editor. Compassion fatigue coping with secondary traumatic stress disorder in those who treat traumatized. New York, NY: Routledge; 1995: 1-20.

[4] McCann IL, Pearlman LA. Vicarious traumatization: a framework for understanding the psychological effects of working with victims. Journal of Traumatic Stress 1990;3(1):131-49. https://doi.org/10.1007/BF00975140

[5] Comstock C, Platania J. The role of media-induced secondary traumatic stress on perceptions of distress. American International Journal of Social Science 2017;16(1).

[6] Figley CR. Compassion fatigue: toward a new understanding of the costs of caring. In: Stamm BH. editor. Secondary traumatic stress: Self-care issues for clinicians, researchers, and educators. Sidran Press; 1999; 3-28.

[7] Jenkins SR, Baird S. Secondary traumatic stress and vicarious trauma: a validational study. J Trauma Stress 2002;15(5):423-32. https://doi.org/10.1023/A:1020193526843

[8] Bride BE. Prevalence of secondary traumatic stress among social workers. Soc Work 2007;52(1):63-70. https://doi.org/10.1093/sw/52.1.63

[9] Holman EA, Garfin DR, Silver RC. Media's role in broadcasting acute stress following the Boston Marathon bombings. Proc Natl Acad Sci USA 2014;111(1):93-8. https://doi.org/10.1073/pnas.1316265110

[10] T.C. İçişleri Bakanlığı Afet ve Acil Durum Yönetimi Başkanlığı (AFAD). 06 Şubat 2023 Kahramanmaraş (Pazarcık ve Elbistan) depremleri saha çalışmaları ön değerlendirme raporu. Deprem Dairesi Başkanlığı; 2023. Available at: https://deprem.afad.gov.tr/earthquake-reports

[11] BBC News Türkçe. 6 Şubat'taki depremlerde hayatını kaybedenlerin sayısı 46 bin 104'e yükseldi. BBC News Türkçe. Available at: https://www.bbc.com/turkce/articles/c51kdv8d15jo

[12] Boztaş H, Aker T, Munir K, et al. Post traumatic stress disorder among adults in the aftermath of 2011 Van-Erciş earthquake in Turkey. Turkish J Clin Psy 2019;22(4):380–8. https://doi.org/10.5505/kpd.2019.62534

[13] Ünal Karaçam S, Ada M, Gönen T, Yıldırım H. Uşak ilinin afet farkındalığı ve afete karşı hazırlık durum araştırması. Uşak Üniversitesi Fen ve Doğa Bilimleri Dergisi 2022;6(2):113-25. https://doi.org/10.47137/usufedbid.1191514

[14] Timisi N, Dursun Ç. Medya ve deprem, 17 Ağustos 1999 depreminin medyada temsili. Öncü Basımevi; 2008.

[15] Kay L, Reilly RC, Connolly K, Cohen S. Help or harm? Symbolic violence, secondary trauma and the impact of press coverage in a community. Journalism Practice 2010;4(4):421-38. https://doi.org/10.1080/17512780903429829

[16] Thompson RW, Arnkoff DB, Glass CR. Conceptualizing mindfulness and acceptance as components of psychological resilience to trauma. Trauma Violence Abuse 2011;12(4):220-35. https://doi.org/10.1177/1524838011416375

[17] Kabat-Zinn J. Coming to our senses: healing ourselves and the world through mindfulness. New York, NY: Hyperion; 2005.

[18] Baer RA. Mindfulness training as a clinical intervention: a conceptual and empirical review. Clinical Psychology: Science and Practice 2003;10(2):125-43. https://doi.org/10.1093/clipsy.bpg015

[19] Shapiro SL, Oman D, Thoresen CE, Plante TG, Flinders T. Cultivating mindfulness: effects on well-being. J Clin Psychol 2008;64(7):840-62. https://doi.org/10.1002/jclp.20491

[20] Setti I, Argentero P. The role of mindfulness in protecting firefighters from psychosomatic malaise. Traumatology: An International Journal 2014;20(2):134-41. https://doi.org/10.1037/h0099398

[21] Szoke D, Lancaster C, Hazlett-Stevens H. Relationships between burnout, secondary traumatic stress, mindfulness, and self-compassion in victim advocates. Violence Against Women 2023;29(12-13):2551-68. https://doi.org/10.1177/10778012231185535

[22] Greenberg J, Solomon S, Pyszczynski T. The causes and consequences of a need for self-esteem: a terror management theory. In: Baumeister RF, editor. Public self and private self. New York, NY: Springer-Verlag; 1986: 189-212. https://doi.org/10.1007/978-1-4613-9564-5_10

[23] Greenberg J, Solomon S, Pyszczynski T. Terror management theory of self-esteem and social behavior: empirical assessments and conceptual refinements. In: Zanna MP, editor. Advances in experimental social psychology. New York, NY: Academic Press; 1997: 61-139. https://doi.org/10.1016/S0065-2601(08)60016-7

[24] Bulut MB, McDermott M, McEwan O. Çok Boyutlu Ölüm Farkındalığı Ölçeği'nin Türkçeye uyarlanması: geçerlik ve güvenirlik çalışması. Uluslararası Sosyal Araştırmalar Dergisi 2017;10(49):268-75. https://doi.org/10.17719/jisr.2017.1578

[25] Bromet E, Sonnega A, Kessler RC. Risk factors for DSM-III-R posttraumatic stress disorder: findings from the National Comorbidity Survey. Am J Epidemiol 1998;147(4):353-61. https://doi.org/10.1093/oxfordjournals.aje.a009457

[26] Hensel JM, Ruiz C, Finney C, Dewa CS. Meta-analysis of risk factors for secondary traumatic stress in therapeutic work with trauma victims. J Trauma Stress 2015;28(2):83-91. https://doi.org/10.1002/jts.21998

[27] Bock C, Heitland I, Zimmermann T, Winter L, Kahl KG. Secondary traumatic stress, mental state, and work ability in nurses-results of a psychological risk assessment at a university hospital. Front Psychiatry 2020;11:298. https://doi.org/10.3389/fpsyt.2020.00298

[28] Yazıcı H, Özdemir M. Predictors of secondary traumatic stress in mental health professionals: trauma history, self-compassion, emotional intelligence. J Rat-Emo Cognitive-Behav Ther 2022;41:162-75. https://doi.org/10.1007/s10942-022-00458-y

[29] Henderson A, Jewell T, Huang X, Simpson A. Personal trauma history and secondary traumatic stress in mental health professionals: a systematic review. J Psychiatr Ment Health Nurs 2025;32(1):13-30. https://doi.org/10.1111/jpm.13082

[30] Stark EA, Parsons CE, Van Hartevelt TJ, et al. Post-traumatic stress influences the brain even in the absence of symptoms: a systematic, quantitative meta-analysis of neuroimaging studies. Neurosci Biobehav Rev 2015;56:207-21. https://doi.org/10.1016/j.neubiorev.2015.07.007

[31] Lazarus RS, Folkman S. Stress, appraisal, and coping. Springer; 1984.

[32] Bonanno GA. Loss, trauma, and human resilience: have we underestimated the human capacity to thrive after extremely aversive events? Am Psychol 2004;59(1):20-8. https://doi.org/10.1037/0003-066X.59.1.20

[33] Kalisch R, Müller MB, Tüscher O. A conceptual framework for the neurobiological study of resilience. Behav Brain Sci 2015;38:e92. https://doi.org/10.1017/S0140525X1400082X

[34] Garfin DR, Silver RC, Holman EA. The novel coronavirus (COVID-2019) outbreak: amplification of public health consequences by media exposure. Health Psychol 2020;39(5):355-7. https://doi.org/10.1037/hea0000875

[35] Pyszczynski T, Greenberg J, Solomon S. Thirty years of terror management theory: from genesis to revelation. Adv Exp Soc Psychol 2015;52:1-70. https://doi.org/10.1016/bs.aesp.2015.03.001

[36] Keng SL, Smoski MJ, Robins CJ. Effects of mindfulness on psychological health: a review of empirical studies. Clin Psychol Rev 2011;31(6):1041-56. https://doi.org/10.1016/j.cpr.2011.04.006

[37] Creswell JD. Mindfulness interventions. Annu Rev Psychol 2017;68:491-516. https://doi.org/10.1146/annurev-psych-042716-051139

[38] Hölzel BK, Lazar SW, Gard T, Schuman-Olivier Z, Vago DR, Ott U. How does mindfulness meditation work? Proposing mechanisms of action from a conceptual and neural perspective. Perspect Psychol Sci 2011;6(6):537-59. https://doi.org/10.1177/1745691611419671

[39] Blais M, Blagys MD, Rivas-Vazquez R, Bello I, Sinclair SJ. Development and initial validation of a brief symptom measure. Clin Psychol Psychother 2015;22(3):267-75; quiz 276-7. https://doi.org/10.1002/cpp.1876

[40] Gülüm İV, Soygüt G. Psychometric properties of the turkish brief symptom measure-25. Curr Psychol 2017;38(6),1558-63. https://doi.org/10.1007/s12144-017-9707-4

[41] Levasseur O, McDermott MR, Lafreniere KD. The multidimensional mortality awareness measure and model: development and validation of a new self-report questionnaire and psychological framework. Omega (Westport) 2015;70(3):317-41. https://doi.org/10.1177/0030222815569440

[42] Mancini MN. Development and validation of the secondary traumatic stress scale in a sample of social media users [Doctoral dissertation]. Cleveland State University; 2019.

[43] Balcı Çelik S, Altınışık MS. Adaptation of secondary traumatic stress scale to Turkish for social media users: reliability and validity study. Turkish Psychological Counseling and Guidance Journal 2021;11(60),1-12.

[44] Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. Assessment 2006;13(1):27-45. https://doi.org/10.1177/1073191105283504

[45] Tran US, Glück TM, Nader IW. Investigating the Five Facet Mindfulness Questionnaire (FFMQ): construction of a short form and evidence of a two-factor higher order structure of mindfulness. J Clin Psychol 2013;69(9):951-65. https://doi.org/10.1002/jclp.21996

[46] Ayalp HD, Hisli Şahin N. Beş Faktörlü Bilgece Farkındalık Ölçeği-Kısa Formu'nun (BFBFÖ-K) Türkçe uyarlaması. Klinik Psikoloji Dergisi 2018;2(3),117-27. https://doi.org/10.31828/kpd2602443807092018m000002

[47] Mishra P, Pandey CM, Singh U, Gupta A, Sahu C, Keshri A. Descriptive statistics and normality tests for statistical data. Ann Card Anaesth 2019;22(1):67-72. https://doi.org/10.4103/aca.ACA_157_18

[48] Bangasser DA, Wicks B. Sex-specific mechanisms for responding to stress. J Neurosci Res 2017;95(1-2):75-82. https://doi.org/10.1002/jnr.23812

[49] Bangasser DA, Valentino RJ. Sex differences in stress-related psychiatric disorders: neurobiological perspectives. Front Neuroendocrinol 2014;35(3):303-19. https://doi.org/10.1016/j.yfrne.2014.03.008

[50] McDonald B, Kanske P. Gender differences in empathy, compassion, and prosocial donations, but not theory of mind in a naturalistic social task. Sci Rep 2023;13(1):20748. https://doi.org/10.1038/s41598-023-47747-9

[51] Frewen PA, Evans EM, Maraj N, Dozois DJA, Partridge K. Letting Go: mindfulness and negative automatic thinking. Cognitive Therapy Research 2008;32(6):758-74. https://doi.org/10.1007/s10608-007-9142-1

[52] Follette VM, Palm KM, Pearson AN. Mindfulness and trauma: implications for treatment. J Ration Emot Cogn Behav Ther 2006;24(1):45-61. https://doi.org/10.1007/s10942-006-0025-2

[53] Becker R. Gender and survey participation: an event history analysis of the gender effects of survey participation in a probability-based multi-wave panel study with a sequential mixed-mode design. methods, data, analyses 2022;16(1):3-32. https://doi.org/10.12758/mda.2021.08

acta medica

CASE REPORT

Pseudomonas-driven amyloid storm: a tale of two cases with rapidly progressive kidney injury

Saliha Yıldırım[1]
ORCID: 0000-0002-2693-1167

Betül Öğüt[2]
ORCID: 0000-0002-1385-7324

İpek Işık Gönül[2]
ORCID: 0000-0003-0058-5136

Özant Helvacı[1]
ORCID: 0000-0002-1382-2439

Yasemin Erten[1]
ORCID: 0000-0002-9741-6779

[1]Gazi University Faculty of Medicine, Department of Nephrology, Ankara, Türkiye

[2]Gazi University Faculty of Medicine, Department of Pathology, Ankara, Türkiye

Corresponding Author: Saliha Yıldırım
E-mail: dr.saliha@gmail.com

Received: 2 April 2025, Accepted: 20 June 2025, Published online: 30 September 2025

ABSTRACT

AA amyloidosis is a significant cause of chronic kidney disease and, if untreated, often leads to progressive kidney damage. This study aims to illustrate how AA amyloidosis can manifest as both slowly progressing chronic kidney injury and rapidly progressive acute kidney injury triggered by secondary conditions.

We describe two patients experiencing an amyloid storm related to Pseudomonas aeruginosa infection: one with bronchiectasis-related amyloidosis and another with paraplegia and decubitus ulcer-related amyloidosis. Clinical, laboratory, and kidney biopsy findings were analyzed.

Both cases demonstrated accelerated kidney failure within two weeks. The first case involved chronic decubitus ulcers and osteomyelitis, while the second had bronchiectasis with pneumonia. Despite infection control and colchicine therapy, both patients experienced irreversible renal damage.

These cases underscore the importance of aggressive infection control in preventing amyloid storm and highlight the interplay between chronic inflammation and acute infections in AA amyloidosis.

Keywords: amyloidosis, amyloid storm, bronchiectasis, decubitus ulcer, pseudomonas aeroginosa

INTRODUCTION

AA amyloidosis, also known as reactive or secondary amyloidosis, is a systemic disease resulting from elevated hepatic production of serum amyloid A (SAA), triggered by cytokine release—especially interleukin-1 (IL-1)—from activated macrophages [1,2]. It often arises secondary to genetic disorders (e.g., familial Mediterranean fever), rheumatoid arthritis, inflammatory bowel disease, connective tissue disorders, or chronic infections (e.g., osteomyelitis, decubitus ulcers, bronchiectasis) [3]. The kidney is a common target organ, with clinical presentations often including nephrotic syndrome [4]. While AA amyloidosis typically progresses to chronic kidney disease unless the underlying cause is adequately addressed, certain conditions can precipitate rapid renal failure [4]. An amyloid storm is a rare complication seen in patients with amyloidosis. It describes a sudden and overwhelming organ involvement by AA amyloid, presumably driven by an acute inflammatory trigger such as infection [5].

This report highlights two cases of AA amyloidosis complicated by accelerated kidney failure within two weeks. Both cases showed hallmark findings of AA amyloidosis on kidney biopsy and Pseudomonas aeruginosa infection. This study was conducted by the Declaration of Helsinki and approved by the Ethical Committee of Gazi University Faculty of Medicine (approval number 2024-1115, 12 July 2024). Written informed consent was obtained from all participants.

CASE PRESENTATION

Case 1: Paraplegic male with decubitis ulcer

A 45-year-old male was admitted to the emergency department with a one-month history of progressively worsening pretibial edema and a recurrent pressure ulcer over the right gluteal region. His medical history included paraplegia following a childhood traffic accident and surgical intervention for the same decubitus ulcer ten years ago. The ulcer was grade four with dark yellow discharge and a seven-centimeter diameter wound. The patient appeared pallor and cachectic and had grade three pretibial edema (BP: 110/60 mmHg).

Laboratory tests revealed severe anemia (hemoglobin: 7.8 g/dL), leukocytosis (13,700/µL with 88.6% neutrophils), and markedly elevated inflammatory markers (CRP: 242 mg/L, ESR: 130 mm/h). Renal function tests indicated acute kidney injury with a serum creatinine of 5.2 mg/dL and BUN of 38.9 mg/dL (Serum creatinine level three months before admission was 1.0 mg/dL). Hypokalemia (serum potassium: 2.7 mmol/L) and hypoalbuminemia (serum albumin: 1.1 g/dL) were also noted. Urinalysis showed nephrotic-range proteinuria (+3 protein dipstick, urine protein-to-creatinine ratio of 76,121 mg/g).

Leukocyte scintigraphy indicated osteomyelitis near the pressure wound, and wound cultures grew

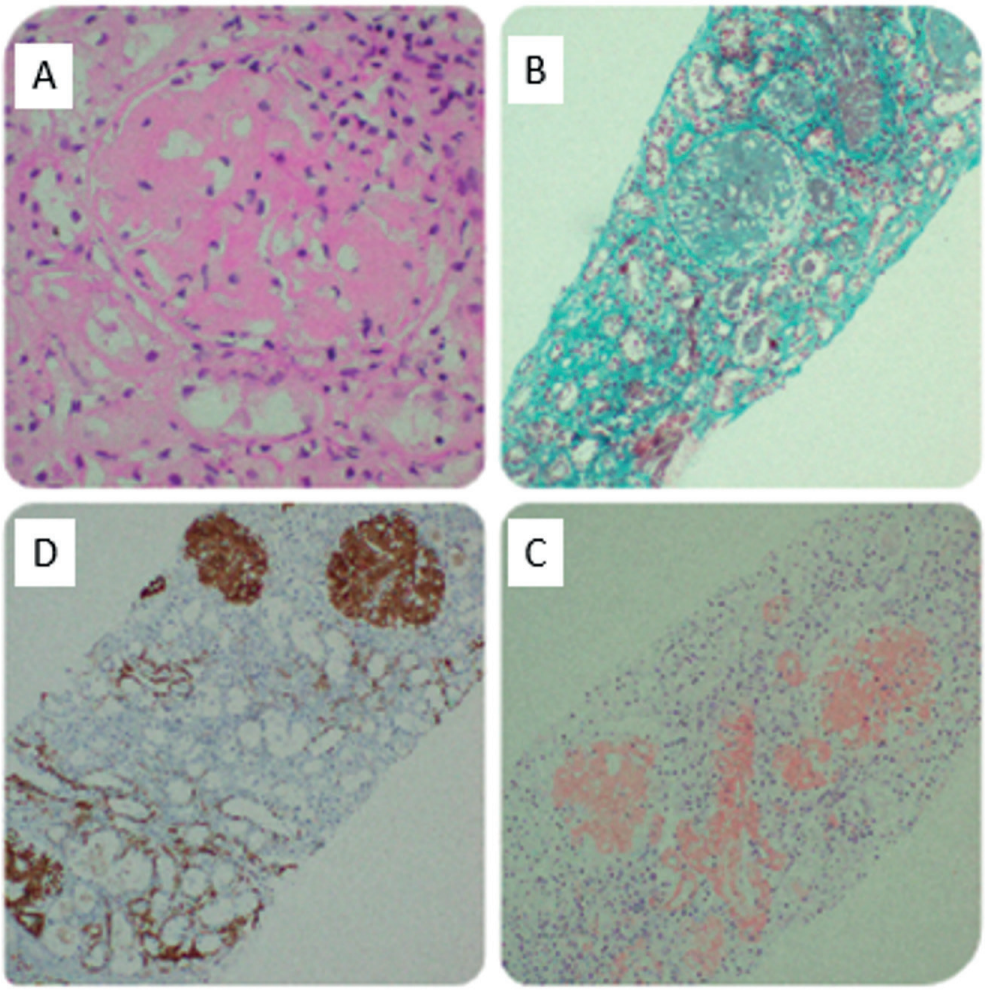


Figure 1. Kidney biopsy findings of case 1. A) Hematoxylin and Eosin (H&E) staining demonstrating amorphous eosinophilic material in the glomerulus. Glomerular tufts are expanded by acellular, eosinophilic, amorphous material suggestive of amyloid. There is associated interstitial inflammation and tubular atrophy. B) Masson's Trichrome staining of renal cortex reveals prominent mesangial expansion and sclerosis. There is moderate interstitial fibrosis and tubular atrophy (IFTA) with collagen deposition (green staining). Glomeruli demonstrate mesangial matrix expansion. C) Congo Red stain under bright-field microscopy showing amyloid deposits. Homogeneous, amorphous deposits are seen in glomerular mesangium and vessel walls, consistent with amyloid deposition. D) Immunohistochemistry for Serum Amyloid A (SAA) showing strong positive staining in glomerular and vascular deposits. There is diffuse, intense SAA positivity in glomerular deposits, confirming the diagnosis of AA-type amyloidosis.

Morganella morganii, Pseudomonas aeruginosa, and Escherichia coli. Intravenous meropenem was initiated.

The biopsy revealed positive staining for AA amyloid, with diffuse polymorphonuclear leukocyte-predominant tubulointerstitial inflammation. Moderate tubular atrophy and interstitial fibrosis were observed, along with 2/30 global glomerulosclerosis. These findings were consistent with AA amyloidosis and ongoing acute kidney injury (Figure 1).

Despite broad-spectrum antibiotics and colchicine therapy, serum creatinine rose from 5.2 mg/dL to 7.8 mg/dL over five days, accompanied by worsening edema and refractory hyperkalemia. Hemodialysis was initiated on day six. The patient remains on thrice-weekly hemodialysis six months post-discharge.

Case 2: Female with bronchiectasis

A 54-year-old female with bronchiectasis and immotile cilia syndrome presented to the emergency department with altered mental status and worsening respiratory symptoms. Her medical history included chronic bronchiectasis, occasional NSAID use, and recurrent lower respiratory tract infections.

Initial tests revealed mild renal impairment (serum creatinine: 0.85 mg/dL, BUN: 22 mg/dL) and elevated inflammatory markers (CRP: 197.2

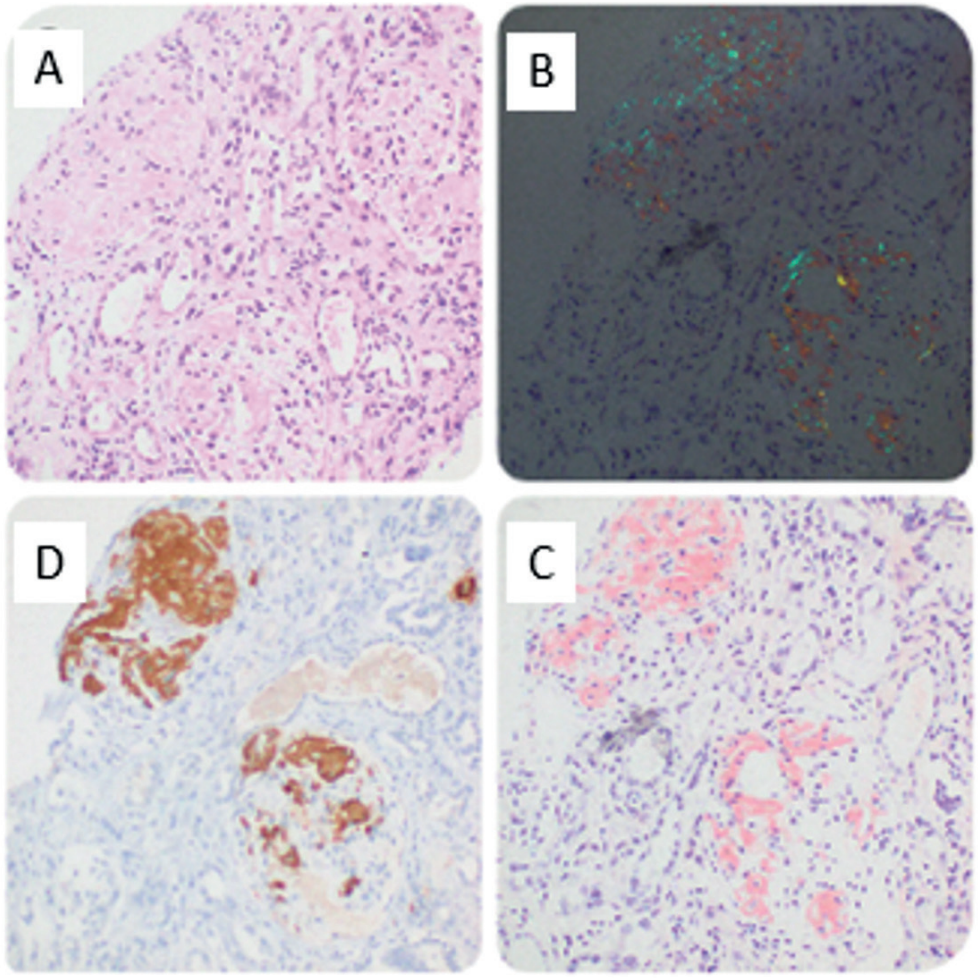


Figure 2. Kidney biopsy findings of case 2. A) Hematoxylin and Eosin (H&E) staining showing glomerular involvement by amyloid. Glomeruli appear expanded by acellular, pale eosinophilic material, with associated interstitial inflammation and tubular atrophy. B) Congo Red staining under polarized light showing apple-green birefringence of amyloid deposits. Glomerular and vascular deposits demonstrate characteristic apple-green birefringence under polarized light, confirming the presence of amyloid. C) Congo Red staining under bright-field microscopy highlights amorphous amyloid deposit in the glomeruli and vessel walls. D) Immunohistochemical staining for Serum Amyloid A (SAA) protein demonstrates positive staining in glomerular amyloid deposits. Strong SAA immunoreactivity in glomerular areas confirms the diagnosis of AA amyloidosis.

mg/L, procalcitonin: 4.6 ng/mL). Hemoglobin was 13.9 g/dL, and leukocytosis was noted (15,590/μL). Urinalysis demonstrated subnephrotic-range proteinuria (2358 mg/day) and microscopic hematuria (8 erythrocytes per high-power field). Sputum cultures isolated Pseudomonas aeruginosa. Chest CT revealed diffuse bronchiectasis with pneumonic infiltrations in the right lower lobe. Intravenous meropenem was initiated.

The biopsy showed positive staining for AA amyloid, tubulointerstitial mononuclear inflammation, moderate tubular atrophy, and interstitial fibrosis supporting the diagnosis of AA amyloidosis with acute kidney injury. Additionally, 2/29 global glomerulosclerosis was observed (Figure 2).

During hospitalization, serum creatinine rose to 2.17 mg/dL. Proteinuria at presentation was subnephrotic (2.4 g/day), which later progressed into the nephrotic range during hospitalization. Two months post-discharge, renal function declined (serum creatinine: 3.14 mg/dL) despite infection control and colchicine therapy.

DISCUSSION

AA amyloidosis arises from systemic deposition of SAA protein, which increases dramatically during acute inflammatory episodes [2]. Bronchiectasis, hemiplegia, and decubitus ulcers may be associated with amyloidosis through different mechanisms [6,7]. Infectious triggers, particularly Pseudomonas aeruginosa, are crucial in exacerbating this process. Pseudomonas aeruginosa infection is a potent inflammatory stimulus associated with functional amyloid biogenesis, a process by which bacterial amyloids can accelerate systemic amyloid deposition [8]. This dual mechanism likely amplifies the risk of amyloid storm, characterized by rapid and severe kidney injury.

In these cases, the presence of Pseudomonas aeruginosa coincided with significant elevations in inflammatory markers such as CRP and procalcitonin, driving an environment conducive to accelerated SAA production and tissue deposition. Furthermore, its involvement in chronic infections such as bronchiectasis and osteomyelitis provides a persistent source of inflammatory signaling, increasing susceptibility to amyloidogenic triggers [9,10]. Experimental studies have highlighted the role of Pseudomonas aeruginosa in secreting curli-like proteins that may directly interact with human amyloid precursors, potentially accelerating the aggregation process [8,10].

Clinically, the rapid renal decline observed in both cases underscores the importance of early identification and aggressive management of Pseudomonas aeruginosa infections. Standard antimicrobial treatments, while crucial, may not fully address the downstream amyloidogenic effects, suggesting a need for adjunct therapies targeting SAA production or amyloid deposition. Emerging research into anti-inflammatory agents, SAA-targeted therapies, and interventions aimed at bacterial amyloid pathways could offer new avenues for mitigating amyloid storm in similar clinical scenarios. These findings suggest that Pseudomonas aeruginosa is more than an inflammatory trigger; it may play a direct pathogenic role in the amyloidogenic cascade. As a result, infection prevention strategies and the need for multidisciplinary approaches to managing high-risk patients with AA amyloidosis are important.

In conclsion these cases highlight the critical role of Pseudomonas aeruginosa in precipitating amyloid storm in patients with AA amyloidosis. Its association with functional amyloid biogenesis raises the possibility of directly contributing to amyloidogenic processes beyond serving as an inflammatory trigger. Preventing and promptly treating Pseudomonas aeruginosa infections in high-risk patients is essential to mitigate the risk of catastrophic renal outcomes. Future research should explore targeted therapies addressing the infection and the amyloidogenic cascade.

Author contribution

Study conception and design: SY, BÖ; data collection: SY, BÖ, and ÖH; analysis and interpretation of results: SY, BÖ; draft manuscript preparation: SY, BÖ, YE. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ethical Committee of Gazi University Faculty of Medicine (Protocol no. 2024-1115/12.07.2024).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Gillmore JD, Lovat LB, Persey MR, Pepys MB, Hawkins PN. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. Lancet 2001;358(9275):24-9. https://doi.org/10.1016/S0140-6736(00)05252-1

[2] Lachmann HJ, Goodman HJB, Gilbertson JA, et al. Natural history and outcome in systemic AA amyloidosis. N Engl J Med 2007;356(23):2361-71. https://doi.org/10.1056/NEJMoa070265

[3] Mirioglu S, Uludag O, Hurdogan O, et al. AA amyloidosis: A contemporary view. Curr Rheumatol Rep 2024;26(7):248-59. https://doi.org/10.1007/s11926-024-01147-8

[4] Feitosa VA, Neves PDMM, Jorge LB, Noronha IL, Onuchic LF. Renal amyloidosis: A new time for a complete diagnosis. Braz J Med Biol Res 2022;55:e12284. https://doi.org/10.1590/1414-431X2022e12284

[5] Kukuy OL, Beckerman P, Dinour D, Ben-Zvi I, Livneh A. Amyloid storm: Acute kidney injury and massive proteinuria, rapidly progressing to end-stage kidney disease in AA amyloidosis of familial Mediterranean fever. Rheumatology (Oxford) 2021;60(7):3235-42. https://doi.org/10.1093/rheumatology/keaa772

[6] Akçay S, Akman B, Ozdemir H, Eyüboğlu FO, Karacan O, Ozdemir N. Bronchiectasis-related amyloidosis as a cause of chronic renal failure. Ren Fail 2002;24(6):815-23. https://doi.org/10.1081/jdi-120015683

[7] Comarr AE. Amyloidosis in paraplegia correlation with decubitus ulcers. Calif Med 1955;82(4):332-4.

[8] Dueholm MS, Petersen SV, Sønderkær M, et al. Functional amyloid in Pseudomonas. Mol Microbiol 2010;77(4):1009-20. https://doi.org/10.1111/j.1365-2958.2010.07269.x

[9] Legger GE, Dermer CWE, Brunger AF, van Daele PLA, Nienhuis HLA. The relation between C-reactive protein and serum amyloid A in patients with autoinflammatory diseases. Pediatr Rheumatol Online J 2022;20(1):106. https://doi.org/10.1186/s12969-022-00757-9

[10] Rouse SL, Matthews SJ, Dueholm MS. Ecology and biogenesis of functional amyloids in pseudomonas. J Mol Biol 2018;430(20):3685-95. https://doi.org/10.1016/j.jmb.2018.05.004

acta medica

CASE REPORT

A case of tadalafil-induced fixed drug eruption

Ecem Bostan[1,2]
ORCID: 0000-0002-8296-4836

Fulya Gökalp[3]
ORCID: 0000-0002-0930-3871

[1]Ankara Medipol University Faculty of Medicine, Dermatology Deparment, Ankara, Türkiye

[2]Private Bilgi Hospital, Dermatology Clinic, Ankara, Türkiye

[3]Konya Beyhekim Research and Training Hospital, Pathology Department, Konya, Türkiye

Corresponding Author: Ecem Bostan
E-mail: bostanecem@gmail.com

Received: 12 April 2025, Accepted: 7 July 2025, Published online: 30 September 2025

ABSTRACT

Fixed drug eruption is a variant of adverse cutaneous drug eruptions which is characterized by the formation of dusky patches and plaques involving the skin and mucosa, following the ingestion of certain drugs such as non-steroidal anti-inflammatory drugs, metronidazole and cotrimoxazole. Herein, we would like to report an unusual case of tadalafil-induced fixed drug eruption.

Keywords: drug eruptions, phosphodiesterase 5 inhibitors, skin

INTRODUCTION

Fixed drug eruption (FDE) is a type of cutaneous adverse drug eruptions characterized by the emergence of single or multiple erythematous-to-purpuric, nummular patches and plaques after exposure to certain drugs [1]. The skin lesions tend to recur each time at the same localization with the consumption of that particular medication [1]. The cutaneous eruption begins within weeks after the drug exposure, however rapid reappearance of the lesions occurs within 1 or 2 days following the repeated ingestions. The most frequently affected sites are limbs, hands, feet and mucosae [1]. A study from France which encompassed three year evaluation of FDE, paracetamol and other non-steroidal anti-inflammatory drugs were the most commonly implicated medications [1]. Herein, we would like to report an uncommon case of FDE following tadalafil ingestion.

CASE PRESENTATION

A 51-year old man was seen at the dermatology outpatient clinic due to multiple, enlarging, non-pruritic skin eruption seen upon the lower extremities. The lesions had begun two days ago in the form of small red papules which later turned into hyperpigmented plaques. Dermatological examination revealed multiple, well-circumscribed, erythematous-to-purpuric patches and plaques involving the lower legs and inner ankles (Figure 1). There were no associated pruritus or pain and no mucosal involvement was present. The patient did not have any other systemic disease and was not using any regular medication. However one day prior to the onset of the skin lesions, he took 5 mg tadalafil pill to enhance intercourse satisfaction. He denied any other recent drug intake other than tadalafil. The patient was using tadalafil on occasion and he recalled that he had developed similar

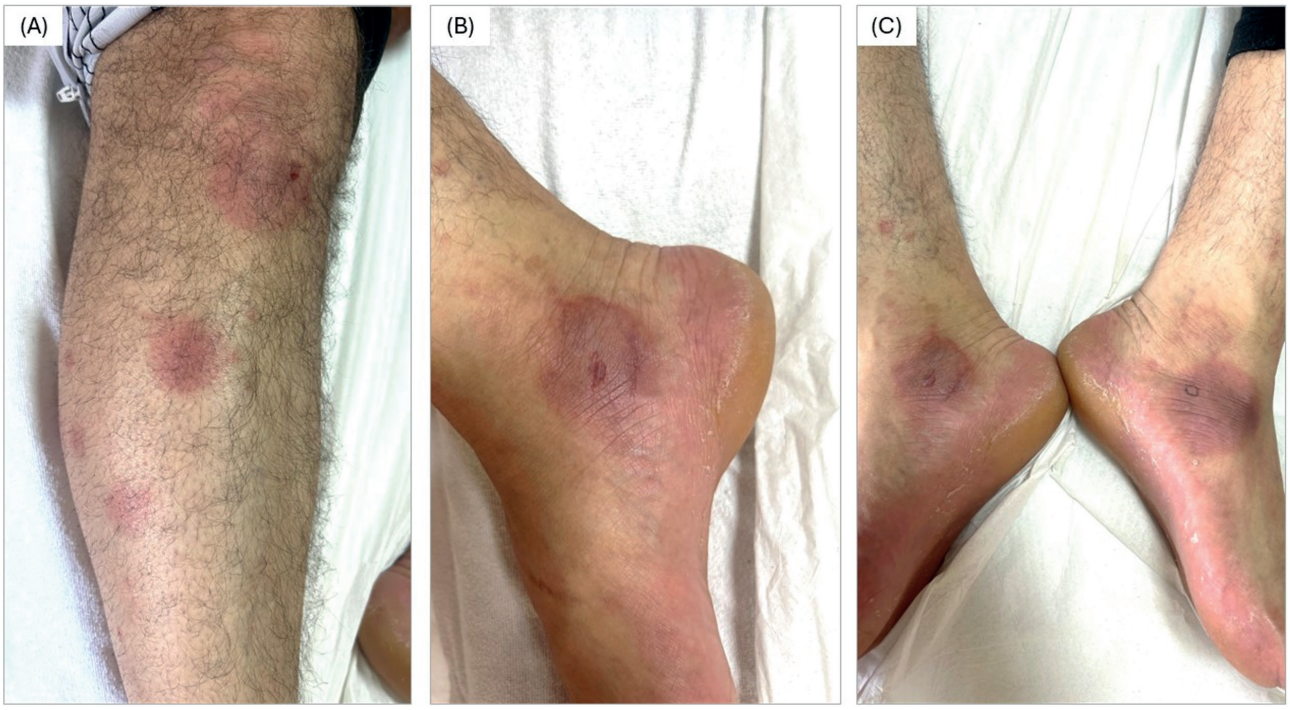


Figure 1. Well defined, erythematous patches and plaques with central violaceous color change present upon the lower extremities (A) and inner ankles (B,C).

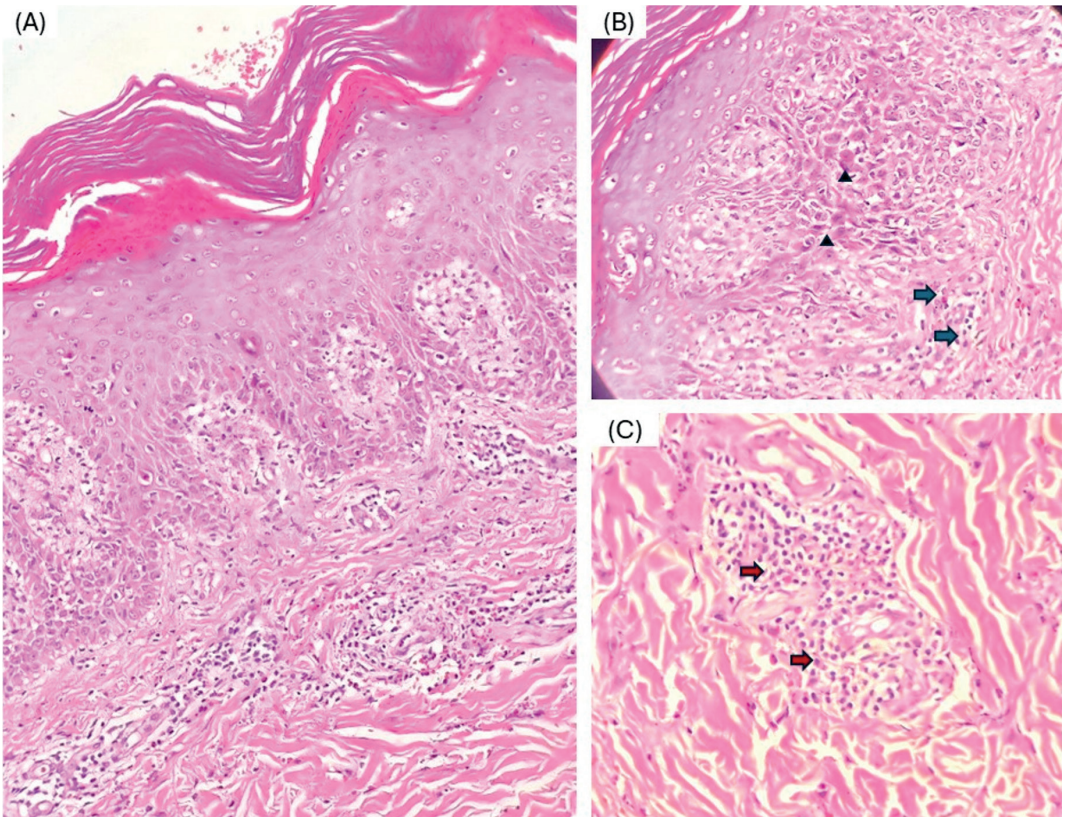


Figure 2. (A) The epidermis has patchy parakeratosis. Scattered necrotic keratinocytes with eosinophilic cytoplasm and pyknotic nuclei are seen in the epidermis. There is superficial and deep dermal perivascular lymphocytic and eosinophilic infiltrate (H&E, x200). (B) Epidermal necrosis and colloid body formation are seen (arrowheads), and dermal lymphocytic and eosinophilic infiltrate (blue arrows) (H&E, x400). (C) Dermal perivascular lymphocytic and eosinophilic infiltrate (red arrows) (H&E, x400).

eruption located at the same locations once again, when he had taken tadalafil previously. Based on the clinical history and dermatological examination findings, FDE was the initial diagnosis. According to the Naranjo Adverse Drug Reaction Probability Scale [2], the present case received a total score of 5 [Are there previous conclusive reports on this reaction? (1 point); Did the adverse event appear after the suspected drug was administered? (2 point); Did the adverse reaction improve when the drug was discontinued? (1 point); Was the adverse event confirmed by any objective evidence? (1 point)] which points out to a 'propable' drug reaction caused by tadalafil. Due to the feasibility restrictions, we were not able to perform an oral provocation or patch testing, which was the limitation of the present report. Skin biopsy was taken and histopathological examination showed scattered necrotic keratinocytes with eosinophilic cytoplasm and pyknotic nuclei in the epidermis, a lichenoid infiltrate composed of lymphocytes and eosinophils in dermis along with superficial and deep dermal perivascular lymphocytic and eosinophilic infiltrate (Figure 2). The diagnosis of FDE was confirmed. Topical application of mometasone furoate ointment and urea-containing emollient for two weeks resulted in the regression of the lesions; minimal residual hyperpigmentation was noted at the end of tenth day. The Informed consent was taken from the patient for the publication of the case details.

DISCUSSION

FDE is a sort of delayed-type of hypersensitivity reaction which is mediated by CD8+ memory cells settled in the epidermis [3]. The distinctive feature of FDE is the repetition of the erythematous, hyperpigmented or bullous skin lesions at the same body localization following the exposure of a particular drug. According to a 20-year cross-sectional study which included 191 patients from Türkiye; cotrimoxazole, naproxen, metronidazole/ornidazole, piroxicam/tenoxicam and dipyrone were among the most common causative drugs of FDE [4]. Another study which investigated 182 adult FDE patients from Türkiye between the years 1996-2018, showed that non-steroidal anti-inflammatory drugs and trimethoprim-sulfamethoxazole were the most frequently blamed agents [5]. Tadalafil is a phosphodiesterase-5 inhibitor generally used for erectile dysfunction or increasing coital pleasure and erection time.Tadalafil-induced FDE cases were reported rarely in the literature; the clinical features

Table 1. The summary of the some reported tadalafil-induced fixed drug eruption in literature with comparison to the present case

Parameter	The present study	Bjekic et al. [6]	Sarawgi & Rudra [7]	Zhang et al.[8]	Das et al.[3]
Age (years)	51	30	46	29	Case 1: 36 Case 2: 17
Sex	Male	Male	Male	Male	Male
Recurrent drug exposure	Yes	Yes	Yes	Yes	Case 1:Yes Case 2: Yes
Multiple/single lesions	Multiple	Multiple	Multiple	Multiple	Case 1:Multiple Case 2: Single
Localization of skin lesions	Lower extremities, ankles	Penile shaft, oral mucosa, elbow, elbow, periorbital lesion	Lip, chest, back, upper and lower extremities, genitalia, buttocks	Oral mucosa, arm, legs, penis, hand and feet	Case 1: Glans penis Case 2: Tongue
Time between the drug exposure and skin eruption	24 hours	-	A few days	Hours	Case 1: A day Case 2: ---
Any accompanying symptom	None	Mild pruritus	Itch and mild pain	Pain	Case 1: Mild tender Case 2: Mild pain
Intervention	Topical mometasone furoate ointment and urea-containing emollients	Topical corticosteroid therapy and gingival hyaluronic acid 0.2% gel	Oral prednisolone	Topical triamcinolone 0.1% ointment	Case 1: A low potent topical steroid Case 2: N/A

along with the characteristics of the some patients reported in the literature are shown in Table 1. The offending drugs such as cotrimoxazole, naproxen and tadalafil act as haptens that attach to the basal keratinocytes and create an inflammatory response by inducing CD8+ T cell expansion and production of cytokines [3]. As clearly seen Table 1, the elapsed time between the start of FDE and drug exposure is usually short (hours to a few days) and skin lesions tend to be multiple [3-8], even though a case reported by Das et al. [3] presented by a single erosion upon the corner of the tongue. Even though, no mucosal involvement is observed in our patient, the reported cases in the literature presented with one or more mucosal site involvement [3-8]. Therefore, FDE can easily be confused with venereal diseases, autoimmune bullous diseases and other drug eruptions such as Stevens-Johnson syndrome. The accurate diagnosis of FDE along with abrupt interruption of the offending medication is significant in the management of FDE.

All in all, we would like to emphasize that tadalafil can be a cause of FDE by inducing the formation of recurrent, fixated violaceous to hyperpigmented, nummular patches and plaques involving the skin and mucosa.

Author contribution

Study conception and design: EB and FG; data collection: EB and FG; analysis and interpretation of results: EB; draft manuscript preparation: EB. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

Infomed consent was taken from the patients for the publication of the case details and images.

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Brahimi N, Routier E, Raison-Peyron N, et al. A three-year-analysis of fixed drug eruptions in hospital settings in France. Eur J Dermatol 2010;20(4):461-464. https://doi.org/10.1684/ejd.2010.0980

[2] Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30(2):239-245. https://doi.org/10.1038/clpt.1981.154

[3] Das S, Das S, Chowdhury J, Bhanja DC. Non pigmenting mucosal fixed drug eruption due to tadalafil: A report of two cases. Indian Dermatol Online J 2014;5(2):167-169. https://doi.org/10.4103/2229-5178.131091

[4] Özkaya E. Changing trends in inducer drugs of fixed drug eruption: A 20-year cross-sectional study from Turkey. J Dtsch Dermatol Ges 2018;16(4):474-476. https://doi.org/10.1111/ddg.13468

[5] Babuna Kobaner G, Ozkaya E. Epidemiological and clinical characteristics, causative drugs, and diagnostic challenges of fixed drug eruption in elderly patients: is bullous type a more common clinical phenotype? J Ist Faculty Med 2021;84(4):559-567. https://doi.org/10.26650/IUITFD.2021.934957

[6] Bjekic M, Markovic M, Sipetic S. Fixed drug eruption caused by tadalafil-case report. An Bras Dermatol 2013;88(4):617-619. https://doi.org/10.1590/abd1806-4841.20131994

[7] Sarawgi D, Rudra O. Tadalafil-Induced generalized bullous fixed drug eruption: A rare side effect of a common drug. Cureus 2023;15(5):e39649. https://doi.org/10.7759/cureus.39649

[8] Zhang JS, Aggarwal I, Bain M. A case of bullous fixed drug eruption caused by tadalafil. JAAD Case Rep 2023;45:44-46. https://doi.org/10.1016/j.jdcr.2023.10.024