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Original Article

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Retracted Articles in the Field of Public, Environmental and Occupational Health: A Descriptive Study

Halk Sağlığı, Çevre Sağlığı ve İş Sağlığı Alanlarında Retrakte Edilen Makaleler: Tanımlayıcı Bir Çalışma

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ABSTRACT

Objective: Retraction is a process brought up when concerns about the integrity of a paper arise. It is widely accepted that a notable increase occurred in the last years. This study aims to explore retractions in public, environmental and occupational health research.

Material and Methods: The type of this study is descriptive. The authors searched the Web of Science database for retractions in public, environmental and occupational health research. Publication date, retraction date, the number of days between the publication and retraction dates, journal names, document type, the country of the corresponding author, reasons for retraction, the source of the retraction request, journal index, and citation count of the retracted papers were recorded.

Results: A total of 192 papers were evaluated. The median time between the papers' publication date and the retraction date was 498 days. The median citation count was 1. A notable increase in the number of retracted papers over recent years was observed, with a peak in 2015. The most commonly identified reasons for retraction were: error (n=59), plagiarism (n=43), and duplication (n=25).

Conclusion: The increasing number of retractions indicates both challenges and improvements in scientific publishing. Editorial and peer-review practices should be improved, awareness among the authors needs to be raised, and more effective post-publication monitoring systems should be implemented.

Keywords: Retraction, public health, occupational health, environmental health

ÖZ

Amaç: Retrakte etme, bir makalenin güvenilirliği ilgili endişeler ortaya çıktığında gündeme gelen bir süreçtir. Son yıllarda retrakte edilen yayın sayısında önemli bir artış olduğu yaygın olarak kabul edilmektedir. Bu çalışmanın amacı halk sağlığı, çevre ve iş sağlığı alanında retrakte edilmiş yayınları incelemektir.

Gereç ve Yöntemler: Bu çalışma tanımlayıcı bir çalışmadır. Halk sağlığı, çevre ve iş sağlığı alanında retrakte edilen yayınlar için Web of Science veritabanı taranmıştır. Basım tarihi, retrakte edilme tarihi, basım ve retrakte edilme tarihleri arasındaki kalan gün sayısı, dergi adları, makale tipi, sorumlu yazarın ülkesi, retrakte edilme nedenleri, geri çekme talebinin kimden geldiği, derginin dizini ve retrakte edilen makalelerin atıf sayısı kaydedildi.

Bulgular: Toplamda 192 makale değerlendirildi. Makaleler için yayın tarihi ile retrakte edilme tarihi arasındaki medyan süre 498 gündü. Medyan atıf sayısı 1'di. Son yıllarda retrakte edilen makale sayısında önemli bir artış olduğu gözlemlendi. Retrakte edilen makale sayısının en fazla olduğu yıl ise 2015 olarak bulundu. En sık retrakte edilme sebepleri; hata (n=59), intihal (n=43) ve duplikasyondu (n=25).

Sonuç: Retrakte edilme sayısının artması bilimsel yazında hem birtakım zorluklara hem de süreçteki gelişmelere işaret etmektedir. Editöryal ve hakem değerlendirme süreçleri iyileştirilmeli, yazarların konu hakkında farkındalığı artırılmalı ve etkin basım sonrası bildirim sistemleri süreçlere dahil edilmelidir.

Anahtar Kelimeler: Retrakte edilme, halk sağlığı, iş sağlığı, çevre sağlığı

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INTRODUCTION

The publication process of a scientific paper relies heavily on the trust and cooperation of several stakeholders: the authors, the readers, the publishers the peer reviewers, and editors who play active roles in ensuring the reliability and integrity of the research. At any stage of this process, if the mutual trust between these parties is compromised, retraction may be considered (1). Retraction is a formal process initiated when concerns arise about the reliability of a scientific study. These concerns can stem from a variety of issues, including errors, data duplication, plagiarism, and ethical violations (2). In this context, retraction serves as an important correction mechanism within the scientific literature, addressing and rectifying any discrepancies or misconduct that may have undermined the credibility of the published work (3).

However, recent years have witnessed a notable increase in the number of retractions across various fields of science (4). This trend is closely tied to the pressures of the "publish or perish" culture, which has become a driving force in academia. With an ever-growing emphasis on publishing frequently and quickly to secure academic advancement and funding, many researchers find themselves under immense pressure to produce results (1-3). This pressure can lead to shortcuts in research practices, including data manipulation, misreporting, and even ethical lapses, all of which can ultimately result in retraction.

The consequences of retractions in scientific publishing can be far-reaching, particularly in fields like medicine, where research directly informs clinical practices and patient care. When a study is retracted, it signals that the findings are unreliable or flawed, which can undermine public trust in the medical literature (5). For clinicians and healthcare providers who rely on published research to guide treatment decisions, a retracted study can create confusion, delays in adopting best practices, or, in some cases, even harm patients (6). In the medical field, where the stakes are literally life and death, ensuring the accuracy and trustworthiness of published research is of utmost importance, not only for the advancement of science but also for patient well-being.

This study aims to explore retractions in public, environmental, and occupational health research. By analyzing retracted studies, we seek to identify common reasons behind these retractions and raise awareness of the importance of scientific integrity in research, underlining its implications for evidence-based decision-making.

MATERIALS and METHODS

This is a descriptive study. Due to the challenges of integrating databases and accessing specific information, we decided to work with a single database and chose Web of Science (WoS) because it is the oldest database, with wide coverage and high data reliability. The authors used the WoS database on July 20, 2023, and filtered by category "public, environmental and occupational health," document type "retraction, retracted publication, withdrawn publication" to identify a series of retracted publications. No exclusions were made based on the publication date, and all articles from all time periods available in the database were included in the study. In total, 246 retracted articles along with their retraction notes were saved in a file for further evaluation. Articles that were repeated, had unverified retractions, or were book chapters were excluded from the study. There were no humans or animals involved in the study. Since open data analysis was used, ethics committee approval was not required.

The classification of retraction reasons was applied according to the following explanations, taking into account the current literature (3,7):

i) Error (improper study design, insufficient data collection, presentation, or report)

ii) Fraud (data, figure, case, or image manipulation, fabrication, and falsification)

iii) Author disagreements and conflicts (publication without an author's knowledge or approval, identification of fictitious authors, or conflict between authors and funders)

iv) Duplication (double publication of the same article)

v) Ethical issues (absence of ethics committee permission, failure to obtain consent from participants)

vi) Peer-review issues (fake or biased peer-review methods, as well as other issues concerning this process)

vii) Plagiarism (misuse of individuals' scientific properties, such as papers, texts, study designs, tables, graphs, figures, and ideas. This category also includes self-plagiarism)

viii) Unknown (not specified)

Statistical Analysis

The data evaluated included the publication date, retraction date, the number of days between the publication and retraction dates, journal names, document type, the country of the corresponding author, reasons for retraction, the source of the retraction request, journal index, and citation count.

Two researchers (EK and RG) independently assessed the reasons for retraction and compared their evaluations. In case of discrepancies, the two researchers collaborated to make a final decision. For continuous variables, mean, standard deviation, median, minimum, and maximum values were calculated, while frequencies and percentages were used for categorical variables.

To examine changes in the number of retracted publications over the years, linear regression analysis was applied. Minitab software was used to visualize linear changes and to forecast the number of retracted publications in future years.

RESULTS

After applying the WoS-based search strategy, 246 retracted papers were recorded in the public, environmental and occupational health category. After applying the exclusion criteria, a total of 192 papers remained for the final analysis, excluding 52 repeated papers, 1 non-retracted paper, and 1 book chapter. The flow chart of the study algorithm is shown in Figure 1.

The median time between the publication date and the retraction date for the papers was 498 days (min=0, max=5497). The median citation count was 1 (min=0, max=158) (Table 1).

Regarding the retracted papers, the highest number was observed in 2015. Regression and trend analysis indicated an increase in the number of retracted papers in recent years ($Yt=-2.51 + 1.261 \times t$). The expected numbers of retracted papers in the public, environmental and occupational health category for the years 2023, 2024, and 2025 were estimated to be 22.7, 23.9, and 25.2, respectively (Figure 2).

Table 2 lists the top 10 journals with the most retractions. Toxicology and industrial health (n=12), European journal of contraception and reproductive health care (n=9), and frontiers in public health (n=8) were the top journals in this field.

Table 3 lists the top 10 countries with the most retracted papers. The United States of America had the most retracted papers, with 38 publications, accounting for 19.8% of all retracted publications worldwide. Iran followed with 20 (10.4%) retracted papers, and China was third with 17 (8.9%) retracted papers.

The retracted papers were categorized based on the reasons for retraction, which were evaluated by researchers who reviewed the retraction notes. The most commonly identified reasons for retraction were error (n=59), plagiarism (n=43), duplication (n=25), unknown (n=16), peer review issues (n=14), ethical issues (n=14), fraud (n=13), and author disagreements or conflicts (n=8) (Figure 3).

Seventy percent of the retracted papers were original articles, 18% were reviews, and 12% were other types of documents. When examining the decision-making points for retraction requests, it was found that 71% of the decisions were made by publishers, 24% by authors, 2% by both publishers and authors, and 3% by unknown parties. The types of retracted documents, retraction requests and decisions, the journal index of the articles are shown in Figure 4.

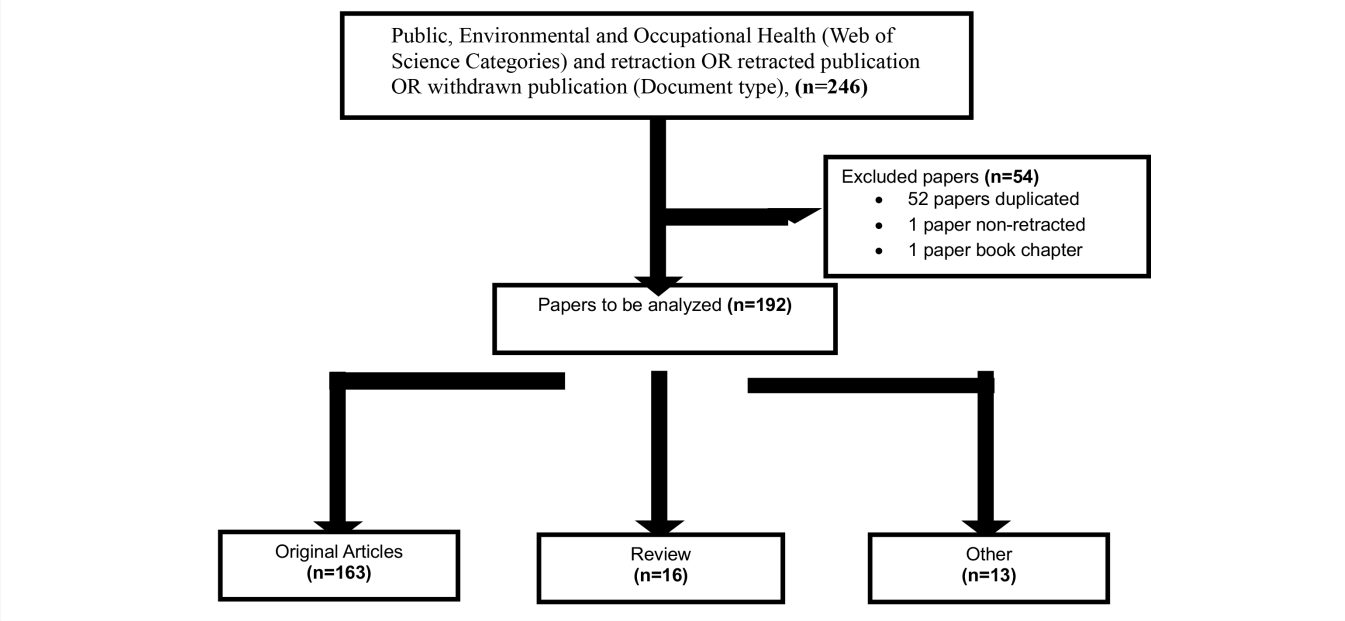

Figure 1. The algorithm of study

Table 1. Publication duration and citation count of retracted papers

	Mean	SD	Median	Minimum	Maximum
Duration of publication (days)	806.1	881.8	498	0	5437
Citation count	7.1	18.1	1	0	158

SD: Standard deviation

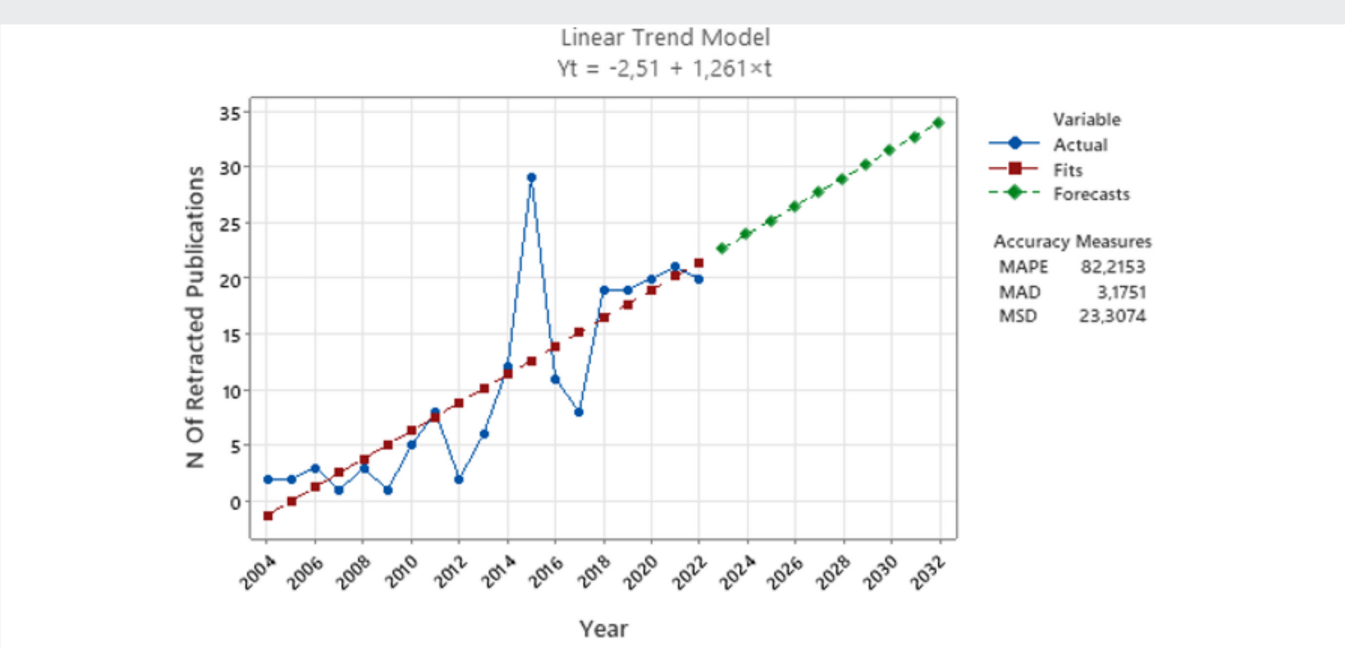

Figure 2. Trend analysis for retracted paper
MAPE: Mean absolute percentage error, MAD: Mean absolute deviation, MSD: Mean square deviation

Table 2. Top 10 journals with the most retractions

	N	%
Toxicology and Industrial Health	12	6.3
European Journal of Contraception and Reproductive Health Care	9	4.7
Frontıers in Public Health	8	4.2
Pan African Medical Journal	7	3.6
International Journal of Environmental Research and Public Health	6	3.1
BMC Public Health	5	2.6
Journal of Community Psychology	5	2.6
Environmental Geochemistry and Health	5	2.6
Environmental Health Perspectives	5	2.6
Cancer Epidemiology Biomarkers & Prevention	4	2.1
N: Number		

Table 3. Top 10 countries with the most retracted papers

	N	%
Usa	38	19.8
Iran	20	10.4
China	17	8.9
India	15	7.8
Egypt	14	7.3
UK	14	7.3
Australia	6	3.1
Kenya	5	2.6
Cameroun	4	2.1
Russia	4	2.1
N: Number		

DISCUSSION

Our findings indicate a notable increase in the number of retracted papers over recent years, with a peak observed in 2015. Many publications examining retracted articles mentioned an increase over the recent years (3,4,8-13). It is not surprising that we have also found, in our study examining retracted articles in the field of public health, an increase over the years. One reason for this may be that published research can be easily reached by everyone, which increases the auditability of the literature, thanks to developing technology and the internet. Another reason may be the increase in the volume of published research, which naturally can lead to more retractions in a larger pool of papers. Another issue that should be emphasized is that articles that are retracted in the field of medicine may also affect the treatments given to patients, and this requires special sensitivity during evaluation. The retraction of some articles related to treatment during the COVID-19 pandemic that we have recently experienced has threatened the trust that society has in science (14-18).

The median time between publication and retraction was found to be 498 days, which highlights that, on average, retracted papers remain in the literature for over a year before being flagged. The lag between the publication dates and retraction of articles was found to be of varying duration

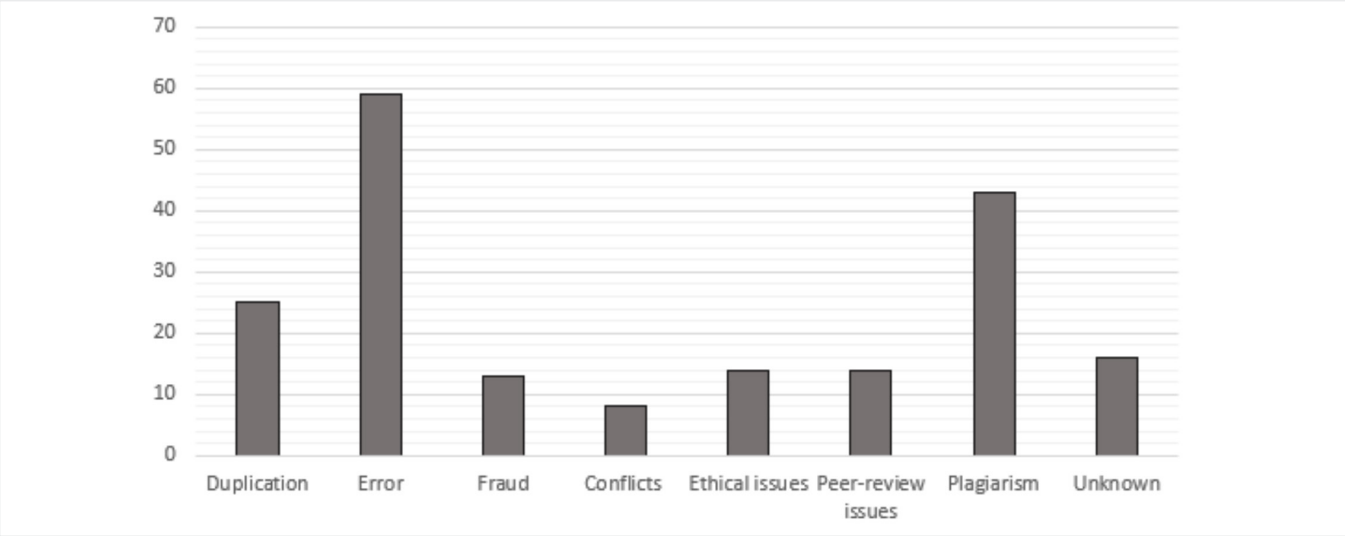

Figure 3. The most common reasons for retraction

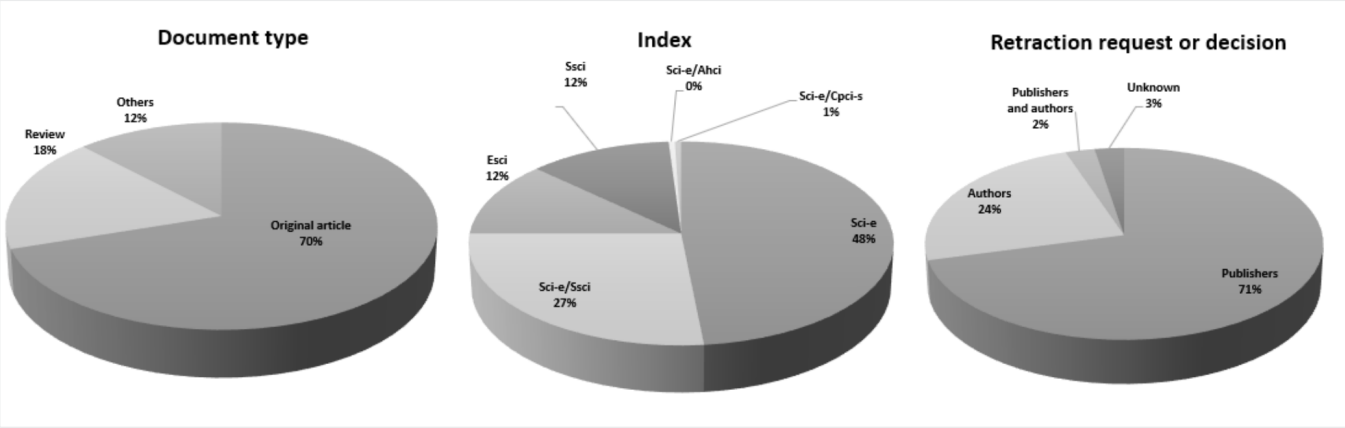

Figure 4. Document types, indexes and sources of retraction decisions of papers

when looking at studies examining this topic (3,8,19,20). This may be due to the different methodologies used in examining various research fields (e.g., life sciences) and the types of articles (e.g., original articles). Nevertheless, the delay in retraction is a concerning issue, since it means that flawed research may be disseminated and cited by other researchers before it is officially retracted. luckily, for public, environmental and occupational health papers, we found the median citation count for retracted papers is just 1, which may suggest that most retracted papers had a minimal impact on the scientific community in terms of citations, though a small proportion had a significant influence before being retracted. It is expected that a retracted article will be cited only in the context of the retraction. However, in practice, this is not the case and sometimes these articles may be cited by inexperienced authors (3). To prevent this, retraction notes must be published swiftly and accessible to all authors openly. The use of databases such as the Retraction Watch Database allows for earlier detection of retracted articles and thus prevents these articles from being mistakenly cited in another article (21).

The most common reasons for retraction were error, plagiarism, and duplication. These findings are similar to previous literature, where duplication and plagiarism have been frequently identified as the primary causes for retraction (22-24). However, we found scientific errors to be more frequent in the field of public, environmental and occupational health. Errors in data analysis, miscalculations, or misinterpretations of data are sometimes identified post-publication, leading to retraction. Plagiarism and duplication are particularly concerning, as they point to ethical breaches that undermine the credibility of the research process. Most of the retracted papers were original research articles. This distribution reflects the higher volume of original

research published in scientific journals. Original articles are also thought to be more prone to errors or misconduct; therefore, higher retraction rates are not quite surprising (3,7). Interestingly, retraction decisions were primarily made by publishers, rather than authors, suggesting that publishers play a crucial role in overseeing the integrity of the literature after publication.

Study Limitation

This study highlights the ongoing challenges faced by the scientific community in maintaining the integrity of published research. The main strength of this study is the examination and evaluation of a relatively large number of publications regarding their retraction. Several limitations, however, can be identified in the current paper. We only searched one database, so our results cannot be extrapolated to all publications in the field of public, environmental and occupational health. Secondly, we only selected a specific field, which also obstructs generalizability. Finally, as with the COVID-19 pandemic, trends in retraction may change over time. This article examined only a specific time period.

CONCLUSION

The increasing number of retractions indicates both challenges and improvements in scientific publishing. While the majority of retracted papers appear to have had minimal impact in the field of public, environmental and occupational health, considering the low value of the median citation number, the influence of widely cited retracted papers can be profound. Another feature that should be underlined about the publications in the field of public, environmental, and occupational health was that the retraction was primarily due to scientific errors rather than on more serious ethical grounds. Continuous efforts are needed to refine editorial and peer-review practices, increase transparency, raise awareness among the authors, and implement more effective post-publication monitoring systems.

Ethics

Ethics Committee Approval: There were no humans or animals involved in the study. Since open data analysis was used, ethics committee approval was not required.

Informed Consent: Since no humans or animals were involved in the study, patient consent information is not required.

Footnotes

Author Contributions

Concept: R.A.O., E.K., Design: R.A.O., R.G., E.K., Data Collection or Processing: R.G., Analysis or Interpretation: R.A.O., E.K., Literature Search: R.A.O., Writing: R.A.O., R.G., E.K.

Conflict of Interest: All authors declare that they have no conflict of interest.

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Original Article

Evaluation of Clinics and Prognoses of COVID-19 Patients with Ferritin, D-Dimer, FAD-85 Score in Intensive Care Unit

COVID-19 Hastalarının Yoğun Bakıma Yatış Sırasında Ferritin, D-Dimer Değerleri ve FAD-85 Skorları ile Klinik Seyir ve Prognozları Arasındaki İlişkinin Değerlendirilmesi

Melek DOĞANCI

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ABSTRACT

Objective: COVID-19 is a serious disease that can cause severe acute respiratory distress syndrome and end-stage organ failure. Clinicians need early and effective indicators to evaluate prognosis and prevent mortality in such infections. The FAD-85 score is used as an early marker calculated by the patient's age, ferritin level, and D-dimer level. This study aimed to investigate the effects of the FAD-85 score, D-dimer, and ferritin values on prognosis and mortality during admission to the intensive care unit (ICU).

Material and Methods: The data of 204 patients hospitalized with the diagnosis of COVID-19 in the tertiary ICU between April 1, 2021-March 31, 2022 were retrospectively analyzed. Demographic characteristics of the patients, invasive/non-invasive mechanical ventilator or high flow oxygen requirement and duration, tracheostomy and intubation status, length of stay in hospital and ICU and 1-month mortality were evaluated. From laboratory parameters, leukocyte, lymphocyte, ferritin, D-dimer, procalcitonin, C-reactive protein (CRP), lactate dehydrogenase levels were recorded. Age + 0.01 x ferritin + D-dimer formula was used for the FAD-85 score.

Results: In this study, in which 204 COVID-19 patients were examined, the conditions predicting 1-month mortality: male gender (p=0.029), presence of intubation (p<0.001), increased CRP (p=0.002), low lymphocyte levels (p=0.009), FAD-85>85 (p=0.001) and high ferritin (p= 0.044) were found. In addition, the presence of intubation [odds ratio (OR) 95% confidence interval (CI): 3.941 (2.115-7.343)], high CRP [OR (95% CI): 1.004 (1.000-1.008)], and FAD-85>85 [OR (95% (CI) (2.462 (1.313-4.617)] were found to predict mortality.

It has been determined that the FAD-85 score, a simple metric, is effective in forecasting mortality among COVID-19 patients. It was observed that patients with a FAD-85 score greater than 85, patients with elevated CRP, and patients requiring intubation have higher mortality rates.

Conclusion: Elevated FAD-85 scores, increased CRP levels, and the necessity of intubation all serve as significant indicators of the severity and prognosis for ICU-admitted COVID-19 patients.

Keywords: COVID-19, D-dimer, FAD-85 score, ferritin

ÖZ

Amaç: COVID-19 sadece birkaç gün içerisinde şiddetli akut respiratuar distress sendromuna ve son dönem organ yetmezliğine neden olabilen ciddi bir hastalıktır. Bu nedenle hastalığın erken evrelerinde prognozu değerlendirmek için kolayca erişilebilen göstergeler, doktorların hastalığın alevlenmesini veya ölüm oranını önlemek için zamanında ve etkili önlemler almasını sağlar. Bu çalışmada yoğun bakıma yatış sırasında bakılan FAD-85 skoru, D-dimer ve ferritin değerlerinin prognoz ve mortalite üzerine etkisinin araştırılması amaçlandı.

Gereç ve Yöntemler: Erişkin 3. basamak genel yoğun bakımda 1 Nisan 2021-31 Mart 2022 tarihleri arasında COVID-19 tanısı ile yatmış 204 hastanın verileri retrospektif olarak incelendi. Hastaların yaşı, cinsiyeti, altta yatan hastalıkları, Charlson Komorbidite İndeksi, akut fizyoloji ve kronik sağlık değerlendirmesi skoru, aşı durumu, SARS-CoV-2 PCR testi, beslenme durumu (parenteral, enteral), yoğun bakımda takipleri sürecince kan, idrar ve trakeal aspirat kültürlerinde üreme durumları, trakeostomi ve entübasyon durumu, invaziv/non-invaziv mekanik ventilatör ihtiyacı ve süresi, yüksek akım oksijen ihtiyacı ve süresi, yoğun bakımda ve hastanede kalış süresi ve 1 aylık mortaliteleri değerlendirildi. Laboratuvar parametrelerinden yoğun bakım ünitesine yatış sırasında lökosit, lenfosit, ferritin, D-dimer, prokalsitonin, C-reaktif protein (CRP), laktat dehidrogenaz düzeyleri kaydedildi. FAD-85 skorunun hesaplanması için yaş + 0,01 x ferritin + D-dimer formulü kullanıldı.

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ÖZ

Bulgular: İki yüz dört COVID-19 hastasının incelendiği bu çalışmada, 1 aylık mortaliteyi öngören faktörler; erkek cinsiyet (p=0,029), entübasyon varlığı (p<0,001), CRP artışı (p=0,002), lenfosit düşüklüğü (p=0,009), FAD-85 değerinin 85'in üstünde olması (p=0,001) ve ferritin yüksekliği (p=0,044) olarak bulunmuştur. Ayrıca entübasyon varlığı [odds oranı (OR) (%95 güven aralığı (GA): 3,941 (2,115-7,343)], CRP yüksekliği [OR (%95 GA): 1,004 (1,000-1,008] ve FAD-85 değerinin 85'in üstünde olmasının (OR (%95 GA): 2,462 (1,313-4,617) mortaliteyi öngördüğü anlaşılmıştır. Basit bir şekilde hesaplanabilen FAD-85 skorunun COVID-19 hastalarında mortaliteyi öngörmede etkin olduğu anlaşılmıştır. FAD-85>85 olan, CRP yüksekliği olan ve yoğun bakımda yatış sırasında entübe takip edilen hastalarda mortalite oranı daha yüksek olduğu için bu hastalarda zamanında ve etkin tedavi son derece önemlidir.

Sonuç: Yoğun bakımda takip edilen COVID-19 hastalarında FAD-85 skoru ve CRP yüksekliği ile entübasyon varlığı hastalığın şiddeti ve prognozu hakkında önemli bilgiler sağlar.

Anahtar Kelimeler: COVID-19, D-dimer, FAD-85 skoru, ferritin

INTRODUCTION

COVID-19, a severe disease that has rapidly spread across numerous countries, was declared a global pandemic by the World Health Organization in 2020. This infection can result in severe acute respiratory distress syndrome (ARDS) and terminal organ failure (1). Patients diagnosed with COVID-19 pneumonia can experience a rapid escalation in symptoms within just a few days, potentially progressing to ARDS. Therefore, readily available early-stage indicators allow physicians to implement timely and effective strategies to mitigate disease progression and reduce mortality rates.

Existing literature has indicated that elevated levels of ferritin and D-dimer, which signify the thrombo-inflammatory nature of COVID-19, are associated with increased mortality and morbidity rates, as well as prolonged hospital stays (2-4). Nevertheless, the prognosis and mortality of patients cannot be solely determined by ferritin and D-dimer levels. Factors such as patient age and comorbid conditions also significantly influence the outcome.

Numerous factors have been assessed for their ability to predict mortality in COVID-19 patients. The FAD-85 score, comprising D-dimer, ferritin, and age, has been identified as highly predictive when investigating the efficacy of various combinations of variables in predicting mortality. The FAD-85 score demonstrated a sensitivity, specificity, positive predictive value, negative predictive value, false-positive rate, and false-negative rate of 86.4%, 81.8%, 39.6%, 97.7%, 16.0%, and 13.6%, respectively (5).

In the case of COVID-19 patients, assessing predictive factors upon admission to the intensive care unit (ICU) can aid in predicting mortality, facilitating the introduction of suitable measures to reduce them. Consequently, the objective of this study was to explore the influence of the FAD-85 score, D-dimer, and ferritin levels, evaluated upon ICU admission, on the prognosis and mortality of COVID-19 patients.

MATERIALS and METHODS

This study encompassed a total of 204 adult patients who were admitted to the adult general ICU with a diagnosis of COVID-19 between April 1, 2021, and March 31, 2022. Following approval from the Institutional Ethics Committee, the patients' data were retrospectively reviewed. The approval of the Clinical Research Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital has been obtained (decision number: 2012-KAEK-15/2666, date: 08.03.2023).

The patients' age, gender, pre-existing conditions, Charlson Comorbidity Index Score (CCIS), acute physiology and chronic health evaluation II (APACHE-II) score, nutritional status (parenteral, enteral), tracheostomy and intubation status, necessity invasive mechanic ventilation (IMV), non-invasive mechanic ventilation (NIMV) and the duration thereof, high flow nasal oxygen ($HFNO_2$) requirement and its duration, duration of ICU and hospital stays, and one-month mortality rates were all recorded.

The patients' COVID-19 vaccination status was reviewed, and they were subsequently categorized as either vaccinated or unvaccinated. For the vaccinated group, the first and second doses of the COVID-19 vaccine were noted and categorized as either inactive or active vaccines.

The diagnosis of COVID-19 was established based on clinical symptoms, contact history, SARS-CoV-2 PCR tests, and typical COVID-19 findings on chest computed tomography. In cases where the SARS-CoV-2 PCR test was negative, but there was clinical suspicion of COVID-19 based on other diagnostic methods, patients were admitted to the COVID ICU and subsequent SARS-CoV-2 PCR tests were conducted. Consequently, patients who initially tested negative on the SARS-CoV-2 PCR test but later tested positive or were diagnosed with COVID-19 based on other diagnostic methods were also included in the study.

Cultures of blood, urine, and endotracheal aspirate samples collected upon ICU admission and throughout the ICU stay were examined. Instances of positive growth in the cultures and the specific microorganisms isolated were documented.

Laboratory parameters, including white blood cell count, lymphocyte count, ferritin, D-dimer, procalcitonin, C-reactive protein (CRP), and lactate dehydrogenase (LDH) levels, were recorded upon ICU admission. Given that the reference range for ferritin in our hospital is 4.6-274 µg/L, the values above 274 µg/L were considered as high ferritin levels. For D-dimer, the reference range is below 550 ng/mL, so values above

550 ng/mL were considered high D-dimer levels. The FAD-85 score was computed using the formula: age + 0.01 x ferritin + D-dimer patients with an FAD-85 score below 85 were classified as low-risk, while those with scores above or equal to 85 were considered high-risk.

Statistical Analysis

Data analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). The normality of the distribution of continuous variables was assessed by the Kolmogorov-Smirnov test. The Levene test was used to evaluate the homogeneity of variances. Unless specified otherwise, continuous data were presented as mean±SD and median (interquartile range). Categorical data were presented as the number of cases (%). Differences in normally distributed variables between two independent groups were compared using Student's t-test, while the Mann-Whitney U test was used for comparisons of non-normally distributed data. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, with a $p<0.05$ accepted as the level of significance in all statistical analyses.

RESULTS

This retrospective study involved 204 patients diagnosed with COVID-19 who were admitted to a level 3 adult ICU. Of these, 92 were female and 112 were male, with a mean age of 68.27±13.92.

When the relationship between the demographic characteristics, clinical findings, treatments, laboratory values and one-month mortality was analyzed, male sex ($p=0.028$), intubation rate ($p<0.001$), FAD-85 (both continuous and categorical) ($p<0.001$), ferritin (both continuous and categorical) ($p=0.001$), APACHE-II score ($p=0.013$), leukocyte ($p<0.001$), procalcitonin ($p=0.001$), LDH ($p=0.001$), CRP ($p=0.001$), and D-dimer (both continuous) value ($p=0.031$) were statistically significantly higher in patients with and without one-month mortality. Notably, hospital stay duration ($p<0.001$), oral feeding status ($p=0.001$), history of a previous cerebrovascular event ($p=0.046$), duration of $HFNO^2$ application ($p=0.013$), duration of NIMV application ($p=0.007$), and lymphocyte count ($p<0.001$) were significantly lower in patients with one-month mortality (Table 1).

Table 1. The relationship between demographic characteristics, clinical findings and laboratory values of the patients and 1-month mortality

		1 month mortality				p-value
		Yes (n=113)		No (n=91)		
		$\bar{X}$±SD/n	Med (IQR)/(%)	$\bar{X}$±SD/n	Med (IQR)/(%)	
Gender$^{\Phi}$	Female	43	(38.4%)	49	(53.8%)	**0.028**
	Male	70	(61.6%)	42	(46.2%)	
Age (year)$^{\beta}$		69.75±13.47	71 (20)	66.44±14.31	67 (22)	0.091
Length of stay ICU (day)*		7.75±6.77	6 (8)	10.87±11.58	6 (13)	0.366
Length of stay in hospital (day)*		12.91±7.92	11 (11)	24.21±18.68	21 (24)	**<0.001**
DM$^{\Phi}$	No	71	(62.8%)	68	(74.7%)	0.070
	yes	42	(37.2%)	23	(25.3%)	
HT$^{\Phi}$	No	64	(56.6%)	55	(60.4%)	0.840
	Yes	49	(43.4%)	36	(39.6%)	
CAD$^{\Phi}$	No	97	(85.8%)	83	(91.2%)	0.237
	Yes	16	(14.2%)	8	(8.8%)	
CHF$^{\Phi}$	No	105	(92.9%)	85	(93.4%)	0.891
	Yes	8	(7.1%)	6	(6.6%)	
CKD$^{\Phi}$	No	111	(98.2%)	90	(98.9%)	0.692
	Yes	2	(1.8%)	1	(1.1%)	
Parenteral nutrition$^{\Phi}$	No	92	(81.4%)	81	(89.0%)	0.133
	Yes	21	(18.6%)	10	(11.0%)	
Oral nutrition$^{\Phi}$	No	30	(26.5%)	11	(12.1%)	**0.010**
	Yes	83	(73.5%)	80	(87.9%)	
Intubation$^{\Phi}$	No	33	(29.2%)	59	(64.8%)	**<0.001**
	Yes	80	(70.8%)	32	(35.2%)	
Previous PTE	No	107	(94.7%)	87	(95.6%)	0.999
	Yes	6	(5.3%)	4	(4.4%)	

Table 1. Continued

		1 month mortality				p-value
		Yes (n=113)		No (n=91)		
		±SD/n	Med (IQR)/(%)	±SD/n	Med (IQR)/(%)	
Previous CVD	No	112	(99.1%)	85	(93.4%)	0.046
	Yes	1	(0.9%)	6	(6.6%)	
1st dose vaccine$^{\Phi}$	No	62	(54.9%)	51	(56.0%)	0.240
	Inactivated vaccine	39	(34.5%)	36	(39.6%)	
	Active vaccine	12	(10.6%)	4	(4.4%)	
2nd dose vaccine$^{\Phi}$	No	67	(59.3%)	54	(59.3%)	0.971
	Inactivated vaccine	31	(27.4%)	24	(26.4%)	
	Active vaccine	15	(13.3%)	13	(14.3%)	
PCR test$^{\Phi}$	PCR +	105	(92.9%)	82	(90.1%)	0.470
	PCR -	8	(71%)	9	(9.9%)	
FAD-85$^{\Phi}$		86.81±16.31	88.18 (18.85)	77.78±16.71	78.39 (22.29)	**<0.001**
	No	48	(42.5%)	61	(67.0%)	**<0.001**
	Yes	65	(57.5%)	30	(33.0%)	
Ferritin (μg/L)$^{\Phi}$		969.9±579.32	906(1182)	682.17±546.66	551.5 (760.78)	**0.001**
	No	10	(8.8%)	17	(18.7%)	**0.039**
	Yes	103	(91.2%)	74	(81.3%)	
D-dimer (ng/mL)$^{\Phi}$		7.37±10.6	2.46 (4.89)	4.89±8.05	1.96 (2.76)	**0.031**
	No	7	(6.2%)	12	(13.2%)	0.081
	Yes	106	(93.8%)	79	(86.8%)	
High Flow O_2 days*		3.5±4.27	2 (4)	5.47±6.56	4 (5)	**0.013**
NIMV days*		3.42±4.24	2 (3)	5.48±6.56	4 (5)	**0.007**
CCIS*		4.15±2.12	4 (2)	3.7±2.43	4 (3)	0.220
APACHE-II*		24.77±8.47	23 (11)	21.33±7.92	19 (12)	**0.013**
Leukocyte (x10^3 / mL)*		14.21±6.51	13.3 (7.55)	12.56±7.37	10.66 (6.66)	**<0.001**
Lymphocyte (%)*		6.21±5.82	4.38 (4.77)	8.68±6.77	6.42 (7.55)	**<0.001**
Procalcitonin (ng/mL)*		7.97±31.46	0.53 (2.26)	1.6±6.66	0.11 (0.34)	**0.001**
LDH (IU/L)*		716.37±856.46	551 (363)	482.2±217.86	457 (286)	**0.001**
CRP (mg/L)*		143.79±87.16	135.44 (108.94)	104.34±82.93	87.36 (124.54)	**0.001**

Student's t-test $^{\beta}$ or the Mann-Whitney U test*, Pearson's chi-square test or Fisher's exact test $^{\Phi}$.
Statistically significant p-values are in bold.
DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, PTE: Pulmonary thromboembolism, CVD: Cerebrovascular disease, NIMV: Non-invasive mechanical ventilation, CCIS: Charlson Comorbidity Index, APACHE-II: Acute physiology and chronic health assessment score, LDH: Lactate dehydrogenase, CRP: C-reactive protein, IQR: Interquartile range,
PCR: Polymerase chain reaction, ICU: Intensive care unit, SD: Standard deviation

FAD-85 score. it is calculated using the formula age + 0.01 x ferritin + D-dimer. In patients with FAD-85>85, advanced age (p<0.001), second dose vaccine inactivity (p=0.011), CCIS (p<0.001), APACHE-II score (p<0.001), leukocyte count (p=0.017), procalcitonin (p=0.001) and CRP (p=0.009) values were statistically significantly higher than those with FAD-85<85. Compared to those with FAD-85<85, patients with FAD-85>85 had lower rates of oral feeding (p=0.002) and shorter durations of HFNO[2] (p=0.006) and NIMV (p=0.002) (Table 2).

For patients with ferritin levels above 274 μg/L, significantly higher values of procalcitonin (p=0.026) and LDH (p=0.008) were observed. In contrast, the rate of inactivated vaccination (p=0.011, p=0.013) was significantly lower compared to those with ferritin levels below 274 μg/L (Table 3).

In patients with a D-dimer level above 550 ng/mL, female sex (p=0.026), age (p=0.013), CCIS (p=0.012), APACHE-II score (p=0.011), procalcitonin (p=0.03), LDH (p=0.003), and CRP (p=0.002) levels were found to be statistically significantly higher, and the oral feeding rate (p=0.009) was lower than those with a D-dimer level below 550 ng/mL (Table 4).

Table 2. Evaluation of the factors affecting the FAD-85 result of the patients

		FAD-85				p-value
		>85 (n=95)		<85 (n=109)		
		X̄±SD/n	Med (IQR)/(%)	X̄±SD/n	Med (IQR)/(%)	
Gender$^{\Phi}$	Female	38	(40.0%)	54	(50.0%)	0.153
	Male	57	(60.0%)	54	(50.0%)	
Age (year)$^{\beta}$		76.69±10.95	79 (13)	60.94±11.95	61 (16)	**<0.001**
Length of stay ICU (day)*		8.91±9.4	6 (9)	9.35±9.31	6 (9)	0.826
Length of stay in hospital*		17.34±13.01	15 (14)	18.49±16.35	14 (18)	0.969
DM$^{\Phi}$	No	69	(72.6%)	70	(64.2%)	0.198
	Yes	26	(27.4%)	39	(35.8%)	
HT$^{\Phi}$	No	53	(55.8%)	66	(60.6%)	0.491
	Yes	42	(44.2%)	43	(39.4%)	
CAD$^{\Phi}$	No	82	(86.3%)	98	(89.9%)	0.427
	Yes	13	(13.7%)	11	(10.1%)	
CHF$^{\Phi}$	No	87	(91.6%)	103	(94.5%)	0.411
	Yes	8	(8.4%)	6	(5.5%)	
CKD$^{\Phi}$	No	93	(97.9%)	108	(99.1%)	0.599
	Yes	2	(2.1%)	1	(0.9%)	
Parenteral nutrition$^{\Phi}$	No	77	(81.1%)	96	(88.1%)	0.164
	Yes	18	(18.9%)	13	(11.9%)	
Oral nutrition$^{\Phi}$	No	28	(29.5%)	13	(11.9%)	**0.002**
	Yes	67	(70.5%)	96	(88.1%)	
Intubation$^{\Phi}$	No	36	(37.9%)	56	(51.4%)	0.054
	Yes	59	(62.1%)	53	(48.6%)	
Previous PTE$^{\Phi}$	No	91	(95.8%)	103	(94.5%)	0.754
	Yes	4	(4.2%)	6	(5.5%)	
Previous CVD$^{\Phi}$	No	92	(96.8%)	105	(96.3%)	0.999
	Yes	3	(3.2%)	4	(3.7%)	
1st dose vaccine$^{\Phi}$	No	48	(50.5%)	65	(59.6%)	0.195
	Inactivated vaccine	41	(43.2%)	34	(31.2%)	
	Active vaccine	6	(6.3%)	10	(9.2%)	
2nd dose vaccine$^{\Phi}$	No	50	(52.6%)	71	(65.1%)	**0.011**
	Inactivated vaccine	35	(36.8%)	20	(18.3%)	
	Active vaccine	10	(10.5%)	18	(16.5%)	
PCR test$^{\Phi}$	PCR +	90	(94.7%)	97	(89.0%)	0.139
	PCR -	5	(5.3%)	12	(11.0%)	
High flow O_2 days*		3.54±4.76	2 (5)	5.11±5.98	3 (5)	**0.006**
NIMV days*		3.45±4.75	2 (5)	5.11±5.96	3 (5)	**0.002**
CCIS*		4.93±2.04	5 (2)	3.1±2.13	3 (4)	**<0.001**
APACHE-II*		26.03±8.14	26 (11)	20.8±7.85	19 (6)	**<0.001**
Leukocyte (x10^3 / mL)*		14.74±7.82	13.3 (8.26)	12.37±5.89	11.09 (6.49)	**0.017**
Lymphocyte (%)*		6.16±4.46	4.42 (4.83)	8.32±7.53	6.3 (6.83)	0.053
Procalcitonin (ng/mL)*		8.34±33.56	0.46 (1.57)	2.3±8.93	0.13 (0.73)	**0.001**
LDH (IU/L)*		692.66±911.3	509 (366)	543.46±315.77	(5028290)	0.287
CRP (mg/L)$^{\beta}$		143.12±94.4	135.44 (125.58)	111.44±78.14	98.16 (114.67)	**0.009**

Student's t-test $^{\beta}$ or the Mann-Whitney U test*, Pearson's chi-square test or Fisher's exact test $^{\Phi}$.
Statistically significant p-values are in bold.
DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, PTE: Pulmonary thromboembolism, CVD: Cerebrovascular disease, NIMV: Non-invasive mechanical ventilation, CCIS: Charlson Comorbidity Index, APACHE-II: Acute physiology and chronic health assessment score, LDH: Lactate dehydrogenase, CRP: C-reactive protein, IQR: Interquartile range, PCR: Polymerase chain reaction, ICU: Intensive care unit, SD: Standard deviation

Table 3. Evaluation of the factors affecting the ferritin result of the patients

		Ferritin				p-value
		>274 mg/L (n=177)		<274 mg/L (n=27)		
		$\bar{X}$±SD/n	Med (IQR)/(%)	$\bar{X}$±SD/n	Med (IQR)/(%)	
Gender$^{\Phi}$	Female	76	(42.9%)	16	(61.5%)	0.075
	Male	101	(57.1%)	10	(38.5%)	
Age (year)$^{\beta}$		67.84±13.89	69 (22)	71.15±13.95	74 (17)	0.250
Length of stay ICU (day)*		8.94±8.96	6 (9)	10.44±11.59	5 (17)	0.905
Length of stay in hospital*		17.34±13.96	14 (14)	21.96±19.69	15 (20)	0.459
DM$^{\Phi}$	No	122	(6.9%)	17	(63.0%)	0.536
	Yes	55	(31.1%)	10	(37.0%)	
HT$^{\Phi}$	No	105	(59.3%)	14	(51.9%)	0.463
	Yes	72	(40.7%)	13	(48.1%)	
CAD$^{\Phi}$	No	158	(89.3%)	22	(81.5%)	0.330
	Yes	19	(10.7%)	5	(18.5%)	
CHF$^{\Phi}$	No	166	(93.8%)	24	(88.9%)	0.405
	Yes	11	(6.2%)	3	(11.1%)	
CKD$^{\Phi}$	No	175	(98.9%)	26	(96.3%)	0.348
	Yes	2	(1.1%)	1	(3.7%)	
Parenteral nutrition$^{\Phi}$	No	153	(86.4%)	20	(74.1%)	0.144
	Yes	24	(13.6%)	7	(25.9%)	
Oral nutrition$^{\Phi}$	No	38	(21.5%)	3	(11.1%)	0.211
	Yes	139	(78.5%)	24	(88.9%)	
Intubation$^{\Phi}$	No	77	(43.5%)	15	(55.6%)	0.241
	Yes	100	(56.5%)	12	(44.4%)	
Previous PTE$^{\Phi}$	No	170	(96.0%)	24	(88.9%)	0.131
	Yes	7	(4.0%)	3	(11.1%)	
Previous CVD$^{\Phi}$	No	171	(96.6%)	26	(96.3%)	0.999
	Yes	6	(3.4%)	1	(3.7%)	
1st dose vaccine$^{\Phi}$	No	105	(59.3%)	8	(29.6%)	**0.013**
	Inactivated vaccine	60	(33.9%)	15	(55.6%)	
	Active vaccine	12	(6.8%)	4	(14.8%)	
2nd dose vaccine$^{\Phi}$	No	112	(63.3%)	9	(33.3%)	**0.011**
	Inactivated vaccine	44	(24.9%)	11	(40.7%)	
	Active vaccine	21	(11.9%)	7	(25.9%)	
PCR test$^{\Phi}$	PCR +	161	(91.0%)	26	(96.3%)	0.706
	PCR -	16	(9.0%)	1	(3.7%)	
High flow O_2 days*		4.28±5.34	3 (5)	5.00±6.46	3 (5)	0.606
NIMV days*		4.25±0.33	3 (5)	4.93±6.44	3 (4)	0.590
CCIS*		3.85±2.25	4 (3)	4.59±2.37	4 (2)	0.136
APACHE-II*		23.36±8.61	21 (11)	22.41±6.81	19 (10)	0.543
Leukocyte (x10^3 / mL)*		13.54±7.04	12.32 (8.03)	13.05±6.35	12.21 (6.5)	0.775
Lymphocyte (%)*		7.13±6.45	5 08(5,2)	8.54±5.79	7.24 (7.32)	0.081
Procalcitonin (ng/mL)*		5.75±25.64	0.32 (1.01)	0.94±2.54	0.11 (0.39)	**0.026**
LDH (IU/L)*		639.59±705.83	520.5 (358)	436.33±193.78	418 (252)	**0.008**
CRP (mg/L)$^{\beta}$		130.83±88.07	124.91(124.24)	95.8±77.07	85.07 (132.25)	0.052

Student's t-test $^{\beta}$ or the Mann-Whitney U test*, Pearson's chi-square test or Fisher's exact test $^{\Phi}$.
Statistically significant p-values are in bold.
DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, PTE: Pulmonary thromboembolism, CVD: Cerebrovascular disease, NIMV: Non invasive mechanical ventilation, CCIS: Charlson Comorbidity Index, APACHE-II: Acute physiology and chronic health assessment score, LDH: Lactate dehydrogenase, CRP: C-reactive protein, IQR: Interquartile range, PCR: Polymerase chain reactio, ICU: Intensive care uni, SD: Standard deviation

A single-variable logistic regression analysis was performed to identify factors influencing mortality in patients. Variables with a p-value less than 0.05, were identified as having a high likelihood of predicting mortality based on the single-variable analysis. Male sex (p=0.029), intubation (p<0.001), elevated CRP (p=0.002), decreased lymphocyte count (p=0.009), FAD-85 score greater than 85 (p=0.001), and ferritin value above 274 µg/L (p=0.044) were determined to be predictive of mortality. Variables with a p-value less than 0.25 in the single-variable logistic regression analysis were included in the multivariable logistic regression analysis. The Forward LR method was applied. The results of the multivariable logistic regression analysis showed that the presence of intubation odds ratio (OR): (5% confidence interval (CI): 3.941 (2.115-7.343)], elevated CRP levels (OR): (95% CI): 1.004 (1.000-1.008)], and FAD-85 score greater than 85 OR: (95% CI): 2.462 (1.313-4.617)] were predictors of mortality (Table 5).

DISCUSSION

In the study aimed at exploring the prognostic and predictive effects of D-dimer, ferritin levels, and the FAD-85 score at the time of admission to the COVID ICU among 204 patients, findings indicated that male sex, intubation, a high CCIS, increased CRP, decreased lymphocyte count, and an FAD-85 score greater than 85 were predictive of mortality. This study brings valuable insights for healthcare professionals by identifying parameters that can assist in early stratification of patients at higher risk, thus enabling targeted treatment strategies to improve patient outcomes.

The risk of mortality from COVID-19 does indeed increase with age in both genders, but men over the age of 30 have a higher risk of death compared to women (6,7). This discrepancy has been attributed to factors such as differences in sex hormones, variations in immune responses, and disparities in vaccine response (8). The Global Health 50/50 project, the world's most extensive gender-disaggregated database on COVID-19, clearly substantiates the increased case fatality rate in men (9). A study conducted by qeadan and colleagues has also demonstrated that ferritin levels are more elevated in men than in women among COVID-19 patients (4). In line with these findings, the current study also detected higher 1-month mortality rates and elevations in ferritin, in male patients. This highlights the need for potential gender-specific considerations when managing COVID-19 patients and when considering the impact of biomarkers like ferritin on disease severity and prognosis.

COVID-19 patients pose a higher risk of disease transmission to healthcare workers, especially when interventions like $HFNO^2$ or NIMV are used. Elective intubation is often preferred, based on expert recommendations, as a way to minimize clinical risks, including contamination of healthcare workers, when NIMV fails in patients (10).

In Northern Italy, it has been reported that more than 10% of COVID-19 patients experiencing hypoxia were intubated in the ICU (11). The rates of intubation in COVID-19 patients have varied greatly in different studies, with reports ranging from as low as 5% to as high as 88%. This considerable variability can be attributed to differences in the study populations, settings, and criteria for intubation (12).

However, it is generally recognized that the mortality rate is higher in intubated COVID-19 patients than in those who are not intubated (13). This underscores the severity of patients requiring intubation, and the importance of careful patient selection and timing for this intervention. Intubation is a significant procedure that comes with its own risks, and these must be balanced against the potential benefits for each individual patient.

In patients with COVID-19, NIMV has been reported to be associated with lower mortality compared to patients who are not intubated or those who require intubation, suggesting that NIMV may confer survival benefits (14). $HFNO^2$, on the other hand, is currently recommended by clinical practice guidelines for critically ill patients with acute hypoxemic respiratory failure, as it has been shown to decrease the need for intubation compared to standard oxygen (15).

In this study, we found that the duration of $HFNO^2$ and NIMV application was shorter in patients with higher mortality and an FAD-85 score>85, suggesting that these patients were rapidly intubated. In our cohort, the intubation rate was 54.9%, and intubation was found to be a predictive factor for 1-month mortality.

Advanced age, diabetes mellitus, respiratory rate, increased CRP levels, and oxygen saturation have been found to have significant predictive value for the need for IMV in patients with COVID-19 (16). The research conducted by Alroomi has indicated that individuals with ferritin levels exceeding 1000 ng/mL tend to have higher concentrations of CRP than those with lower levels (3). Research indicates that along with an increase in CRP, other markers associated with COVID-19 include lymphopenia, leukocytosis, elevated levels of procalcitonin, D-dimer, ferritin, and LDH (17,18). Wang et al. (19) highlighted that a significant number of COVID-19 patients experienced a pronounced decrease in lymphocyte count during their hospital stay, and this lymphopenia became more severe over time in those patients who did not survive.

In this study, it was determined that patients with a FAD-85 score greater than 85 and a higher 1-month mortality exhibited leukocytosis, elevated procalcitonin, and CRP levels. Notable associations were discovered between raised ferritin and D-dimer levels, and increased LDH levels, along with increased 1-month mortality. A decrease in lymphocytes and elevated CRP were identified as factors predicting mortality. We think these changes in blood parameters are related to the continued inflammatory response, cytokine storm, and tendency to coagulation disorders.

Hyperferritinemia has been proposed as a mortality indicator in COVID-19 patients (20,21), with studies showing a significant link to the severity of the disease (22). Increased

Table 4. Evaluation of the factors affecting the D-dimer result of the patients

		D-dimer				p-value
		>550ng/mL (n=185)		<550ng/mL (n=19)		
		X̄±SD/n	Med (IQR)/(%)	X̄±SD/n	Med (IQR)/(%)	
Gender$^{\Phi}$	Female	88	(47.8%)	4	(21.1%)	**0.026**
	Male	96	(52.2%)	15	(78.9%)	
Age (year)$^{\beta}$		69.04±13.69	71 (22)	60.79±14.24	67 (25)	**0.013**
Length of stay ICU (day)*		9.38±9.46	6 (9)	6.79±7.89	4 (8)	0.131
Length of stay in hospital*		18.4±15.31	15 (15)	13.58±8.53	10 (12)	0.278
DM$^{\Phi}$	No	124	(67.0%)	15	(78.9%)	0.288
	Yes	61	(33.0%)	4	(21.1%)	
HT$^{\Phi}$	No	106	(57.3%)	13	(68.4%)	0.349
	Yes	79	(42.7%)	6	(31.6%)	
CAD$^{\Phi}$	No	162	(87.6%)	18	(94.7%)	0.706
	Yes	23	(12.4%)	1	(5.3%)	
CHF$^{\Phi}$	No	171	(92.4%)	19	(100.0%)	0.371
	Yes	14	(7.6%)	0	(0.0%)	
CKD$^{\Phi}$	No	182	(98.4%)	19	(100.0%)	0.999
	Yes	3	(1.6%)	0	(0.0%)	
Parenteral nutrition$^{\Phi}$	No	157	(84.9%)	16	(84.2%)	0.376
	Yes	28	(15.1%)	3	(15.8%)	
Oral nutrition$^{\Phi}$	No	39	(21.1%)	2	(10.5%)	**0.009**
	Yes	146	(78.9%)	17	(89.5%)	
Intubation$^{\Phi}$	No	78	(42.2%)	14	(73.7%)	0.501
	Yes	107	(57.8%)	5	(26.3%)	
Previous PTE$^{\Phi}$	No	177	(95.7%)	17	(89.5%)	0.236
	Yes	8	(4.3%)	2	(10.5%)	
Previous CVD$^{\Phi}$	No	179	(96.8%)	18	(94.7%)	0.501
	Yes	6	(3.2%)	1	(5.3%)	
1st dose vaccine$^{\Phi}$	No	101	(54.6%)	12	(63.2%)	0.756
	Inactivated vaccine	69	(37.3%)	6	(31.6%)	
	Active vaccine	15	(8.1%)	1	(5.3%)	
2nd dose vaccine$^{\Phi}$	No	107	(57.8%)	14	(73.7%)	0.235
	Inactivated vaccine	53	(28.6%)	2	(10.5%)	
	Active vaccine	25	(13.5%)	3	(15.8%)	
PCR test$^{\Phi}$	PCR +	169	(91.4%)	18	(94,7%)	0.999
	PCR -	16	(8.6%)	1	(5.3%)	
High flow O_2 days*		4.43±5.66	3 (5)	3.89±3.41	4 (3)	0.670
NIMV days*		4.38±5.66	3 (5)	3.89±3.41	4 (3)	0.630
CCIS*		4.08±2.23	4 (2)	2.68±2.38	3 (4)	**0.012**
APACHE-II*		23.6±8.15	21 (11)	19.68±9.96	18 (6)	**0.011**
Leukocyte (x10^3 / mL)*		13.48±6.83	12.37 (7.95)	13.39±8.14	11.9 (7.09)	0.494
Lymphocyte (%)*		7.12±6.28	4.91 (5.7)	9.15±7.1	6.3 (7.16)	0.139
Procalcitonin (ng/mL)*		5.2±24.62	0.3 (0.95)	4.35±16.55	0.08 (0.31)	**0.030**
LDH (IU/L)*		636.71±691.19	521 (364.5)	378.56±175.19	399 (187)	**0.003**
CRP (mg/L)$^{\beta}$		130.85±88.61	124.91 (122.09)	80.88±57.97	64.4 (90.34)	**0.002**

Student's t-test $^{\beta}$ or the Mann-Whitney U test*; Pearson's chi-square test or Fisher's exact test $^{\Phi}$.
Statistically significant p-values are in bold.
DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, PTE: Pulmonary thromboembolism, CVD: Cerebrovascular disease, NIMV: Non invasive mechanical ventilation, CCIS: Charlson Comorbidity Index, APACHE-II: Acute physiology and chronic health assessment score, LDH: Lactate dehydrogenase, CRP: C-reactive protein, IQR: Interquartile range, PCR: Polymerase chain reactio, ICU: Intensive care uni, SD: Standard deviation

Table 5. Univariate and multivariate logistic regression analysis

	Univariate logistic regression					Multivariate logistic regression (forward LR)				
	Wald	p	OR	95% CI for OR		Wald	p	OR	95% CI for OR	
				Lower	Upper				Lower	Upper
Age	2.836	0.092	1.017	0.997	1.038					
Gender (ref: female)	4.797	**0.029**	1.872	1.068	3.281					
İntubation	24.636	**<0.001**	4.470	2.475	8.073	18.661	**<0.001**	3.941	2.115	7.343
CCIS	1.947	0.163	1.092	0.965	1.235					
Lymphocyte	6.869	**0.009**	0.937	0.892	0.984					
CRP	9.825	**0.002**	1.006	1.002	1.009	4.378	**0.036**	1.004	1.000	1.008
Procalcitonin	2.652	0.103	1.033	0.993	1.074					
Unvaccinated (ref: vaccinated 1)	0.028	0.867	0.953	0.547	1.662					
Unvaccinated (ref: vaccinated 2)	0.001	0.994	0.998	0.569	1.751					
FAD-85 (ref: <85)	11.937	**0.001**	2.753	1.550	4.891	7.884	**0.005**	2.462	1.313	4.617
Ferritin (ref: <274)	4.075	**0.044**	2.366	1.025	5.461					
D-dimer (ref: <550)	2.795	0.095	2.300	0.866	6.108					

Wald: Test statistics, OR: Odds radio, Statistically significant p-values are in bold. CCIS: Charlson Comorbidity Index, CRP: C-reactive protein, CI: Confidence interval

D-dimer levels are thought to help in the early detection of patients who are likely to have a poor outcome (2). Elderly individuals have a higher risk of developing ARDS, and their immune response tends to be less robust, resulting in a more severe progression of the disease (23). The FAD-85 score, a calculation that considers a patient's age, ferritin, and D-dimer levels, serves as an early predictive tool for assessing patient outcomes. The FAD-85 score demonstrates significant predictive power in determining the likelihood of mortality. All the parameters included in the FAD-85 score are easily attainable through standard clinical procedures, and it is recommended that these lab tests are carried out upon a patient's admission to the hospital (5). In our research, we observed a substantial association between increased levels of ferritin and D-dimer, and mortality at one month. Additionally, we identified a FAD-85 score exceeding 85 as an indicator of mortality risk. This score, which is simple to calculate, can provide early indications about the severity and potential fatality of a COVID-19 case.

Besides laboratory parameters, the presence of comorbidities is another crucial aspect to consider in patients with COVID-19. A study involving 134.209 patients hospitalized due to COVID-19 revealed that individuals with obesity and diabetes experienced higher mortality rates. Additionally, the need for IMV was more prevalent among patients who were obese, diabetic, and hypertensive (24).

CCIS, which is an indicator of multiple comorbidities, has been consistently demonstrated to be a potent predictor of mortality in various studies (25). In the context of this study, it was observed that patients with a FAD-85 score exceeding the threshold of 85 and those exhibiting elevated D-dimer levels, had notably higher CCIS.

Another frequently employed scoring system in the ICU is the APACHE-II score. Studies have demonstrated that the APACHE-II score is a more reliable indicator of illness severity and mortality when compared to MuLBSTA (multi-lobar infiltrates, hypo-lymphocytosis, bacterial co-infection, smoking history, hypertension, and age) and CURB-65 (confusion, uremia, respiratory rate, blood pressure, age≥65 years) in COVID-19 patients (26). In this study, it was observed that patients with increased 1-month mortality, elevated d-dimer levels, and FAD-85>85 also exhibited higher APACHE-II scores. These findings suggest that the APACHE-II score can be reliably utilized as a scoring system for predicting mortality in COVID-19 patients.

Study Limitation

There are some limitations to our study. It is a single-center retrospective study with a small number of patients, which limits the generalizability of our findings. We used only admission laboratory values to evaluate the clinical prognosis and mortality of patients. The consequences of fluctuations in laboratory values during the follow-up in the ICU were not studied. Complications such as thrombotic events and sepsis, that might emerge as a result of the increase in laboratory markers, were not examined. Because our hospital is a tertiary care center with multiple COVID ICUs, and because our study was carried out in a third-level COVID ICU, these factors could potentially contribute to the elevated mortality rate.

CONCLUSION

In summary, COVID-19 is characterized by a rapidly evolving clinical course, underscoring the importance of early prognostic markers. Such markers play a vital role in risk prediction and guiding the implementation of prophylactic treatments to prevent complications. We propose that the FAD-85 score can serve as a valuable predictive factor for the clinical prognosis of COVID-19. However, the FAD-85 score is not widely utilized currently, and to strengthen the evidence for its utility, additional multicenter studies are warranted. These future investigations will help corroborate and validate our findings, leading to more informed and effective management strategies for COVID-19 patients.

Ethics

Ethics Committee Approval: The approval of the Clinical Research Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital has been obtained. (decision number: 2012-KAEK-15/2666, date: 08.03.2023).

Informed Consent: Retrospective study.

Footnotes

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Original Article

Evaluation of Family Medicine Residents Knowledge Levels, Attitudes and Behaviors About Rotavirus Infection and Vaccines

Aile Hekimliği Asistanlarının Rotavirüs Enfeksiyonu ve Aşıları Hakkındaki Bilgi Düzeyleri, Tutum ve Davranışlarının Değerlendirilmesi

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ABSTRACT

Objective: In children under 5 years of age, vaccines developed against rotavirus (RV) infection, one of the most important viral diarrhea agents, prevent hundreds of thousands of deaths. The short time interval in which the vaccine can be given and the fact that it is not included in the national vaccination calendar impose a special responsibility on family physicians. The aim of this study was to evaluate the level of knowledge, attitudes, and behaviors of family medicine residents about RV infection and RV vaccines and to update the educational content with these data.

Material and Methods: With the permission of the Ethics Committee of Adana City Training and Research Hospital (ACTR), the study was conducted with the family medicine residents of ACTR hospital. Demographic data of the participants, their attitude towards the RV vaccine, and 22 questions measuring the level of knowledge about RV infection and vaccines were collected, and the data obtained were analyzed.

Results: The study included 106 participants, 48.1% of whom were women. The mean age of the participants was 30.69±3.87 years and the mean duration of practice was 5.59±3.55 years. While 80.2% of the participants stated that they had previously experienced a patient with RV infection, 85.8% said that they recommended RV vaccination to families. The mean correct response of the participants to the 22-item questionnaire measuring their knowledge was 14.98±3.51. The knowledge level of the participants who stated that they had sufficient knowledge about RV, and recommended RV vaccine to families, was significantly higher than that of the other participants.

Conclusion: RV vaccine, which significantly reduces the incidence and severity of RV-associated gastroenteritis, hospitalization rate, and disease-related mortality, is not currently included in the national vaccine program and is not yet adequately applied despite its proven efficacy and safety. The data obtained in the study revealed the necessity to emphasize issues such as the route of administration, doses, time of administration, contraindications, and use of RV vaccines together with other vaccines to be included in the prepared training program.

Keywords: Rotavirus vaccine, family medicine, gastroenteritis

ÖZ

Amaç: Beş yaş altı çocuklarda en önemli viral ishal etkenlerinden olan rotavirüs (RV) enfeksiyonuna karşı geliştirilen aşılar yüzbinlerce ölümü engellemektedir. Aşının uygulanabileceği zaman aralığının kısalığı ve ulusal aşı takviminde bulunmaması aile hekimlerine özel bir sorumluluk yüklemektedir. Bu çalışmanın amacı aile hekimliği asistanlarının RV enfeksiyonu ve RV aşıları hakkındaki bilgi düzeylerini, tutum ve davranışlarını değerlendirmek ve bu verilerle eğitim içeriklerini güncellemektir.

Gereç ve Yöntemler: Adana Şehir Eğitim ve Araştırma Hastanesi (AŞEAH) Etik Kurulu'ndan alınan izin ile AŞEAH aile hekimliği asistanları ile gerçekleştirilmiştir. Katılımcıların demografik verileri, RV aşısına karşı tutumu ve 22 sorudan oluşan RV enfeksiyonu ve aşıları hakkındaki bilgi düzeyini ölçen sorular yöneltilerek elde edilen veriler analiz edildi.

Bulgular: Çalışma %48,1'i kadın olan 106 katılımcı dahil oldu. Katılımcıların yaş ortalaması 30,69±3,87 iken ortalama hekimlik süresi 5,59±3,55 yıl olarak gözlendi. Katılımcıların %80,2'si daha önceden RV enfeksiyonu ile karşılaştığını belirtirken, %85,8'i ise ailelere RV aşısını önerdiğini söyledi. Katılımcıların 22 maddeden oluşan ve bilgilerini ölçen ankete verdikleri doğru yanıt ortalaması 14,98±3,51 olarak saptandı. RV hakkında yeterli bilgi düzeyi olduğunu belirten ve ailelere RV aşısı önerdiğini belirten katılımcıların bilgi düzeyi, diğer katılımcılara göre anlamlı ölçüde yüksek saptandı.

Sonuç: Rotavirüse bağlı gastroenterit sıklık ve şiddetini, hastaneye yatış oranını, hastalığa bağlı mortaliteyi önemli ölçüde azaltan RV aşısı ulusal aşı programında hâlihazırda bulunmaması nedeniyle oldukça etkin ve güvenilirliği kanıtlanmış olmasına rağmen henüz yeterince

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ÖZ

uygulanmamaktadır. Çalışmada elde edilen veriler hazırlanacak eğitim programında RV aşılarının uygulama yolu, dozları, uygulama zamanı, kontrendikasyonları, diğer aşılarla birlikte kullanımı gibi konularını vurgulanması gerekliliğini ortaya koymuştur.
Anahtar Kelimeler: Rotavirüs aşısı, aile hekimliği, gastroenterit

INTRODUCTION

Family medicine is an open and unlimited entry point for those seeking health care. The relationship of trust that physicians have with their patients through repeated contact creates a unique opportunity for the delivery of preventive health services. Vaccinations are one of the most important forms of preventive health care. Family physicians have personal education, immunization, hygiene, and diagnosis and treatment responsibilities, not only for individual patients but also for this disease, which concerns public health and can rapidly cause epidemics. Family physicians have a great responsibility for rotavirus (RV) infection, which can be prevented by vaccination today and which frequently causes severe dehydration in children under 5 years of age, according to World Health Organization (WHO) data (1).

RV are non-enveloped, double-stranded, RNA viruses belonging to the family Reoviridae. In the literature, 10 different RV types are classified from A to J according to VP6 sequence and antigenic differences. Type A roRV are the most common cause of childhood infections, while there are geographical differences between strains (2-4). RV infect intestinal enterocytes. Epithelial cell interactions with the virus, malabsorption secondary to enterocyte damage, villus ischemia and released vasoactive agents play a role in pathophysiology (5). A decrease in intestinal enzymes including maltase, sucrase, and lactase occurs with acute infection. This leads to malabsorption and transport of an osmotically active food bolus into the large intestine, resulting in osmotic diarrhea occurs (6,7). The incubation period of the disease is 1-3 days,and symptoms start suddenly following this period. The onset of the disease occurs with vomiting followed by secretory diarrhea. Approximately one-third of the patients may also have a fever that accompanies the symptoms. In the presentation of the disease, diarrhea without blood and mucus is yellow-green. Symptoms may last for 1 week (8,9). In the diagnosis of RV, a RV antigen can be found in stool samples using Enzyme-Linked Immunosorbent Assay (ELISA) or immunochromatography. One of the most commonly used tests in daily practice is the stool ELISA test (2,10). The main aim in the treatment of RV infection is to correct fluid loss and electrolyte disturbance, and to ensure adequate hydration and nutrition. Treatment should be given to alleviate dehydration symptoms. Specific antiviral treatment for RV is not available. Dehydration should be prevented with oral rehydration solutions, but if oral treatment is not possible, hospitalization and intravenous hydration should be considered. Most patients admitted to outpatient clinics and emergency departments can be discharged with oral rehydration solutions (11). Rarely progressing from isolated form to systemic infection, RV may also cause neurologic pictures including meningitis, encephalitis and seizures (2).

RV, which has the potential to cause disease even with low viral load, can remain viable on surfaces for a long time and is contagious even during asymptomatic periods of the disease. It is an infectious agent that is difficult to protect against using only general hygiene rules, although it is transmitted via the fecal-oral route. In 2016, it was reported to cause 258 million cases of diarrhea and more than 128 thousand deaths in children under 5 years of age (12). The high mortality rate of the disease has led to vaccine development efforts, and two types of RV vaccines that are widely used today have been included in the national vaccination schedule in some countries. The pentavalent human-bovine reassortant RV vaccine (Rotateq) was licensed in 2006 and is used in 3 doses, while the monovalent human RV (Rotarix) vaccine was licensed in 2008 and is used in 2 doses. Both oral vaccines are used in our country (13-15). As of 2020, 107 countries have included the RV vaccine in their national vaccination calendars, preventing 30,000 deaths each year (16).

In this study, the study aimed to evaluate the level of knowledge, attitudes, and behaviors of family medicine residents about RV vaccines and infection, which are not yet included in the national vaccination calendar and whose efficacy and safety have been proven.

MATERIALS and METHODS

Study Type

Before the study was started, written permissions were obtained from the administrations of the universities whose students were included in the study sample. The approval of the Clinical Research Ethics Committee of Adana City Training and Research Hospital has been obtained (decision number: 2527, date: 27.04.2023).

Our cross-sectional study was conducted between 01.05.2023-31.06.2023 with 106 family medicine residents working in ACTR hospital.

Study Group

The population of the research consisted of 141 family medicine residents working in the ACTR hospital. In the calculation made with the Epi-Info statistical program, the sample size was found to be 103 people with 80% power, 95% confidence interval, and 5% margin of error. Residents who agreed to participate and completed the consent form

were included in the study; participants who did not agree to participate or later withdrew consent were excluded.

Procedures

In the questionnaire, 33 questions were asked to measure the demographic data of the participants, their thoughts about RV infection, and their level of knowledge about vaccines. The first 6 questions of the questionnaire were about demographic data, the next 5 questions were about attitudes, behaviors, and disease experience, and the remaining 22 questions measured the level of RV knowledge. The answers were coded and the data obtained were analyzed. Some questions (16, 17, 21, 23, 25, 31, 33) were reverse coded. In statistical analysis, item difficulty index, item discrimination, and reliability of the questions were analyzed. Cronbach's Alpha value was calculated (0.721). The 22 questions used in our study were included due to their item discrimination power, validity and reliability. The calculated item difficulty index and item discrimination of the questions in the prepared scale were evaluated (Table 1).

Statistical Analysis

SPSS version 23.0 statistical software was used to analyze the data obtained. Descriptive statistics related to the socio-demographic characteristics of the participants were calculated. Student's t-test was used for two-group comparisons of normally distributed parameters, and the Mann-Whitney U test was used for two-group comparisons of non-normally distributed parameters. For comparisons of numerical data between more than two groups, the Kruskal Wallis test was used for those not showing normal distribution. Categorical data were compared by the chi-square test. Pearson correlation analysis was used to evaluate the relationships between numerical data. The p-value <0.05 was considered statistically significant.

RESULTS

48.1% of the participants were female. The mean age was 30.69±3.87 years; 66 percent were married and 34 percent had children. The mean duration of medical practice was 5.59±3.87 years, and the mean duration of residency was 2.57±1.22 years. 80.2% of the participating physicians had previously diagnosed patients with RV, and there was no statistical difference between the mean scores of the knowledge questions compared to the group of physicians who had not previously diagnosed patients with RV (p>0.05).

The rate of those who thought that RV vaccine should be included in the national vaccination schedule was 91.5%, and there was a statistically significant difference between the mean scores of those who answered no to this question and those who answered yes (p<0.05) (Table 2). The proportion of those who thought that they had sufficient information about RV vaccines was 45.3%. There was no statistically significant difference, 3%, between the group who answered no to this question and the mean scores of the answers given to the questions prepared about RV infection and vaccine (p>0.05). While the rate of physicians who routinely recommended the RV vaccine to families was 85.3%, a statistically significant difference was observed in the mean scores of the answers given to the questions prepared about RV infection and vaccine between the group who did not recommend it (p<0.05) (Table 2).

Participants were asked 22 questions about RV infection and vaccination. The 5 questions with the most correct answers were RV may cause diarrhea, nausea, vomiting, dehydration and electrolyte abnormalities. The main goal in the treatment of RV infection is to correct fluid loss and electrolyte disturbance and to ensure hydration and nutrition. Sanitation and hygiene reduce the likelihood of transmission. RV is one of the most important causes of diarrhea that can lead to

Table 1. According to the answers to the questions related to rotavirus infection and vaccines item Discrimination Index (rjx) and item Difficulty Index (Pj)

Question number	pj	rjx	c%	Question number	pj	rjx	c%
1	0.67	0.11	66.98	12	0.6	0.39	60.38
2	0.75	0.11	75.47	13	0.86	0.24	85.85
3	0.95	0.04	95.28	14	0.19	0.2	18.87
4	0.99	0.02	99.06	15	0.58	0.43	58.49
5	0.94	0.06	94.34	16	0.58	0.43	57.55
6	0.33	0.19	33.02	17	0.58	0.46	57.55
7	0.97	0.04	97.17	18	0.79	0.33	75.47
8	0.75	0.09	75.47	19	0.72	0.28	71.70
9	0.98	0.04	98.11	20	0.1	0.15	10.38
10	0.86	0.17	85.85	21	0.57	0.3	56.60
11	0.65	0.3	65.09	22	0.57	0.37	56.60

rjx: Discrimination Index, Pj: Difficulty Index

death in young children and infants. RV is transmitted through blood. The questions with the least correct answers were RV vaccines are absolutely contraindicated in severe combined immunodeficiencies. RV vaccines cannot be administered simultaneously with parenteral or nasal vaccines. RV occurs frequently in the summer season in our country. Rotarix® is a pentavalent human bovine reassortant vaccine while Rotateq® is a monovalent human RV vaccine, Since Rotateq® contains latex, Rotarix® should be preferred for those with latex allergy (Table 3).

The score on the knowledge questions about RV infection and vaccines was 14.98±3.51. There was a weak negative correlation between the knowledge scores of the physicians in the study group about RV infection and vaccines and the duration of their residency (r=-0.215, p=0.027). There was no correlation between the knowledge scores of the physicians regarding RV infection and vaccines and the duration of residency (r=0.135, p=0.168).

DISCUSSION

In our study, the average correct response rate to questions about RV infection was 84.27%. The level of knowledge of family medicine residents about the disease seems to be sufficient. In the study by Yıldız (17) this rate was found to be 84.27% in family physicians, while in this study, a relationship was found between specialty training, vaccination status of their own children, and knowledge level. In the Avcı (18) study, physicians who thought that they had sufficient knowledge about RV had a significantly higher mean response rate. A similar relationship was not found in our study. Studies in the literature conducted with nurses show that the rates of

Table 2. Participants' RV experience, attitudes and mean knowledge scores

	n	(%)	Mean ± SD	P
Have you ever seen a rotavirus infected patient?				
No	21	19.8	14.38±2.94	0.385
Yes	85	80.2	15.12±3.64	
Should rotavirus vaccine be on the routine vaccination schedule?				
No	9	8.5	13.81±3.39	0.001
Yes	97	91.5	16.39±3.14	
Do you think you have the adequate level of knowledge about rotavirus vaccine?				
No	58	54.7	13.22±3.52	0.117
Yes	48	45.3	15.14±3.48	
Do you recommend rotavirus vaccine to families?				
No	15	14.2	13.20±2.51	0.011
Yes	91	85.8	15.27±3.58	

RV: Rotavirus, SD: Standard deviation, n: Number

Table 3. The questions that the participants answered most and least correctly

The number of correct answers, (n%)		RV infection & vaccine knowledge level items
105	99.06	RV may cause diarrhea, nausea, vomiting, dehydration and electrolyte abnormalities.
104	98.11	The main goal in the treatment of RV infection is to correct fluid loss and electrolyte disturbance and to ensure hydration and nutrition.
103	97.17	Sanitation and hygiene reduce the likelihood of transmission.
101	95.28	RV is one of the most important causes of diarrhea that can lead to death in young children and infants.
100	94.34	RV is transmitted through blood.
60	56.60	RV vaccines are absolutely contraindicated in severe combined immunodeficiencies.
60	56.60	RV vaccines cannot be administered simultaneously with parenteral or nasal vaccines.
35	33.02	RV occurs frequently in the summer season in our country.
20	18.87	Rotarix® is a pentavalent human bovine reassortant vaccine while Rotateq® is a monovalent human RV vaccine.
11	10.38	Since Rotateq® contains latex, Rotarix® should be preferred for those with latex allergy.

RV: Rotavirus, n: Number

pre-education knowledge were below 50% and increased to 90% and above after the education programs (19,20). Many studies show that a higher number of correct answers were given to questions about the clinical aspects of RV gastroenteritis.

The low rate of correct answers to the question about the time of onset of RV enteritis is noteworthy. Only 33% of physicians answered this question correctly. The fact that most gastroenteritis is seen in the summer may have led to confusion. Dinç et al. (21) in our country, the most common months of RV enteritis were reported as winter. It was observed that marital status, having children, and gender of the physicians participating in our study had no effect on RV knowledge. This situation was found to be different from previous studies in the literature. The main reason for this may be the difference between the study populations. Since the population in our study received a medical education, they had more knowledge about RVs infection and vaccines than the participants from the general public (22).

The prevalence of the disease in our country was demonstrated within the scope of the Turkish demographic and health survey. It was found that 23% of children under the age of five had diarrhea in the last 2 weeks before the survey period. This rate is higher in children younger than 6 months and older than 23 months (23). In our study, we observed a negative correlation between the increase in the professional duration of physicians and the level of knowledge (24). It is thought that the inconsistency between the findings of our study and the literature stems from the type and quality of postgraduate education (24). In the study of Avcı (18) 74.8% of the physicians answered yes to the question "Do you recommend RV vaccination?" >10.6% of the physicians stated that they did not recommend any non-scheduled vaccines. Among the family physicians who did not recommend private vaccines to their patients, 58.7% stated that they did so because it was not included in the routine vaccination calendar of the Ministry of Health. 30.4% of the participants stated that they did not recommend the vaccine because it required payment. In the study conducted by Kolcu (25) when asked whether family physicians recommended RV vaccine to individuals, 56.5% stated that they did. In the same study, 62.6% of the participants reported that they would consider vaccinating their own children. In this study, 33.7% of the participants stated that they did not have enough time to educate families and patients about the vaccine and therefore did not recommend it. 53.1% of the participants stated that they did not have enough information to provide education about vaccination, and therefore did not recommend vaccination. 18.4% of the participants stated that they did not recommend the vaccine because the disease it targets was not severe (25). In the Yıldız (17) study, 37.2% of family physicians stated that they recommended vaccines not included in the routine vaccination schedule to the patients they followed. Among these vaccines, the RV vaccine had the highest recommendation rate at 85.7%. In this study, 76% of physicians who did not recommend the vaccine stated that they did not recommend it because it was not included in the routine vaccination schedule, 15% because it required payment, 13.6% because they did not have enough information, and 1.7% because of its side effect profile (17).

MacDougall et al. (26) reported that 55.7% of participating physicians recommended RVs vaccine to their patients in their study conducted in Canada. O'Leary et al. (27) found that 65% of family physicians recommended the vaccine to families in their study conducted in the USA in 2013. The study investigated the necessity of routine vaccine administration and the reasons for the current attitudes of pediatricians and family physicians. In 2007, it was reported that 70% of family physicians were concerned about the RV vaccine due to safety issues, and 5% stopped recommending the vaccine altogether. Later, the FDA's statements regarding the applicability of the vaccine and the elimination of the existing risk brought the vaccine recommendations back to their previous levels (27). In the study conducted by Özkaya et al. (28) in our country, 82.8% of physicians stated that they recommended the RV vaccine to families. In this study, it was found that reasons such as increased migration-related disease burden, cost, and the idea of early immunization, affected vaccination recommendations. In addition, in this study it was found that parents most frequently refused vaccines for reasons such as ingredients, side effects, concern about autism, and religious beliefs.

In our study, 91.5% of the participants answered "yes" to the question of whether RV vaccine should be included in the routine vaccination schedule. In 2009, WHO recommended that all countries include live oral RV vaccine in routine infant vaccination programs, and more than 100 countries have introduced RV vaccines to date (29). In the Almış et al. (30) study conducted in our country, 15 (39.5%) primary care physicians thought that the RV vaccine should be added to the routine vaccination schedule, while 10 (26.3%) thought that it was not necessary.

In a study conducted by Agyeman et al. (31) in 2009 to evaluate the attitudes of primary care physicians toward implementing RV vaccination into the swiss vaccination program, only 15% of the participating family physicians stated that they accepted routine RV vaccination. However, 48.5% of the same participant group stated that they would recommend the vaccine for their patients if the Ministry of Health authorities supported it and if it was included in the reimbursement program. The higher rate of RV vaccine recommendation and the necessity to include it in the routine vaccination schedule in our study compared to the studies in the literature may have resulted from the fact that it was conducted more recently than other studies. In our study, 91.5% of the participants thought that the RV vaccine should be included in the routine vaccination schedule, while the rate of recommending it to patients was 85.8%. The reason for

the difference may be because recommending a vaccine that has not yet been added to the national vaccination schedule is seen as a defensive medicine preference or is influenced by private vaccine fees.

In our study, the average correct response rate to questions about RV vaccines was 58.78%. Questions about RV vaccine were answered with less accuracy than questions about RV infection. In our study, 42.45% of the participants could not give correct answers to the questions about the route of administration, doses and time of administration of both types of RV vaccine. Contraindications of the vaccine, special patient groups for whom the vaccine should not be used, and the use of the vaccine with other vaccines were the questions with the least number of correct answers in our study. Adding information about RV vaccines to postgraduate education programs may increase the level of knowledge of the participants. In vaccine presentation meetings in our country, pediatricians are predominantly preferred chosen as the working group for paid vaccines such as the RV vaccine, which is not included in the national vaccination schedule.

Study Limitations

This study was conducted in a single center as a survey. With a multicenter design, it is possible to define the state of knowledge about RV infection and vaccination in family medicine education, both in other centers and nationally, in a more inclusive manner. The strength of our study is that it was conducted among family medicine residents who will actively assume immunization responsibility in primary care. In addition, opportunistic education was provided indirectly and awareness was raised by assessing infection, clinical, vaccine knowledge, and attitude at the same time is one of the strengths of our study.

CONCLUSION

RV infection is important for family physicians because it is a vaccine-preventable disease with a short vaccination period. The last dose of the vaccine can be administered up to a maximum of 24-32 weeks, and vaccination is not recommended after this period. If the necessary awareness is not created during this period, this opportunity will be missed because parents are not informed about the vaccine. In our study, the fact that the questions answered least correctly by family physicians consisted of basic points that should be known about the subject, such as the time period when the disease is frequently seen, the route of administration of the vaccine, the time of application of the vaccine, its applicability with other vaccines, and the fact that it is a live vaccine, led to the conclusion. It was concluded that a reminder and reinforcing education program should be organized at various intervals. For all vaccines, the type of vaccine, the time of application, the place of application, and possible side effects should be clearly known by family physicians, who are most likely the primary providers of the vaccine. The most common questions answered correctly by the participants were those related to the route of transmission, clinical aspects, and treatment. These responses may indicate that the participants prioritized the therapeutic approach rather than the preventive approach to RV infection. Nevertheless, it is important to emphasize that the primary duty of family physicians is to provide protective and preventive healthcare. In our country, there are vaccines with high efficacy and safety in the current medical literature that are not included in the routine vaccination schedule. Residency associations should work to ensure that the RV vaccine, which is applied routinely in many countries, is also applied routinely in our country. Although family medicine residents had adequate knowledge about RV infection, their knowledge about RV vaccines was limited. Training can be organized to increase the level of knowledge about vaccines that are not included in the expanded immunization program. It should be emphasized that the main duty of family physicians is preventive and protective medicine.

Ethics

Ethics Committee Approval: The approval of the Clinical Research Ethics Committee of Adana City Training and Research Hospital has been obtained (decision number: 2527, date: 27.04.2023).

Informed Consent: Residents who agreed to participate and completed the consent form were included in the study.

Footnotes

Author Contributions

Surgical and Medical Practices: M.T., Concept: M.T., S.K., Design: M.T., S.K., Data Collection or Processing: M.T., Analysis or Interpretation: M.T., S.K., Literature Search: M.T., S.K., Writing: M.T., S.K.

Conflict of Interest: All authors declare that they have no conflict of interest.

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Case Report

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Transient Hematuria Associated with Modified-Release Methylphenidate

Modifiye Salınımlı Metilfenidat ile İlişkili Geçici Hematüri

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that often requires pharmacological treatment, with methylphenidate (MPH) being a first-line therapy. While generally well-tolerated, MPH is associated with a range of side effects, some of which are rare and poorly understood. This article presents a case of hematuria in a pediatric patient who is using MPH, aiming to explore the potential link between MPH use and hematological side effects, such as bleeding. A 7-year-old female patient with ADHD and conduct disorder developed hematuria following an increase in the dose of modified-release MPH. The hematuria resolved after discontinuation of the modified-release formulation and switching to immediate-release MPH. Extensive medical evaluation revealed no other underlying causes for the hematuria. Although rare, hematological side effects, including hematuria, can occur in patients using MPH. The potential mechanisms underlying these effects may involve dopamine-induced changes in platelet aggregation, possibly contributing to bleeding or thrombocytopenia. While only a few cases have been reported, the connection between MPH and bleeding diatheses remains unclear. Further clinical studies are needed to explore the pathophysiological mechanisms of these rare side effects. MPH induced hematuria, although rare, should not be overlooked, particularly in patients who have difficulty expressing their symptoms. A better understanding of the mechanisms and regular monitoring of patients receiving MPH treatment may help identify and manage this rare side effect more effectively.

Keywords: Attention deficit hyperactivity disorder, methylphenidate, hematuria

ÖZ

Dikkat eksikliği/hiperaktivite bozukluğu (DEHB), yaygın bir nörogelişimsel bozukluktur ve tedavisinde genellikle metilfenidat (MPH) ilk tercih edilen ilaçtır. Genellikle iyi tolere edilse de MPH bazı yaygın yan etkilerle ilişkilidir ve bunlardan bazıları nadir olup tam olarak anlaşılmamıştır. Bu makale, MPH kullanımına bağlı olarak gelişen hematuri olgusunu sunmakta ve MPH hematolojik yan etkileri, özellikle kanama ile olan olası bağlantısını incelemeyi amaçlamaktadır. Yedi yaşında DEHB ve davranım bozukluğu tanılı bir kız çocuk, modifiye salım MPH dozunun arttırılmasının ardından hematuri gelişmiştir. Hematuri, modifiye salım formülasyonu kesildikten ve kısa etkili MPH geçildikten sonra düzelmiştir. Yapılan kapsamlı tıbbi değerlendirmede, hematuriye yol açabilecek başka bir altta yatan neden bulunmamıştır. Her ne kadar nadir olsa da MPH kullanımında hematolojik yan etkiler, özellikle hematuri görülebilir. Bu etkilerin olası mekanizmaları, dopaminin platelet agregasyonunda yarattığı değişikliklerle ilişkilendirilebilir ve bu durum kanama veya trombositopeniye yol açabilir. Ancak, MPH kanama yatkınlıklarıyla olan bağlantısı hala netleşmemiştir. Bu nadir yan etkilerin patofizyolojik mekanizmalarını araştırmak için daha fazla klinik çalışmaya ihtiyaç vardır. MPH neden olduğu hematuri, nadir olmasına rağmen, özellikle şikayetlerini ifade etmekte zorlanan hastalarda göz ardı edilmemelidir. Bu nadir yan etkinin mekanizmalarının daha iyi anlaşılması ve izlenmesi, bu yan etkinin daha etkin bir şekilde yönetilmesine yardımcı olabilir.

Anahtar Kelimeler: Dikkat eksikliği hiperaktivite bozukluğu, metilfenidat, hematüri

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD, as defined by the DSM-5) and hyperkinetic disorder (HKD, as outlined in the ICD-10) refers to a developmental condition that begins in childhood and persists for at least six months across various contexts. This condition is characterized by three main symptoms: inattention, impulsivity, and motor restlessness (1). While inattention and poor planning skills are often persistent and may negatively impact daily functioning, impulsivity also frequently continues. Motor restlessness, on the other hand, may decrease from adolescence onward, with overt hyperactivity being replaced by an internal sense of restlessness and a constant urge to move (2).

ADHD is a condition that is often overlooked and insufficiently treated (3). Studies have shown that, when ADHD is left untreated, there is an increase in risky behaviors, more frequent accidents, more prominent relationship issues, and a higher prevalence of substance abuse behaviors in individuals (4,5). Particularly, these individuals face significant challenges in social and academic domains, which increases the risk of developing psychological issues such as depression and anxiety. In the long term, this condition can negatively affect individuals' quality of life and reduce their workforce participation (6). According to the guidelines published by the National Institute for Health and Care Excellence in March 2018 and updated in September 2019, pharmacological treatment is recommended for children aged 5 and older, as well as adolescents, when ADHD symptoms persist in at least one area of daily life (e.g., social, academic, or interpersonal relationships), despite environmental adjustments (7).

Methylphenidate (MPH) is ADHD. It has been shown to result in significant improvements in 70% to 80% of individuals with ADHD (8,9). However, MPH is associated with common side effects such as insomnia, headaches, exacerbation of tics, irritability, anxiety, appetite loss, abdominal discomfort, and weight loss. Additionally, although rarer, more severe adverse effects, including psychotic episodes, seizures, tachycardia, weight gain, and drowsiness, have also been reported in the literature (10,11). This article aims to present a case of hematuria, which is suspected to be related to the use of MPH, in light of existing research.

CASE REPORT

A 7-year-old female patient presented to the Child and Adolescent Psychiatry Clinic at AUniversity of Health Sciences Türkiye, Adana City Training and Research Hospital with complaints of irritability, hyperactivity, dangerous behaviors, and self-mutilation. According to information from her parents, the patient was harming others at home and school, becoming angry when things did not go as she wanted, feeling restless shortly after starting to study, and exhibiting a high level of lack of attention, leading to falls and injuries. Additionally, she frequently lost or forgot her belongings at school. Following clinical evaluation and psychometric tests, the patient was diagnosed with ADHD and conduct disorder (CD). Treatment was initiated with 10 mg of modified-release MPH and 1 mg of risperidone, which resulted in significant improvement in her symptoms. MPH was supplemented with risperidone, an atypical antipsychotic, to address the comorbidity of CD.

However, after two weeks, the patient's symptoms began to flare up again, and the modified-release MPH dose was increased to 20 mg/day. After two months of treatment with 20 mg/day modified-release MPH the patient reported noticing bloody stains on her underwear, blood in her urine, and a burning sensation during urination. The complaints were absent during weekends when only risperidone 1 mg was administered without the modified-release MPH. No food or medications were consumed that could cause red urine.

The patient underwent a comprehensive medical evaluation, which included urinary system ultrasonography, X-rays, and detailed urine and blood tests. No underlying pathology was found. Laboratory tests conducted during the pediatric consultation showed no signs of infection, such as elevated white blood cells or C-reactive protein levels. Urine microscopy revealed the presence of erythrocytes, but no leukocytes were found, and no bacterial growth was observed in the urine culture.

The patient was referred to the pediatric hematology clinic. In the peripheral smear, erythrocytes appeared normochromic-normocytic, and the platelet count was within the normal range. No abnormalities were found in the bleeding disorder tests. During the pediatric nephrology consultation, kidney function tests were normal. The urinary ultrasound showed normal positioning of both kidneys bladder wall thickness, and the findings were within normal limits.

The patient had no history of hypertension or bleeding disorders, and she had not recently used non-steroidal anti-inflammatory drugs, warfarin, or any antiplatelet agents. No physical causes that could explain the urinary bleeding, such as genital trauma, surgery, or infection, were identified. When the modified-release MPH was discontinued and replaced with 10 mg immediate-release MPH, no further issues were observed.

DISCUSSION

Existing literature and clinical observations indicate that MPH is generally well tolerated in the treatment of ADHD. Most of the common side effects are temporary and do not require discontinuation of treatment (12). To the best of our knowledge, only one case of hematuria associated with MPH use in children and adolescents with ADHD has been reported, which occurred after an increase in the dose of Osmotic Release Oral System-Methylphenidate Hydrochloride (OROS-

MPH) (13). However, there are few reports of hematological side effects and bleeding, and a definitive causal relationship has not been firmly established (14).

Some case reports suggest a potential link between MPH and thrombocytopenia (15). In a case reported by Coskun and Adak (16) excessive and frequent menstruation occurred in an adolescent girl with ADHD while using OROS-MPH. Regarding the potential mechanisms of bleeding associated with MPH, it is plausible that in this case, OROS-MPH could have triggered a bleeding diathesis, such as thrombocytopenia, which may have led to bleeding. Another study hypothesized that MPH-induced thrombocytopenia might be related to peripheral platelet destruction. Under normal conditions, dopamine acts as a co-agonist for adenosine diphosphate (ADP)-induced aggregation, exerting a pro-thrombotic effect. However, prior studies have shown that at elevated dopamine levels, it acts as an anti-thrombotic agent. We propose that the increased dopamine levels, induced by MPH, could contribute to an anti-thrombotic state, which might result in hematuria (17-19).

It is well established that MPH enhances dopaminergic transmission by inhibiting dopamine transporters (20). The various effects of dopamine on platelet aggregation have been documented in earlier studies. These include dopamine-induced platelet aggregation at micromolar concentrations, enhanced ADP-induced platelet aggregation, and inhibition of epinephrine-induced aggregation (21). In another case report, it was noted that a decrease in platelet count occurred after the use of MPH, which led to a switch to atomoxetine treatment. Subsequently, the platelet count returned to baseline levels (22). Monozygotic twin sisters, experienced menorrhagia after starting MPH, despite their platelet levels being normal. The condition improved after they discontinued the medication, suggesting a possible connection between MPH and a genetic predisposition rather than an idiosyncratic reaction (23).

In our case, hematuria was observed following the increased doses, of long-acting modified-release MPH, and it did not recur when the medication was discontinued or when switched to the short-acting form, IR- MPH. Furthermore, no other medical causes were identified during the investigation. In this context, we may conclude that the hematuria was likely associated with modified-release MPH treatment, similar to the previously reported case (24).

CONCLUSION

Although there are limited reports in the literature regarding MPH causing hematuria or bleeding, this side effect should not be overlooked, especially in patients who have difficulty expressing their complaints. Further clinical studies are needed to better understand and monitor the mechanisms of this rare effect. Additionally, research on the hematological side effects of MPH could help in developing safer treatment strategies.

Ethics

Informed Consent: Written assent from the patient and consent from his parents/guardians were received for publication of this case report.

Footnotes

Author Contributions

Surgical and Medical Practices: C.K., Y.K., S.G., Concept: C.K., Y.K., S.G., Data Collection or Processing: C.K., Y.K., S.G., Analysis or Interpretation: S.G., Literature Search: C.K., Y.K., S.G., Writing: C.K.

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