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University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, Şişli Hamidiye Etfal Training and Research Hospital, Department of Obstetrics and Gynecology, İstanbul, Türkiye
E-mail: nura.topbasselcuki@wrh.ox.ac.uk
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Zeynep Betül ÖZCAN, PhD Candidate
University of Health Sciences Türkiye, Hamidiye Institute of Health Sciences, Department of Physiotherapy and Rehabilitation, İstanbul, Türkiye
E-mail: 211002002@ogrenci.sbu.edu.tr
ORCID: https://orcid.org/ 0000-0003-1788-7755

Language Editor

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Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Türkiye
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Merve KABASAKAL
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University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, İstanbul Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, Türkiye

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University of Health Sciences Türkiye, Hamidiye Faculty of Medicine; İstanbul Sultan 2. Abdulhamid Han Training and Research Hospital, İstanbul, Türkiye

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University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, İstanbul Ümraniye Training and Research Hospital, İstanbul, Türkiye

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University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, İstanbul Erenköy Mental and Nervous Diseases Training and Research Hospital, İstanbul, Türkiye

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EDITORIAL

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Will Artificial Intelligence Replace Biostatisticians? Evolving Tools and Enduring Responsibilities

Yapay Zekâ Biyoistatistikçilerin Yerini Alacak mı? Gelişen Araçlar ve Kalıcı Sorumluluklar

Özge Pasin

University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, Department of Biostatistics, İstanbul, Türkiye

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In recent years, as biostatisticians, we have increasingly encountered similar questions from researchers and students: "With the rapid advancement of artificial intelligence (AI) applications, biostatistical analyses can now be performed using systems such as ChatGPT and similar tools. In this context, will the need for biostatisticians decrease in the future? Can statistical analyses be conducted reliably and accurately solely through AI tools without consulting an expert?"

By generating tables and outputs through prompts, it may appear that analyses are being conducted correctly. However, the reality is not as straightforward as it seems. Statistical analysis is not merely a process of entering data into a model and obtaining result tables. What truly matters is asking the correct research question, selecting the appropriate methodology, verifying underlying assumptions, and accurately interpreting the clinical significance of the findings. There is no doubt that AI accelerates many processes. Nevertheless, it does not assume the scientific responsibility arising from the analysis itself. Incorporating AI-generated outputs directly into scientific manuscripts without critical evaluation can be highly misleading and, in some cases, may contribute to the dissemination of scientifically inaccurate conclusions. Consequently, researchers may unknowingly produce manuscripts based on erroneous statistical analyses. At precisely this point, it becomes essential to explain why academics and experts specializing in biostatistics are still indispensable in scientific research. AI systems may perform certain statistical calculations, and the resulting outputs may appear highly convincing. However, determining whether these evaluations are accurate, valid, reliable, and scientifically defensible still requires the expertise of a qualified biostatistician. Furthermore, it is important to recognize that "statistics is the invisible backbone of science." Statistics constitutes the fundamental framework that ensures the reliability of scientific knowledge, yet because it often remains in the background, its critical role may go unnoticed.

From past to present, the field of biostatistics has continuously evolved. In earlier periods, analyses were performed manually using calculators; this was later replaced by statistical package software, and more recently by programming-based platforms such as R, which allow researchers to conduct advanced analyses through coding. Just as the transition from calculators to statistical software required rapid adaptation to technological progress, AI has now emerged as a new collaborative tool in the analytical process. At times, AI systems may appear almost like highly talkative, fast-responding, self-confident, rigid, yet creatively decisive individuals. While these characteristics may provide advantages in certain situations, they may also be misleading in others. Producing analyses and presenting results rapidly without critically filtering and evaluating every stage of the process can create a false sense of accuracy and reliability. Consequently, the speed and fluency of AI-generated outputs should not be mistaken for methodological correctness or scientific validity.

When we honestly ask ourselves this question, whether AI will completely eliminate our profession emerges as an important topic of discussion. From my personal perspective, however, the answer to this question is "no." AI is capable of taking over certain tasks, accelerating various processes, and creating substantial transformations in some areas of

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work. Nevertheless, it should not be regarded as a force capable of entirely replacing the fundamental nature and essence of the profession.

Biostatistics is a discipline that involves distinguishing meaningful signals from noise within data, ensuring that appropriate research questions are addressed using suitable methodologies, and evaluating the difference between statistically possible findings and scientifically defensible conclusions. AI applications may accelerate analytical workflows and simplify technical procedures; however, the ultimate judgment regarding which research questions should be asked, how reliable the obtained findings truly are, and whether these findings carry genuine clinical significance still fundamentally depends on human expertise.

In a study conducted by Bin Zhu, it was reported that although ChatGPT-4o was capable of solving certain biostatistical problems, this was achievable only after careful prompting and multiple iterative attempts. The study emphasized that biostatisticians play a crucial role in recognizing when the model produces inaccurate outputs, guiding the system in the correct direction, and managing complex analytical tasks through precise and structured instructions. In this context, the role of the biostatistician in the era of AI is expected to center on guidance, supervision, and critical evaluation. Furthermore, the study suggested that AI-assisted workflows may reduce the burden of repetitive and time-consuming tasks, thereby allowing experts to devote greater attention to problem-solving, formulating appropriate research questions, and developing scientifically robust analytical strategies (1). Similarly, Kim SN argued that AI systems should not be regarded as independent decision-making mechanisms capable of replacing biostatisticians. Rather, these systems should be considered supportive tools that assist research activities, reduce workload, and accelerate analytical processes (2).

In the study conducted by Aleksandar Ignjatović and colleagues, the reliability of ChatGPT as a supportive tool for medical students solving biostatistical problems was investigated. For this purpose, ten biostatistical problems were randomly selected from the Oxford Handbook of Medical Statistics, and different versions of ChatGPT were compared. GPT-3.5 correctly answered only five out of ten questions on the first attempt, whereas GPT-4 correctly solved six out of ten questions during the initial trial. The authors observed that although the responses were presented in a highly organized, logical, and convincing manner, the models were still capable of producing mathematically incorrect results. This issue was considered particularly critical because students may easily be persuaded by answers that are fluent, coherent, and expressed with high confidence. Moreover, error rates increased substantially when the models were confronted with more complex problems. In multi-step analytical tasks, the systems were found to select inappropriate formulas and misinterpret tabular data. The authors ultimately emphasized that AI may serve as a supportive educational tool that facilitates learning; however, it cannot replace the learning process itself (3).

The study published by Dobler and colleagues provides a highly instructive framework and a comprehensive perspective on this issue. Rather than discussing ChatGPT solely from a theoretical standpoint, the article evaluates the system directly through the types of tasks encountered in the routine practice of biostatisticians. Across a wide range of application areas—including meta-analysis, latent class analysis, sample size calculations, causal inference, data analysis, and code generation—ChatGPT demonstrated remarkably successful performance in certain tasks, while in other situations it produced incorrect or misleading outputs with a high degree of confidence. The diverse use cases presented in the study illustrate that generative large language models (LLMs) may serve as practical and time-saving tools in biostatistical practice. Nevertheless, several fundamental principles must be considered in order to use these tools safely and effectively. First, although LLMs are particularly useful for accelerating routine tasks, it is essential to provide the model with sufficient contextual information to ensure that the task is performed appropriately. Furthermore, these systems should not be assumed to consistently reflect human expertise accurately; therefore, all generated outputs must be critically re-evaluated. Not only textual explanations, but also the consistency between analytical outputs produced in the data analysis environment and the accompanying narrative interpretations should be carefully verified. The study also emphasized that results may often be improved by explicitly pointing out previous errors to the model or by providing clearer and more structured prompts. In addition, due to the inherent stochastic nature of LLMs, the same task may yield different responses across separate sessions; consequently, output stability should, when necessary, be assessed through multiple independent attempts. Finally, the authors noted that the obtained results may vary depending on the programming language used and the specific model version, highlighting that the use of LLMs should not be viewed as a static process, but rather as a dynamic practice that requires continuous adaptation to evolving technological conditions (4).

AI applications provide substantial time advantages for researchers, particularly in routine statistical

processes. They can assist with data cleaning procedures, offer guidance regarding appropriate analytical methods, and facilitate exploratory data analyses in a manner that establishes a shared communicative framework with the researcher. Certain preparatory stages that traditionally required hours to complete may now be carried out within minutes through AI-assisted workflows. Nevertheless, it should be recognized that interpretations presented in a fluent and convincing manner do not necessarily correspond to scientifically accurate or reliable conclusions. In some instances, AI systems may present erroneous or scientifically questionable findings with a high degree of consistency and confidence. Consequently, the apparent coherence and persuasiveness of AI-generated outputs should not be automatically interpreted as indicators of methodological validity or scientific reliability. AI systems often do not independently question whether the fundamental assumptions required for the application of statistical methods have been satisfied. Core assumptions—such as homogeneity of variances, the assumption of normality, and the suitability of the data structure for the selected analytical method—represent critical components of the statistical analysis process. Although AI systems may recommend potentially applicable statistical tests, determining whether these methods are truly appropriate and valid for a given dataset constitutes a separate process that requires specialized expertise. Consequently, the investigation and verification of these methodological considerations should be supervised by qualified experts. In this context, it may be argued that with the advancement of AI technologies, the role of the biostatistician is becoming not less important, but increasingly essential. In the future, less time may be devoted to writing code itself; however, greater intellectual and analytical effort will likely be required for planning analytical workflows, evaluating the validity of statistical methods, and interpreting findings within their appropriate scientific and clinical contexts. Although fewer mechanical and repetitive tasks may remain, the need for methodological supervision, validation, and the development of innovative analytical approaches is expected to increase. This is because the primary aim of biostatistics is not merely to generate numerical outputs, but also to correctly interpret what the data truly represent, evaluate the reliability of the findings, and identify the most appropriate methodological approach for the underlying data structure. AI can generate code for biostatistical analyses and assist with data cleaning procedures, thereby providing substantial advantages in routine and repetitive tasks. However, the fluent and persuasive language of AI does not necessarily indicate that the statistical analyses it produces are reliable. In statistics, the most dangerous errors are often not the obvious ones, but rather those that appear reasonable and convincing at first glance.

As technology continues to advance, it is essential not to resist these developments, but instead to adapt to them. In this context, the role of the biostatistician will likely evolve: becoming less focused on mechanical coding and more centered on managing critical decision points; less occupied with repetitive technical operations and more engaged in constructing analytical frameworks; less concerned with determining "which command works," and more focused on answering "which inference is scientifically defensible." Consequently, biostatisticians will increasingly devote their efforts to interpreting, questioning, and contextualizing data. AI models may generate text, write code, and produce tables. Nevertheless, the ultimate responsibility for determining whether an analysis is truly correct still belongs to humans. Therefore, rather than eliminating the field of biostatistics, the integration of AI is more likely to replace simpler and routine tasks within biostatistical practice.

In conclusion, researchers may substantially benefit from AI in biostatistical analyses. When researchers formulate appropriate questions and construct effective prompts, AI systems can provide access to basic statistical guidance and analytical code generation. Nevertheless, these systems are not consistently reliable and should therefore be considered preliminary supportive tools rather than definitive authorities. Accordingly, all stages of the research process should ultimately be reviewed and critically evaluated in collaboration with a domain expert. Furthermore, teaching students and researchers solely how to use statistical software packages no longer appears sufficient in the current era. Contemporary educational approaches should also encompass AI literacy, including the ability to communicate effectively with AI systems, construct accurate and meaningful prompts, and critically evaluate the correctness and appropriateness of AI-generated outputs. Equally important is equipping researchers with the ability to question whether the responses generated by AI systems are genuinely appropriate for the underlying research question. In this context, the integration of AI applications within a collaborative framework involving both researchers and biostatisticians may represent one of the most effective strategies for achieving faster, more accurate, and more reliable scientific outcomes.

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Serum Albumin Levels on Admission Predict Clinical Outcomes in Hospitalized COVID-19 Patients

Hastanede Yatan COVID-19 Hastalarında Klinik Sonuçlarının Öngörülmesinde Hastaneye Yatış Sırasındaki Serum Albümin Düzeyinin Yeri

Beyza Keleş[1], Refik Demirtunç[2], Kürşad Nuri Baydili[3]

[1]*University of Health Sciences Türkiye, Darıca Farabi Training and Research Hospital, Department of Internal Medicine, Kocaeli, Türkiye*

[2]*University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital, Department of Internal Medicine, İstanbul, Türkiye*

[3]*University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, Department of Biostatistics, İstanbul, Türkiye*

ABSTRACT

Background: To evaluate whether serum albumin levels at hospital admission independently predict clinical outcomes—specifically in-hospital mortality, length of stay, and need for respiratory support—in hospitalized Coronavirus Disease 2019 (COVID-19) patients after adjustment for age, comorbidities, and disease severity.

Materials and Methods: A retrospective study was conducted among adult patients with confirmed COVID-19 at University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital between February 2020 and February 2021. Patients were categorized into two groups based on their serum albumin levels measured within the first 24 hours of admission: hypoalbuminemia (<3.5 g/dL) and normoalbuminemia (≥3.5 g/dL). Sociodemographic and clinical characteristics, laboratory parameters, hospital stay, in-hospital mortality, and intensive care unit needs were compared between the groups. Multivariate logistic regression was performed with mortality, respiratory support requirements, and prolonged hospital stay as outcomes and albumin status as a primary predictor, adjusting for age, comorbidities, and disease severity.

Results: The study included 208 adult patients with a median age of 56 years (range, 20–91 years). Patients with hypoalbuminemia experienced significantly longer hospital stays (median 12 days vs. 7.5 days, $p < 0.001$), a higher rate of in-hospital mortality (21.8% vs. 5.9%, $p = 0.001$), and a greater need for oxygen support (37.3% vs. 16%, $p = 0.001$) and for non-invasive mechanical ventilation (NIMV) (85.7% vs. 22.2%, $p < 0.001$). In multivariate analysis adjusting for age, disease severity, and inflammatory markers, hypoalbuminemia remained an independent predictor of mortality (adjusted odds ratio [OR] = 3.127, 95% confidence interval 1.156–8.457, $p = 0.025$), a 37.4% longer hospital stay ($p < 0.001$), and increased respiratory support requirements (adjusted OR = 3.245 for oxygen therapy and OR = 18.734 for NIMV). Age-stratified analysis confirmed the albumin-mortality association in both younger patients (<60 years: OR = 6.197, $p = 0.023$) and older patients (≥60 years: OR = 2.672, $p = 0.082$), with no significant age-albumin interaction ($p = 0.377$). In an exploratory analysis, multivariate regression identified D-dimer (OR = 1.001, $p = 0.008$) and neutrophil count (OR = 1.909, $p = 0.048$) as independent predictors of hypoalbuminemia. Multivariate regression analysis identified D-dimer and neutrophil count as independent predictors of hypoalbuminemia. Survival analysis revealed that older age, lower peripheral oxygen saturation, lower albumin levels, and higher levels of C-reactive protein, lactate dehydrogenase, procalcitonin, D-dimer, blood urea nitrogen, and aspartate aminotransferase were significantly associated with increased mortality.

Conclusion: Hypoalbuminemia at admission independently predicted in-hospital mortality, prolonged hospitalization (37% longer hospital stay), and greater requirements for respiratory support, thereby establishing hypoalbuminemia as a valuable prognostic marker for early risk stratification in COVID-19 patients.

Keywords: COVID-19, hypoalbuminemia, prognosis, serum albumin, mortality

Address for Correspondence: Beyza Keleş, University of Health Sciences Türkiye, Darıca Farabi Training and Research Hospital, Department of Internal Medicine, Kocaeli, Türkiye

E-mail: byzklsdr@gmail.com **ORCID ID:** orcid.org/0000-0003-1380-5388

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ÖZ

Amaç: Hastaneye yatış sırasında serum albümin düzeylerinin, yaş, komorbiditeler ve hastalık şiddeti düzeltildikten sonra, hastanede yatan Koronavirüs Hastalığı 2019 (COVID-19) hastalarında klinik sonuçların, özellikle hastane içi mortalite, yatış süresi ve solunum desteği ihtiyacının bağımsız bir öngörücüsü olup olmadığını incelemektir.

Gereç ve Yöntemler: Bu retrospektif çalışma, Şubat 2020 ile Şubat 2021 tarihleri arasında Sağlık Bilimleri Üniversitesi, Haydarpaşa Numune Eğitim ve Araştırma Hastanesi'nde kesin COVID-19 tanısı alan erişkin hastalar üzerinde yürütülmüştür. Hastalar, yatış sonrası ilk 24 saat içinde ölçülen serum albümin düzeylerine göre iki gruba ayrılmıştır: Hipoalbüminemi (<3,5 g/dL) ve normoalbüminemi (≥3,5 g/dL). İki grup arasında sosyodemografik ve klinik özellikler, laboratuvar parametreleri, hastanede kalış süresi, hastane içi mortalite ve yoğun bakım ihtiyacı karşılaştırılmıştır.

Bulgular: Çalışmaya medyan yaşı 56 olan toplam 208 erişkin hasta dahil edilmiştir. Hipoalbüminemisi olan hastalar, anlamlı şekilde daha uzun hastanede kalış süresi (medyan 12 gün vs. 7,5 gün, p < 0,001), daha yüksek hastane içi mortalite oranı (%21,8 vs. %5,9, p = 0,001) ve daha fazla oksijen desteği (%37,3 vs. %16, p = 0,001) ve non-invaziv mekanik ventilasyon (NIMV) ihtiyacı (%85,7 vs. %22,2, p < 0,001) göstermiştir. Yaş, hastalık şiddeti ve inflamatuar belirteçler için ayarlama yapılan çok değişkenli analizde, hipoalbüminemi mortalitenin bağımsız bir öngörücüsü olarak kaldı (ayarlanmış olasılık oranı [OR] = 3,127, %95 güven aralığı 1,156–8,457, p = 0,025), uzun süreli hastanede kalış (%37,4 daha uzun kalış, p < 0,001) ve artan solunum desteği gereksinimi (düzeltilmiş OR = 3,245 oksijen tedavisi için, OR = 18,734 NIMV için) için bağımsız bir öngörücü olarak kaldı. Yaşa göre sınıflandırılmış analiz, hem genç (<60 yaş: OR = 6,197, p = 0,023) hem de yaşlı hastalarda (≥60 yaş: OR = 2,672, p = 0,082) albümin-mortalite ilişkisini doğruladı ve yaş-albümin etkileşimi açısından anlamlı bir fark bulunmadı (p = 0,377).

Sonuç: Hastaneye yatışta hipoalbüminemi, hastane içi mortaliteyi, uzun süreli yatış süresini (%37 daha uzun kalış süresi) ve solunum desteği ihtiyacının artmasını bağımsız olarak öngörerek, COVID-19 hastalarında erken risk sınıflandırması için değerli bir prognostik belirteç olarak kabul edilebilir.

Anahtar Kelimeler: COVID-19, hipoalbüminemi, prognoz, serum albümin, mortalite

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2–driven Coronavirus Disease 2019 (COVID-19) has imposed an unprecedented burden on healthcare systems worldwide (1). Identifying reliable and readily available prognostic markers is crucial for predicting disease severity, guiding clinical management, and ultimately improving patient outcomes (2).

Serum albumin, the predominant plasma protein, is essential for colloid osmotic pressure regulation and the transport of a wide range of endogenous and exogenous substances. Beyond its transport functions, albumin also exhibits significant antioxidant and anti-inflammatory properties. Systemic inflammation, a key characteristic of severe COVID-19, can significantly impact serum albumin levels. This reduction, termed hypoalbuminemia, can occur through several mechanisms, including increased capillary permeability leading to albumin leakage into the interstitial space; decreased hepatic synthesis due to cytokine dysregulation; and potentially increased albumin catabolism. Inflammation-induced cytokines, notably interleukin-6 and tumor necrosis factor-alpha, suppress albumin gene transcription, exacerbating hypoalbuminemia (3).

Hypoalbuminemia is a well-established prognostic indicator in various critical illnesses, including sepsis, trauma, and other infectious diseases (4). In these settings, lower serum albumin levels have been linked to increased morbidity, prolonged hospitalization, and increased mortality, serving as a key indicator of physiological dysfunction and as a predictor of adverse outcomes (5).

Given the existing evidence highlighting the prognostic significance of serum albumin in various diseases, this study aimed to evaluate whether initial serum albumin levels, measured within 24 hours of admission, independently predict clinical outcomes, specifically in-hospital mortality, length of hospital stay (LOS), and need for respiratory support, in patients hospitalized with COVID-19 at University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital, after adjusting for age, comorbidity burden, and disease severity. The objective was to determine whether hypoalbuminemia could serve as a readily accessible and cost-effective biomarker for early risk assessment and clinical management in this specific patient population.

Materials and Methods

Study Design and Setting

This retrospective study analyzed data from confirmed COVID-19 patients admitted to the pandemic clinics at the Haydarpaşa Numune Training and Research Hospital between February 2020, and February 2021. The study protocol received ethical approval from the University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (decision number: HNEAH-KAEK 2022/202, dated: 24.10.2022).

Patient Selection

The inclusion criteria were as follows: [1] Age ⩾ 18 years; [2] hospitalization in the pandemic services or the intensive care unit (ICU) of University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital between February 1, 2020, and December 31, 2021; [3] measurement of serum albumin level within the first 24 hours of hospital admission; and [4] confirmed COVID-19 diagnosis via reverse transcription polymerase chain reaction (PCR) assay of nasopharyngeal or oropharyngeal swabs.

The exclusion criteria were as follows: [1] patients without a serum albumin measurement within the first 24 hours of admission; [2] patients with a negative COVID-19 PCR test result; [3] pregnant patients; [4] patients with a history of blood or blood-product transfusion, or albumin replacement therapy within the three months preceding hospital admission; [5] patients with a known history of chronic liver disease; [6] patients diagnosed with nephrotic syndrome or chronic kidney disease; [7] patients with active malignancy; and [8] patients who were discharged from the hospital at their own request.

Of 932 patients initially screened, 724 were excluded according to the study criteria. The final analysis comprised 208 adult patients.

Data Collection and Definitions

Data were collected retrospectively by reviewing electronic medical records and patient files available through the hospital's Health Information System. The variables extracted included demographic characteristics, LOS, in-hospital mortality, need for ICU admission, presence of chronic comorbidities, clinical parameters recorded during hospitalization, and laboratory parameters measured upon admission.

Patients were dichotomized based on their serum albumin levels measured within the first 24 hours of admission: the hypoalbuminemia group (serum albumin <3.5 g/dL) and the normoalbuminemia group (serum albumin ⩾3.5 g/dL). This cut-off value is commonly used in clinical practice to define hypoalbuminemia (1).

Serum albumin and total protein levels were measured using the Bromocresol Green dye-binding method and the Biuret method, respectively, on the Abbott Architect Ci 4100 analyzer (Architect-Aeroset-Abbott Diagnostics, IL, USA). C-reactive protein (CRP) was measured using an immunoturbidimetric assay on the same platform. Complete blood count parameters were measured using impedance and colorimetric methods on the Mindray BC-5800 hematology analyzer (Mindray BioMedical Electronics Co., Ltd., Shenzhen, China). Biochemical parameters were measured using standard methods on the Abbott Architect Ci 4100 analyzer. The Charlson Comorbidity Index (CCI) was calculated for each patient using their preexisting chronic medical conditions as documented in their medical records.

Statistical Analysis

Statistical analyses were conducted with SPSS Statistics software (version 25.0; IBM Corp., Armonk, NY, USA).

Normality of continuous variables was evaluated using the Shapiro–Wilk test supplemented by visual inspection of Q-Q plots and histograms. Based on a normality assessment, the following variables were approximately normally distributed and were compared between groups using independent-samples t-tests: body temperature, heart rate, systolic blood pressure, and diastolic blood pressure.

All other continuous variables exhibited non-normal distributions (Shapiro–Wilk test, $p < 0.05$) and were therefore compared using nonparametric Mann–Whitney U tests. These variables included age, LOS, peripheral capillary oxygen saturation (SpO_2), albumin, CRP, lactate dehydrogenase (LDH), procalcitonin, D-dimer, blood urea nitrogen (BUN), creatinine, alanine aminotransferase, aspartate aminotransferase (AST), total protein, white blood cell count (WBC), neutrophils, lymphocytes, hemoglobin, platelet count, ferritin, international normalized ratio (INR), troponin, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and CCI.

Group differences in categorical variables were assessed using Pearson's chi-square test when all expected cell frequencies were ⩾5. In cases where expected cell frequencies were less than 5, Fisher's exact test was employed instead to ensure valid inference. Hospital LOS, exhibiting a non-normal distribution, was analyzed using the Mann–Whitney U test.

For the multivariable logistic regression analyses, we employed a systematic variable selection approach. Variables were considered for inclusion in the multivariate models based on the following criteria: [1] clinical relevance based on established pathophysiological mechanisms in COVID-19; [2] statistical significance at $p < 0.25$ in univariate analyses, as recommended by Hosmer and Lemeshow for screening potential predictors; and [3] absence of severe multicollinearity (variance inflation factor [VIF] <5).

Three multivariable logistic regression models were constructed: Model 1 to identify independent predictors of in-hospital mortality (with albumin status as a primary predictor); Model 2 to identify independent predictors of respiratory support requirements; and Model 3 to identify factors associated with hypoalbuminemia (exploratory analysis). For Model 1 (predictors of mortality), the following

variables, which met the $p < 0.25$ threshold in univariate analyses, were entered: age, SpO_2, hypoalbuminemia (<3.5 g/dL), CRP, LDH, D-dimer, severity of CT involvement, and presence of comorbidity. For Model 2 (respiratory support), age, sex, CCI, SpO_2, CRP, computed tomography (CT) severity, and albumin status were included. For Model 3 (predictors of hypoalbuminemia), variables were selected using the same $p < 0.25$ criterion from the albumin group comparisons.

Variables were entered simultaneously into the model using the enter method. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test, and discriminative ability was evaluated using the area under the receiver operating characteristic curve (AUC). Multicollinearity was assessed through VIF and tolerance statistics. For age-stratified analysis, we calculated stratum-specific odds ratios and used the Cochran-Mantel-Haenszel test to obtain a common odds ratio adjusted for age strata. The Breslow-Day test was used to assess the homogeneity of the odds ratios across age strata (i.e., to test for an age-albumin interaction). Model discrimination improvement was assessed using DeLong's test for comparing AUC values. Net Reclassification Improvement was calculated to quantify the improvement in risk classification when adding albumin to the base model. A statistical significance threshold of $p < 0.05$ was applied for all tests.

Given the retrospective nature of this study, a formal a priori sample size calculation was not performed. However, we conducted a post-hoc power analysis to assess the adequacy of our sample size for detecting clinically meaningful differences. Based on our primary outcome of in-hospital mortality and an observed mortality rate of 21.8% in the hypoalbuminemia group versus 5.9% in the normoalbuminemia group, our sample of 208 patients (55 with hypoalbuminemia and 153 without) had >90% power to detect this difference at $\alpha = 0.05$ (two-tailed).

Results

Among 932 patients initially screened, 624 were excluded per study criteria. The final analysis comprised 208 adult patients.

Patient demographics are detailed in Table 1. The study included 112 (53.8%) males and 96 (46.2%) females, with a median age of 56 years (range, 20–91 years). Comorbidities were present in 114 patients (54.8%). Severe lung involvement on CT was observed in 132 patients (63.5%), and in-hospital complications occurred in 94 patients (45.2%). Oxygen therapy was required by 102 (49%) patients, while only 5 (2.4%) required non-invasive mechanical ventilation (NIMV). The overall prevalence of hypoalbuminemia (<3.5 g/dL) was 26.4% (55 patients). The in-hospital mortality rate was 10.1% (21 patients). The median hospital LOS was 8 days (range 1–47 days).

Patients with hypoalbuminemia exhibited significantly longer median LOS (12 days vs. 7.5 days; $p < 0.001$), higher median age (66 years vs. 53 years; $p < 0.001$), and lower median SpO_2 (95% vs. 97%; $p < 0.001$) compared to the normoalbuminemia group. They also exhibited significantly higher levels of CRP, LDH, procalcitonin, D-dimer, BUN, and AST, and significantly lower levels of total protein, WBC, neutrophils, lymphocytes, and hemoglobin. Ferritin, INR, CCI, troponin levels, NLR, and PLR were also significantly higher in the hypoalbuminemia group. Furthermore, the hypoalbuminemia group had a significantly higher prevalence of comorbidities and in-hospital complications, more severe lung involvement on CT, and a greater need for oxygen therapy (Table 2).

Primary Outcome: Albumin as Predictor of in-Hospital Mortality

In univariate logistic regression analysis, hypoalbuminemia was significantly associated with in-hospital mortality (odds ratio [OR] = 4.389, 95% confidence interval [CI] = 1.774–10.858, $p = 0.001$), as were age, lower SpO_2, elevated inflammatory markers, and severe CT involvement (Table 3).

In the multivariate model, after adjusting for age, SpO_2, CRP, LDH, D-dimer, severity of CT involvement, and the presence of comorbidities, hypoalbuminemia remained a significant independent predictor of mortality (adjusted OR = 3.127; 95% CI = 1.156–8.457; $p = 0.025$). Other independent predictors in the final model included age (adjusted OR = 1.048 per year, 95% CI = 1.006–1.092, $p = 0.025$) and severe CT involvement (adjusted OR = 5.234, 95% CI = 1.845–14.846, $p = 0.002$). The model demonstrated excellent discrimination (AUC = 0.892; 95% CI = 0.826–0.958) and good calibration (Hosmer-Lemeshow $\chi^2 = 6.84$, $p = 0.553$), indicating robust predictive performance (Table 3).

Age-Stratified Analysis

To address potential confounding by age, we performed age-stratified analysis using 60 years as the cut-off (median age of the study population). Hypoalbuminemia was associated with increased mortality in both younger patients (<60 years: OR = 6.197, 95% CI = 1.189–32.305, $p = 0.023$; n = 115, of whom 18 were hypoalbuminemic; deaths: 3 among hypoalbuminemic vs. 3 among normoalbuminemic) and older patients (≥60 years: OR = 2.672, 95% CI = 0.865–8.257, $p = 0.082$; n = 93, of whom 37 were hypoalbuminemic; deaths: 9 among hypoalbuminemic vs. 6 among normoalbuminemic), with no significant age-albumin interaction (Breslow-Day test $\chi^2 = 0.78$, $p = 0.377$).

The Cochran-Mantel-Haenszel common odds ratio, adjusted for age strata, was 3.418 (95% CI = 1.289–9.067; p = 0.011), closely matching our multivariate-adjusted estimate and confirming that albumin provides prognostic value beyond age stratification.

When comparing effect sizes for clinically meaningful changes, severe CT involvement was the strongest predictor (adjusted OR = 5.234, Wald χ^2 = 9.84), followed by hypoalbuminemia (adjusted OR = 3.127, Wald χ^2 = 5.03) and age (adjusted OR = 1.048 per year; corresponding to OR = 2.91 for a one-standard-deviation increase of 18 years; Wald χ^2 = 5.02). The nearly identical Wald χ^2 values for albumin and age demonstrate that albumin is not a minor contributor but rather is of comparable prognostic importance to age (Table 3).

Secondary Outcome: Albumin and LOS

Patients with hypoalbuminemia exhibited significantly longer median LOS compared with those with normal albumin levels (12 days, IQR = 9–17, range 2–47 vs. 7.5 days, IQR = 6–10, range 1–32; Mann–Whitney U Z = -4.719, p < 0.001). In a linear regression analysis with log-transformed LOS as the dependent variable, after adjusting for age, presence of comorbidities, and CT disease severity, hypoalbuminemia was independently associated with a 37.4% longer hospital stay (β = 0.316, 95% CI = 0.148–0.484, p < 0.001) (Table 4).

Secondary Outcome: Albumin and Respiratory Support Requirements

In separate multivariate logistic regression models adjusting for age, sex, CCI, SpO_2 at admission, CRP, and CT severity, hypoalbuminemia independently predicted an increased need for oxygen therapy (adjusted OR = 3.245, 95% CI = 1.532-6.874, p = 0.002), NIMV (adjusted OR = 18.734, 95% CI = 3.256–107.773, p = 0.001), and combined respiratory support (adjusted OR = 4.127, 95% CI = 1.891–9.006, p < 0.001) (Table 5).

Table 1. Descriptive statistics of the study population.

Variable	n (%)	Variable	Median (range)
Sex		LOS (days)	8 (1–47)
Male	112 (53.8)	Age (years)	56 (20–91)
Female	96 (46.2)	CCI	1 (0–8)
Comorbidity		Body temperature (°C)	36.6 (35.8–39.8)
Absent	94 (45.2)	Heart rate (bpm)	85 (56–124)
Present	114 (54.8)	SpO_2 (%)	96 (56–99)
Chest CT involvement		Systolic BP (mmHg)	124 (69–170)
Moderate	76 (36.5)	Diastolic BP (mmHg)	76.5 (45–113)
Severe	132 (63.5)	Albumin (g/dL)	3.8 (1.8–4.6)
In-hospital complications		CRP (mg/dL)	3.0 (0.2–29)
Absent	114 (54.8)	LDH (U/L)	257 (103–874)
Present	94 (45.2)	Procalcitonin (ng/mL)	0.005 (0–2.9)
Oxygen requirement		D-dimer (ng/mL)	578.5 (30–6013)
No	106 (51.0)	BUN (mg/dL)	14 (6–48)
Yes	102 (49.0)	Creatinine (mg/dL)	0.83 (0.3–2.3)
NIMV requirement		ALT (U/L)	22 (6–183)
No	203 (97.6)	AST (U/L)	25 (11–109)
Yes	5 (2.4)	Total protein (g/dL)	6.8 (5–71)
Serum albumin (g/dL)		WBC (10^3/μL)	5.61 (1.2–22.04)
<3.5	55 (26.4)	Neutrophils (10^3/μL)	3.63 (0.46–20.39)
≥3.5	153 (73.6)	Lymphocytes (10^3/μL)	1.39 (0.18–3.89)
Survival status		Hemoglobin (g/dL)	13.1 (7.2–16.9)
Survived	187 (89.9)	Platelet count (10^3/μL)	197.5 (54–520)
Deceased	21 (10.1)	Ferritin (ng/mL)	335 (5.7–4676)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; CT, computed tomography; LDH, lactate dehydrogenase; LOS, length of stay; NIMV, non-invasive mechanical ventilation; SpO_2, peripheral oxygen saturation; WBC, white blood cell count.

Table 2. Comparison of clinical and laboratory parameters between the hypoalbuminemia and normoalbuminemia groups (<3.5 g/dL vs. ≥3.5 g/dL).

Variable	Hypoalbuminemia group, <3.5 g/dL	Normoalbuminemia group, ≥3.5 g/dL	Z	p-value
LOS	12 (2–47)	7.5 (1–32)	-4.719	<0.001*
Age	66 (30–91)	53 (20–91)	-4.949	<0.001*
SpO_2 (%)	95 (74–99)	97 (56–99)	-3.490	<0.001*
CRP	7.9 (0.2–29)	1.8 (0.2–20.9)	-5.780	<0.001*
LDH	280 (144–874)	238 (103–620)	-3.491	<0.001*
Procalcitonin	0.05 (0.01–2.9)	0.01 (0–1.45)	-5.685	<0.001*
D-dimer	925 (260–6013)	500 (30–5671)	-6.032	<0.001*
BUN	15 (8–48)	13 (6–36)	-2.038	0.042*
AST	29 (11–87)	24 (11–109)	-2.500	0.012*
Total protein	6.3 (5.1–71)	7.0 (5–61)	-5.051	<0.001*
WBC	6.2 (1.2–22.04)	5.41 (2.2–12.24)	-2.108	0.035*
Neutrophils	4.65 (0.46–20.39)	3.3 (1.3–10.18)	-3.528	<0.001*
Lymphocytes	1.2 (0.18–2.8)	1.47 (0.38–3.89)	-2.941	0.003*
Hemoglobin	12.3 (7.2–16.9)	13.7 (8.3–16.4)	-3.938	<0.001*
Ferritin	433 (6–4676)	292 (5.7–3720)	-3.047	0.002*
INR	1.06 (0.42–1.89)	1.00 (0.18–3.14)	-4.141	<0.001*
Charlson index	3 (0–8)	1 (0–7)	-4.749	<0.001*
Troponin	0.01 (0–2.39)	0.00 (0–0.08)	-4.381	<0.001*
NLR	3.87 (0.69–18.69)	2.31 (0.65–9.98)	-4.067	<0.001*
PLR	159.1 (8.68–722.4)	135.0 (45.5–602.6)	-2.339	0.019*
Variable	**Hypoalbuminemia group <3.5 g/dL**	**Normoalbuminemia group, ≥3.5 g/dL**	**χ^2**	**p-value**
Comorbidity present, n (%)	39 (34.2)	75 (65.8)	7.826	0.005*
CT Involvement Severe, n (%)	47 (35.6)	85 (64.4)	15.597	<0.001*
Complications present, n (%)	32 (34.0)	62 (66.0)	5.093	0.024*
Oxygen required, n (%)	38 (37.3)	64 (62.7)	12.031	0.001*

Continuous variables, median (minimum–maximum), Z test; Categorical variables presented as n (% within albumin group). Percentages calculated as: (number in subgroup/total number in albumin group) × 100.
Categorical variables analyzed using Pearson's chi-square test (all expected frequencies ≥5). Significant differences ($p < 0.05$) are indicated by an asterisk (*). AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; CT, computed tomography; INR, international normalized ratio; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SpO_2, peripheral oxygen saturation; WBC, white blood cell count; LOS, length of stay.

Table 3. Predictors of in-hospital mortality: univariate and multivariate logistic regression analysis.

Variable	Univariate analysis OR (95% CI)	Univariate p-value	Multivariate analysis adjusted OR (95% CI)	Multivariate p-value
Hypoalbuminemia (<3.5 g/dL)	4.389 (1.774–10.858)	0.001*	3.127 (1.156–8.457)	0.025*
Age (per year increase)	1.065 (1.029–1.102)	<0.001*	1.048 (1.006–1.092)	0.025*
SpO_2 (per % increase)	0.897 (0.831–0.968)	0.005*	0.932 (0.851–1.021)	0.130
CRP (per mg/dL)	1.183 (1.089–1.286)	<0.001*	1.098 (0.991–1.217)	0.074
LDH (per U/L)	1.006 (1.003–1.009)	<0.001*	1.003 (0.999–1.007)	0.156
D-dimer (per 100 ng/mL)	1.042 (1.024–1.061)	<0.001*	1.018 (0.998–1.039)	0.078
Severe CT involvement	7.826 (3.187–19.213)	<0.001*	5.234 (1.845–14.846)	0.002*
Presence of comorbidity	3.889 (1.283–11.785)	0.016*	2.145 (0.625–7.361)	0.227

*Significant at $p < 0.05$. CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; LDH, lactate dehydrogenase; OR, odds ratio; SpO_2, peripheral oxygen saturation.

Exploratory Analysis: Predictors of Hypoalbuminemia

As an exploratory analysis aimed at identifying the pathophysiological correlates of hypoalbuminemia in COVID-19, we investigated which admission parameters were independently associated with hypoalbuminemia. In multivariate logistic regression analysis, after adjusting for age, SpO_2, inflammatory markers, and disease severity, higher D-dimer levels (OR = 1.001 per ng/mL, 95% CI = 1.000–1.001, p = 0.008) and higher neutrophil counts (OR = 1.909 per 10^3/μL, 95% CI = 1.005–3.627, p = 0.048) were independently associated with hypoalbuminemia. This suggests that the procoagulant state and intense neutrophilic inflammation may contribute to albumin depletion in severe COVID-19 (Table 6).

Survival Analysis by Clinical Characteristics

Deceased patients were significantly older and had significantly lower SpO_2 and albumin levels. They also exhibited significantly higher levels of CRP, LDH, procalcitonin, D-dimer, BUN, and AST, as well as lower levels of lymphocytes and hemoglobin. Ferritin, troponin, and NLR were also significantly higher in non-survivors, while platelet counts were lower. Non-survivors had a significantly higher comorbidity rate, a higher prevalence of hypoalbuminemia, more severe lung involvement on CT, more in-hospital complications, and a greater need for oxygen therapy and mechanical ventilation.

Discussion

Our study demonstrates that hypoalbuminemia at hospital admission is an independent predictor of adverse clinical outcomes in COVID-19 patients. Critically, this association persists after rigorous adjustment for age, comorbidity burden, and radiological disease severity, suggesting that albumin provides prognostic information beyond these established risk factors. Specifically, patients with albumin levels <3.5 g/dL had a 3.1-fold increase in the

Table 4. Association between albumin status and LOS.

Albumin group	Median LOS (days)	IQR (days)	Range (days)	Mann–Whitney U	p-value
Hypoalbuminemia (<3.5 g/dL)	12	9–17	2–47	Z = -4.719	<0.001*
Normoalbuminemia (≥3.5 g/dL)	7.5	6–10	1–32		

*Significant at p < 0.05. IQR, interquartile range; LOS, length of stay.

Table 5. Association between albumin status and respiratory support requirements: multivariate analysis.

Outcome	Hypoalbuminemia effect adjusted OR (95% CI)	p-value
Oxygen therapy requirement	3.245 (1.532–6.874)	0.002*
NIMV requirement	18.734 (3.256–107.773)	0.001*
Combined respiratory support	4.127 (1.891–9.006)	<0.001*

All models adjusted for: Age, sex, CCI, SpO_2 at admission, CRP, and CT severity. *Significant at p < 0.05. CCI, Charlson Comorbidity Index; CI, confidence interval; CT, computed tomography; NIMV, non-invasive mechanical ventilation; OR, odds ratio; SpO_2, peripheral oxygen saturation; CRP, C-reactive protein.

Table 6. Exploratory analysis-factors associated with hypoalbuminemia.

Variable	B	S.E.	Wald	p-value	OR (95% CI)
Age	-0.009	0.025	0.129	0.720	0.991 (0.943-1.041)
SpO_2	-0.016	0.041	0.149	0.699	0.984 (0.908-1.067)
CRP	0.052	0.048	1.212	0.271	1.054 (0.960-1.157)
LDH	-0.001	0.002	0.224	0.636	0.999 (0.994-1.004)
D-dimer	**0.001**	**0.000**	**7.110**	**0.008***	**1.001 (1.000-1.001)**
Neutrophil	**0.647**	**0.327**	**3.902**	**0.048***	**1.909 (1.005-3.627)**
Hemoglobin	-0.228	0.138	2.746	0.097	0.796 (0.608-1.043)
CCI	0.388	0.213	3.325	0.068	1.474 (0.971-2.236)
CT involvement	0.324	0.573	0.321	0.571	1.383 (0.450-4.249)
Oxygen requirement	1.515	0.783	3.741	0.053	4.551 (0.980-21.137)

*Significant at p < 0.05. B, regression coefficient; CCI, Charlson Comorbidity Index; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; LDH, lactate dehydrogenase; OR, odds ratio; S.E., standard error; SpO_2, peripheral oxygen saturation; Wald, Wald chi-square statistic.

odds of in-hospital mortality (adjusted OR = 3.127, 95% CI = 1.156–8.457, p = 0.025), a 37% longer hospital stay (p < 0.001), and a 3–4-fold higher risk of requiring respiratory support (adjusted OR = 3.245 for oxygen therapy, OR = 18.734 for NIMV), all independent of age and disease severity.

Our findings are consistent with a substantial body of existing literature that has established the prognostic value of serum albumin in COVID-19 (6). Meta-analyses have demonstrated a significant association between lower albumin levels and increased mortality risk in COVID-19 patients (7). Our observation of an increased mortality rate in the hypoalbuminemia group (21.8% vs. 5.9%) aligns with these findings. Similarly, the association between lower albumin and longer hospital stays and an increased need for respiratory support is consistent with findings from Chen et al. (8) and de la Rica et al. (9).

In our exploratory analysis examining factors associated with hypoalbuminemia, the identification of D-dimer and neutrophil count as independent predictors may reflect the intense inflammatory and procoagulant state characteristic of COVID-19 (10). Elevated D-dimer levels are indicative of activation of coagulation, which is frequently observed in severe COVID-19 and can contribute to endothelial dysfunction and increased vascular permeability, potentially leading to albumin extravasation (11,12). Similarly, a higher neutrophil count suggests a more pronounced inflammatory response, which can also contribute to albumin consumption and leakage (13).

The association between hypoalbuminemia and poor outcomes in COVID-19 can be attributed to several pathophysiological mechanisms. The systemic inflammatory response in COVID-19 triggers the release of pro-inflammatory cytokines, which can decrease hepatic albumin synthesis and increase capillary permeability, leading to albumin leakage into the interstitial space (14). Reduced serum albumin levels can impair crucial physiological functions, including maintaining oncotic pressure (loss of which can contribute to fluid overload and respiratory distress), transporting essential nutrients, hormones, and medications, and losing its antioxidant and anti-inflammatory properties, potentially exacerbating tissue damage and organ dysfunction (3,15-17).

A critical consideration in interpreting our findings is the potential confounding effect of age, given the substantial age difference between survivors (median 55 years) and non-survivors (median 70 years) in our cohort. We addressed this through multiple complementary analytical approaches. First, in multivariate regression with simultaneous adjustment, both age and hypoalbuminemia remained statistically significant independent predictors with comparable effect sizes. When standardized to clinically meaningful increments, age demonstrates similar prognostic importance. Second, an age-stratified analysis demonstrated that the albumin-mortality association persisted in both younger (<60 years) and older (≥60 years) patients, with no significant age-albumin interaction, confirming that albumin provides prognostic value beyond age stratification. Third, this indicates that the effect of hypoalbuminemia on mortality does not vary significantly by age. Both younger and older patients with hypoalbuminemia face increased mortality risk. Fourth, to assess the incremental predictive value of albumin beyond age-based risk assessment, we compared nested models and demonstrated that albumin significantly enhances risk stratification beyond age alone. Fifth, age-adjusted predicted probabilities illustrate the clinical significance: at age 55, predicted mortality was 2.1% with normal albumin versus 6.3% with hypoalbuminemia; at age 70, predicted mortality was 8.7% with normal albumin versus 23.5% with hypoalbuminemia. These calculations demonstrate that, even among patients of the same age, hypoalbuminemia substantially increases mortality risk, with the absolute effect more pronounced in older patients.

These findings indicate that albumin is not merely a marker of age-related frailty but rather captures distinct pathophysiological processes—specifically inflammation-driven protein loss, hepatic synthetic dysfunction, and oxidative stress—that contribute to COVID-19 mortality, independent of chronological age. Indeed, the comparable effect sizes of age and hypoalbuminemia suggest that albumin status is of similar prognostic importance to a nearly 20-year age difference. This is clinically significant because while age is immutable, hypoalbuminemia is potentially modifiable through nutritional support, targeted anti-inflammatory therapy, or albumin replacement, thereby offering potential therapeutic targets that age alone does not provide.

Mounting evidence supports the prognostic value of serum albumin in COVID-19. Numerous meta-analyses and large cohort studies have demonstrated an association between hypoalbuminemia at hospital admission and an increased risk of mortality, greater disease severity, higher rates of ICU admission, and prolonged hospitalization (18). These findings, observed across diverse populations and geographical locations, highlight the potential utility of serum albumin as a readily accessible biomarker in the management of COVID-19. For instance, Abdeen et al. (1) confirmed a robust link between hypoalbuminemia and elevated in-hospital mortality, while Paliogiannis et al. (19) demonstrated significant associations between

hypoalbuminemia and both disease severity and adverse outcomes.

This study has several strengths, including its real-world setting; inclusion of a well-defined cohort of hospitalized COVID-19 patients during a specific period of the pandemic; measurement of serum albumin within the first 24 hours of admission; comprehensive adjustment for age as a confounder using multiple analytical approaches; and thorough analysis of a range of relevant clinical and laboratory parameters. However, it has limitations. The retrospective, single-center design may limit the generalizability. A single albumin measurement at admission does not capture the dynamic changes in albumin levels during the illness, which have also been shown to be prognostically relevant (20). The relatively small sample size for some subgroup analyses may have limited statistical power to detect significant differences, particularly in the age-stratified analysis, in which the older stratum showed a trend toward significance ($p = 0.082$) but did not reach conventional statistical significance, likely reflecting the reduced sample size in this subgroup.

This study identifies serum albumin, a routinely measured and low-cost biomarker, as an independent prognostic tool for the early risk stratification of hospitalized COVID-19 patients, providing information beyond age and conventional disease severity markers. Patients presenting with hypoalbuminemia may be at higher risk of adverse outcomes and may benefit from closer monitoring and, potentially, more aggressive therapeutic interventions. Longitudinal studies examining the trajectory of serum albumin levels during hospitalization and their association with outcomes would also be valuable. Furthermore, research exploring the potential therapeutic role of albumin infusion in improving outcomes for hypoalbuminemic COVID-19 patients is warranted.

Conclusion

This study demonstrates that hypoalbuminemia at hospital admission is a significant independent predictor of adverse clinical outcomes in patients hospitalized with COVID-19, including prolonged in-hospital stay (37% longer) and increased respiratory support requirements. The prognostic value of albumin persists after rigorous adjustment for age and disease severity, with effect sizes comparable to age itself, and is consistent across age groups. These findings underscore the potential utility of serum albumin as a simple, cost-effective, and readily available prognostic marker for early risk stratification, and they may help guide clinical decision-making in the management of COVID-19.

Ethics

Ethics Committee Approval: The study protocol received ethical approval from the University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (decision number: HNEAH-KAEK 2022/202, dated: 24.10.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.K., R.D., Concept: B.K., R.D., Design: B.K., R.D., Data Collection or Processing: B.K., K.N.B., Analysis or Interpretation: B.K., R.D., K.N.B., Literature Search: B.K., R.D., K.N.B., Writing: B.K., R.D., K.N.B.

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Forensic Evaluation of Informed Consent Deficiencies in Medical Practices

Tıbbi Uygulamalardaki Aydınlatılmış Onam Eksikliklerinin Adli Tıbbi Açıdan Değerlendirilmesi

Caner Beşkoç

The Council of Forensic Medicine, 7th Specialization Board, İstanbul, Türkiye

ABSTRACT

Background: Informed consent is a fundamental element of medical ethics and legal accountability. However, in many healthcare institutions, consent forms are still treated as a formality rather than a meaningful communication process between physicians and patients. In Türkiye, malpractice allegations and compensation claims related to incomplete or missing consent have increased in recent years, highlighting the need for standardized documentation and physician-led consent practices. This study aimed to evaluate the quality, completeness, and common deficiencies of informed consent documents referred to the *Adli Tıp Kurumu* (Council of Forensic Medicine) for forensic assessment.

Materials and Methods: A total of 441 medico-legal case files sent by judicial authorities to the Council of Forensic Medicine for expert evaluation of informed consent were retrospectively analyzed over a five-year period from January 2020 to December 2024. The Data included demographics, medical specialty, intervention type, hospital type, presence of written consent, risk and complication information, person obtaining consent, and identified deficiencies.

Results: Written informed consent was present in 201 cases (45.6%) and absent in 240 cases (54.4%). The most frequent deficiencies were missing physician's signature (10%), missing diagnosis (7.5%), and missing date (6%). Risk information was present in 98.5% of forms. Deficiencies were significantly higher when consent was obtained by nurses or other personnel ($p < 0.01$) and in private hospitals, where rates of deficiencies were about twice those in public institutions ($p < 0.01$).

Conclusion: Deficiencies in informed consent documentation remain common in Türkiye. Lack of physician involvement and incomplete forms undermine both patient autonomy and legal validity. Standardized, physician-led, and procedure-specific consent processes, supported by institutional oversight, are essential to ensure ethical and legal protection.

Keywords: Informed consent, verbal consent, forensic medicine, medical law, patient rights

ÖZ

Amaç: Aydınlatılmış onam, tıbbi etiğin ve hukuki sorumluluğun temel bir unsurudur. Ancak birçok sağlık kuruluşunda onam formları, hekim ile hasta arasındaki anlamlı bir iletişim süreci olmaktan ziyade, hâlen biçimsel bir gereklilik olarak ele alınmaktadır. Türkiye'de son yıllarda eksik veya hiç alınmamış onama bağlı malpraktis iddiaları ve tazminat taleplerinin artması, standartlaştırılmış dokümantasyonun ve hekim tarafından yürütülen onam uygulamalarının gerekliliğini ortaya koymaktadır. Bu çalışmanın amacı, Adli Tıp Kurumu'na adli değerlendirme amacıyla gönderilen aydınlatılmış onam belgelerinin kalite, bütünlük ve sık görülen eksiklikler açısından değerlendirilmesidir.

Gereç ve Yöntemler: Ocak 2020–Aralık 2024 tarihleri arasındaki beş yıllık dönemde, aydınlatılmış onamın adli bilirkişi incelemesi amacıyla yargı mercileri tarafından Adli Tıp Kurumu'na gönderilen toplam 441 adli tıbbi dosya retrospektif olarak analiz edildi. Veriler; demografik özellikler, tıbbi uzmanlık alanı, girişim türü, hastane türü, yazılı onamın varlığı, risk ve komplikasyonlara ilişkin bilgilendirme, onamı alan kişi ve saptanan eksiklikleri içermektedir.

Bulgular: Yazılı aydınlatılmış onam 201 olguda (%45,6) mevcutken, 240 olguda (%54,4) bulunmamaktaydı. En sık saptanan eksiklikler; hekimin imzasının bulunmaması (%10), tanının yer almaması (%7,5) ve tarihin bulunmaması (%6) idi. Risk bilgilendirmesi formların %98,5'inde mevcuttu. Onamın hemşireler veya diğer personel tarafından alındığı durumlarda eksikliklerin anlamlı derecede daha

Address for Correspondence: Caner Beşkoç, The Council of Forensic Medicine, 7th Specialization Board, İstanbul, Türkiye
E-mail: canbeskoc@yahoo.com **ORCID ID:** orcid.org/0000-0003-1336-0358

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ÖZ

fazla olduğu (p < 0,01) ve özel hastanelerde eksiklik oranlarının kamu kurumlarına kıyasla yaklaşık iki kat daha yüksek olduğu (p < 0,01) saptandı.

Sonuç: Türkiye'de aydınlatılmış onam dokümantasyonundaki eksiklikler yaygınlığını sürdürmektedir. Hekim katılımının yetersizliği ve eksik doldurulmuş formlar, hem hasta özerkliğini hem de hukuki geçerliliği zedelemektedir. Etik ve hukuki korumanın sağlanabilmesi için, kurumsal denetimle desteklenen, standartlaştırılmış, hekim tarafından yürütülen ve işleme özgü aydınlatılmış onam süreçleri gereklidir.

Anahtar Kelimeler: Aydınlatılmış onam, sözlü onam, adli tıp, tıp hukuku, hasta hakları

Introduction

Informed consent is one of the cornerstones of modern medicine, both ethically and legally. While it is a basic principle in clinical practice, it has also gained increasing importance in the field of forensic medicine. This process, which protects patient autonomy, ensures that the nature, benefits, risks, and alternatives to a medical intervention are clearly explained to the patient and that the patient makes a conscious and voluntary decision based on this information (1).

Consent can be classified as written, verbal, or implied, depending on how it is obtained. Written consent ensures complete information flow and traceability; documents that explicitly include risks and complications offer clarity for both physicians and forensic evaluators, regardless of whether malpractice has occurred. By contrast, verbal consent often lacks supporting evidence, making it difficult to prove in court and more vulnerable to legal challenge. Implied consent is accepted in simple and routine procedures, such as when a patient attends for a physical examination (2,3).

Although informed consent is a medical obligation, it also has a legal basis. In Türkiye, the Law on the Practice of Medicine and Its Branches (Tababet ve Şuabatı Sanatlarının Tarzı İcrasına Dair Kanun, Law No. 1219, enacted on 11 April 1928) stipulates in Article 70 that "written consent must be obtained before any surgical intervention." This legal obligation is further reinforced by the ethical rules of the Türk Tabipleri Birliği (Turkish Medical Association) and by the Hasta Hakları Yönetmeliği (Patient Rights Regulation, 1998/2014) (4).

Prior work in Türkiye indicates that perceived service quality and patient satisfaction are often higher in private hospitals and clinics than in public institutions; this difference may shape expectations regarding documentation and consent processes (5).

As frequently noted in decisions of the Yargıtay (Court of Cassation), "lack of consent" or "insufficient consent" is often regarded a deficiency in expert reports and has given rise to legal liability. Recently, deficiencies in consent have increasingly been used as grounds for malpractice lawsuits (6).

In forensic medicine, unlike in some medical contexts, the issue of consent is often evaluated in terms of its legal validity. While obtaining consent before intervention is ethically mandatory, the evaluation of cases where no malpractice is alleged but the consent form is incomplete remains controversial among experts. Therefore, in such cases, the content of the file is of significant importance (7).

The aim of this study is to assess the presence, content, and adequacy of informed consent forms that were referred to the *Adli Tıp Kurumu* (Council of Forensic Medicine) for expert evaluation.

In Türkiye, the number of malpractice allegations and compensation claims related to insufficient or missing consent has markedly increased in recent years, yet there is still no nationwide standard for consent documentation or audit.

Therefore, this study was designed to highlight the current deficiencies in informed consent practices, to raise awareness among physicians and healthcare institutions, to provide an evidence base for developing national consent standards, and to strengthen the role of forensic medicine in the legal assessment of medical practice.

Materials and Methods

Study Design

A total of 47,500 case files referred by judicial authorities to the Adli Tıp Kurumu (Council of Forensic Medicine) between December 2024 and January 2025 for expert opinion on alleged medical malpractice were reviewed. Among these, 441 files specifically requested expert evaluation of the presence or adequacy of informed consent and were included in the study. Due to conflicts between the parties, cases involving claims of verbal consent could not be assessed. A detailed analysis of the content and deficiencies of the consent documents was conducted for only the 201 cases with written informed consent. All data were anonymized before analysis, and only variables directly related to informed consent were included to ensure consistency and confidentiality.

Data Collection and Variables

Files were obtained from the institutional archives, and only documents submitted by judicial authorities were examined. For each case, the following variables were recorded:

- Demographics: Age, sex
- Specialty and type of intervention: Cardiology, plastic surgery, general surgery, dentistry, orthopedics, ear, nose and throat (ENT), neurosurgery, ophthalmology, emergency medicine, oncology, urology, etc.; surgery, anesthesia, drug treatment, hospitalization, and other procedures
- Hospital type: Public or private healthcare institutions
- Consent information: Presence of written consent, person obtaining consent (physician, nurse, other healthcare staff), person providing consent (patient or relative), and whether complication/risk information was included in the form
- Deficiencies: Missing patient/relative signature, name, date, diagnosis, physician signature, and other documentation issues

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 29.0. Descriptive statistics were presented as numbers (n) and percentages (%). Pearson's chi-square test was used for bivariate comparisons, and Fisher's exact test was applied when cell frequencies were low. Effect sizes were calculated with Cramer's V. In analyses of associations between multi-categorical variables, cell contributions were examined through standardized residuals. When necessary, deficiency types were combined and reanalyzed. A multivariable logistic regression model was planned; however, because of low frequencies in some cells, the model was restricted and the results focused primarily on significant bivariate findings. Statistical significance was set at $p < 0.05$.

Results

Among the 441 cases evaluated, females constituted 59.0% and males 41.0%. The ages of the cases ranged from 0 to 89 years. According to the World Health Organization (WHO) classification, 13.2% were adolescents (0–17 years), 72.3% were adults (18–64 years), and 14.5% were elderly (≥65 years). The majority of cases were working-age adults, corresponding to the period during which surgical and interventional procedures are most common.

The largest share of cases originated in surgical and interventional specialties, notably obstetrics and gynecology, plastic surgery, and general surgery (Figure 1). Surgical procedures accounted for 68.5% of interventions, followed by drug treatments, anesthesia procedures, and other interventions such as hospitalization or diagnostic tests (Table 1).

Private hospitals represented 61.5% of all cases, with deficiency rates nearly twice as high as those in public hospitals ($p < 0.01$).

Table 2 summarizes the presence of written consent and the inclusion of complication/risk information. Overall, 201 (45.6%) had written consent, while 240 (54.4%) lacked documentation. Complication or risk information was present in 98.5% of the written forms.

Consent was obtained primarily by physicians (94.5%), whereas deficiencies were significantly more frequent when consent was obtained by nurses or administrative staff ($p < 0.01$). Overall, 67 of the 201 written consent forms (33.3%) had at least one deficiency, and 21 forms (10.4%) contained two or more missing elements (Table 3).

No statistically significant associations were observed with patient age, sex, or the person providing consent.

Discussion

This study presents important findings regarding the practice of obtaining informed consent within healthcare delivery in Türkiye. Our results showed that cases without written consent (54.4%) were more common than those with written consent (45.6%). This finding suggests that informed consent is still not a fully standardized practice with respect to patient autonomy and the physician–patient relationship. Previous studies across different medical disciplines in Türkiye have similarly emphasized that obtaining formal consent is often neglected (8,9). International literature also indicates that in developing countries, written consent is often obtained only as a formality, and patients are not adequately aware of their right to refuse or withdraw consent. In contrast, in developed healthcare systems, these

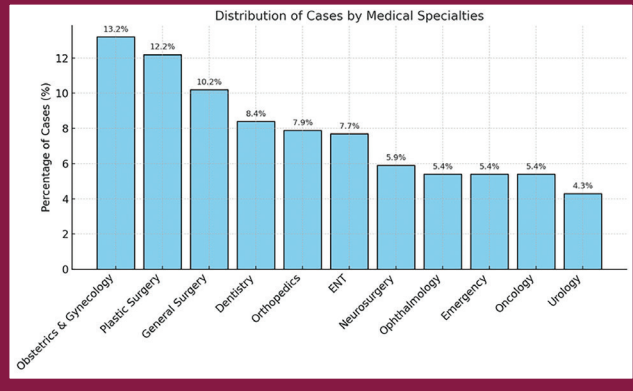


Figure 1. Distribution of cases by medical specialties. The most frequent specialties were obstetrics and gynecology (13.2%), plastic surgery (12.2%), and general surgery (10.2%).

Table 1. Demographic distribution of cases (n = 441).

Variables	Category	n	%
Gender	Female	260	59.0
	Male	181	41.0
Age	0–17	58	13.2
	18–64	319	72.3
	64–74	41	9.3
	75–84	18	4.1
	≥85	5	1.1
Hospital	Private	271	61.5
	Public	170	38.5
Type of procedure	Surgery	302	68.5
	Drug administration	51	11.6
	Anesthesia	35	7.9
	Other	53	12.0

Other includes hospitalization, diagnostic tests, reproductive health, and organ donation.

Table 2. Distribution of consent presence and risk/complication information.

Variables	Category	n	%
Consent	Present	201	45.6
	Absent	240	54.4
Risk/complication information	Present	198	98.5
	Absent	3	1.5

Table 3. Distribution of personnel obtaining consent, person providing consent, and deficiencies (n = 201).

Variables	Category	n	%
Obtained by	Physician	190	94.5
	Nurse	10	5.0
	Other (hospital staff)	1	0.5
Provided by	Patient	173	86.1
	Relative	27	13.4
	Not recorded	1	0.5
Deficiencies in written consent	Physician's signature missing	20	10
	Diagnosis missing	15	7.5
	Date missing	12	6.0
	Patient/relative signature missing	10	5.0
	Patient name missing	5	2.5

rights are more strictly protected, and informed consent is regarded as an integral part of patient autonomy (10,11).

In our study, women represented 59% of cases and men 41%. This distribution may be explained by the greater representation of specialties that are frequently accessed by female patients, such as gynecology, obstetrics, plastic surgery, and cosmetic procedures. The Literature also reports that women seek healthcare services more frequently than men and therefore participate more often in the consent process (12). However, no statistically significant difference was found between genders in the presence of deficiencies.

When age groups were reclassified according to the WHO standard, the majority of cases (72.3%) were adults aged 18–64 years, reflecting that most malpractice-related evaluations involve the active working-age population, who are the primary users of healthcare services. International studies also report that consent is most frequently obtained from young and middle-aged adults, especially in obstetric and general surgical procedures (13). In our series, however, age was not significantly associated with the presence of consent deficiencies. Overall, demographic data suggest that deficiencies are not specific to any age or gender group, but rather related to institutional, professional, and specialty-based factors.

This highlights the importance of focusing on process-related shortcomings in forensic evaluation rather than individual patient characteristics.

The specialties most commonly evaluated with respect to consent were obstetrics and gynecology (13.2%), plastic surgery (12.2%), and general surgery (10.2%), followed by dentistry, orthopedics, ENT, neurosurgery, ophthalmology, emergency medicine, oncology, and urology. This distribution reflects a predominance of malpractice claims among surgical and interventional specialties in Türkiye. These areas inherently carry a higher risk of complications, making the consent process particularly critical. Similarly, the literature underscores the importance of informed consent in surgical specialties, where complications are often unavoidable and patients' expectations are high (14,15). In plastic surgery, particularly cosmetic procedures, patient satisfaction is highly subjective, which further emphasizes the need for complete documentation of risks and complications. In our study, deficiencies were more common in surgical specialties (χ^2 test, $p < 0.05$), highlighting the need to strengthen consent practices in these fields.

Regarding types of procedures, surgical procedures were the most frequent, followed by drug treatments, anesthesia, and other interventions (hospitalization, diagnostic tests, reproductive health, organ donation). This was expected, as surgery carries the highest risk of complications and legal liability. The Literature also states that surgical procedures are the most frequent context in which informed consent is obtained, and that such documents serve as the most critical evidence in legal disputes (2). In our study, non-surgical procedures were associated with fewer written

consents. In particular, chemotherapy, anesthesia, and high-risk drug therapies were often obtained by verbal rather than written consent, which constitutes a serious deficiency. The Literature has emphasized that written consent is mandatory for these high-risk interventions (16).

By hospital type, 61.5% of consents were obtained from private hospitals and 38.5% from public hospitals. This may be related to differing patient expectations and institutional practices in the private sector, where service quality and satisfaction are generally perceived to be higher. Deficiencies were nearly twice as frequent in private hospitals (χ^2 test, $p < 0.01$; Cramer's $V \approx 0.20$). This suggests that consent in private institutions often remains a formality rather than a substantive process. The Literature has similarly noted that pressure to maintain patient satisfaction in private hospitals may result in superficial consent practices (17). Studies in Türkiye also report that private hospitals tend to use standardized forms that provide inadequate individualized information on risks and complications (8). In contrast, documents from public hospitals appear more formal and subject to oversight, with lower deficiency rates.

Deficiencies were strongly linked to institutional and professional factors and were higher in private hospitals and when recorded by non-physician staff, particularly in surgical specialties.

In discussions of malpractice and consent deficiencies, attention is primarily focused on the individual physician. However, from a forensic and legal perspective, the responsibility for obtaining and documenting informed consent lies not only with the practitioner but also with the institution where the medical procedure is performed. The consent process has three essential components: the patient, who must be adequately informed and make a voluntary decision; the physician, who has the professional duty to disclose and explain; and the institution, which must ensure the availability of standardized forms, proper record-keeping, and administrative oversight. Institutional deficiencies—such as the absence of updated consent templates, the lack of training for staff involved in documentation, or insufficient auditing mechanisms—may directly contribute to the legal vulnerability of both the physician and the healthcare facility. Therefore, strengthening institutional policies and ensuring active monitoring of consent procedures are as crucial as physician-level diligence in preventing malpractice disputes.

It should also be acknowledged that there are exceptional circumstances in which the process of obtaining informed consent may be limited or temporarily bypassed. These include emergency interventions where immediate action is required to save lives or prevent serious harm; unforeseen complications that arise during a standard course of treatment and must be controlled promptly; and legal obligations where examination or intervention is mandated by law—such as in forensic cases or infectious diseases that pose a public health risk. In such contexts, the physician's priority is to act in the patient's best interest and in accordance with legal mandates, while still providing information to the extent possible. These exceptional situations illustrate that responsibility for consent cannot rest solely on the individual physician but must be considered within the broader context of institutional and legal frameworks.

Content analysis of written consents revealed that 198 of 201 cases (98.5%) included information on complications or risks, while only three cases (1.5%) lacked such information. While this indicates that risk information is usually present, the key issue is whether it is sufficiently detailed and individualized. The literature suggests that information about complications is often provided in generic terms, and patients frequently fail to fully understand the real risks. In one study, only 34% of patients recalled the risks and only 26% recalled alternatives (2). Thus, the mere presence of risk information is not enough; it must also be clear, comprehensive, and tailored to the patient. Evaluations from Türkiye confirm that consent is often based on standard templates rather than individualized communication. Kurt (4) emphasized the need for forms adapted to patients' social and psychological conditions, while Yıldırım et al. (18) showed that, especially in surgical specialties, consent in practice is usually delivered in generalized terms. Forensic assessments must consider this distinction, since courts evaluate not only the existence of a consent form but also its adequacy.

Although most consents were obtained by physicians, deficiencies were significantly lower when physicians were directly involved and significantly higher when consents were obtained by nurses or other personnel (χ^2 test, $p < 0.01$; Cramer's $V \approx 0.30$). This underscores that informed consent is not merely a signature but a professional responsibility that requires explanation, disclosure of risks, and patient–physician communication. The literature also reports that non-physician staff often obtain consent beyond their scope of authority, thereby reducing the quality of consent documentation (19). Our findings reinforce that the consent process must remain the responsibility of physicians. In practice, certain emergency or high-workload situations may require assistance from nurses or other healthcare staff during the consent process. This support typically involves logistical help—such as form preparation or witness documentation—rather than assuming the physician's ethical and legal responsibility for disclosure. Recognizing these circumstances is important for distinguishing

between delegation of tasks and of responsibility, ensuring that physicians remain primarily accountable while acknowledging the practical realities of healthcare delivery.

In our series, the majority of consents (86.1%) were signed directly by the patients, while 13.4% were signed by relatives. This generally reflects respect for patient autonomy. However, obtaining consent from relatives when patients are competent raises ethical concerns. The Literature states that consent should be obtained directly from adult patients with decision-making capacity and from legal representatives only in cases of unconsciousness, severe mental impairment, or when the patient is a minor (2,10).

The most frequent deficiency observed in written consents was the absence of physician signatures. This directly undermines the medical and legal validity of the form, since the physician's signature is proof that they personally conducted the informed consent process. The literature also emphasizes that consent forms lacking a physician's signature are often deemed invalid in court, thereby increasing physician liability (19). Missing diagnoses, dates, and patient signatures are also important. In particular, the absence of a diagnosis leaves unclear what the patient has agreed to, while missing dates undermine the legal validity of the document. The absence of a patient signature renders the form entirely null.

In forensic practice, consent forms are not only ethical tools but also critical documents defining legal accountability. The Court of Cassation frequently classifies lack of consent or incomplete consent as "fault," leading to liability (7). Especially in surgical cases, deficiencies in form and content are often considered to constitute insufficient disclosure. Our findings are consistent with this perspective: nearly one-third of forms had at least one deficiency and one-tenth had multiple deficiencies. These shortcomings may seriously disadvantage physicians and institutions in legal proceedings. Moreover, consent obtained by non-physician staff is particularly problematic with regard to legal validity.

Study Limitations

This study has certain limitations. The analysis was based solely on case files referred to the Adli Tıp Kurumu (Council of Forensic Medicine) for expert evaluation, which inherently limits access to comprehensive demographic or clinical information. In particular, variables such as education level, occupation, and marital status were not consistently documented in the judicial referral files and therefore could not be analyzed. This reflects a structural limitation of medico-legal data systems in Türkiye rather than a study-specific omission. Despite these constraints, the dataset represents a large and nationally relevant sample that accurately reflects the forensic perspective on informed consent practices.

The study was designed to evaluate the adequacy and completeness of informed consent forms from a forensic perspective, not to re-assess the medical indications or diagnostic decisions underlying the interventions. Information on clinical indications was not consistently available in the judicial referral files and was therefore excluded from the analysis to maintain a focused and standardized evaluation of consent quality.

It should be noted that the present study focused solely on written informed consent forms. In cases without written documentation, it was not possible to verify whether verbal consent had been provided, as the case files contained conflicting statements from the parties and lacked objective evidence. The assessment of verbal consent belongs primarily to the legal domain, and its verification requires a different methodological framework. Therefore, this study evaluated only the existence and adequacy of written consent documents.

Conclusion

This study provides evidence that deficiencies in informed consent documentation are still common among cases referred for forensic evaluation in Türkiye.

However, since the analysis was limited to the content and completeness of consent forms, the findings should not be generalized to all clinical settings. The results primarily reflect the documentation quality of cases under legal scrutiny, rather than the overall performance of the healthcare system.

This study demonstrated that significant deficiencies remain in the practice of obtaining written informed consent in Türkiye. The higher frequency of deficiencies in private hospitals, and of deficiencies in consents obtained by non-physician personnel, is particularly noteworthy. The most common deficiencies involved the absence of physicians' signatures, diagnoses, and dates, all of which weaken both the medical and legal validity of the documents. From a forensic medical perspective, not only the presence but also the content and completeness of consent forms are of critical importance. Considering that such deficiencies are often regarded as "fault" in court decisions, physicians and institutions must treat the consent process not as a formality, but as a process that directly affects patient rights and their own legal accountability.

Accordingly, several steps should be taken: the national standardization of consent forms; the adaptation of documents to the specific specialty and procedure; the restriction of the consent process to physicians; the provision

of complication and risk information in a clear, detailed, and patient-specific manner; and the establishment of regular institutional audit mechanisms.

Ethics

Ethics Committee Approval: This study was reviewed by the Scientific Research and Training Commission, Adli Tıp Kurumu (Council of Forensic Medicine) and approved (decision number: 21589509/2025/949, dated: 12.08.2025).

Informed Consent: Since this study was retrospective and based on archived judicial case files, individual informed consent was waived.

Footnotes

Conflict of Interest: No conflict of interest was declared by the author(s).

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ORIGINAL ARTICLE

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Health Promoting Lifestyle of Older Adults Living in Public Nursing Homes: A Cross-Sectional Study from İstanbul, Türkiye

Kamu Huzurevlerinde Yaşayan Yaşlıların Sağlığı Geliştirici Yaşam Biçimleri: İstanbul, Türkiye'den Bir Kesitsel Çalışma

Ayşe Nur Balcı Yapalak[1,2], Bedia Özyıldırım[3]

[1]İstanbul Medipol University School of Medicine, Department of Public Health, İstanbul, Türkiye

[2]İstanbul Medipol University Graduate School of Health Sciences, Department of Epidemiology, İstanbul, Türkiye

[3]Bezmialem Vakıf University Faculty of Medicine, Department of Public Health, İstanbul, Türkiye

ABSTRACT

Background: Preventing the progression of non-communicable diseases, which are the most common health problems in old age, is possible by developing healthy habits. This study aims to assess the healthy lifestyle behaviors of older adults residing in nursing homes.

Materials and Methods: In this cross-sectional study, a questionnaire that contained socio-demographic information, the Health-Promoting Lifestyle Profile-II (HPLP-II), and the first part of the Nottingham health profile (NHP) was administered to 120 accessible participants (31.3% of 383 residents) in five public nursing homes in İstanbul.

Results: The mean age of participants was 75.8 ± 7.8 years; 40% were women. Participants' highest per-question scores on the HPLP-II sub-dimensions were for spiritual growth and stress management (2.7 ± 0.5 and 2.6 ± 0.4, respectively), whereas the lowest were for health responsibility (HR) and physical activity (1.5 ± 0.4 and 1.6 ± 0.4, respectively). The NHP sub-dimensions in which participants scored best were pain, energy level, and emotional reaction (9.0 ± 15.5, 9.0 ± 21.4, and 10.6 ± 14.1, respectively), while the worst were sleep and social isolation (19.2 ± 27.6 and 18.8 ± 19.7, respectively).

Conclusion: Habits such as HR, PA, and sleep were poorer than emotional domains. More suitable and wide-ranging interventions are required to improve lifestyle habits among nursing home residents and promote better health.

Keywords: Healthy aging, nursing homes, healthy lifestyle, health facilities

ÖZ

Amaç: Yaşlılık döneminde en sık görülen sağlık sorunları arasında yer alan bulaşıcı olmayan hastalıkların ilerlemesinin önlenmesi, sağlıklı alışkanlıkların geliştirilmesiyle mümkündür. Bu çalışma, huzurevlerinde yaşayan yaşlı bireylerin sağlığı geliştirici yaşam biçimi davranışlarını belirlemeyi amaçlamaktadır.

Gereç ve Yöntemler: Bu kesitsel çalışmada, İstanbul'daki beş kamu huzurevinde yaşayan 383 bireyden ulaşılabilen 120 katılımcıya (%31,3) sosyodemografik bilgileri içeren bir anket, Sağlığı Geliştirici Yaşam Biçimi Ölçeği II (HPLP-II) ve Nottingham sağlık profili ölçeği'nin (NHP) birinci bölümü uygulanmıştır.

Bulgular: Katılımcıların yaş ortalaması 75,8 ± 7,8 olup, %40'ı kadındır. HPLP-II alt boyutlarından en yüksek puan ortalamaları "manevi gelişim" (2,7 ± 0,5) ve "stres yönetimi" (2,6 ± 0,4) alanlarında, en düşük puan ortalamaları ise "sağlık sorumluluğu" (1,5 ± 0,4) ve "fiziksel aktivite" (1,6 ± 0,4) alanlarında saptanmıştır. NHP alt boyutları arasında en iyi sonuçlar "ağrı", "enerji düzeyi" ve "duygusal reaksiyon" (sırasıyla 9,0 ± 15,5; 9,0 ± 21,4 ve 10,6 ± 14,1) iken, en olumsuz sonuçlar "uyku" ve "sosyal izolasyon" (19,2 ± 27,6 ve 18,8 ± 19,7) alt boyutlarında bulunmuştur.

Sonuç: Sağlık sorumluluğu, fiziksel aktivite ve uyku gibi alışkanlıklar, maneviyatı değerlendiren alt boyutlardan daha kötüydü. Huzurevinde kalanların daha sağlıklı alışkanlıklar ile yaşamasını sağlamak ve yaşam biçimi davranışlarının iyileştirilmesi için uygun ve geniş kapsamlı müdahalelere ihtiyaç vardır.

Anahtar Kelimeler: Sağlıklı yaşlanma, bakım evleri, sağlıklı yaşam tarzı, sağlık tesisleri

Address for Correspondence: Ayşe Nur Balcı Yapalak, İstanbul Medipol University School of Medicine, Department of Public Health, İstanbul, Türkiye

E-mail: ayse.balci@medipol.edu.tr **ORCID ID:** orcid.org/0000-0003-1323-4511

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Introduction

Türkiye is aging rapidly, as people aged 65 and over made up 8% of Türkiye's population in 2014, increasing to 9.1% by 2019 (1). Life expectancy is increasing for various reasons, and the number of births per woman is decreasing. The main reasons for this demographic change are industrialization, technological development, urbanization, and other related factors, which create a vicious cycle in which these factors reinforce one another. These changes also affect the family structure, and extended families are beginning to give way to nuclear families. As family size shrinks, the roles of older adults are changing: the number of family members available to meet their needs is decreasing, which negatively affects their mental health (2).

It has become necessary for older adults to meet their needs by receiving services from external providers, especially those living apart from their children in the city. Long-term care systems, such as home care services and institutional care, have begun to develop, as have their associated difficulties, such as unprofessional caregivers and the isolation of older adults from their homes and communities (2). The situation is slightly different in Türkiye. Although children do not typically live in the same household as their parents, they generally prefer to live close to them and do not completely isolate themselves from their parents' care. Despite this, both the number of nursing homes and their occupancy rates are gradually increasing, especially in large cities (3).

The trend of increasing life expectancy at birth is a great success, but the extension of lifespan should be qualified. Life expectancy increases, but so does the number of years over which one is unhealthy; Türkiye experienced an average of 9.69 years of poor health in 1990 and 11.09 years in 2017 (4). The World Health Organization defines healthy aging as developing and maintaining functional abilities that provide well-being in older age (2). In line with this, the Ministry of Health developed the "Türkiye Healthy Aging Action Plan and Implementation Program 2015–2020," which highlights the importance of promoting healthy lifestyle behaviors to prevent non-communicable diseases (NCDs) among older adults (5). This is particularly relevant because NCD risk increases substantially with age (6).

In Türkiye, healthy lifestyle behaviors among older adults living in nursing homes have been insufficiently studied, even though the number of institutionalized older adults and the burden of NCDs continue to increase (7–10). Existing evidence does not adequately describe key daily behaviors such as physical activity (PA), sleep, and health responsibility (HR) within institutional settings. Given these gaps, identifying the Health-Promoting Lifestyle Profile II (HPLP-II) of residents in public nursing homes is important for guiding targeted interventions and supporting healthier ageing.

The aim of this study is to describe the health-promoting lifestyle behaviors of older adults living in public nursing homes and to examine how these behaviors vary according to demographic characteristics.

Materials and Methods

The study is conducted in public nursing homes, as their residents are a disadvantaged group but are also more amenable to intervention. Nine nursing homes in İstanbul are affiliated with the Ministry of Family and Social Services (MoFS). At the time of the study, one of the nursing homes was under renovation, and its residents were transferred to other nursing homes. This cross-sectional study was conducted in five of these that agreed to allow this research to be carried out in their facilities. Of these five nursing homes, three are on the European side of İstanbul and two on the Asian side; all are located in different districts. Nursing homes affiliated with the MoFS provide standard or specialized care to people over the age of 60 who are mentally healthy, free of infectious diseases and drug or alcohol addictions, and economically or socially deprived, depending on their health status (11). Three hundred eighty-three residents, 159 (41.5%) of whom were women, were residing in these five nursing homes and receiving routine care.

People who received special care services in institutions, or who received normal care but had amnesia, loss of limbs, hearing or speech problems, were not included in the study. Random selection could not be achieved because entering a resident's room is forbidden, and identifying them by name alone was not possible, since photographs were not included in every file. Hence, participants who consented were selected by convenience sampling from the common areas of nursing homes. The survey was administered face-to-face by one of the researchers, who read each question aloud and recorded participants' responses, because most residents were unable to complete the form independently.

A a priori sample size estimation was conducted using effect size information from a previous study of Turkish nursing home residents (12). Using a significance level of 0.05 and 80% power, the calculation indicated that approximately 60 participants would be adequate. However, because probability-based sampling was not possible and convenience sampling was used, this estimate was considered useful only for planning the study and was not used to support statistical interpretation (13).

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2013. Ethics approval was obtained from the Bezmialem Vakıf University

Non-Invasive Research Ethics Committee (approval number: 15/286, dated: 30.07.2019). Verbal informed consent was obtained from all participants prior to data collection. Out of 383 residents, 140 were reachable, and 120 of them agreed to participate in the study. One hundred twenty of them agreed to participate in the study. While 1 participant did not provide a reason for his/her refusal, the remaining 19 participants cited the following reasons for non-participation: 7 participants indicated they were unavailable due to prior commitments or other engagements; 3 participants stated that they were overwhelmed by participating in the surveys; 3 participants reported feeling unwell or indisposed; 1 participant declined to share personal information; 1 participant expressed skepticism about the sincerity of the survey responses; 1 participant felt uncomfortable with the appearance of the interviewer; 1 participant lacked confidence in his/her ability to complete the survey; 1 participant simply stated he/she was not interested in participating; and 1 participant declined to participate due to an ongoing conversation he/she did not want to interrupt.

A questionnaire that included socio-demographic information, HPLP-II, and the first part of the Nottingham health profile (NHP) was administered to the participants between December 2019 and January 2020 by a single interviewer, who also scored the Likert-scale responses based on the participants' answers. Sociodemographic characteristics were treated as independent variables, and the HPLP-II and NHP scale scores were considered as dependent variables.

The Turkish validity and reliability study of the HPLP-II was conducted by Bahar et al. (14). The scale comprises 52 four-point Likert items, all of which are positively worded. On the scale, 1 point = never; 2 points = sometimes; 3 points = often; and 4 points = regularly. HPLP-II comprises six subscales: HR, PA, nutrition (N), spiritual growth (SG), interpersonal relationships (IR), and stress management (SM). PA and SM have eight items; the others have nine items (15). The Cronbach's alpha coefficient was calculated to be 0.92.

The Turkish validity and reliability study for NHP was conducted by Küçükdeveci et al. (16). The first part of the NHP has six subscales and a total of 38 items: eight items for pain, eight for mobility, nine for emotional reactions (ER), five for sleep, five for social isolation (SI), and three for energy. The answer to each item is yes or no. The items in each subscale are weighted within the subscale to total 100 points, where higher scores indicate a lower health profile (17).

Statistical Analysis

Descriptive statistics are presented as frequencies and percentages for categorical variables, and as means and standard deviations for quantitative variables. Normality was tested using the Kolmogorov–Smirnov test. Categorical variables are compared by an appropriate chi-squared test. The Mann–Whitney U or Kruskal–Wallis test was used to compare non-normally distributed data across categorical groups, depending on the number of groups. Spearman correlation was used to evaluate the relationship between non-normally distributed or ordinal data. Cronbach's alpha was used to assess the reliability of the scales. Analyses were conducted using the IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA). A two-sided significance level of 0.05 was used.

Results

Of 120 participants, 40% (n = 48) were women. The gender distribution in the universe (41.5%) and in the sample are statistically similar (p = 0.77). The mean age of participants was 75.8 ± 7.8 years, and 17 of them (14.8%) had no NCD. Ninety-one older adults (75.8%) had at least one living child. İstanbul was the place where 104 participants (87.4%) spent most of their lives. The mean length of stay in a nursing home was 53.9 ± 45.5 months (range: two days to 19 years). The distributions of other demographic characteristics are presented in Table 1.

Table 1. The distribution of demographics of participants.

	n (%)
Education status	
Never went to school	17 (14.3)
Primary school	34 (28.6)
Middle school	17 (14.3)
High school	36 (30.3)
Undergraduate or higher	15 (12.6)
Total	119* (100.0)
Income status	
None	9 (7.5)
Retirement pay	106 (88.3)
Retirement pay + side income	5 (4.2)
Total	120 (100.0)
Smoking status	
Never smoked	45 (40.2)
Quit smoking	34 (30.4)
Still smoking	33 (29.5)
Total	112* (100.0)
*There were missing values.	

Participant HPLP-II scores are presented in Table 2. Since the number of items included in each subscale may differ, the mean score per item was also calculated. The highest subscale score per question was SG, and the lowest score was HR.

The reliability of the HPLP-II and the subscales was good, except for the N subscale. When the item "I consume limited sugar and dessert" (item N) was removed, Cronbach's alpha increased to 0.452. When the items "I have breakfast" and "I eat 6-11 servings of bread, cereal, rice, and pasta every day" were removed, it increased to 0.520. However, the associated reliability remained unacceptable.

Comparisons of HPLP-II scores across demographic variables are presented in Table 3. Overall, education emerged as the most influential demographic factor associated with HPLP-II. However, no difference was found between the groups in the post-hoc tests. The SG was significantly higher among participants with a high school education and those with an undergraduate degree or higher compared with those with secondary school education or who never attended school. In addition, scores for participants with undergraduate or higher education were higher than those for participants who attended primary school.

The NHP subscales on which participants scored best were pain and energy, and the worst was the sleep subscale. The reliability coefficients of the subscales were suboptimal but acceptable, except for SI. When the item "I think I am a burden on people" was removed from SI, Cronbach's alpha increased to 0.568. When the item "I feel lonely" was removed, the associated Cronbach's alpha increased to 0.625, but remained unacceptable (Table 4).

Comparisons of NHP scores according to demographic variables are given in Table 5. Among NHP subscales, age

Table 2. Mean scores and reliability of HPLP-II.

	Mean ± SD	Mean ± SD per question	Cronbach alpha
Scores of subscales			
HR	13.8 ± 3.9	1.5 ± 0.4	0.834
PA	12.9 ± 3.7	1.6 ± 0.5	0.785
N	21.0 ± 2.3	2.3 ± 0.3	0.385
SG	24.2 ± 4.3	2.7 ± 0.5	0.880
IR	21.9 ± 4.1	2.4 ± 0.5	0.890
SM	20.5 ± 3.2	2.6 ± 0.4	0.738
The total score of HPLP-II	114.4 ± 13.5	2.2 ± 0.3	0.892

HPLP-II, Health-Promoting Lifestyle Profile-II; HR, health responsibility; IR, interpersonal relationships; N, nutrition; PA, physical activity; SD, standard deviation; SG, spiritual growth; SM, stress management.

Table 3. Change in HPLP-II scores by demographics.

	HR	PA	N	SG	IR	SM	Total HPLP-II
Gender							
Women	15.1 ± 4.0	12.7 ± 4.0	21.5 ± 2.4	24.9 ± 4.5	22.4 ± 4.1	20.5 ± 3.5	117.1 ± 13.7
Men	13.0 ± 3.6	13.1 ± 3.6	20.7 ± 2.1	23.8 ± 4.2	21.5 ± 4.2	20.5 ± 3.0	112.6 ± 13.1
p	0.001*	0.373	0.117	0.203	0.258	0.871	0.061
Age							
r	-0.044	-0.127	-0.132	-0.108	0.009	0.138	-0.061
p	0.631	0.170	0.152	0.242	0.925	0.135	0.507
Education grade							
Never went to school	13.9 ± 4.4	12.2 ± 3.0	20.9 ± 2.9	21.2 ± 4.5	21.0 ± 5.1	19.1 ± 4.0	108.4 ± 18.2
Primary school	14.3 ± 3.8	13.7 ± 3.5	21.2 ± 2.3	23.7 ± 3.6	21.9 ± 3.8	20.7 ± 3.1	115.2 ± 13.3
Middle school	13.1 ± 3.4	12.2 ± 3.7	21.5 ± 2.0	22.2 ± 3.5	21.1 ± 5.2	19.8 ± 2.8	109.9 ± 10.2
High school	13.9 ± 4.6	13.3 ± 4.5	21.0 ± 2.3	25.9 ± 4.4	22.3 ± 3.4	20.9 ± 3.0	117.5 ± 13.5
Undergraduate or higher	13.2 ± 1.7	12.3 ± 3.1	20.5 ± 1.6	27.3 ± 2.8	23.1 ± 3.5	21.7 ± 3.0	118.1 ± 7.8
p	0.865	0.477	0.854	<0.001*	0.548	0.178	0.016*
Income							
None	13.0 ± 3.8	12.6 ± 5.3	20.6 ± 2.4	24.6 ± 3.6	22.9 ± 3.0	21.2 ± 3.3	114.8 ± 11.1
Retirement pay	13.8 ± 3.8	12.9 ± 3.5	21.0 ± 2.2	24.1 ± 4.3	21.8 ± 4.2	20.4 ± 3.2	113.9 ± 13.3
Retirement pay + side income	16.2 ± 5.1	13.2 ± 6.1	21.6 ± 3.9	27.2 ± 5.5	23.0 ± 3.6	22.4 ± 3.1	123.6 ± 20.0
p	0.319	0.607	0.799	0.222	0.820	0.463	0.516

Table 3. Continued

	HR	PA	N	SG	IR	SM	Total HPLP-II
Where most of life takes place							
İstanbul	14.0 ± 3.8	13.0 ± 3.8	21.1 ± 2.4	24.4 ± 4.1	22.1 ± 4.0	20.6 ± 3.2	115.2 ± 13.3
Out of İstanbul	13.1 ± 4.4	12.5 ± 3.4	20.4 ± 1.5	23.9 ± 4.5	21.4 ± 3.4	20.3 ± 2.8	111.5 ± 12.3
p	0.188	0.757	0.247	0.682	0.353	0.640	0.276
Children							
None	13.4 ± 3.5	11.8 ± 3.2	21.0 ± 1.8	23.5 ± 5.0	21.9 ± 5.2	20.3 ± 3.6	111.8 ± 14.7
Exist	14.0 ± 4.0	13.3 ± 3.9	21.0 ± 2.4	24.5 ± 4.1	21.9 ± 3.7	20.6 ± 3.0	115.2 ± 13.1
p	0.583	0.045*	0.649	0.803	0.382	0.863	0.481
NCDs							
None	11.5 ± 2.8	15.2 ± 3.9	21.6 ± 2.0	24.8 ± 5.5	21.5 ± 5.2	20.7 ± 3.6	115.3 ± 16.4
Exist	14.2 ± 3.9	12.6 ± 3.6	20.9 ± 2.3	24.1 ± 4.1	21.9 ± 3.9	20.5 ± 3.1	114.3 ± 13.0
p	0.003*	0.006*	0.188	0.210	0.910	0.649	0.660
Smoking							
Never smoked	14.4 ± 4.1	12.3 ± 3.3	20.7 ± 2.4	24.4 ± 4.4	21.8 ± 3.9	20.1 ± 3.4	113.8 ± 12.8
Quit smoking	13.0 ± 3.2	13.5 ± 4.4	21.1 ± 2.0	24.9 ± 3.0	23.1 ± 2.9	21.2 ± 2.7	116.8 ± 10.0
Still smoking	13.4 ± 4.0	13.3 ± 3.4	21.2 ± 1.8	23.2 ± 4.9	20.9 ± 4.9	20.5 ± 3.0	112.6 ± 15.5
p	0.247	0.348	0.222	0.529	0.227	0.334	0.615

*p < 0.05. HPLP-II, Health-Promoting Lifestyle Profile-II; HR, health responsibility; IR, interpersonal relationships; N, nutrition; PA, physical activity; SD, standard deviation; SG, spiritual growth; SM, stress management.

and smoking status showed the clearest differences. In the post-hoc analysis, non-smokers had worse pain (p = 0.03) and mobility (p = 0.01) profiles than smokers and had worse energy profiles than those who had stopped smoking (p = 0.03).

Exploratory correlation analyses are presented in Table 6. PA was moderately associated with pain, mobility, energy and the total NHP score, indicating that more active residents tended to report fewer functional limitations. Psychosocial domains, such as SG, IR, and SM, were most strongly correlated with ER, SI, energy, and overall health profile. The total HPLP-II score was moderately correlated with the total NHP score. These relationships suggest that both physical and emotional aspects of health-promoting behaviors are linked to perceived health status.

Table 4. Mean score and reliability of NHP.

	Mean ± SD	Cronbach alfa
Scores of subscales		
Pain	9.0 ± 15.5	0.774
ER	10.6 ± 14.1	0.643
SI	18.8 ± 19.7	0.410
Mobility	16.1 ± 16.9	0.685
Energy	9.0 ± 21.4	0.602
Sleep	19.2 ± 27.6	0.697
The total score of NHP	82.6 ± 70.8	0.791

ER, emotional reaction; NHP, Nottingham Health Profile; SD, standard deviation; SI, social isolation.

Discussion

This study examined the health-promoting lifestyle behaviors of older adults residing in public nursing homes in İstanbul. The overall lifestyle scores of the participants were at a moderate level, with the highest mean score observed in the IR subscale and the lowest in the PA subscale. In addition, significant associations were identified between health-promoting behaviors and sociodemographic characteristics such as age, education level, and length of stay in the institution. These findings provide important insights into the health behaviors of institutionalized older adults and indicate potential areas for targeted interventions.

Globally, women have a longer life expectancy at birth than men (1). Therefore, the proportion of female residents in nursing homes is expected to be higher than that of males. However, men outnumbered women in all five nursing homes where this study was conducted. In Turkish culture, older men in particular believe that a man cannot do anything without his wife, which may explain why they choose to stay in nursing homes (18,19). It is a common belief in Türkiye that living with children is easier for mothers than for fathers (20).

Table 5. Change in NHP scores by demographics.

	Pain	ER	SI	Mobility	Energy	Sleep	Total NHP
Gender							
Women	12.4 ± 20.3	12.9 ± 17.3	17.7 ± 21.1	20.5 ± 18.7	10.3 ± 22.1	20.5 ± 27.7	94.3 ± 83.7
Men	6.7 ± 10.7	9.1 ± 11.4	19.5 ± 18.9	13.1 ± 15.0	8.1 ± 21.1	18.3 ± 27.6	74.7 ± 60.0
p	0.437	0.531	0.549	0.037*	0.536	0.631	0.309
Age							
r	0.230	0.029	0.001	0.307	0.217	-0.041	0.161
p	0.012*	0.754	0.990	0.001*	0.018*	0.655	0.080
Education grade							
Never went to school	13.4 ± 22.4	17.7 ± 16.8	23.6 ± 24.7	20.0 ± 15.9	23.5 ± 34.8	20.5 ± 28.4	118.8 ± 96.6
Primary school	6.8 ± 13.0	9.3 ± 13.1	20.3 ± 18.0	14.6 ± 16.0	5.0 ± 12.5	18.6 ± 23.8	74.6 ± 52.5
Middle school	10.8 ± 16.0	11.2 ± 15.0	18.8 ± 15.8	14.7 ± 15.4	6.4 ± 12.2	18.2 ± 32.1	80.2 ± 51.5
High school	7.9 ± 14.9	10.4 ± 13.9	17.8 ± 20.5	14.7 ± 18.6	9.3 ± 24.7	22.1 ± 32.1	82.2 ± 81.5
Undergraduate or higher	7.5 ± 10.4	3.9 ± 8.0	9.4 ± 16.5	16.9 ± 15.7	1.6 ± 6.2	14.2 ± 19.2	53.6 ± 40.7
p	0.700	0.100	0.237	0.683	0.142	0.965	0.257
Income							
None	4.7 ± 11.9	11.6 ± 14.1	14.6 ± 20.7	18.2 ± 15.5	8.2 ± 16.2	26.0 ± 35.9	83.2 ± 69.7
Retirement pay	9.7 ± 16.0	10.8 ± 14.4	19.2 ± 19.7	16.3 ± 17.2	9.5 ± 22.3	18.1 ± 27.2	83.6 ± 72.4
Retirement pay + side income	2.3 ± 3.2	6.1 ± 5.6	16.1 ± 22.1	6.4 ± 9.6	-	29.5 ± 20.7	60.5 ± 34.0
p	0.395	0.924	0.645	0.310	0.554	0.291	0.904
Where most of life takes place							
İstanbul	9.1 ± 16.0	11.0 ± 14.8	17.0 ± 18.6	16.6 ± 16.6	8.7 ± 21.8	19.0 ± 28.0	81.3 ± 72.0
Out of İstanbul	8.2 ± 12.2	7.3 ± 8.4	28.7 ± 23.0	13.4 ± 19.3	9.0 ± 19.3	21.8 ± 25.5	88.3 ± 65.8
p	0.928	0.611	0.047*	0.358	0.809	0.386	0.522
Children							
None	10.0 ± 16.7	7.8 ± 11.2	15.0 ± 22.8	17.5 ± 18.4	11.0 ± 23.5	13.9 ± 22.6	75.2 ± 72.7
Exist	8.7 ± 15.1	11.5 ± 14.9	20.0 ± 18.6	15.6 ± 16.5	8.3 ± 20.9	20.9 ± 28.9	84.9 ± 70.4
p	0.790	0.265	0.078	0.737	0.406	0.222	0.255
NCDs							
None	1.5 ± 4.4	7.2 ± 9.7	20.4 ± 20.6	6.5 ± 14.4	13.8 ± 28.7	17.7 ± 30.0	67.1 ± 72.7
Exist	10.2 ± 16.3	11.2 ± 14.7	18.5 ± 19.7	17.6 ± 16.8	8.2 ± 20.1	19.4 ± 27.3	85.1 ± 70.5
p	0.009*	0.390	0.763	0.002*	0.486	0.560	0.142
Smoking							
Never smoked	14.0 ± 20.0	12.7 ± 16.2	16.3 ± 20.7	21.1 ± 18.9	13.2 ± 24.0	19.7 ± 26.3	96.9 ± 87.0
Quit smoking	6.5 ± 12.1	7.5 ± 13.0	14.1 ± 12.0	15.8 ± 14.9	1.4 ± 5.7	18.7 ± 29.8	64.0 ± 47.1
Still smoking	3.8 ± 6.5	11.0 ± 12.4	22.4 ± 20.8	8.6 ± 10.8	9.0 ± 25.4	21.4 ± 29.4	76.1 ± 62.2
p	0.019*	0.196	0.287	0.011*	0.039*	0.795	0.371

*p < 0.05. ER, emotional reaction; NCD, non-communicable diseases; NHP, Nottingham health profile; SI, social isolation.

The reliability of the HPLP-II subscales, with the exception of the N subscale, was measured by the Cronbach's alpha coefficient and found to be good (Table 2). Even after the statements that reduced reliability were removed, Cronbach's alpha did not exceed 0.520 for the N subscale. This may be because the portion, as expressed on the scale, is not explicitly stated. Although a single interviewer was expected to reduce this ambiguity, this expectation did not sufficiently increase reliability.

Participants had higher scores on the SG, IR, and SM subscales, which provide information about their inner world, than on the PA and HR subscales, which are related to their habits. Since N was mostly provided through meals in nursing homes, it was usually not affected by preferences; therefore, the score of this N subscale was average. Therefore, it was observed that participants' nutritional status was not affected by demographic, social, or economic factors in this study, although education and income have been reported as the most important factors affecting N in other studies (21,22).

A gender difference was observed only for the HR subscale, with higher scores in women than in men. Although a meta-analysis that included all theses in Türkiye usually found higher total HPLP-II scores for women, this difference has also been shown to be purely incidental (23).

Higher levels of education have been the most frequently mentioned factor for its positive effect on healthy behaviors, especially in total HPLP-II, N, and PA (9,21,22,24). However, in this study, PA and N were not affected by education level. The reason could be that everyone lives under nursing-home conditions. Unlike these, SG score was higher in those with a higher level of education.

Another factor mentioned in the literature as having a positive impact on healthy behaviors is a high income level, especially for total HPLP-II, N, and PA (9,21,22). Since the income levels of the participants were similar, it was not possible to draw meaningful conclusions regarding income; however, participants with higher incomes had higher scores.

In this study of older adults, those with children were more physically active than those without children. Interviews revealed that older adults usually went outside the nursing home, which could be the underlying reason (20).

Table 6. Correlation between HPLP-II and NHP.

	Pain	ER	SI	Mobility	Energy	Sleep	Total NHP
HR							
r	0.161	0.138	0.046	0.077	-0.014	-0.144	0.014
p	0.080	0.132	0.622	0.406	0.875	0.117	0.882
PA							
r	-0.270	-0.205	-0.165	-0.382	-0.241	0.043	-0.305
p	0.003*	0.025*	0.072	<0.001*	0.008*	0.644	0.001*
N							
r	-0.115	-0.117	0.033	-0.132	-0.116	-0.051	-0.138
p	0.209	0.201	0.718	0.150	0.206	0.582	0.133
SG							
r	-0.111	-0.466	-0.439	-0.116	-0.434	-0.124	-0.491
p	0.229	<0.001*	<0.001*	0.205	<0.001*	0.178	<0.001*
IR							
r	0.054	-0.440	-0.538	0.065	-0.333	-0.175	-0.431
p	0.555	<0.001*	<0.001*	0.483	<0.001*	0.056	<0.001*
SM							
r	-0.069	-0.603	-0.471	-0.039	-0.391	-0.409	-0.602
p	0.454	<0.001*	<0.001*	0.671	<0.001*	<0.001*	<0.001*
Total HPLP-II							
r	-0.061	-0.466	-0.404	-0.136	-0.431	-0.230	-0.544
p	0.506	<0.001*	<0.001*	0.138	<0.001*	0.011*	<0.001*

*p < 0.05. ER, emotional reaction; HPLP-II, Health-Promoting Lifestyle Profile-II; HR, health responsibility; IR, interpersonal relationships; N, nutrition; NHP, Nottingham health profile; PA, physical activity; SG, spiritual growth; SI, social isolation; SM, stress management.

Since physical inactivity can lead to NCDs and NCDs can cause certain disabilities, people with NCDs are expected to be less physically active (25). Contrary to expectations, this study found that people with NCDs had better HR. Paying greater attention to their own health after having the disease may explain this.

The reliability of the NHP subscales, as measured by Cronbach's alpha coefficient, was good, with the exception of the SI subscale (Table 4). Cronbach's alpha increased after removing the items "I think I am a burden on people" and "I feel lonely" from the SI subgroup of five items. These items may have been similar among the participants because they were in nursing homes; consequently, their correlations with the other items of the scale may have been lower.

In this study, the NHP subscales with better scores were pain and energy, whereas the worse subscales were sleep, SI, and mobility; by contrast, in other studies among older adults, energy was the worst subscale and SI the best (26–28). However, none of these studies was conducted in nursing homes, and living in an institution far from home and community may explain why SI was worse in this instance (2). Participants were likely to be more extroverted because they were selected from common areas and agreed to participate in the study. Hence, the better results for energy may be purely due to the selection of participants in this study.

Although all subscales and total NHP were worse for women, the difference was statistically significant only for mobility. To the best of our knowledge, no studies in the literature have found that older men have worse NHP results than older women (26,28,29).

As expected, pain, mobility, and energy were worse in advanced age. This study also showed that the presence of NCDs worsened pain and impaired mobility. Similarly, studies conducted in older adults have shown that the general health profile worsens with age, particularly in the mobility and pain subscales, and that NCDs in old age are detrimental to the health profile (26–28). Interestingly, pain, mobility, and energy were found to be worse among non-smokers. Smoking is also used as a socializing tool, and nicotine has a pain-relieving effect (30,31).

It has been observed that those who have not spent most of their lives in İstanbul are more socially isolated than those who have. Given that people, especially older adults, are happier and more self-confident in familiar environments, leaving both their homes and their hometowns may have made it difficult for those unfamiliar with İstanbul to adapt to the city and its environment (2,32,33).

In exploratory analyses, several HPLP-II subscales showed moderate associations with NHP domains, particularly those reflecting psychosocial aspects of lifestyle. SG, IR, and SM were related to better emotional responses, lower SI, and more favorable overall health profiles. These patterns are consistent with previous research showing that psychosocial well-being and social connectedness are associated with improved quality of life and self-rated health among older adults (34,35). These findings are in line with previous evidence showing that psychosocial lifestyle factors are closely linked to how older adults perceive their health.

Study Limitations

This study has several limitations. First, because it employs a cross-sectional design, it is not possible to determine causal relationships between sociodemographic characteristics, lifestyle behaviors, and health profiles. Second, the study was conducted in public nursing homes in İstanbul, and convenience sampling was used; therefore, the findings cannot be generalized to other institutions or to the full resident population of the participating nursing homes. Third, both HPLP-II and NHP are self-reported scales; during data collection, some participants had difficulty distinguishing past experiences from their current health status, which may have influenced the accuracy of responses. In addition, healthy lifestyle behaviors develop over a lifetime, yet information about participants' earlier habits was not collected; therefore, the extent to which past behaviors contributed to current health profiles remains unknown. Finally, institutional factors were not evaluated and may have contributed to variations in lifestyle behaviors.

Conclusion

Scores for Habits related to HR, PA, and sleep were notably lower than scores for subscales reflecting emotional and psychosocial domains, such as SG, SM, IR, energy, and ER. In addition, 30% of older adults in the sample continued to smoke.

These findings are consistent with Türkiye's Healthy Ageing Action Plans. Both the 2015–2020 and 2021–2026 programs identify low PA, limited HR, and challenges in chronic disease self-management as priority areas for institutional action. Based on these priorities, simple daily exercise routines, guided walking sessions, or chair-based activity groups could be incorporated into weekly schedules. Education on basic sleep hygiene, regular screening for sleep problems, and follow-up of residents with poor sleep scores may also support better outcomes. Short and practical sessions that increase awareness of medication use, chronic disease monitoring, and healthy N may help strengthen HR.

Spiritual well-being and social relationships were relatively strong in this sample; therefore, existing activities

in these areas can be maintained rather than expanded. Implementing such culturally appropriate and feasible programs may contribute to healthier daily behaviors among nursing home residents.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the Bezmialem Vakıf University Non-Invasive Research Ethics Committee (approval number: 15/286, dated: 30.07.2019).

Informed Consent: Informed consent was obtained from all participants prior to data collection.

Footnotes

Authorship Contributions

Concept: A.N.B.Y., B.Ö., Design: A.N.B.Y., B.Ö., Data Collection or Processing: A.N.B.Y., Analysis or Interpretation: A.N.B.Y., Literature Search: A.N.B.Y., Writing: A.N.B.Y., B.Ö.

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Using Scoring Systems to Predict Thoracic Trauma Mortality in Emergency Department Management

Acil Servis Yönetiminde Torasik Travma Mortalitesini Tahmin Etmek için Puanlama Sistemlerinin Kullanılması

Abidin Musa Kapcı[1], Mümin Murat Yazıcı[2], Gökhan Ersunan[2], Özlem Bilir[2]

[1]*Bursa Kestel State Hospital, Department of Emergency Medicine, Bursa, Türkiye*

[2]*Recep Tayyip Erdoğan University Training and Research Hospital, Department of Emergency Medicine, Rize, Türkiye*

ABSTRACT

Background: Thoracic trauma accounts for approximately one-third of trauma cases admitted to the hospital, and approximately 20–25% of trauma-related deaths can be attributed to this type of injury. Given the significant morbidity and mortality associated with thoracic trauma, this study investigates the predictive value of trauma scoring systems for complications and mortality in affected patients.

Materials and Methods: This was a single-center, retrospective study. Patients who presented to the emergency department of a tertiary care hospital in Türkiye between January 1, 2021 and December 31, 2022 with trauma were consulted by the thoracic surgery clinic, and those who did not meet the exclusion criteria were included in the study. The diagnostic value of trauma scoring systems for predicting complications and mortality associated with thoracic trauma has been evaluated.

Results: A total of 329 patients were enrolled: 226 males (68.7%) and 103 females (31.3%); median age was 59 years (interquartile range: 48–70). Compared with the non-complication group, patients with complications had significantly higher Abbreviated Injury Scale (AIS), American Association for the Surgery of Trauma (AAST) score, Rib Fracture Scoring System, Chest Trauma Score (CTS), and Rib Score values, and lower Revised Trauma Score (RTS) values (all $p < 0.001$). In the mortality analysis, decedents demonstrated significantly lower RTS and higher AIS and AAST scores (all $p < 0.001$).

Conclusion: Our findings suggest that the AIS and the RTS may be more appropriate for predicting mortality, whereas the CTS may be more suitable for predicting complications.

Keywords: Thoracic trauma, trauma scoring systems, emergency department, mortality

ÖZ

Amaç: Göğüs travması, hastaneye yatırılan travma vakalarının yaklaşık üçte birini oluşturur ve travma ile ilişkili ölümlerin yaklaşık %20–25'i bu tür yaralanmalara atfedilebilir. Göğüs travması ile ilişkili önemli morbidite ve mortalite göz önüne alındığında, bu çalışma göğüs travması olan hastalarda komplikasyonları ve mortaliteyi öngörmede travma skorlama sistemlerinin öngörü değerini araştırmayı amaçlamaktadır.

Gereç ve Yöntemler: Bu çalışma tek merkezli ve retrospektif bir çalışmadır. 1 Ocak 2021 ile 31 Aralık 2022 tarihleri arasında Türkiye'deki bir üçüncü basamak hastanenin acil servisine travma ile başvuran, daha sonra göğüs cerrahisi kliniğine sevk edilen ve dışlama kriterlerine uymayan hastalar çalışmaya dahil edilmiştir. Göğüs travmasında komplikasyonları ve mortaliteyi öngörmede travma skorlama sistemlerinin tanısal değeri hesaplanmıştır.

Bulgular: Toplam 329 hasta çalışmaya dahil edildi; bunların 226'sı erkek (%68,7) ve 103'ü kadın (%31,3) idi ve yaş ortalaması 59 idi (çeyrekler arası aralık: 48–70). Komplikasyon olmayan grupla karşılaştırıldığında, komplikasyonlu hastalar önemli ölçüde daha yüksek Kısaltılmış Yaralanma Ölçeği (AIS), Amerikan Travma Cerrahisi Derneği Puanlama Sistemi (AAST), Kaburga Kırığı Puanlama Sistemi, Göğüs Travması Puanlama Sistemi (CTS) ve Kaburga Puanı (RS) değerlerine ve daha düşük Revize Travma Puanı (RTS) değerlerine sahipti (tümü $p < 0,001$). Mortalite analizinde, ölen hastalar önemli ölçüde daha düşük RTS ve daha yüksek AIS ve AAST skorları gösterdi (tümü $p < 0,001$).

Address for Correspondence: Mümin Murat Yazıcı, Recep Tayyip Erdoğan University Training and Research Hospital, Department of Emergency Medicine, Rize, Türkiye

E-mail: mmuratyazici53@gmail.com **ORCID ID:** orcid.org/0000-0003-1957-7283

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ÖZ

Sonuç: Bulgularımız, AIS ve RTS'nin mortaliteyi tahmin etmek için daha uygun olabileceğini, CTS'nin ise komplikasyonları tahmin etmek için daha uygun olabileceğini göstermektedir.

Anahtar Kelimeler: Torasik travma, travma skorlarma sistemleri, acil servis, mortalite

Introduction

Trauma patients present with a wide range of symptoms in the emergency department (ED) (1). Trauma is the leading cause of death among young adults (2). Thoracic trauma accounts for one-third of hospitalized trauma cases, and approximately 20–25% of trauma-related deaths are due to thoracic injuries (3,4). Rib fractures are the most common thoracic injury; they typically result from blunt chest trauma and most often involve four to nine ribs. Other common injuries include pneumothorax, hemothorax, and lung contusion (5,6). Early detection of thoracic injuries, which can cause significant morbidity and death, is crucial in the ED.

Emergency management of trauma patients depends on a comprehensive assessment of their medical history, physical examination, vital signs, laboratory results, and imaging findings. Advanced Trauma Life Support guidelines serve as the foundation of this patient's care (7). Evaluating vital signs, certain laboratory parameters, scoring systems, and imaging results helps guide management and inform prognosis in trauma patients (8,9). Likewise, the presence of concomitant thoracic trauma in a multi-trauma patient is important for both ED management and follow-up and treatment strategies. Trauma patients should undergo rapid, thorough triage beginning at the initial assessment, and trauma scoring systems should be used to determine injury severity. Prompt and appropriate initial interventions can reduce mortality and morbidity (10,11).

Given the high morbidity and mortality rates associated with thoracic trauma, it is crucial to determine the severity of thoracic injuries in the ED. To this end, we aimed to evaluate the ability of the Revised Trauma Score (RTS), Abbreviated Injury Scale (AIS), American Association for the Surgery of Trauma (AAST), Rib Fracture Scoring System (RFS), Chest Trauma Score (CTS), and Rib Score (RS) to predict mortality in patients with thoracic trauma.

Materials and Methods

Study Design and Population

This study was single-center, cross-sectional, and retrospective. Approval was obtained from the Recep Tayyip Erdoğan University Non-Interventional Clinical Research Ethics Committee before data collection (decision number: 2023/177, dated: 03.08.2023).

Historically, morbidity and mortality rates associated with different thoracic trauma scores have been observed to range from 10 to 20 per cent (4,12). Similarly, different trauma scores have acceptable accuracy in predicting morbidity and mortality (area under the curve [AUC]: 0.600–0.900) (10,12,13). Based on these studies, we estimated that a sample size of 200–400 patients would be required to use thoracic trauma scores to predict morbidity and mortality, assuming an expected AUC of at least 0.60, an outcome prevalence of 10–20%, and 80% power. After estimating a 10% dropout rate, the final sample size was 223–445 participants.

Patients who presented with trauma to the ED of a tertiary care hospital in Türkiye between January 1, 2021, and December 31, 2022, were evaluated by the thoracic surgery clinic. Those who did not meet any exclusion criteria were included in the study.

Patients under the age of 18, patients aged 90 years and older (excluded because of high comorbidity), patients with chest trauma who did not undergo advanced imaging by computed tomography, patients with minor trauma who did not require consultation with a thoracic surgery clinic, and patients with terminal-stage cancer were excluded from the study.

The study population (n = 329) was selected based on the inclusion and exclusion criteria.

Study Protocol

The study population was defined after applying the inclusion and exclusion criteria.

Demographic data, anamnesis and background information, vital parameters at admission, trauma mechanisms, thoracic examination findings, additional trauma, rib fractures (presence, number, and locations), pneumothorax, hemothorax, pulmonary contusion, sternal fracture, scapular fracture, ED outcome, complications (pneumonia, pulmonary embolism, deep vein thrombosis, acute respiratory failure, tracheostomy, and atelectasis), and hospital outcome were analyzed. All patient data were obtained from the hospital information management system.

Furthermore, RTS, AIS, AAST, RFS, CTS, and RS for the patients included in the study were calculated and analyzed.

Endpoints

The primary endpoint of the study was the diagnostic value of thoracic scoring systems for predicting mortality. The

secondary endpoints were defined as the diagnostic values of thoracic scoring systems for predicting complications.

Statistical Analysis

All analyses were performed using Jamovi statistical software (The Jamovi Project [2021] Computer Software, version 1.6. Sidney, Australia). Categorical data were expressed as frequencies (n) and percentages. Normally distributed continuous variables were presented as mean and standard deviation and non-normally distributed continuous variables were presented as median and interquartile range (IQR). The normality of the distribution was evaluated using the Shapiro-Wilk test.

When comparing continuous variables, groups with a normal distribution were compared using the t-test, and those lacking a normal distribution were compared using the Mann-Whitney U test. The chi-square and Fisher's exact tests were used to compare the categorical variables between groups. A receiver operating characteristic (ROC) curve was created to determine the cut-off levels of RTS, AIS, AAST, RFS, CTS, and RS for predicting complications and mortality. In ROC analysis, the maximum value of Youden's index was used to select the cut-off value. Finally, sensitivity, specificity, likelihood ratios (+LR and -LR), and positive and negative predictive values were calculated for the RTS, AIS, AAST, RFS, CTS, and RS. Logistic regression was used for univariate analysis to estimate odds ratios (ORs) and p-values for associations with complications and mortality.

Results

A total of 329 patients were enrolled, comprising 226 males (68.7%) and 103 females (31.3%), with a median age of 59 years (IQR = 48–70). The most common comorbidities were hypertension (34.7%), diabetes mellitus (15.2%), and coronary artery disease (14.0%), whereas congestive heart failure (2.1%), chronic obstructive pulmonary disease (3.0%), atrial fibrillation (3.6%), and prior stroke (2.1%) were less prevalent. At presentation, median systolic and diastolic blood pressures were 120 mmHg (IQR = 120–130) and 80 mmHg (IQR =80–80), respectively; the median pulse rate was 77/min (IQR = 69–87), the respiratory rate was 15/min (IQR = 14–16), and the oxygen saturation (SO_2) was 97% (IQR = 96–98). Falls and roll-type injuries were the leading trauma mechanisms (66.6%), followed by in-vehicle traffic accidents (19.8%), non-vehicle traffic accidents (4.0%), and gunshot wounds (2.4%). Extra-thoracic injuries were most commonly localized to the head and neck (25.5%) and the extremities (30.0%), with smaller proportions affecting the abdomen (7.9%) and pelvis (4.2%); no cardiac injuries were reported. The median number of rib fractures was 3 (IQR = 0–15). Overall, 47 patients (14.3%) developed complications, and 12 (3.6%) died. There was no statistically significant difference in gender between participants who developed complications and those who did not; however, age differed significantly between the two groups (p = 0.109 for gender, p = 0.038 for age). Furthermore, there were no statistically significant differences in gender or age between the mortality and non-mortality groups (p = 0.265 for gender, p = 0.419 for age). The demographic data and other baseline characteristics of the patients are presented in Tables 1 and 2.

Trauma scores were analyzed: median RTS, 12 (IQR = 12–12); AIS, 3 (IQR = 2–5); AAST, 2 (IQR = 1–2); RFS, 5 (IQR = 3–7); CTS, 4 (IQR = 3–6); RS, 0 (IQR = 0–1). The median RTS, AIS, AAST, RFS, CTS, and RS values measured in the included groups showed a statistically significant difference between the complication and non-complication groups (p = 0.001 for RTS, p = 0.001 for AIS, p = 0.001 for AAST, p = 0.001 for RFS, p = 0.001 for CTS, and p = 0.001 for RS). The median RTS, AIS, and AAST values measured in the included groups differed significantly between the mortality and non-mortality groups (p = 0.001 for RTS, AIS, and AAST). The trauma scores and statistical analyses are presented in Table 3.

ROC analysis identified CTS (AUC: 0.702 ± 0.036; cut-off: 6) as the most accurate predictor of complications, followed closely by AIS (AUC: 0.694 ± 0.040; cut-off: 6) and RFS (AUC: 0.672 ± 0.044; cut-off: 8). AAST demonstrated the highest sensitivity (89.4%) but poor specificity (31.0%), whereas RS achieved the highest specificity (90.6%) but low sensitivity (21.2%). RTS, despite its widespread use, showed limited discriminatory power (AUC: 0.577 ± 0.049). For mortality prediction, AIS outperformed other scores with the highest AUC (0.774 ± 0.075; cut-off: 6) and a balanced sensitivity–specificity profile (66.7% and 79.5%, respectively). RTS ranked second (AUC: 0.742 ± 0.094; cut-off: 7), offering excellent specificity (97.8%) but moderate sensitivity (50.0%). AAST achieved 100% sensitivity but only 29.1% specificity. CTS, RFS, and RS demonstrated modest predictive value, with AUCs ranging from 0.527 to 0.604. ROC curve analyses for complications and mortality are presented in Tables 4 and 5 and Figures 1 and 2.

Of the 329 patients analyzed, 47 developed complications (14.3%) and 12 died (3.6%). All trauma scores were significant predictors of complications. Similarly, RTS, AIS, and AAST scores were statistically significant predictors of mortality. The AAST score was identified as the best score for predicting both complications and mortality (OR for complications: 2.304, 95% confidence interval [CI]: 1.524–3.483, p = 0.001; OR for mortality: 2.329, 95% CI: 1.160–4.677, p = 0.017). The summary of the logistic regression analysis is shown in Table 6.

Discussion

In the present study, we evaluated the prognostic utility of scoring systems in predicting complications and mortality among patients presenting to the ED with thoracic trauma. This study contributes to the literature by simultaneously evaluating multiple scoring systems and assessing their predictive value for both complications and mortality. Our findings suggest that the CTS provides superior predictive value for complications compared with other trauma scoring systems, while the AIS and RTS demonstrate greater suitability for predicting mortality. This observation is consistent with previous reports in the literature (13–15).

In the study by Harde et al. (16), conducted at a tertiary care trauma center in India, the CTS was evaluated for its ability to predict outcomes in patients with chest trauma. Patients with a CTS ⩾5 were found to have significantly higher rates of complications and mortality. ROC analysis demonstrated that CTS had acceptable accuracy in predicting mortality (AUC: 0.75). Consequently, a CTS ⩾5 was interpreted as an indicator of poor prognosis and may be utilized to identify patients who require early, intensive, and focused management (16). In the study by Elsaied Hussein et al. (17), patients with chest trauma were evaluated using the CTS. The CTS demonstrated a significant association with the need for mechanical ventilation, the development of pneumonia, intensive care unit stay, and mortality. ROC analysis showed that a CTS score ⩾6.5 predicted mortality with high sensitivity (100%) and acceptable specificity (62.2%), whereas a CTS score ⩾5.5 predicted pneumonia with 80% accuracy. Consequently, CTS was concluded to be a valuable prognostic tool to assess the risk of complications and mortality in patients with blunt chest trauma (17). In our

Table 1. The patients' demographic data and baseline characteristics (according to develop complications).

	Analysis of groups with and without complications			
Characteristics	**All patients (n = 329)**	**Complication group (n = 47)**	**Non-complication group (n = 282)**	**p-value**
Gender				
Male, n (%)	226 (68.7)	37 (78.7)	189 (67.0)	0.109
Female, n (%)	103 (31.3)	10 (21.3)	93 (33.0)	
Age (years), median (IQR)	59 (IQR: 48–70)	65 (IQR: 54–74)	58 (IQR: 47–68)	**0.038**
Comorbidities				
Hypertension, n (%)	114 (34.7)	23 (48.9)	91 (32.3)	**0.026**
Diabetes, n (%)	50 (15.2)	10 (21.3)	40 (14.2)	0.210
CAD, n (%)	46 (14.0)	9 (19.1)	37 (13.1)	0.270
CHF, n (%)	7 (2.1)	1 (2.1)	6 (2.1)	1.000
COPD, n (%)	10 (3.0)	3 (6.4)	7 (2.5)	0.159
Atrial fibrillation, n (%)	12 (3.6)	3 (6.4)	9 (3.2)	0.390
Stroke, n (%)	7 (2.1)	2 (4.3)	5 (1.8)	0.263
Vital signs				
SBP (mmHg), median (IQR)	120 (IQR: 120–130)	120 (IQR: 110–130)	120 (IQR: 120–130)	0.058
DBP (mmHg), median (IQR)	80 (IQR: 80–80)	80 (IQR: 70–80)	80 (IQR: 80–90)	**0.020**
Pulse (/min), median (IQR)	77 (IQR: 69–87)	80 (IQR: 74–95)	77 (IQR: 69–85)	**0.010**
RR (/min), median (IQR)	15 (IQR: 14–16)	16 (IQR: 14–18)	15 (IQR: 14–16)	**0.043**
SO_2 (%), median (IQR)	97 (IQR: 96–98)	96 (IQR: 94–98)	97 (IQR: 96–99)	**0.001**
Trauma Mechanisms				
In-vehicle traffic accident, n (%)	65 (19.8)	8 (17.9)	57 (20.2)	
Non-vehicle traffic accident, n (%)	13 (4.0)	2 (4.3)	11 (3.9)	**0.043**
Fall and roll, n (%)	219 (66.6)	33 (70.2)	210 (74.5)	
Gunshot wound, n (%)	8 (2.4)	4 (8.6)	4 (1.4)	
Presence of extra-thoracic trauma				
Head-neck, n (%)	84 (25.5)	19 (40.4)	65 (23.0)	**0.011**
Abdominal, n (%)	26 (7.9)	8 (17.0)	18 (6.4)	**0.012**
Pelvic, n (%)	14 (4.2)	4 (8.5)	10 (3.6)	0.124
Cardiac, n (%)	0 (0)	0 (0.0)	0 (0.0)	-
Extremity, n (%)	69 (30.0)	12 (25.5)	57 (20.2)	0.407
Number of hip fractures (number), median (IQR)	3 (IQR: 0–15)	4 (IQR: 3–8)	3 (IQR: 1–5)	**0.001**

CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; IQR, interquartile range (25p, 75p); RR, respiratory rate; SBP, systolic blood pressure.

study, the CTS demonstrated a sensitivity of 78.7% and a specificity of 56.0% at a cut-off value of ⩾ 6 for predicting complications in patients with thoracic trauma. Similarly, CTS showed a sensitivity of 75.0% and a specificity of 53.0% at the same cut-off value for predicting mortality. Based on our findings, CTS may be superior to other scoring systems in forecasting complications among thoracic trauma patients. The variability in reported cut-off values, sensitivities, and specificities in the literature may be attributed to differences in study populations, including sex distribution, comorbidities, and mechanisms of trauma.

In the study by Bayer et al. (18), greater severity of thoracic trauma was associated with a higher incidence of thoracic injuries and an increased need for prehospital intubation (58%), chest tube placement (22%), cardiopulmonary resuscitation (11%), massive transfusion (12%), and emergency surgery (17%). Patients with an AIS-thorax score ⩾4 required more complex early management and had higher mortality and complication rates (18). Similarly, in the study by Benhamed et al. (19), AIS ⩾3 was strongly associated with mortality. In another study by Besra et al. (20), the effectiveness of different trauma scoring systems in predicting mortality among patients with chest and abdominal trauma was evaluated. The authors concluded that, in particular, the RTS and several comprehensive trauma-scoring systems are reliable prognostic methods for chest and abdominal trauma (20). In our study, the AIS demonstrated a sensitivity of 66.7% and a specificity of 79.5% at a cut-off value of ⩾6 for predicting mortality in thoracic trauma patients. Similarly, the RTS showed a sensitivity of 50.0% and a specificity of 97.8% at a cut-off value of less than 7 for predicting mortality. Based on our findings, AIS and RTS may be superior to other scoring

Table 2. The patients' demographic data and baseline characteristics (according to mortality).

	Analysis of groups with and without mortality			
Characteristics	**All patients (n = 329)**	**Mortality group (n = 12)**	**Non-mortality group (n = 317)**	**p-value**
Gender				
Male, n (%)	226 (68.7)	10 (83.3)	216 (68.1)	0.265
Female, n (%)	103 (31.3)	2 (16.7)	101 (31.9)	
Age (years), median (IQR)	59 (IQR: 48–70)	68 (IQR: 39–76)	59 (IQR: 48–70)	0.419
Comorbidities				
Hypertension, n (%)	114 (34.7)	7 (58.3)	107 (33.8)	0.079
Diabetes, n (%)	50 (15.2)	3 (25.0)	47 (14.8)	0.403
CAD, n (%)	46 (14.0)	3 (25.0)	43 (13.6)	0.227
CHF, n (%)	7 (2.1)	1 (8.3)	6 (1.9)	0.231
COPD, n (%)	10 (3.0)	2 (16.7)	8 (2.5)	**0.047**
Atrial fibrillation, n (%)	12 (3.6)	1 (8.3)	11 (3.5)	0.365
Stroke, n (%)	7 (2.1)	0 (0.0)	7 (2.2)	1.000
Vital signs				
SBP (mmHg), median (IQR)	120 (IQR: 120–130)	93 (IQR: 80–120)	120 (IQR: 120-130)	**0.001**
DBP (mmHg), median (IQR)	80 (IQR: 80–80)	63 (IQR: 50–80)	80 (IQR: 80–80)	**0.001**
Pulse (/min), median (IQR)	77 (IQR: 69–87)	93 (IQR: 82–104)	77 (IQR: 60–85)	**0.019**
RR (/min), median (IQR)	15 (IQR: 14–16)	18 (IQR: 16–21)	15 (IQR: 14–16)	**0.013**
SO_2 (%), median (IQR)	97 (IQR: 96–98)	92 (IQR: 68–96)	97 (IQR: 96–99)	**0.001**
Trauma mechanisms				
In-vehicle traffic accident, n (%)	65 (19.8)	3 (25.0)	62 (19.6)	
Non-vehicle traffic accident, n (%)	13 (4.0)	1 (8.3)	12 (3.8)	**0.023**
Fall and roll, n (%)	219 (66.6)	6 (50.0)	213 (67.2)	
Gunshot wound, n (%)	8 (2.4)	3 (25.0)	5 (1.6)	
Presence of extra-thoracic trauma				
Head-neck, n (%)	84 (25.5)	5 (41.7)	79 (25.0)	0.192
Abdominal, n (%)	26 (7.9)	4 (33.4)	22 (6.9)	**0.010**
Pelvic, n (%)	14 (4.2)	2 (16.7)	12 (3.8)	0.087
Cardiac, n (%)	0 (0)	0 (0.0)	0 (0.0)	-
Extremity, n (%)	69 (30.0)	5 (41.7)	64 (20.2)	0.073
Number of hip fractures (number), median (IQR)	3 (IQR: 0–15)	4 (IQR: 2–4)	3 (IQR: 2–5)	0.998

CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; IQR, interquartile range (25p, 75p); RR, respiratory rate; SBP, systolic blood pressure.

systems in predicting mortality among thoracic trauma patients. Furthermore, our results suggest that general trauma scoring systems may outperform specific scoring systems in predicting mortality.

In our study, RFS demonstrated 50.0% sensitivity and 67.5% specificity in predicting mortality in patients with thoracic trauma at a cut-off value of ⩾8. Similarly, RS demonstrated a sensitivity of 50.0% and a specificity of 58.8% in predicting mortality in patients with ⩾2 cut-off values. However, RFS demonstrated a sensitivity of 59.6% and a specificity of 71.3% in predicting complications in patients with ⩾8 cut-off values in thoracic trauma. Similarly, RS demonstrated 21.2% sensitivity and 90.6% specificity in predicting complications at a cut-off value of ⩾2. Our

Table 3. Statistical analysis of trauma scores.

	Analysis of groups with and without complications			
Trauma scoring	**All patients (n= 329)**	**Complication group (n = 47)**	**Non-complication group (n = 282)**	**p-value**
RTS, median (IQR)	12 (12–12)	12 (12–12)	12 (12–12)	**0.001**
AIS, median (IQR)	3 (2–5)	5 (3–8)	3 (2–5)	**0.001**
AAST, median (IQR)	2 (1–2)	2 (2–3)	2 (1–2)	**0.001**
RFS, median (IQR)	5 (3–7)	7 (5–10)	5 (3–7)	**0.001**
CTS, median (IQR)	4 (3–6)	5 (5–7)	4 (3–6)	**0.001**
RS, median (IQR)	0 (0–1)	1 (0–2)	0 (0–1)	**0.001**
	Analysis of groups with and without mortality			
Trauma scoring	**All patients (n = 329)**	**Mortality group (n = 12)**	**Non-mortality group (317)**	**p-value**
RTS, median (IQR)	12 (12–12)	12 (7–12)	12 (12–12)	**0.001**
AIS, median (IQR)	3 (2–5)	7 (5–10)	3 (2–5)	**0.001**
AAST, median (IQR)	2 (1–2)	2 (2–3)	2 (1–2)	**0.001**
RFS, median (IQR)	5 (3–7)	7 (2–7)	5 (3–7)	0.752
CTS, median (IQR)	4 (3–6)	5 (5–5)	4 (3–6)	0.215
RS, median (IQR)	0 (0–1)	1 (0–1)	0 (0–1)	0.572

AAST, American Association for the Surgery of Trauma; AIS, Abbreviated Injury Scale; CTS, chest trauma scoring; IQR, interquartile range (25p, 75p); RFS, Rib Fracture Scoring System; RS, Rib Score; RTS, Revised Trauma Score.

Table 4. The cut-off values for complication of ROC curve analysis.

	RTS	**AIS**	**AAST**
AUC ± SD	0.577 ± 0.049	0.694 ± 0.040	0.648 ± 0.042
Cutoff	7	6	3
Sensitivity (%), (95% CI)	17.0 (7.6–30.8)	44.7 (30.2–59.9)	89.4 (76.9–96.4)
Specificity (%), (95% CI)	98.2 (95.9–99.4)	81.5 (76.5–85.9)	31.0 (25.6–36.7)
+LR, (95% CI)	9.6 (3.3–28.1)	2.83 (1.62–3.62)	1.29 (1.1–1.5)
-LR, (95% CI)	0.84 (0.7–1.0)	0.79 (0.5–0.9)	0.34 (0.2–0.8)
PPV (%), (95% CI)	61.5 (35.3–82.4)	28.8 (21.3–37.6)	17.8 (16.0–19.7)
NPV (%), (95% CI)	87.7 (86.2–89.0)	89.9 (87.2–92.0)	94.6 (88.2–97.6)
Accuracy (%), (95% CI)	86.6 (82.5–90.1)	76.2 (71.3–80.8)	39.3 (34.0–44.9)
	RFS	**CTS**	**RS**
AUC ± SD	0.672 ± 0.044	0.702 ± 0.036	0.630 ± 0.045
Cutoff	8	6	2
Sensitivity (%), (95% CI)	59.6 (44.3–73.6)	78.7 (64.3–89.3)	21.2 (14.7–29.0)
Specificity (%), (95% CI)	71.3 (65.6–76.5)	56.0 (50.0–61.9)	90.6 (85.6–94.4)
+LR, (95% CI)	2.07 (1.5–2.8)	1.79 (1.5–2.9)	2.26 (1.3–3.9)
-LR, (95% CI)	0.57 (0.4–0.8)	0.38 (0.2–0.7)	0.87 (0.8–1.0)
PPV (%), (95% CI)	25.7 (20.4–31.8)	23.0 (19.7–26.7)	61.7 (48.3–73.6)
NPV (%), (95% CI)	91.4 (88.1–93.8)	94.0 (90.0–96.5)	61.7 (59.4–64.0)
Accuracy (%), (95% CI)	69.6 (64.3–74.5)	59.2 (53.7–64.6)	61.7 (56.2–67.0)

AAST, American Association for the Surgery of Trauma; AIS, Abbreviated Injury Scale; AUC, area under the curve; CI, confidence interval; CTS, chest trauma scoring; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; RFS, Rib Fracture Scoring System; ROC, receiver operating curve; RS, Rib Score; RTS, Revised Trauma Score; SD, standard deviation.

Table 5. The cut-off values for mortality of ROC curve analysis.

	RTS	AIS	AAST
AUC ± SD	0.742 ± 0.094	0.774 ± 0.075	0.686 ± 0.065
Cutoff	7	6	3
Sensitivity (%), (95% CI)	50.0 (21.1–78.9)	66.7 (34.9–90.1)	100.0 (73.5–100.0)
Specificity (%), (95% CI)	97.8 (95.5–99.1)	79.5 (74.6–83.8)	29.1 (24.2–34.5)
+LR, (95% CI)	22.6 (9.0–57.1)	3.3 (2.1–5.1)	1.4 (1.3–1.5)
-LR, (95% CI)	0.51 (0.3–0.9)	0.42 (0.2–0.9)	0 (0.0–0.0)
PPV (%), (95% CI)	46.2 (25.4–68.4)	11.0 (7.2–16.3)	5.1 (4.7–5.4)
NPV (%), (95% CI)	98.1 (96.7–98.9)	98.4 (96.6–99.3)	100.0 (100.0-100.0)
Accuracy (%), (95% CI)	96.1 (93.3–97.8)	79.0 (74.2–83.3)	31.7 (26.7–37.0)
	RFS	**CTS**	**RS**
AUC ± SD	0.527 ± 0.094	0.604 ± 0.063	0.543 ± 0.085
Cutoff	8	6	2
Sensitivity (%), (95% CI)	50.0 (21.1–78.9)	75.0 (42.8–94.5)	50.0 (21.1–78.9)
Specificity (%), (95% CI)	67.5 (62.1–72.6)	52.0 (46.4–57.7)	58.7 (53.0–64.2)
+LR, (95% CI)	1.5 (0.9–2.8)	1.6 (1.1–2.2)	1.2 (0.7–2.2)
-LR, (95% CI)	0.7 (0.4–1.3)	0.5 (0.2–1.3)	0.9 (0.5–1.5)
PPV (%), (95% CI)	5.5 (3.1–9.5)	5.6 (4.0–7.7)	4.4 (2.5–7.6)
NPV (%), (95% CI)	97.3 (95.3–98.4)	98.2 (95.4–99.3)	96.9 (94.6–98.2)
Accuracy (%), (95% CI)	66.8 (61.5–71.9)	52.9 (47.3–58.4)	58.4 (52.8–63.2)

AAST, American Association for the Surgery of Trauma; AIS, Abbreviated Injury Scale; AUC, area under the curve; CI, confidence interval; CTS, chest trauma scoring; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; RFS, Rib Fracture Scoring System; ROC, receiver operating curve; RS, Rib Score; RTS, Revised Trauma Score; SD, standard deviation.

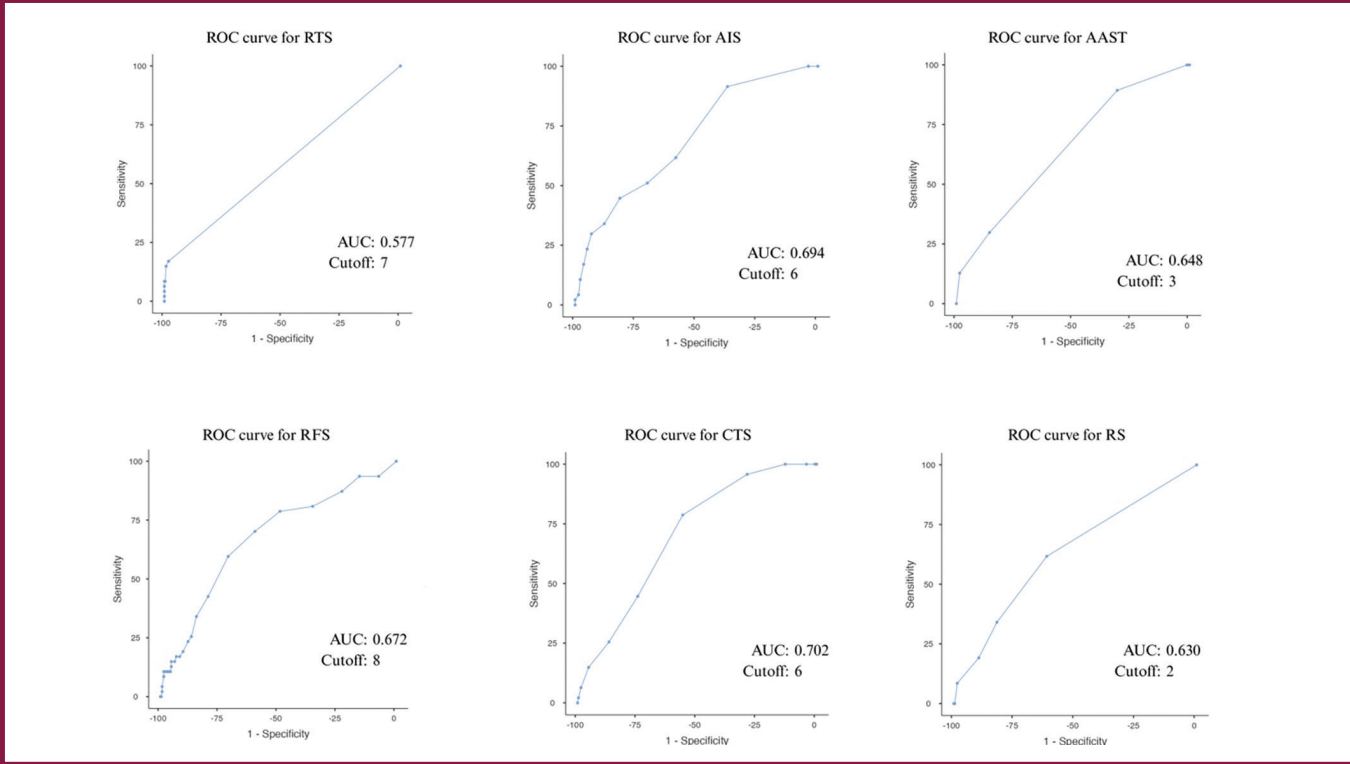


Figure 1. ROC analysis for complications.
AAST, American Association for the Surgery of Trauma; AIS, Abbreviated Injury Scale; AUC, area under the curve; CTS, chest trauma scoring; RFS, Rib Fracture Scoring System; ROC, receiver operating curve; RS, Rib Score; RTS, Revised Trauma Score.

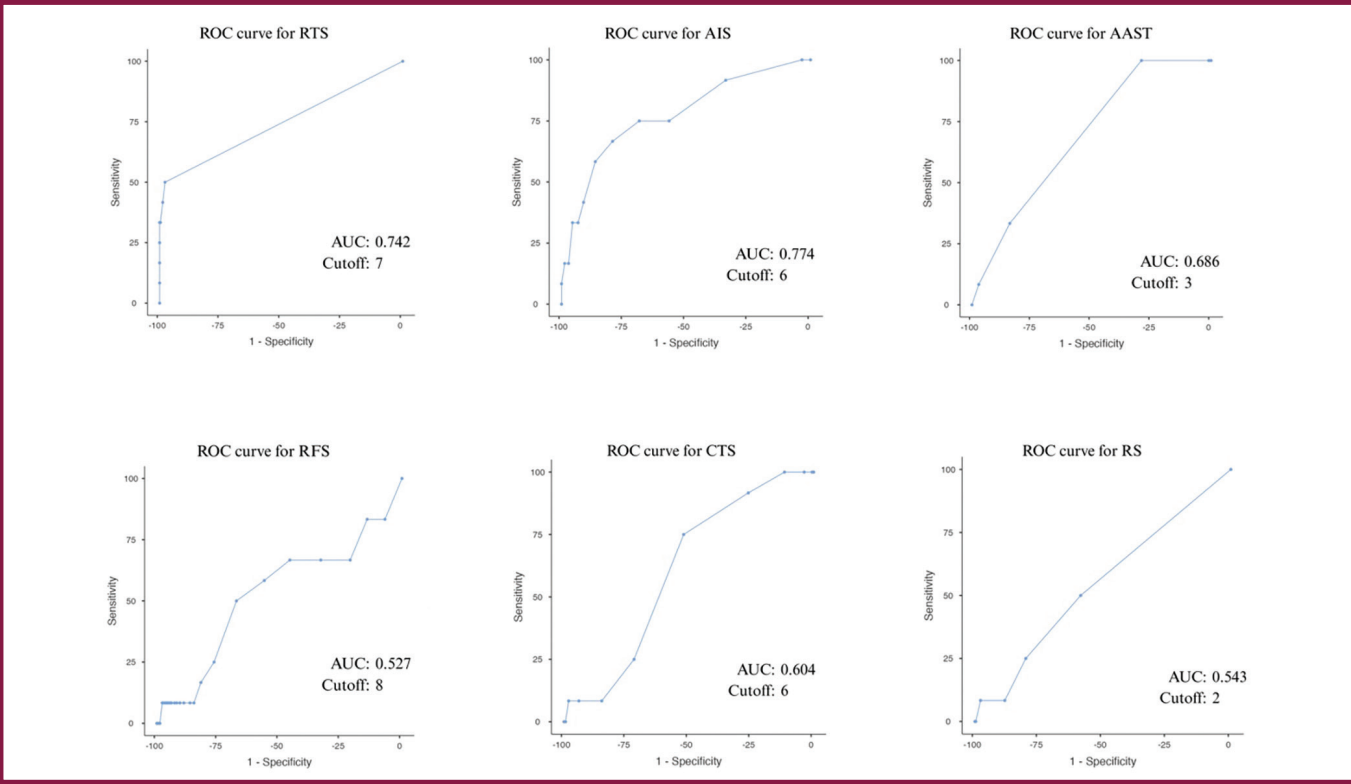


Figure 2. ROC analysis for mortality.
AAST, American Association for the Surgery of Trauma; AIS, Abbreviated Injury Scale; AUC, area under the curve; CTS, chest trauma scoring; RFS, Rib Fracture Scoring System; ROC, receiver operating curve; RS, Rib Score; RTS, Revised Trauma Score.

Table 6. Logistic regression analysis for trauma scores.

	Univariate analysis to predict complications			
Predictor	**OR**	**95% CI**		**p-value**
		Lower	**Upper**	
RTS, median (IQR)	0.371	0.186	0.739	**0.005**
AIS, median (IQR)	1.285	1.153	1.432	**0.001**
AAST, median (IQR)	2.304	1.524	3.483	**0.001**
RFS, median (IQR)	1.090	1.038	1.144	**0.001**
CTS, median (IQR)	1.487	1.241	1.781	**0.001**
RS, median (IQR)	1.450	1.139	1.846	**0.003**
	Univariate analysis to predict mortality			
Predictor	**OR**	**95% CI**		**p-value**
		Lower	**Upper**	
RTS, median (IQR)	0.276	0.129	0.590	**0.001**
AIS, median (IQR)	1.415	1.191	1.683	**0.001**
AAST, median (IQR)	2.329	1.160	4.677	**0.017**
RFS, median (IQR)	1.012	0.914	1.121	0.809
CTS, median (IQR)	1.194	0.874	1.632	0.263
RS, median (IQR)	1.124	0.700	1.805	0.628

AAST, American Association for the Surgery of Trauma; AIS, Abbreviated Injury Scale; CI, confidence interval; CTS, chest trauma scoring; OR, odds raito; RFS, Rib Fracture Scoring System; RS, Rib Score; RTS, Revised Trauma Score; SD, standard deviation.

findings support that the specific scoring systems RFS and RS are not sufficiently robust in predicting complications and mortality in thoracic trauma.

In our study, all trauma scores were statistically significant predictors of complications. Similarly, RTS, AIS, and AAST scores were statistically significant predictors of mortality. The lack of significance of thoracic-only trauma scores as predictors of mortality indicates that trauma scores incorporating a more general assessment would have better predictive value. This situation should be taken into account in mortality assessments.

In our study, gender was not associated with complications or mortality, whereas age was associated with complications. Among comorbid conditions, hypertension was found to be associated with complications, while chronic obstructive pulmonary disease was found to be associated with mortality. This finding is consistent with previous studies (21–24). In the literature, mortality rates associated with thoracic trauma have been reported to vary considerably (25,26). In our study, the mortality rate was 3.6%, and we believe that the differences observed in other studies may have also influenced the mortality outcomes in our cohort.

Study Limitations

This study has several limitations. In particular, it was conducted on a small scale, at a single center, and in a retrospective design. Due to its retrospective nature, patient data could not be comprehensively assessed, raising concerns about selection bias, as is common in other retrospective studies. However, the study population was designed to minimize this concern by excluding conditions that could potentially introduce bias. Another limitation is that, while some scoring systems (e.g., AIS) assess trauma comprehensively, others (e.g., RS) are restricted to thoracic evaluation. Regarding mortality, this makes holistic scoring systems more effective, whereas those focused only on the thorax seem less so. This situation could potentially bias approaches to comprehensive scoring systems when considering mortality. Finally, the sample size was calculated based on the morbidity and mortality rates in previous studies, whereas our study observed lower morbidity and mortality. This may have affected our results. Further studies with larger patient cohorts and the inclusion of multiple centers are necessary to validate our findings.

Conclusion

In thoracic trauma, general trauma scoring systems appear to be superior to specific trauma scoring systems in predicting both complications and mortality. Our findings suggest that the AIS and the RTS may be more appropriate for predicting mortality, whereas the CTS may be more suitable for predicting complications.

Ethics

Ethics Committee Approval: Approval was obtained from the Recep Tayyip Erdoğan University Non-Interventional Clinical Research Ethics Committee before data collection (decision number: 2023/177, dated: 03.08.2023).

Informed Consent: This study was single-center, cross-sectional, and retrospective.

Footnotes

Authorship Contributions

Concept: A.M.K., M.M.Y., G.E., Ö.B., Design: A.M.K., M.M.Y., Data Collection or Processing: A.M.K., Analysis or Interpretation: M.M.Y., G.E., Ö.B., Literature Search: A.M.K., Writing: A.M.K., M.M.Y.

Conflict of Interest: No conflict of interest was declared by the author(s).

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ORIGINAL ARTICLE

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Can Complete Blood Count Parameters Analyzed in Early Pregnancy Predict Threatened Abortion and Spontaneous Abortion: A Retrospective Study

Erken Gebelikte Analiz Edilen Tam Kan Sayımı Parametreleri Düşük Tehdidi ve Gebelik Kaybını Öngörebilir mi: Retrospektif Bir Çalışma

Orhan Ay[1], Fethiye Şahin[1], Ali Acar[1], Pelin Bahçeci[1], Deniz Taşkıran[2]

[1]Necmettin Erbakan University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Perinatology, Konya, Türkiye

[2]Giresun University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Perinatology, Giresun, Türkiye

ABSTRACT

Background: To evaluate whether first-trimester complete blood count (CBC) parameters predict the risk of spontaneous abortion and threatened abortion.

Materials and Methods: We retrospectively analyzed 90 pregnant women who presented to our hospital in 2024. Participants were equally divided into three groups: spontaneous abortion (n = 30), threatened abortion (n = 30), and healthy controls with no history of bleeding or miscarriage (n = 30). First-trimester CBC parameters assessed included hemoglobin, total white blood cell count (WBC), neutrophil count, and platelet count. Platelet indices (mean platelet volume [MPV], platelet distribution width [PDW]) and inflammatory ratios (MPV/platelet ratio, PDW/platelet ratio, platelet-to-lymphocyte ratio [PLR], neutrophil-to-lymphocyte ratio [NLR], and monocyte-to-lymphocyte ratio [MLR]) were evaluated for their ability to distinguish normal early pregnancies from pathological early pregnancies.

Results: Maternal age was comparable across groups; however, gravidity, parity, gestational age at assessment, and body mass index (BMI) differed significantly. In univariate analyses, WBC (p = 0.040), neutrophil count (p = 0.018), NLR (p = 0.045), and MLR (p = 0.032) differed among groups, whereas hemoglobin, platelet count, MPV, PDW, and PLR did not differ significantly (all p > 0.05). After Bonferroni correction, statistical significance remained for only three comparisons: gestational age (spontaneous abortion vs. controls, p = 0.001), neutrophil count (spontaneous abortion vs. threatened abortion, p = 0.015), and BMI (spontaneous abortion vs. controls, p = 0.008). In a multinomial logistic regression model adjusted for gestational age, BMI, and gravidity (reference: controls), neutrophil count (adjusted odds ratio [aOR] = 0.487; 95% confidence interval [CI]: 0.251–0.946; p = 0.034), NLR (aOR = 0.194; 95% CI: 0.041–0.919; p = 0.039), and MLR (aOR = 0.433; 95% CI 0.214–0.875; p = 0.020) were inversely associated with the odds of spontaneous abortion per 1 standard deviation. No independent associations were observed for the other parameters.

Conclusion: Neutrophil count and CBC-derived indices (NLR, MLR) may independently predict spontaneous abortion after adjustment; platelet-related parameters were not significant predictors. These markers should not be used in isolation but may complement clinical and sonographic assessments. Larger prospective studies are needed.

Keywords: Neutrophil-to-lymphocyte ratio, spontaneous abortion, threatened abortion

ÖZ

Amaç: Birinci trimester tam kan sayımı (TKS) parametrelerinin spontan abortus ve düşük tehdidi riskini öngörmedeki değerini araştırmak.

Gereç ve Yöntemler: 2024 yılında hastanemize başvuran 90 gebe kadın retrospektif olarak analiz edildi. Katılımcılar eşit üç gruba ayrıldı: spontan abortus (n = 30), düşük tehdidi (n = 30) ve kanama ya da düşük öyküsü olmayan sağlıklı gebeliğe sahip kontroller (n = 30). Hematolojik değerlendirme için birinci trimester kan sonuçları kullanıldı. Analize hemoglobin, toplam lökosit sayısı (WBC),

Address for Correspondence: Orhan Ay, Necmettin Erbakan University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Perinatology, Konya, Türkiye

E-mail: orhan.ay.5561@gmail.com **ORCID ID:** orcid.org/0000-0002-9685-5374

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ÖZ

nötrofil sayısı ve trombosit sayısı dâhil edildi. Ortalama trombosit hacmi (MPV) ve trombosit dağılım genişliği (PDW) gibi trombosit indeksleri ile birlikte MPV/trombosit, PDW/trombosit, trombosit/lenfosit oranı (TLO), nötrofil/lenfosit oranı (NLO) ve monosit/lenfosit oranı (MLO) gibi inflamatuvar oranlar incelendi. Bu değişkenler, normal ve patolojik erken gebelikleri ayırt etmedeki ilişkilerini değerlendirmek amacıyla analiz edildi.

Bulgular: Maternal yaş gruplar arasında benzerdi; ancak gravide, parite, değerlendirme sırasındaki gebelik haftası ve vücut kitle indeksi (VKİ) anlamlı farklıydı. Tek değişkenli analizlerde WBC (p = 0,040), nötrofil (p = 0,018), NLO (p = 0,045) ve MLO (p = 0,032) gruplar arasında farklılık gösterdi; hemoglobin, trombosit, MPV, PDW ve TLO anlamlı değildi (tümü p > 0,05). Bonferroni düzeltmesi sonrası yalnızca üç karşılaştırmada anlamlılık korundu: gebelik haftası (spontan abortus–kontrol, p = 0,001), nötrofil (spontan abortus–düşük tehdidi, p = 0,015) ve VKİ (spontan abortus–kontrol, p = 0,008). Gebelik haftası, VKİ ve gravideye göre düzeltilmiş multinomiyal lojistik regresyonda (referans: kontrol) nötrofil (düzeltilmiş olasılık oranı [aOR] = 0,487; %95 güven aralığı [GA]: 0,251–0,946; p = 0,034), NLO (aOR = 0,194; %95 GA 0,041–0,919; p = 0,039) ve MLO (aOR = 0,433; %95 GA 0,214–0,875; p = 0,020) her 1 standart sapma artış için spontan abortus olasılığıyla ters ilişkili bulundu; diğer parametrelerde bağımsız ilişki yoktu.

Sonuç: Nötrofil sayısı ve TKS-türevi indeksler (NLO, MLO), karıştırıcı değişkenler için düzeltme yapıldıktan sonra spontan abortusu öngörmede bağımsız bir değere sahip olabilirken, trombosit parametreleri ve diğer indeksler anlamlı bulunmadı. Bu bulgular, hematolojik belirteçlerin klinik karar vermede tek başına kullanılmaması, ancak klinik ve ultrasonografik değerlendirmeyi tamamlayıcı nitelikte olabileceğini düşündürmektedir. Daha büyük, prospektif çalışmalar gereklidir.

Anahtar Kelimeler: Nötrofil/lenfosit oranı, spontan abortus, düşük tehdidi

Introduction

First-tirmester vaginal bleeding occurs in about 7–27% of pregnancies, and roughly 12% of these cases end in miscarriage (1). During this period, the leading causes of vaginal bleeding include spontaneous abortion, threatened abortion, ectopic pregnancy, and cervical disorders. A thorough medical history, a detailed physical examination, ultrasound, and laboratory tests are used to determine the cause of bleeding during pregnancy.

Spontaneous abortion refers to a nonviable intrauterine pregnancy before 20 weeks of gestation. In clinical practice, it is also termed miscarriage or pregnancy loss. The pathophysiology of spontaneous abortion is complex. In addition, the identified risk factors include a previous miscarriage, young maternal age (<20 years), advanced maternal age (>35 years), uncontrolled diabetes, hypertension, thyroid disease, chromosomal abnormalities, smoking, alcohol use, obesity or extremely low body weight, uterine anomalies (uterine septum, uterus didelphys, etc.), and cervical insufficiency (2). Threatened abortion is a condition occurring before the 20th week of gestation, characterized by vaginal bleeding with a closed cervix. Under these conditions, approximately 15–20% of pregnancies may result in miscarriage (3).

The complete blood count (CBC), a simple and widely used test during pregnancy, has been evaluated in numerous studies for its role in predicting spontaneous or threatened abortion. These parameters included the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), investigated for their association with inflammation, platelet distribution width (PDW)/platelet ratio, mean platelet volume (MPV)/platelet ratio, MPV, and PDW, examined to determine their association with thrombosis. Other biochemical markers that have been examined in some studies to assess the risk of miscarriage (spontaneous abortion) include progesterone, serum beta-human chorionic gonadotropin alpha-fetoprotein, follistatin, and activin A. However reliable biochemical markers that can predict the risk of miscarriage and threatened abortion have not yet been established due to the complexity of the underlying mechanisms.

Pregnancy is inherently prothrombotic, and disturbances in placental vascular hemostasis are considered major contributors to spontaneous abortion. Decreased platelet function has been reported in the patient group (4). In this regard, many studies have examined parameters such as PDW, MPV, PDW/platelet count ratio, and MPV/platelet count ratio to demonstrate this prothrombotic state. Platelets also play an important role in inflammation by increasing the secretion of cytokines.

Bleeding in the first trimester is common; both threatened and spontaneous abortion are significant causes of early pregnancy loss. Currently, reliable biomarkers that can predict which cases of bleeding will result in miscarriage are limited. In recent years, inexpensive hematological indices have received increasing attention. For instance, meta-analyses have demonstrated that the neutrophil-to-lymphocyte ratio (NLR) is significantly higher in women with abortion than in healthy controls (5). Similarly, markers of platelet activation such as MPV and PDW have been associated with spontaneous abortion in systematic reviews (6). However, the evidence is inconsistent because other studies have demonstrated no significant difference

in platelet indices among women with recurrent pregnancy loss (7).

We set out to evaluate the roles of PDW, MPV, PDW/platelet ratio, MPV/platelet ratio, platelet-to-lymphocyte ratio (PLR), NLR, and monocyte-to-lymphocyte ratio (MLR) as predictors of the risk of spontaneous and threatened abortion, and of selected inflammatory and thrombotic markers among CBC indices.

Materials and Methods

This retrospective analysis included 90 pregnant women admitted to our hospital between January and October 2024. Participants were divided into three equal groups of 30 each: women with threatened abortion, women who experienced spontaneous abortion, and healthy controls without vaginal bleeding. Eligible gestational ages ranged from 6 to 14 weeks. The threatened-abortion group included patients with vaginal bleeding, an intact cervical os, and an ongoing intrauterine pregnancy. The spontaneous abortion group consisted of women diagnosed with pregnancy loss before 14 weeks' gestation. Controls were randomly chosen from women attending the same clinic period with viable first-trimester pregnancies and no bleeding complaints.

Clinical and laboratory data were extracted from archived files and electronic medical records. Demographic variables included maternal age, gravidity, parity, gestational week, and body mass index (BMI). Hematological parameters include hemoglobin, white blood cell (WBC) count, neutrophil, lymphocyte, monocyte, and platelet counts, MPV, and PDW.

Women with systemic conditions likely to influence hematologic indices, including hematologic disorders, multiple pregnancy, smoking, diabetes, chronic hypertension, thyroid dysfunction, autoimmune diseases, or acute or chronic infection were excluded from the study. Ethical approval was obtained from the Non-Interventional Research Ethics Committee of Necmettin Erbakan University (decision number: 2024/5333, dated: 15.11.2024), and the study complied with the principles of the Declaration of Helsinki.

Statistical Analysis

Data were analyzed using version 22.0 of IBM SPSS Statistics. The normality of continuous variables was first examined using the Shapiro–Wilk test, and the homogeneity of variances was evaluated using Levene's test. Continuous variables that had a normal distribution and equal variances were reported as mean ± standard deviation (SD) and compared between groups using one-way analysis of variance (ANOVA). When the assumptions of normality or homogeneity of variances were not met, data were reported as medians and analyzed using the Kruskal–Wallis test. When overall tests were significant, post hoc pairwise comparisons were conducted using an independent-samples t-test or a Mann–Whitney U test, with the Bonferroni procedure applied to adjust for multiple comparisons.

Effect sizes were also reported to accompany p-values and were expressed as eta squared (η^2) for ANOVA and and ε^2 for Kruskal–Wallis test. Multinomial logistic regression analyses were used to further establish independent associations between hematological measurements and study outcomes. Models were adjusted for potential confounders (gestational age, BMI, and gravidity), and the control group was used as a reference category. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were provided. A two-sided p-value <0.05 was considered statistically significant.

Power Analysis

Because this was a retrospective study, we included all women who met the inclusion criteria during the study period (n = 90; 30 per group). A post-hoc sensitivity analysis using G*Power (v3.1, one-way ANOVA, $\alpha = 0.05$) indicated approximately 80% power to detect a medium effect size (Cohen's f ≈ 0.30) and more than 95% power to detect a large effect size (Cohen's f ≈ 0.40). Accordingly, the study was adequately powered for moderate-to-large effects but may be underpowered for small effects.

Results

A total of 90 women were evaluated: 30 with spontaneous abortion, 30 with threatened abortion, and 30 healthy controls.

Demographic Characteristics (Table 1)

There was no significant difference in maternal age among the groups (p = 0.730). In contrast, gravidity (p = 0.007), parity (p = 0.028), BMI (p = 0.006), and gestational age at evaluation (p = 0.015) differed significantly across groups. Overall, the control group was assessed at a more advanced gestational age and had a lower BMI than the spontaneous abortion group.

Hematological Parameters (Table 2)

As shown in Table 2, 90 women were evaluated (spontaneous abortion, n = 30; threatened abortion, n = 30; controls, n = 30). WBC levels differed significantly among the groups (medians [interquartile range]: 7.82 [7.05–10.00], 9.77 [8.84–10.39], and 9.65 [7.06–11.56], respectively; p = 0.040; η^2/ε^2 = 0.05). Neutrophil counts also differed significantly across groups (5.25 [4.13–6.62], 6.75 [6.05–7.63], and 6.87 [4.79–8.57], respectively; p = 0.018; η^2/ε^2 =

0.07). Among inflammatory indices, both NLR (2.55 [1.85–3.35], 3.02 [2.41–4.00], and 3.27 [2.44–4.68], respectively; p=0.045, η^2/ε^2=0.05) and MLR (0.24 [0.21–0.32], 0.28 [0.24–0.34], and 0.29 [0.24–0.40], respectively; p=0.032, η^2/ε^2=0.06) differed significantly among groups. In contrast, no significant between-group differences were observed for hemoglobin (p = 0.108), platelet count (p = 0.778), MPV (p = 0.542), PDW (p = 0.574), PLR (p = 0.904), or the MPV/platelet (p = 0.965) and PDW/platelet (p = 0.997) ratios (all p > 0.05). Overall, the observed significant differences were associated with small effect sizes ($\eta^2/\varepsilon^2 \approx 0.05–0.07$).

PostHoc Comparisons (Supplementary Table 1)

According to Bonferroni-adjusted analyses using a significance threshold of p < 0.017, only three comparisons reached statistical significance. Gestational age differed significantly between the spontaneous abortion and control groups (p = 0.001), while neutrophil counts differed significantly between the spontaneous abortion and threatened abortion groups (p = 0.015). In addition, BMI differed significantly between the spontaneous abortion and control groups (p = 0.008). In contrast, the initially observed differences in gravidity (p = 0.027, p = 0.019), WBC count (p = 0.021), and MLR (p = 0.042) did not remain statistically significant after Bonferroni correction.

Multinomial Logistic Regression (Table 3).

To minimize multicollinearity between leukocyte subtype counts and derived ratios (e.g., NLR and MLR), we fitted separate adjusted multinomial logistic regression models for each CBC-related marker, expressed per 1-SD increase. Models were adjusted for potential confounders (gestational age, BMI, and gravidity), and the control group was used as a reference category. In these models, no marker was significantly associated with threatened abortion compared with controls (all p > 0.05). Compared with controls, neutrophil count (aOR = 0.487, 95% CI 0.251–0.946; p = 0.034), NLR (aOR = 0.194, 95% CI 0.041–0.919;

Table 1. Demographic characteristics across groups.

Variable	Spontaneous abortion (n = 30)	Threatened abortion (n = 30)	Control (n = 30)	p-value	Effect size (η^2/ε^2)
Age (year)	29.60 ± 5.39	28.50 ± 5.26	29.07 ± 5.43	0.730[a]	0.01
Gravidity	2.00 (2.00–3.00)	1.50 (1.00–2.00)	3.00 (1.25–4.00)	**0.007**[b]	0.09
Parity	1.00 (0.00–2.00)	0.00 (0.00–1.00)	1.00 (0.00–2.00)	**0.028**[b]	0.06
BMI (kg/m^2)	29.74 (27.01–34.30)	28.19 (25.47–31.45)	24.79 (23.23–29.83)	**0.006**[b]	0.10
Gestational age (week)	10.00 (8.25–10.00)	9.00 (7.00–13.00)	12.00 (10.25–13.00)	**0.015**[b]	0.07

Reporting rule: mean ± SD if normality and homoscedasticity were satisfied; otherwise median (IQR). Test selection based on Shapiro–Wilk and Levene's tests. Effect sizes are η^2 (ANOVA) or ε^2 (Kruskal–Wallis). [a]ANOVA test, [b]Kruskal-Wallis test, p < 0.05 was considered statistically significant. ANOVA, analysis of variance; BMI, body mass index; IQR, interquartile range; SD, standard deviation.

Table 2. CBC parameters across groups.

Variable	Spontaneous abortion (n = 30)	Threatened abortion (n = 30)	Control (n = 30)	p-value	Effect size (η^2/ε^2)
Hemoglobin	13.20 (12.30–13.57)	12.80 (11.80–13.57)	11.90 (11.27–13.40)	0.108[b]	0.03
Platelets	277.50 (228.50–331.25)	273.00 (238.25–314.50)	263.00 (227.25–290.75)	0.778[b]	0.00
WBC	7.82 (7.05–10.00)	9.77 (8.84–10.39)	9.65 (7.06–11.56)	**0.040**[b]	0.05
Neutrophil	5.25 (4.13–6.62)	6.75 (6.05–7.63)	6.87 (4.79–8.57)	**0.018**[b]	0.07
MPV	10.48 ± 0.89	10.36 ± 0.84	10.25 ± 0.71	0.542[a]	0.01
PDW	11.80 (10.83–13.38)	11.65 (10.50–13.47)	11.55 (10.80–12.57)	0.574[b]	0.00
PLR	121.75 (94.66–162.31)	125.84 (105.34–144.69)	131.91 (100.36–167.01)	0.904[b]	0.00
NLR	2.55 (1.85–3.35)	3.02 (2.41–4.00)	3.27 (2.44–4.68)	**0.045**[b]	0.05
MLR	0.24 (0.21–0.32)	0.28 (0.24–0.34)	0.29 (0.24–0.40)	**0.032**[b]	0.06
MPV/platelet	0.04 (0.03–0.05)	0.04 (0.03–0.05)	0.04 (0.03–0.05)	0.965[b]	0.00
PDW/platelet	0.04 (0.03–0.05)	0.04 (0.04–0.06)	0.05 (0.04–0.05)	0.997[b]	0.00

[a]ANOVA test, [b]Kruskal-Wallis test, p < 0.05 was considered statistically significant. Negative ε^2 values (which may occur due to sampling variability) were truncated to 0.00 for reporting. ANOVA, analysis of variance; CBC, complete blood count; MLR, monocyte-to-lymphocyte ratio; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PDW, platelet distribution width; PLR, platelet-to-lymphocyte ratio; WBC, white blood cell count.

Table 3. Adjusted multinomial logistic regression results for CBC-related markers across groups (reference: control).

Marker (per 1 SD increase)	Threatened abortion vs. control adjusted OR (95% CI)	p-value	Spontaneous abortion vs. control adjusted OR (95% CI)	p-value
Hemoglobin	1.267 (0.737–2.179)	0.393	1.592 (0.882–2.875)	0.123
Platelets	0.876 (0.511–1.501)	0.630	0.871 (0.470–1.617)	0.662
WBC	1.118 (0.631–1.980)	0.702	0.617 (0.334–1.142)	0.125
Neutrophil	1.020 (0.567–1.835)	0.948	**0.487 (0.251–0.946)**	**0.034**
MPV	1.076 (0.600–1.929)	0.807	1.221 (0.680–2.192)	0.504
PDW	1.139 (0.620–2.096)	0.674	1.345 (0.731–2.473)	0.341
PLR	0.956 (0.580–1.574)	0.859	0.894 (0.484–1.650)	0.719
NLR	1.155 (0.547–2.438)	0.706	**0.194 (0.041–0.919)**	**0.039**
MLR	0.924 (0.531–1.607)	0.780	**0.433 (0.214–0.875)**	**0.020**

Each marker was evaluated in a separate adjusted multinomial logistic regression model (per 1-SD increase) to avoid multicollinearity among mathematically related predictors (e.g., leukocyte subtype counts and derived ratios). Models were adjusted for gestational age, BMI, and gravidity. BMI, body mass index; CI, confidence interval; MLR, monocyte-to-lymphocyte ratio; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PDW, platelet distribution width; PLR, platelet-to-lymphocyte ratio; SD, standard deviation; WBC, white blood cell count.

p = 0.039), and MLR (aOR = 0.433, 95% CI 0.214–0.875; p = 0.020) were inversely associated with spontaneous abortion.

Discussion

Based on the assumption that prothrombotic events may affect the hemostatic balance in placental vessels and that chronic inflammation may cause spontaneous and threatened abortion, we evaluated various hematologic parameters in our study. PDW, MPV, PDW/platelet ratio, MPV/platelet ratio, PLR, NLR, and MLR were examined in this context.

Many studies have shown that threatened miscarriage is associated with an increased risk of complications later in pregnancy (8). These complications can be avoided if the cause of threatened miscarriage is elucidated. Chronic decidual inflammation with hemorrhage has been proposed in the pathophysiology of threatened abortion (8). Therefore, we analyzed the levels of the inflammatory markers NLR, PLR, and MLR.

Inconsistencies exist among studies examining NLR and PLR values in patients with spontaneous abortion and in those with threatened abortion. In a study of 300 patients that compared threatened abortion, spontaneous abortion, and healthy pregnancies, NLR did not differ between groups, whereas PLR was higher in the threatened abortion and spontaneous abortion groups (9). In another study of 285 patients with spontaneous abortion and healthy pregnant women as the control group, no difference was found between NLR and PLR (10).

Recent evidence from systematic reviews further contextualizes our findings. A 2024 systematic review and meta-analysis evaluating NLR and PLR across early pregnancy loss phenotypes (including threatened abortion, missed abortion, and RPL) reported that NLR was often higher in early pregnancy loss, whereas PLR did not show a consistent difference, and rated the certainty of evidence as moderate while noting substantial between-study heterogeneity (e.g., variations in definitions, timing of sampling, and populations) (11). In our cohort, NLR (and MLR) varied across groups; however, the direction of association for spontaneous abortion differed from some reports, with lower NLR in spontaneous abortion compared with controls and an inverse association in adjusted analyses. These discrepancies may reflect differences in study populations, gestational age at sampling, and measurement timing.

More recently, additional meta-analyses have suggested that NLR may be higher in some early pregnancy loss phenotypes, while noting heterogeneity and the influence of study design, geographic region, and cut-off selection (5). Conversely, a systematic review and meta-analysis of PLR concluded that PLR does not appear to have reliable predictive value for early miscarriage (12). Taken together, these data suggest that inflammatory ratios, particularly NLR, may reflect a systemic inflammatory milieu associated with early pregnancy loss, but their direction and discriminative performance are likely context-dependent and sensitive to methodological differences.

A notable finding of our study was an inverse association between neutrophil count and spontaneous abortion in adjusted models (per 1-SD increase in neutrophil count). Although inflammation plays an important role in the pathophysiology of early pregnancy loss, peripheral neutrophil levels can be influenced by several factors, including gestational age–related physiological changes, hemodilution, stress response, and the timing of blood sampling relative to symptom onset. In addition,

assessment of the control group at a more advanced gestational age and differences in BMI across groups may have affected baseline leukocyte profiles and, consequently, the direction of the association. In this context, the similarly inverse associations observed for NLR and MLR suggest that CBC-derived indices may reflect context-dependent inflammatory dynamics rather than a uniform inflammatory signature. Therefore, these parameters should not be used in isolation for clinical decision-making; rather, they should be interpreted as supportive markers alongside clinical assessment and ultrasound findings.

In addition to their well-established role in blood clotting, platelets contribute significantly to angiogenesis and cellular proliferation. They release several growth factors, including vascular endothelial growth factor, epidermal growth factor, and basic fibroblast growth factor, which are essential for tissue development. Research has shown that the levels of these molecules are reduced in women who experience pregnancy loss. This reduction suggests that compromised platelet function may hinder the development of decidual blood vessels, interfere with the formation of the uteroplacental unit, and impair trophoblast differentiation. Such disruptions in early placental development can increase the likelihood of miscarriages. Therefore, diminished platelet functionality during pregnancy may serve as a biomarker for miscarriage or threatened miscarriage (4). The key indicators of platelet activity include MPV, PDW, and platelet count.

An increased MPV indicates platelet activation and growth. In addition, MPV is increased in conditions such as myocardial infarction and venous thromboembolism (13). In addition, from an obstetric perspective, MPV has been found to be associated with recurrent pregnancy loss and spontaneous abortion (14–16). For example, another study of 200 patients found no difference in MPV and platelet values between the spontaneous abortion group and the control group (17).

The MPV/platelet ratio has been associated with thrombosis and inflammation in previous studies (18). However, our study found no relationship between the MPV/platelet ratio and the prediction of miscarriage risk. We assessed that this difference was due to a variety of factors predisposing to miscarriage.

The PDW value provides information on the variability in platelet volume. Increased PDW may be an indicator of abnormal thrombus formation. In our study, we did not observe a significant difference in PDW values between the groups. Supporting this, another study found no difference in PDW values between the threatened abortion and control groups (15). In another study of 300 patients, the PDW/platelet and MPV/platelet ratios did not differ between the spontaneous abortion and threatened abortion groups (19).

Our analysis confirms partial alignment with recent literature. While many univariate comparisons in our study did not reach statistical significance, multinomial logistic regression revealed that neutrophil count, NLR, and MLR remained independent predictors after adjustment for gestational age, BMI, and gravidity. Although several meta-analyses report higher NLR in early pregnancy loss compared with controls (5), our adjusted analyses suggested an inverse association with spontaneous abortion, highlighting that the direction of CBC-derived inflammatory indices may be context-dependent. Conversely, some studies found no significant differences in platelet parameters (MPV, PDW) between patients with recurrent pregnancy loss and controls, suggesting that these indices may have limited predictive value or that their effects are context-dependent (7).

Our findings similarly show limited utility of platelet-derived parameters when considered alongside inflammatory markers. The discrepancy between univariate findings and regression-based outcomes underscores the role of confounding variables. Some differences that seem modest or non-significant on their own become meaningful once gestational age, BMI, or gravidity are controlled for. This implies that hematological indices like NLR and MLR may be masked by clinical variation unless analyzed in multivariable frameworks. Other parameters did not demonstrate significant predictive value, underscoring the need for larger prospective studies to validate these findings and to clarify the clinical utility of hematological indices for predicting early pregnancy outcomes.

Although the retrospective nature of our study was a limitation, a strength of our study was that PDW, MPV, PDW/platelet ratio, MPV/platelet ratio, NLR, PLR, and CBC parameters were evaluated simultaneously. However, because CBC parameters were based on a single measurement obtained in early pregnancy, the timing of sampling relative to symptom onset and physiological gestational age–related hematologic changes may have introduced variability into the results. Moreover, due to the etiologic heterogeneity of early pregnancy loss (e.g., chromosomal or pathological causes) and the lack of consistent availability of certain ultrasound markers (e.g., subchorionic hematoma characteristics), stratified analyses were not feasible. Additionally, gestational age and BMI differed across groups, and these variables are potential confounders that may influence hematological indices. Although statistical adjustments were applied, these differences may still affect the results. Moreover, the balanced three-arm design (n=30 per group) provided sufficient power to detect moderate-to-large effects. However, the total sample size (n = 90) may be insufficient to reliably detect small effects. Therefore, non-

significant findings should not be interpreted as evidence of no effect. Larger, prospective studies are warranted.

Conclusion

In this study, we evaluated a wide spectrum of CBC parameters and their derivatives in women with spontaneous abortion, threatened abortion, and healthy pregnancies during the first trimester. Although most indices did not show significant differences across groups, neutrophil count, NLR, and MLR retained independent predictive value for spontaneous abortion after adjustment for gestational age, BMI, and gravidity. These results emphasize that CBC-derived indices cannot serve as standalone diagnostic tools but may provide additional support when interpreted alongside ultrasound findings and clinical assessment.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Non-Interventional Research Ethics Committee of Necmettin Erbakan University (decision number: 2024/5333, dated: 15.11.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: O.A., F.Ş., Design: O.A., A.A., P.B., Data Collection or Processing: F.Ş., P.B., Analysis or Interpretation: O.A., D.T., Literature Search: O.A., Writing: O.A., F.Ş., D.T.

Conflict of Interest: No conflict of interest was declared by the author(s).

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Supplementary Table 1. Pairwise post-hoc comparisons (Bonferroni-adjusted).

Variable	Pairwise comparison	Bonferroni p
Gravidity	Spontaneous abortion vs. threatened abortion	0.027
Gravidity	Spontaneous abortion vs. control	1.000
Gravidity	Threatened abortion vs. control	0.019
Parity	Spontaneous abortion vs. threatened abortion	0.058
Parity	Spontaneous abortion vs. control	1.000
Parity	Threatened abortion vs. control	0.057
BMI	Spontaneous abortion vs. threatened abortion	0.676
BMI	Spontaneous abortion vs. control	**0.008**
BMI	Threatened abortion vs. control	0.078
Gestational age (week)	Spontaneous abortion vs. threatened abortion	1.000
Gestational age (week)	Spontaneous abortion vs. control	**0.001**
Gestational age (week)	Threatened abortion vs. control	0.448
WBC	Spontaneous abortion vs. threatened abortion	0.021
WBC	Spontaneous abortion vs. control	0.474
WBC	Threatened abortion vs. control	1.000
Neutrophil	Spontaneous abortion vs. threatened abortion	**0.015**
Neutrophil	Spontaneous abortion vs. control	0.126
Neutrophil	Threatened abortion vs. control	1.000
NLR	Spontaneous abortion vs. threatened abortion	0.086
NLR	Spontaneous abortion vs. control	0.117
NLR	Threatened abortion vs. control	1.000
MLR	Spontaneous abortion vs. threatened abortion	0.177
MLR	Spontaneous abortion vs. control	0.042
MLR	Threatened abortion vs. control	1.000

Post-hoc pairwise tests (t-test or Mann–Whitney with Bonferroni correction) were performed when the overall tests were significant. $p < 0.017$ was considered statistically significant. Power context: With total n = 90 (n = 30/group), achieved power is ~80% for medium effects (Cohen's $f \approx 0.30$; $\eta^2 \approx 0.08$) and >95% for large effects ($f \approx 0.40$) at $\alpha = 0.05$.
BMI, body mass index; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell count.

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Maternal Psychological Responses to Retinopathy of Prematurity Diagnosis and Treatment: Anxiety, Rumination, and Resilience–A Cross-Sectional Study

Prematüre Retinopatisi Tanısı ve Tedavisine Annelerin Psikolojik Tepkileri: Kaygı, Ruminasyon ve Dayanıklılığın İncelenmesi–Kesitsel Araştırma

Duygu Kınay Ermiş[1], Cengiz Gül[2]

[1]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Department of Child and Adolescent Psychiatry, İstanbul, Türkiye

[2]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Department of Ophthalmology, İstanbul, Türkiye

ABSTRACT

Background: This study investigated the psychological impact of retinopathy of prematurity (ROP) diagnosis and treatment on mothers, focusing on anxiety, intolerance of uncertainty, rumination, resilience, and parenting self-efficacy.

Materials and Methods: This cross-sectional study included 267 mothers of preterm infants who underwent routine ROP screening. Participants were categorized into three groups: mothers of infants with ROP not requiring treatment (n = 93), mothers of infants with ROP requiring treatment (n = 47), and mothers of infants without ROP (n = 127). Validated scales, including the State–Trait Anxiety Inventory, Edinburgh Postnatal Depression Scale, Intolerance of Uncertainty Scale, Connor–Davidson Resilience Scale, and Perceived Maternal Parenting Self-Efficacy Scale, were used for assessment. Statistical analyses included analysis of variance, Mann–Whitney U tests, and correlation analyses.

Results: Mothers in the ROP–no treatment and ROP–treated groups exhibited significantly higher levels of state anxiety ($p < 0.001$) and negative rumination ($p = 0.007$) than those in the no ROP group. Anxiety levels were highest in the ROP–no treatment group, whereas mothers in the ROP–treated group demonstrated significantly greater psychological resilience ($p = 0.044$). No significant group differences were observed in depressive symptoms or intolerance of uncertainty. Higher psychological resilience was significantly associated with lower levels of anxiety ($p < 0.001$) and rumination ($p < 0.05$).

Conclusion: ROP diagnosis and treatment have significant effects on maternal anxiety and resilience. Structured psychosocial interventions such as resilience training and cognitive reframing may alleviate maternal distress. These findings emphasize the need for integrated psychological support in the care of preterm infants with ROP.

Keywords: Retinopathy of prematurity, maternal anxiety, psychological resilience, rumination, parenting self-efficacy

ÖZ

Amaç: Bu çalışma, prematüre bebeklerin annelerinde retinopati prematürelik (ROP) tanı ve tedavi sürecinin psikolojik etkilerini; anksiyete, belirsizliğe tahammülsüzlük, ruminasyon, psikolojik dayanıklılık ve ebeveynlik öz-yeterliği odağında incelemeyi amaçlamıştır.

Gereç ve Yöntemler: Bu kesitsel çalışmaya, rutin ROP taramasından geçen 267 prematüre bebeğin annesi dahil edilmiştir. Katılımcılar üç gruba ayrılmıştır: Tedavi gerektirmeyen ROP tanılı bebeklerin anneleri (n = 93), tedavi gerektiren ROP tanılı bebeklerin anneleri (n = 47) ve ROP tanısı olmayan bebeklerin anneleri (n = 127). Değerlendirmede Durumluk-Sürekli Kaygı Envanteri, Edinburgh Doğum Sonrası Depresyon Ölçeği, Belirsizliğe Tahammülsüzlük Ölçeği-12, Connor–Davidson Psikolojik Dayanıklılık Ölçeği ve Algılanan Maternal Ebeveynlik Öz-Yeterliği Ölçeği kullanılmıştır. İstatistiksel analizlerde varyans analizi, Mann–Whitney U testi ve korelasyon analizleri uygulanmıştır.

Address for Correspondence: Duygu Kınay Ermiş, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Department of Child and Adolescent Psychiatry, İstanbul, Türkiye

E-mail: duygukinayy@hotmail.com **ORCID ID:** orcid.org/0000-0002-6586-2838

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öz

Bulgular: ROP–tedavi gerektirmeyen ve ROP–tedavi edilen gruplardaki annelerin durumluk anksiyete ($p < 0,001$) ve olumsuz ruminasyon ($p = 0,007$) düzeyleri, ROP olmayan gruba kıyasla anlamlı düzeyde daha yüksek bulunmuştur. Anksiyete düzeyleri en yüksek ROP–tedavi gerektirmeyen grupta saptanırken, ROP–tedavi edilen gruptaki annelerin psikolojik dayanıklılık düzeyleri anlamlı olarak daha yüksek bulunmuştur ($p = 0,044$). Depresif belirtiler ve belirsizliğe tahammülsüzlük açısından gruplar arasında anlamlı bir fark gözlenmemiştir. Daha yüksek psikolojik dayanıklılık düzeyleri, daha düşük anksiyete ($p < 0,001$) ve ruminasyon ($p < 0,05$) düzeyleri ile anlamlı olarak ilişkili bulunmuştur.

Sonuç: ROP tanı ve tedavi süreci, annelerin anksiyete düzeyleri ve psikolojik dayanıklılığı üzerinde anlamlı etkilere sahiptir. Dayanıklılığı artırmaya yönelik yapılandırılmış psikososyal müdahaleler (örneğin; dayanıklılık eğitimi ve bilişsel yeniden çerçeveleme), maternal psikolojik sıkıntının azaltılmasına katkı sağlayabilir. Bu bulgular, ROP tanılı prematüre bebeklerin bakım sürecinde bütüncül psikolojik destek yaklaşımlarının gerekliliğini vurgulamaktadır.

Anahtar Kelimeler: Prematüre retinopatisi, anne kaygısı, psikolojik dayanıklılık, ruminasyon, ebeveynlik öz-yeterliliği

Introduction

Prematurity, which affects approximately 15 million infants annually, is a significant global health issue and a leading cause of neonatal morbidity and mortality. Retinopathy of prematurity (ROP) is a significant concern, as it remains one of the leading preventable causes of blindness in preterm infants worldwide (1). Advances in neonatal intensive care have improved the survival rates of preterm infants; however, this has also increased the risk of long-term health challenges, including neurological, auditory, and visual impairments (2,3).

While the medical challenges faced by preterm infants are well documented, the emotional and psychological burden on their parents, particularly mothers, remains underexplored. Caring for a preterm infant diagnosed with ROP can be overwhelming and marked by uncertainty, heightened anxiety,and the need for psychological resilience. These emotional challenges are further amplified during medical procedures, with some mothers reporting increased anxiety when witnessing their infant's discomfort and others experiencing relief by avoiding such situations (4-7). Lack of social support and low psychological resilience exacerbate these struggles, contributing to higher levels of anxiety and depression than those in the general population (8,9).

Previous studies have emphasized the role of parental support groups and educational interventions in improving maternal coping mechanisms (10,11). However, specific psychological constructs, such as intolerance of uncertainty, rumination, resilience, and parenting self-efficacy, remain insufficiently explored in the context of ROP. Intolerance of uncertainty, characterized by difficulty in managing unpredictable outcomes, is closely linked to stress and anxiety in medical settings (12). Rumination, particularly negative rumination (NRS), intensifies emotional distress by fostering repetitive and intrusive thoughts (13). Conversely, psychological resilience is a protective factor that enables individuals to adapt to and recover from adversity (14). Parenting self-efficacy, a parent's belief in their ability to effectively fulfill caregiving responsibilities, is another critical factor influencing maternal responses to ROP-related challenges (6,15).

This study aimed to examine the psychological impact of ROP diagnosis and treatment on the mothers of preterm infants. Specifically, we sought to compare levels of state anxiety, trait anxiety, rumination, intolerance of uncertainty, psychological resilience, and parenting self-efficacy among mothers in the ROP—no treatment, ROP—treated, and no-ROP groups.

Additionally, this study aimed to explore associations among maternal anxiety, depressive symptoms, rumination styles, psychological resilience, and parenting self-efficacy while adjusting for potential clinical confounders such as maternal education level and number of ophthalmologic examinations.

Based on the existing literature, we hypothesized that:

(1) Mothers in the ROP–no treatment and ROP–treated groups exhibited higher levels of state anxiety and rumination than did mothers in the ROP group.

(2) Mothers in the ROP–treated group demonstrated greater psychological resilience than mothers in the ROP–no treatment group.

(3) Higher psychological resilience and parenting self-efficacy were associated with lower anxiety and maladaptive cognitive processes across the sample.

Materials and Methods

This cross-sectional study included mothers of preterm infants whose infants underwent routine ROP screening at the ophthalmology clinic of a University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital between November 1 and December 20, 2024. Ethics committee approval was obtained from the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital,

Institutional Clinical Research Ethics Committee prior to study initiation (decision number: KAEK-11/25.09.2024.167, dated: 06.11.2024). This study was conducted in accordance with the principles of the Declaration of Helsinki. Before participation, written informed consent was obtained from all participants, following the provision of comprehensive information regarding the objectives and scope of the study.

Participants and Group Classification

A total of 267 biological mothers of preterm infants who met the ROP screening criteria according to the International Classification of ROP (ICROP) guidelines were enrolled (16). Eligible infants were those born at ⩽32 weeks' gestational age and/or with a birth weight ⩽1500 g, or who had an unstable clinical course warranting ROP screening, as determined by the attending neonatologist. The infants were examined by two experienced ophthalmologists specializing in ROP. Based on the infant's final ROP status at the time of the survey (reflecting the current disease and treatment status rather than the initial diagnosis), mothers were categorized into three groups:

ROP–no treatment (n = 93): Mothers of infants diagnosed with any stage of ROP who did not require treatment until the survey date.

ROP–treated (n = 47): Mothers of infants with type 1 or aggressive posterior ROP who underwent treatment (intravitreal anti-vascular endothelial growth factor [VEGF], laser photocoagulation, or both).

No ROP (n = 127): Mothers of preterm infants who met the screening criteria but had never developed ROP at any examination or were documented as having mature retinal vasculature at their first examination.

The exclusion criteria were maternal illiteracy, pre-existing psychiatric disorders preventing reliable self-reporting, refugee or immigrant status limiting follow-up, suspected or confirmed syndromic conditions in the infant, a history of caring for another preterm infant, and inability to complete the study instruments. Only one mother per infant was included in this study.

ROP Screening Protocol

ROP screening was performed according to the ICROP recommendations. Examinations were performed by two experienced ophthalmologists using binocular indirect ophthalmoscopy with scleral indentation after pharmacological pupil dilation. Screening was initiated at 4–6 weeks of chronological age or at 31–33 weeks of postmenstrual age, whichever occurred later. Follow-up examinations were scheduled at intervals determined by disease severity and continued until either full retinal vascularization was achieved or the treatment criteria were met. For each infant, the total number of ophthalmological examinations completed prior to the survey date was recorded from the medical charts and later included as a covariate in the statistical analyses.

Timing of Questionnaire Administration

The mothers completed the questionnaires on the same day as their infants' scheduled ROP examinations within the study period. In the ROP-treated group, this typically occurred during routine post-treatment follow-up. For the ROP–no treatment group, screening was ongoing. For the no-ROP group, questionnaires were administered at a scheduled screening visit at which infants were confirmed to have no signs of ROP or, in some cases, to have mature retinal vasculature. This same-day administration minimized recall bias by capturing maternal psychological responses directly related to clinical encounters.

The data collection tools used in this study were as follows:

1. Sociodemographic Information Form: Designed by the researchers, this form gathered essential background information, such as maternal age, education level, socioeconomic status, and family structure.

2. State-Trait Anxiety Inventory (STAI): Developed by Spielberger (17) and adapted into Turkish by Öner and Le Compte (18) in 1985, this inventory measures anxiety on two dimensions: State Anxiety (STAI-S), which evaluates temporary anxiety triggered by specific situations (e.g., the stress of a medical diagnosis), and Trait Anxiety (STAI-T), which reflects a general tendency toward anxiety. Each subscale contains 20 items; subscale scores range from 20 to 80, with higher scores indicating greater anxiety.

3. The Intolerance of Uncertainty Scale-12 (IUS-12) is a 12-item scale that assesses the tendency to perceive uncertain or unpredictable situations as distressing. Responses are rated on a 5-point Likert scale, with total scores ranging from 12–60. High scores indicate low tolerance for uncertainty, which is a common challenge for mothers coping with their infants' unpredictable medical outcomes.

4. Perceived Maternal Parenting Self-Efficacy Scale (PMPS-E), developed by Barnes and Adamson-Macedo (19) and validated in Turkish by Kahya and Uluc (20) measures a mother's confidence in her ability to effectively fulfill parenting roles, particularly in the context of preterm infant care. The scores ranged from 20 to 80, with higher scores reflecting greater self-efficacy and confidence.

5. Edinburgh Postnatal Depression Scale (EPDS): A 10-item screening tool created by Cox et al. (21) and validated in Turkish by Engindeniz et al. (22). It is used to screen for

depressive symptoms during the postnatal period, with higher scores indicating greater severity .

6. Ruminative Response Scale–Short Form: The NRS and positive rumination (PRS) subscales were used to assess maladaptive and adaptive ruminative thinking styles. Higher scores indicate greater engagement in the rumination style.

7. The Connor-Davidson Resilience Scale (CD-RISC), a 25-item measure that evaluates psychological resilience (defined as the ability to cope effectively with stress and adversity), was used. The scores were rated on a 5-point Likert scale, with higher scores indicating greater resilience. The validity and reliability of the Turkish version of the scale were established by Karaırmak (23). Resilience is crucial for mothers in managing the emotional challenges posed by the medical needs of their infants.

Statistical Analysis

Analyses were performed using SPSS version 29.0 (IBM Corp., Armonk, NY, USA). Categorical variables are presented as frequencies and percentages, whereas continuous variables are expressed as means with standard deviations or medians with interquartile ranges, as appropriate. Normality was assessed using the Kolmogorov–Smirnov test, skewness and kurtosis values, and visual inspection of box plots and histograms. Depending on the distribution of the data, comparisons between two groups were conducted using the Student's t-test or the Mann–Whitney U test, while comparisons across three groups were performed using one-way ANOVA or the Kruskal–Wallis H test; Bonferroni correction was applied for multiple comparisons. Associations between categorical variables were examined using the chi-square test, and correlations among numerical variables were assessed using Spearman's rank correlation coefficients. To control for potential confounding factors, a multivariate analysis of covariance (MANCOVA) was conducted with maternal education level and the number of ophthalmologic examinations as covariates. The dependent variables in the MANCOVA model were psychological scale scores (STAI-S, STAI-T, EPDS, NRS, PRS, IUS-12, CD-RISC, and PMPS-E). Pillai's Trace was used as the multivariate test statistic, and significant multivariate effects were followed by univariate analysis of covariances with post-hoc pairwise comparisons. A two-tailed p-value of <0.05 was considered statistically significant.

Results

A total of 267 infants were included in the study, of whom 140 were diagnosed with ROP (ROP [+]) and 127 were without ROP (no ROP). In the ROP [+] group, 47 infants were classified as having type 1 or aggressive ROP and received anti-VEGF injections, laser ablation, or combination therapy. Infants in the ROP [+] group had significantly lower gestational age (28.84 ± 2.93 vs. 31.72 ± 1.56 weeks; $p < 0.001$), lower birth weight, and longer hospital stays (63.01 ± 31.24 vs. 25.92 ± 15.33 days; $p < 0.001$). While most sociodemographic variables showed no significant differences between the groups, maternal education was higher in the No ROP group ($p = 0.008$). Demographic characteristics are summarized in Table 1.

When psychological scale scores were compared across the three groups, state anxiety (STAI-S) and trait anxiety (STAI-T) were highest in the ROP–no treatment group compared with both the ROP–treated and No ROP groups ($p < 0.001$). Mothers in the ROP–treated group demonstrated significantly higher psychological resilience (CD-RISC) scores than mothers in the ROP–no treatment group ($p = 0.044$). For NRS, both the ROP (no treatment) and ROP (treated) groups scored significantly higher than the No ROP group ($p = 0.008$). No significant group differences were observed in depressive symptoms (EPDS), PRS, intolerance of uncertainty (IUS-12), or parenting self-efficacy (PMPS-E) in the unadjusted analysis (Table 2).

The distribution of ophthalmologic examination numbers differed significantly across groups, with the highest frequency observed in the ROP–treated group, followed by the ROP–no treatment group, and the lowest frequency in the no ROP group ($p < 0.001$), as illustrated in Figure 1.

Correlation analyses showed that STAI-S correlated positively with STAI-T ($r = 0.53$, $p < 0.001$) and with EPDS scores ($r = 0.46$, $p < 0.001$), whereas resilience (CD-RISC) correlated negatively with both anxiety and depression ($p < 0.001$). NRS correlated positively with STAI-T and EPDS scores, whereas PRS correlated positively with resilience and negatively with depression (Table 3). These findings highlight the strong interrelationships between maternal anxiety, depression, resilience, and cognitive processing.

To account for confounders, a MANCOVA was performed, controlling for maternal education and the number of ophthalmological examinations. After adjustment, significant group differences persisted for state anxiety ($p < 0.001$), trait anxiety ($p = 0.001$), and parenting self-efficacy ($p = 0.006$). Specifically, both the ROP–no treatment and ROP–treated groups had higher STAI-S scores than the No ROP group, whereas trait anxiety remained highest in the ROP–no treatment group. Importantly, parenting self-efficacy scores, which did not differ significantly in unadjusted analyses, were significantly higher in both ROP groups after adjustment for confounders.

Table 1. Demographic characteristics.

	ROP (+)*, (n = 140)	ROP (–), (n = 127)	p-value
Age of infant (days), mean ± SD	160.9 ± 144.3	69.8 ± 52.4	<0.001
Gender of the infant, n (%) Girls Boys	 66 (47.1%) 74 (52.9%)	 61 (48.0%) 66 (52.0%)	0.885
Gestational age of the infant (weeks), mean ± SD	28.84 ± 2.93	31.72 ± 1.56	<0.001
Birth weight of the infant (g), mean ± SD	1228.5 ± 502.3	1839.7 ± 495.7	<0.001
The length of hospitalization (days), mean ± SD	63.01 ± 31.24	25.92 ± 15.33	<0.001
Socioeconomic status, n (%) Low Middle High	 21 (15.0%) 106 (75.7%) 13 (9.3%)	 14 (11.0%) 109 (85.8%) 4 (3.2%)	0.062
Maternal age (years), mean ± SD	26.41 ± 7.30	26.44 ± 7.88	0.272
Maternal education, n (%) High school or below University	 77 (55.0%) 63 (45.0%)	 89 (70.1%) 38 (29.9%)	0.008
Maternal job status, n (%) Working Not working	 36 (25.7%) 104 (74.3%)	 37 (29.1%) 90 (70.9%)	0.531
Family type, n (%) Nuclear Large Single	 117 (83.6%) 19 (13.6%) 4 (2.8%)	 93 (73.3%) 29 (22.8%) 5 (3.9%)	0.116
Birth type, n (%) Cesarean Vaginal	 133 (95.0%) 7 (5.0%)	 111 (87.4%) 16 (12.6%)	0.027

*ROP (+) group includes both treated and untreated cases. ROP, retinopathy of prematurity; SD, standard deviation.

Table 2. Comparing the groups based on their scale scores.

	ROP (+)		ROP (–)	p-value*
	ROP–no treatment	ROP–treated	No ROP	
STAI–S score	36.03 ± 8.28 (37.0)[b]	32.15 ± 5.86 (30.0)[a]	31.58 ± 7.75 (31.0)[a]	<0.001
STAI–T score	41.32 ± 8.58 (42.0)[b]	35.81 ± 5.34 (34.0)[a]	37.41 ± 9.52 (36.0)[a]	<0.001
EPDS score	6.68 ± 5.57 (5.0)	5.87 ± 4.39 (4.0)	5.63 ± 5.06 (5.0)	0.328
NRS score	20.49 ± 4.62 (20.0)[a,b]	20.87 ± 2.14 (21.0)[a]	19.61 ± 3.03 (19.0)[b]	0.008
PRS score	26.42 ± 5.00 (26.0)	28.11 ± 4.77 (28.0)	27.02 ± 4.82 (27.0)	0.146
IUS-12_total	30.28 ± 9.21 (29.0)	28.79 ± 9.01 (29.0)	29.72 ± 11.65 (27.0)	0.591
PMPS-E	57.32 ± 8.647 (57.0)	58.11 ± 8.69 (61.0)	55.18 ± 8.10 (55.0)	0.159
CD-RISC_total	94.68 ± 12.50 (97.0)[b]	100.21 ± 10.51 (103.0)[a]	97.85 ± 17.57 (99.0)[a,b]	0.044

Mean ± SD (median), *Kruskal–Wallis H test. Superscript letters [(a, b)] indicate post-hoc pairwise comparisons between groups: values sharing the same letter do not differ significantly, whereas values with different letters indicate statistically significant differences. Significance values have been adjusted by the Bonferroni correction for multiple tests. CD-RISC_total, Connor-Davidson Resilience Scale – total score; EPDS, Edinburgh Postnatal Depression Scale; IUS-12_total, Intolerance of Uncertainty Scale – 12 items, total score; NRS, Numeric Rating Scale; PMPS-E, Parents' Postoperative Pain Measure – Extended; PRS, Pain Relief Scale; ROP, retinopathy of prematurity; SD, standard deviation; STAI–S, State-Trait Anxiety Inventory – State; STAI–T, State-Trait Anxiety Inventory – Trait.

Discussion

This study examined the psychological impact of the diagnosis and treatment of ROP on mothers of preterm infants. Three main findings emerged. First, mothers in the ROP–no treatment and ROP–treated groups exhibited significantly higher levels of state anxiety and NRS than mothers in the no ROP group, indicating that the ROP diagnostic process itself is a substantial source of situational psychological distress.

Second, the highest anxiety levels were observed among mothers in the ROP—no treatment group, whereas mothers in the ROP—treated group demonstrated significantly greater psychological resilience. Third, psychological resilience was negatively associated with anxiety, depressive symptoms, and NRS, suggesting a potential protective role of maternal psychological adjustment during the ROP care process. Taken together, these findings indicate that the psychological burden experienced by mothers of infants with ROP is shaped not only by disease severity but also by treatment status and by the structure and intensity of medical follow-up and support services.

The elevated levels of state anxiety observed among mothers of infants diagnosed with ROP are consistent with previous studies emphasizing the psychological burden associated with uncertainty and prolonged medical monitoring in the care of preterm infants (4–6). The absence of significant differences in trait anxiety across groups suggests that the heightened anxiety observed in these mothers reflects a situational response to stressors specific to the ROP diagnosis and care process, rather than stable personality characteristics. Although the literature examining mothers of infants with ROP remains limited, existing studies generally report increased maternal anxiety with greater ROP severity (5-7). Notably, the highest anxiety levels were observed among mothers in the ROP No Treatment group. This finding suggests that more frequent medical examinations and more structured follow-ups in the ROP-treated group may have mitigated uncertainty and alleviated psychological distress.

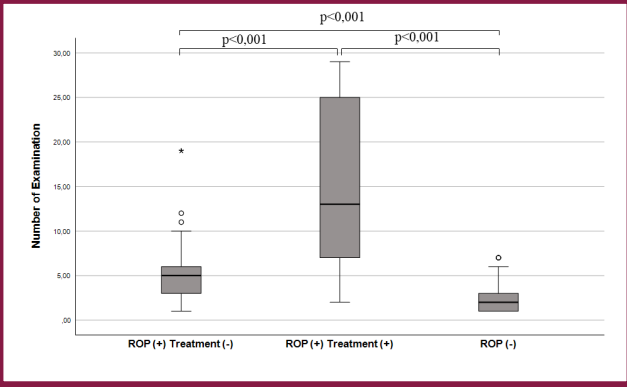


Figure 1. Comparison of examination numbers among infants with ROP requiring treatment, not requiring treatment, and without ROP. *ROP (+) includes both treated and untreated cases. *ROP, retinopathy of prematurity; SD: standard deviation.*

A systematic review of interventions aimed at reducing parenting stress in families of children with pediatric conditions highlighted that consistent and structured communication with healthcare professionals alleviates parental uncertainty and stress by providing clear, regular updates about the child's condition and care (24). Similarly, in our study, mothers in the ROP-treated group engaged more frequently with healthcare providers and received more detailed information about their infants' status. This may have contributed to reduced anxiety and facilitated better psychological adaptation to treatment. Furthermore, routine follow-ups and structured care plans appear to enhance mothers' sense of control, thereby supporting lower anxiety levels (25,26).

The study's findings indicate that mothers in the ROP–treated group, who faced more severe challenges related to ROP, demonstrated higher psychological resilience than mothers in the ROP–no treatment group, as reflected in their CD-RISC scores. Resilience is a protective mechanism that facilitates adaptation to complex caregiving demands, promotes positive coping strategies, and mitigates maladaptive patterns of thought (14).

Table 3. Correlations among study variables.

	STAI–S	STAI–T	EPDS	NRS	PRS	IUS-12_total	PMPS-E	CD-RISC_total
STAI–S	—							
STAI–T	0.530***	—						
EPDS	0.464***	0.627***	—					
NRS	0.046	0.319***	0.237***	—				
PRS	−0.275***	−0.290***	−0.332***	0.069	—			
IUS-12_total	0.189**	0.482***	0.403***	0.160**	−0.223***	—		
PMPS-E	0.170**	0.085	0.071	0.025	−0.137*	0.087	—	
CD-RISC_total	−0.349***	−0.312***	−0.207***	−0.062	0.261***	−0.141*	0.080	—

Spearman correlation analysis, *p < 0.05, **p < 0.01, ***p < 0.001. All correlations are based on the total sample (n = 267). CD-RISC_total, Connor-Davidson Resilience Scale – total score; EPDS, Edinburgh Postnatal Depression Scale; IUS-12_total, Intolerance of Uncertainty Scale – 12 items, total score; NRS, Numeric Rating Scale; PMPS-E, Parents' Postoperative Pain Measure – Extended; PRS, Pain Relief Scale; ROP, retinopathy of prematurity; STAI–S, State-Trait Anxiety Inventory – State; STAI–T, State-Trait Anxiety Inventory – Trait.

Previous studies have not explicitly examined the relationship between ROP-related challenges and resilience. However, these findings differ from those reported by Xie et al. (7), who identified lower resilience levels among the parents of infants with severe ROP. Such discrepancies may stem from contextual differences, including cultural factors, healthcare systems, and participant characteristics (27). For instance, a study conducted in China found that low levels of social support and high stress during outpatient fundus examinations were associated with reduced resilience (7). In contrast, a study in Türkiye observed that low-income mothers were better able to cope with uncertainty owing to the support provided by the healthcare system and extended family networks (28). These findings suggest that regular and structured information flow from healthcare professionals is crucial to helping mothers manage uncertainty and strengthen their psychological resilience (29).

The NRS was significantly associated with higher anxiety and depression scores, highlighting its role as a mediator of emotional distress. This finding underscores the importance of addressing maladaptive cognitive processes in interventions aimed at improving mental health. However, the lack of significant differences in EPDS scores between the groups suggests that depression may not vary substantially across diagnostic categories, it remains a critical underlying concern. This contrasts with the findings of Duman et al. (5). Özyurt et al. (6) reported higher EPDS scores in mothers of infants with ROP. The absence of differences in our study may indicate that depression is a widespread issue among mothers, independent of ROP severity or treatment.

While unadjusted analyses showed no significant group differences in PMPS-E and IUS-12, adjusted analyses revealed that self-efficacy scores were significantly higher in both ROP groups than in the No ROP group. This suggests that maternal education and examination frequency may partially mask between-group differences in self-efficacy. Nevertheless, the relatively low levels of self-efficacy observed in the sample highlight the need for targeted interventions to strengthen maternal caregiving confidence, particularly through educational and structured support programs (6).

This study highlights the need for psychological interventions for mothers of preterm infants with ROP. Programs that build resilience, such as mindfulness-based and cognitive-behavioral techniques, may help mothers cope more effectively with caregiving challenges. Addressing negative thought patterns and promoting adaptive cognitive strategies can reduce emotional distress, while parent support groups and educational initiatives may foster a sense of community and shared understanding among affected families.

Study Limitations

This study had several limitations. First, the cross-sectional design prevented causal inferences regarding the relationships between the psychological constructs. Longitudinal studies are required to clarify how maternal mental health evolves over time and in response to various interventions. Second, the exclusion of fathers limits the generalizability of the findings, as paternal experiences may differ and require further investigation. Third, although maternal education and the number of ophthalmological examinations were statistically controlled, other unmeasured confounders (e.g., social support, parity, and socioeconomic factors) may also affect maternal psychological outcomes. Additionally, variations in examination frequency may have contributed to differences in anxiety and resilience, underscoring the need for standardized follow-up protocols in future research. Finally, future studies should consider the broader role of cultural factors and healthcare system characteristics in shaping maternal responses to the ROP.

Conclusion

This study demonstrated a complex interplay among anxiety, resilience, and cognitive processing in mothers of preterm infants with ROP. By identifying key psychological challenges and protective factors, this study provides a foundation for developing targeted interventions to support mothers' mental health. Addressing the unique needs of this vulnerable population is essential not only for improving maternal well-being, but also for optimizing infant health outcomes.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Institutional Clinical Research Ethics Committee prior to study initiation (decision number: KAEK-11/25.09.2024.167, dated: 06.11.2024).

Informed Consent: Before participation, written informed consent was obtained from all participants.

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Footnotes

Authorship Contributions

Concept: D.K.E., C.G., Design: D.K.E., C.G., Data Collection or Processing: C.G., Analysis or Interpretation: D.K.E., C.G., Literature Search: D.K.E., Writing: D.K.E.

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ORIGINAL ARTICLE

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Newly Diagnosed Monoclonal Gammopathies in 2024 in a Single Center: A Retrospective Study from a Perspective of Initial Testing in Diagnosis

2024 Yılında Yeni Tanı Alan Monoklonal Gamopatiler: Tanısal Testler Perspektifinden Retrospektif Bir Çalışma

Merve Dinçer[1], Özgür Aydın[1], Volkan Karakuş[2]

[1]University of Health Sciences Türkiye, Antalya Training and Research Hospital, Biochemistry Laboratory, Antalya, Türkiye

[2]University of Health Sciences Türkiye, Antalya Training and Research Hospital, Department of Hematology, Antalya, Türkiye

ABSTRACT

Background: There is no consensus on the initial testing in diagnosing monoclonal gammopathies (MG). This retrospective analysis reports on newly diagnosed MG patients at the University of Health Sciences Türkiye, Antalya Training and Research Hospital and assesses the necessity of serum immunofixation electrophoresis (SIFE) as an initial diagnostic test.

Materials and Methods: All serum protein electrophoresis (SPE) tests performed and reported between 1 January 2024 and 31 December 2024 were retrospectively reviewed from the institute's archival database. Patients with any electrophoresis test results and patients without any previous electrophoresis test results were included in the study.

Results: Our laboratory diagnosed 115 new patients with MG in 2024. Of these 115 patients, 67 (58%) were male and 48 (42%) were female, with mean ages of 65.98 ± 10.78 years in men and 66.22 ± 10.37 years in women. Sixty-three of 115 patients were positive on both the SPE and the serum free lightchain ratio (rFLC). Of 115 patients, 31 were positive only for SPE and negative for rFLC, whereas 5 were positive only for rFLC and negative for SPE. Six of 115 patients were negative for both SPE and rFLC, but were diagnosed by a positive SIFE.

Conclusion: After a retrospective review of 115 newly diagnosed MG patients in 2024, we concluded that 6 of these patients might have been missed (undiagnosed) if a combination of SPE + rFLC tests had been used as the initial diagnostic tests. None of these six cases showed a measurable M protein on SPE, nor did they receive medication for MG.

Keywords: Serum-free light chain ratio, multiple myeloma, general practice, diagnostic work-up, reflective test

ÖZ

Amaç: Monoklonal gamopatilerin (MG) tanısında ilk test yöntemi konusunda bir fikir birliği yoktur. Bu retrospektif analiz, Sağlık Bilimleri Üniversitesi, Antalya Eğitim ve Araştırma Hastanesi'nde yeni tanı almış MG hastalarını sunmakta ve ilk tanı testi olarak serum immünfiksasyon elektroforezinin (SIFE) gerekliliğine odaklanmaktadır.

Gereç ve Yöntemler: 1 Ocak 2024 ile 31 Aralık 2024 tarihleri arasında gerçekleştirilen ve raporlanan tüm serum protein elektroforez (SPE) testleri arşiv veri tabanından retrospektif olarak incelenmiştir. Herhangi bir elektroforez testi sonucu olan ve daha önce elektroforez testi sonucu olmayan hastalar çalışmaya dahil edilmiştir.

Bulgular: Laboratuvarım sonuçları ile 2024 yılında 115 yeni MG hastası tanı almıştır. Bu 115 hastanın 67'si (%58) erkek, 48'i (%42) kadın olup, erkeklerde ortalama yaş 65,98 (±10,78), kadınlarda ise 66,22 (±10,37) idi. Yüz on beş hastanın 63'ü hem SPE hem de serum serbest hafif zincir oranı (rFLC) açısından pozitifti. Yüz on beş hastanın 31'i sadece SPE pozitif, rFLC negatifken, 115 hastanın 5'i sadece rFLC pozitif, SPE negatifti. Yüz on beş hastanın 6'sı hem SPE hem de rFLC negatifti ve bu hastalara pozitif SIFE ile tanı konuldu.

Sonuç: 2024 yılında yeni tanı almış 115 MG hastası retrospektif olarak incelendiğinde, ilk tanı testleri olarak SPE + rFLC testlerinin kombinasyonu kullanılırsa, bu hastalardan 6'sının muhtemelen gözden kaçabileceği (tanı konulamayacağı) sonucuna vardık. Bu 6 vakanın hiçbiri SPE'de ölçülebilir bir M proteini göstermedi veya MG için herhangi bir tedavi almadı.

Anahtar Kelimeler: Serum serbest hafif zincir oranı, multiple myelom, genel uygulamalar, tanısal testler, reflektif test

Address for Correspondence: Özgür Aydın, University of Health Sciences Türkiye, Antalya Training and Research Hospital, Biochemistry Laboratory, Antalya, Türkiye

E-mail: belozgur@hotmail.com **ORCID ID:** orcid.org/0000-0002-6123-6186

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Introduction

According to the latest Global Cancer Observatory statistics, there were an estimated 190,000 cases of multiple myeloma (MM) in 2022, ranking 21st in disease incidence and 17th in mortality globally (1). Lifetime risk of developing MM is 0.24% in men and 0.17% in women, indicating a higher risk in men (2). With the introduction of proteasome inhibitors and immunomodulatory drugs, the 5-year overall survival of MM patients has increased significantly. However, MM remains incurable (3).

MM is a member of the large family of monoclonal gammopathies (MG). Serum protein electrophoresis (SPE), by gel or capillary methods, has been the most widely used laboratory test for diagnosing MG (4). Serum immunofixation electrophoresis (SIFE) and immunosubtraction have been used to identify and characterize the detected monoclonal neoplastic immunoglobulin protein (M protein). After a quarter of a century, serum free light chain (FLC) assays are now recognized as essential in all diagnostic protocols for MG. Mass spectrometry and quantitative measurements of heavy- and light-chain isotypes are emerging diagnostic tests for MG. Laboratories may choose to use one, all, or a combination of these diagnostic test panels (5). In May 2022, Keren et al. (6) published their paper on laboratory detection and initial diagnosis of MG. The paper presented evidence-based recommendations from an expert panel established by the College of American Pathologists (CAP). Besides recommendations on specimen requirements and appropriate tests for the initial laboratory detection of M proteins, they concluded their work with a flowchart outlining diagnostic testing for MG.

There have been attempts to ensure appropriate initial test requests for the diagnosis of MG in line with good laboratory practice (5–8). Appropriate testing is part of good laboratory practice, and "requesting the right test with the right method, at the right time, for the right patient, to produce the right result at the right (reasonable) cost" has been a major goal of modern laboratories (9). This study aimed to provide feedback and information to support future efforts to regulate test protocols used in the diagnosis of MG, with a particular focus on the SIFE test.

Materials and Methods

All SPE test results between 1 January 2024 and 31 December 2024 were retrospectively retrieved from the laboratory information system and reviewed. Age, sex, and electrophoresis test results for each patient were recorded. It was recorded whether the electrophoresis tests were used alone or in various combinations. SPE showing a depressed gamma region was subjected to reflective SIFE and FLC tests. M protein measurements were performed using the perpendicular-drop method. M protein concentrations >1 g/dL were considered measurable. SPE and SIFE results were reported as "monoclonal band not detected" (negative) or "monoclonal band detected" (positive). The immunophenotype of the positive monoclonal band was included in the report. FLC tests were reported as Kappa and Lambda FLC quantities in the patient's serum, and as the ratio of Kappa to Lambda test results FLC ratio (rFLC). Values outside the normal range (0.31–1.56) were considered positive. Only patients with first-time electrophoresis test results were included; patients with any prior electrophoresis test results were excluded.

SPE were performed using the serum protein 6-band format on agarose gel (Helena Diagnostics, UK) platform with SAS plus and SAS-2 24 SB kit. SIFE was performed on the same platform using the Helena Biosciences SAS-1 IFE-4 kit to confirm the presence of M protein and to characterize isotypes, employing monospecific antisera against immunoglobulin G (IgG), IgM, and IgA heavy chains and κ and λ light chains. Serum FLC were measured in batch mode using N Latex FLC Kappa and Lambda assays (Siemens Healthcare Diagnostics, Marburg, Germany) on a Siemens BNII nephelometer, according to the manufacturer's instructions.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Antalya Training and Research Hospital Scientific Research Ethics Committee (decision number: 4/15, dated: 27.02.2025).

Statistical Analysis

Windows Excel 2013 (Microsoft, USA) was used to perform calculations and generate statistical data.

Results

The study was conducted at a 1,270-bed tertiary-care medical center affiliated with a medical school. Our laboratory diagnosed 115 new MG patients in 2024. Of these 115 patients, 67 (58%) were male and 48 (42%) were female, with a mean age of 65.98 (± 10.78) in men and 66.22 (± 10.37) in women. When patients were examined in types of paraproteinemia, in order of frequency, we detected IgG-Kappa in 44 patients (38.2%), IgG-Lambda in 32 patients (27.8%), IgA-Kappa in 8 patients (7%), IgA-Lambda in 8 patients (7%), IgM-Kappa in 6 patients (5.2%), IgM Lambda in 2 patients (1.7%), light chain Kappa in 5 (4.3%), light chain Lambda in 6 (5.2%) patients, heavy chain IgA in 2 patients (1.7%), biclonal IgG Kappa + IgG Lambda and IgG Kappa + IgA Kappa in 2 patients (1.7%). In 103 of these patients, a combination of SPE, SIFE, and

rFLC tests was requested as initial testing. 7 patients, diagnosed with the combination of SPE + SIFE test while 3 patients were diagnosed only with SIFE and 2 patients were diagnosed with only SPE test.

The positive and negative initial electrophoresis tests were as follows (Figure 1):

Of 109 patients with a positive SPE and/or rFLC, 63 were positive for both SPE and rFLC. 31 of 109 patients were positive for SPE but negative for rFLC, whereas 5 of 109 patients were positive for rFLC but negative for SPE. Heavy-chain components were observed in SIFE in these five cases.

Of 115 patients, 6 were negative for both SPE and rFLC. They were diagnosed based on a positive SIFE.

Ten of 116 patients were positive for monoclonal FLC only and negative for IgG, IgM, and IgA antisera. IgD or IgE positivity could not be excluded. rFLC values were significantly abnormal (either elevated or reduced, depending on the affected light chain) in all cases. SIFE were negative, and SPE were depressed or apparently normal, without a visible M protein.

Discussion

In the vast majority of our patients (95.5%), a combination of SPE, SIFE, and rFLC was requested by clinicians as initial diagnostic tests. The combination was in line with the recommendations of International Myeloma Foundation's International Myeloma Working Group (IMWG) for diagnostic testing for MG (6). After retrospectively reviewing the 115 newly diagnosed MG patients in 2024, we concluded that 6 of these patients could have been missed (undiagnosed) if any combination of initial diagnostic tests that did not include SIFE had been used. None of the six cases showed a measurable M protein on SPE, and their rFLC values were within the normal range. In two of the six cases that showed a monoclonal IgA band in the beta region, the SPE tests were nearly normal. In the other four cases with a monoclonal band in the gamma region (2 IgG Lambda, 1 IgG Kappa , and 1 IgA Lambda), slight irregularities in the SPE tests were detectable only with a high index of suspicion. All six cases were re-evaluated by an expert hematologist; all were diagnosed with MG of undetermined significance (MGUS) and did not receive any treatment for MGUS (Table 1).

One of the main reasons for including sFLC tests as essential first-line tests is the detection of FLC MM (6,10). In 2024, we diagnosed 10 patients with FLC MM. Although IgE- or IgD-heavy-chain components were not detected serologically, these cases were classified and treated as FLC MM. In 7 of 10 FLC MM cases, the gamma region on SPE was depressed and reported as positive. Particularly, considering FLC MM single SPE without rFLC or SIFE tests

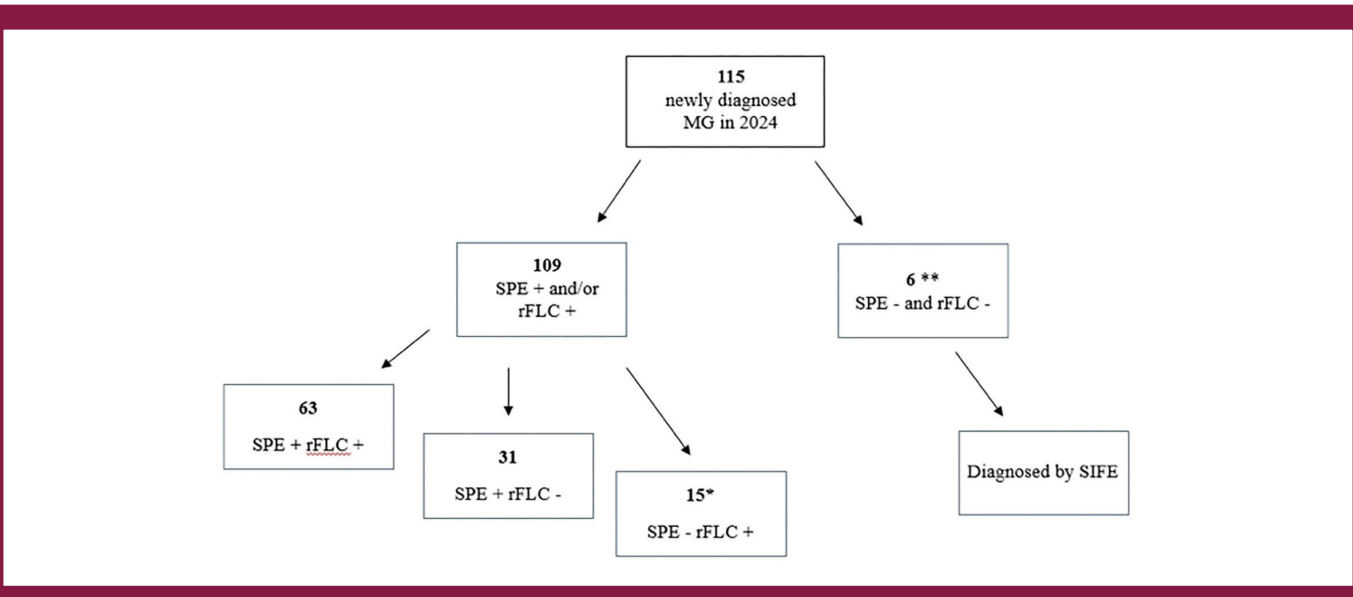


Figure 1. Our laboratory diagnosed 115 new MG patients in 2024. One hundred nine patients were positive for SPE and/or rFLC, which meant that the SPE and rFLC combination was sufficient as an initial diagnostic test. Sixty-three of 109 patients were positive for both SPE and rFLC; 31 of 109 patients were positive for SPE and negative for rFLC; and 15 of 115 patients were positive only for rFLC and negative for SPE. In the last group of 15 patients, 10 were positive for monoclonal FLCs only, without a heavy-chain component, after SIFE (*). Six of the 115 patients were negative for both SPE and rFLC (**). They were diagnosed based on a positive SIFE performed as the initial test. These six cases could be missed when a combination of SPE and rFLC is used as the initial test. MG, monoclonal gammopathy; rFLC, ratio of free light chains; SIFE, serum immunofixation electrophoresis; SPE, serum protein electrophoresis.

Table 1. In retrospective analysis of 115 newly diagnosed MG patients, in 6 patients SIFE was the diagnostic test and these cases could have been missed by initial SPE + rFLC tests (without SIFE). Three of the patients underwent bone marrow biopsy and diagnosed as MGUS. Patients 1 was without a follow-up, no further investigations were performed on patient 3 because of old age and patient 4 was followed-up by electrophoresis and treated like MGUS.

Patient	rFLC	SPE	SIFE	Details	Diagnosis
1	0.95	A distorsion at the center of a normodense gamma region.	Vague IgG Kappa	No follow-up.	Treated like MGUS*
2	0.85	Invisible in the beta region.	Clear IgA Lambda	Undergone bone marrow biopsy.	MGUS
3	0.34	A distorsion at the anodal end of normodense gamma region.	Vague IgA Kappa	92 years old, no further investigation.	Treated like MGUS*
4	0.38	Invisible in the beta region.	Clear IgA Lambda	Followed by electrophoresis.	Treated like MGUS*
5	0.79	A distorsion at the cathodal end of normodense gamma region.	Vague IgG Lambda	Undergone bone marrow biopsy.	MGUS
6	0.36	A distorsion at the cathodal end of normodense gamma region.	Vague IgG Lambda	Undergone bone marrow biopsy.	MGUS

MGUS, monoclonal gammopathy of undetermined significance; rFLC, serum free light chain ratio; SIFE, serum immunofixation electrophoresis; SPE, serum protein electrophoresis; treated like MGUS*, final diagnosis was not confirmed by bone marrow biopsy; Ig, immunoglobulin.

may be challenging for inexperienced laboratory specialists when diagnosing MG. In 3 of the 10 FLC MM patients, SPE did not show any aberrant signs of positivity. In all cases of FLC, MM rFLC were extremely alarming. We can confidently conclude that the performance of the rFLC test was highly satisfactory for detecting FLC MM in these patients.

Many cost-effective applications advise clinicians to use stepwise testing when diagnosing MG. In 2017, Genzen et al. (5) reported results from a survey of 774 laboratories in 38 countries that quantified patterns of electrophoresis test use for detecting M protein. The findings indicated substantial variation in practice compared with current IMWG guidelines. They reported SPE, used as a first-line screening test followed by other confirmatory tests, as the most common application. To support a stepwise approach, the laboratory must maintain reflex or reflective testing capabilities to avoid repeated sampling. In our study, reflective SIFE was performed in two cases with positive SPE to avoid repeat sampling. Although performed in only two patients, our study showed that stepwise testing was successful with reflective testing of SIFE.

Appropriate testing is a part of good laboratory practices. "Requesting the right test with the right method, at the right time, for the right patient, to produce the right result at the right (reasonable) cost" has been defined as an appropriate test request. Particularly for SPE and SIFE, a major concern, in addition to the high cost of the tests, is the time and effort required of a highly specialized technician or laboratory specialist (9,11). Gel electrophoresis remains one of the last conventional tests used in the clinical laboratory. Semi-automated gel electrophoresis requires substantial manual work by a specialized, experienced technician, while reporting the tests requires additional time and effort from a specialized, experienced laboratory specialist. In the absence of an evidence-based guideline from a systematic review, laboratories have developed disparate practices for M protein detection and quantitative measurement, complicating harmonization of results (6–8,12).

In May 2022, Keren et al. (6) published their paper on laboratory detection and initial diagnosis of MG. The paper presented evidence-based recommendations from an expert panel established by the CAP. The expert panel included a broad representation of experts in the diagnosis and treatment of MG and in the laboratory procedures used for their initial detection. They called their work a contemporary guideline and a first step toward harmonizing the initial detection of MG. They finalized their work with a flowchart for stepwise diagnostic testing to detect MG, in which SPE and rFLC were the first-line tests, followed by confirmatory SIFE if needed. Compared with the recommendations by Keren et al. (6), the IMWG recommendations include SIFE testing as an initial diagnostic test in addition to SPE and rFLC. Willrich and Katzmann (13) demonstrated that the combined use of SPE and rFLC identified 94.3% of M proteins in 1877 patients (100% for MM and 88.7% for MGUS). This retrospective study demonstrated that the combined use of SPE and rFLC could miss some cases of MG that would be diagnosed by adding SIFE to the first-line diagnostic test panel. Our six had no measurable M protein on SPE, did not receive any medication for MG, and were confirmed or accepted as MGUS. Although considering SIFE as a first-line test in the screening and diagnosis of MG is a matter

of debate, we believe our findings will be valuable. The guideline by Keren et al. (6) was declared to be reviewed every four years after its publication. The expert panel is expected to discuss potential changes and recommend revision of the guideline if necessary.

Our findings should be considered and discussed from a cost-effectiveness perspective. Pressure on hospitals to restrain health-care expenditure has resulted in cost-cutting strategies. In this regard, the Turkish Ministry of Health launched the "Good Laboratory Practices Project" in 2018. A practical guide for requesting appropriate tests was included in this project. In practice, attempts to reduce unnecessary laboratory test requests include two major approaches: educating clinicians and designing test requests. Our experience showed that the educational approach was short-lived, with effects disappearing soon after the educational effort ceased. On the other hand, efforts to design clinicians' test-ordering practices are likely to result in longer-lasting effects. Designing test ordering practices necessitates close co-operation between the clinicians and the laboratory (9).

Study Limitations

The main limitation of our study was its retrospective nature. The cases were actually not missed, but our judgment was that they could have been missed. We did not consider urine IFE because its use across departments was limited. Our findings were based on gel electrophoresis, and results from capillary electrophoresis could differ from our conclusions.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and approved by the Antalya Training and Research Hospital Scientific Research Ethics Committee (decision number: 4/15, dated: 27.02.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: V.K., Concept: Ö.A., V.K., Design: Ö.A., Data Collection or Processing: M.D., Ö.A., Analysis or Interpretation: Ö.A., V.K., Literature Search: M.D., Ö.A., Writing: V.K.

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ORIGINAL ARTICLE

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Investigation of the Strengthening Effect of Toyocamycin on Docetaxel in Human Ovarian Cancer Cells

İnsan Ovaryum Kanseri Hücrelerinde Toyokamisinin Dosetaksel Üzerindeki Güçlendirici Etkisinin Araştırılması

Yalçın Erzurumlu, Yağmur Doğanlar

Süleyman Demirel University Faculty of Pharmacy, Department of Biochemistry, Isparta, Türkiye

ABSTRACT

Background: Docetaxel is an anti-microtubule chemotherapeutic agent classified in the taxane group and is widely used in the treatment of many types of cancer. However, systemic toxic effects can be observed in patients treated with docetaxel, and the development of *de novo* or acquired resistance limits its use and therapeutic efficacy. Thus, investigation of adjuvant treatment approaches has attracted interest. This study aimed to investigate the effects of toyocamycin-mediated inhibition of the Inositol-Requiring Enzyme 1 alpha (IRE1α)-X-box Binding Protein 1 (XBP-1) pathway, a physiological mechanism in mammalian cells, on the sensitivity of ovarian cancer cells to docetaxel.

Materials and Methods: Human ovarian adenocarcinoma cell lines SKOV3 and Caov-3 were used in the studies. The effects of toyocamycin and docetaxel on cell viability were investigated using the Water-Soluble Tetrazolium-1 assay. The inhibitory effect of toyocamycin on the IRE1α-XBP-1 pathway was confirmed by immunoblotting studies. The impact of combined treatment with toyocamycin and docetaxel on migration and invasion was evaluated using wound-healing and Matrigel-coated Boyden-chamber invasion assays. The expression levels of some pro-apoptotic and anti-apoptotic genes, such as B-cell lymphoma 2 (*BCL2*)-associated X apoptosis regulator, BH3-interacting domain death agonist, *BCL2* and *BCL2*-like 1, were analyzed by quantitative real-time polymerase chain reaction (qRT-PCR).

Results: Our results showed that toyocamycin-mediated inhibition of IRE1α-XBP-1 signaling significantly suppressed cell viability, migration, and invasion in ovarian cancer cells. In combined treatment with toyocamycin and docetaxel, it was determined that the viability, migration, and invasion were more effectively suppressed in a dose-dependent manner with increasing concentrations of toyocamycin than with either agent alone. Similar results were obtained from qRT-PCR studies. Combination treatments upregulated pro-apoptotic genes and downregulated anti-apoptotic genes in both cell lines.

Conclusion: The present data suggest that pharmacological targeting of IRE1α/XBP-1 signaling could significantly enhance the sensitivity of ovarian cancer cells to docetaxel.

Keywords: Docetaxel, ovarian cancer, toyocamycin, unfolded protein response

ÖZ

Amaç: Anti-mikrotübül ajanı olan dosetaksel taksan grubu sınıfındaki kemoterapötik ajanlardan birisidir ve çok sayıdaki kanser türünün tedavisinde yaygın olarak kullanılmaktadır. Ancak, dosetaksel'in kullanımına bağlı olarak hastalarda sistemik toksik etkiler gözlenebilmektedir. Bununla birlikte *de novo* veya edinilmiş direnci gelişimi dosetaksel'in kullanımını ve terapötik etkinliğini sınırlamaktadır. Bu nedenle adjuvan tedavi yaklaşımlarının araştırılması ilgi çekici hale gelmiştir. Bu çalışmada memeli hücrelerinde fizyolojik bir mekanizma olan İnozitol Gerektiren Enzim 1 alfa (IRE1α)-X-kutusu Bağlayıcı Protein 1 (XBP-1) yolunun *Streptomyces diastatochromogenes*'ten elde edilen bir adenozin analoğu olan toyokamisin aracılı inhibisyonunun ovaryum kanseri hücrelerinin dosetaksel'e olan duyarlılığı üzerine olan etkilerinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmalarda insan ovaryum adenokarsinoma hücre hatları SKOV3 ve Caov-3 kullanılmıştır. Toyokamisin ve dosetakselin hücre canlılığı üzerine olan etkileri Suda Çözünebilen Tetrazolyum-1 hücre canlılık testi ile incelendi.

Address for Correspondence: Yalçın Erzurumlu, Süleyman Demirel University Faculty of Pharmacy, Department of Biochemistry, Isparta, Türkiye
E-mail: yalcin.erzurumlu@gmail.com **ORCID ID:** orcid.org/0000-0001-6835-4436

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ÖZ

Toyokamisinin IRE1α-XBP-1 yolu üzerindeki inhibe edici etkisi immünoblotlama çalışmaları ile doğrulandı. Toyokamisin ve dosetakselin kombinasyonel uygulamalarının migrasyon ve invazyon üzerine olan etkileri yara iyileşme ve matrijel-kaplı Boyden-chamber invazyon testleri ile değerlendirildi. Kantitatif gerçek zamanlı polimeraz zincir reaksiyonu (qRT-PCR) çalışmaları ile B-cell lymphoma 2 (*BCL2*)-associated X apoptosis regulator, BH3-interacting domain death agonist, *BCL2* ve *BCL2*-like 1 gibi bazı pro-apoptotik ve anti-apoptotik genlerin ifade düzeyleri analiz edildi.

Bulgular: Sonuçlarımız IRE1α-XBP-1 sinyalinin toyokamisin aracılı inhibisyonunun ovaryum kanseri hücrelerinin canlılığını, migrasyonunu ve invazyonunu önemli ölçüde baskıladığını gösterdi. Toyokamisin ve dosetakselin kombinasyonel uygulamalarında artan konsantrasyonlardaki toyokamisin uygulamasına bağlı olarak daha etkili hücrelerin canlılığını, migrasyonunu ve invazyonunun yalnız başına uygulamalara kıyasla daha etkili olarak baskılandığı belirlendi. Benzer sonuçlar qRT-PCR çalışmalarından da elde edildi. Her iki hücre hattında da kombinasyonel uygulamaların pro-apoptotik genleri yukarı regüle ettiğini, anti-apoptotik genleri ise aşağı regüle ettiğini gösterdi.

Sonuç: Mevcut araştırma verileri ovaryum kanseri hücrelerinin dosetaksel'e olan duyarlılığının geliştirilmesinde IRE1α/XBP-1 sinyalizasyonunun farmakolojik olarak hedeflenmesinin önemli bir potansiyele sahip olduğunu önermektedir.

Anahtar Kelimeler: Dosetaksel, ovaryum kanseri, toyokamisin, katlanmamış protein yanıtı sinyali

Introduction

Ovarian cancer is one of the leading causes of cancer-related deaths in women. According to the American Cancer Society, an estimated 20,890 women in the United States will be diagnosed with ovarian cancer in 2025, and approximately 12,730 of these women will die from ovarian cancer (1). Currently, many risk factors for ovarian cancer have been identified, including androgen levels, body weight, postmenopausal hormone therapy, and familial cancer syndromes (2). Local treatments, such as surgery and radiation therapy, and systemic treatment approaches, such as chemotherapy, hormone therapy, targeted drug therapy, and immunotherapy, are widely used in the treatment of ovarian cancer. However, the heterogeneity of cancer cells in tumor tissues, the development of resistance to systemic treatments, and recurrence after treatment may limit the effectiveness of treatment for ovarian cancer (3). Therefore, improving the utilization of existing agents with confirmed efficacy and enhancing the sensitivity of cancer cells to these agents continue to be important priorities. Adjuvant approaches remain important in this regard (4).

Docetaxel, an anti-microtubule agent belonging to the taxane family, is used as a first-line treatment for many cancers, including prostate and breast cancer. Docetaxel is a semi-synthetic, second-generation taxane with cytotoxic effects, derived from the needles of European yew trees (5). It blocks tubulin polymerization, leading to cell cycle arrest in ovarian cancer cells. However, patients develop *de novo* or acquired resistance to docetaxel following high-dose administration. This situation limits the use and therapeutic efficacy of docetaxel (6). We aimed to investigate the effects of combined application of docetaxel and toyocamycin, an adenosine analog obtained from *Streptomyces diastatochromogenes*, on the sensitivity of ovarian cancer cells to docetaxel.

Recent studies have reported that mechanisms involved in the control of endoplasmic reticulum (ER) stress, the unfolded protein response (UPR), and cellular proteostasis play a key role in tumor progression and the acquisition of drug resistance by cancer cells (7). UPR signaling is controlled by three main regulatory pathways: Inositol-Requiring Enzyme 1 alpha (IRE1α), PKR-like ER kinase, and activating transcription factor 6. Toyocamycin selectively inhibits the IRE1α–X-box Binding Protein 1 (XBP-1) signaling pathway (8). Under ER stress, IRE1α, localized in the ER membrane, oligomerizes, undergoes autophosphorylation of its cytosolic kinase domain, and mediates removal of a 26-bp intron from XBP-1 mRNA by alternative splicing through activation of its endoribonuclease domain. In this way, the expression of UPR target genes is selectively regulated by the formation of XBP-1s, the spliced form of XBP-1 (9,10). Studies have reported that alterations in the activity of the IRE1α-XBP1 signaling pathway significantly affect tumorigenic properties of cancer cells, including survival, drug resistance, invasion, metastasis, and epithelial-mesenchymal transition (9-12). Although the UPR signal serves as an adaptive mechanism in mammalian cells, reprogramming cells in response to stress, it can also activate programmed cell death when cellular stress is insurmountable (13). Given these regulatory roles, the IRE1α-XBP-1 signaling pathway has been suggested as an important target for the development of cancer therapeutics.

Toyocamycin was originally isolated from *Streptomyces* species and is a nucleoside antibiotic analogue of adenosine (14). It blocks RNA synthesis and ribosomal function, and programmed cell death. Toyocamycin also negatively

modulates the IRE1α-XBP1 pathway by affecting IRE1α autophosphorylation—a step required for IRE1α activation—thereby inhibiting the splicing of XBP-1 mRNA (14). Current *in vitro* and *in vivo* studies have revealed that it has potent anti-cancer activity against cancer cells (14-16). Considering this evidence, investigating the effect of toyocamycin as an adjuvant treatment is of particular interest.

Herein, we evaluated whether toyocamycin potentiates the anticancer activity of docetaxel in SKOV3 and Caov-3 human ovarian adenocarcinoma cell lines. For this purpose, their effects on cell viability and on the migratory and invasive abilities of ovarian cancer cells were assessed using several methods. Moreover, the effects on the expression levels of some pro-apoptotic and anti-apoptotic genes were examined by quantitative real-time polymerase chain reaction (qRT-PCR). Our results showed that combined treatment with docetaxel and toyocamycin has the potential to significantly enhance docetaxel's anticancer effects in ovarian cancer cells. Taken together, these findings suggest that simultaneous pharmacological targeting of the IRE1α-XBP1 arm of the UPR signaling may significantly improve the sensitivity of ovarian cancer cells to docetaxel.

Materials and Methods

Materials

All cell culture-compatible plastic materials were supplied by Sarsdeth. The culture medium, fetal bovine serum (FBS), trypsin (0.25% and 0.05%), and other supplements were purchased from Lonza Bioscience. Dimethyl sulfoxide (#20385.01), of suitable quality for cell culture studies, was purchased from SERVA. Rabbit polyclonal antibody XBP-1s (#24868-1-AP) (1:2500), one of the primary antibodies used in immunoblotting studies, was supplied by Proteintech. Mouse monoclonal beta-actin antibody (#A5316) (1:10.000) was purchased from Sigma-Aldrich. Horseradish peroxidase (HRP)-conjugated anti-mouse (#31430) (1:500) or anti-rabbit (#31460) (1:500) immunoglobulin G (H+L) secondary antibodies were obtained from Thermo Fisher Scientific. Toyocamycin (#sc-362812) and docetaxel (#sc-201436) were obtained from Santa Cruz Biotechnology. Thapsigargin (#T9033) was provided by Sigma-Aldrich.

Methods

Cell Culture

SKOV3 (HTB-77™) and Caov-3 (HTB-75™) human epithelial ovarian adenocarcinoma cell lines were obtained from the American Type Culture Collection. SKOV3 cells were cultured in McCoy's 5A Medium supplemented with 10% FBS and Caov-3 cells were cultured in Dulbecco's Modified Eagle's Medium containing 10% FBS and 2 mM L-glutamine under conventional cell culture conditions (37 °C and 5% CO_2). Mycoplasma contamination was routinely monitored using the easy PCR™ Mycoplasma Detection Kit (#20-700-20) (Biological Industries). Cell lines used in the studies were passaged between 5 and 10 times.

Water-Soluble Tetrazolium-1 (WST-1)-Based Cell Viability Assay

Cells were seeded into 96-well cell culture dishes at a density of 10,000 cells/well; after 24 hours, toyocamycin, docetaxel or combinations of the two agents were applied to the cells for 48 hours. An equal volume of the solvent was applied as a control. The master stocks of all agents were prepared at a 2000-fold concentration. 48 hours later, cell viability was analyzed using WST-1 reagent (#MK400) (Takara, Japan), following the manufacturer's recommended protocol. 20 µL of WST-1 was added to each well, and the culture dish was incubated for 2 hours at 37 °C. Absorbance was measured at 450 nm using a microplate reader (BioTek Epoch 2). Experimental studies were performed in 3 technical and 3 biological replicates. Results are presented graphically as % viability ± standard deviation (SD). Inhibitory concentration 50 (IC_{50}) values for the agents were calculated using GraphPad Prism 8.0.

Quantitative Real-Time PCR

Total RNA was isolated using the Monoarch® Miniprep Total RNA Isolation Kit (#T2010S) (New England Biolabs, USA), following the manufacturer's recommended protocol. The concentrations and purity of the obtained RNA samples were determined by A260/A280 absorbance measurements using a microspectrophotometer (Allsheng Nano 400A). 1 µg of RNA sample was used to synthesize complementary DNA (cDNA) using the iScript™ cDNA Synthesis kit (#1708890) (Bio-Rad). Real-time PCR analyses were performed on the CFX Connect Real-Time PCR system using iTaq Universal SYBR® Green Master Mix (#1725120; Bio-Rad). mRNA expression levels of BCL2-associated X apoptosis regulator (*BAX*), *BCL2*, *BCL-xL*, and BH3-interacting domain death agonist (*BID*) were analyzed. Expression levels of ribosomal protein lateral stalk subunit P0 were evaluated for use as a housekeeping gene. Relative gene expression changes were calculated using the Livak method. Results are presented as fold change ± SD in a bar graph. qRT-PCR studies were performed with three biological replicates; each cDNA sample was analyzed in three technical replicates. Melting curve analysis was performed at the end of each qRT-PCR run to evaluate the specificity of the PCR.

Western Blotting

Immunoblotting studies were conducted as previously described in Erzurumlu et al. (17). Cell pellets were lysed in radioimmunoprecipitation assay buffer containing 1% mammalian protease inhibitor (SERVA #39102.01) for 30 min. The samples were centrifuged at 14,000 r.p.m. for 20 minutes at 4 °C; the pellet was removed, and the supernatant was stored for use in subsequent steps. Total protein content was determined using bicinchoninic acid (#23225) (Thermo Scientific, MA). Protein samples were denatured in 4x Laemmli protein loading buffer at 70 °C for 15 minutes. Protein samples were loaded onto hand-cast sodium dodecyl sulfate–polyacrylamide gels at approximately 25 µg per lane and were subjected to electrophoresis for 2 h. Protein samples separated on the gel were transferred onto an Immun-Blot® polyvinylidene difluoride (PVDF) membrane (Bio-Rad; #1620177). The PVDF membrane was subjected to blocking, washing, primary antibody treatment, washing, HRP-conjugated secondary antibody treatment, and washing; chemiluminescence imaging was then performed using Clarity™ Western ECL substrate (#1705061) (Bio-Rad). Chemiluminescence imaging was performed on the Fusion Pulse (Vilber Lourmat) system.

Wound-Healing Assay

Cells were seeded into 12-well cell culture dishes at a concentration of 3.5 x 10^5 cells per well. 24 hours later, wound areas were created using a sterile 200-µl micropipette tip. After washing the cells with 1x DPBS, fresh complete medium was added to the cells, and the cells were treated with agents for 72 hours. Wound areas were photographed at 0 and 72 hours using a phase-contrast microscope equipped with a camera system (Sunny SopTop microscope). Wound closure rates (%) were analyzed with ImageJ software (http://imagej.nih.gov/ij/). Each group was studied in three technical and three biological replicates, and the results were presented as % wound-closure area (mean ± SD) in a bar graph.

Matrigel-coated Boyden-Chamber Invasion Assay

Invasion assays were performed as previously described by Erzurumlu et al. (17). Matrigel (BD Biosciences) and serum-free medium were combined in a tube at a ratio of 1:8. 45 µl of the mixture was applied to the surface of a transwell (Sarstedt) with a pore size of 8 µm and incubated at 37 °C for 1 hour. The upper surface of the transwell was filled with 100 µl of serum-free medium and incubated for 30 minutes. 10,000 cells were seeded into each transwell. A culture medium containing 20% FBS was added to the culture dish holding the lower part of the transwell, and then the cells were treated with the agents. After 72 hours, cells that migrated to the lower surface of the membrane filter were fixed, stained with crystal violet, and counted. Each sample was analyzed in three biological and two technical replicates. Results are presented as percent invasion in a bar graph (mean ± SD).

Statistical Analysis

Statistical significance of differences between groups was determined by two-tailed Student's t-test (assuming equal variances) or one-way analysis of variance, with a confidence level of at least 95%, using GraphPad Prism 8.0. Statistical significance was accepted at $p < 0.05$. Results are presented as mean ± SD.

Results

Evaluation of the Effects of Toyocamycin and Docetaxel on Viability in Ovarian Cancer Cells

The effects of toyocamycin and docetaxel on cell viability in SKOV3 and Caov-3 human ovarian adenocarcinoma cells were investigated using the WST-1 cell viability assay. For this purpose, cells were treated with 10, 12.5, 25, 32.5, 40, 50, 62.5, 75, and 100 nM toyocamycin, and with 0.1, 0.125, 0.25, 0.325, 0.45, 0.5, 0.625, 0.75, and 1 nM docetaxel for 48 hours, after which WST-1 viability analysis was performed. Our results show that docetaxel and toyocamycin significantly suppressed cell viability in SKOV3 and Caov-3 cells in a concentration-dependent manner (Figures 1A and 1B). The IC_{50} concentrations of toyocamycin were determined to be 55.08 and 51.33 nM for SKOV3 and Caov-3 cells, respectively, and for docetaxel, they were calculated to be 0.585 and 0.563 nM.

Investigation of the Effects of Co-Administration of Toyocamycin with Docetaxel on the Viability of Ovarian Cancer Cells

To evaluate whether toyocamycin enhances the suppressive effect of docetaxel on the viability of SKOV3 and Caov-3 ovarian cancer cells, toyocamycin at ¼x, ½x, and 1x IC_{50} and docetaxel at 1x IC_{50} were applied simultaneously to the cells, and cell viability was analyzed. We found that combined application of toyocamycin and docetaxel suppressed cell viability more strongly than either agent alone (Figure 2). Our findings revealed that co-administration of toyocamycin and docetaxel resulted in enhanced anticancer responses in ovarian cancer cells.

Confirmation of the Inhibitory Effect of Toyocamycin on XBP-1s Production by Immunoblotting

Toyocamycin, an adenosine analog obtained from *S. diastatochromogenes*, prevents the cleavage of XBP-1

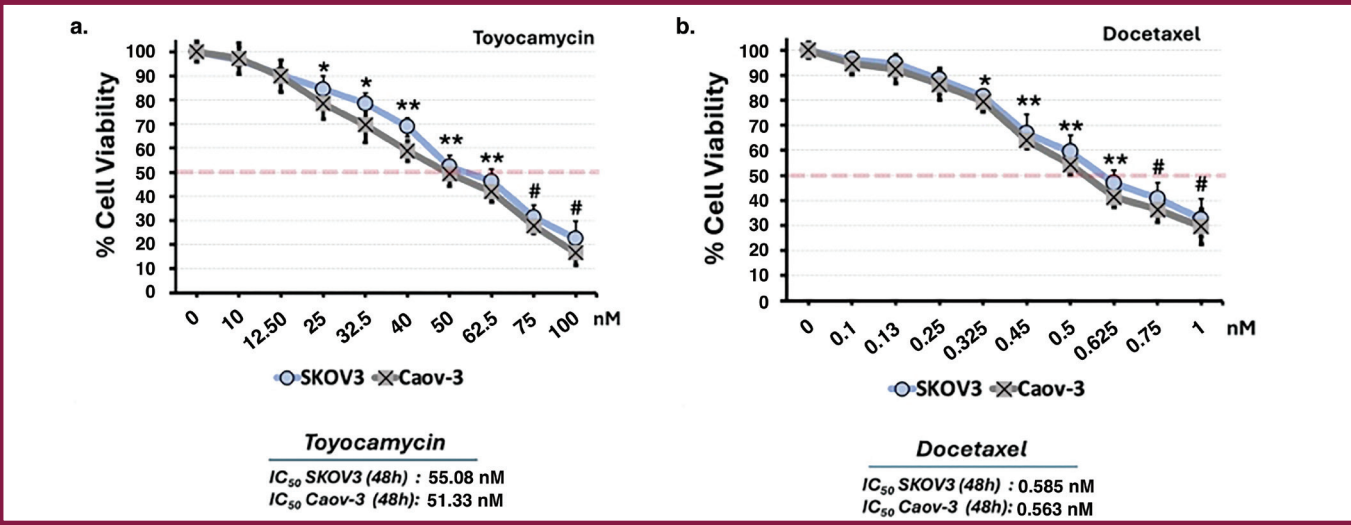


Figure 1. Investigation of the effects of toyocamycin and docetaxel on the viability in SKOV3 and Caov-3 human ovarian adenocarcinoma cells and the determination of IC_{50} concentrations. SKOV3 and Caov-3 cells were treated for 48 hours with (a) 10, 12.5, 25, 32.5, 40, 50, 62.5, 75, and 100 nM toyocamycin and (b) 0.1, 0.125, 0.25, 0.325, 0.45, 0.5, 0.625, 0.75, and 1 nM docetaxel . Cell viability was assessed using the WST-1 assay. Each experiment was performed with three independent biological replicates and three technical replicates. IC_{50} concentrations of the agents were calculated using GraphPad Prism 8.0. Comparisons with control were indicated as: *p < 0.05, **p < 0.005, #p < 0.001. IC_{50}, inhibitory concentration 50; WST-1, Water-Soluble Tetrazolium-1.

mRNA and blocks the formation of XBP-1s, which function as active transcription factors in UPR signaling. (14). Immunoblotting studies were performed to confirm XBP-1 inhibition at the IC_{50} concentrations determined in cell viability assays. In these studies, thapsigargin, which can activate UPR signaling by inducing ER stress, was used as a positive control. SKOV3 and Caov-3 cells were treated with 5 nM thapsigargin for 1 hour to induce ER stress (18). As expected, thapsigargin administration resulted in increased XBP-1s levels in SKOV3 and Caov-3 cells compared to the control group. Thapsigargin-induced increases in XBP-1s levels were suppressed by toyocamycin in a dose-dependent manner (Figure 3). These results confirm that toyocamycin inhibits XBP-1s signaling at the applied concentrations in SKOV3 and Caov-3 ovarian cancer cells.

Investigation of the Effects of Combined Applications of Toyocamycin and Docetaxel on the mRNA Expression Levels of Apoptotic Genes in Ovarian Cancer Cells

To examine the effects of toyocamycin and docetaxel treatments on the expression of pro-apoptotic (*BAX, BID*) and anti-apoptotic (*BCL2, BCL-xL*) genes in SKOV3 and Caov-3 cells, mRNA levels were evaluated by qRT-PCR. For this purpose, cells were treated with docetaxel at 1x IC_{50} and with toyocamycin at ¼x, ½x, and 1x IC_{50} or with combinations of the two agents, for 24 h. Our data revealed that toyocamycin and docetaxel alone significantly up-regulated the expression levels of the pro-apoptotic proteins *BAX* and *BID*, while the expression levels of the anti-apoptotic proteins *BCL2* and *BCL-xL* were down-regulated compared to the control group (Figures 4A and B). Combined treatment with increasing concentrations of toyocamycin and docetaxel strongly upregulated the expression of the pro-apoptotic proteins *BAX* and *BID* and downregulated the expression of the anti-apoptotic proteins *BCL2* and *BCL-xL*, compared with treatment with toyocamycin or docetaxel alone (Figures 4A and B). These results indicate that co-treatment with toyocamycin and docetaxel induces apoptotic responses more effectively than either agent alone in SKOV3 and Caov-3 cells.

Evaluation of the Effects of Co-treatment of Toyocamycin and Docetaxel on the Migration and Invasion Ability of Ovarian Cancer Cells

To evaluate the effects of co-treatments with toyocamycin and docetaxel on the migratory and invasive abilities of ovarian cancer cells, SKOV3 and Caov-3 cells were treated with 1x IC_{50} docetaxel and ¼x, ½x, and 1x IC_{50} toyocamycin, or combinations of both agents, for 48 hours in migration assays and 72 hours in invasion assays. Our results showed that treatment with either toyocamycin or docetaxel alone significantly inhibited the migration and invasion of SKOV3 and Caov-3 cells compared with the control group (Figures 5A and 5B). In our trials in which combinations of

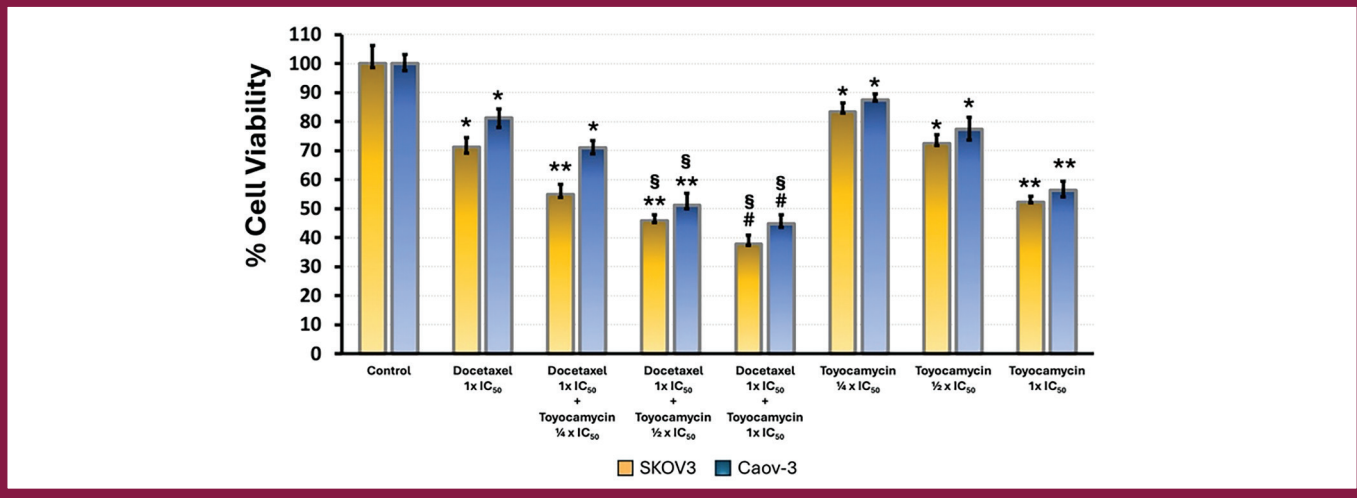


Figure 2. Investigation of the effects of combined application of toyocamycin and docetaxel to SKOV3 and Caov-3 human ovarian adenocarcinoma cells on cell viability. SKOV3 and Caov-3 cells were treated with toyocamycin at ¼x, ½x, and 1x IC_{50}, with docetaxel at 1x IC_{50}, or with combinations thereof for 48 hours. Cell viability was examined by WST-1 assay. Results are presented in the graph as % viability relative to the control group. Each experiment was performed with three independent biological replicates and three technical replicates. Toyocamycin concentrations corresponding to ¼x, ½x, and 1x IC_{50} are 13.77, 27.54, and 55.08 nM for SKOV3 and 12.83, 25.67, and 51.33 nM for Caov-3, respectively. The 1x IC_{50} docetaxel concentrations were 0.585 nM and 0.563 nM for SKOV3 and Caov-3, respectively (comparisons with control: *$p < 0.05$; **$p < 0.005$; #$p < 0.001$, comparisons with docetaxel: §$p < 0.05$; §$p < 0.01$). IC_{50}, inhibitory concentration 50; WST-1, Water-Soluble Tetrazolium-1.

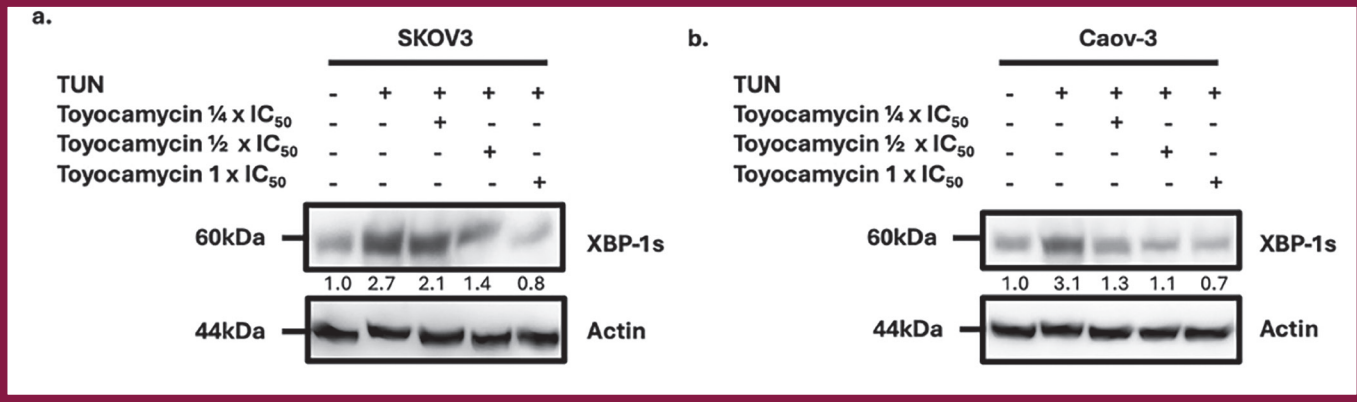


Figure 3. Confirmation of the inhibitory effect of toyocamycin on XBP-1 by immunoblotting studies. (a) SKOV3 and (b) Caov-3 cells were treated with combinations of 5 nM thapsigargin with toyocamycin at ¼x, ½x, and 1x IC_{50} for 24 hours. Total protein was subsequently isolated from the cells, and XBP-1s levels were examined by immunoblotting. Beta-actin was used as a loading control in these studies. Thapsigargin was used as a positive control. Densitometry results of XBP-1s levels, normalized to beta-actin bands, are presented below the blot images. ¼x, ½x and 1x IC_{50} toyocamycin concentrations are 13.77, 27.54 and 55.08 nM for SKOV3 and 12.83, 25.67 and 51.33 nM for Caov-3, respectively. IC_{50}, inhibitory concentration 50; XBP-1, X-box Binding Protein 1.

increasing concentrations of toyocamycin and docetaxel were applied, co-treatment with toyocamycin and docetaxel more strongly inhibited the migratory and invasive abilities of SKOV3 and Caov-3 cells than either agent alone. Our results showed that the combination of toyocamycin and docetaxel produced more potent anti-migratory and anti-invasive effects.

Discussion

Gynecological cancers continue to be a significant health problem; they are commonly diagnosed and are a frequent cause of death (19). In many patients, resistance to conventional therapies or distinct genomic and proteomic profiles of tumor cells limit treatment success (20). Therefore, research on adjuvant approaches has gained importance.

Taxane-class agents are an important group of chemotherapeutic agents used in cancer therapy (21). Responses to treatments with taxane-class drugs may vary depending on whether patients have received previous therapy. Patients may develop resistance to these agents (22). In the present study, the combined effect of the taxane-class drug docetaxel and toyocamycin on improving its anticancer activity was evaluated in an *in vitro* ovarian cancer model using several methodologies.

Toyocamycin, also known as vengicide, is an adenosine analog. Isolated from *S. diastatochromogenes*, toyocamycin exhibits activity against multiple targets and functions as an antibiotic with antitumor activity (14,23). Studies have shown that toyocamycin inhibits the IRE1α-XBP-1 signaling pathway, a physiological signaling mechanism in mammalian cells (14).

IRE1α signaling regulates numerous pathways in mammalian cells, including lipid biogenesis, chaperone synthesis, protein degradation, control of quality-control protein levels, regulation of autophagic responses, and increased expression of pro-survival genes (24,25). Recent studies have revealed that changes in the activity of the IRE1α-XBP-1 signaling pathway promote carcinogenesis (9-12). Thus, it is suggested as one of the important mechanisms to be targeted in cancer therapy. Toyocamycin is a small-molecule agent that inhibits the IRE1α-XBP-1 signaling pathway by blocking the kinase activity of IRE1α (14). Its selective effect on IRE1α-XBP-1 signaling makes it an important agent for investigating its efficacy in anticancer therapies.

Our studies investigating the possible enhancing roles of toyocamycin on the anticancer activity of docetaxel

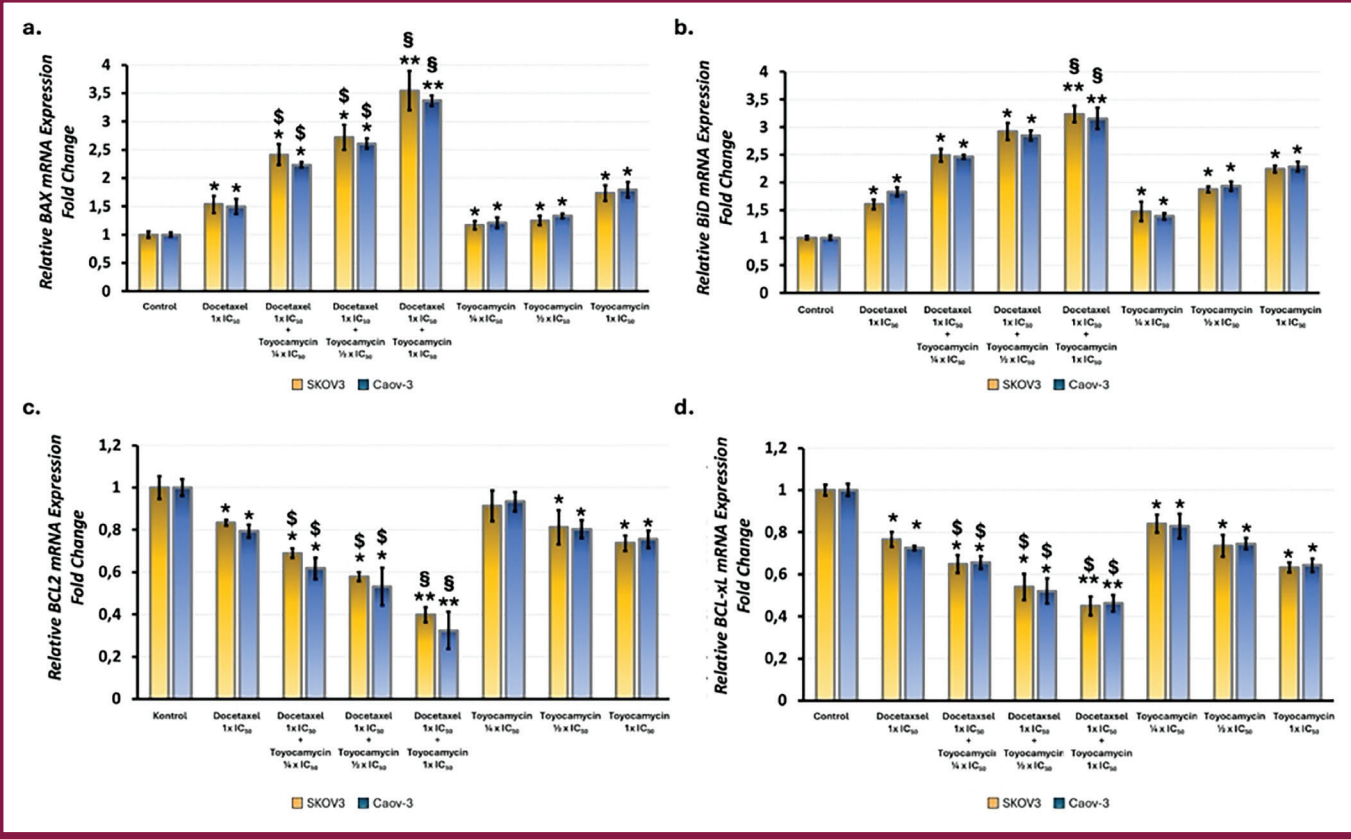


Figure 4. Investigation of mRNA expression levels of pro-apoptotic and apoptotic genes in SKOV3 and Caov-3 cells by qRT-PCR. Cells were treated for 24 hours with toyocamycin at ¼x, ½x, or 1x IC_{50}; with docetaxel at 1x IC_{50}; or with combinations of both agents. mRNA expression levels of the genes (a) *BAX*, (b) *BID*, (c) *BCL2*, and (d) *BCL-xL* were analyzed by qRT-PCR. RPLP0 was used as the housekeeping gene. Results are presented as fold changes with SDs (±) in a bar graph. The control was set to 1. Each experiment was performed in three independent biological and three technical replicates. ¼x, ½x and 1x IC_{50} toyocamycin concentrations are 13.77, 27.54 and 55.08 nM for SKOV3 and 12.83, 25.67 and 51.33 nM for Caov-3, respectively. 1x IC_{50} docetaxel concentration is 0.585 nM and 0.563 nM for SKOV3 and Caov-3, respectively (comparisons with control; *p < 0.05; **p < 0.005; #p < 0.001, comparisons with docetaxel; $p < 0.05; §p < 0.01). *BAX*, BCL2-associated X apoptosis regulator; *BCL-xL*, BCL2-like 1; *BCL2*, B-cell lymphoma 2; *BID*, BH3-interacting domain death agonist; RPLP0, ribosomal protein lateral stalk subunit P0; IC_{50}, inhibitory concentration 50; qRT-PCR, quantitative real-time polymerase chain reaction; SD, standard deviation.

determined that the combination of docetaxel and toyocamycin, across increasing concentrations, suppressed the viability of ovarian cancer cells to a significantly greater extent than docetaxel alone (Figure 1B). These findings suggest that targeting the IRE1α-XBP-1 pathway with toyocamycin, in combination with docetaxel as an adjuvant therapy, may represent an important approach to achieve more effective anticancer responses. Previous reports have shown that UPR signaling is an important mechanism of drug resistance in cancer cells (26). From this perspective, toyocamycin may offer an important approach to preventing resistance to docetaxel. However, our findings, which are limited to an *in vitro* experimental model of simultaneous combination therapy, should be validated in *in vivo* studies of long-term docetaxel treatment to confirm the effect of toyocamycin on docetaxel therapy.

Few studies have examined the combined effects of toyocamycin. Ri et al. (14) demonstrated that toyocamycin exerts therapeutic effects in multiple myeloma (MM) cells by inhibiting IRE1α-XBP-1. These studies also demonstrated that combinations of toyocamycin with bortezomib, a proteasome inhibitor, had greater antitumor activity in an *in vivo* MM model (14). Park et al. (15) reported that toyocamycin induces apoptosis through crosstalk between oxidative stress and the MAPK signaling pathway in human prostate cancer cells. Additionally, a Phase I study was conducted of toyocamycin

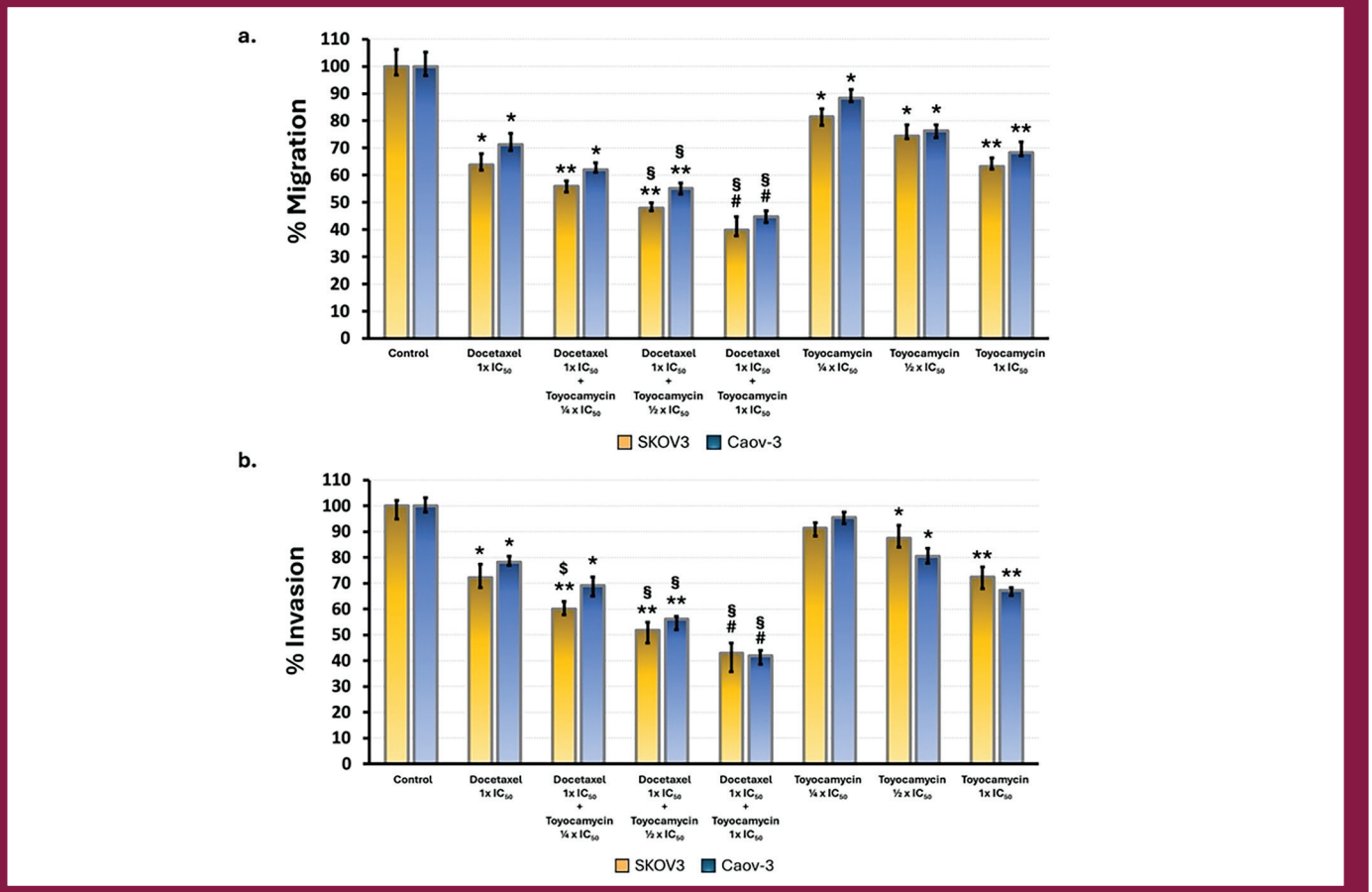


Figure 5. Evaluation of the effects of toyocamycin and docetaxel applications on migration and invasion ability in SKOV3 and Caov-3 cells. (a) SKOV3 and Caov-3 cells were treated with toyocamycin at ¼x, ½x, and 1x IC_{50}, with docetaxel at 1x IC_{50}, or combinations of both agents. Wound areas were monitored for 72 hours during migration experiments. % changes in wound closure were calculated from closure areas measured at 0 and 72 hours using ImageJ software. Each experiment was performed in three independent biological and three technical replicates. (b) In invasion assays, SKOV3 and Caov-3 cells were treated with toyocamycin at ¼x, ½x, and 1x IC_{50}, with docetaxel at 1x IC_{50}, or with combinations of both agents, for 72 hours. Cells exhibiting invasion were stained with crystal violet and counted. Results are presented as fold changes ± SDs in bar graphs. Each experiment was performed in three independent biological and three technical replicates. ¼x, ½x and 1x IC_{50} toyocamycin concentrations are 13.77, 27.54 and 55.08 nM for SKOV3 and 12.83, 25.67 and 51.33 nM for Caov-3, respectively. 1x IC_{50} docetaxel concentration is 0.585 nM and 0.563 nM for SKOV3 and Caov-3, respectively (comparisons with control; *$p < 0.05$; **$p < 0.005$; #$p < 0.001$, comparisons with docetaxel; $^{\$}p < 0.05$; $^{\$}p < 0.01$). IC_{50}, inhibitory concentration 50; SD, standard deviation.

in patients with advanced solid tumors. However, the study results were not carried forward to subsequent stages, in which patients did not demonstrate a significant clinical response to toyocamycin treatment. One important finding of this study was that no systemic side effects, such as organ dysfunction or cytopenia, were observed in association with toyocamycin treatment. Local foci of necrosis were observed only at the infusion sites in tissues treated with toyocamycin. This suggests that the side effects of toyocamycin infusion via central venous catheters would be manageable. This issue paves the way for its clinical use (27). Taken together, these findings suggest that toyocamycin is a promising agent and that further studies are required to examine its effects in different cancer groups and to determine its possible additive effects with different treatments.

Radiotherapy and systemic or targeted cytotoxic agents, commonly used in cancer therapy, stimulate the apoptotic cell-death pathway. Therefore, evasion of apoptosis by cancer cells is one of the main reasons for treatment failure (28). In our studies, we examined the expression levels of the pro-apoptotic genes *BAX* and *BID* and the anti-apoptotic genes *BCL2* and *BCL-xL*. Our findings showed that toyocamycin and docetaxel reprogrammed the cells by upregulating pro-apoptotic gene expression and downregulating anti-apoptotic gene expression in SKOV3 and Caov-3 cells. Moreover, combination therapy induced the expression of apoptotic genes more effectively than either therapy alone (Figures 4A and B). These findings suggest that toyocamycin enhances docetaxel-mediated induction of apoptosis in ovarian cancer cells additively, thereby providing more effective anticancer responses.

Study Limitations

One of the major limitations to successful cancer treatment is that cancer cells become more aggressive, exhibiting increased migration and invasion. This allows cancer cells to spread more rapidly. Furthermore, drug resistance contributes to the failure of currently applied therapies (29,30). In this respect, the simultaneous use of combinatorial approaches alongside traditional treatments is important for improving therapeutic efficacy. Our findings showed that treatment of ovarian cancer cells with increasing concentrations of toyocamycin combined with docetaxel significantly reduced the migratory and invasive abilities of SKOV3 and Caov-3 cells compared with treatment with docetaxel or toyocamycin alone (Figures 5A and B). Previous studies have reported that pharmacological targeting of UPR signaling suppresses the motility-related properties of cancer cells (31). Consistent with this, present data suggest that toyocamycin treatment in combination with docetaxel, which has an inhibitory effect on cell division, results in more effective responses than either agent alone, due to the suppression of tumorigenic properties of ovarian cancer cells and to toyocamycin-mediated disruption of the UPR signal, which functions as an adaptive mechanism. Although our findings are limited to *in vitro* results, studies in the literature emphasize the importance of targeting the IRE1α-XBP-1 arm of the UPR signaling pathway for new therapeutic approaches. The importance of UPR-targeted approaches has been highlighted in numerous *in vitro* and *in vivo* studies, particularly in prostate, breast, pancreatic, ovarian, glioblastoma, and hematological cancers (11,12,32-38). Collectively, our research findings suggest that targeting IRE1α-XBP-1 signaling to improve cellular sensitivity to docetaxel in ovarian cancer may contribute to the development of new treatment protocols.

Conclusion

In conclusion, our *in vitro* findings suggest that the XBP-1 inhibitor toyocamycin, which targets the IRE1α arm of the UPR, has significant potential to sensitize ovarian cancer cells to docetaxel. Our data, limited to *in vitro* experimental findings, support further studies examining the potential use of toyocamycin in cancer cells. Although obtaining data from *in vitro* systems is a significant limitation of our study, the present findings suggest that the potential effects of toyocamycin may guide the design of further *in vivo* experimental models.

Ethics

Ethics Committee Approval: This study does not require any ethical permission.

Informed Consent: Not required.

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Footnotes

Authorship Contributions

Concept: Y.E., Design: Y.E., Data Collection or Processing: Y.E., Y.D., Analysis or Interpretation: Y.E., Literature Search: Y.E., Y.D., Writing: Y.E.

Conflict of Interest: No conflict of interest was declared by the author(s).

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