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From the Editor

Dear Readers,

We are delighted to share with you the second edition of 2025, featuring a diverse collection of articles curated with the interests of healthcare professionals in mind, particularly those in primary care. Our objective is to offer a valuable resource for practitioners, and to that end, this issue comprises 7 original research papers and 1 comprehensive review article focusing on recent advancements in key areas of healthcare.

As Türkiye's foremost journal dedicated to primary care, we take great pride in and feel a deep responsibility for being a trusted source of knowledge for healthcare providers in our region. We sincerely appreciate your ongoing engagement with our publication and reaffirm our dedication to delivering up-to-date research and evidence-based insights relevant to primary care.

We encourage you to explore the insightful articles within this issue, which we are confident will capture your interest and spark new ideas. Your continued support and involvement are vital to our mission of advancing knowledge and fostering innovation in the field of primary care.

Please stay connected for our next issue, where we aim to deliver yet another enriching and intellectually stimulating collection of work.

Prof. Dr. Ahmet Keskin

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Research Article

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BURNOUT IN NURSING: A CROSS-SECTIONAL STUDY IN INDONESIA AND TAIWAN

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Abstract

Objectives: Burnout among nursing professionals has garnered significant international attention in recent years, largely due to its profound implications for nurse well-being, patient satisfaction, and the overall effectiveness of healthcare systems. This phenomenon underscores the urgent necessity for implementing comprehensive strategies to mitigate burnout and promote the well-being of nursing staff. This study examines the prevalence of Burnout Syndrome among nurses in Indonesia and Taiwan using a cross-sectional study approach.

Materials and Methods: The research employs a quantitative method, utilising a questionnaire to collect data and SEM-PLS software to conduct validity tests. The study encompasses 1.327 respondents from Indonesia and 312 respondents from Taiwan. The survey identifies three variables to measure burnout syndrome in nurses: depersonalisation, emotional exhaustion, and personal achievement.

Results: The findings indicate that high levels of depersonalisation, significant emotional exhaustion, and relatively low personal achievement all contribute to the Burnout Syndrome experienced by nurses in both countries. The R-squared value for Indonesia is 36.8%, while Taiwan's is 46.1%. This suggests that the interpretation of the Burnout Syndrome can be categorised as moderate.

Conclusion: The research indicates that the regression model, including independent variables such as depersonalisation, emotional exhaustion, and personal achievement, can explain most of the variations in Burnout Syndrome in nurses in both countries, although not optimally. The study concludes that the results related to Burnout Syndrome in nurses in Indonesia and Taiwan can impact the quality of patient services.

Keywords: Burnout syndrome, nurse, health.

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Introduction

Burnout in nursing has gained international recognition in recent years due to its substantial impact on nurses' well-being, patient satisfaction, and the overall performance of healthcare systems.[1] Nursing is a vital component of the healthcare system in Indonesia and Taiwan, providing essential health services to individuals with diverse needs.[2] The challenges that nurses encounter while fulfilling their duties should not be overlooked. Fatigue in the nursing profession presents a significant challenge. Fatigue is a multifaceted issue that can substantially impact the well-being of individual nurses and the standard of patient care.[3] Burnout in nursing pertains to the physical, emotional, and psychological strain experienced by nurses due to demanding job requirements, substantial workloads, and various factors within their professional environment.[4]

Indonesia and Taiwan, countries with developing healthcare systems influenced by various cultural, economic, and social factors, encounter specific challenges in preserving nurses well-being and addressing burnout within the nursing profession.[5] The provision of health services in Indonesia faces systemic challenges, including limited resources, high workloads, and significant accessibility barriers, particularly in rural areas.[6] Despite boasting a robust healthcare system and solid infrastructure, Taiwan faces challenges stemming from demographic shifts, rising job demands, and mental health concerns in the workplace.[7]

In Indonesian healthcare, the nurse-to-patient ratio is 1:4 for inpatient units and 1:20 for outpatient units.[8] Taiwan's healthcare system includes legislation that mandates minimum hospital nurse-to-patient ratios.[9] Additionally, it is customary for families to accompany and remain with patients during their hospital stay. However, enforcing the minimum ratio of 1 nurse to 8 patients only came into effect in 2009, and this requirement is applicable solely during daytime shifts. This analysis highlights the significant nurse workload disparities between the two countries. In Indonesia, nurses typically adhere to a 12-hour workday schedule, five days a week, resulting in extensive working hours.[10] In comparison, nurses in Taiwan typically work fewer hours, averaging around ten hours per day, five days a week.[7] The prevalence of nurse burnout represents a significant issue that warrants attention and intervention within the healthcare sector. According to recent studies, the prevalence rate of nurse burnout in Indonesia is 63%, whereas in Taiwan, it is slightly lower at 52%.[7] High levels of burnout in nurses can lead to an excessive workload and detrimentally affect their physical and emotional well-being, as well as the standard of patient care.[11] Fatigue in nursing is critical due to its detrimental consequences. Nurses who suffer from burnout often exhibit reduced performance and increased error rates and are more susceptible to experiencing severe burnout. Burnout, characterised by severe exhaustion, can have profound effects, including reduced quality of healthcare, increased nurse turnover rates, and adverse impacts on the healthcare system.[12]

It is essential to delve into the factors contributing to nurse burnout and compare the situations in Indonesia and Taiwan. This can offer valuable insights for enhancing human resource management policies and practices in the health sector of both countries. By comparing Indonesia and Taiwan, we can better understand the cultural disparities, healthcare systems, and other influences on nurse burnout. This study seeks to assess the level of burnout among nurses in both countries using a cross-sectional study approach. Drawing comparisons between the two nations will help us pinpoint both differences and similarities in the factors affecting nurse burnout. The results of this study will serve as the foundation for developing improved policies, human resource management strategies, and mental health interventions in the nursing field.

Materials and Methods

Study Design

This study employs a cross-sectional research design, which enables the collection of data at a single point in time, facilitating a comparative analysis of nurse burnout in Indonesia and Taiwan. The data collection period for the Indonesian cohort spans from January to October 2023, while for Taiwan, it occurs between August and September 2023. By utilising a quantitative research approach, this investigation enables the precise measurement of burnout-related variables, thereby allowing for robust statistical analysis.

This research has received Ethical Approval from the Ethics Committee of Universitas 'Aisyiyah Yogyakarta No. 2536/KEP-UNISA/I/2023, valid from 25 January 2023 to 26 January 2024, and Taipei Medical University (TMU-Joiunt Institutional Review Board) No. N202306070 was valid from August 2, 2023, to August 1, 2024. Before the commencement of data collection, all participants received a thorough explanation of the study's objectives, potential risks, and associated benefits to ensure informed participation. Written informed consent was obtained from all individuals, thereby affirming the voluntary nature of their involvement. To maintain data confidentiality, participant responses were anonymised, and all collected data were securely stored to prevent unauthorised access. The study adhered to the ethical principles outlined in the Declaration of Helsinki and the Indonesian national research ethics guidelines. By adhering to these rigorous methodological and ethical standards, we endeavour to ensure that the research's findings are valid and reproducible, while maintaining an unwavering commitment to integrity in research practices.

Participants and Sampling Size

The study population consists of licensed nurses actively employed in healthcare settings, particularly hospitals, in Indonesia and Taiwan. The inclusion criteria for participation were set as follows: (1) full-time employment status and (2) a minimum of one year of professional experience in the nursing field. Conversely,

the exclusion criteria encompassed (1) part-time nurses or those in trainee positions, (2) nurses on leave during the data collection period, and (3) individuals who declined to participate in the study. These criteria were meticulously established to ensure the relevance of participants and enhance the reliability of the data.

A stratified random sampling method was utilised to ensure representation from various healthcare settings, experience levels, and geographic regions. A flowchart outlining the recruitment process is provided in the appendix. This flowchart delineates the total number of nurses approached, which comprised 1.800 in Indonesia and 500 in Taiwan. It further indicates the number of participants who consented to participate in the study, with 1.500 in Indonesia and 400 in Taiwan. After applying exclusion criteria, the final sample consisted of 1.327 participants from Indonesia and 312 from Taiwan. This structured representation enhances the transparency and rigour of the reporting process. The difference in sample sizes reflects the varied nursing population sizes in the two countries. Power analysis conducted with G*Power software indicated that a minimum sample of 300 per group would be sufficient to identify a medium effect size ($f^2 = 0.15$) with 80% power at a 5% significance level, thereby deeming the sample sizes adequate. The larger sample from Indonesia enhances the robustness of the findings and promotes greater generalizability. To mitigate selection bias, stratified sampling was employed to ensure proportional representation across essential nursing demographics. To address response bias, measures were taken to anonymise participant responses and guarantee data confidentiality. Additionally, measurement bias was minimised through the utilization of a pre-tested and validated instrument that was adapted to align with the specific cultural context of the study.

Data Collection Instruments

Burnout was assessed utilizing a validated survey instrument designed to capture four primary dimensions: Depersonalization (DP), Emotional Exhaustion (EE), Personal Accomplishment (PA), and Overall Burnout Syndrome. The instrument underwent cultural adaptation for relevance in Indonesia and China, with translations provided in Bahasa Indonesia and Mandarin Chinese. To ensure semantic consistency, back-translation procedures were meticulously applied. The validation metrics, including Cronbach's alpha ($\alpha > 0.7$ across all subscales) and confirmatory factor analysis, which demonstrated acceptable factor loadings (exceeding 0.6), corroborated the instrument's reliability and construct validity within both populations.

Data Analysis

Data analysis using appropriate statistical analysis techniques through SmartPLS software version 3.2.9. The study examines the correlation between the leading indicators of nurse burnout and the factors that influence it. Furthermore, path analysis in the SEM framework will enable the assessment of the direct and indirect influences of independent variables on dependent variables, such as DP, EE, and PA. The use of Burnout Syndrome indicators as the primary dependent variables in the SEM model will provide a comprehensive

understanding of the complexity and interaction of these indicators. This study measured the structural model (Inner Model) by examining the R-squared value. The R-squared value is the coefficient of determination on the dependent variable. According to Chin (1998), the R-squared values are 0.67 (strong), 0.33 (moderate), and 0.19 (weak).[13] Hypothesis testing follows the inner model test results, which include R-squared values, parameter coefficients, and t-statistics. A hypothesis is either accepted or rejected based on the t-statistics and p-values. Specifically, suppose the t-statistic exceeds 1.64 at a 0.05 significance level (one-tailed), and the beta coefficient is positive. In that case, H0 will be rejected if the p-value is less than 0.05, indicating a statistically significant influence. Conversely, if the p-value is greater than 0.05, H0 is accepted, suggesting no influence. This analysis examines the impact of workload, social support, and work environment on nurse burnout, offering valuable insights for developing more effective interventions and human resource management policies in both countries.

Hypothesis

H1: Depersonalization (X1) positively and significantly affects Nursing Fatigue (Y).

H2: Emotional Exhaustion (X2) positively and significantly affects Nursing Fatigue (Y).

H3: Personal Accomplishment (X3) positively and significantly affects Nursing Fatigue (Y).

Results

Demographic Respondents

Table 1 indicates that most respondents were female nurses, with 69.02% from Indonesia and 93.91% from Taiwan. The predominant age group for nurses in both countries was 36-45 years, representing 34.99% in Indonesia and 35.90% in Taiwan. Notably, there were no nurses over 65 in Taiwan, while 0.15% of nurses in Indonesia remained active in this age bracket. Regarding educational qualifications, Indonesia had a higher proportion of diplomas (50.38%) and master's graduates (0.60%). In contrast, Taiwan had a larger share of Bachelor of Nursing (46.15%) graduates, with no master's degree holders in practice. Furthermore, 52.78% of nurses in Indonesia and 74.04% in Taiwan had over five years of work experience, with permanent employment significantly higher in Taiwan at 94.23%, compared to 63.07% in Indonesia. Notably, no nurses were occupying professional or managerial positions in Taiwan.

Table 1 indicates that external factors, such as length of service, employment status, and job position, may significantly impact nurse burnout syndrome in Indonesia and Taiwan more than internal factors like age and education. The complexities of work environments, high job demands, and a lack of adequate support from

employers contribute to this phenomenon. For example, nurses with extensive experience may face heightened stress due to the cumulative challenges of their roles. Additionally, those with unstable employment or in lower positions may be at higher risk for burnout due to increased workloads and job insecurity. While age and education can influence stress management, the external pressures of a challenging workplace appear to be more decisive. To effectively address burnout among nurses, it is essential to enhance work conditions, provide sufficient support, and recognise the importance of experience and education in managing stress.

Table 1. Respondents demographic profile

Characteristic		Indonesia (n = 1327)		Taiwan (n = 312)	
		Frequency	**Percentage (%)**	**Frequency**	**Percentage (%)**
Gender	Male	411	30.98	19	6.09
	Female	916	69.02	293	93.91
Age	17-25	35	2.64	48	15.38
	26-35	382	28.79	110	35.26
	36-45	464	34.99	112	35.90
	46-55	346	26.11	34	10.90
	56-65	98	7.39	8	2.56
	> 65	2	0.15	0	0
Education Level	Diploma in Nursing	668	50.38	132	42.31
	Bachelor of Nursing	17	1.28	144	46.15
	Ners	634	47.80	36	11.54
	Master of Nursing	8	0.60	0	0
Length of Work	< 1 Year	100	7.54	19	6.09
	1-2 Years	189	14.26	29	9.29
	3-4 Years	337	25.42	33	10.58
	> 5 Years	701	52.78	231	74.04
Type of work	Regular employees	837	63.07	294	94.23
	Temporary Employees	490	36.93	18	5.77
Position	Professional Nurse	1264	95.30	24	100
	Managerial	8	0.60	0	0
	Both (Professional nurse and Managerial)	55	4.14	0	0

Research Variable Reliability

Table 2 reveals that both Indonesian and Taiwanese nurses experience moderate levels of Burnout Syndrome, with R-squared values of 36.8% for Indonesia and 46.1% for Taiwan. The regression analysis indicates a modest influence of the independent variable on the dependent variable. The inner model results presented in Figure 2 demonstrate positive path coefficients for all indicators except for the Burnout Syndrome indicator in Indonesia. The Depersonalization Indicator exhibits the highest statistical value at 19.687, while the Burnout Syndrome indicator has a low t-statistic of 1.140. Most indicators show a p-value of 0.001, except for the Personal Accomplishment variable (0.003) and the Burnout Syndrome variable (0.255). Hypothesis acceptance in this study is contingent upon p-values below 0.05 (Table 3). Hypothesis 1 supports the conclusion that depersonalization has a positive impact on burnout syndrome among Indonesian nurses. Likewise, Hypothesis 2 confirms that Emotional Exhaustion significantly affects Burnout Syndrome. Finally, Hypothesis 3 substantiates the positive influence of Personal Achievement on Burnout Syndrome within this demographic.

Table 2. R-Square Value on Burnout Syndrome using SEM-PLS

Variable	R-Square	Description
Burnout Syndrome (Taiwan)	0.461	Moderate
Burnout Syndrome (Indonesia)	0.368	Moderate

Description of R-Square value:
Strong : > 67%
Moderate : 33 – 67%
Low : 19 – 33%

Discussion

This study examines the levels of DP, EE, and PA among nurses in Indonesia and Taiwan to compare their experiences with burnout syndrome. Burnout syndrome is a complex psychological condition characterised by emotional exhaustion, depersonalisation, and personal achievement resulting from chronic occupational stress.[14] The issue presents substantial implications for nurses' physical, psychological, and behavioural well-being, frequently resulting in reduced job satisfaction, decreased quality of care provided, and elevated turnover rates within the profession.[15] Burnout syndrome includes a range of psychological problems that have a substantial impact on an individual's physical, psychological, and emotional well-being due to occupational stress.[15] Prolonged burnout syndrome within the nursing profession may ultimately result in the decision to

resign from the role.[15] Individuals experiencing burnout syndrome often exhibit heightened self-awareness regarding their work, including a strong inclination to contemplate leaving their current employment.[15]

Depersonalisation and Burnout Syndrome

The study provided empirical evidence that DP has a significant influence on burnout syndrome among nurses in both Indonesia and Taiwan. Various external factors intensify this issue, including excessive working hours, insecure employment, and entry-level job positions. These conditions significantly undermine nurses' sense of control over their work environment. For instance, nurses in unstable job situations may experience a profound emotional detachment from their patients.[16] This disconnection often stems from job insecurity and a restricted ability to make independent decisions in their roles, ultimately affecting the quality of care they provide.

The findings of this study align with an expanding body of literature that highlights the detrimental impact of extended working hours on the prevalence of burnout syndrome among nursing professionals. A large-scale cross-sectional investigation by Lin et al. (2021) conducted in Taiwan revealed a pronounced dose-response relationship between weekly working hours and burnout among healthcare practitioners.[17] Specifically, nurses who worked beyond 60 hours weekly exhibited a twofold increase in the likelihood of experiencing symptoms of burnout when contrasted with their counterparts working 40 hours. The odds increased by threefold for those engaged in over 74 hours and by fourfold for those exceeding 84 hours per week.[17] Notably, the relationship was partially mediated by reduced sleep duration, which accounted for 7%–29% of the observed incidence of burnout. Thus, sleep deprivation is a pivotal pathway through which prolonged working hours adversely affect mental health.[17]

DP has a significant impact on nurses' mental health and patient outcomes. Research has shown that healthcare professionals experiencing DP exhibit a diminished capacity to deliver empathetic care, resulting in decreased patient satisfaction and erosion of trust in the healthcare system.[18] Addressing DP requires a comprehensive strategy that incorporates several key components. First, improving working conditions is vital to create a more inviting and engaging environment for employees. This includes enhancing the physical workspace, managing workloads, and clarifying job responsibilities and expectations. Encouraging collaboration among colleagues helps foster strong relationships that can counter feelings of isolation and disconnection.[19] Regular counselling sessions offer employees a safe space to express their feelings and seek guidance. These initiatives can reduce feelings of detachment and create a more nurturing and supportive work environment.

Emotional Exhaustion and Burnout Syndrome

EE is recognised as the most significant dimension of burnout and considerably influences nurses in both countries. External factors, such as the length of service, employment status, and nursing position, play a more significant role in shaping the work experience than internal factors, like age and education. Nurses in lower-ranking positions or those in precarious jobs often confront overwhelming workloads.[20] Moreover, they frequently lack the necessary resources and managerial support to manage these demands effectively, resulting in increased emotional exhaustion.[21] This challenging work environment can significantly impact their well-being and job satisfaction.

This study aligns with the study of Jordanian nurses' burnout.[22]. This highlighted the prevalence of EE among nurses working in challenging conditions. EE not only affects nurses' mental health but also significantly undermines their ability to provide high-quality patient care.[22] This fatigue and disengagement can increase the risk of medical errors, thus compromising patient safety. Addressing this critical issue requires a comprehensive approach that includes systemic changes. Improving staff scheduling is essential to ensure that nurses have adequate rest and recovery time. Additionally, implementing fair and equitable workload distribution will help prevent the overburdening of individual nurses while fostering a supportive organisational culture prioritising employee well-being.[23] Furthermore, ensuring access to mental health resources is crucial for supporting nurses who encounter EE.[23] This will ultimately lead to increased job satisfaction and better patient care outcomes.

In alignment with these international data, a recent study conducted in Turkey by Gündüz and Öztürk (2024) examined burnout among intensive care unit nurses, revealing that an alarming 95.5% reported high mental workloads, which were robustly correlated with elevated levels of burnout.[24] This investigation further determined that emotional workload significantly predicted emotional exhaustion, personal accomplishment, and depersonalisation.[24] Although this research primarily focused on mental workload rather than shift duration, it underscores the substantial psychological demands confronting nurses in high-acuity environments. Thus, it reinforces the more general conclusion that excessive job demands—whether manifested through extended hours or high cognitive load—substantially increase burnout risk.[24] A study conducted in Turkey identified that nurses working in cardiac surgery departments were particularly susceptible to high levels of burnout.[25] This phenomenon can be attributed to the high-pressure nature of their work environments, coupled with inadequate rest periods. Furthermore, the study revealed that burnout harmed the nurses' perceived quality of work life.[25]

In light of ongoing global nursing shortages and the intensified healthcare demands in the aftermath of the pandemic, these findings collectively underscore the pressing necessity for systematic reforms. Healthcare institutions must prioritise the implementation of policies that regulate shift lengths, guarantee adequate rest

periods, and address the intensity of workload to safeguard the mental health of nursing professionals while sustaining the quality of care delivered.

Personal Accomplishment and Burnout Syndrome

The study indicated that PA significantly influences burnout syndrome among nurses in Indonesia and Taiwan. Nurses with longer tenures or higher job titles report a stronger sense of personal accomplishment, mainly due to their accumulated experience, skills, and recognition.[26] Conversely, nurses who face limited opportunities for career advancement and receive insufficient acknowledgement for their contributions are more likely to experience feelings of inadequacy.[26] These conditions can heighten the risk of burnout, underscoring the need for a supportive work environment that fosters professional growth and acknowledges individual achievements.

Nurses working in environments with limited opportunities for career advancement often encounter considerable challenges. When pathways for professional growth, such as promotions, specialised training, or leadership roles, are lacking, they may feel stagnant in their current positions.[27] Moreover, a lack of acknowledgement for their contributions, whether through formal recognition, awards, or simple expressions of gratitude from management and colleagues, can further erode their sense of worth in the workplace.[27] An initial investigation revealed significant burnout rates among healthcare professionals, which were attributed to excessive workloads, inadequate administrative support, and an unbalanced work-life balance.[28] The findings underscored the imperative for systemic reforms within hospital management practices to mitigate these issues and enhance overall staff well-being. Consequently, these factors combined may lead to feelings of inadequacy and self-doubt, making it increasingly difficult for them to sustain high levels of motivation and job satisfaction in an already demanding profession.

Cross-Cultural Implications

A comparative analysis of nurses in Indonesia and Taiwan reveals a nuanced interplay of shared and unique factors that contribute to burnout syndrome. In both countries, critical external elements such as job status and working conditions significantly shape the various dimensions of burnout experienced by healthcare professionals. However, cultural and systemic differences between the two nations influence how these factors manifest in practice.[29] In Taiwan, the pressures of an ageing population and high patient volumes place considerable stress on nurses, resulting in overwhelming workloads and EE. Conversely, Indonesia grapples with its challenges, including inefficient resource allocation and workforce instability, which further intensify the difficulties faced by nurses on a daily basis. While burnout is a shared experience, the specific ways it arises and affects nursing professionals can vary significantly between these two countries.

Understanding the intricacies of cultural differences is crucial for developing effective, tailored interventions. In Taiwan, the increasing demands of an ageing population present formidable challenges for healthcare workers. By enhancing staffing levels and allocating additional resources to care facilities, we can help mitigate the emotional and physical burnout that nurses frequently encounter.[30] In Indonesia, the focus should be on enhancing job stability and offering comprehensive professional development opportunities. This shift can significantly improve the overall well-being of nurses, enabling them to excel in their roles. Furthermore, fostering collaborative partnerships among policymakers, healthcare organisations, and educational institutions is essential.[30] Such synergies will facilitate the effective implementation of impactful strategies to address burnout in these varied regions.

Implications for Practice and Policy

The findings of this study underscore the urgent need for comprehensive interventions to tackle burnout among nurses in Indonesia and Taiwan. Essential recommendations include enhancing working conditions by ensuring adequate staffing, equitable workload distribution, and safe working environments to mitigate stress and fatigue. Furthermore, fostering organisational support through access to mental health resources, mentorship programs, and professional development opportunities will cultivate a supportive workplace culture. Promoting work-life balance with flexible work policies, childcare support, and structured leave programs can aid nurses in effectively managing their personal and professional commitments. Strengthening emotional intelligence through targeted training programs will equip nurses with vital stress management skills, resilience-building strategies, and tools for delivering exceptional patient care. Lastly, recognising and rewarding achievements by acknowledging nurses' contributions through awards, promotions, and public recognition is crucial for enhancing morale and fostering a sense of personal accomplishment. These initiatives are imperative for creating a healthier work environment for nurses and improving the overall quality of care.

Several limitations of this study merit acknowledgement. First, while a stratified random sampling method was utilised to enhance representativeness, the research focused exclusively on licensed nurses working in hospital settings in Indonesia and Taiwan. This geographic and contextual limitation may restrict the generalizability of the findings to nurses in other healthcare environments or regions. Second, excluding part-time nurses, trainees, and those on leave may have introduced a selection bias, potentially omitting valuable perspectives from nurses with varying work patterns or employment statuses. Additionally, despite achieving relatively high response rates—with 1.327 participants in Indonesia and 312 in Taiwan—the voluntary nature of participation could lead to self-selection bias, as those who chose to engage may differ significantly from those who opted out. Finally, cultural and systemic differences between the healthcare systems of the two countries may have influenced the responses, and these contextual factors should be carefully considered when interpreting cross-national comparisons.

This study highlights the significant impact of depersonalisation (DP), emotional exhaustion (EE), and personal accomplishment (PA) on burnout syndrome among nurses in Indonesia and Taiwan, underscoring the need for targeted interventions that address these factors from both individual and organisational perspectives. By fostering a supportive work environment and prioritising the well-being of nurses, healthcare organisations can enhance job satisfaction, improve patient care, and reduce burnout rates. The research reveals that all three variables significantly correlate with burnout syndrome, with R-squared values of 0.368% for Indonesia and 46.1% for Taiwan, suggesting a moderate understanding of the phenomenon within these contexts. The differences in findings between the two countries further emphasise the influence of cultural and workplace factors on nurses' burnout experiences. While this study aims to deepen our understanding of these issues in the respective regions, it is essential to note that the survey was conducted over a limited timeframe, indicating a need for further research with a broader scope to thoroughly examine the factors influencing burnout syndrome in nursing.

Ethical Considerations: This research has received Ethical Approval from the Ethics Committee of Universitas 'Aisyiyah Yogyakarta No. 2536/KEP-UNISA/I/2023, valid from 25 January 2023 to 26 January 2024, and Taipei Medical University (TMU-Joiunt Institutional Review Board) No. N202306070 was valid from August 2, 2023, to August 1, 2024.

Conflict of Interest: The authors declare no conflict of interest.

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Research Article

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EVALUATION OF SLEEP QUALITY AND PERCEIVED STRESS LEVELS IN MEDICAL STUDENTS

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Abstract

Objectives: The aim of the study was to determine sleep quality and perceived stress levels in medical students and to develop recommendations for this purpose.

Materials and Methods: There were a total of 1466 students enrolled during the study. A 43-question questionnaire including a sociodemographic data form, Pittsburgh Sleep Quality Index, and Perceived Stress Scale scales was applied to 1217 students (83% of all students).

Results: The mean age of the participants was 21.64 years (±2.26 years), with 56.4% of the participants being female and 43.6% male. The study revealed that 41.2% of the students surveyed reported good sleep quality, while 58.8% indicated poor sleep quality. 6th-grade students' good sleep quality was statistically significantly higher than the other grades ($p<0.001$). Poor sleep quality was found to be significantly higher in students who smoked and drank alcohol than in those who did not ($p<0.05$). As indicated by the Perceived Stress Scale, 0.9% of the participants exhibited no stress, 41.2% demonstrated low stress, 53.2% displayed moderate stress, and 4.7% displayed high stress. Female students had significantly higher perceived stress levels and poor sleep quality than male students ($p<0.05$). Among the students, the perceived stress level of those who used alcohol and did not do physical activity was statistically significantly higher ($p<0.05$).

Conclusion: Medical students have high levels of psychological stress and poor sleep quality due to long and intensive working hours, challenging exam load, life disorganization, and patient management responsibilities.

Keywords: Medical students, sleep quality, stress.

Introduction

Sleep is indispensable for an individual's quality of life and general health. Changes in sleep patterns or quality can negatively affect daily activities and impair physical and mental health.[1] Lack of sleep can have serious consequences, causing work and traffic accidents.[2]

It is reported that sleep problems and fatigue are common in university students and that this fatigue may even be as intense as that of heavy laborers. Students reported that their sleep patterns were inconsistent, that they could not get enough sleep, that their sleep quality was poor, and that they frequently resorted to alcohol or over-the-counter medication to regulate their sleep and used stimulants to stay awake.[3,4]

Stress is a fight or flight response to a trigger that threatens a person's life and harmony with his/her environment.[5] Stress is a ubiquitous problem in many different fields, including business, education, and many others. The exposure of working individuals to numerous stress factors in their daily lives can result in a range of psychological, physical, and social changes.[6]

The medical faculty, in particular, is characterized by its unique challenges, which are a consequence of the protracted and arduous nature of the educational process, the substantial course load, and the anxieties associated with examination pressure. The prevalence of depression, anxiety, burnout levels, and suicidal attempts among medical students is a matter of concern.[7]

This study aimed to examine the quality of sleep and perceived stress levels of medical students, to determine the factors affecting sleep and stress, and to develop recommendations regarding these factors.

Unlike similar studies, this research involves a larger group of participants with a high response rate and examines a wider range of variables such as sleep efficiency, sleep latency, and subjective sleep quality in relation to perceived stress.

Materials and Methods

Study design

The study aimed to include all medical students. However, only 1,217 students (83%) out of the 1,466 enrolled students volunteered and signed the informed consent form. Students who did not attend classes were on

academic leave or refused to participate were excluded. Although random sampling was not performed, the high participation rate was considered sufficient for the sample to be representative of the population. The questionnaire was administered face-to-face to consenting students. Participants were informed of the study's purpose, told that their participation was voluntary, and assured that their responses would remain confidential. No personal identifiers were collected, and all data were anonymized and reported only in aggregate form.

Ethical Approval

The type of this study was descriptive cross-sectional and was conducted at the Faculty of Medicine of Selçuk University Hospital from January to May 2024. The aims and procedures of the study were evaluated and approved by our ethics committee before the relevant analyses were performed (Date: 13 February 2024; No: 2024/85).

Data Collection

Data on participants' age, gender, marital status, class, economic status, alcohol and cigarette use, average sleep duration, physical activity status, presence of chronic diseases, and medications used continuously were collected through a structured self-report-based questionnaire form created by the researchers. These questions are based on self-report methods that are frequently used in similar studies and whose validity is supported in the literature.[8] A 43-question questionnaire was administered to the participants, including the Pittsburg sleep quality index (PSQI) and perceived stress scales (PSS).

Perceived Stress Scale (PSS)

The Turkish validity and reliability study of the PSS-14 was conducted by Eskin et al. The internal consistency coefficient was 0.84 and Cronbach's α coefficient was 0.893. Consisting of 14 questions, the PSS-14 assesses the degree of stress perceived in certain situations in the individual's life on a 5-point Likert-type scale ranging from “Never (0)” to “Very often (4)”. The PSS-14 scores range from 0 to 56, with a higher score indicating more stress perceived by the individual.[9]

Pittsburg Sleep Quality Index (PSQI)

The PSQI was created by Buysse et al. in 1989 to assess the quality of sleep and disturbances over the previous month.[10] Cronbach Alpha amount of the scale is 0.80. The PSQI consists of 7 subcomponents: subjective quality of sleep, habitual efficiency of sleep, disturbances of sleep, latency of sleep, duration of sleep, use of sleep

medication, and daytime dysfunction. The total PSQI score ranges from 0 to 21. A score of 5 or below means sleep quality is good, and a score of 6 or above indicates poor sleep quality.[11]

Statistical Analysis

Data were analyzed using the IBM SPSS 22.0 statistical package program. In descriptive analyses of the data, frequency (n) and percentage (%) were used for categorical variables and mean ± standard deviation was used for normally distributed variables. The results were analyzed at the significance level of $p<0.05$ and 95% confidence interval.

Before the analysis, the compatibility of the variables with normal distribution was checked by the Kolmogorov-Smirnov test ($p>0.05$) and Q-Q plot graphs; skewness and kurtosis values between -1 and +1 supported normal distribution. PSS, PSQI questionnaire scores, and sociodemographic data were evaluated using descriptive statistics. Pearson chi-square test and Fisher's exact test were applied for sociodemographic data, sleep problems, and questionnaire scores. One-way analysis of variance (ANOVA) was performed for the comparison of PSQI subcomponents and PSS scores. In cases where significant differences were found as a result of ANOVA, post hoc analyses were performed in pairwise comparisons between groups, and the Tukey HSD (Honestly Significant Difference) test was used for multiple test corrections. Thus, the risk of type I error in multiple subcomponent comparisons was controlled. The relationship between the subcomponents of the PSQI and the numerical variables in the PSSdata was determined by Pearson correlation analysis ($p<0.05$). Students were categorized according to their curricular stages with the 1st, 2nd, and 3rd grades as “preclinical” and the 4th, 5th, and 6th grades as “clinical” group. The preclinical group includes the lecture-oriented education period in which there is no direct contact with the patient (no clinical internships, shifts, or ward duties), while the clinical group includes clinical rotations involving hospital-based practices and patient care.

Results

Of the 1217 students in the study, 56.4% were female and 43.6% were male. The mean age was 21.64±2.26 (min:17, max:36) years. 15.9% of the students were studying in the first grade, 18.3% in the second grade, 16.3% in the third grade, 20.5% in the fourth grade, 14.2% in the fifth grade, and 14.8% in the sixth grade. 3.8% of the students were married and 96.2% were single. 37.6% of the students did not do physical activity, 40.7% did it 1-2 times a week, 16.7% did it 3-4 times a week, and 5% did it more than 5 times a week. 14.9% of the students reported smoking and 14% reported drinking alcohol. 90.5% of the participants stated that they did not have chronic diseases and 91.9% stated that they did not use any medication regularly.

While 58.8% of the students had poor sleep quality, the perceived stress level was none in 0.9%, low in 41.2%, moderate in 53.2%, and high in 4.7%.

Regarding sleep quality, 6th-grade students had significantly better sleep quality compared to other grades (p<0.001). According to post hoc analysis, the rate of poor sleep quality was significantly higher in 2nd and 4th grade students (p<0.001). According to gender, male students had better sleep quality than females (p=0.019). The rate of poor sleep quality was significantly higher in the smoking (p=0.006) and alcohol users (p=0.018) groups (Table 1).

Table 1. Evaluation of the Relationship Between Sociodemographic Characteristics and Sleep Quality in Medical Students

	Sleep Quality						
	Good (PSQI≤5) (n=502)		Poor (PSQI>6) (n=715)		Total	X^2	p
	n	%	n	%	n		
Grade							
1.grade	80	41.5	113	58.5	193	33.353	**<0.001***
2. grade	74	33.2[a]	149	66.8[b]	223		
3. grade	86	4.4	112	56.6	198		
4. grade	79	3.6[a]	171	68.4[b]	250		
5. grade	85	49.1	88	50.9	173		
6. grade	98	54.4[a]	82	45.6[b]	180		
Gender							
Female	263	38.3	423	61.7	686	5.497	**0.019***
Male	239	45.0	292	55.0	531		
Marital Status							
Married	21	45.7	25	54.3	46	0.217	0.641**
Single	481	41.1	690	58.9	1171		
Cigarette							
Yes	58	32.0	123	68.0	181	7.434	**0.006***
No	444	42.9	592	57.1	1036		
Alcohol							
Yes	56	32.9	114	67.1	170	5.628	**0.018***
No	446	42.6	601	57.4	1047		

* Pearson chi-square analysis ** Continuity correction test was used.

According to the perceived stress level, males were significantly more likely to have low stress than females (p=0.003), whereas females were more likely to experience moderate stress (p=0.003). Students who engaged in physical activity had a higher rate of low stress levels (p<0.001), whereas moderate stress was more common in those who did not (p<0.001). Students who used alcohol had a significantly higher rate of high stress levels (p=0.006). Students without chronic diseases were more likely to have low-stress levels, whereas

students with chronic diseases were significantly more likely to have high stress levels (p<0.001). Students who regularly used medication were significantly more likely to have high stress levels (p<0.001) (Table 2).

Table 2. Evaluation of the Relationship between Sociodemographic Characteristics of Medical Faculty Students and Perceived Stress Levels

	Perceived Stress Level					
	None (0-11)	**Low (12-26)**	**Middle (27-41)**	**High (42-56)**	**X^2**	**p**
	n %	n %	n %	n %		
Grade						
Preclinical	5 %0.8	242 %39.4	333 %54.2	34 %5.5	3.318	0.343*
Clinic	6 %1.0	260 %43.1	314 %52.1	23 %1.4		
Gender						
Female	3 %0.4	257 %37.5[a]	391 %57.0[a]	35 %5.1	14.182	**0.003***
Male	8 %1.5	245 %46.1[b]	256 %48.2[b]	22 %4.1		
Marital Status						
Married	2 %4.3[a]	23 %50.0	21 %45.7	0 %0	8.313	**0.035****
Single	9 %0.8[b]	479 %40.9	626 %53.5	57 %4.9		
Physical Activity						
Yes	11 %1.4[a]	344 %45.3[a]	377 %49.6[a]	28 %3.7[a]	23.657	**<0.001***
No	0 %0[b]	158 %34.6[b]	270 %59.1[b]	29 %6.3[b]		
Cigarette						
Yes	1 %0.5	79 %43.6	89 %49.2	12 %6.6	2.944	0.400*
No	10 %1.0	423 %40.8	558 %53.9	45 %4.3		
Alcohol						
Yes	0 %0	60 %35.3	94 %55.3	16 %9.4[a]	13.085	**0.006***
No	11 %1.1	442 %42.2	553 %52.8	41 %3.9[b]		
Chronic Disease						
There is	0 %0	37 %31.9[a]	64 %55.2	15 %12.9[a]	22.596	**<0.001***
None	11 %1.0	465 %42.2[b]	583 %53.0	42 %3.8[b]		
Regular Medication Use						
There is	0 %0	33 %33.3	51 %51.5	15 %15.2[a]	19.466	**<0.001****
None	11 %1.0	469 %41.9	596 %53.3	42 %3.8[b]		

* Pearson chi-square analysis ** Continuity correction test was used.

Significant relationships were found between perceived stress scores and subcomponents of PSQI in medical students. It was observed that perceived stress scores increased significantly as the frequency of sleep disturbance increased, subjective sleep quality worsened, daytime dysfunction increased, falling asleep time prolonged, sleep duration shortened, and sleep efficiency decreased (p<0.001) (Table 3).

Table 3. Evaluation of the Comparison of the Score Levels of Pittsburg Sleep Quality Subcomponents and Perceived Stress Scale Scores of the Students

	Perceived Stress Scale Score		
Sleep disturbance	**n**	**Mean±S.D**	**p**
Nothing	77	25.56 ± 8.84	
1<time/week	735	27.58 ± 6.78	**<0.001**
1-2 times/week	367	30.53 ± 7.34	
≥3 times/week	38	35.26 ± 7.74	
Subjective Sleep Quality			
Very Good	80	24.75 ± 7.83	
Good	693	27.10 ± 6.73	**<0.001**
Bad	370	30.94 ± 6.59	
Very Bad	74	35.91 ± 7.74	
Daytime Dysfunction			
Never	244	25.14 ± 7.73	
<1 time/week	357	27.06 ± 6.20	**<0.001**
1-2 times/week	424	29.87 ± 6.72	
≥3 times/week	192	33.35 ± 6.95	
Sleep Latency			
0-15 minutes	257	27.30 ± 7.79	
16-30 minutes	432	27.53 ± 7.00	**<0.001**
31-60 minutes	379	29.71 ± 6.93	
>60 minutes	149	31.50 ± 7.29	
Sleep Duration			
7 hours	734	27.80 ± 7.32	
6-7 hours	263	28.99 ± 6.89	**<0.001**
5-6 hours	151	31.12 ± 6.60	
<5 hours	69	30.91 ± 8.76	
Sleep Activity			
>%85	1043	28.25 ± 7.21	
%75-84	116	31.42 ± 7.22	**<0.001**
%65-74	29	31.45 ± 8.84	
<%65	29	29.07 ± 7.83	
Total	1217		

SD:Standart Deviasyon, One-way Analysis of Variance (ANOVA) test was used.

A moderate positive correlation was detected between the PSQI scores and PSS scores (r=0.391; p<0.001). This suggests that as sleep quality worsens, the level of perceived stress increases (Table 4).

Table 4. Analysis of the Relationship Between Age, Grade, PSQI Score and PSS Score

		PSS Score	PSQI Score	Grade	Age
PSS Score	r				
	p				
PSQI Score	r	**0.391****			
	p	**<0.001**			
Grade	r	**-0.098****	**-0.102****		
	p	**<0.001**	**<0.001**		
Age	r	**-0.128****	**-0.077****	**0.786****	
	p	**<0.001**	**0.004**	**<0.001**	

Pearson correlation analysis was used.

Discussion

In this study, sleep quality and perceived stress levels of medical students were evaluated. Factors that may be effective on these variables were analyzed.

When sleep quality was evaluated, 58.8% of the students had poor sleep quality. In a study conducted by Alotaibi et al. in 230 medical students, 77% of the students reported poor sleep quality.[12] Academic intensity, high levels of stress, anxiety and depression, unhealthy lifestyle, extracurricular activities, and active social life harm sleep quality in medical students.

In the study, the good sleep quality of 6th-grade students was significantly higher than that of other grades. In addition, poor sleep quality was significantly higher in 2nd and 4th-grade students compared to other grades. In the study conducted by Sarısaltık et al. it was found that the sleep quality of first-year medical faculty students was worse than other grades. [13] These results may help students to manage their sleep patterns more effectively with increased clinical experience and better adaptation to the medical school environment in the later stages of their education.

In the evaluation by gender, male students were found to have better sleep quality compared to female students. In a 2020 study using the PSQI, female students were found to have a higher rate of poor sleep quality than male students.[13] This difference may be due to stress management, sleep habits, physiological and hormonal effects, cultural and social factors, and methodological differences.

In the study, the proportion of students with poor sleep quality was significantly higher among smokers compared to non-smokers. Similarly, in a study by Shalva et al. with 126 medical students, smokers were found to have lower sleep quality. [14] The stimulant effects of nicotine increase sleep latency and disrupt sleep integrity. Similarly, in our study, the rate of poor sleep quality in students who used alcohol was found to be

significantly higher than those who did not use alcohol. However, no significant relationship was found between alcohol use and sleep quality in the study by Jie et al. [15] The different results between studies suggest that the effects of alcohol use on sleep quality may be complex and multifaceted. The effects of alcohol on sleep may depend on several variables such as the amount and frequency of consumption, individual differences, and other lifestyle factors.

When the perceived stress level of the students was analyzed, it was determined that 53.2% experienced moderate stress, 41.2% had low-stress levels, and 4.7% experienced high stress levels. This finding is consistent with the median score of 27, which was reported in the study conducted by Dağtekin et al. in 2019 with 1002 students [16] These results indicate that the stress levels of medical students are high, similar to the literature and that supportive measures should be taken for stress management.

When the relationship between physical activity and stress level was examined, it was found that students who engaged in physical activity had significantly lower stress levels. In a study conducted in 2022 by Boyd et al. in first-year medical students, it was shown that decreases in physical activity level increased the perceived stress level. [17] Our study shows that physical activity reduces perceived stress in line with the literature. Physical activity is an important stress management tool at the individual and social levels.

Statistically significant relationships were found between the subcomponents of sleep quality and perceived stress. In a study conducted in 2025 with 386 medical students, moderate positive correlations were found between sleep quality and depression, anxiety, and stress levels; increased levels of depression and anxiety were associated with deterioration in sleep quality. [8] These findings indicate that stress levels are high in individuals with poor sleep quality, difficulty falling asleep, insufficient sleep duration, irregular bedtime and wake-up times, insomnia or sleep fragmentation for some reasons, and impaired daytime functioning.

There was a moderate positive correlation between PSQI and PSS scores. Since the increase in sleep quality scores indicates poor sleep quality, poor sleep quality indicates an increase in stress. In a study conducted in 2023 on 795 medical students in India, similar to our study, Pearson's correlation analysis showed a significant positive correlation between perceived stress and sleep quality. [18] High-stress levels disrupt sleep cycles, damaging the individual both physically and mentally.

In this study, the quality of sleep and perceived stress levels of medical students were evaluated. As a result, a significant proportion of students were found to have poor sleep quality and stress levels were generally moderate. Sleep quality was better in 6th-grade and male students, while poor sleep quality was significantly higher in students who smoked and drank alcohol. Perceived stress levels were higher in female students, alcohol users, and those with chronic diseases or regular medication use. Physical activity was observed to reduce stress. There was a significant relationship between sleep disorder components and perceived stress.

Poor sleep quality was associated with increased stress. In order to improve the quality of sleep and decrease stress, recommendations such as sleep hygiene training, stress management techniques, and physical activity promotion should be developed for medical students. In addition, awareness and support programs are recommended to reduce smoking and alcohol use. Large-scale and multicentre studies can make it more understandable of this relationship.

Limitations of the study

The restriction of this study to a single university, in addition to the limitation of the data to a specific period, serves to constrain the generalizability of the results and the traceability of changes over time. The generalisability of the findings is contingent upon the execution of analogous research in diverse cultural and institutional contexts. Moreover, although the study's objective was to encompass the entire population, the participation rate was found to be 83%, thereby precluding the application of random sampling and resulting in the consideration of this as a potential limitation, which might have led to selection bias. It is recommended that future multicentre studies be conducted, employing larger and more culturally diverse samples. These studies will provide more generalizable and stronger evidence on the factors affecting sleep quality and stress levels.

Ethical Considerations: The aims and procedures of the study were re-evaluated and approved by our ethics committee before the relevant analyses were performed (Date: 13 February 2024; No: 2024/85).

Conflict of Interest: The authors declare no conflict of interest.

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Research Article

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PREVALENCE AND THE RISK FACTORS OF POSTPARTUM DEPRESSION IN ANKARA CITY HOSPITAL

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Abstract

Objectives: Pregnancy and postpartum are processes that open to complications, not only gynecological & obstetric but also psychiatric complications are quite risky during the first months. Untreated Postpartum Depression (PPD) is a condition that may lead to mortality. Our aim with this study was to detect the relationship between sociodemographic information, and hemoglobin levels of postpartum women, with PPD levels.

Materials and Methods: This cross-sectional study was conducted with 250 women who were in their postpartum period and admitted to the Ankara City Hospital for 2 months. Volunteers were subjected to a sociodemographic characteristics survey, the Edinburgh Postnatal Depression Scale (EPDS), and their hemoglobin values were recorded.

Results: The prevalence of PPD was found to be 22.8%. The risk of depression is higher in younger mothers ($p=0.042$). There was a significant relationship between a low educational level and depression scores ($p=0.020$). The depression risk groups exhibited statistically significant relationships concerning spousal support during ($p=0.007$) and after ($p=0.009$) pregnancy. The risk of PPD is lower in women who receive spousal support. The EPDS score increased as hemoglobin levels decreased ($p<0.001$, $r=-0.266$). Mothers without depression risk had higher average breastfeeding numbers than others ($p<0.01$).

Conclusion: Young age, early marriage, lack of education associated with high EPDS scores, spousal support during pregnancy and postpartum, breastfeeding practices and frequency, and high hemoglobin levels were found to have significant relationships with low EPDS scores.

Keywords: Postpartum depression, family medicine, anemia.

Introduction

The World Health Organization (WHO) defines Postpartum Depression (PPD) as non-psychotic depressive episodes beginning from the 6th week up to the first year after birth.[1] According to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-4), PPD symptoms start within the first 4 weeks postpartum. The DSM-5 notes that one-third of patients experience symptoms during pregnancy, termed peripartum-onset major depressive disorder. [2-3] PPD is a leading public health issue, and when left undiagnosed or diagnosed late, it's associated with increased risks of maternal mortality and morbidity. Projections suggest that without preventive measures, depression could become one of the top three causes of death by 2030.[4] As a frequent postnatal complication, the American College of Obstetrics and Gynecology recommends at least one screening for postpartum women. Diagnostic tools include the Edinburgh Postnatal Depression Scale (EPDS) and Beck Depression Inventory.[5] Symptoms include low mood, anhedonia, forgetfulness, irritability, anxiety, sleep disturbance, dysfunctionality, and feelings of worthlessness, with some patients potentially posing harm to themselves or their infants.[6] Stress-related factors predominantly contribute to PPD risk.[7] A history of depression, anxiety during or before pregnancy, a failure to bond with the baby due to hospitalization, insufficient environmental support, marital problems, and challenging living conditions can all trigger PPD.[8-9] Research indicates that low socioeconomic status, minority ethnic groups, and young motherhood further increase the PPD risk.[10-11] This study aimed to inspect the relationship between sociodemographic factors and hemoglobin levels in postpartum women with PPD.

Materials and Methods

This cross-sectional study at the Ankara City Hospital involved 250 postpartum women, excluding those with high-risk pregnancy histories. Approval for the study was obtained from the Ankara City Hospital Clinical Research and Ethics Committee (E2-21-794.), and all participants provided oral informed consent before their inclusion. This study was administered following the 1964 Declaration of Helsinki and its later amendments. Participants were selected successively and screened using the EPDS, a 10-item self-rating scale developed by Cox et al. to detect postpartum depression.[13] Turkish validity and reliability were confirmed by Engindeniz et al., with a Cronbach's alpha of 0.87.[12] Each question has four response options, scored from 0 to 3, with a cutoff score of 13 indicating a risk of depression.[13] Anemia status, defined as hemoglobin levels below 12 mg/dl according to WHO, was also evaluated. [14] Hemoglobin measurements were performed by fluorescence flow cytometry method with the XN-100 model of the Sysmex brand device. Data were analyzed using IBM SPSS.23, with normality and variance homogeneity checked using Kolmogorov-Smirnov and Levene's tests. Descriptive statistics included means and standard deviations for continuous variables, and frequencies and percentages

for categorical variables. The Mann-Whitney U test and Wilcoxon signed-rank test were used to analyze non-normally distributed independent and dependent samples, respectively. Chi-square tests were used to examine the relationships between categorical variables, and Spearman's rho was used for continuous variable correlations. A significance level of $p<0.05$ was adopted, and the questionnaire's Cronbach's alpha was 0.860. This value is consistent with the previously validated Turkish version. The slight difference may be due to variations in sample characteristics, cultural adaptation of the scale, or minor procedural differences. Nevertheless, both values indicate a high level of internal consistency, validating the reliability of the instrument.

Results

A total of 250 postpartum women, with an average age of 28.7 years, participated in this study. The sociodemographic information is provided in Table 1. The participants' mean hemoglobin level was 11.37 g/dl, and the average EPDS score was 7.40. Depression risk was high in 22.8% of the participants. A weak but statistically significant negative correlation was detected between EPDS and hemoglobin levels ($p<0.001$, $r=-0.266$). The mean hemoglobin level of those at high risk of PPD was 10.84 g/dl, compared with 11.5 g/dl in those at low risk. There was a significant difference in the risk of PPD in those receiving breastfeeding education ($p=0.017$), with lower depression risk observed in mothers who received breastfeeding education. The depression risk groups showed statistically significant relationships in terms of spousal support during ($p=0.007$) and after ($p=0.009$) pregnancy. The risk of PPD was found to be lower in women who receive spousal support. Sociodemographic characteristics related to PPD are presented in Table 2. Mothers with anemia breastfed an average of 11.36 times/day, while those without anemia breastfed 12.48 times/day, indicating a significant effect of anemia on breastfeeding frequency ($p=0.011$). Mothers without anemia breastfed more frequently than those with anemia did.

Table 1. Sociodemographic characteristics of participants

	Total n (%)
Age	28.37 ± 4.95
Height	161.66 ± 8.55 cm
Weight	68.59 ± 10.86 kg
BMI	25.96 ± 4.43 kg/m2
Marital status	
Married/Marriage age	249 (99.6%)/23.6 ± 3.53
Single	1 (0.4%)
Working status	
Working	2 (0.8%)
Unemployed	176 (70.4)
Maternity leave	72 (28.8%)
Income status	
Income more than expenses	72 (28.8%)
Income equals expenses	129 (51.6%)
Income less than expenses	49 (19.6%)
Birth status	
Vaginal birth	187 (74.8%)
Cesarean section	63 (25.2%)
Planned pregnancy status	
Planned pregnancy	205 (82.0%)
Planned pregnancy	205 (82.0%)
Unplanned pregnancy	45 (18.0%)
Spouse status	
Spouses who wanted the baby	236 (94.4%)
Spouses who did not want the baby	14 (5.6%)
Spouses who supported their partners during pregnancy	200 (80.0%)
Spouses who partially supported their partners during pregnancy	41 (16.4%)
Spouses who did not support their partners during pregnancy	9 (3.6%)
Spouses who supported their partners after birth	197 (78.8%)
Spouses who partially supported their partners after birth	43 (17.2%)
Spouses who did not support their partners after birth	10 (4.0%)
Pregnancy school status	
Attended pregnancy school	13 (5.2%)
Did not attend pregnancy school	237 (94.8%)
Breastfeeding status	
Received breastfeeding training	53 (21.2%)
Did not receive breastfeeding training	197 (78.8%)
Sufficiently breastfeeding	176 (70.4%)

Table 2. The Relationship of Sociodemographic Characteristics with Postpartum Depression

	High risk of depression n (%)	**Low risk of depression n (%)**	**p**
Hemoglobin	10.84 ± 1.52 g/dl	11.50 ± 1.51 mg/dl	**0.011***
Age	27.42 ± 5,86	28.60 ± 4.69	**0.042***
Marriage age	22.77 ± 4.44	23.80 ± 3.26	**0.020***
Educational background			**0.020***
Primary school	12 (25.0)	20 (10.1)	
High school	21 (43.8)	97 (48.7)	
University	15 (31.3)	82 (41.2)	
Spouse who supported during pregnancy			**0.007***
Yes	31 (64.6)	169 (83.7)	
Partially	12 (25.0)	29 (14.4)	
No	5 (10.4)	4 (2.0)	
Spouse who supported after birth			**0.009***
Yes	31 (64.6)	166 (82.2)	
Partially	12 (25.0)	31 (15.3)	
No	5 (10.4)	5 (2.5)	
Breastfeeding Education			**0.017***
Received breastfeeding education	4 (8.3)	49 (24.3)	
Did not receive breastfeeding education	44 (91.7)	153 (75.7)	
Adequately breastfeeding			**<0.001***
Yes	16 (33.3)	160 (79.2)	
No	32 (66.7)	42 (20.8)	
Number of breastfeeding n/day	8.81 ± 3.79	12.57 ± 3.32	**<0.001***

Discussion

Our study identified factors related to PPD, with a prevalence of 22.8%. Hahn Holbrook et al reported a global PPD prevalence of 17.7%.[15] Ahmad et al reviewed 15 Middle Eastern studies (2006-2020) and found a 27% incidence.[16] A 2015 United States study with 4022 women reported a PPD rate of 10.1 %.[17] In China, a study with 2462 women found a 22.2% prevalence.[18] Sociocultural diversity and socioeconomic status likely explain these differences.

Our study found that higher educational levels were correlated with lower depression risk (p=0.020). A Middle Eastern meta-analysis, including Türkiye, Iran, Israel, and the United Arab Emirates, linked low educational levels with PPD.[16] Education may enhance awareness and ease motherhood adjustment, thereby reducing anxiety and depression. Therefore, educating women reduces the risk of depression and ensures the formation of conscious and healthy societies.

There was a significant decrease in the risk of developing depression with spousal support both during pregnancy (p = 0.007) and after pregnancy (p = 0.009). Eslahi et al found similar results in Iran, suggesting spousal support lowers workload and boosts self-efficacy.[19] Desta et al's Ethiopian meta-analysis indicated domestic violence increases PPD risk by 5.46 times, highlighting the impact of an unsettled home environment.[20] Insufficient social support stands out as an environmental factor in the emergence of disorders such as depression and anxiety. The postpartum period is a very challenging process. To prevent depression, spouses need to support women during stressful periods.

Our study showed a weak negative correlation between EPDS and hemoglobin levels, with low hemoglobin linked to higher PPD risk (p=0.011). A Canadian review found that anemia increased PPD risk in 8 out of 10 studies.[21] Each 1 g/dL decrease in hemoglobin increased PPD risk by 10%.[22] As in depression, behavioral symptoms associated with anemia in adults include changes in cognition, emotions, apathy, hypoactivity, fatigue, and irritability. Because anemia may produce these symptoms during pregnancy or the postpartum period has been identified as a possible physiological risk factor for PPD. The mechanisms by which anemia causes depressive symptoms may be explained by changes in myelination and neurotransmitter metabolism.[23]

In our study, breastfeeding education was correlated with a lower risk of depression (p=0.017). Education improves breastfeeding quality and provides the feeling of adequate breastfeeding. Postpartum depression harms the hormones that affect breastfeeding, causing disruption in mothers' performance and reducing their self-efficacy in breastfeeding.[24] Hammond et al. found reduced PPD symptoms in women who were confident about their breastfeeding.[25] Prolonged breastfeeding causes oxytocin levels in the blood to remain high. High oxytocin levels from breastfeeding are known to help prevent PPD.[26] Supporting breastfeeding in mothers and providing adequate training on breastfeeding both reduce the risk of depression and ensure the healthy development of the baby.

Limitations

One limitation of our study is the varying postpartum periods of the participating women. Additionally, we used the EPDS, which only indicates the risk of depression rather than providing a diagnosis. However, one strength of our research is the lack of comparative studies on PPD and anemia in Türkiye, and our results align with the existing literature.

Conclusion

The postpartum period critically influences both the mother and baby's neuropsychosocial development, with untreated PPD potentially resulting in severe outcomes, such as suicide. Factors such as young age, early marriage, lack of education, spousal support, breastfeeding practices, and hemoglobin levels were significantly correlated with EPDS scores. These factors can be detected in clinical practice, identifying mothers at risk through screening. Postpartum mood changes require close monitoring. Every woman should be screened for depression during this period. Spousal support during and after pregnancy can help prevent PPD while encouraging and educating mothers about breastfeeding is crucial for maternal and child health. The treatment of postpartum anemia may also protect against PPD onset. Family physicians play a crucial role in identifying PPD risk factors by monitoring pregnancy and the postpartum period, ensuring early diagnosis, and appropriate treatment.

Ethical Considerations: Approval for the study was obtained from the Ankara City Hospital Clinical Research and Ethics Committee (E E2-21-794)

Conflict of Interest: The authors declare no conflict of interest.

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Research Article

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EXAMINATION OF FACIAL EMOTION RECOGNITION SKILLS OF INDIVIDUALS WITH SOCIAL ANXIETY

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Abstract

Objectives: The ability to figure out emotions very quickly while interacting and reacting appropriately is essential for acceptable social behavior. This study assessed the effect of social anxiety level on emotion recognition in facial expressions in a large cross-sectional case population, without a time limitation to avoid the negative effect of reaction time.

Materials and Methods: The data collection tools involved the sociodemographic characteristics data form, the Brief Fear of Negative Evaluation Scale (BFNE), the Brief Social Phobia Scale (BSPS), and the Emotion Identification Test from Facial Expressions.

Results: A total of 641 university students with a mean age of 21.36 ± 2.98 years participated in the study. There was a positive correlation between the BFNE and BSPS and its subdimensions. The BFNE had a negative relationship with the neutral emotion. There was a positive correlation between the BSPS and the feeling of disgust. There was a significant difference between individuals with high social anxiety and individuals with low social anxiety in recognizing anger and disgust emotions. There was no difference between the socially anxious groups and non-socially anxious groups in the overall misclassification of identifying facial expressions. Individuals with high social anxiety had a significantly higher fear of being negatively evaluated than those with low social anxiety.

Conclusion: Considering that facial expressions convey basic social information, understanding the interpretation of facial expressions is important for understanding social anxiety. Therefore, comprehensively understanding face recognition-oriented biases will guide future intervention strategies through cognitive processing in social anxiety.

Keywords: Social phobia, social anxiety disorder, emotion, face.

Introduction

Social phobia (social anxiety disorder, SAD) is a common disorder characterized by a disproportionate fear and anxiety of social performance and social situations that negatively affect functioning. Individuals with pathological SAD may develop disproportionate fears about the potential danger associated with social interactions and may avoid eye contact and looking at the faces of other individuals.[1] Considering that many of the social clues encountered in everyday life are ambiguous or irrelevant, biases for negatively misinterpreting these clues may serve to maintain anxiety about interacting with the world.

Wells et al. suggest from a cognitive perspective that SAD is characterized by addressing social situations in a negatively biased manner.[2] Individuals with SAD tend to interpret ambiguous and unfavorable social events more negatively or as a sign of disapproval than individuals without anxiety.[2,3] Biased information processing includes biased attention to social threats, excessive attention to internal clues, and negative interpretation of ambiguous social events.[4] Individuals with SAD are assumed to preferentially direct their attention to potential social threats in the environment, in other words, to indicators of being negatively evaluated or rejected. Threat detection occurs at an early stage of information processing, which occurs automatically and involves the unconscious, rapid, and involuntary recognition of stimuli.[5,6] Anxiety causes mild or ambiguous social disapproval to be interpreted as destructive.[3] Studies have found that socially anxious individuals interpret depictions of ambiguous social scenes more negatively or less favorably than individuals without anxiety.[4-7]

Recognizing emotions from facial expressions is particularly important when processing relevant social information. Facial expressions provide an important reference for information about other people's emotions and intentions during social interactions.[8] The ability to figure out emotions very quickly while interacting and reacting appropriately is essential for acceptable social behavior.[9] Facial expressions typically include clues for different categories of emotions and are therefore ambiguous in nature.[10] Because socially anxious individuals tend to interpret social responses as a sign of disapproval, the ambiguity in facial expressions is prone to misinterpretation.[11] Individuals with SAD have a high level of bias in interpreting facial expressions, especially increased sensitivity to facial expressions that evoke a threat or scrutiny.[12,13] Patients with SAD tend to evaluate neutral faces negatively, remember critical faces better, and scan facial expressions with a different eye movement pattern than those without SAD.[1,14,15] People with high SAD who interpret social interactions catastrophically recognize negative expressions more accurately than other expressions and are more likely to categorize a neutral or positive expression as negative.[16]

The issue in recognizing facial expressions is a bias in information processing, and biases in information processing play a central role in the development and maintenance of psychiatric disorders.[17] Considering that facial expressions convey basic social information, understanding the interpretation of facial expressions is

important for understanding SAD. Therefore, comprehensively understanding face recognition-oriented biases will guide future intervention strategies through cognitive processing in SAD. Given that the duration of presentation of facial expressions and emotional intensity vary simultaneously, we cannot determine whether differences across individuals are due to the isolated effect of only one of these variables or their combined effect. This study assessed the effect of SAD level on emotion recognition in facial expressions in a large cross-sectional case population, without a time limitation to avoid the negative effect of reaction time.

Study hypotheses

There is a positive relationship between the SAD scores and the fear of being negatively evaluated.

The performance in the identification of facial expressions of emotions differs between socially anxious groups and non-anxious groups.

There is a positive relationship between SAD scores and facial expressions showing threatening emotions (i.e., anger, fear, or disgust).

Materials and Methods

This study was conducted in two universities in Turkey between April 01 and June 01, 2024. The total number of students enrolled in these two universities is 35471. The estimated sample size was 381 based on the population sample calculation (alpha = 0.05, confidence interval = 95%). Of the university students, 641 participated in the study. The sample included undergraduate students who responded to self-report questionnaires. For the social anxiety group, we used the following clinical cut-off score: ≥20 on the BSPS. The criteria for participation in the study included being a university student, being 18 years of age or older, having access to the internet, and volunteering for the study. Participants who gave incomplete responses to the study scales were excluded.

The study was granted ethical approval by the Ankara Yıldırım Beyazıt University (03-612) and was conducted following the Declaration of Helsinki.

Procedure

All data were collected via Google Forms, an online survey site. The study link was sent to the e-mail addresses of the students by the Information Technology units of the departments where they were studying. Upon accessing the link with a self-report questionnaire, participants were shown an informed consent form. The data collection tools covered the variables studied, including the Sociodemographic Characteristics Data Form,

the Brief Fear of Negative Evaluation Scale (BFNE), the Brief Social Phobia Scale (BSPS), and the Emotion Identification Test from Facial Expressions of Healthy Individuals in Turkish Society (EITTS). Each participant was presented with 70 color images of emotional expressions. Participants had to identify the emotions depicted by each face. To avoid habituation, a participant was presented with each person displaying each of the seven emotions (happiness, sadness, surprise, fear, disgust, anger, and neutral) only once. Completion of the questionnaires took approximately 15 to 30 minutes. The study was approved by the Ethics Committee (Date: 21.03.2024; No: 03-612) and conducted following the Declaration of Helsinki. The principles of "Confidentiality and Protection of Privacy" and "Respect for Autonomy" were adopted. Participation in the study was voluntary, and no incentives were offered.

Measurements

Sociodemographic Characteristics Data Form: This form included questions to collect information about the participants' age, sex, education, marital status, socio-economic status, and where and with whom they live.

The Brief Fear of Negative Evaluation Scale: The twelve-item scale was developed by Leary (1983). It was adapted to Turkish culture by Çetin et al.[18] It is a self-report scale measuring an individual's tolerance to negative or hostile evaluations by others. The responses to statements are rated on a 5-point Likert scale, ranging from 1 (Not at all characteristic of me) to 5 (Extremely characteristic of me). In the adaptation process, 1 item with a factor load value below the acceptable level was removed, the analyses were repeated, and an 11-item measurement tool was obtained. There are three reverse items on the scale. Cronbach alpha internal consistency coefficient, split-half reliability, and test-retest reliability were tested for the scale's reliability. The internal consistency coefficient of the scale was 0.84, and the split-half reliability coefficient was 0.83. The test-retest procedure was performed at an interval of two weeks, and the test-retest reliability coefficient was reported as 0.82. Factor loads ranged from 0.34 to 0.74.[18] The Cronbach Alpha coefficient of the scale was calculated at 0.90 for the current study.

Brief Social Phobia Scale: The BSPS, which is administered by the clinician, evaluates the fear and avoidance associated with the seven social situations and the severity of the four physiological manifestations. It was developed by JR Davidson in 1991. It was adapted to Turkish culture by Cengiz et al.[19] In the first chapter, the clinician questions the severity of fear and avoidance within the past week with a Likert-type scale between 0 and 4 points. Scores range from 20–72. This accorded with a total score of 20 has been judged to reflect social phobia symptoms severe enough to warrant treatment. If people have not experienced any fear and avoidance within the past week, they are asked to respond by thinking about how they would feel if they encountered such a situation. In the second part, the physical signs are scored again in the same way. Thus, a total of three

scores on three fields including fear, avoidance, and physical symptoms are obtained. The Cronbach's alpha coefficient was 0.87.[19] The Cronbach Alpha coefficient of the scale was calculated at 0.94 for the current study.

The Emotion Identification Test from Facial Expressions of Healthy Individuals in Turkish Society: This test was developed by Turan.[20] To create the data set for the test, the researcher took facial photographs expressing six basic emotions (happiness, sadness, surprise, fear, disgust, and anger) and neutral emotions. The photographs deemed appropriate according to expert opinion were collated and a test setup was created in the computer environment. Participants were asked to evaluate which emotion the facial expression they saw on the computer screen expressed for them. Sex, sex range, and geographical region criteria were kept equal, and each emotion expression that had a recognition rate of 80% and above was included in the test. Finally, facial photographs of facial 10 expressions of each emotion were gathered and a test setup consisting of a total of 70 photographs was prepared. In scoring, 1 point is given for correct and 0 points are given for incorrect answers. The maximum score on the test is 70. The correlation values of (EITTS) test-retest scores were examined and the r-value of the test total score was 0.58 ($p<0.001$). The Cronbach's alpha coefficient of the scale was 0.90 for the present study.

Statistical analysis

All statistical analyses were performed using SPSS (version 22). The normality distribution was tested with a histogram and the Shapiro–Wilk test. Descriptive statistics including frequencies and percentages, as well as measures of mean and standard deviation, were used to describe the data. For the social anxiety group, we used the following clinical cut-off score:≥20 on the BSPS. Due to the non-normal distribution of the data, relationships were analyzed between all variables using bivariate Spearman rank correlation. To evaluate the outcomes, the students were divided into two groups: socially anxious and non-anxious. The Mann-Whitney U test was used to evaluate whether there was a difference between the fear of being negatively evaluated and the recognition of emotions from facial expressions between the groups. A p-value <0.05 was considered statistically significant.

Results

A total of 641 university students with a mean age of 21.36±2.98 years participated in the study. The participants' subjective economic perception level was 5.41±1.57 (the level is scored from 1 to 10, with 1 being those who perceive they have the least amount of money, and 10 being those with the perception of having the most money). Most were female (85.2%), while 14.8% were male. Of the participants, 64.4% had no romantic relationship, 51.8% lived in a student dormitory, 33.4% were at the first-year level, 91.9% had no chronic disease, and 90.6% had no mental illness. The BSPS score of 66.0% of the participants was above 20 points.

Demographic characteristics of the participants are shown in Table 1. Descriptive statistics and correlations between all variables are presented in Table 2. Briefly, the mean self-reported BFNE scores were 30.8 (SD = 8.9), mean BSPS scores were 26.9 (SD = 14.3; scored out of 20, with greater scores indicating greater SAD), and mean identification of facial expressions of emotions scores were 59.2 (SD = 8.1)

Table 1. Descriptive Characteristics (n=641)

Variable	n	%
Gender		
Female	546	85.2
Male	95	14.8
Marital status		
Single	413	64.4
Committed dating relationship	228	35.6
Residential area		
Student dormitory	332	51.8
At home with family	219	34.2
At home with friends	36	5.6
Alone at home	28	4.4
At home with relatives	26	4.0
Grade		
1	214	33.4
2	142	22.2
3	106	16.5
4	175	27.3
5	2	0.3
6	2	0.3
Having a chronic illness		
Yes	52	8.1
No	589	91.9
Having a mental illness		
Yes	60	9.4
No	581	90.6
BSPS* score		
<20	218	34.0
≥20	423	66.0

*BSPS: Brief Social Phobia Scale; This accorded with a total score of 20 has been judged to reflect social phobia symptoms severe enough to warrant treatment.

Descriptive statistics and correlations between all variables are presented in Table 2. Briefly, the mean self-reported BFNE scores were 30.8 (SD = 8.9), mean BSPS scores were 26.9 (SD = 14.3; scored out of 20, with greater scores indicating greater SAD), and mean identification of facial expressions of emotions scores were 59.2 (SD = 8.1).

There was a positive correlation between the BFNE and BSPS and its subdimensions ($p < 0.01$). In addition, the BFNE had a negative relationship with the neutral emotion ($r = -0.09$, $p<0.01$). There was a positive correlation between the BSPS and the feeling of disgust ($r=0.10$, $p<0.01$). Anxiety and avoidance, subdimensions of the BSPS, had a positive correlation with disgust ($r=0.11$, $p<0.01$; $r=0.10$, $p<0.05$, respectively); however, physiological reactions, another subdimension of the BSPS, had a negative correlation with the neutral emotion ($r=-0.09$, $p<0.05$) (Table 2).

Table 3 shows the results of the evaluation of whether there was a difference between fear of being negatively evaluated and recognition of emotions from facial expressions between groups with high and low SAD. The BFNE score was significantly higher in the individuals with SAD ($z=-13.489$, $p=0.000$). There was a significant difference between individuals with high SAD and individuals with low SAD in recognizing anger and disgust emotions ($z=-2.266$, $p=0.023$; $z=-2.224$, $p=0.026$) (Figure 1). As shown in Figure. 2 there was no difference between the socially anxious groups and non-socially anxious groups in the overall misclassification of identifying facial expressions.

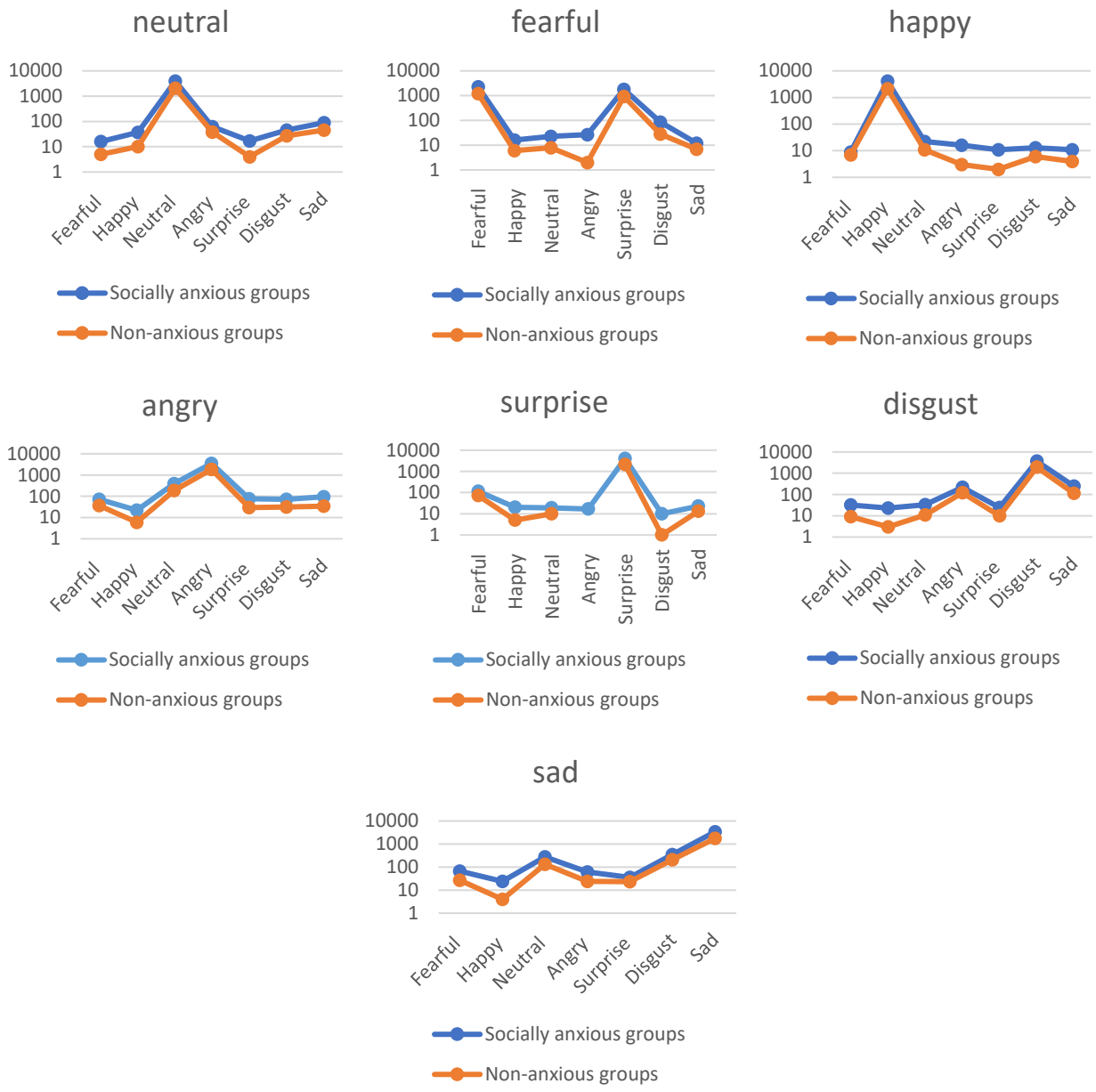

Figure 1. Distribution of misclassification by emotion type

Table 2. Correlation, means, and standard deviation table

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13
M	30.8	26.9[a]	11.5	10.8	4.6	59.2	5.4	9.5	8.0	9.8	8.3	9.3	8.7
SD	8.9	14.3	6.1	5.9	3.6	8.1	3.0	1.3	2.0	0.9	1.9	1.3	1.4
Cronbach's α	0.90	0.94	0.89	0.87	0.84	0.90	0.82	0.82	0.71	0.91	0.73	0.74	0.60
1. BFNE	-												
2. BSPS	0.693**	-											
3. Fear	0.674**	0.963**	-										
4. Avoidance	0.653**	0.957**	0.919**	-									
5. Physiological reactions	0.530**	0.755**	0.615**	0.599**	-								
6. EITTS	0.032	0.050	0.096*	0.047	-0.043	-							
7. Fearful	0.029	0.032	0.070	0.020	-0.031	0.802**	-						
8. Surprise	-0.030	0.010	0.026	0.011	-0.024	0.251**	0.019	-					
9. Sad	-0.024	-0.010	0.023	-0.003	-0.068	0.570**	0.290**	0.126**	-				
10. Happy	-0.027	0.017	0.053	0.008	-0.034	0.294**	0.176**	0.292**	0.216**	-			
11. Angry	0.014	0.040	0.069	0.047	-0.025	0.559**	0.247**	0.218**	0.253**	0.225**	-		
12. Neutral	-0.096*	-0.064	-0.046	-0.050	-0.092*	0.265**	0.117**	0.243**	0.097*	0.285**	0.027	-	
13. Disgust	0.048	0.109**	0.117**	0.100*	0.064	0.349**	0.122**	0.111**	0.087*	0.204**	0.222**	0.126**	-

BFNE: Brief Fear of Negative Evaluation Scale; BSPS: Brief Social Phobia Scale; EITTS: Emotion Identification Test from Facial Expressions of Healthy Individuals in Turkish Society. M and SD are used to represent mean and standard deviation respectively.

[a] Scores range from 20–72, This accorded with a total score of 20 has been judged to reflect social phobia symptoms severe enough to warrant treatment.

*indicates $p < 0.05$. ** indicates $p < 0.01$

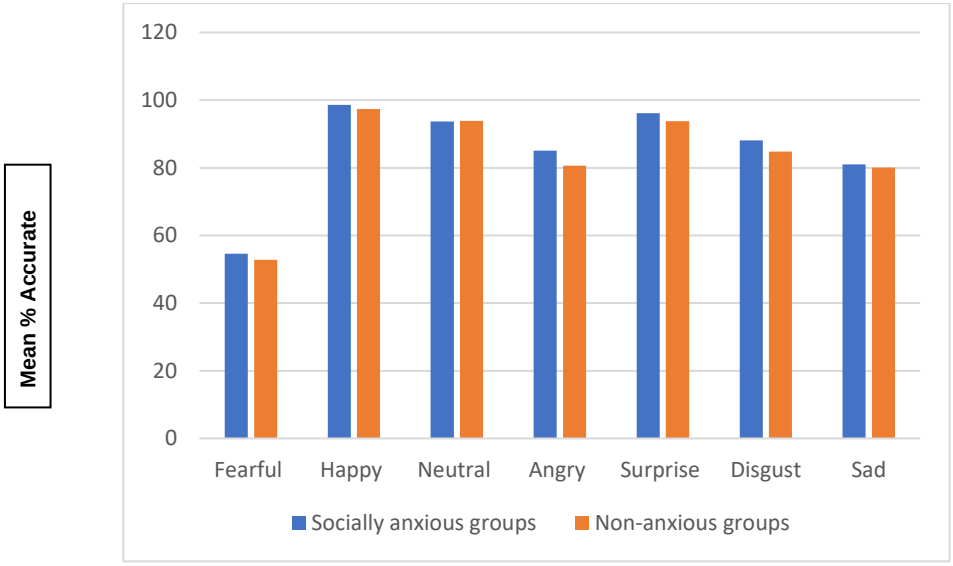

Figure 2. Mean % (SE) accuracy of facial expression recognition by emotion type

Table 3. Distribution of emotion recognition scores from face expressions between socially anxious and non-socially anxious groups

Variable	Socially anxious groups	Non-socially anxious groups	Statistical analysis *	
	Mean± SD	Mean± SD	z	p
BFNE	34.03±8.47	24.53±5.97	**-13.489***	0.000
EITTS	59.72±7.24	58.34±9.60	-1.652	0.098
Fearful	5.46±3.09	5.28±3.03	-0.779	0.436
Surprise	9.61±1.05	9.38±1.70	-0.957	0.339
Sad	8.10±1.98	8.01±2.16	-0.011	0.991
Happy	9.86±0.76	9.74±1.31	-0.096	0.924
Angry	8.51±1.76	8.06±2.19	**-2.266***	0.023
Neutral	9.37±1.24	9.39±1.41	-0.849	0.396
Disgust	8.81±1.32	8.48±1.71	**-2.224***	0.026

*Mann-Whitney U Test; SD: Standard Deviation; p: Significance ($p \leq 0.05$).

Discussion

This study was conducted to investigate the emotion recognition performance from facial expressions of individuals with high SAD levels. Consistent with the study's hypotheses, individuals with high SAD had a significantly higher fear of being negatively evaluated than those with low SAD. A positive relationship was

found between fear of being evaluated negatively and SAD. A significant difference was found between the groups with high SAD and low SAD in recognizing feelings of anger and disgust. There was a positive correlation between anxiety and avoidance, the subdimensions of the BSPS, with the feeling of disgust; however, there was a negative correlation between the physiological reactions subdimension and the feeling of neutrality. Fear of being evaluated negatively had a negative correlation with neutral emotions.

Fear of being evaluated negatively is an underlying element of SAD.[6] Individuals afraid of being evaluated negatively may also experience the fear that this will be noticed by others, which may increase their SAD level.[9] Sigurvinsdottir and colleagues found that individuals with SAD have high levels of fear of being evaluated negatively.[14] Previous studies have shown a positive correlation between being afraid of being negatively evaluated and SAD.[21,22] SAD is characterized by a negative interpretation bias toward ambiguous social stimuli.[11] Individuals with SAD exaggerate the likelihood of others' negative evaluations of their performance and catastrophize the consequences of being negatively evaluated. Biased information processing contributes to the continuation of SAD.

Processing facial expressions is an important source of interpersonal information about positive or negative evaluations of others in the process of evaluating and responding to unexpected environmental situations.[8,10] In the present study, individuals with high levels of SAD performed better than those with low levels of SAD in recognizing feelings of anger and disgust. Previous studies found no difference between individuals with and without SAD correctly recognizing emotions from facial expressions, individuals with SAD have more correct responses in recognizing facial expressions, individuals with SAD have more correct responses in recognizing angry facial expressions, and individuals with SAD evaluate angry and disgusted faces as more unreliable than those without SAD and need more information to recognize facial expressions.[23-26] Individuals with SAD pay more attention to angry faces.[13] Liang and colleagues found that the eye movements of individuals with SAD are more fixed on angry facial expressions than other emotions.[24] Gentili and colleagues reported that individuals with SAD have high amygdala activity in response to negative facial expressions (e.g., anger, disgust, and fear).[26] Individuals in a feared social situation feel that they are being negatively evaluated by others to an exaggerated and unrealistic extent, and expect to be negatively evaluated and rejected. Thus, individuals with SAD tend to focus their attention on themselves. This situation interferes with addressing external social clues normally. This can lead to attention and interpretation biases in detecting social threats, resulting in hypervigilance to negative emotions.[23]

Better addressing threat clues may emerge as a result of increased perception or selective attention. Therefore, higher levels of SAD may be associated with an increased ability to detect negative emotions in others beyond a negative response bias.[14] In the present study, anxiety and avoidance, the subdimensions of the BSPS, had a positive correlation with the feeling of disgust. The expression of anger and disgust is one of the main emotional

components of hostility.[1] Therefore, facial expressions of disgust can be quite threatening for individuals with SAD as they may signal disapproval or rejection.[10,12] Individuals with SAD exhibit a pattern called hypervigilance or avoidance. Hypervigilance-avoidance models define hypervigilance as an initial attention bias toward threatening stimuli (e.g., angry facial expressions) followed by avoidance of these stimuli.[27] According to this pattern, individuals with SAD show the first stage (hypervigilance), which is characterized by increased attention to expressions of negative emotions such as disgust and angry faces.[1]

Bodily manifestations of anxiety during interpersonal interactions, and especially their visibility, also become a central object of fear in individuals with SAD. This results in the individual exhibiting high levels of self-focused attention.[2] Stimuli that are neutral or only mildly aversive to most people can lead to hyperarousal, increased vigilance, emotional distress, and attempts to escape or avoid the anxiety-provoking object or situation.[11] Biased attention to social threats, excessive attention to internal clues, and negative interpretation of ambiguous social events contribute to biased information processing in individuals with SAD.[28] The present study found that fear of being evaluated negatively and the physiological reaction subdimension of the BSPS had a negative correlation with neutral emotions. As the fear of individuals with SAD being evaluated negatively increases, the rate of correct perception of neutral facial expressions decreases. Neutral faces presented in combination with a negative sense of smell lead to increased activation in the amygdala and hippocampus of patients with SAD.[29] Israelashvili and colleagues found that individuals with SAD misclassify neutral expressions more often as angry and less often as sad.[23] A meta-analysis study conducted by Günther and colleagues showed that individuals with SAD tend to misinterpret neutral faces as angry.[30] Neutral faces typically are evaluated as emotionally ambiguous stimuli, but individuals with SAD perceive them as threatening.[15] Individuals with SAD may be alert to subtle facial expressions indicating untrustworthiness or overinterpret ambiguous clues as signs of untrustworthiness to avoid feared negative evaluations.[25] In addition, when these individuals make judgments about how others see them, they may attach more importance to their impressions than to others' negative clues.

The strongest aspect of this study is that it applied facial expressions including seven different emotions in a large sample. However, the results need to be interpreted in light of the limitations of the study. First, the study focused only on the correct recognition of facial expressions reflecting emotional expressions. No assessment was made in terms of emotional intensity. All instruments were self-reported questionnaires, resulting in the possibility of response bias. Second, no time constraints were used when the participants evaluated facial expressions. This could have prevented individuals with SAD from experiencing anxiety about being evaluated and provided a sense of safety. Thirdly, the study data were administered online, and individuals evaluated their facial expressions without feeling any pressure under any supervision. Future studies should address the extent to which individuals with SAD accurately evaluate facial expressions when their anxiety levels increase.

In addition, study designs in which there is emotional intensity in facial expressions and evaluations made in a defined period should be used.

Ethical Considerations: The study was approved by the Ethics Committee at the Ankara Yıldırım Beyazıt University (Date: 21.03.2024; No: 03-612).

Conflict of Interest: The authors declare no conflict of interest.

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Research Article

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HEPATIC SAFETY OF ORAL TERBINAFINE IN ONYCHOMYCOSIS: IS ROUTINE MONITORING OF LIVER FUNCTION TESTS NECESSARY?

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Abstract

Objectives: Onychomycosis is the most common disease of the nail treated commonly with oral antifungals mainly with terbinafine, itraconazole, and fluconazole. Given concerns regarding the potential hepatotoxic effects of systemic antifungal therapy, our study aims to investigate the hepatic safety profile of terbinafine in patients with onychomycosis.

Materials and Methods: A retrospective study was carried out at our dermatology clinic between October 2024 and February 2025. 150 patients (aged 18–65 years) with onychomycosis, who underwent liver function tests before and after two months of terbinafine (250 mg daily) treatment were included. Patients with known renal, liver, biliary, or pancreatic diseases, abnormal baseline liver function tests, or potential drug interactions were excluded. Aspartate transaminase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) were analyzed. P-values < 0.05 are considered as a level of significance.

Results: 52 (34.7%) of the patients were female 98 (65.3%) were male, and the mean age was 48.53 ± 7.85 years. The mean age for females was 49.38 ± 7.73 years and 48.07 ± 7.91 years for males (p = 0.329). The mean ALT values were 30.74 ± 11.94 IU/L pre-treatment and 32.41 ± 12.15 IU/L post-treatment (p = 0.169). AST values were 26.45 ± 10.46 IU/L pre-treatment and 28.17 ± 8.60 IU/L post-treatment (p = 0.055), while GGT levels were 35.21 ± 13.65 IU/L pre-treatment and 35.87 ± 13.35 IU/L post-treatment (p = 0.084).

Conclusion: After two months of treatment, oral terbinafine did not cause significant alterations in laboratory values among patients with onychomycosis. Based on our limited patient sample and short follow-up duration, baseline liver function testing may not be necessary in otherwise healthy patients; however, further prospective studies are needed to confirm this finding.

Keywords: Onychomycosis, liver, terbinafine.

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Introduction

Onychomycosis (OM) is a chronic infection of the nail plate and nail bed, caused mainly by dermatophytes, less frequently molds other than dermatophytes, and rarely yeasts.[1] As the most prevalent nail disease, OM is considered for over half of nail pathologies, and its global prevalence is approximately 5.5 %, varying depending on geographic and population-based factors.[2, 3] Clinically, OM manifests as nail discoloration, hyperkeratosis, and detachment of the nail bed. It is observed more frequently in males than in females, and the likelihood of occurrence increases significantly with advancing age. [4] Multiple risk factors contribute to the development of OM, including diabetes, peripheral arterial pathologies, psoriasis, immunosuppressive condition, concomitant tinea pedis, tobacco smoking, repetitive nail trauma or traumatic nail conditions, use of occlusive footwear, sports participation, peripheral neuropathies, and other traumatic nail conditions.[3] The infection can be transmitted via direct contact or through fomites contaminated with the keratin or skin scales of infected individuals.[1] OM can considerably impair the quality of life, both due to cosmetic deformities and their psychological implications.[5]

OM treatment is often delayed or avoided because of the prolonged treatment duration, costs, and the potential adverse effects associated with systemic antifungals.[6] Oral treatments, mainly terbinafine, less commonly itraconazole, and fluconazole, are the first choices for OM treatment due to their high efficacy and accessibility. However, these medications may have some adverse effects: terbinafine may rarely lead to gastrointestinal upset, hepatotoxicity, gustatory and visual alterations, and rashes—all usually self-limiting. Itraconazole shares a similar side effect profile, including upper respiratory tract infections and gastrointestinal discomfort. Fluconazole use is frequently associated with gastrointestinal discomfort and other adverse events are myalgia, dizziness, paresthesia, QT prolongation, agranulocytosis, gustatory disturbances, and drug eruptions. Additionally, elevated liver enzymes and hepatotoxicity were reported previously with fluconazole, terbinafine, and itraconazole use.[7,8,9] Nonetheless, adverse effects of systemic antifungal medications are mild, transient, and reversible with the cessation of the drug in general.

Standard dosing of OM includes 250 mg daily terbinafine, and 200 mg daily itraconazole with a duration of 6 weeks for fingers or 12 weeks for toes, with itraconazole also available with a pulse dosing option. Fluconazole is also used for OM treatment 150 mg/week for 6 to 9 months for fingers, and 12 to 18 months for toes.[10]

A meta-analysis has shown that asymptomatic elevation in transaminases occurs in approximately less than 2% of patients receiving oral antifungals, and half of those required treatment discontinuation. As such, liver function monitoring is recommended at baseline and again one month after initiating treatment.[11]

Despite terbinafine's widespread use and general safety profile, there is a gap in knowledge regarding the necessity of routine liver function test monitoring during treatment. Current guidelines suggest baseline and follow-up testing, yet the clinical value of these recommendations in asymptomatic patients without liver disease remains unclear. This uncertainty highlights the need for updated real-world data on the hepatic safety of terbinafine.

In this study, changes in liver function tests before treatment and at the second month of treatment will be examined in patients receiving terbinafine due to onychomycosis, and the effect of terbinafine treatment on these changes will be investigated. In this way, the study will contribute to the literature regarding the necessity of routine liver function test monitoring in patients receiving terbinafine treatment.

Materials and Methods

This retrospective study is performed in the dermatology clinic between October 2024 and February 2025 with the approval of the ethics committee (number: 1-24-601 date: 25/09/2024). Onychomycosis-diagnosed patients prescribed with terbinafine 250 mg daily were screened from the database. Patients aged between 18 and 65 years who underwent blood tests both before and during the second month of terbinafine treatment were included in the study. Patients with a diagnosis of onychomycosis through clinical evaluation and/or potassium hydroxide (KOH) examination were enrolled. Patients with known renal, hepatic, biliary, or pancreatic diseases, those with abnormally elevated liver function tests before treatment, and those taking medications known to interact with terbinafine and pregnant individuals were excluded from the archive screening. Additionally, patients who did not have venous blood drawn after at least 8 hours of fasting were excluded from our study.

Age, gender, known diseases, and chronic medications were obtained from the hospital's database. Laboratory values of aspartate transaminase (AST), alanine aminotransferase (ALT) levels, and GGT (gamma-glutamyl transferase) were retrospectively evaluated before and after the second month of therapy. The normal range was 5-30 IU/L for AST, 4-36 IU/L for ALT, and 6-50 IU/L for GGT.[12] Patients with elevated levels of ALT, AST, or GGT before or during therapy are referred to internal medicine.

A power analysis was conducted to determine the required sample size for evaluating pre- and post-treatment changes in liver function tests using paired t-tests. Assuming a medium effect size (Cohen's d= 0,5), a significance level adjusted for multiple comparisons (Bonferroni correction; $\alpha = 0{,}0167$), and a desired statistical power of 95 % ($1-\beta = 0{,}95$), the minimum required sample size was calculated as 54 patients. The

analysis of the data was performed with SPSS 26.0 (IBM, Armonk, NY). The data distribution was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests as appropriate. Categorical data were presented as counts and percentages. Laboratory parameters and continuous variables were expressed as mean and standard deviation. To compare laboratory values before and after treatment, the paired t-test was applied for normally distributed data, while the Wilcoxon signed-rank test was employed for those not meeting normality assumptions. Pearson correlation analysis was used for the evaluation of correlations between age and laboratory values. A p-value of lower than 0.05 is considered a threshold for statistical significance.

Results

In total, 150 patients prescribed oral terbinafine were eligible for the study, with 52 females (34.7%) and 98 males (65.3%). The mean age of the population was 48.53 ±7.85 years (range: 22–67). The mean age for females was 49.38 ±7.73 years, while for males it was slightly lower at 48.07 ±7.91 years; however, this was not considered a statistically significant difference (p = 0.329). Among the 150 patients, 28 had diabetes mellitus (18.7%), 31 had hypertension (20.7%), and 18 had venous insufficiency (12.0%). The mean ALT value was 30.74 ±11.94 before treatment and 32.41 ±12.15 after treatment, with no significant difference between them (p = 0.169). The mean AST value was 26.45 ±10.46 before treatment and 28.17 ±8.60 after treatment, and the difference was also not statistically significant (p = 0.055). The mean GGT value was 35.21 ±13.65 before treatment and 35.87 ±13.35 after treatment, with no statistically significant difference observed (p = 0.084). The changes in the laboratory values are presented in Table 1. No significant difference was observed between genders in liver function tests before and after treatment (Table 2). No correlations were found between patient age and ALT, AST, and ALT values (p= 0.074, 0.684, and 0.625, respectively). Adverse effects included gastrointestinal upset in 14 patients, altered taste sensation in 10 patients, headache in 6 patients, and tinnitus in 1 patient.

Table 1. Laboratory changes in liver enzymes after the second month of terbinafine therapy

	Before treatment	The second month of treatment	p-value
ALT	30.74±11.94	32.41±12.15	0.169
AST	26.45±10.46	28.17±8.6	0.055
GGT	35.21±13.65	35.87±13.35	0.084

AST: Aspartate transaminase; ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase.

Table 2. Comparison of liver enzymes between genders before and after therapy

	Before treatment			After treatment		
	Women (n=52)	Men (n=98)	p-value	Women (n=52)	Men (n=98)	p-value
ALT	32.4±12.5	29.8±11.6	0.210	32.7±11.4	32.3±12.5	0.839
AST	26.2±10.7	26.6±10.3	0.812	28.4±8.4	28.0±8.7	0.797
GGT	32.3±12.0	36.8±14.2	0.056	33.1±11.8	37.3±13.9	0.068

AST: Aspartate transaminase; ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase.

Discussion

This study demonstrated that oral terbinafine therapy did not lead to any clinically significant hepatotoxicity in patients with onychomycosis. Although mild increases in AST and ALT levels were observed in some patients, none of these elevations exceeded three times the upper limit of normal, and no cases required treatment discontinuation due to liver-related adverse effects. These findings support the growing evidence suggesting that serious liver injury from terbinafine is rare and often idiosyncratic.

While severe drug-induced liver injury (DILI) is uncommon, a retrospective analysis of the United Network for Organ Sharing (UNOS) liver transplant registry, covering approximately 51,000 transplants between 1990 and 2002, identified only 492 cases of medication-related acute liver failure requiring transplantation in adult and pediatric patients. Notably, none of these cases were attributed to terbinafine.[13]

DILI remains the main cause of post-marketing drug withdrawal, with individuals suffering from conditions such as nonalcoholic fatty liver, hepatitis C, iron overload, cholestasis, or alcohol use being at greater risk.[14] While terbinafine has been associated with hepatotoxicity, its underlying mechanism remains poorly understood.[15] A study performed by Chalasani et al. documented 300 DILI cases, among which terbinafine was implicated in 4 cases, while no cases were associated with griseofulvin.[16] Similarly, another study by Kao et al., among patients using oral antifungals observed that 8 among 18,677 patients treated with griseofulvin, and 2 among 12,376 patients treated with terbinafine had DILI.[17]

According to a study by Fontana et al., terbinafine hepatotoxicity is uncommon but can present with significant liver injury in susceptible individuals, particularly those with the HLA-A*33:01 allele which is more prevalent

among Caucasian and African American patients.[18] However, the overall incidence of severe liver injury remains low.

Stolmeier et al. performed a retrospective study assessing the utility of laboratory monitoring in patients taking terbinafine. They found that the frequency of elevated ALT and AST were low and comparable to baseline values, suggesting that routine liver enzyme monitoring may not be necessary without a history of pre-existing liver conditions.[19]

Kramer and Albrecht reviewed cases of severe liver injury associated with terbinafine and observed that most patients were symptomatic, presenting with abdominal distress, malaise, and jaundice. They found no evidence supporting the utility of routine liver function test monitoring in asymptomatic patients.[20] In addition to this study, Etgü has observed that patients with onychomycosis who were prescribed either terbinafine or itraconazole showed no signs of hepatotoxicity.[21]

In a meta-analysis encompassing 19,298 immunocompetent patients, treatment discontinuation due to adverse events was reported in 3.4% of patients receiving terbinafine, 2.6% with the pulsed regimen of itraconazole, and 4.2% with daily itraconazole therapy. Furthermore, no association was found between extended duration of terbinafine use and elevated risk of liver injury.[11] This finding may reinforce the notion that adverse reactions to oral antifungal agents are largely idiosyncratic, typically emerging within the initial weeks of therapy and showing no linear relationship with treatment duration.

Certain populations are more prone to terbinafine-induced liver toxicity. In a previous review, of 24 cases of terbinafine-related acute liver injury, more than 90% of affected individuals were over 40 years old, and most of these patients were taking the drug for three to four weeks. The majority of cases are resolved following drug discontinuation and/or appropriate medical management.[22] Preexisting hepatic disorders are considered an important risk factor for terbinafine-induced liver toxicity.[19]

A retrospective study by Wang et al which involves 944 patients undergoing terbinafine therapy for onychomycosis found that isolated elevations in AST and ALT accounted for approximately 90% of liver test alterations, respectively. These findings suggest that monitoring ALT alone, along with baseline testing, could detect most hepatic changes and reduce monitoring costs.[23]

This study has some limitations. First, its retrospective design limits the ability to establish causality. Second, the lack of long-term follow-up prevents the evaluation of delayed hepatotoxicity. Third, the relatively small sample size may limit the generalizability of the findings. Lastly, the absence of genetic data, such as HLA typing, restricts the assessment of individual susceptibility to terbinafine-induced liver injury.

Laboratory testing is a convenient and rapid method for family physicians and dermatologists to obtain objective data. In today's clinical setting, where time limitations and medicolegal concerns are increasingly prominent, lab tests offer a practical approach to exclude serious complications. However, abnormal lab findings are frequently clinically insignificant. Controlled studies have shown that even widely used over-the-counter drugs like acetaminophen can cause frequent, asymptomatic lab abnormalities—often at rates exceeding those seen with terbinafine and griseofulvin in this study—which typically resolve upon cessation of the drug.[24] There is a growing tendency among physicians to prioritize lab results over thorough history-taking and physical examination. Additionally, hepatotoxicity associated with terbinafine is considered idiosyncratic. Due to the rare and unpredictable nature of severe DILI, routine liver enzyme monitoring lacks reliability as a screening method. Tests with normal range do not rule out the risk of future idiosyncratic reactions, and minor abnormalities rarely require clinical action.

In conclusion, this study evaluated liver enzymes before and after terbinafine therapy and revealed no significant differences in liver enzyme levels. This finding aligns with existing literature that suggests terbinafine-associated hepatotoxicity is relatively rare and often idiosyncratic.

Ethical Considerations: The study was approved by the local Ethics Committee on 25/09/2024 (number: 1-24-601). This study was prepared following the principles of the Declaration of Helsinki.

Conflict of Interest: The authors declare no conflict of interest.

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Research Article

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IS IT TIME TO REVISE CERVICAL CANCER SCREENING GUIDELINES?

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Abstract

Objectives: In our retrospective study, we tried to determine whether cervical smear screening is necessary in patients over 65 years of age by comparing the cytological and histological results of patients over 65 years of age.

Materials and Methods: A retrospective review of the cytological and histological results of 3465 patients over the age of 65 who underwent cervical cytology between September 2017 and September 2022 was conducted.

Results: It was established that 547 of the 3,361 patients with normal Pap smear results had irregular screening follow-ups, while 2,814 patients were undergoing regular follow-ups following the screening program. Of the 104 patients with abnormal Pap smear results, 54 had irregular follow-ups and 50 had regular screening. Among the 601 patients aged 65 and above who did not undergo regular cervical screening, 8.98% exhibited abnormal smear results and 3.16% displayed abnormal histological findings. When abnormal Pap-Smear results and abnormal biopsy results were analyzed, it was found to be significantly higher in women over 65 years of age without regular follow-up. ($p<0.001$),($p<0.05$)

Conclusion: Significant differences were observed in the frequency of abnormal smear results and the severity of diagnosis in women over 65 years of age who were followed up irregularly in line with the cervical cancer screening program compared to those who were followed up regularly. The results of our study indicate that the screening cut-off age should be revised for patients with irregular cervical screening to reduce the incidence of cervical cancer and precursor lesions.

Keywords: Pap smear, cervical cancer, HPV.

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Introduction

Cervical cancer remains a significant public health concern, despite a decline in its prevalence due to screening and prophylactic vaccination. According to the 2020 global estimates, it is the fourth most common cancer in women and a leading cause of cancer-related mortality. The majority of cervical cancer cases are attributed to persistent infections with high-risk oncogenic types of sexually transmitted human papillomavirus.[1]

Cervical cancers are largely preventable through three main avenues: primary prevention with HPV vaccination, secondary prevention with cervical screening and treatment of precancerous lesions, and tertiary prevention with early diagnosis and treatment of cancer. The most effective methods for reducing the incidence of cervical cancer and associated mortality are primary prevention and screening. The high cost of the HPV vaccine, the failure of most countries to implement a free vaccine program, and the lack of compliance with screening programs present significant challenges to the effective prevention and control of cervical cancer.

According to the National Cancer Screening Program of the Ministry of Health of Turkey, women between the ages of 30 and 65 are advised to undergo a smear and HPV-DNA test every five years to detect cervical cancer. This recommendation is based on the evidence that cervical cancer is most prevalent in women in this age range and that regular screening can facilitate early detection and improve outcomes. Despite current screening guidelines, opportunistic cervical smears are frequently performed in older women during routine gynecological visits, especially in the absence of reliable screening history documentation.

The growing proportion of older people in the global population is influencing the development of new research methods for analyzing the incidence of cervical cancer and cancer-related mortality. The current guidelines may be insufficient in anticipating these changes. They may be failing to identify crucial opportunities for the prevention of cervical cancer incidence and mortality in women over the age of 65.

According to national and international guidelines, the patient's screening history should be taken into account when deciding whether to discontinue cervical smear screenings. It is obligatory that the patient has undergone at least two negative tests in the preceding five years and has no prior history of preinvasive neoplastic disease. The proposal to cease routine cervical cancer screening at the age of 65 among women who have undergone regular and adequate screening has been put forth since 2012.[2]

According to the American College of Obstetricians and Gynaecologists (ACOG), a woman aged 65 years or older is considered to be adequately screened if she has had three or more consecutive negative cytology tests or two consecutive negative test results within the last ten years, with the most recent test being within the last five years. In the present study, the retrospective results were analyzed, with patients who met the specified

conditions deemed to have been adequately screened. Conversely, patients who did not meet these conditions were considered to have been inadequately and irregularly screened. Patients classified as having regular screening had a documented history of normal cytology or test results and no prior diagnosis of abnormal smear or preinvasive cervical lesions.

The objective of our study was to investigate the frequency of abnormal cytology in women over the age of 65 whose previous follow-ups were classified as either "regular, adequate" or "inadequate, irregular" by the established recommendations.

Materials and Methods

This study was conducted by the ethical principles set forth in the Declaration of Helsinki. The data for our single-center retrospective study were obtained from the archives of SBÜ İzmir Tepecik Training Research Hospital. The study commenced after obtaining approval from the SBÜ İzmir Tepecik Training Research Hospital Ethics Committee with approval number 2023/01-21.

A retrospective review of the files of 3465 patients who had undergone a Pap smear test between September 2017 and September 2022 and met the inclusion criteria was conducted. The histological results of patients who underwent biopsy were duly recorded in the case report form. Only asymptomatic women undergoing routine gynecologic care were included. No smear was obtained based on a suspicious clinical finding.

Inclusion criteria for patients: individuals aged 65 years and above, patients with adequate cervical cytology, and patients without pathologically confirmed preinvasive cervical lesions. Patients who are excluded from the study are those under the age of 65, those with inadequate cervical cytology, those with a history of preinvasive lesions, those with a pathologically confirmed history of gynecological malignancy, and patients who have undergone hysterectomy for non-malignant reasons.

The data were analyzed using IBM Statistics 21.0. Comparisons between groups were performed using the chi-square test. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to evaluate associations. A p-value < 0.05 was considered statistically significant. The strength of the association was evaluated using the odds ratio (OR) with a 95% confidence interval (CI). The data were expressed as absolute (n) and relative (%) frequencies to assess the relationship between the diagnostic categories. A significance level of 5% was deemed appropriate for this study.

Results

The mean age of the 3,361 patients with normal Pap smear results was 69.9 years, while the mean age of the 104 patients with abnormal Pap smear results was 70.1 years. No statistically significant difference was observed in the mean age between the two groups.

A total of 547 patients out of 3,361 whose Pap smear results were reported as normal were found to have undergone an 'irregular, inadequate' follow-up, while 2,814 patients had received 'regular, adequate' follow-up by the national cancer screening program. It was established that 54 of the 104 patients who had been identified with abnormal Pap smear results were monitored in an "irregular and inadequate" manner, whereas 50 patients were monitored "regularly and adequately" by the national cancer screening program.

It was established that the prevalence of abnormal Pap smear results in patients aged 65 and above was markedly elevated in those who were monitored irregularly in comparison to those who were monitored regularly within the framework of the national cancer screening program. ($p < 0.001$). Among the 601 patients aged 65 and above who did not undergo regular cervical screening, 8.98% exhibited abnormal smear results and 3.16% displayed abnormal histological findings. Of the 104 patients with abnormal smear results, 61 were diagnosed with ASCUS (58.6%), 16 with ASC-H (15.3%), 8 with LGSIL (7.7%), 7 with HGSIL (6.7%), and 12 with AGC (11.5%). At follow-up, 60 patients (57.6%) underwent repeat cytology, 36 (34.6%) underwent colposcopy and 64 (61.4%) underwent diagnostic biopsy. Table 1 presents the distribution of abnormal cytology and the rate of repeated cytology, colposcopy, biopsy, and abnormal biopsy rates.

Table 1: The distribution of abnormal cytology, along with the rates of repeat cytology, colposcopy, biopsy, and abnormal biopsy, is presented according to the types involved.

First Cytology Results	n (%)	Repeat Cytology	Colposcopy	Abnormal Colposcopy	Biopsy	Abnormal Biopsy
ASCUS	61 (58.6%)	55 (90.1%)	14 (22.9%)	11 (18.0%)	28 (45.9%)	10 (16.4%)
ASC-H	16 (15.3%)	0	9 (56.2%)	6 (37.5%)	16 (100%)	7 (43.7%)
LSIL	8 (7.7%)	3 (37.5%)	1 (12.5%)	0	3 (37.5%)	0
HSIL	7 (6.7%)	2 (28.5%)	4 (57.1%)	2 (28.5%)	7 (100%)	4 (57.1%)
AGC	12 (11.5%)	0	4 (33.3%)	2 (16.6%)	10 (83.3%)	5 (41.6%)
Total	**104**	**60 (57.6%)**	**36 (34.6%)**	**21 (20.1%)**	**64 (61.4%)**	**26 (25.0%)**

Abbreviations: ASCUS, Atypical Squamous Cells of Undetermined Significance; ASC-H, Atypical Squamous Cells-cannot exclude HSIL; LSIL, Low-grade Squamous Intraepithelial Lesion; HSIL, High-grade Squamous Intraepithelial Lesion; AGC, Atypical Glandular Cells.

An abnormal biopsy result was observed in 26 of the 64 patients. It was determined that 7 of the 26 patients who underwent biopsy and were followed up due to abnormal biopsy results were under regular follow-up and 19 were under irregular follow-up. Abnormal biopsy results were observed in seven of the 27 patients with abnormal smear results and regular follow-up, and 19 of the 37 patients with abnormal smear results and irregular follow-up. Although statistical significance was not reached in odds ratio analysis (OR: 3.02, $p = 0.070$), the frequency of abnormal cytology and biopsy findings was significantly higher in the irregular screening group ($p < 0.05$). This trend suggests a potential association that warrants further investigation in larger cohorts.

Amongst the cohort of patients who were monitored regularly, one patient was diagnosed with cervical intraepithelial neoplasia I (CIN), three patients with CIN III, one patient with squamous cell carcinoma, and two patients with endometrial adenocarcinoma. In the irregularly followed-up patient group, eight patients were diagnosed with cervical intraepithelial neoplasia I (CIN), two with CIN II, one with CIN III, five with squamous cell carcinoma, and three with endometrial adenocarcinoma. Table 2 presents the abnormal biopsy rates observed in patients with regular and irregular follow-up.

Table 2: Abnormal biopsy rates in patients with regular and irregular follow-up.

	Abnormal Biopsy Results	
	Regular Follow-up	**Irregular Follow-up**
ASCUS (n:28)	CIN I (n:1) CIN III (n:2)	CIN I (n:3) CIN II (n:2) SCC (n:2)
ASC-H (n:16)	CIN III (n:1) SCC (n:1)	CIN I (n:2) EA (n:1) SCC (n:2)
LGSIL (n:3)	0	0
HGSIL (n:7)	0	CIN I (n:2) CIN III (n:1) SCC (n:1)
AGC (n:10)	EA (n:2)	EA (n:2) CIN I (n:1)
Total (n:64)	**7**	**19**

Abbreviations: CIN, Cervical Intraepithelial Neoplasia; EA, Endometrial Adenocarcinoma; SCC, Squamous Cell Carcinoma.

A total of six patients diagnosed with squamous cell carcinoma were examined. Staging was performed using the FIGO 2018 classification system. One patient was classified as Stage 1A2, while the remaining five patients were categorized as Stage IIB or higher. The remaining five patients exhibited advanced-stage cervical cancer, classified as Stage IIB or above. A review of medical records revealed that all patients with advanced-stage cervical cancer had been irregularly followed up. One patient was recommended for radical hysterectomy, while five patients were advised to undergo concomitant chemoradiotherapy and brachytherapy. The stages of patients diagnosed with squamous cell carcinoma (SCC) were classified according to the International Federation of Gynecology and Obstetrics (FIGO) 2018 staging system and are presented in Table 3.

Table 3: The distribution of patients with squamous cell carcinoma (SCC) according to the International Federation of Gynecology and Obstetrics (FIGO) 2018 staging system.

	Regular Follow-up	**Irregular Follow-up**
SCC	Stage 1A2 (n) 1	Stage IIB ≥ (n) 5

SCC, Squamous Cell Carcinoma

Discussion

There is currently no definitive evidence regarding the optimal age and population for cessation of cervical cancer screening.[4] Approximately 20% of cases of cervical cancer are diagnosed in women over the age of 65. Although the diagnosis is made at a more advanced stage in older women, this results in a worse prognosis and a higher cancer-related mortality rate.[5,6,7]

However, current screening guidelines recommend stopping routine cervical cancer screening at age 65 in "adequately screened, regularly screened" women, and aim to balance the benefits, harms, and costs for women over 65.[2] Nevertheless, a growing number of studies suggest that screening also reduces cancer incidence and mortality in women aged 65 and older.[8,9]

Most cervical cancers and pre-cancerous lesions are known to result from persistent human papillomavirus (HPV) infection. One of the hypotheses put forward to justify the cessation of screening in women over 65 years of age is the age-related decline in the prevalence of HPV.

Furthermore, the incidence of cervical cancer is relatively low in older women with a history of negative screening results. Castanon et al. demonstrated that it may be safe for women with three negative tests after

the age of 50 to undergo cervical screening at the age of 65.[10] The American Cancer Society (ACS) advises that individuals aged 65 years and over with no history of grade 2 or more severe cervical intraepithelial neoplasia within the past 25 years and documented adequate negative screening results within the previous 10 years should cease cervical cancer screening.[11] These recommendations are predominantly founded upon theoretical modeling and the opinions of experts in the field. Nevertheless, the majority of modeling exercises concentrate on the influence of expenses and detriments resulting from augmented screening and colposcopies, as opposed to the harm caused by the consequences of unidentified cervical cancer cases.

Nevertheless, evidence indicates that the risk of developing cervical cancer following multiple consecutive negative screening results is comparable between women aged 50 and younger.[12] Consequently, a history of negative results at older ages may not be a sufficient rationale for discontinuing screening.

In the present study, 8.98% of 601 patients aged 65 and above who had not undergone regular cervical screening exhibited abnormal smear results, while 3.16% displayed abnormal histological results. Furthermore, the decline in participation in screening programs with increasing age contributes to the higher incidence of cervical cancer observed in older women.[13]

The decline in screening participation with increasing age also contributes to the higher incidence of cervical cancer observed in older women, particularly in settings where screening programs are opportunistic. These same explanations have also been put forward to explain the frequency of abnormal tests in older women with inadequate screening histories in Australia and Finland.

The persistence of cervical cancer diagnoses in patients aged 65 and above, despite the availability of effective preliminary screening, may be attributed to the diminished sensitivity of these screening methods and the age-related decline in the efficacy of colposcopic examination. Cytological tests may become less sensitive because of recession, vulvovaginal atrophy, and cervical atrophy of the squamocolumnar junction that occurs after menopause.[14,15]

Population aging and increasing life expectancy are likely to influence the future prevalence of cervical cancer in older women. Cervical cancer is more severe and has a worse prognosis in older patients than in younger patients.[7] In our study, five patients whose diagnosis of cervical cancer was confirmed by biopsy results were diagnosed with advanced-stage cervical cancer (Stage IIB and above).

Some studies in the literature posit that the aging population will not impact the incidence of cervical cancer. The aforementioned studies posit that older women are less likely to be exposed to new HPV infections, do not have sufficient time to develop pre-invasive or invasive disease, and therefore will not benefit from cervical cancer screening.[16] However, it has been shown that the number of lifetime sexual partners may be more

important for HPV infection than recent new partners.[17] The results of these studies indicate that a significant proportion of new HPV infections are the result of reactivation of previously acquired HPV infections.

In women aged 65 years, the average life expectancy is more than 15 years. Consequently, early diagnosis of cervical cancer can prevent cervical cancer-related deaths. Although adequate negative screening between 50 and 64 years of age has been demonstrated to be protective against cervical cancer, the effectiveness of this protection gradually decreases after 69 years of age.[18] This evidence indicates that screening should be maintained, given that life expectancy for women aged 65 and above has increased by approximately 20 years.

Cervical premalignant lesions and cervical cancer are not exclusive to young women. Notably, more than 20% of women diagnosed with cervical cancer are aged 65 or above. As the population continues to age, the prevalence of HPV infection and associated cervical lesions in older women will undoubtedly remain a significant challenge for the prevention and control of cervical cancer. It is therefore beneficial to diagnose cancer in the elderly population at an early stage, as this will help to reduce the disease burden and mortality.

The most significant limitation of our study is the absence of integration between smear results and HPV DNA results, as well as the lack of evaluation of abnormal smear results in conjunction with HPV results. Three options are available for the screening of cervical cancer in individuals between the ages of 30 and 65. These include primary HPV testing every five years, cervical cytology alone every three years, or co-testing with a combination of cytology and HPV testing every five years.[19] While all three screening strategies have demonstrated efficacy, with a reasonable balance of benefits and potential harms, HPV DNA testing is strongly recommended, particularly for new or changing partners. One of the main limitations of our study is the absence of HPV DNA results due to the lack of systematic HPV testing in our center during the study period.

A further limitation of this study is that the results were derived from a single center, which may not be representative of the general population. However, our center is in one of the most populous cities in our country, and our current study demonstrates the prevalence of abnormal cervical smear results in individuals aged 65 and above in our population.

Consequently, the rise in the average life expectancy of women has resulted in an increase in the population of older women at risk of developing cervical cancer and dying from this disease The findings of our study indicate that the detection rates for premalignant and invasive neoplasms were significantly higher in women who did not undergo regular follow-up compared to those who did.

In conclusion, the current screening guidelines stipulate that a patient who has undergone adequate screening and has received a negative result may opt out of further screening after reaching the age of 65. These findings highlight the potential clinical benefit of extending cervical cancer screening beyond the age of 65 in women

without an adequate screening history. Revising current guidelines considering increased life expectancy and inconsistent follow-up records may reduce the burden of undiagnosed cervical cancer in the elderly population.

Ethical Considerations: The study was approved by SBÜ İzmir Tepecik Training Research Hospital Ethics Committee with the date and approval number 07.02.2023-2023/01-21

Conflict of Interest: The authors declare no conflict of interest.

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Research Article

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INVESTIGATION OF THE RELATIONSHIP BETWEEN HYPOMAGNESEMIA AND INFECTION IN PATIENTS HOUSED IN ONCOLOGY PALLIATIVE CARE CENTER

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Abstract

Objectives: Hypomagnesemia is a serum magnesium (Mg+2) level of <1.8 mg/dl. Hospitalized or critically ill patients, especially cancer patients, are at risk of hypomagnesemia. In the literature, studies on this subject have only been conducted in intensive care units. Therefore, in our study, we aimed to investigate the relationship between serum magnesium levels and infection status in patients with hypomagnesemia admitted to an oncology palliative care center.

Materials and Methods: The age, cancer type, infection status, and biochemical values of 211 patients admitted to the Oncology Palliative Care Service between 01/01/2022 and 31/12/2022 were retrospectively examined. In cases with suspected infection, tests requested by an infectious disease specialist were performed, and according to the results, patients diagnosed with various infections and started on antibiotics were included in the infected group. Data were analyzed using SPSS 25. P values less than 0.05 were considered statistically significant.

Results: The mean age of the participants was determined as 63.41±12.38 years. The mean magnesium (Mg+2) level was measured as 1.82±0.28 mg/dl. Infection was diagnosed in 55.5% of the patients, and the most common infection was a urinary system infection. It was observed that the Mg+2 value was significantly lower in patients with infection than in those without infection ($p<0.001$). While the frequency of infection was 81.1% in patients with low serum Mg+2 levels, this rate was found to be 29.5% in those without low serum Mg+2 levels.

Conclusion: The statistical relationship observed between hypomagnesemia and infection status in our screened cancer patients suggests that there is a connection between the inflammatory changes caused by the infection and the patient's magnesium levels.

Keywords: Cancer, hypomagnesemia, infection, palliative care.

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Introduction

Magnesium (Mg^{2+}) is the fourth most abundant element in the human body ($Ca^{2+} > K^{+} > Na^{+} > Mg^{2+}$) and the second most abundant intracellular cation after potassium. At birth, the human body contains approximately 760 mg of magnesium, which increases to around 5 grams by the age of 4–5 months.[1] The total amount of Mg^{2+} in the body ranges between 20 and 28 grams.[2] More than 99% of total body magnesium is found in the intracellular compartment, with the majority (approximately 53%) stored in the bones.[3] Serum magnesium levels below 1.7–1.8 mg/dL (0.75 mmol/L) are defined as hypomagnesemia.[4] Magnesium homeostasis is regulated by hormonal mechanisms involving the intestines, bones, and kidneys. Serum Mg^{2+} is filtered by the renal glomeruli and then reabsorbed along the nephron. It is abundantly present in tissues such as the heart, liver, kidneys, skeletal muscles, red blood cells, and the brain.[5] The $MgATP^{2-}$ complex is essential for the activity of many enzymes. In general, Mg^{2+} acts as a cofactor in all reactions involving the utilization and transfer of ATP, including cellular responses to growth factors and cell proliferation, thus being related to almost every process in the cell.[6] In addition, Mg^{2+} is vital for maintaining genomic and genetic stability, stabilizing the natural conformation of DNA, and acting as a cofactor for nearly all enzymes involved in nucleotide excision repair, base excision repair, and mismatch repair. Given these effects, low Mg^{2+} levels may be a contributing factor in cancer development.[7] Some studies have shown a significant relationship between Mg^{2+} and the inflammatory response. These studies observed effects on pro-inflammatory cytokines.[8]

Mg^{2+} deficiency may be associated with the activation of cells such as macrophages, neutrophils, and endothelial cells. In Mg^{2}-deficient rats, macrophages have been found in the peritoneal cavity. These macrophages, considering their histological appearance and reactive oxygen production detected via chemiluminescence activity, appear to be endogenously activated and may partially contribute to increased production of pro-inflammatory cytokines.[9] One of the most remarkable findings regarding the effects of magnesium deficiency on the organism is the observation of higher levels of apoptosis in the thymus of magnesium-deficient rats compared to controls.[10] A study conducted by Dominguez and colleagues discusses the relationship between Mg^{2+} and infection in the geriatric patient population. It has been shown that magnesium-induced calcium channel blockade plays a role in preventing the release of inflammatory cytokines from immunocompetent cells and in suppressing systemic inflammation.[11] Infectious complications are a major cause of morbidity and mortality in cancer patients, particularly those with underlying hematological malignancies. Autopsy studies have shown that approximately 60% of deaths are associated with infections.[12]

Hypomagnesemia frequently develops in cancer patients, hospitalized patients, or critically ill individuals, with incidence rates reaching as high as 50–60%.[13] Factors contributing to the etiology of hypomagnesemia include:

Dietary magnesium deficiency (due to factors such as fasting, protein-calorie malnutrition, total parenteral nutrition)

Factors related to the redistribution of magnesium from the extracellular to the intracellular space (e.g., blood transfusion, acute pancreatitis), gastrointestinal, renal, and transdermal losses. Hypomagnesemia is associated with immune dysfunction, including both acute and chronic infections.[14]

In a study evaluating patients diagnosed with sepsis, a significant decrease in serum Mg^{2+} concentrations was observed in patients with acute bacterial infections (bronchopneumonia and urinary tract infections). These changes in Mg^{2+} concentration occurred within a few days, persisted for several weeks, were independent of the bacteria causing the infection, and were not correlated with disease severity. Therefore, this study suggests that measuring serum Mg^{2+} levels may be useful in bacterial infections.[15] Another meta-analysis demonstrated that hypomagnesemia in critically ill patients was associated with an increased incidence of sepsis and prolonged mechanical ventilation.[14] Most studies have been conducted in intensive care units, and there is a lack of research on oncology patients in the terminal phase. Therefore, considering that patients in oncology palliative care centers frequently face infectious diseases, we aimed to investigate the relationship between serum magnesium levels and infection status in this patient group.

Materials and Methods

This retrospective study was conducted using a screening method on 211 patients who were hospitalized in the Oncology Palliative Care Unit between 01/01/2022 and 31/12/2022, after obtaining approval from the Non-Interventional Clinical Studies Ethics Committee on 13/07/2023 with the decision number 2023/06-17. It was determined that the sample size was appropriate based on power analysis. Demographic data, medical records, biochemical results, infection status, and outcomes of the patients were collected through the hospital information management system and analyzed. Since CRP (C-reactive Protein) levels may be directly affected by malignancy, CRP values were excluded from the data. According to the hospital laboratory, reference ranges for biochemical parameters were determined as follows: magnesium 1.8–2.6 mg/dL, white blood cells (WBC) 4.2–10.6×10^3/μL, procalcitonin 0–0.065 ng/mL.

Inclusion criteria for the study were being over the age of 18 and having a diagnosis of malignancy. Patients who stayed in the hospital for less than 24 hours, those who were not tested for serum magnesium, complete blood count, or procalcitonin at admission, patients who had received chemotherapy in the last month, those with hematological malignancies, chronic kidney failure, corticosteroid use, or who did not meet the inclusion criteria were excluded from the study. Patients receiving corticosteroid therapy and those with hematologic malignancies were excluded because such conditions may directly affect leukocyte levels.

In our hospital, an infectious diseases consultation is required to initiate antibiotic therapy. Therefore, patients with clinical signs of infection or suspected infection based on laboratory findings such as WBC, procalcitonin, or culture results were referred to the infectious diseases department. The tests requested by the infectious diseases specialist were performed, and based on the results, various infection diagnoses were made, and antibiotic therapy was initiated. These patients were classified as the infected group.

Statistical Analysis

Descriptive statistics such as frequency, percentage, mean, and standard deviation were used in the data analysis via the SPSS 22.0 software package. Relationships between categorical parametric variables were examined using Pearson Chi-Square and Fisher's Exact Test, while the relationship between scale scores and categorical variables was investigated using the Independent Samples t-test and One-Way ANOVA. The results were evaluated at a 95% confidence interval. A p-value of less than 0.05 was considered statistically significant.

Results

After screening through the hospital information management system and excluding patients who met the exclusion criteria, a total of 211 individuals were included in the study. The demographic data of the participants and the distribution of cancer types are presented in Table 1.

The levels of Mg^{2+}, WBC, and procalcitonin of the participants were analyzed. The mean magnesium level was determined as 1.82±0.28 mg/dL. Magnesium, leukocyte, and procalcitonin values are presented in Table 2. According to the grouping based on infection status, 94 patients (44.5%) were found to have no infection. The most frequently observed infection was urinary tract infection in 44 patients (20.9%), followed by pneumonia, which was also detected in 44 patients (20.9%) (Figure 1).

Table 1. Distribution of demographic data and cancer groups among participants.

Variables	Mean	SD
Age	63.41	12.38
Gender	**n**	**%**
Female	107	50.7
Male	104	49.3
Cancer Type		
Gastric Cancer	24	11.4
Breast Cancer	21	10
Oropharyngeal Cancer, Laryngeal Cancer, Tongue Base Cancer	20	9.5
Lung Cancer	17	8.1
Pancreatic Cancer	15	7.1
Endometrial Cancer	14	6.6
Colon Cancer	14	6.6
Brain Cancer	13	6.2
Rectal Cancer	13	6.2
Cervical Cancer	12	5.7
Prostate Cancer	9	4.3
Nasopharyngeal Cancer	8	3.8
Esophageal Cancer	6	2.8
Other	6	2.8
Ovarian Cancer	5	2.4
Liver Cancer	5	2.4
Biliary Tract Cancer	3	1.4
Bladder Cancer	3	1.4
Kidney Cancer	3	1.4
Head and Neck Region	44	20.9
Supradiaphragmatic	45	21.3
Infradiaphragmatic	122	57.8

Table 2. Magnesium, WBC, and procalcitonin levels

	Unit	Mean	SD
Magnesium	mg/dL	1.82	0.28
WBC	10^3/mikroL	8877.25	4472.96
Procalcitonin	ng/mL	0.148*	0.49**

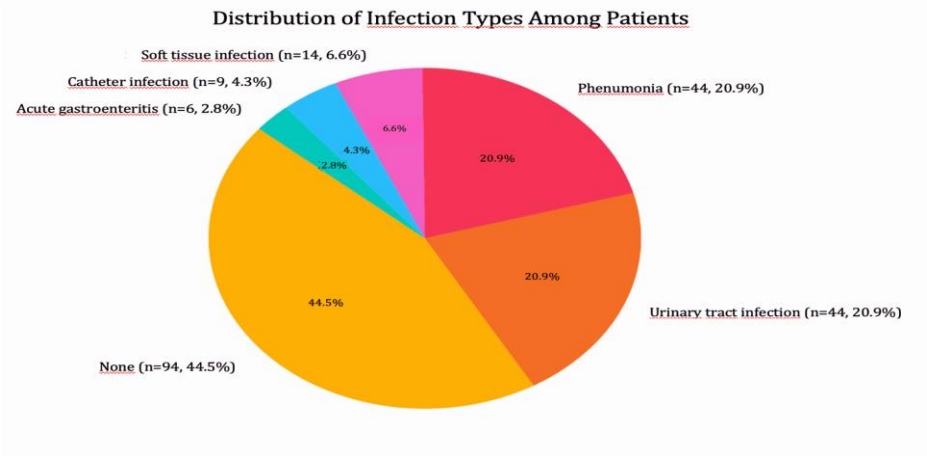

Figure 1. Distribution of Infection Types Among Patients

A comparison was made between magnesium, leukocyte (WBC), and procalcitonin levels and the infection status of the patients. Significant differences were observed in WBC and procalcitonin levels between infected and non-infected patients ($p<0.001$, $p<0.001$) (Table 3).

When grouped according to participants' gender, no statistically significant differences were found in magnesium, leukocyte (WBC), and procalcitonin levels (Table 4).

When magnesium levels were examined according to different types of infections, the mean Mg^{2+} level in patients with urinary tract infections was found to be 1.7±0.28 mg/dL. Significant differences were found in mean Mg^{2+} levels among different infection types ($p<0.001$) (Table 5).

Table 3. Comparison of magnesium, WBC, and procalcitonin levels according to the presence of infection

		Infection				
		None (94)		Present (117)		
	Unit	Mean	SD	Mean	SD	p-value
Magnesium	mg/dL	1.95	0.2	1.72	0.29	**<0.001**
WBC	10^3/mikroL	7632.97	3365.04	9876.92	4987.92	**<0.001**
Procalcitonin	ng/ml	0.052*	0.11**	0.368*	1.13**	**<0.001*** **

*Median, **IQR, ***Mann-Whitney U test p-value less than 0.05 were considered significant

Table 4. Comparison of magnesium, WBC, and procalcitonin levels according to gender

		Gender				
		Female		Male		
	Unit	Mean	SD	Mean	SD	p-value
Magnesium	mg/dL	1.8	0.27	1.84	0.28	0.896
WBC	10^3/mikroL	8340.18	4478.01	9429.8	4421.21	0.56
Procalcitonin	ng/ml	0.135*	0.44**	0.165*	0.49**	**0.144*** **

*Median, **IQR, ***Mann-Whitney U test p-value less than 0.05 were considered significant

Table 5. Comparison of Mg levels according to infection types

	n	Unit	Mean	SD	p-value
No infection	94	mg/dL	1.95	0.2	**<0.001***
Urinary tract infection	44	mg/dL	1.7	0.28	
Catheter infection	9	mg/dL	1.89	0.17	
Pneumonia	44	mg/dL	1.71	0.29	
Soft tissue infection	14	mg/dL	1.72	0.32	
Acute gastroenteritis	6	mg/dL	1.72	0.4	

*P-values less than 0.05 were considered significant

Table 6. Comparison of infections according to magnesium level

	Magnesium level				
	Normomagnesemia (1,8-2,6 mg/dL)		Hypomagnesemia (<1,8 mg/dL)		
Presence of infection	**n**	**%**	**n**	**%**	**p-value**
None	74	70.5	20	18.9	**<0.001***
Present	31	29.5	86	81.1	

* P-values less than 0.05 were considered significant

According to the hospital laboratory reference values, levels below 1.8 mg/dL were considered suggestive of hypomagnesemia. When patients were grouped as hypomagnesemic and normomagnesemic, the frequency of infection was found to be significantly higher among patients with hypomagnesemia ($p<0.001$, Table 6). In the analysis of procalcitonin levels according to magnesium status, the median procalcitonin level was found to be 0.091 ng/mL in patients with normal magnesium levels, whereas it was 0.215 ng/mL in patients with low magnesium levels. A significant increase in procalcitonin levels was observed in patients with low magnesium levels ($p<0.001$) (Figure 2).

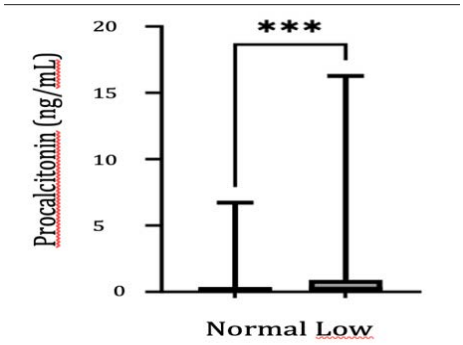

Figure 2. Procalcitonin Levels According to Magnesium Status

Discussion

In our study, cancer types were compared among patients admitted to the oncology palliative care center. While subdiaphragmatic cancers were frequently detected, the most common cancer type was gastric cancer. This was followed by breast and pharyngeal region tumors. Lung cancer ranked third. Although there are similarities between the most frequently encountered cancers in our study and those observed in the literature, the main reason for the lack of complete alignment is thought to be that the clinic where the study was conducted provides diagnosis and treatment services to advanced-stage cancer patients who require hospitalization.

In a study conducted in the USA, it was observed that the majority of cancer patients aged 30 and older were women, and this trend continued in the geriatric age group.[16] In our study, the mean age of the included patients was found to be 63.41 ± 12.38 years. The majority of the participants were female patients. Compared to studies in the literature, we observed that female dominance was consistent with the literature. Infection is a significant cause of morbidity and mortality in cancer patients. Autopsy series of patients with hematologic malignancies have reported infection rates of 60%. In patients with solid organ tumors, this rate was found to be 50%.[17]

In a study by Elfaituri et al., which investigated infection-related cancer deaths between 1973 and 2014, 141,440 cancer patients were retrospectively analyzed, and the most commonly identified infections were pneumonia and influenza along with sepsis. Prostate cancer was identified as the most common disease associated with infection-related deaths.[18] In a study by Zheng et al., infection-related deaths among cancer patients in the United States were examined. Although pneumonia-related deaths were the most common, sepsis was observed as the second most important cause.[19] In our study, the most frequently observed infections were urinary tract infections (20.9%) and pneumonia (20.9%). As seen in the literature, pneumonia, the most frequently observed infectious agent in cancer patients, was similarly identified in our study.[18,19]

Oncological conditions are among the leading causes of death worldwide. According to the 2021–2022 data in our country, they are seen as the second most important cause of death with 14% and 15.2%, respectively.[20] In the geriatric population, cancer and cancer-related conditions significantly contribute to mortality. Cancer-related conditions may account for up to 70% of the observed mortality in this patient group.[21] According to WHO GLOBOCAN 2022 data, the most common cancer types in geriatric patients worldwide are breast, lung, and colorectal cancers in women; and prostate, lung, and colorectal cancers in men. According to the WHO's incidence projections made in 2020, lung, prostate, and colorectal cancers are predicted to be the most prevalent cancers by 2045.[22] In our study, while no difference was observed in magnesium levels between genders, magnesium levels were found to be significantly lower in patients with infections compared to those without. The frequency of infection in patients with hypomagnesemia was 81.1%, while it was 29.5% in those without hypomagnesemia, demonstrating that hypomagnesemia significantly increases the risk of infection. While there was no significant difference between hypomagnesemia and WBC, patients with low magnesium levels had significantly higher procalcitonin levels. In our study, increased procalcitonin levels were observed in association with inflammation due to infection, and the development of hypomagnesemia was also observed, consistent with the literature. In a prospective observational study conducted by Limaye et al. on 100 adult ICU patients, hypomagnesemia was detected in 52% of patients admitted to the ICU, and an increase in sepsis incidence and mortality was reported in patients with hypomagnesemia.[14] In another study, a significant relationship was found between hypomagnesemia and high levels of C-reactive protein (CRP) and procalcitonin in pediatric intensive care units.[23] Magnesium is required for steps related to cell growth. It is essential at every stage, from receptor-mediated intracellular signaling and transphosphorylation reactions to gene transcription, protein synthesis, DNA replication, and cell division.[24] One study showed that serum magnesium levels frequently decreased in patients with solid tumors, and decreased independently of treatments, and this decrease was associated with the stage of the malignant tumor.[25]

In a study by Marciniak et al., it was stated that magnesium levels could be used as a biomarker in the identification of cancers and that impaired magnesium levels should be evaluated as a cancer trigger.[26] In a meta-analysis examining electrolyte disturbances in patients with solid tumors treated with anti-EGFR monoclonal antibodies, colorectal cancer patients receiving anti-EGFR monoclonal antibody treatment showed the highest risk of electrolyte imbalance compared to their controls. In addition, colorectal cancer patients receiving panitumumab were shown to be more susceptible to severe hypomagnesemia.[27] In a study conducted in mice, magnesium chloride supplementation was observed to reduce the expression of inflammation-related genes such as TNF-α and TGF-β1 and slow tumor progression.[28] In a randomized clinical study, oral magnesium supplementation in children receiving cisplatin-based chemotherapy was shown to reduce febrile neutropenia (FN) attacks by 47% and also decrease the incidence of septic shock.[29] In another study, the use of magnesium sulfate in critically ill patients with sepsis was associated with a lower all-cause mortality rate in 28-day follow-up.[30]

These findings suggest that magnesium may support the immune system with its anti-inflammatory effects and provide protection against infections.

Limitations

This study was conducted retrospectively. While a prospective and multicenter design provides advantages in terms of patient distribution and data evaluation, retrospective analyses may offer an opportunity to reach a broader group for the interpretation of findings. Our study was conducted with a limited sample of oncology palliative care patients, and patients using diuretics could not be excluded due to the widespread use of diuretics in this population. The laboratory values at the time of patient admission were included in the study. To clarify the relationship between hypomagnesemia and infection and to exclude all potential causes of hypomagnesemia, prospective studies are needed. However, consistent with the literature, our study demonstrated a link between Mg^{2+} and infection in oncology palliative care patients.

In conclusion, a total of 211 participants were included in our study, 50.7% of whom were female, with a mean age of 63.41 ± 12.38 years. Among the participants, the most common type of cancer was gastric cancer, followed by breast and laryngeal cancers. The most frequently observed cancer types were located below the diaphragm.

While no infection was detected in 44.5% of the participants, pneumonia was present in 20.9% and urinary tract infection in 20.9%. The magnesium levels in patients diagnosed with infection were found to be significantly lower compared to those without infection. Although there was no significant change in white blood cell count in patients with hypomagnesemia, procalcitonin levels were significantly higher, and hypomagnesemia was more frequently observed in the presence of infection. Given its role in enzymatic reactions and nuclear functions, magnesium may serve as a biomarker associated with inflammation in cancer patients. A relationship was observed between inflammation-related changes caused by infection and magnesium levels in patients. Serum magnesium levels should be monitored in the follow-up of oncological patients. If magnesium levels are low, patients should be evaluated for infections. Even in the absence of infection, magnesium replacement should be considered, as hypomagnesemia may potentially increase the risk of infection. More comprehensive studies with larger sample sizes are needed to evaluate the effect of hypomagnesemia on infection development and the impact of magnesium replacement in cancer patients.

Ethical Considerations: The local ethics committee approval numbered 2023/06-17 was obtained from the Ethics Committee of the University of Health Sciences Tepecik Education and Research Hospital.

Conflict of Interest: The authors declare no conflict of interest.

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Review

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INADEQUATE VITAMIN D LEVELS AND ASSOCIATED RISK FACTORS AMONG CHILDREN UNDER FIVE YEARS IN SOUTHEAST ASIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Vitamin D deficiency (VDD) and Vitamin D insufficiency (VDI) in children in Southeast Asia (SEA) pose significant public health concerns, impacting growth and non-skeletal health. This study aimed to (1) assess the prevalence of inadequate Vitamin D levels among children under five years in SEA and (2) identify associated risk factors. A meta-analysis was conducted, systematically reviewing articles from ProQuest, EBSCO, and PubMed (January 2013–October 2024). Inclusion criteria encompassed original, English-language, cross-sectional studies focusing on children under five years with documented serum 25(OH)D levels. Studies conducted outside SEA, lacking full text, addressing irrelevant topics, or containing insufficient data were excluded. Statistical analysis employed the DerSimonian and Laird random-effects model, with 95% CI calculated using the Clopper-Pearson method. A total of 13 cross-sectional studies from Thailand, Malaysia, Indonesia, Philippines, Cambodia, and Vietnam were included, with a combined sample size of 4,321 subjects. The prevalence of VDD among children under five years in SEA was 35% (95% CI, 24%-45%; I2, 98.15%), and VDI was found in 34% (25%-44%; I2, 89.67%). The mean serum vitamin D level (nmol/L) was 57.97 (48.83–67.10; I2, 99.99%). Maternal VDD or VDI was found to be associated with inadequate Vitamin D levels among children under five years in SEA, with a Pooled Odds Ratio of 4.25 (95% CI: 1.76–6.74; I2 =87.57%). This study underscores the high prevalence of inadequate Vitamin D levels among children under five in SEA, highlighting the urgent need for targeted public health interventions to mitigate this growing concern.

Keywords: Children, Southeast Asia, vitamin D deficiency, vitamin D insufficiency.

Introduction

Vitamin D deficiency (VDD) and Vitamin D insufficiency (VDI) are notable health issues, particularly in regions like Southeast Asia (SEA), where they can lead to severe health consequences such as rickets, a condition characterized by skeletal demineralization and deformities.[1] VDD and VDI are commonly seen in children during phases of rapid growth like infancy and prepuberty, leading to symptoms such as bowed legs, delayed tooth development, seizures due to low calcium levels, and muscle weakness during adolescence.[2,3] The recurrence of VDD and VDI has been noted in children with darker skin tones, inadequate sunlight exposure, and insufficient vitamin D consumption.[3,4]

Apart from bone-related issues, VDD and VDI are associated with non-bone complications such as higher rates of acute respiratory infections, cardiovascular conditions, and overall mortality.[5-7] Children suffering from VDD and VDI face an increased risk of severe pneumonia or inadequate response to typical pneumonia treatments due to compromised immunity and a weakened rib structure.[7,8]

Although SEA receives ample sunlight, lifestyle choices, and cultural beliefs play a significant role in the prevalence of VDD and VDI in the area.[9,10] It is essential to implement public health initiatives that promote sufficient vitamin D levels through cost-effective, realistic, and enduring approaches.[9] Identifying vulnerable age groups prone to VDD and VDI and the factors influencing this condition is vital for planning successful preventive or intervention strategies.[11] This study aimed to: 1) assess the prevalence of inadequate Vitamin D levels among children under five years in SEA, and 2) identify the factors associated with inadequate Vitamin D levels in this population.

Materials and Methods

Study design and sample

The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] Searches were conducted in three databases; ProQuest, EBSCO, and PubMed to identify relevant studies published from January 2013 to October 2024.

Study selection

The research aimed to analyze the mean blood vitamin D levels in children under five years within the region and to identify the factors associated with inadequate levels. For this investigation, VDD was defined as a serum 25(OH)D level <20 ng/mL or <50 nmol/L, while VDI was between 20-29 ng/mL or 50-74.9 nmol/L, and hypovitaminosis D (VDD and VDI).[14] The search strategy employed specific keywords to identify original articles published between January 2013 and October 2024: "((Children[MeSH Terms]) AND (Risk factors[MeSH Terms])) AND (Vitamin D deficiency[MeSH Terms])". Only original English-language articles involving human subjects were included, with a focus on cross-sectional studies. Studies conducted outside Southeast Asia (Thailand, Malaysia, Indonesia, Philippines, Cambodia, Vietnam, Myanmar, Singapore, Brunei Darussalam, and Laos) were excluded during the filtering process. Additionally, articles were excluded if they lacked full text, addressed irrelevant topics, or contained data unsuitable for extraction or analysis. Two authors (RDN and NPS) independently reviewed the titles and abstracts of potentially relevant articles. Studies meeting the inclusion criteria underwent a full-text assessment to facilitate the meta-analysis, with disagreements resolved through consensus.

Data extraction and quality assessment

The information from the articles was organized into tables containing details such as author names, country of origin, study designs, subjects' ages, sample sizes, Vitamin D measurement methods, prevalence of Vitamin D status, average Vitamin D levels, and risk factors. Data extraction was conducted independently by two authors (RDN and NPS), with any discrepancies resolved through consultation with a third author (LCM). In cases where additional data were needed, the study authors were contacted for clarification. Visual representations in the form of PRISMA flowcharts were utilized to outline the article retrieval process (Figure 1).

The assessment of bias risk in prevalence studies was carried out using the Joanna Briggs Institute (JBI) criteria. Studies were categorized based on their scores: 0 to 3 as low-risk, 4 to 6 as moderate-risk, and 7 to 9 as high-risk (Figure 2).[14]

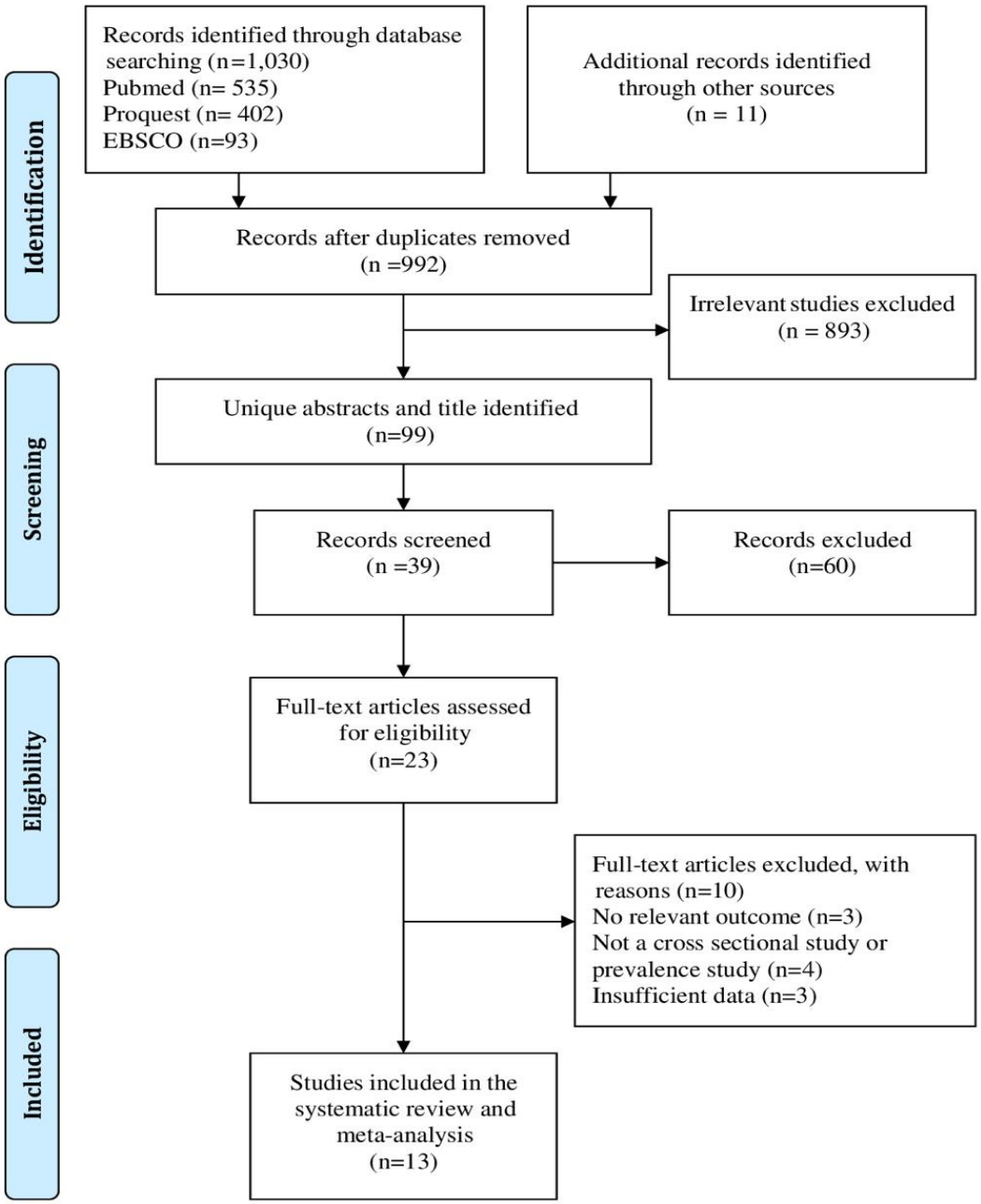

Figure 1. PRISMA flow chart

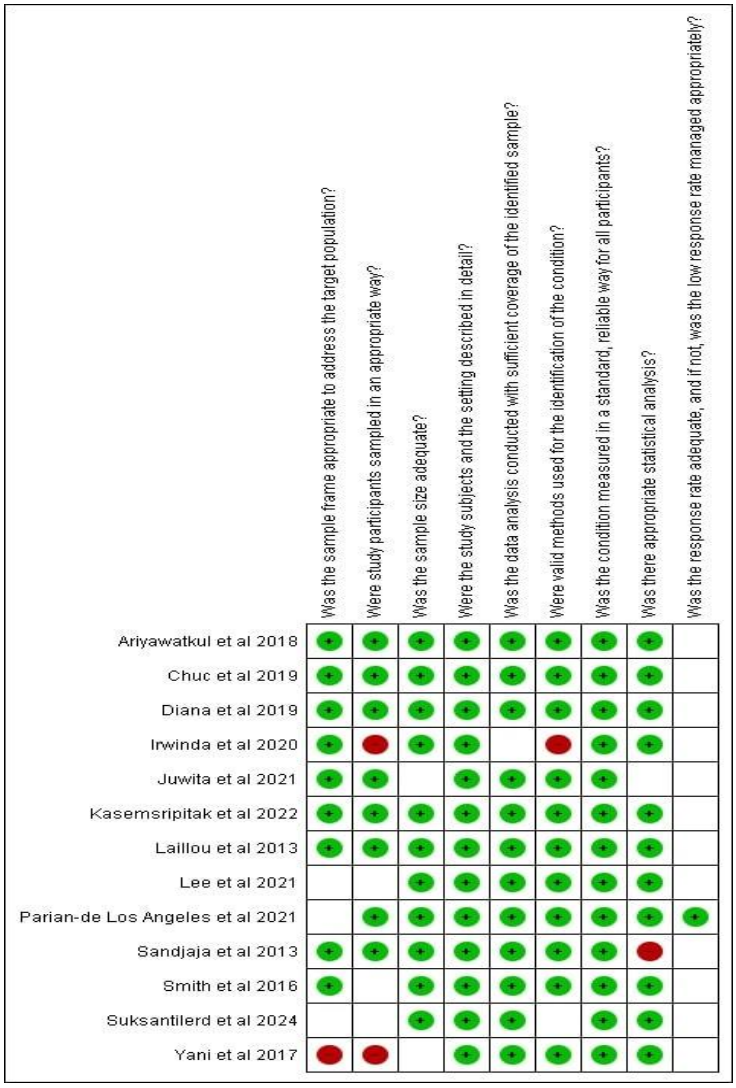

Figure 2. Quality of the publications using Joanna Briggs Institute (JBI) criteria

Data analysis

To calculate the prevalence rate, the total count of children under five years old with documented vitamin D levels was divided by the number identified as VDD and VDI. The statistical analysis utilized the DerSimonian and Laird random-effects model, and the 95% confidence interval (CI) was calculated using the Clopper-Pearson method.[15] Publication bias was assessed using Egger's test. The analysis of the data was conducted utilizing Stata 17.0 software.

Results

The review of the studies identified 13 cross-sectional studies conducted in regions including Thailand, Malaysia, Indonesia, the Philippines, Cambodia, and Vietnam, with a combined sample size of 4,321 subjects (Table 1).[16-28]

Table 1. Review of included studies

Author	Year	Country	Study design	Subject's age	Sample size	Method of measuring Vitamin D	Prevalence of Vitamin D status (%)			Mean of Vitamin D level (nmol/L)	Risk factors
							VDD	VDI	HVD		
Suksantilerd et al[16]	2024	Thailand	Cross-sectional	4 mo	109	ECLIA	35.78	33.03	68.81	35.93±8.4	Child sun exposure (≤ 15 min/day), maternal Vitamin D supplement
Kasemsripitak et al[17]	2022	Thailand	Cross-sectional	6-12 mo	120	CMIA	9	19	28	64±24.5	Child sun exposure (≤ 15 min/day), maternal VDD or VDI
Lee et al[18]	2021	Malaysia	Cross-sectional	Newborn	110	ECLIA	N/A	42.7	N/A	36.9±15.3	Child sun exposure (≤ 15 min/day)
Juwita et al[19]	2021	Indonesia	Cross-sectional	23-29 mo	109	ELISA	50.5	36.7	87.2	50.7±10.5	N/A
Parian-de Los Angeles et al[20]	2021	Philippines	Cross-sectional	<6 mo	131	ECLIA	77	N/A	N/A	N/A	Infant age ≤ 11 mo, maternal VDD or VDI
Irwinda et al[21]	2020	Indonesia	Cross-sectional	Newborn	30	LCMS	52.4	N/A	N/A	53.75±12.5	N/A
Diana et al[22]	2019	Indonesia	Cross-sectional	6 mo	116	LCMS	10	N/A	N/A	89.71±1.57	N/A
Chuc et al[23]	2019	Vietnam	Cross-sectional	1-3 y	327	ELISA	47.7	N/A	N/A	81.3±26.48	N/A
Ariyawatkul et al[24]	2018	Thailand	Cross-sectional	Newborn	94	CMIA	33.3	54.2	87.5	37.1±12.83	Maternal VDD or VDI
Yani et al[25]	2017	Indonesia	Cross-sectional	<5 y	100	ELISA	21	N/A	N/A	N/A	N/A
Smith et al[26]	2016	Cambodia	Cross-sectional	24-59 mo	495	ELISA	10.3	24.4	34.7	87.9±35.4	Infant age ≤ 11 mo, maternal Vitamin D supplement
Laillou et al[27]	2013	Vietnam	Cross-sectional	<5 y	532	HPLC	36.7	N/A	N/A	44.50±0.74	N/A
Sandjaja et al[28]	2013	Indonesia	Cross-sectional	2-4.9 y	2,048	ELISA	34.9	N/A	N/A	56.0±3.0	N/A
Total sample					**4,321**						

CMIA, Chemiluminescent microparticle immunoassay; ECLIA, Electrochemiluminescence immunoassay; ELISA, Enzyme-linked immunosorbent assay; HPLC, High-performance liquid chromatography; LCMS, Liquid chromatography-tandem mass spectroscopy; N/A, not available; y, years; mo, months; VDD, Vitamin D Deficiency; VDI, Vitamin D insufficiency; HVD, hypovitaminosis D.

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In Figure 3, the prevalence of VDD among children under five years in SEA was 35% (95% CI, 24%-45%; I^2, 98.15%), while VDI was found in 34% (25%-44%; I^2, 89.67%), and HVD was present in 61% (35%-88%; I^2, 98.71%). The average serum vitamin D level (nmol/L) was 57.97 (48.83– 67.10; I^2, 99.99%) (Figure 3).

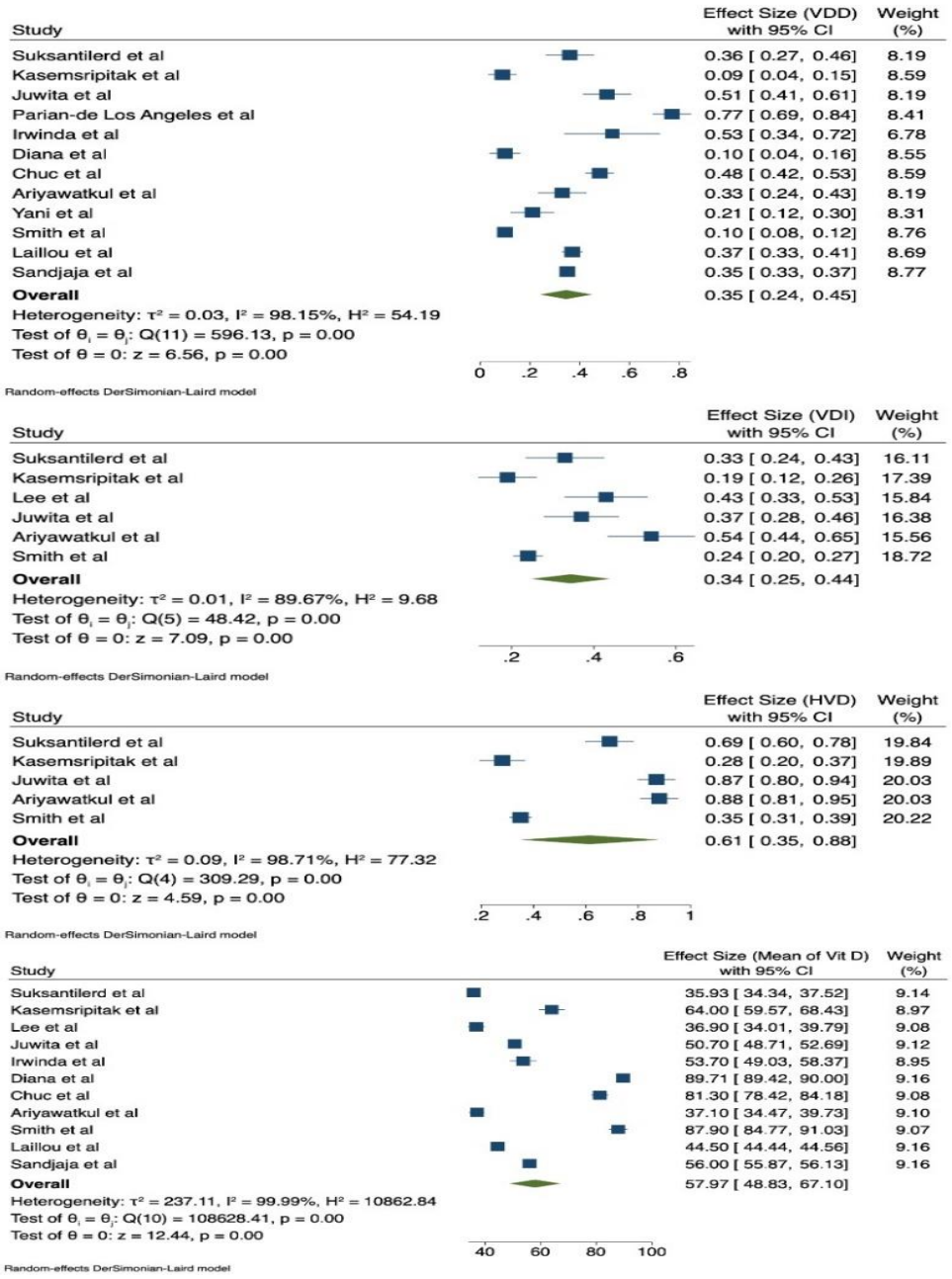

Figure 3. Prevalence of inadequate Vitamin D levels among children under five years in SEA

Figure 4 displays the factors associated with inadequate Vitamin D levels among children under five years in SEA. Maternal VDD or VDI is associated with inadequate Vitamin D levels among children under five years in SEA, with a Pooled Odds Ratio of 4.25 (95% CI, 1.76–6.74; I^2, 87.57%) (Figure 4).

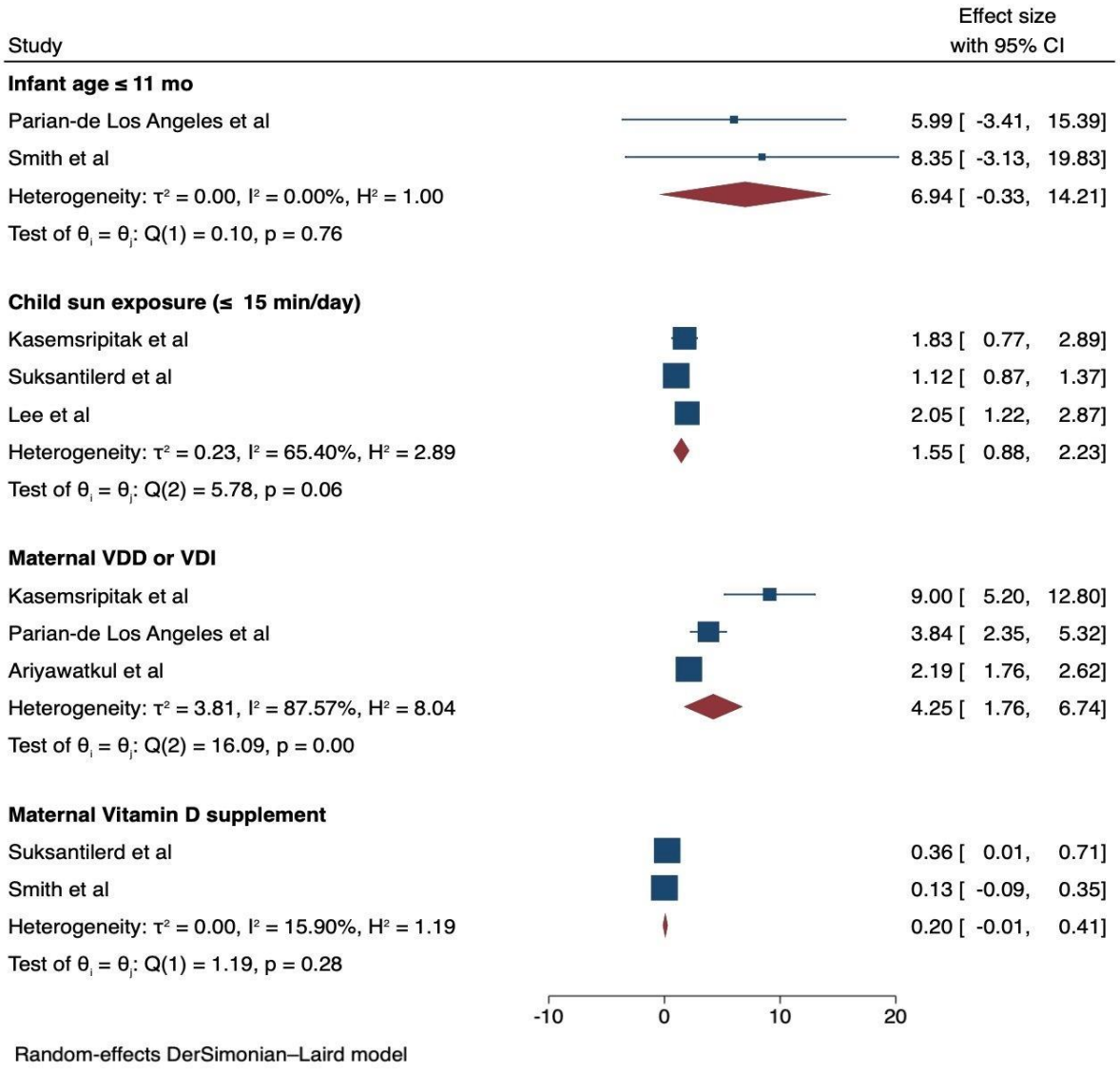

Figure 4. Factors associated with inadequate Vitamin D levels among children under five years in SEA

Meta-regression analysis outcomes presented in Table 2 indicate the prevalence of VDD based on different factors. When measuring Vitamin D using ELISA, the prevalence was 33% (95% CI, 17%-48%; I^2, 98.76%),

which was slightly lower compared to non-ELISA methods at 36% (19%-54%; I^2, 97.76%). Moreover, for sample sizes less than 100, the prevalence was 41% (22%-61%; I^2, 70.63%), higher than sample sizes of 100 or more, which showed a prevalence of 33% (22%-45%; I^2, 98.74%). According to the JBI criteria, the prevalence in the low category was 34% (22%-46%; I^2, 98.63%), lower than the moderate category at 35% (19%-51%; I^2, 82.55%). The study also revealed that newborns had the highest prevalence of VDD at 41% (22%-61%; I^2, 70.63%), followed by children under five years old at 34% (21%-46%; I^2, 98.53%), and infants at 33% (2%-64%; I^2, 98.78%). Additionally, there was no evidence of publication bias among the studies included in the analysis, as assessed across various factors (Table 2).

Table 2. Meta-regression analysis results

Criteria	Prevalence (95% CI)	p-value	I^2	Egger's test
Method of measuring Vitamin D				
ELISA	33 (17-48)	<0.001	98.76	0.362
Non-ELISA	36 (19-54)	<0.001	97.76	0.376
Sample size				
<100	41 (22-61)	<0.001	70.63	0.065
≥100	33 (22-45)	<0.001	98.74	0.258
JBI criteria				
Low	34 (22-46)	<0.001	98.63	0.238
Moderate	35 (19-51)	<0.001	82.55	0.055
Age groups				
Newborn (0-28 days)	41 (22-61)	<0.001	70.63	0.065
Infant (28 days-12 months)	33 (2-64)	<0.001	98.78	0.319
Under-five years old (1-5 years)	34 (21-46)	<0.001	98.53	0.411

Discussion

The research emphasizes the critical necessity of tackling VDD and VDI among SEA children under five years, given its substantial health repercussions and prevalent occurrence. Vitamin D plays a pivotal role in maintaining the health of both skeletal and non-skeletal organs, with its inadequacy linked to a diverse array of health issues such as rickets, psoriasis, muscle weakness, and an elevated risk of various conditions including infections, autoimmune diseases, and cancer.[4,5]

The COVID-19 pandemic has further accentuated the significance of Vitamin D inadequacy, as studies have indicated a potential correlation between VDD and heightened mortality rates in severe COVID-19 cases.[1,13,29]

This underscores the vital role of ensuring optimal Vitamin D levels in Indonesian children not only for their overall well-being but also for potentially mitigating the severity of infectious diseases like COVID-19. Consequently, it is imperative to implement initiatives and targeted programs focusing on increasing Vitamin D sufficiency in SEA children through strategies like supplementation programs, dietary guidance, increased sunlight exposure, and educational campaigns emphasizing the importance of Vitamin D.[1,29] By raising awareness and enacting specific measures, the health outcomes and quality of life for SEA can be significantly enhanced, thereby reducing the burden of preventable health conditions associated with VDD and VDI.[1,13]

In contrast to our findings, South Asia, which includes countries like India, Pakistan, and Bangladesh, has also reported high prevalence rates of VDD. For instance, in India, despite the country's geographical latitude allowing for ample sunshine, studies have reported a prevalence of over 70% of VDD in all age groups, including toddlers. This is particularly concerning in urban areas and among lower socioeconomic strata, where the prevalence of VDD is even higher.[9]

In the United States, approximately 5.9% of the population is affected by severe VDD, characterized by 25(OH)D levels below 30 nmol/L. Furthermore, the prevalence of individuals with levels below 50 nmol/L is reported to be 24%, indicating a substantial portion of the U.S. population, including children, may be vulnerable to VDD.[30]

Programs of vitamin D supplementation, dietary modification, and educational campaigns play a crucial role in effectively addressing VDD and VDI in the pediatric population.[1] Firstly, implementing routine Vitamin D supplementation programs for children at high risk of inadequate Vitamin D levels, such as those with dark skin, limited sunlight exposure, or diets low in Vitamin D content, is essential.[2,5]

Secondly, educating individuals on the importance of consuming Vitamin D-rich foods, such as fatty fish, eggs, fortified dairy products, and other sources of Vitamin D, is vital. Promoting a balanced diet that includes sufficient Vitamin D intake to support children's bone health and immune systems is crucial.[13,15]

Thirdly, conducting educational campaigns on the significance of adequate sunlight exposure for Vitamin D synthesis in the skin is essential. Providing information to the public about the symptoms of VDD and VDI in children under five years, as well as the long-term health consequences of VDD, is imperative.[8,9] Furthermore, collaborating with educational institutions, healthcare services, and governmental bodies to disseminate information on preventing and addressing VDD and VDI at the community level is essential. By integrating and sustaining programs focused on supplementation, dietary adjustments, and educational initiatives, it is anticipated that community awareness will increase, access to Vitamin D sources will improve, and the occurrence of VDD and VDI in children under five years will decrease significantly.[10,11,13]

Our study also found that maternal VDD or VDI is associated with inadequate Vitamin D levels among children under five years in SEA, with a Pooled Odds Ratio of 4.25. Maternal Vitamin D status during pregnancy and breastfeeding directly influences the fetal and neonatal Vitamin D supply, as the fetus relies entirely on maternal stores for its Vitamin D needs.[3,4,6] Insufficient maternal Vitamin D levels can result in suboptimal transfer of this essential nutrient to the child, predisposing them to deficiency or insufficiency. Previous studies in SEA have reported high rates of maternal VDD and VDI due to limited sun exposure, cultural practices, and inadequate dietary intake of Vitamin D-rich foods.[1,2]

The study's strength lies in its pioneering role as the first to perform a meta-analysis evaluating the prevalence of VDD, VDI, and hypovitaminosis in children under five years across SEA. Furthermore, it successfully identified instances of inadequate Vitamin D levels by meticulously analyzing a broad spectrum of studies, each boasting substantial sample sizes and encompassing a wide array of demographic characteristics within the Southeast Asian region.

It is important to note that this meta-analysis has several limitations. The included studies were cross-sectional in nature, which limits the ability to establish causality between vitamin D levels and associated factors. Additionally, there was substantial heterogeneity among the studies, which may be attributed to variations in study populations, methodologies, and geographical locations. Despite these limitations, this study provides valuable insights into the occurrence of inadequate vitamin D levels among children under five years in SEA and underscores the need for further research and public health interventions to address this issue.

The study's findings have significant implications for public health interventions in SEA. Targeted strategies such as supplementation programs, dietary modifications, and educational campaigns are essential to address VDI and VDI effectively and improve the overall health outcomes of children under five years in the region. Future studies in this area could assess the long-term impact of VDD and VDI on children's health outcomes in SEA. Additionally, exploring the effectiveness of different intervention strategies and their impact on reducing the prevalence of VDD and VDI would be valuable for guiding public health policies and practices.

Ethical Considerations: As this study utilized publicly available data and previously published literature, no ethical concerns or violations were involved.

Conflict of Interest: The authors declare no conflict of interest.

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