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Message from the Editor-in-Chief

Message from the Editor-in-Chief,

Dear Colleagues,

As the GMJ team, we will be happy to share the 2nd issue of 2024 with you in June, the herald of summer. As it is known, the most reliable data in scientific developments in the field of medicine is provided by the evidence-based medicine approach. At this point, research published in journals with high accessibility and citation probability has the potential to provide guiding effects on the medicine of the future.

In this issue, we aimed to provide a perspective on current developments and inspire future studies by including very interesting research and case reports from our colleagues from different branches.

We would like to express our gratitude to our editors, editorial board, authors and referees who worked meticulously in the preparation of this issue.

Finally, we would like to thank you, our valued readers, for your interest.

M. Ali Gülçelik, M.D., Prof.
Editor-in-Chief

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Latent profile analysis for the classification of OECD countries with health indicators

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Keywords: Classification, health equipment, healthcare workers, latent profile analysis, OECD

ABSTRACT

Aims: Health indicators provide up-to-date information on the health status of a population. This study aimed to classify the Organization for Economic Co-operation and Development (OECD) countries according to health indicators and assess their status.

Methods: The dataset was obtained from the OECD and World Bank databases. The most recent data from 2018 to 2022 were used. The dataset included the number of hospital beds, computed tomography scanners, magnetic resonance imaging (MRI) units, mammography machines, and radiotherapy machines as indicators of health equipment and the number of doctors, nurses, medical graduates, and nursing graduates as indicators of healthcare workers. The classification was performed using latent profile analysis (LPA). Estimated classes were compared using ANOVA or the Kruskal-Wallis test.

Results: Three distinct classes were obtained from the models constructed with LPA (Akaike information criteria: 1674.91, Bayesian information criteria: 1726.87, Lo-Mendell-Rubin adjusted likelihood ratio test: $p<0.001$). The number of countries in the classes was 11, 14, and 4, respectively. The number of MRI units was the most prominent variable in separating the classes ($p=0.001$). Türkiye was in the same class as Canada, Chile, the Czech Republic, Estonia, Hungary, Israel, Luxembourg, Mexico, Poland, and Slovenia. The numbers for all indicators in Türkiye were below the average of its class, except for the numbers of MRI units and medical graduates.

Conclusions: This study found the number of MRI units to be the most prominent indicator in categorizing OECD countries into three different classes, whereas the number of hospital beds and nurses did not differ across the defined classes.

Introduction

Healthcare systems play an active role in the development and welfare of a country. Social and economic conditions and health policies influence access to healthcare systems. Health indicators are important tools for monitoring and improving health systems. Governments use health indicators to guide healthcare system policies, set targets for improving population health, monitor public health programs, and make efficient plans. Researchers also use health indicators as supporting evidence to describe the state of a population's health (1). Indicators such as mortality rate, disease prevalence, and life expectancy can provide quantitative data to evaluate progress in healthcare systems. Health indicators can also highlight health inequalities in a community. Differences between genders, races, ethnic groups, socioeconomic classes, and other groups in health indicators can be used to guide policies and interventions to bring about health equity in the future. Not only governments or researchers but also many institutions, including international organizations such as the United Nations, the World Health Organization, and the Organization for Economic Cooperation and Development (OECD), utilize health indicators (2).

The OECD is an international organization that began its activities in 1961 and includes 38 members. It works with governments to establish evidence-based international standards and find solutions to social, economic, and environmental challenges. Its objectives include improving

economic performance, creating jobs, promoting stronger education, exchanging experiences, advising on public policies, and setting international standards (3). In line with these objectives, it collects and shares data from member countries regularly. Health indicators have an important place in the data categories that include main headings such as agriculture, development, economy, education, and finance. OECD publishes various indicators of countries under the headings of health care utilization, health equipment, health resources, health risks, and health status.

Evaluating the efficiency of healthcare systems is crucial for resource allocation, cost control, quality improvement, equitable access, evidence-based decision-making, and international comparisons. In addition, it may support the optimal use of healthcare resources, improve quality of care, promote equitable access, make informed decisions, and learn from global best practices. It would be beneficial to classify OECD countries into homogenous subgroups using various health indicators for focused policy interventions, benchmarking and comparison, resource allocation, and progress monitoring. Previous studies have tested data envelopment and panel tobit methods to assess the efficiency of healthcare systems by grouping various health indicators as input and output variables (4-6). Cluster analysis (7-12), Application of Additive Ratio Assessment (ARAS), and Simple Additive Weightings (SAW) (13) methods have also been used to identify homogenous classes of member countries.

This study aimed to (i) allocate OECD countries into similar sub-classes using latent profile analysis (LPA) according to the number of health equipment and healthcare workers, (ii) determine the health indicators that are effective in the formation of the classes, and (iii) evaluate the status of Türkiye in its class.

Methods

Data Set

Data were collected for 38 OECD members, creating and collecting nine variables for each, covering the most recent values between 2018 and 2022. Open-access databases from the OECD Statistics and the World Bank were used (3,14). The dataset includes the number of hospital beds, computed tomography (CT) scanners, magnetic resonance imaging (MRI) units, mammography machines, and radiotherapy machines as health equipment indicators, and the numbers of doctors, nurses, medical graduates, and nursing graduates as healthcare workers indicators. The number of health equipment is presented per million inhabitants. The numbers of doctors and nurses are presented per thousand residents, whereas the numbers of graduates are presented per hundred thousand residents. Nine OECD countries, namely Costa Rica, Colombia, France, Germany, Japan, the Netherlands, Portugal, Switzerland, and the United Kingdom, were excluded from the analysis because of missing data for one or more indicators. Previous authors also reported issues in data availability for some indicators and members of OECD countries (10,13,15).

Statistical Analysis

LPA was used to identify classes of OECD countries with similar health equipment and healthcare workers indicators. It is a person-centered statistical method that uses individual differences and similarities above relationships between variables and aims to divide individuals from a heterogeneous population into smaller, more homogeneous subgroups or classes based on continuous indicator variables (16).

LPA classifies observations using building models and is most interested in two parameters: (i) class or profile membership probabilities describing the class prevalence in the sample and (ii) means and variances of the indicator variables within each class. A widely used model equation for LPA is:

$$\sigma_i^2 = \sum_{k=1}^{K} \pi_k (\mu_{ik} - \mu_i)^2 + \sum_{k=1}^{K} \pi_k \sigma_{ik}^2,$$

In this formula, μ_{ik} and σ_{ik} indicate profile-specific (k) means and variances for indicator variable i, and π_k denotes the proportion of the individuals belonging to profile k.

LPA operates under the following assumptions: (i) samples drawn from a heterogeneous population produce data that are a mixture of K profile-specific distributions, (ii) each indicator variable follows a normal distribution, (iii) the profile-specific mean vectors represents the observed variable means for each profile (k), and (iv) indicator variables are uncorrelated within the identified latent profiles.

Determining the number of profiles (classes) (k) is a crucial step in LPA. Expectations of researchers, clinical relevance, theories generated from earlier studies, or statistical methods may all be considered when determining the number of profiles (17). Choosing the best model is a gradual process. The first step is to build a one-class LPA model that calculates the observed item proportions in the sample. This one-class model is a comparative baseline point for models with multiple classes. In the next step, the number of classes is increased by one, and the result is evaluated to determine whether the new solution outperforms the prior one conceptually and significantly. Building new models stops when convergence issues arise, or insufficient data exists to estimate all the model parameters (18).

Evaluation indices are used to select the best model among the models created. We employed the Akaike information criteria (AIC) (19), Bayesian information criteria (BIC) (20), and Lo-Mendell-Rubin adjusted likelihood ratio test (LMRT) (21) in this study. AIC and BIC are goodness-of-fit indices used to compare models. Lower values of AIC and BIC indicate a better fit of the model on the dataset (19,20). The LMRT compares the fit of a

target model with that of a model with one less class. A p-value <0.05 indicates that the target model fits significantly better (16).

Once the best model is determined, (i) researchers can investigate associations between indicator variables and the classes and, (ii) assign an individual to the most likely class based on posterior probabilities. Classes can be labeled according to the mean of each indicator variable in the profile (16,17). Those with less than 5% in the sample are misleading and tend to overfit the data (22).

All calculations were performed with Stata 18 (23), R studio (24), and the tidyLPA (Easily perform LPA Using Open-Source or Commercial Software) package (v1.1.0) (25). Parameter estimations of the LPA models were made with the Expected Maximization algorithm. Descriptive statistics of health indicators are displayed as mean±standard deviation and median (Q_1-Q_3). The normality of the health indicators was assessed using the Shapiro-Wilk test. Comparison of classes based on health indicators was performed using one-way analysis of variance (ANOVA) and Kruskal-Wallis test for normally and non-normally distributed data, respectively. Pairwise comparisons were performed with the Bonferroni test for ANOVA, while Dunn's test was used for significant Kruskal-Wallis test results. A p value < 0.05 was considered significant.

Results

We built a series of LPAs from one class to five. The AIC, BIC, and LMRT results are shown in Table 1. As more classes were introduced, the values of AIC and BIC decreased until the three latent-class solutions. Evaluation indices indicated the choice of the three-latent-class model by rejecting the one-latent-class and two-latent-class models. The three-latent-class model was selected as the final model because it provided the best fit to the dataset.

The posterior probabilities of the members were calculated based on the three-class model. Class 1 countries had 11 (38%) members, while Class 2 and Class 3 countries had 14 (48%) and 4 (14%) members, respectively. The members of the classes are listed in Table 2. Türkiye was in Class 1 countries with countries from different regions. Class 2 countries mostly included members from European Union countries, whereas Class 3 countries included members from geographically diverse countries.

The health indicator values of the estimated latent classes were evaluated. Table 3 shows the comparisons of the estimated classes. The number of hospital beds (p=0.990) and nurses (p=0.076) did not significantly differ between the classes. Concerning the health equipment indicators, Class 1 countries had the lowest numbers of CT scanners (p=0.001), mammography (p<0.001), and radiotherapy units (p=0.003). The numbers of MRI units were significantly different among all classes (p=0.001). The highest number of MRI units belonged to Class 3 countries, followed by Class 2 countries (p<0.001) and Class 1 countries (p<0.001) (Table 3). Pairwise comparisons indicated no significant differences between the Class 2 and Class 3 countries in the number of CT scanners, mammography, and radiotherapy (p>0.05). Concerning the relationship between the estimated classes and indicators of healthcare workers, Class 2 countries had significantly higher numbers of doctors (p=0.004) and medical graduates (p=0.010) than Class 1 countries. Class 3 countries had the highest number of nursing graduates among the classes, whereas Class 1 and Class 2 countries had similar values (p=0.011).

Table 1. Comparisons of LPA models with different number of classes

Number of classes	Log Likelihood statistics	AIC	BIC	LMRT (p value)
1	-846.9345	1729.869	1754.480	-
2	-819.6528	1695.306	1733.590	**<0.001**
3	-799.4537	1674.907	1726.865	**<0.001**
4	-791.1796	1678.359	1743.989	0.130
5	-784.9831	1685.966	1765.269	0.336

AIC: Akaike information criterion, BIC: Bayesian information criterion, LMRT: Lo-Mendell-Rubin test

Table 2. Distribution of OECD countries in estimated classes

Class 1 countries (n=11)		Class 2 countries (n=14)		Class 3 countries (n=4)
Canada	Mexico	Australia	Lithuania	Finland
Chile	Poland	Austria	Latvia	Greece
Czech Republic	Slovenia	Belgium	Norway	Korea
Estonia	Türkiye	Denmark	New Zealand	The United States of America
Hungary		Ireland	Slovak Republic	
Israel		Iceland	Spain	
Luxembourg		Italy	Sweden	

OECD: Organization for Economic Co-operation and Development

Finally, we derived the estimated marginal means of the classes from the three-class LPA model. Values of all health indicators were converted to a scale of 0-100 for a better trend comparison on the latent profile plot shown in Figure 1. Class 3 countries showed a better trend for health equipment indicators while losing superiority in healthcare workers' indicators. Class 1 countries presented the lowest figures for all indicators.

Discussion

This study classified the OECD countries based on health indicators using LPA. Although there are different groups of indicators under the health heading on the OECD website, we prioritized the indicators of health equipment and healthcare workers to examine the status of healthcare systems. Some studies based on the classification of OECD countries focused mainly on indicators such as the number of nurses, doctors, hospital beds (7,8,10,11), health expenditure (7-9,11), or health

Table 3. Comparison of estimated classes by health indicators

Health indicators	Class 1 countries Mean±SD Median (Q_1-Q_3)	Class 2 countries Mean±SD Median (Q_1-Q_3)	Class 3 countries Mean±SD Median (Q_1-Q_3)	p
Hospital beds	3.99±1.92	4±1.59	5.62±4.73	0.990
	4.18 (2.55-6.19)	3.3 (2.84-5.51)	3.51 (2.82-8.42)	
CT scanners	16.16±5.62^{A}	34.05±14.01^{B}	35.99±12.73^{B}	**0.001**
	16.26 (9.82-20.31)	29.69 (22.96-43.66)	41.61 (28.8-43.19)	
MRI unit	10.43±4.47^{A}	18.14±7.42^{B}	34.17±2.92^{C}	**0.001**
	11.41 (5.34-13.28)	16.33 (14.31-19.1)	33.9 (32.23-36.12)	
Mammography	12.52±2.57	20.46±7.63	58.87±18.82	**<0.001**
	11.28 (10.78-14.79)^{A}	17.37 (16.34-21.1)^{B}	66.94 (47.98-69.76)^{B}	
Radiotherapy	4.94±2.34	9.39±3.45	8.82±2.37	**0.003**
	4.7 (2.77-6.64)^{A}	8.2 (7.32-11.75)^{B}	8.64 (6.8-10.83)^{B}	
Doctors	3.12±0.57^{A}	4.18±0.64^{B}	3.7±1.79^{A,B}	**0.004**
	3.3 (2.7-3.48)	4.19 (3.67-4.48)	3.06 (2.52-4.89)	
Nurses	6.83±3.14	10.31±4	9.32±4.53	0.076
	6.38 (4.3-10.06)	10.67 (6.6-12.26)	10.18 (5.87-12.78)	
Medical graduate	10.49±4.64^{A}	16.73±4.71^{B}	10.37±2.97^{A,B}	**0.010**
	11.37 (7.55-14.28)	15.69 (13.57-21.04)	10.37 (7.88-12.85)	
Nursing graduate	32.12±14.85^{A}	42.69±26.83^{A}	118.44±64.05^{B}	**0.011**
	30.19 (18.48-37.36)	37.01 (24.27-46.15)	97.87 (78.54-158.35)	

$^{A, B, C}$: Different letters on the same line represent significant differences ($p<0.05$).
SD: Standard deviation, CT: Computed tomography, MRI: Magnetic resonance imaging

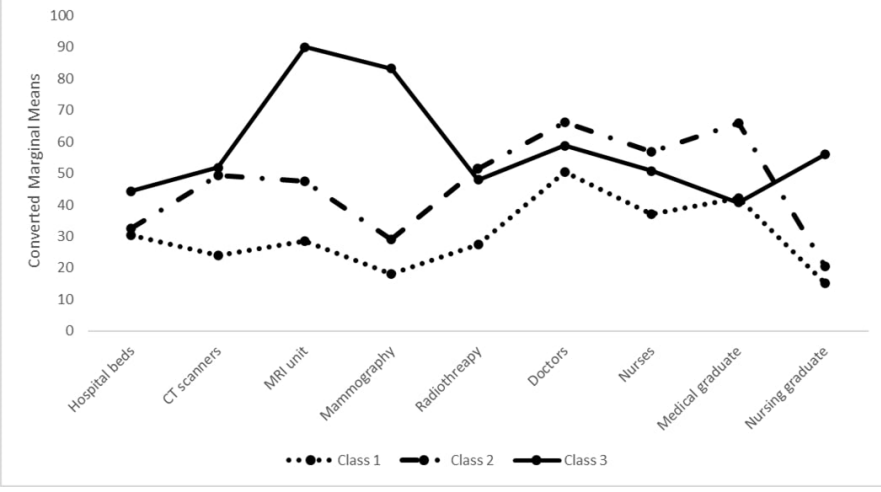

Figure 1. Latent profile plot of estimated classes based on the health indicators
CT: Computed tomography, MRI: Magnetic resonance imaging

status indicators such as infant mortality rates and life expectancy (8,12). However, few studies have been interested in indicators of health equipment (13). In this study, we included more health equipment indicators in the dataset. Unlike the previous studies, we focused on the indicators of both healthcare workers and health equipment to assess the current healthcare system status provided by OECD countries.

Another difference in the current work was utilizing the LPA during the classification process. To our knowledge, this is the first study classifying the OECD countries with LPA using health indicators. Unlike conventional classification methods (e.g., k-means clustering, hierarchical clustering), this method provides more objective and probability-based inferences (16,17). LPA estimates probabilities directly from the model to identify class membership and produces estimated marginal means to provide insight into the role of variables in creating classes (16-18). In addition, the appropriate number of classes is selected in a more realistic way using statistical methods such as LMRT (21).

Three distinct classes were derived from 29 countries, and there were significant differences between the estimated classes in health indicators, except for the number of hospital beds and nurses. The most prominent variable in separating the classes was the number of MRI units. These differences between estimated classes suggest that OECD countries are a heterogeneous population and that three distinct classes were created successfully. Using LPA in this study was an appropriate choice because it discriminates heterogeneous populations into more homogenous subclasses (16-18).

Türkiye was classified as a member of Class 1 countries in the study, while Canada, Chile, Czech Republic, Estonia, Hungary, Israel, Luxembourg, Mexico, Poland, and Slovenia were the others. This result is consistent with previous studies that classified OECD countries by health indicators. In these studies, Türkiye was placed in the same class as the Czech Republic, Chile, Israel, Mexico, Estonia, and Poland (8,10-12). The numbers of both health equipment and healthcare workers per capita in Class 1 countries were significantly lower than in other classes. Assessment of the current demographic, population growth rate and provision of health services may be an appropriate starting point to enhance healthcare systems in countries that require improvement. New policies to increase the quantity of healthcare workers and equipment may be subject to further review. An assessment of Türkiye's status in Class 1 countries revealed that the number of medical graduates and MRI units was higher than the average of its class. However, the remaining health indicators were below the class average. This situation illustrates that implementing new policies to increase the amount of health equipment and healthcare workers may enhance Türkiye's standing among OECD countries. Class 2 countries may be considered the most homogeneous class in the study because it included European Union countries, Australia, and New Zealand. Class 3 countries were the group with the least number of countries from the most diverse geographical regions. The common feature of Class 3 countries was that they included countries with high numbers of MRI units and nursing graduates. The highest number of MRI units among the OECD countries belonged to the United States of America, followed by South Korea and Greece. Finland had the highest number of nursing graduates, followed by Australia and South Korea.

The lack of data on health indicators for some countries in the OECD and World Bank databases could lead to bias in the study results.

Conclusion

This study categorized OECD countries into three classes. The number of MRI units was the most prominent indicator used in categorizing OECD countries into three classes. The number of hospital beds and nurses did not differ across the defined classes.

Ethics

Ethics Committee Approval: Ethical approval was not required.

Informed Consent: Informed consent was not required.

Authorship Contributions

Concept: H.Ö., D.Ö., Design: H.Ö., D.Ö., Data Collection or Processing: H.Ö., Analysis or Interpretation: H.Ö., D.Ö., Literature Search H.Ö., Writing: H.Ö., D.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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Novel low-grade inflammation markers in children with attention deficit hyperactivity disorder

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Keywords: ADHD, inflammation, proinflammatory marker, monocyte-lymphocyte ratio, platelet-lymphocyte ratio

ABSTRACT

Aims: The course of low-grade inflammation markers, including platelet-monocyte ratio (PMR), mean platelet volume-lymphocyte ratio (MPVLR), and the mean platelet volume-platelet ratio (MPVPR), is not known in children with Attention Deficit Hyperactivity Disorder (ADHD). The primary objective of this study was to compare PMR, MPVLR, and MPVPR in children with ADHD versus healthy controls.

Methods: A retrospective, case-control, cross-sectional study was performed with children aged 6-18 years with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. An age, gender, and body mass index-matched healthy control group was formed. Platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), basophil-lymphocyte ratio (BLR), PMR, MPVLR, MPVPR, and systemic immunity-inflammation index (SII) were compared between the two groups.

Results: The study included 79 children with ADHD and 70 controls. NLR, BLR, SII, PMR, and MPVPR were not significantly different between the two groups. However, the PLR was higher in the ADHD group than in the control group ($p<0.001$). Additionally, the MLR ($p=0.048$) and the MPVLR ($p=0.018$) were higher in the ADHD group than in the control group. Receiver operating characteristic analysis demonstrated that the MPVLR level was not significantly associated with predicting the presence of ADHD [area under the curve (AUC): 0.58, $p=0.077$]. However, PLR (AUC: 0.68, $p<0.001$) and MLR (AUC: 0.59, $p=0.048$) values showed predictive potential for ADHD, with cut-off values of 110.23 and 0.19, respectively.

Conclusions: Of the variables evaluated, significant increases in PLR and MLR support the hypothesis that an altered inflammatory response may be associated with ADHD. Further research is needed to confirm these findings in prospectively designed studies.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most widespread neurodevelopmental disorders that affect the lives of children and adolescents (1). The global prevalence of ADHD is approximately 5.3% among children of school age, exhibiting a variability that spans from 2.5% to 12.5% (2). Characterized by inattention, hyperactivity, and impulsivity, ADHD not only poses significant challenges for affected individuals but also places a substantial burden on their families and society (3). ADHD symptoms are not confined to childhood; they persist into adulthood at a rate ranging from 15% to 80% (4,5). Additionally, individuals with ADHD may often experience comorbid psychiatric disorders, including learning disorders, oppositional defiant disorder, conduct disorder, depression, and anxiety. ADHD and its comorbid conditions can result in significant social, academic, and psychological challenges in all stages of child and adolescent development (3). While extensive research has explored the neurobiological and genetic underpinnings of ADHD, the involvement of immune system dysregulation and inflammatory processes in the pathogenesis of this condition has received increasing attention in recent years (6).

White blood cells (WBCs), including lymphocytes, basophils, monocytes, and neutrophils, along with parameters such as mean platelet volume (MPV) and red blood cell distribution width (RDW), in conjunction with various derived ratios, such as the platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), neutrophil-lymphocyte ratio (NLR), basophil-lymphocyte ratio (BLR), and the systemic immunity-inflammation index (SII), have emerged as indicative biomarkers of systemic inflammation (7-10). These markers are derived from the complete blood count (CBC) and offer a cost-effective means of assessing an individual's inflammatory status. Furthermore, novel prognostic indicators, including the platelet-monocyte ratio (PMR), MPV-to-platelet ratio (MPVPR), and MPV-lymphocyte ratio (MPVLR), have shown promise as innovative predictors of cardiovascular disorders and seizures (11-13).

Neuroinflammation, characterized by the activation of immune cells within the central nervous system, has been implicated in various neuropsychiatric conditions, including ADHD (14). Emerging evidence suggests that chronic inflammation may disrupt neurodevelopmental processes, alter neurotransmitter systems, and impair cognitive functions, all of which may contribute to ADHD symptomatology (15,16). Empirical findings indicate a heightened incidence of ADHD in individuals with rheumatic disorders (17). However, the relationship between low-grade inflammation markers and ADHD in pediatric populations remains an area of ongoing investigation (14).

A study on the relationship between ADHD and hematological parameters revealed elevated WBC counts, neutrophil counts, MPV, PLR, NLR, and PDW in individuals with ADHD compared with healthy controls (18). Different authors have also reported higher MPV levels in individuals with ADHD (19,20). A recent study showed increased PLR and NLR in adolescents with ADHD compared with healthy controls (21). Another study involving children with ADHD in Turkey showed statistically significant increases in NLR, PLR, MLR, MPV and neutrophil counts and lower lymphocyte counts in individuals with ADHD compared to controls (22). On the other hand, several studies have found no significant differences in CBC parameters in individuals with ADHD (23,24).

The above mentioned inconsistent findings are noteworthy, and the potential roles of PMR, MPVLR, and MPVPR as novel prognostic indicators in children with ADHD remain unknown. Therefore, the current study aimed to examine the circulating inflammation markers, including NLR, PLR, MLR, BLR, PMR, MPVLR, MPVPR, and SII in a pediatric cohort of patients with ADHD diagnosis and healthy controls.

Methods

Participants and procedures

This retrospective, cross-sectional, case-control study included children of 6 to 18 years admitted to the child psychiatry outpatient clinic at Başkent University Faculty of Medicine between August 2022 and August 2023. The patients met the diagnostic criteria for ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. The exclusion criteria were having received previous treatment for ADHD, having psychiatric comorbidities (mental retardation, learning disability, autism, psychosis, depression, anxiety disorders or bipolar affective disorder), having a chronic medical illness (such as autoimmune disease, allergic disease, hypertension, diabetes mellitus, etc.), acute or chronic infectious diseases, and having CBC values outside the normal limits [anemia (hemoglobin <11 g/dL), leukocytosis (>10,000/μL) or leukopenia (<4000/μL), thrombocytopenia (<150.000 mm^3/dL), or thrombocytosis (>400.000 mm^3/dL)], obesity (at or above the 95th percentile for age and gender), or the use of any drugs, substances, or cigarettes. The control group consisted of individuals with no known acute or chronic physical or psychiatric diseases and who were admitted for a routine check-up at the pediatric outpatient clinic on similar dates. They were matched with children with ADHD for gender, age, and body mass index (BMI). The study was approved by Başkent University, Medical and Health Sciences Research and Ethics Committee (project number: KA23/313, date: 19.09.2021). The procedures conformed to the principles of the Declaration of Helsinki revised in 2013.

All data were obtained from hospital records, including age, gender, body weight, height, BMI, and hematological parameters (leukocyte, thrombocyte, neutrophil, lymphocyte, monocyte, basophil count, RDW, MPV). Subsequently, NLR (absolute neutrophil count/absolute lymphocyte count), PLR (absolute platelet count/absolute lymphocyte count), MLR (absolute monocyte count/absolute lymphocyte count), BLR (absolute basophil count/absolute lymphocyte count), SII (platelet count × neutrophil count/lymphocyte count), PMR (absolute platelet count/absolute monocyte count), MPVLR (mean platelet volume/absolute lymphocyte count), and MPVPR (mean platelet volume/absolute platelet count) were calculated.

Statistical Analysis

A priori power analysis for sample size calculation was conducted using G Power analysis (25), which determined that a minimum of 64 participants per group was required, based on a two-tailed t-test for means (effect size d=0.50, α=0.05, 1-β=0.80). Data analysis was performed using Statistical Package for Social Sciences 25.0 (Armonk, New York: IBM corporation).

The normality of distribution was tested using the Shapiro-Wilk test, histogram plots, mean-median values, skewness, and kurtosis statistics. The chi-square test was used to compare categorical variables, and the Student's t-test was used to compare continuous variables showing normal distribution. The Mann-Whitney U test was used to compare non-normally distributed continuous variables. Pearson correlation analysis was used to check the correlations between age, gender, BMI, and inflammation markers. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic thresholds of serum inflammatory marker levels. P<0.05 was considered statistically significant.

Results

Of the 168 ADHD diagnoses, 89 subjects were excluded, primarily because of psychiatric comorbidities (62%). The ADHD group included 79 individuals with a mean age of 10.35 years [standard deviation (SD)=3.22] and male predominance (69.6%). The control group also included 79 individuals, with a mean age of 10.64 years (SD=3.63) and 72.9% male predominance. Age, gender, and BMI were not significantly different between the two groups (Table 1).

Table 1. Comparison of the groups in terms of age, gender, and BMI

Variables	ADHD (n=79)	Controls (n=70)	p
Age (years)*	10.35±3.22	10.64±3.63	0.613[a]
Gender**			
Female	24 (30.4)	19 (27.1)	0.663[b]
Male	55 (69.6)	51 (72.9)	
BMI (kg/m^2)*	19.88±4.91	19.10±2.47	0.215[a]

Data are expressed as *mean±standard deviation or **number (%).
[a]Independent sample t-test was used, [b]Pearson's chi-squared test was used.
ADHD: Attention-deficit/hyperactivity disorder, BMI: Body mass index

Age displayed statistically significant positive correlations with MPV, MPVLR, and MPVPR values (r=0.282, p<0.001; r=0.391, p<0.001; r=0.393, p<0.001, respectively), and inverse correlations with platelet count, lymphocyte count, and basophil count (r=-0.301, p<0.001; r=-0.337, p<0.001; r=-0.215, p=0.008, respectively). No significant correlations were found between age and RDW, neutrophils, monocytes, NLR, PLR, MLR, BLR, PMR, or SII levels.

The PLR was significantly higher in the ADHD group than in the control group [123.8 (SD=37.5) vs. 103.0 (SD=31.1), p<0.001]. Additionally, the median MLR [0.20 (IQR=0.08) vs. 0.19 (IQR=0.07), p=0.048], and the median MPVLR [3.2 (IQR=1.2) vs. 2.8 (IQR=0.7), p=0.018] were higher in the ADHD group than in the control group. However, there were no statistically significant between-group differences in leukocyte, platelet, neutrophil, lymphocyte, monocyte and basophil counts, RDW, and MPV (Table 2). In the ADHD group, NLR, SII, and PMR were higher (Table 2), but the differences did not reach statistical significance (p>0.05).

Serum MPVLR level was a predictor of ADHD [AUC: 0.58, 95% confidence interval (CI): 0.49-0.68, p=0.077]. On the other hand, PLR (AUC: 0.68, 95% CI: 0.59-0.77, p<0.001) and MLR (AUC: 0.59, 95% CI: 0.50-0.69, p=0.048) exhibited predictive

Table 2. Comparison of the groups in terms of laboratory parameters

Laboratory parameters	ADHD (n=79) Mean±SD/Median (IQR)	Controls (n=70) Mean±SD/Median (IQR)	p
White blood cell count (10^3/mm^3)	7.2±1.9	7.6±1.58	0.202[a]
Platelet count (10^9/L)	312.4±71.1	291.2±65.1	0.061[a]
Red blood cell distribution width (%)	12.2±1.5	12.5±1.1	0.182[a]
Mean platelet volume (fL)	7.7±1.3	7.8±1.1	0.517[a]
Neutrophils count (10^3/mm^3)	3.7±1.4	3.8±1.3	0.606[a]
Lymphocyte count (10^3/mm^3)	2.7±0.9	2.9±0.6	0.077[a]
Monocytes count (10^3/mm^3)	0.6±0.2	0.6±0.1	0.836[a]
Basophils count (10^3/mm^3)	0.05 (0.05)	0.06 (0.04)	0.400[b]
Neutrophil-lymphocyte ratio	1.5±0.7	1.4±0.6	0.244[a]
Platelet-lymphocyte ratio	123.8±37.5	103.0±31.1	**<0.001**[a]
Monocyte-lymphocyte ratio	0.20 (0.08)	0.19 (0.07)	**0.048**[b]
Basophil-lymphocyte ratio	0.02±0.01	0.02±0.01	0.732[a]
Systemic immunity-inflammation index	389.9 (276.5)	337.5 (200.9)	0.109[b]
Platelet-monocyte ratio	524.5 (292.5)	499.8 (220.92)	0.272[b]
MPV-lymphocyte ratio	3.2±1.2	2.8±0.7	**0.018**[a]
MPV-to-platelet ratio	0.03±0.01	0.03±0.01	0.087[a]

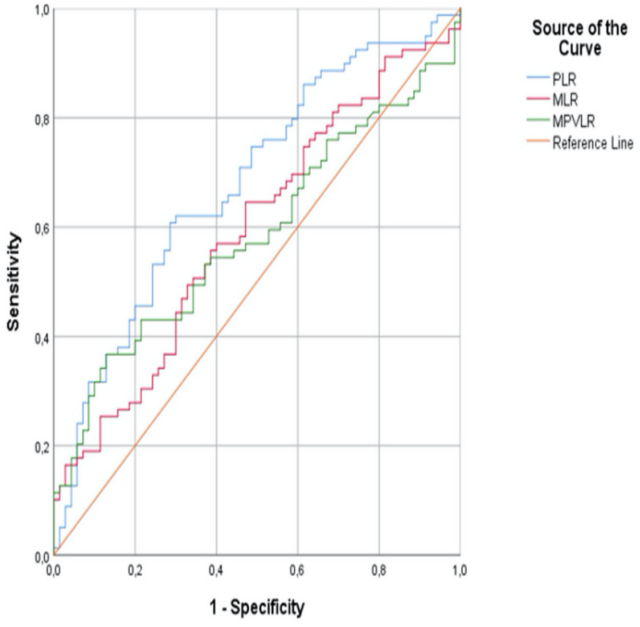
[a]: Independent sample t-test was used, and [b]:Mann-Whitney U-test was used. Bold values are significant.
SD: Standard deviation, IQR: Interquartile range, ADHD: Attention-deficit/hyperactivity disorder

value for diagnosing ADHD in ROC analysis. The recommended threshold value for PLR was 110.23, with a sensitivity of 62.9%, specificity of 70%, positive predictive value of 70%, and negative predictive value of 62%. A threshold of 0.19 was calculated for MLR, with a sensitivity of 64.6% and a specificity of 52.9% (Figure 1).

Discussion

Low-grade inflammation has been an investigation field concerning the underlying mechanisms and potential biomarkers associated with ADHD (26). One of the key features of this study is its pioneering evaluation of the relationship between PMR, MPVLR, and MPVPR with ADHD. Additionally, it is one of the rare studies in Turkey that simultaneously assessed multiple inflammation markers in children with ADHD. Based on the ROC analysis results, serum PLR and MLR have emerged as potential diagnostic markers for ADHD.

AUC values of 0.68 for PLR and 0.59 for MLR indicate moderate and fair discriminative abilities, respectively. While the AUC for PLR signifies a higher degree of discriminatory power, both ratios show statistical significance in differentiating between individuals with and without ADHD. It should be emphasized that the diagnostic capacity of PLR appears particularly promising, with an AUC well above the 0.5 threshold commonly associated with random chance. Previous studies have reported a higher predictive power of PLR than MLR, which is consistent with the current results (22,27).



Test variables	Area	p value	95% confidence interval	
			Lower bound	Upper bound
PLR	0.680	<0.001	0.594	0.765
MLR	0.594	0.048	0.503	0.685
MPVLR	0.584	0.077	0.492	0.676

Figure 1. ROC curve analysis for PLR, MLR, and MPVLR to discriminate ADHD and healthy control

PLR: Platelet-lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, MPVLR: MPV-lymphocyte ratio, ADHD: Attention Deficit Hyperactivity Disorder

The current results align with prior research that indicated a relationship between PLR and ADHD (21,22) and between MLR and ADHD (22,27). In addition to leukocytes, platelets play a crucial role in inflammation. Similar to various disorders characterized by inflammation, ADHD has been associated with elevated levels of MPV and platelets (19,20). In our study, both groups showed MPV levels, platelet count, and lymphocyte counts within the normal range, with no significant between-group differences. However, a notably elevated PLR was observed within the ADHD group, emphasizing the relevance of this inflammatory ratio in the context of ADHD. However, previous studies have reported that these inflammation markers could not predict specific ADHD subtypes (22,27,28) or the severity of the condition (21,22,28). Moreover, Önder et al. (21) reported no statistically significant differences in the levels of inflammatory markers (NLR and PLR) between patients with and without psychopharmacological treatment for ADHD. Therefore, higher levels of low-grade inflammation markers, including PLR, may indicate ADHD. However, inflammation at a certain level or above may not be related to the severity or subtype of the disease.

While ADHD occurs due to various environmental causes in the presence of a genetic predisposition, the neurobiological basis of these interactions has not been elucidated (29). Brain development in neurodevelopmental disorders such as ADHD is most sensitive to environmental factors during the early stages (30). A cohort of over 1,500 preterm and low birth weight newborns showed that infants with elevated serum inflammation-related proteins during the first 2 postnatal weeks exhibited more attention problems at 2 years of age (31). Similarly, a prospective follow-up study determined that an increased systemic inflammatory response during the first month of life in children with a history of preterm birth was associated with a higher risk of ADHD (32). Many environmental risk factors are known to play a role in the etiology of ADHD (33), and ADHD seems to be associated with the inflammatory response, at least in a subgroup (23).

One inherent limitation of this investigation is its cross-sectional and retrospective design, which hinders causal relationships. Moreover, although the diagnostic accuracy of PLR and MLR is promising, they may not be sufficient standalone tools for diagnosing ADHD.

Conclusion

In summary, PLR and MLR may offer a cost-effective and easily accessible tool for the early detection of children

with ADHD. Future research may investigate the underlying biological mechanisms and validate our findings across diverse populations to establish broader clinical applicability. Ultimately, a multidimensional approach that integrates clinical evaluation, neuroimaging, and inflammation markers may provide a more precise and comprehensive diagnostic framework for ADHD.

Ethics

Ethics Committee Approval: The study was approved by Başkent University, Medical and Health Sciences Research and Ethics Committee (project number: KA23/313, date: 19.09.2021).

Informed Consent: Retrospective study.

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Relationship between changes in hemoglobin level in cesarean section and delta neutrophil index

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ABSTRACT

Aims: Accurate prediction of changes in hemoglobin (Hb) levels, an indicator of blood loss, in cesarean deliveries is critical for reducing maternal morbidity and mortality. This study evaluated the potential relationship between the preoperative delta neutrophil index (DNI), an inflammatory marker, and changes in Hb levels after cesarean section.

Methods: Women with a history of a single cesarean section and who underwent a second cesarean section for delivery between 2018 and 2020 were retrospectively analyzed. The difference between the preoperative and postoperative 6th-hour and 24th-hour Hb levels was defined as the delta Hb 1 (ΔHb1) level and delta Hb 2 (ΔHb2) level, respectively. The primary outcome was the relationship between preoperative DNI with ΔHb1 level and ΔHb2 level. We also investigated the relationships of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) with DNI and changes in Hb levels.

Results: The study included 368 women with a mean age of 28 (19 to 45) years. The mean DNI was -0.82±5.62, NLR was 4.31±2.16, and PLR was 141.89±55.22. A positive correlation was found between DNI and ΔHb1 level ($r=0.624$, $p<0.05$) and ΔHb2 level ($r=0.372$, $p=0.05$). No significant correlation was found between PLR and NLR.

Conclusions: Among women who underwent cesarean section, preoperative DNI showed a positive relationship with changes in postoperative Hb levels. The significance of DNI in predicting changes in Hb levels after cesarean section needs to be explored.

Introduction

Early diagnosis of pregnancies at high risk for postpartum hemorrhage, timely interventions to prevent intrapartum hemorrhage and appropriate treatment are key in reducing maternal morbidity and mortality (1). Yefet et al. (2) showed that a decrease in hemoglobin (Hb) of ≥2 g/dL was compatible with the diagnosis of postpartum hemorrhage, and the maximum rate of decrease in Hb exchange as a laboratory indicator of blood loss is in the first 6-12 hours after birth, reaching a plateau in 24-48 hours. Therefore, it is important for clinicians not to miss the possible intrapartum and postpartum blood losses, as well as the follow-up of postpartum changes in Hb level and the prediction of possible over-falls.

Inflammation and inflammatory conditions are common in gynecology and obstetrics. Chorioamnionitis, inflammation of the umbilical vessels (umbilical vasculitis), and funisitis are

common in patients undergoing postpartum hysterectomy due to postpartum hemorrhage (3). To this end, numerous inflammatory markers have been studied in gynecology and obstetrics, and studies focusing on cost-effective markers have increased. Recently, the focus has shifted to the delta neutrophil index (DNI), which indicates the number of immature granulocytes in complete blood count (CBC) from peripheral venous blood (4). DNI reflects the ratio of immature granulocytes to the total neutrophil count and is known to be associated with infection and inflammation (5) and may be predictive in various infectious diseases such as peritonitis, bacterial infections, and sepsis (6-8). Previously, DNI was associated with preeclampsia and eclampsia in obstetrics (9,10) and was considered a histopathological marker for chorioamnionitis in pregnant women with a rupture of membranes (10).

CBC shows systemic inflammation and hemostasis (11). CBC parameters like neutrophil-to-lymphocyte ratio (NLR) (12) and platelet-to-lymphocyte ratio (PLR) (13) are easily assessable markers that can be associated with prognosis in various diseases.

Recently, postpartum hemorrhage has been redefined as a cumulative blood loss of 1,000 mL or more or any blood loss associated with the signs and symptoms of hypovolemia, regardless of the delivery route (14). It is clinically advantageous to predict changes in Hb levels as an indicator of blood loss (2,11). Consequently, we examined the relationship between preoperative DNI and postoperative changes in Hb levels in pregnant women undergoing cesarean section.

Methods

Study population

This retrospective study was conducted at the Etlik Zübeyde Hanım Maternity and Women's Health Training and Research Hospital. Women with a previous history of one cesarean section and who underwent a second cesarean section between January 2018 and January 2020 were identified from the hospital's registration system and those who underwent a second cesarean delivery at 37-42 weeks of gestation were included. To obtain a more homogeneous cohort, we included only cesarean deliveries performed with a lower segment transverse incision in the abdomen with a Pfannenstiel incision as a standard procedure. Patients with a history of multiple (>1) cesarean section, multiple pregnancies, fetal anomalies, pregnancies followed in the perinatology department, maternal comorbidity, preterm and post-term pregnancies, and placental invasion anomalies were excluded. Additionally, to exclude potential confounding factors with DNI, women with signs of systemic infection during hospitalization (e.g., cystitis, tonsillitis, influenza, prolonged rupture of membranes), preoperative infection using anticoagulants and antiaggregators, who developed drug-dependent hemolysis, or with hematological diseases were excluded. Ethical approval was obtained from the Etlik Zübeyde Hanım Maternity and Women's Health Training and Research Hospital Local Ethics Committee (06.08.2020-12).

Laboratory and instrumental investigations

An initial hemogram test is routine in all hospitalized patients at our center. Hemograms are also routine at the 6th and 24th hour postoperatively in patients undergoing cesarean section. DNI was obtained using an automated cell analyzer (ADVIA 2120 Hematology System, Siemens, Healthcare Diagnostics, Forchheim, Germany). This flow cytometer-sensitive hematological analyzer uses two independent methods to count leukocytes: myeloperoxidase and the lobule/nuclear density channel. The DNI is calculated using the following formula: (leukocyte subfraction measured by the cytochemical reaction in the myeloperoxidase channel) – (leukocyte subfraction measured by the weak radiation reflectance in the nuclear lobular channel) (10,15). Hemograms were analyzed using a MINDRAY BC-6000 (Mindray, China). NLR was calculated by dividing the neutrophil count by the lymphocyte count, and PLR was calculated by dividing the platelet count by the lymphocyte count. DNI, PLR, and NLR were obtained from the initial CBC test during hospitalization.

The delta Hb 1 (ΔHb1) level was calculated by subtracting the Hb levels at the postoperative 6th hour from the initial Hb values on admission. The delta Hb 2 (ΔHb2) level was calculated by subtracting the Hb levels at the postpartum 24th hour from the initial Hb values on admission. Demographics, age, obstetric history, body mass index (BMI) (kg/m^2), and neonatal data (birth weight, sex) were recorded. The primary outcome was the relationship of DNI with ΔHb1 level and ΔHb2 level, corresponding to the amount of blood loss during cesarean section. As secondary outcomes, NLR and PLR were also investigated for their relationship with ΔHb1 level and ΔHb2 level.

Statistical Analysis

All analyses were performed using Statistical Package for Social Sciences (SPSS) (version 20; IBM Corp., Armonk, NY, USA). After testing the normality assumptions, the variables were expressed as median and minimum-maximum (min-max), mean±standard deviation, or frequency (%). The t-test or Mann-Whitney test was used to compare numerical data based on the normality analyses. The relationships between continuous variables were analyzed using Pearson correlation analysis. $P<0.05$ was considered statistically significant.

Results

The study included 368 women [mean age: 28 (19 to 45)] years. The mean birth weight was 3380 (2450 to 4900) g, and

the mean birth week was 39 (37 to 40). The mean BMI was 30 (22 to 39) kg/m^2. The male-to-female ratio of the fetuses was 51.1/48.9% (Table 1).

The mean DNI in the preoperative period was -0.82±5.62. The mean Hb value in the preoperative blood counts was 11.69±1.40 g/dL. The mean Hb value at the 6th hour after the cesarean section was 10.32±1.33 g/dL and 10.09±1.29 g/dL at the 24th hour. The mean ΔHb1 level was 1.37 and the mean ΔHb2 level was 1.6. The mean PLR was 141.89±55.22, and the mean NLR was 4.31±2.16 (Table 2).

A positive correlation was observed between DNI and ΔHb1 level (r=0.624, p<0.001) and ΔHb2 level (r=0.372, p<0.001) (Table 3). No correlation of PLR or NLR with ΔHb1 level and ΔHb2 level was noted.

Table 1. Demographic and obstetrics data of the cases in the study (n=368)

Age, median (min-max)	28 (19-45)
Body mass index (kg/m²), median (min-max)	30 (22-39)
Gravida, median (min-max)	2 (2-9)
Parity, median (min-max)	1 (1-5)
Placental localization, n (%)	
Anterior	242 (65.8)
Posterior	109 (29.6)
Fundal	17 (4.6)
Birth week, median (min-max)	39 (37-40)
Birth weight (g), median (min-max)	3380 (2450-4900)
Sex of the newborn, n (%)	
Female	180 (48.9)
Male	188 (51.1)

min-max: Minimum-maximum

Table 2. Hemogram test results of the cases in the study (n=368)

Hemoglobin initial value (g/dL), mean±SD	11.69±1.40
Hemoglobin 6th hour (g/dL), mean±SD	10.32±1.33
Hemoglobin 24th hour (g/dL), mean±SD	10.09±1.29
Delta hemoglobin 1 (g/dL), mean±SD	1.37±0.83
Delta hemoglobin 2 (g/dL), mean±SD	1.60±0.93
Platelet lymphocyte ratio (%), mean±SD	141.89±55.22
Neutrophil lymphocyte ratio (%), mean±SD	4.31±2.16
Delta neutrophil index, mean±SD	-0.82±5.62

SD: Standard deviation

Discussion

Accurate prediction and early diagnosis of blood loss in cesarean deliveries can help clinicians arrange timely interventions and appropriate management to prevent morbidity and mortality (1). We examined the relationship between preoperative DIN and changes in Hb levels before and after cesarean section. We observed that DNI increased significantly in patients with larger differences in pre-and postoperative Hb levels. There was no correlation between ΔHb1 level, ΔHb2 level, and PLR or NLR. However, a positive correlation was found between DNI and ΔHb1 level or ΔHb2 level. To the best of our knowledge, this is the first study to use DNI to assess changes in Hb associated with the amount of blood loss.

Postpartum hemorrhage occupies an important place in obstetric practice as it is a frequent cause of maternal mortality in developing countries (16,17). To reduce maternal mortality, prenatal education and the availability of an experienced team with a multidisciplinary approach are crucial for pregnancies with risk factors for obstetric hemorrhage. A European-based study found that the risk of hysterectomy after cesarean section was nine-fold higher (18). Therefore, clinicians need to predict the risk of bleeding after cesarean section, and it is essential to take the necessary precautions for such an event. Unfortunately, there are no known risk factors for blood loss due to postpartum and intrapartum hemorrhage, especially for most cases of uterine atony; therefore, a substantial proportion of hemorrhages occurs in the absence of recognized risk factors (19). Although inflammation in the uterus and placenta appears to be associated with postpartum hemorrhage due to inadequate contractility of the myometrium, the exact mechanism is not clear (20). Inflammation also supports the formation of residual placenta and placental invasion abnormalities, which pose a significant risk for uterine atony (21). Inflammation, endothelial damage, infarcts, fibrotic villi, and placental septal cysts dramatically increase in the residual placenta. In addition, placental inflammation and decidual defects between uterine smooth muscle fibers are present in placental invasion abnormalities, which carry a very high risk of postpartum hemorrhage (22).

An increase in the immature/total granulocyte ratio resulting from incomplete maturity of circulating neutrophils during inflammation and an increase in neutrophil banding is named left shift and, is used to demonstrate systemic inflammatory responses (23). DNI, which indicates the percentage of immature granulocytes in the cardiovascular system by a dissimilar method, is considered an indicator of inflammation.

Table 3. Investigation of the relationship between hemogram values and delta neutrophil index in pregnant women

	Platelet-lymphocyte ratio	Neutrophil-lymphocyte ratio	Delta neutrophil index
Delta hemoglobin 1	0.28*/-0.056**	0.31*/0.052**	**<0.001*/0.624****
Delta hemoglobin 2	0.67*/-0.022**	0.38*/0.046**	**<0.001*/0.372****

*p value; **r value; Pearson correlation test, bold is statistically significant

It has been shown to predict pneumonia and acute appendicitis as well as sepsis in adult and pediatric populations (3,7). It was reported to predict chorioamnionitis with a sensitivity and specificity of 93% at a cut-off of 1, making DNI a more potent parameter than other commonly used maternal serum markers in predicting chorioamnionitis (24). Cho et al. (9) showed that DNI could be used as a serum marker to predict chorioamnionitis in patients with preterm premature rupture of membranes, and lymphocyte count, C-reactive protein, and DNI could be used to predict inflammatory responses in the placenta. A meta-analysis reported the high diagnostic accuracy of DNI as a predictive and prognostic factor in infected patients (7). Additionally, DNI was shown to be an effective parameter in estimating the mortality of these patients and suggested to be useful in clinical practice (25).

In a study with 278 patients that defined massive transfusion as a transfusion of ≥10 units of red blood cells within 24 hours after postpartum hemorrhage, massive transfusion was detected in 60 participants (26). In the current study, an optimal cut-off value of 3.3 for DNI was found to be significantly associated with an increased risk of massive transfusion (with an AUC of 0.74), as well as a cut-off value of 3.54 for PLR and 0.48 for NLR (26). In addition, Kong et al. (27) demonstrated that the optimal cut-off value of DNI was 1 at admission and 2.6 on day 1 to predict 30-day mortality in patients with upper gastrointestinal bleeding. Considering the results of these studies (26,27), DNI is seen as a parameter related to the amount of blood loss, the need for transfusion, and mortality due to blood loss. We found a positive correlation between preoperative DNI and ΔHb1 level and ΔHb2 level.

The strength of the current study is the investigation of the relationship between changes in postpartum Hb levels and widely recognized markers DNI, PLR, and NLR in a homogeneous group of patients undergoing cesarean section. In addition, most potential causes that may affect these markers were excluded. The large sample size reflected its high statistical power. A limitation of the study is that DNI is a hematological marker that may not be useful in each patient. Because postpartum hemorrhage can be associated with various factors, DNI may be misleading in comorbid conditions. The most important factor in preventing postpartum hemorrhage is to be cautious of the risk and to take the necessary measures early (1,13,14). However, predicting the risk of blood loss in the preoperative period is not easy. Based on the data obtained in our study, DNI may help predict the extent of blood loss during cesarean section and thus can assist the physician in taking the necessary precautions.

Conclusion

This study found a positive correlation between DNI and changes in Hb levels at the 6th and 12th h in the post-cesarean period.

Ethics

Ethics Committee Approval: The study was approved by Etlik Zübeyde Hanım Maternity and Women's Health Training and Research Hospital Local Ethics Committee (decision no: 12, date: 06.05.2020). The study protocol was in accordance with the Declaration of Helsinki on the ethical conduct of studies involving human subjects.

Informed Consent: All study participants provided written informed consent.

Authorship Contributions

Surgical and Medical Practices: Y.A.R., E.N.V., F.B.F., R.S.K. Concept: Y.A.R., A.A., Design: Y.A.R., A.A., E.N.V., Data Collection or Processing: E.N.V., H.E.T., Analysis or Interpretation: Y.A.R., E.N.V., R.E.P. Literature Search: Y.A.R., A.A., E.N.V. Writing: Y.A.R., A.A., E.N.V., F.B.F., H.E.T., S.Y.E., R.E.P., R.S.K.

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Relationship between social media addiction level and nutritional status in students of the faculty of health sciences

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ABSTRACT

Aims: University students widely use social media applications to acquire a social environment and access/share information. However, more time spent on social media may put individuals at risk of addiction and indirectly affect their nutritional status. This study investigated the relationship between social media addiction and the nutritional habits of university students.

Methods: We enrolled volunteers using an online questionnaire. The Social Media Addiction Scale-Student Form (SMA-SF) and the Attitude Scale for Healthy Nutrition (ASHN) were administered online. The primary outcomes were the SMA-SF and ASHN total scores and their correlation.

Results: The study included 957 subjects (mean age: 19.8±1.4; 91.3% female). A low but significant negative correlation was found between SMA-SF and ASHN scores (r=-0.245, p=0.001). Concerning the time spent daily on social media, we identified that taking less than 1 hour/day as the reference, spending 1 to 3 or above 3 hours/day on social media was significantly associated with higher SMA-SF scores [beta=0.387, t(956)=12.951, p<0.001, 95% confidence interval (CI): 8.814 to 11.962]. Similarly, taking less than 1 hour/day as the reference, spending 1 to 3 or above 3 hours/day on social media was significantly associated with a lower ASHN scale for healthy nutrition scores [beta=-0.173, t(956)=-5.437, p<0.001, 95% CI: -3.725 to -1.749].

Conclusions: Our findings show that increasing time spent on social media during university may increase social media addiction and negatively affect attitudes toward healthy eating.

Introduction

Healthy eating is one of the most important determinants of individual and societal well-being. Maintaining a healthy diet throughout life protects individuals from malnutrition and diet-related chronic diseases (1). Failure to maintain an adequate and balanced diet can lead to poor quality of life and many health problems.

Even if university students know nutrition, factors such as the difficulty of the academic program, limited food options, or economic conditions impact healthy food choices and eating habits (2). Students who leave the family home eat more unhealthy (3). Moreover, higher prices of healthy food, lack of healthy food in the canteen, and inability to find a suitable time for cooking cause students to have an unhealthy diet (4). Therefore, university students need more information on adequate and balanced nutrition, more nutritional information on ideal body weight, and effective intervention programs (5-7).

Thanks to rapidly developing technology, access to social media tools has become quite easier. While social media applications offer benefits such as access to all kinds of information, networking with people, having fun, participating in events, playing online, and being able to access them on the go, they also pose risks such as misinformation, invasion of privacy, and social media addiction (8-10). The ability to use social media anytime, anywhere and the use of the social media

platform by mobile phones also increases the time spent on these applications (11). Increased long-term use may lead to social media addiction (11).

Students can access all kinds of information about nutrition in social media applications. Food-related posts by individuals or food companies and the sharing of nutrition-related posts by non-experts on this platform result in misleading nutrition information (12). In addition, the use of social media can negatively impact an individual's body image and lead to eating disorders (13-15). A previous study found a correlation between the use of social media tools and eating disorders in individuals aged 19-32 (16). Easier access to these applications anytime, anywhere allows individuals to view other people's posts and compare their appearance with others (13). As a result, the risk of obsession with healthy eating may increase (17,18). It is also thought that as people spend more time on social media, they skimp on meals and replace them with unhealthy options because they do not have time to cook, on top of an inactive lifestyle (15,19,20), raising the question of whether the students are influenced by posts about nutrition and food on social media, and whether the time they spend on social media affects their nutritional status. Therefore, this study investigated the relationship between social media addiction and the dietary habits of university students.

Methods

The study included students from the departments of nutrition and dietetics, child development, midwifery, occupational therapy, physiotherapy and rehabilitation, audiology, orthotics-prosthetics, health management, and social work, Gülhane Faculty of Medicine, University of Health Sciences Türkiye, Ankara, Türkiye. They were enrolled through an online survey because of the COVID-19 pandemic from December 2020 to January 2021. Invitations were sent via e-mail and phone text messages. Ethical approval was obtained from the Non-interventional Research Ethics Committee of Gülhane University of Health Sciences Türkiye (decision no: 2020-437, date: 05.11.2020).

Survey Questionnaire

The online survey included anthropometric measures, duration and content of social media use, the Social Media Addiction Scale-Student Form (SMA-SF) and the Attitude Scale for Healthy Nutrition (ASHN) (21,22). In the first part, individuals were asked about the time they spent daily on the internet and social media and which social media application they used most. In the second part, the volunteers were asked to report their height and weight to calculate the body mass index (BMI) (23).

SMA-SF

In the third part of the questionnaire, SMA-SF was applied online to measure social media addiction level of the students, which was developed previously to determine social media addiction levels of middle school, high school, and university students (21). The total variance of the scale was 53.2%. Cronbach's alpha coefficient was 0.93 on average and 0.81, 0.81, 0.86, and 0.82 for virtual tolerance, virtual communication, virtual problem, and virtual information, respectively (21). SMA-SF is a 5-point Likert-type scale comprising 29 questions. It consists of four factors: virtual tolerance, virtual communication, virtual problem, and virtual information. Virtual Tolerance consists of items 1-5, Virtual Communication 6-14, Virtual Problems 15-23, and Virtual Information 24-29. Each item is rated "1-Not at all suitable for me," "2-Not suitable for me," "3-I am undecided," "4-It is suitable for me," and "5-Very suitable for me." Scores range between 29 and 145. Addiction levels were determined by dividing the minimum and maximum score intervals into five levels. These were classified as "no dependency (29-51 points), "low dependency (52-74 points), "moderate dependency (75-97 points), "high dependency (98-120 points)' and 'very highly dependent (121-145 points)'.

ASHN

In the fourth part of the questionnaire, the students' ASHN was administered online, which was developed and validated previously (22). The ASHN consists of 21 questions and four factors. The factors are 'Information on Nutrition', for items 1-5, 'Emotion for Nutrition', for items 6-11, 'Positive Nutrition' for items 12-16, and 'Malnutrition' for items 17-21. The scale is a 5-point Likert-type and consists of "Strongly Disagree," "Disagree," "Undecided," "Agree," and "Strongly Agree" options. Items 1-5 and 12-16 are positive, and items 6-11 and 17-21 are negative. Scores range between 21 and 105. The scores are classified into very low (21 points), low (23-42 points), moderate (43-63 points), high (64-84 points), and ideally high (85-110 points) attitudes toward healthy eating. The total variance of the scale was 57.8% and 0.90, 0.84, 0.75, and 0.83 for "Information on Nutrition," "Emotion for Nutrition," "Positive Nutrition," and "Malnutrition," respectively (22).

Statistical Analysis

The data were analyzed using the IBM Statistical Package for the Social Sciences statistics (22.0.0.0). Data were summarized as mean±standard deviation. Skewness and kurtosis values were used to assess the data distribution. The chi-square test was used to compare the categorical variables. Pearson's correlation coefficients were calculated to assess potential correlations. Linear regression analysis was used to evaluate the potential correlations of the SMA-SF and ASHN scores with categorical variables above two levels. $P<0.05$ was considered statistically significant.

Results

A total of 1,856 students were invited from the departments of nutrition and dietetics (n=243), child development (n=245),

midwifery (n=220), occupational therapy (n=223), physiotherapy and rehabilitation (n=240), audiology (n=222), orthotics-prosthetics (n=53), health management (n=187) and social work (n=223), and 957 (mean age: 19.8±1.4 years; 91.3% female) completed the questionnaire. Table 1 shows the time volunteers spent daily on the internet and social media and the applications they used most. The rates were similar between genders, and 68.3% of students spent more than 3 hours/day on the internet. Concerning time spent on social media, 58% of students spent 1-3 hours on social media applications, while 24.8% spent more than 3 h. Seventy percent were of normal weight.

There was a relationship between the ASHN scores and the most followed topic about nutrition and food on social media. Individuals who follow accounts that share information about healthy nutrition and healthy nutrition recipes on social media have achieved higher ASHN scores than those who do not. On the other hand, there was also an association between the ASHN scores and the most followed people on nutrition and food on social media. The students who followed doctors' and dietitians' accounts received higher ASHN scores than those who did not follow (Table 2).

There was a correlation between the SMA-SF total score and its four factors with the ASHN total score (Table 3) (p=0.001). Furthermore, there were correlations between BMI and virtual communication (p=0.04) and virtual problems (p=0.049).

Figure 1 shows weak, negative correlations between the SMA-SF total score and its four factors, virtual tolerance, virtual communication, virtual problems, and virtual information scores, with the ASHN total scores. There was a positive and very weak correlation between BMI and the virtual communication and virtual problem sub-dimensions.

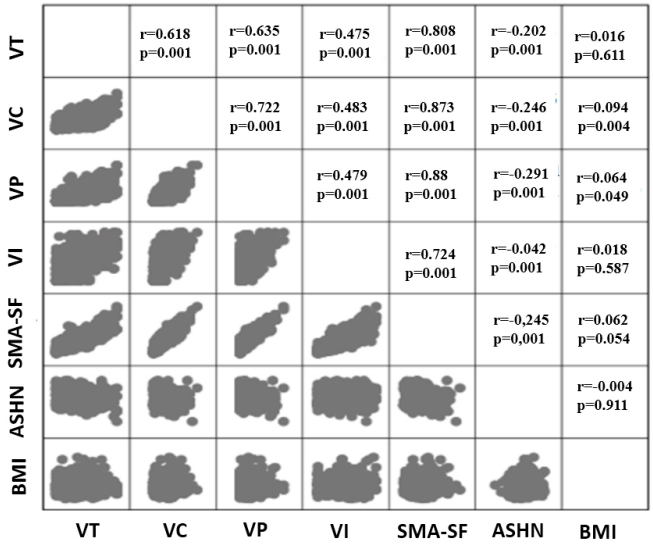

Figure 1. Matrix scatter plot of correlation between SMA-SF total score and its four factors, virtual tolerance, virtual communication, virtual problem and virtual information scores, and ASHN total scores and BMI values

VT: Virtual tolerance, VC: Virtual communication, VP: Virtual problems, VI: Virtual information, SMA-SF: Social Media Addiction Scale-Student Form, ASHN: Attitude Scale for Healthy Nutrition, BMI: Body mass index

Table 1. Internet-social media use and BMI levels

	Gender					
	Male		Female		Total	
Variables	**n**	**%**	**n**	**%**	**n**	**%**
Internet use (daily)						
<1 hour	1	1.3	22	2.5	23	2.4
1-3 hours	28	35.4	252	28.7	280	29.3
>3 hours	50	63.3	604	68.8	654	68.3
Total	79	100	878	100	957	100
Social media use (daily)						
<1 hour	19	24.0	146	16.6	165	17.2
1-3 hours	47	59.5	508	57.9	555	58
>3 hours	13	16.5	224	25.5	237	24.8
Total	79	100	878	100	957	100
Body mass index (kg/m²)						
Underweight (≤18.4)	8	10.1	151	17.2	159	16.6
Normal weight (18.5-24.9)	46	58.2	626	71.3	672	70.2
Pre-obesity (25.0-29.9)	25	31.7	86	9.8	111	11.6
Obesity (≥30.0)	0	0	15	1.7	15	1.6
Total	79	100	878	100	957	100

BMI: Body mass index

Table 2. ASHN classification with the most followed topics/people related to nutrition and food on social media

Classification of ASHN	a) The most followed topic about nutrition and food on social media											b) The most followed people on nutrition and food on social media										
	Not interested		Healthy eating		Recipes		Weight loss		Total		p	Not following		Dietitians		Doctors		Social media and magazine celebrities		Total		p
	n	%	n	%	n	%	n	%	n	%	0.001	n	%	n	%	n	%	n	%	n	%	0.001
Very low, low and moderate	22	17.2	17	5.6	30	7.9	18	12.2	87	9.1		42	9.6	24	6.6	5	7.4	16	18.4	87	9.1	
High	88	68.8	171	56.8	284	74.7	94	63.5	637	66.6		328	75.1	213	58.4	40	58.8	56	64.4	637	66.6	
Ideal	18	14.1	113	37.5	66	17.4	36	24.3	233	24.3		67	15.3	128	35.1	23	33.8	15	17.2	233	24.3	
Total	128	100	301	100	380	100	148	100	957	100		437	100	365	100	68	100	87	100	957	100	

The chi-square test was used to calculate the p value.
ASHN: Attitude Scale for Healthy Nutrition

Concerning the time spent daily on social media, we identified that taking less than 1 hour/day as the reference, spending 1 to 3 or more hours/day on social media was significantly associated with higher social media addiction scores [beta=0.387, t(956)=12.951, p<0.001, 95% confidence interval (CI): 8.814 to 11.962]. Similarly, taking less than 1 hour/day as the reference, spending 1 to 3 or more hours/day on social media was significantly associated with lower ASHN scores [beta=-0.173, t(956)=-5.437, p<0.001, 95% CI: -3.725 to -1.749].

Discussion

The results showed that most university students (58%) spent 1-3 hours on social media, while 24.8% spent more than 3 hours. In a study conducted in the USA, 45% of students spent 6-8 hours on social media applications (24). However, although a significant proportion of students spend considerable time on social media, it should be noted that social media use might have increased during the pandemic (25). As time spent on social media increases, so do social media addiction scores (26-28). Salari et al. (29) found that the global social media addiction prevalence was 18.4% among university students. These results indicate that social media addiction among university students is becoming a public health problem, and it is necessary to take the necessary measures to prevent this issue.

In this study, subjects who followed healthy eating and recipes on social media applications were less likely to have a low level of healthy eating attitudes than those who did not. Those who followed weight loss posts were more likely to have a low level of healthy eating attitudes than those who followed healthy eating posts. In particular, subjects who followed celebrities' nutrition-related social media posts were more likely to have low levels of healthy eating attitudes. It can be assumed that posts by people who are not experts in the field of weight loss cause a negative perception in the followers and negatively affect healthy eating attitudes. In addition, exposure to photos of celebrities or peers on social media might be harmful to women's body image, and affect the physical and mental health of individuals by causing a negative body image and psychological problems (26,30-32). In contrast, in this study, we observed that students who followed dietitians' and doctors' posts about healthy eating on social media were more likely to have ideal healthy eating attitudes. This finding suggests that since posts about nutrition and food on social media may influence individuals' healthy eating attitudes, they should be made by experts in the field.

Although social media addiction is not related to healthy eating attitudes, there is a relationship between social media addiction and eating disorder risk among university students (21). Social media addiction also has negative effects on eating behavior among adolescents and young individuals (33). As the time spent on social media increases, healthy eating

Table 3. Correlations of SMA-SF total score and its four factors virtual tolerance, virtual communication, virtual problem and virtual information scores with ASHN total score and BMI

		Virtual tolerance	Virtual communication	Virtual problems	Virtual information	SMA-SF	ASHN	BMI
Virtual tolerance	**r**		0.618	0.635	0.475	0.808	-0.202	0.016
	p		**0.001**	**0.001**	**0.001**	**0.001**	**0.001**	0.611
Virtual communication	**r**	0.618		0.722	0.483	0.873	-0.246	0.094
	p	**0.001**		0.001	**0.001**	**0.001**	**0.001**	**0.004**
Virtual problems	**r**	0.635	0.722		0.479	0.88	-0.291	0.064
	p	**0.001**	**0.001**		**0.001**	**0.001**	**0.001**	**0.049**
Virtual information	**r**	0.475	0.483	0.479		0.724	-0.042	0.018
	p	**0.001**	**0.001**	**0.001**		**0.001**	0.193	0.587
SMA-SF	**r**	0.808	0.873	0.88	0.724		-0.245	0.062
	p	**0.001**	**0.001**	**0.001**	**0.001**		**0.001**	0.054
ASHN	**r**	-0.202	-0.246	-0.291	-0.042	-0.245		-0.004
	p	**0.001**	**0.001**	**0.001**	0.193	**0.001**		0.911
BMI	**r**	0.016	0.094	0.064	0.018	0.062	-0.004	
	p	0.611	**0.004**	**0.049**	0.587	0.054	0.911	

Pearson correlation analysis was used to calculate the p value.
SMA-SF: Social Media Addiction Scale-Student Form, ASHN: Attitude Scale for Healthy Nutrition, BMI: Body mass index

behaviors are affected negatively, leading to young individuals' involvement with social media, skipping breakfast and drinking sugary soft drinks (34,35). As the amount of time spent on social media increases, young people's exposure to high-calorie, low-nutrient food posts increases, which is thought to impact food preferences negatively, which can lead to disordered eating behaviors (32,36).

Limitations and Future Directions

This study was conducted with volunteer university students using an online survey. The results may not reflect all students of the faculty and all students studying in Türkiye. Because of the pandemic, the survey could not be conducted face-to-face and was distributed online. Therefore, the height and weight information of the individuals was self-reported, which may be less reliable. In addition, the students were studying online because of the pandemic, which may have affected their daily internet and social use (37). Studies with larger samples and follow-up are needed to examine the effects of social media addiction and dietary habits among university students. Moreover, social media addiction education should be provided at universities, and policies should be developed to support healthy nutrition and access to healthy food.

Conclusion

Although social media offers many benefits to university students, spending too much time on social media platforms increases the risk of addiction and negatively affects individuals' attitudes toward healthy eating. Students should be informed about social media use, and necessary protection programs should be implemented. Some studies have shown that nutrition education through social media tools has a positive impact on the nutritional status of individuals (38-41). The social media platform can be the cheapest, fastest, and most comprehensive tool for implementing these protective programs.

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Ethics

Ethics Committee Approval: Ethical approval was obtained from the Non-interventional Research Ethics Committee of Gülhane University of Health Sciences Türkiye (decision no: 2020-437, date: 05.11.2020).

Informed Consent: This study is an online questionnaire.

Authorship Contributions

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

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Associations between circadian preference, social jetlag, and diabetes mellitus risk in nurses working shifts

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ABSTRACT

Aims: This study uncovered the links between circadian preferences, social jet lag, and diabetes mellitus (DM) risk screening results of nurses working shifts.

Methods: In this cross-sectional study design, sociodemographic data, the American Diabetes Association (ADA) Diabetes Risk Test, Morningness-Eveningness Stability Scale Improved (MESSi), sleep awake and bedtimes, and shift count were collected via survey. Participants were split into DM risk-positive and negative groups to compare them for MESSi scores, circadian preference and social jetlag.

Results: Short sleep keepers were 61.8% of all 212 nurses aged 32.25±6.99 years. Abnormal social jetlag was detected in 18.9% of the study population. The group that experienced abnormal social jetlag exhibited a significantly lower morning affect and a higher eveningness (EV) compared with the normal jetlag group (p=0.003 and p=0.004, respectively). DM risk was present in 6.6% of all. A higher risk of DM was observed in individuals with older age, longer job experience, higher body mass index (BMI), male gender, and lower EV score (p<0.001, p<0.001, p<0.001, p=0.006 and p=0.042, respectively). Distinctness scores were positively correlated with DM risk scores (r=0.168; p=0.014), whereas they inversely correlated with night shift count (r=-0.149; p=0.022). Higher values of BMI (odds ratio=1.255; 95% confidence interval=1.036-1.520; p=0.020) and male sex (odds ratio=7.350; 95% confidence interval=1.265-42,161; p=0.026) were associated with increased risk for DM.

Conclusions: This study reports that circadian preference, but not social jetlag time, may be related to DM risk among nurses working shifts.

Introduction

The timing of daily behaviors within the 24-hour day defines our chronotype (1). Sleep chronotype is the sleep pattern related to the preference for sleeping in the morning and evening during circadian rhythm, and it shows differences between individuals in the morning, intermediate, or evening form (2). Those in the morning sleep chronotype go to bed early and those in the evening sleep chronotype late (3). The evening chronotype is associated with the possibility of unhealthy food and nutrient intake, which may predict a higher risk of obesity than the morning preference (3). The prevalence of type 2 diabetes (T2D) and prediabetes is increasing worldwide, and by the end of 2030, more than 470 million people will be affected by prediabetes because of insulin resistance (4). In addition, sleep shorter than 8 hours is associated with obesity and glucose intolerance via increased appetite for high-energy foods (5,6).

Disruption of sleep patterns and sagging of the midpoint of sleep time due to changes in social obligations such as school or work is called social jetlag (2,7). Social jetlag is calculated as the continuously measured and bisected absolute difference

in the midpoint of the sleep period between weekdays and weekend days. Values of 2 h or more are considered abnormal and indicate more shifts in sleep timing during the week (7-10). It is assumed that individuals with evening chronotypes are prone to abnormal jetlag (3) and sleep deprivation due to night and shift work will be compensated on free days (11).

Nursing is characterized by a working articulation in shifts to ensure continuity of care throughout the 24 hours (12). Several studies examined sleep quality, daytime sleepiness, or sleep chronotypes due to the work schedule of health workers, including night shifts (13). It has been explained among female workers that with prolonged years of exposure to shift work, the risk of T2D might increase (14).

The screening of nurses for diabetes risk was the focus of this study, which used the American Diabetes Association (ADA) Diabetes Risk tool. Additionally, the study sought to establish links between social jetlag, circadian preferences, and diabetes risk. Specifically, the effects of shift work and sleep patterns on the DM risk among nurses were investigated.

Methods

Study design, setting, and sample

This cross-sectional study was conducted face-to-face with the nurses between September and November 2021. The research population consisted of 1200 nurses working at a tertiary hospital. The required number for the sample group was calculated as at least 197 people using the calculation tool on the https://sampsize.sourceforge.net/ site, taking the diabetes risk rate as 32% in the sample literature (15), type 1 error rate 5% and power level as 90%. A target of 300 participants was randomly determined through the randomizer.org website based on a work date list obtained from the hospital's human resource management department, and the study was terminated when 212 nurses meeting the inclusion criteria were reached.

Study subjects included participants; nurses who volunteered to participate in the study as shift workers, nurses who did not suffer from psychiatric and neurological conditions, nurses who had not been previously diagnosed with diabetes and/or sleep disorders, pregnancy, and nurses who were not taking nutritional supplements (such as melatonin) or medications impairing sleep.

Instruments and data collection

The sociodemographic data form (age, gender, marital status, smoking, working profession, number of shifts), height, weight, sleep length, time to sleep, time to get up in the morning, Morningness-Eveningness Stability Scale improved (MESSi) and ADA diabetes risk assessment questionnaire were applied in line with the literature (15-17).

American Diabetes Association type 2 diabetes risk score calculation

When the total score obtained from the responses related to age, waist circumference, gestational diabetes, height, race/ethnicity, hypertension, family history, and exercise in the ADA T2D risk score is five or higher, it indicates a higher risk for diabetes, probability of pre-diabetes or undiagnosed diabetes and needs to be administered to a physician (16-19).

Morningness-Eveningness Stability Scale Improved

MESS is a novel instrument that consists of subscales of morning affect (MA), eveningness (EV), and stability/distinctness (DI) and is used to define participants' morningness-EV preference. The scale was developed by Randler et al. (18) in 2016 and adopted into Turkish by Demirhan et al. (16) in 2019. MESSi comprises 15 items with five choices (16). Questions 3, 4, 11, and 12 are reverse questions. Circadian fluctuations are related to mood or activation. The DI (amplitude of diurnal variation) subscale represents the subjective feeling of DI of daily changes. As the total score from the stability dimension increases, DI decreases; in other words, stability in mood increases (16,18). The Turkish form of the scale's Cronbach's alpha values for MA, EV, and DI were 0.84, 0.81, and 0.58, respectively (16). In our study, the MESSi scale's Cronbach's alpha values for MA, EV, and DI were found to be 0.83, 0.79, and 0.66.

Social jetlag calculation

"Social jetlag" was defined as the absolute difference in the midpoint of the sleep period between weekdays and weekends, measured continuously and dichotomized (2:2 hours), with higher values indicating more displacement of sleep timing across the week (7). For example, if a participant reported a sleep onset of 8:00 pm and wake time of 6:00 am on weekdays (midpoint: 1:00 am) and a 10:00 pm sleep onset and 10:00 am wake time on weekends (midpoint: 4:00 am), their social jetlag was 3 h (7).

Ethical approval

For the implementation of the study, permission was obtained from the İstanbul Provincial Health Directorate Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee with the date 08/09/2021 and no 324. The participants provided written informed consent.

Statistical Analysis

The collected research data were analyzed using the MediCres E-Picos Calculator online statistical program. The numerical data are shown as mean and standard deviation. The categorical data were given as numbers and percentages between groups with normal and abnormal jetlag and were compared using the chi-square and Fisher's exact test, and

continuous data were compared using the Student's t-test. The Pearson correlation test was used to determine the relationships among circadian preferences, jetlag times, and diabetes risk score. Risk factors for diabetes mellitus (DM) risk probability were assessed using a binary logistic regression model. Statistical significance limit p<0.05 was accepted.

Results

The characteristics of the participants, sleep patterns and comparisons of normal and abnormal social jetlag groups are shown in Table 1. The mean age of the 212 nurses was 32.25±6.99 years. 83.5% (n=177) were female and 43.9% (n=93) were married. The average shift count of our study population was 4.21±3.78 (median=4) shifts. The rate of short sleepers whose sleep duration was less than 8 hours was 61.8%. The presence of social jetlag was detected in 18.9% (n=40). Participants with normal sleep duration and those with lower EV and higher MA scores had a higher likelihood of normal social jetlag than those with short sleep keepers, those with higher EV, and those with lower MA (p=0.009, p=0.004, p=0.003). Furthermore, those who slept longer on weekdays had a significantly higher chance of normal social jetlag than short sleep keepers (p<0.001). Additionally, nonsmokers were more inclined to experience normal social jetlag than smokers (p=0.029). It was observed that nurses with fewer than four monthly shifts had a lower diabetes risk than others (p=0.004).

In Table 2, comparisons of groups with and without diabetes risk are presented. ADA diabetes risk presence was 6.6% (n=14).

Table 1. Comparison of sociodemographic characteristics, sleep duration, circadian preferences and diabetes risk presence between groups with normal and abnormal social jetlag

Variables	Total n=212 (100%)	Normal social jetlag (<2 hours) n=172 (81.1%)	Abnormal social jetlag (≥2 hours) n=40 (18.9%)	p
Age, years, mean±SD	32.25±6.99	32.59±6.99	30.75±6.93	0.134*
Profession, years, mean±SD	10.13±7.19	10.37±7.20	9.10±7.12	0.324*
Monthly shift count, mean±SD	4.21±3.78	4.11±3.86	4.76±3.45	0.416*
≤4 shifts, n (%)	109 (52.4)	93 (54.1)	18 (45.0)	0.301
>4 shifts, n (%)	101 (47.6)	79 (45.9)	22 (55.0)	
BMI, mean±SD	23.67±4.70	23.69±4.76	23.58±4.53	0.900
Sex, n (%)				
Female	177 (83.5)	144 (83.7)	33 (82.5)	0.851
Male	35 (16.5)	28 (16.3)	7 (17.5)	
Marital status, n (%)				
Married	93 (43.9)	76 (44.2)	17 (42.5)	0.847
Single/divorced	119 (56.1)	96 (55.8)	23 (57.5)	
Smoking, n (%)				
Smoker	65 (30.7)	47 (27.3)	18 (45.0)	**0.029***
Non-smoker	147 (69.3)	125 (72.7)	22 (55.0)	
Sleep duration, n (%)				
Short (<8 hour) sleep	131 (61.8)	99 (57.6)	32 (80.0)	**0.009***
Normal sleep	81 (38.2)	73 (42.4)	8 (20.0)	
Weekday sleep duration, mean±SD	7.54±1.62	7.74±1.59	6.65±1.44	**<0.001***
Weekend sleep duration, mean±SD	8.9±1.42	8.84±1.38	9.17±1.55	0.187
MA score, mean±SD	16.66±3.55	17.01±3.39	15.15±3.84	**0.003***
EV score, mean±SD	15.15±3.97	14.78±3.97	16.75±3.59	**0.004***
DI score, mean±SD	14.95±3.31	15.11±3.28	14.25±3.39	0.137
ADA diabetes risk screening, n (%)				
DM risk positive	14 (6.6)	12 (7.0)	2 (5.0)	0.650***
DM risk negative	198 (93.4)	160 (93.0)	38 (95.0)	

*Student's t-test, **chi-square test, ***Fisher's exact test, p<0.05 is significant MA, EV, and stability/DI.
MA: Morning affect, EV: Eveningness, DI: Distinctness, BMI: Body mass index, ADA: American Diabetes Association, DM: Diabetes mellitus, SD: Standard deviation

It was observed that nurses with fewer than four monthly shifts had a higher risk of diabetes than others (p=0.004). Participants with diabetes risk had an older age (p<0.001), longer job experience (p<0.001), lower night shift count (p=0.010), higher body mass index (BMI) (p<0.001), and male sex (p=0.006) versus diabetes risk negative group (Table 2). No significant difference was observed in the presence of abnormal jetlag between the groups with and without DM risk, as presented in Table 1.

Table 3 shows the comparison of social jetlag, MA, EV, and DI scores between groups of sex, marital status, smoking, sleep duration (hour) and diabetes risk. Males had a higher DI score than females (p=0.014). MA score was higher in married nurses than in single/divorced group (17.23±3.04 vs. 16.21±385; p=0.040). Short sleep keepers had a higher social jetlag time than normal sleep keepers (1.34±0.89 vs. 0.92±0.97; p=0.005). The DM risk-positive group had a lower EV than the negative group (13.07±3.56 vs. 15.29±3.96; p=0.042). Furthermore, smokers had longer social jetlag than non-smokers (1.40±0.99 vs. 1.09±0.91; p=0.026), higher EV scores (16.23±3.82 vs. 14.67±3.96; p=0.011), and lower MA scores (15.46±4.28 vs. 17.19±3.04; p=0.005). The group of rare shifts (≤4 shift count) had higher MA (17.35±3.44 vs. 15.90±3.52; p=0.003) and DI (15.55±3.12 vs. 14.29±3.40; p=0.006) scores than those with over four shifts.

Table 2. Comparison of sociodemographic characteristics, sleep duration, and circadian preferences between ADA diabetes risk screening questionnaire groups with and without diabetes risk

Variables	ADA diabetes risk positive n=14 (6.6%)	ADA diabetes risk negative n=198 (93.4%)	p
Age, years, mean±SD	43.43±5.21	31.45±6.42	**<0.001***
Profession, years, mean±SD	22.36±5.70	9.25±6.45	**<0.001***
Monthly shift count, mean±SD	1.68±2.75	4.50±3.78	**0.010***
≤4 shifts, n (%)	13 (92.9)	98 (49.5)	**0.004*****
>4 shifts, n (%)	1 (7.1)	100 (50.5)	
BMI, mean±SD	29.28±4.31	23.24±4.48	**<0.001***
Sex, n (%)			
Female	8 (57.1)	169 (85.4)	**0.006****
Male	6 (42.9)	29 (14.6)	
Marital status, n (%)			
Married	9 (64.3)	84 (42.4)	0.111
Single/divorced	5 (35.7)	114 (57.6)	
Smoking, n (%)			
Smoker	4 (28.6)	61 (30.8)	0.861
Non-smoker	10 (71.4)	137 (69.2)	
Sleep duration, n (%)			
Short sleep keepers	9 (64.3)	122 (61.6)	0.843
Normal sleep keepers	5 (35.7)	76 (38.4)	
Weekday sleep duration, mean±SD	7.21±1.11	7.57±1.65	0.431
Weekend sleep duration, mean±SD	8.37±1.28	8.94±1.42	0.146

*Student's t-test, **chi-square test, ***Fisher's exact test, p<0.05 is significant. BMI: Body mass index, ADA: American Diabetes Association, SD: Standard deviation

Table 4 shows the correlation analysis of social jetlag duration and circadian preferences toward age, weekday sleep duration, weekend sleep duration, BMI, and ADA T2D screening scores. The DI score positively correlated with the ADA score (r=0.168; p=0.014), age (r=0.140; p=0.031), and a negative correlation with the monthly shift count (r=-0.149; p=0.022). The MA negatively correlated with the shift count (r=-0.164; p=0.018).

However, there was a negative relationship between age and night shift count (r=-0.395; p<0.001).

The risk factors for DM risk were assessed with a binary logistic regression model (Table 5). Higher values of BMI [odds ratio (OR)=1.255; 95% confidence interval (CI): 1.036-1.520; p=0.020] and male sex (OR: 7.350; 95% CI: 1.265-42.161; p=0.026) were associated with increased risk of DM.

Discussion

The current research achieved associations between circadian sleep preferences, social jet lag, and diabetes risk screening results among nurses working shifts. The DM risk was 6.6% and the frequency of abnormal social jetlag was 18.9%. A higher risk of DM was related to lower EV and had a positive relationship with DI. It was concluded that circadian preference, but not social jetlag time, may be related to DM risk. Male nurses with a higher BMI were found to be at the highest risk of developing DM.

A literature review for nurse health has shown that shift working is a risk factor for DM (12). Globally, 41 million individuals are estimated to have prediabetes, defined as impaired fasting glucose or impaired glucose tolerance. Prediabetes implies an increased risk of development of T2D on the order of 30% over 4 years (20). In the region where this study was conducted, İğci and Basat (15) performed ADA T2D screening and found the DM risk to be 32% in the general population who applied to the same hospital's family medicine clinic. Kulak et al. (21) found a high to very high risk for DM (19.3%) and a moderate risk (22.2%) in another study. The prevalence of prediabetes among young adults was 24.0% in the United States (22). Therefore, a DM screening risk of 6.6% may be considered as a low incidence. This result may be associated with the fact that our sample included health professionals.

Table 3. Comparison of social jetlag, MA, EV, and DI scores between groups of sex, shift count, marital status, smoking, sleep duration (hours) and diabetes risk

		Social jetlag (hours)	MA	EV	DI
Sex	Female	1.16±0.93	16.55±3.54	15.24±4.06	14.71±3.20
	Male	1.31±0.99	17.22±3.55	14.71±3.55	16.20±3.64
p		0.392	0.300	0.478	**0.014***
Monthly shift count	≤4 shifts	1.18±0.80	17.35±3.44	14.82±4.50	15.55±3.12
	>4 shifts	1.19±1.07	15.90±3.52	15.52±3.29	14.29±3.40
p		0.928	**0.003***	0.198	**0.006***
Marital status	Married	1.20±0.88	17.23±3.04	14.91±4.42	15.28±3.26
	Single/divorced	1.18±0.98	16.21±385	15.34±3.59	14.69±3.35
p		0.888	**0.040***	0.444	0.205
Smoking	Smoker	1.40±0.99	15.46±4.28	16.23±3.82	14.80±3.58
	Non-smoker	1.09±0.91	17.19±3.04	14.67±3.96	15.02±3.19
p		**0.026***	**0.005***	**0.011***	0.729
Sleep duration (hour)	Short sleep keepers (%)	1.34±0.89	16.81±3.53	15.09±4.10	15.06±3.26
	Normal sleep keepers (%)	0.92±0.97	16.41±3.58	15.23±3.78	14.78±3.41
p		**<0.001***	0.415	0.810	0.546
ADA diabetes risk screening test result	DM risk positive	1.21±0.70	17.57±3.25	13.07±3.56	15.57±4.16
	DM risk negative	1.18±0.96	16.59±3.56	15.29±3.96	14.91±3.25
p		0.908	0.321	**0.042***	0.471

*Student's t-test, p<0.05.
MA: Morning affect, EV: Eveningness, DI: Distinctness, ADA: American Diabetes Association, DM: Diabetes mellitus

Table 4. Correlation analysis of social jetlag duration and circadian preferences towards age, weekday sleep duration, weekend sleep duration, BMI, and ADA type 2 diabetes screening score

Variables	Social jetlag (hours)	MA	EV	DI
Age	r=0.014 p=0.834	r=0.111 p=0.109	r=-0.129 p=0.060	**r=0.140** **p=0.042**
Profession, years	r=0.013 p=0.855	r=0.131 p=0.060	r=-0.130 p=0.064	r=0.062 p=0.062
Monthly shift count	r=-0.006 p=0.926	**r=-0.164** **p=0.018***	r=0.084 p=0.229	**r=-0.149** **p=0.031***
Weekday sleep duration	**r=-0.293** **p<0.001***	r=0.007 p=0.916	r=-0.059 p=0.396	r=-0.025 p=0.715
Weekend sleep duration	**r=0.190** **p=0.005***	r=-0.045 p=0.511	r=-0.044 p=0.520	r=-0.052 p=0.455
ADA diabetes risk screening score	r=-0.005 p=0.941	r=0.111 p=0.109	r=-0.118 p=0.086	**r=0.168** **p=0.014***
BMI	r=0.014 p=0.996	r=0.165 p=0.165	r=0.028 p=0.690	r=0.087 p=0.206

*p<0.05 Pearson correlation test.
MA: Morning affect, EV: Eveningness, DI: Distinctness, BMI: Body mass index, ADA: American Diabetes Association, DM: Diabetes mellitus

Morningness is usually associated with well-being, better sleep quality, and more conscientiousness, whereas EV is associated with negative emotionality, poorer sleep quality, and less conscientiousness (23). In addition, evening-oriented sleep timing preferences have been related to the risk of diabetes, cardiovascular diseases, obesity, psychiatric disorders, and increased mortality (1). In contrast, the DM risk-positive nurse group had a lower EV and higher DI (amplitude of diurnal variation) score than the other groups in our study. In addition, DM risk presence was significant for longer work experience and less night shift count versus others. We thought it might be related to older nurses having higher DM risk, longer work

Table 5. Evaluation of ADA diabetes risk entity with logistic regression test

Variables	Presence of risk in ADA type 2 diabetes screening test result		
	OR	95% CI	p
Age, year	1.065	0.797-1.423	0.669
Sex (reference: male)	7.350	1.265-42.161	**0.026***
Profession, year	1.192	0.916-1.550	0.191
Monthly shift count (reference: ≤4 shifts)	10.185	0.425-244.066	0.152
BMI kg/m²	1.255	1.036-1.520	**0.020***
EV score	0.927	0.762-1.138	0.488

*p<0.05 binary logistic regression test.
EV: Eveningness, BMI: Body mass index, ADA: American Diabetes Association, OR: Odds ratio, CI: Confidence interval

experience, and fewer night shifts than younger nurses, as expected. Usually, 90% of the adult population is diagnosed with T2D at over 45 years of age (24). Similarly, in our study, the mean age of participants with diabetes risk was 43.43±5.21 years while the mean age of our study population was 32.25±6.99 years.

The prevalence of prediabetic syndrome, which means diabetes risk, is sexually biased in all populations studied (25). The male gender was significant for our study's DM risk screening results, but our search did not confirm it with glucose measures confirming prediabetic syndrome.

Vagos et al. (26) demonstrated that both EV and DI negatively correlated with age. Females are not different from males in MA but score significantly lower on EV and higher on DI. In the study by Rahafar et al. (27), men reported higher MA than women, whereas women reported higher DI than men. Regarding the country effect, Iranian participants reported the highest MA compared to Spaniards and Germans, whereas Germans reported higher DI than Iranians and Spaniards. Díaz-Morales and Puig-Navarro (28) showed in adolescents that boys reported higher morningness, whereas girls reported higher DI. In contrast, our study found that females had a lower DI score, and age had a positive correlation with the DI score. MA and EV scores were similar between males and females. We thought that gender and DI could change according to cultural features or occupations to explain the opposite results of our study.

Maidstone et al (29). divided a study population as day workers, shift workers, irregular shift workers and permanent night shift workers. They observed higher odds of asthma as a chronic disease in shift workers who never or rarely worked night shifts when compared with day workers. In our study, DI was related to older age and rare shift counts. However, age was negatively related to shift counts. Rare shift working may explain the association between older age and higher DI cause of rare shift counts of older nurses in our sampling.

The risk of developing T2D is 30% higher in those who slept 5 hours a day than in those who slept 7-8 hours (30). In our study, short sleep duration was accepted below 8 hours, but there was no difference in DM risk between short sleep keepers and other nurses.

In a study conducted with university students, the level of social jetlag was associated with a loss of sleep duration and increased BMI (31). A cohort study found that social jetlag was associated with an increased risk of diabetes/prediabetes (32) and predicted higher HbA1c levels in patients with T2D (33). Our study did not find any difference in social jetlag between the groups with and without DM risk.

A high level of social jetlag was linked to EV (34). Similarly, we found that nurses with abnormal social jetlag had higher EV. Didikoglu et al. (1) showed that an evening-type cluster was associated with traits related to increased smoking. The study of Başpınar and Basat (35) showed that while the ADA diabetes risk of smokers is 20.5%, there would be an increased risk of diabetes due to weight gain after quitting. Therefore, combining never-smokers and ex-smokers may have been a limitation for screening DM risk in this study. However, we found that smokers had a prolonged social jetlag time, higher EV, and lower MA than nonsmokers.

This study has several limitations. We performed screening through self-report. MESSi is a self-report questionnaire, but the gold methods for detecting chronotypes are monitoring techniques (e.g., core body temperature and melatonin levels) or altimetry as a noninvasive method (36). Similarly, the ADA T2D risk screening test is another self-report questionnaire. Therefore, self-reporting is a limitation of this present study, but MESSi and ADA tools were chosen because they are fairly simple and economically cost-effective methods. Finally, the number of people at risk of diabetes was low. Therefore, using a small sample size and a limited study group caused the results of our study not to be generalized. Studies with larger sample groups are required.

Conclusion

Participants with abnormal jetlag had circadian preference differences compared with normal subjects. No relationship was detected between social jetlag and DM risk. However, we concluded that circadian preferences such as DI and lower EV may be related to DM risk among nurses working shifts.

Ethics

Ethics Committee Approval: Ethical approval was obtained from İstanbul Provincial Health Directorate Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee with the date 08/09/2021 and no 324.

Informed Consent: The nurses included in the study were informed about the study, and their written consent was obtained.

Authorship Contributions

Concept: M.M., M.M.B., Y.T., Design: M.M., M.M.B., Y.T., Data Collection or Processing: M.M., M.M.B., Y.T., Analysis or Interpretation: M.M., M.M.B., Literature Search: M.M., M.M.B., Y.T., Writing: M.M., M.M.B., Y.T.

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Factors associated with unscheduled venous access port removal in cancer patients

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ABSTRACT

Aims: Implantable venous access ports (IVAP) are used in cancer patients to provide central venous circulation access. This study investigated the prognostic factors for IVAP removal among cancer patients.

Methods: A retrospective cohort study was conducted on cancer patients implanted with IVAP in the Hospital Universiti Sains Malaysia and followed up with at least one cycle of chemotherapy. The primary endpoint was unscheduled IVAP removal due to complications. Kaplan-Meier curves were used to estimate removal probability, and the log-rank test and Cox proportional hazards regression model were used to explore independent predictors.

Results: A total of 205 patients were included [mean, standard deviation (SD) age: 31.55 (22.45)]. More than half of the patients were male (53.2%) and of Malay ethnicity (91.2%). During the observation period, 222 IVAPs were implanted in 205 patients with predominantly solid cancers. During the mean follow-up of 15.03 (SD: 18.45) months, 28 complications were recorded. Prognostic factors for unscheduled IVAP removal were kidney disease [hazard ratio (HR): 8.33; 95% confidence interval (CI): 2.78, 24.90; p<0.001] and receiving no radiotherapy (HR: 5.25; 95% CI: 1.44, 19.11; p<0.012).

Conclusions: Cancer patients with kidney disease records or those who were not planned for radiotherapy were at higher risk of unscheduled IVAP removal.

Introduction

Due to the frequent infusions and the medication's severe vasculature irritancy, cancer patients taking chemotherapy require a central vascular device. The most popular option is implanted venous access ports (IVAP). In cancer settings, the use of IVAPs has recently increased, allowing easier repeated injections, infusions, and, optionally, blood collection (1). It is placed beneath the dermis where a catheter extends to the central vein and a needle is used to reach the subdermal reservoir (2).

IVAP was initially introduced by Niederhuber et al. (3) at the MD Anderson Cancer Center in Houston in 1982. Since then, it has been used for treating oncology diseases. The single BardPort with Grosong catheter has been used in the Hospital Universiti Sains Malaysia (USM), Kelantan, in cancer patients requiring long-term venous access to administer chemotherapy. Its port is made of plastic and titanium with single and dual lumens (power-injectable). An 8-F Grosong catheter is connected to single-lumen ports (4). The distal tip of the Grosong catheter, which was invented in 1978, featured a pressure-sensitive valve

with three positions. The valve opens under positive or negative pressure, effectively preventing unintended air embolism and spontaneous blood reflux. Because of its distinctive characteristics, it is more expensive.

Although IVAP allows convenient prolonged access to central veins with minimal disruption of lifestyle and discomfort (5), it is also associated with several complications, albeit less frequent than other venous access routes (6). IVAP-related complications not only prolong the length of hospital stay and reduce the life of infusion ports but also increase costs (6).

Several authors have reported that 46.2% of patients had their infusion port removed because of catheter-associated infections (7,8). Although infusion ports reduce the chance of bacterial infections, 3-10% of infusion ports are removed because of port-associated infections (9).

Various factors have been linked to IVAP complications, including age, gender, surgical technique, choice of puncture route, type of tumor (solid or hematologic), physical condition, chemotherapy type and care level (10,11). Hematologic malignancies are the most significant risk factors for catheter-associated infections (10), particularly in younger patients, which are linked to intense chemotherapy and neutropenia (12). In the current study, we explored the prognostic factors for IVAP removal due to complications among cancer patients.

Methods

Study design and sample size

This retrospective cohort study was conducted among cancer patients with IVAP at Hospital USM, Kelantan, Malaysia, between 1st January 2008 and 31st December 2014. Ethical approval was obtained from the Human Research and Ethics Committee of USM (USM/JEPeM/15090289 on 4th January 2016). Personal details, disease status, clinical characteristics, and other retrieved information were secured by identification number instead of patient name, registration number, and identification card number in the data collection form.

Inclusion and exclusion criteria

The inclusion criteria were a cancer diagnosis, an IVAP implant, and receipt of at least one cycle of chemotherapy. IVAP implantations in non-malignant diseases were excluded. In the case of IVAP renewal due to a complication, only the first procedure was recorded in the analyses. Patients transferred to other hospitals without a single chemotherapy cycle were excluded.

In the Hospital USM, orthopedic surgeons use the operating room to implant IVAP in cancer patients under aseptic conditions and general anesthesia. Depending on the patient's condition, a single type of IVAP (Bardport) made up of titanium and silicon rubber and connected with a 6-8 F silastic Grosong catheter in the cephalic vein, internal jugular vein, or femoral vein was placed in the enrolled patients. The position of the catheter tip was examined by fluoroscopy.

Data collection

Between January 2008 and December 2014, 420 cancer patients were implanted with an IVAP. From this pool, 220 patients were identified using a simple random selection procedure (Simple Random Sampling Generator in Microsoft Excel). After further exclusions, 205 patients formed the final study sample.

The endpoint was the removal of IVAP in patients with cancer due to complications. The observation was censored when the IVAP was not removed until study completion, or when the patient died, refused chemotherapy, was lost to follow-up, or was still under follow-up at the time of study completion.

Complications were classified as early and late. Early complications were those that occurred within 30 days of the procedure, including infections, malposition, and malfunction. Late complications were defined as complications that occurred after 30 days of the procedure, including infections, malposition, malfunction, and thrombosis.

Statistical Analysis

Data were evaluated using Stata SE version 11 (Stata Corp, 2009). Descriptive analysis was used to report sociodemographics, comorbidities, clinical characteristics, surgery type, and complications. Results are presented as frequency [percentage (%)] for categorical variables and mean [standard deviation (SD)] for numerical variables.

Kaplan-Meier curves were used to estimate the removal probability, and the log-rank test and Cox proportional hazard regression model were used to explore independent predictors. The results are shown as the hazard ratio (HR), 95% confidence interval (CI), and p-value. The cut-off for statistical significance was $p<0.05$.

Results

The mean age was 31.55 years (SD 22.45), with male (53.2%) and Malay predominance (91.2%) (Table 1). The majority of cases were lung cancer (22.9%). Of the 205 patients, 9.8% had diabetes mellitus, 17.6% had hypertension, 12.7% had liver disease, and 4.4% had heart disease.

Table 2 shows the clinical characteristics of cancer patients treated with IVAP. The insertion site of the catheter was the cephalic vein in most patients (97.6%). The majority of insertions were on the right side (92.7%). The oncology ward was the primary care site after implantation (61.9%), followed by the general ward.

Approximately two-thirds of the patients had solid cancer (68.3%), of which 36.6% were carcinoma type and 31.7% were sarcoma type. Hematologic malignancies were recorded

by 31.7%, of which 18.0% were lymphoma and 13.7% were leukemia. The most common cancer types were bone cancer (31.7%), lymphoma (18.0%), leukemia (13.7%), and gastrointestinal tract (17.6%). Other cancer types (19.0%) were hepatobiliary, gynecologic, nasopharyngeal, breast, genitourinary, and neuroblastoma. Most cancers were in the advanced stage (68.3%). Metastases were recorded by 42.9%. Relapse was 5.9%. Chemotherapy was completed in 56.6% of the patients. A history of surgery was recorded by 10.7% and radiotherapy was recorded by 49.8%.

Table 1. Socio-demographic characteristics of cancer patients with IVAP in Hospital Universiti Sains Malaysia (n=205)

Variables	n (%)
Age (years)*	31.55 (22.45)
Gender, male	109 (53.2)
Ethnicity	
Malay	187 (91.2)
Non-Malay	18 (8.8)
Educational level	
Tertiary	29 (14.1)
Secondary	79 (38.5)
Primary	59 (28.8)

IVAP: Implantable venous access ports

Table 2. Clinical characteristics of cancer patients with IVAP (n=205)

Variables	n (%)
Insertion site	
Cephalic vein	200 (97.6)
Others	5 (2.4)
Insertion side	
Right	190 (92.7)
Left	15 (7.3)
Ward of care	
General	80 (39.0)
Oncology	125 (61.0)
Types of cancer	
Solid	140 (68.3)
Hematologic	65 (31.7)
Stage of cancer	
I-II	65 (31.7)
III-IV	140 (68.3)
Metastases of cancer	88 (42.9)
Relapsed of cancer	12 (5.9)
Chemotherapy regime, complete	116 (56.6)
Surgery	
Yes	22 (10.7)
Not applicable	183 (89.3)
Radiotherapy	
Yes	102 (49.8)
Not applicable	103 (50.2)

IVAP: Implantable venous access ports

During the observation period, 222 IVAPs were implanted in 205 patients with predominantly solid cancers. During the mean follow-up of 15.03 (SD: 18.45) months, 28 complications were recorded. IVAP removal was recorded in 17 of these complications, and a second port was implanted. All patients received at least one cycle of chemotherapy through the device after insertion.

Four of the 28 complications were classified as early, and one was infection leading to IVAP renewal. Three were due to the malposition of the port. Two malpositions did not require port removal but required intervention for readjustment. One malposition resulted in IVAP renewal.

Delayed or late complications were recorded in 24 (11.7%) patients. Eleven (45.8%) were infected, 6 (25.0%) were malfunctioned, 4 (16.7%) were thrombosed, 2 (8.3%) were malpositioned, and 1 (4.2%) was dislodged (Table 3). Five (45.5%) of infected ports required IVAP removal, while the remaining cases were successfully treated with antibiotics. All four thrombosed catheters required removal because anticoagulants were ineffective. Only one (16.7%) malfunctioning port did not require removal. There was only one case of a dislodged port necessitating removal.

Up to 1 month, the probability of IVAP removal was 0.98 due to complications, whereas it was 0.92 up to 6 months, 0.91 up to 12 months, and 0.88 up to 24 and 36 months (Table 4). The removal probabilities decreased over time. The maximum time for IVAP removal was 27 months.

Table 5 shows the prognostic factors associated with IVAP removal due to complications. Kidney disease (adjusted HR: 8.33; 95% CI: 2.78, 24.90; p<0.001) and receiving radiotherapy (adjusted HR: 5.25; 95% CI: 1.44, 19.11; p=0.012) were the two independent factors.

Table 3. Complications of cancer patients with IVAP (n=205)

Complications, n (%)	177 (86.3)
Early complications	4 (2.0)
Infected port	1 (25.0)
Malposition	3 (75.0)
Late complications	24 (11.7)
Catheter dislodge	1 (4.2)
Malposition	2 (8.3)
Malfunction	6 (25.0)
Thrombosed-catheter	4 (16.7)
Infected port	11 (45.8)

IVAP: Implantable venous access ports

Discussion

IVAP is used more frequently than in the past, mostly in cancer patients for its benefits in preventing repetitive punctures and irritation and safety in long-lasting treatment schedules (13). It is suitable for high-concentration medications, reduces the discomfort caused by frequent venipuncture, prevents damage to peripheral superficial veins, and reduces restrictions in daily activities, ultimately improving quality of life (13). Its maintenance is also easier after wound healing. Such benefits encourage IVAP placements, particularly for cancer patients requiring long-term, ambulatory chemotherapy.

The introduction of IVAP has resolved many challenges in venous access in patients with cancer (14). However, IVAPs may also cause harm through infections, wound gaping and thrombosis (15), requiring their removal before the completion of chemotherapy. Numerous studies have shown that 10% of patients may require IVAP removal because of catheter-related infections and thrombotic events (16-19). Catheter removal may also be necessary because of thrombotic occlusion. In case of potential recurrence, the port is sometimes maintained during follow-up (20-22).

The overall complication rate in our study was 13.7%, similar to previous studies, which reported rates between 6.9% and 17.7% (23). In the worst case, IVAP-associated complications lead to IVAP removal. Nevertheless, every single removal puts the patient at additional risk by delaying ongoing chemotherapy and making parenteral nutrition difficult, ultimately resulting in increased morbidity, mortality, and costs (24).

With the progress in the types of equipment and surgical techniques, the most frequent complications became catheter-associated infections and thrombosis (17,25). In the current study, infections occurred in 12 patients, and it as the most common complication and reason for IVAP removal. A total of 17 catheters were removed and required renewal. These results align with those of earlier studies that indicated IVAP-related infections as the most frequent reason for port removal (26-28). The other complications included port malfunction, malposition, thrombosed catheter, and catheter dislodging from the port.

No immediate or procedural complications were recorded in the current study. This finding may be related to the improved surgical practices in the Hospital USM. The cut-down surgical technique was reported as the only approach to prevent possible fatal complications compared with other techniques (29).

This study suggests that IVAPs implanted on the left side may be particularly vulnerable to catheter thrombosis. Additionally, IVAPs implanted on the right side were associated with fewer complications and lasted longer than IVAPs implanted on the left. This finding may be explained by the fact that the left brachiocephalic vein forms a wider angle with the superior vena cava. When the catheter is positioned on the left side, downward pressing of the catheter may harm the endothelium. However, in this study, out of four patients with the thrombosed catheter, only one patient had a catheter inserted on the left side, and only one of 15 left-sided catheters was related to a complication.

Complications of IVAP often result in removal, prolonged hospital stay, intensive care unit admission, and death (30). Infection is the most common complication associated with IVAP (31). In particular, IVAP infection has a high morbidity rate and can result in early removal of IVAP (30). In addition, infections increase the length of hospital stay, morbidity, mortality, long-term antibiotic use, and costs (31,32).

Kidney disease was a prognostic factor for IVAP removal in the present study. This observation suggests that cancer patients with kidney disease had a higher risk of IVAP removal

Table 4. The overall removal probabilities of IVAP due to complications among cancer patients (n=205)

Time	Overall removal probabilities (95% CI)
1 month	0.98 (0.95, 0.99)
6 months	0.92 (0.87, 0.95)
12 months	0.91 (0.86, 0.95)
24 months	0.88 (0.81, 0.93)
36 months	0.88 (0.81, 0.93)

IVAP: Implantable venous access ports, CI: Confidence interval

Table 5. Prognostic factors of IVAP removal due to complications among cancer patients (n=205)

	Simple Cox regression			Multiple Cox regression		
	B	Crude HR (95% CI)	p	B	Adjusted HR (95% CI)	p
Kidney disease						
No	-	1.00	-	-	1.00	-
Yes	1.85	6.33 (2.16, 18.56)	**0.001**	2.12	8.33 (2.78, 24.90)	**<0.001**
Radiotherapy						
Yes	-	1.00	-	-	1.00	-
Not indicated	1.41	4.08 (1.15, 14.48)	**0.029**	1.66	5.25 (1.44, 19.11)	**0.012**

Backward log-rank Cox proportional hazard regression model applied.
Log-minus log plot, hazard function plot and partial residual were used to check the model assumptions.
IVAP: Implantable venous access ports, CI: Confidence interval, HR: Hazard ratio

due to complications. However, the explanation for this novel finding is difficult; because no previous study has reported a similar finding.

Another significant factor for IVAP removal was no radiotherapy treatment. Radiotherapy may not be suitable for patients with advanced cancer, cachexia, significant weight loss, severe dehydration, and inadequate nutrition. The current findings suggest that cancer patients with worse health conditions may be more prone to complications resulting from IVAP removal. In our dataset, some esophageal cancer patients had perforations precluding radiotherapy.

Some limitations of this study should be acknowledged. First, the retrospective cohort design may cause selection bias. Consistent with this, we identified up to 50% loss to follow-up in the registry. Improper follow-up may be related to late complications that can be prevented early. Second, the data retrieved from the medical records may cause information bias. Clinical records may not always be suitable for research. Finally, missing or unrecorded data (e.g., body mass index) reduces the number of critical variables in the adjusted analyses.

Conclusion

This study found that cancer patients with kidney disease and those who were not planned for radiotherapy had a higher risk of IVAP removal due to complications. Further studies with prospective enrollment and targeted follow-up are required to confirm these results and identify other predictors of unscheduled IVAP removal.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Human Research and Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/15090289 on 4th January 2016).

Informed Consent: Retrospective cohort study.

Authorship Contributions

Surgical and Medical Practices: N.N.N., A.H.S-A., S.Y., Concept: N.M.M., N.N.N., A.H.S-A., S.Y., Design: N.M.M., N.N.N., A.H.S-A., S.Y., Data Collection or Processing: N.M.M., A.H.S-A., Analysis or Interpretation: N.M.M., N.N.N., A.H.S-A., S.Y., W.N.A.W.A., Literature Search: N.M.M., N.N.N., A.H.S-A., S.Y., W.N.A.W.A., Writing: N.M.M., W.N.A.W.A.

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Adenocarcinoma of the lung mimicking interstitial lung disease

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Keywords: Adenocarcinoma, interstitial, pneumonia

ABSTRACT

Atypical radiologic and clinical patterns may be observed within subgroups of lung adenocarcinoma. A 74-year-old man with progressive dyspnea and productive cough unresponsive to antibiotherapy showed bilateral interstitial changes in the lung parenchyma on computed tomography. We here report a patient followed up with a prediagnosis of interstitial lung disease but eventually diagnosed with lung adenocarcinoma following transthoracic lung biopsy.

Introduction

Adenocarcinoma is the most common histological subtype of non-small-cell lung cancer. In our country, lung cancer is the most common subtype, constituting approximately 45-50% of lung cancer cases, and its relative frequency is increasing. More than 70% of cases are diagnosed at an advanced stage (1). Primary lung carcinomas may present with various radiological appearances. In particular, in subgroups of lung adenocarcinoma, atypical radiologic and clinical patterns may be observed (2). While lung adenocarcinomas frequently present as solitary nodules, patchy, lobar, or multilobar infiltration with air bronchograms that are often indistinguishable from pneumonia and rarely as bilateral reticulonodular involvement, giving the impression of interstitial lung disease (ILD) may also be observed (3,4). In such situations, the most precise and rapid methods for diagnosis should be the priority, and definite treatment should start as soon as possible. In this article, we report a patient under follow-up with a prediagnosis of ILD but eventually diagnosed as primary lung carcinoma by transthoracic lung biopsy (TTLB).

Case Presentation

A 74-year-old man was admitted to the outpatient clinic with complaints of cough with sputum and increasing dyspnea that did not improve despite antimicrobial treatment with cephalosporin. He had a history of working in a cement factory many years ago and was diagnosed with hypertension, diabetes mellitus, and

chronic renal failure. He had no history of smoking or alcohol use. Physical examination revealed only diffuse rales in bilateral lungs. FEV1, FVC, and FEV1/FVC were 60% (1.52L), 60% (2L) and 73.40, respectively. Arterial blood gas analysis revealed no hypoxia or hypercarbia. The biochemical test results were within the normal range. Procalcitonin and C-reactive protein levels were normal. Radiography revealed bilateral diffuse nonhomogeneous opacity in the middle and lower zones (Figure 1). Thorax computed tomography (CT), including high-resolution CT sections, revealed diffuse ground-glass areas (GGA), interstitial changes in bilateral lung parenchyma, and marked emphysematous changes in the upper lobes (Figure 1). On the other hand, similar findings with some progressions were observed on the thoracic CT obtained 9 months ago.

Severe acute respiratory syndrome-coronavirus-2-polymerase chain reaction tests were negative, and the patient was hospitalized with a preliminary diagnosis of pneumonia. Despite antimicrobial treatment with a combination of macrolide and cephalosporin, no improvement was observed in lung images. Bronchoalveolar lavage (BAL) was obtained from the right middle lobe. BAL fluid-based cytology showed increased polymorphonuclear leukocyte count, no microbial growth on culture, and no atypical cells, leaving no definitive diagnosis. Rheumatologic markers were also negative. To exclude ILD and malignancy, a tru-cut parenchymal biopsy using a transthoracic approach was performed from the middle lobe of the right lung because of diffuse bilateral interstitial and alveolar infiltration on thorax CT. ILD was not confirmed on histological examination. On the other hand, the specimens were positive for TTF-1 and napsin A. In addition, a lepidic, micropapillary lesion was reported (Figure 2). According to the pathologist, the biopsy revealed a limited area, and the morphologic findings were consistent

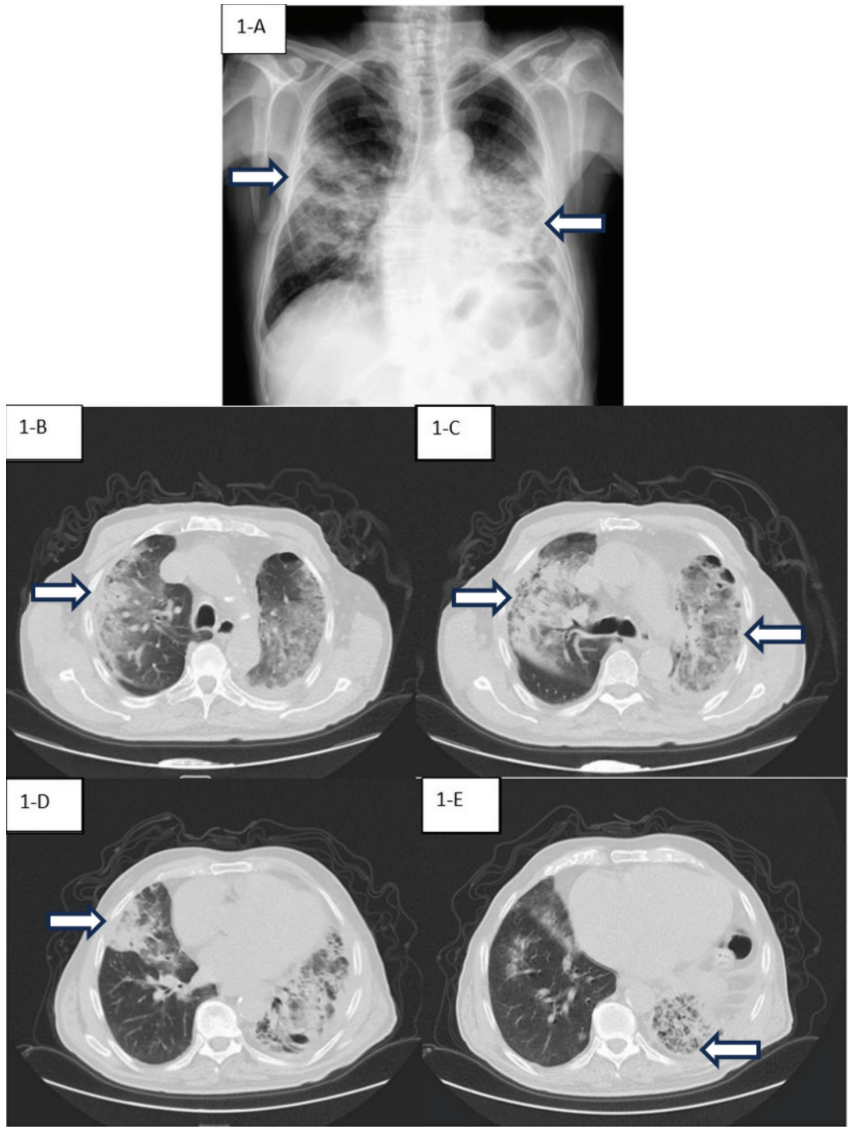

Figure 1. A) Non-homogeneous opacity increase in bilateral middle and lower zones on chest radiography. B-E) Bilateral ground-glass opacities, consolidation areas, and interstitial pattern on thoracic computed tomography

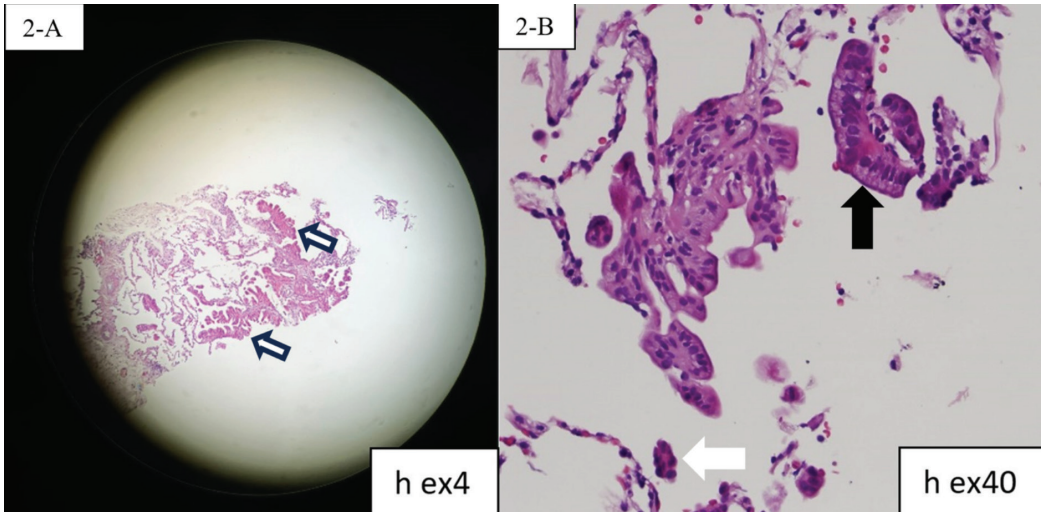

Figure 2. A) Pathological image; both arrows point to lepidic pattern and micropapillary pattern (right lung middle lobe tru-cut biopsy) [hematoxylin-eosin (H-E), x4]. B) Lepidic pattern (black arrow), micropapillary pattern (white arrow) (H-E, x40)

with minimally invasive adenocarcinoma when combined with the patient's epicrisis. Based on clinical, radiological, and pathological findings, the patient was diagnosed with lung adenocarcinoma. Rebiopsy was not planned. The sample obtained by the tru-cut biopsy was insufficient for a mutation analysis and, therefore, could not be performed. The patient was referred to the chemotherapy unit.

Discussion

Adenocarcinoma is the most common histologic subtype of lung cancer and is the leading cause of mortality worldwide. Approximately 90% of invasive lung adenocarcinomas have a complex heterogeneous histopathological structure (5). Depending on the histologic subtype, radiological appearances may vary broadly. Radiologically, it is most often a solitary or multiple nodule. However, lobar or multilobar localization, consolidation, GGA, centrilobular or bronchocentric lesions with a nodule or mass appearance, or reticular opacities may develop (1).

Detterbeck et al. (6) described a pneumonic-type lung adenocarcinoma presenting with pneumonia-like infiltration or consolidations in the lung that may present with dyspnea, cough, and fever and is characterized by GGA or consolidation resembling infectious or ILD on thorax CT. Because of these features, lung adenocarcinomas are often called "masqueraders" (7). In these cases, diagnosis should be made as soon as possible using the most accurate tools to provide timely treatment.

The current study presents a rare case of lung adenocarcinoma with bilateral GGA, consolidated areas, and a reticular interstitial pattern (3). In the differential diagnosis, infectious causes, collagen vascular diseases, and acute exacerbations of ILD were considered prediagnosis. Mir et al. (8) made a diagnosis of adenocarcinoma after 2 years of follow-up of a consolidation covering almost the entire left lower lobe without worsening the patient's clinical status and without significant change in the size of the lesion. Despite antimicrobial therapy, the existence of bilateral multilobar consolidation and GGA on lung imaging suggested malignancy. Detailed anamnesis (occupational-environmental exposure), radiologic imaging, sputum analysis, serologic tests, pulmonary function tests, bronchoscopy, BAL, transbronchial lung biopsy, and video-assisted thoracoscopic surgery (VATS) are the recommended diagnostic methods (9). A prompt tissue sampling should be performed to provide a clear diagnosis. In this study, the diagnosis was TTLB. At the diagnostic stage, VATS may be preferred to TTLB because a mutation analysis will require more samples.

Conclusion

Adenocarcinoma of the lung may present with atypical radiologic and clinical findings. This report emphasizes the importance of adenocarcinoma in the differential diagnosis of ILD.

Ethics

Informed Consent: The patient provided written, informed consent.

Authorship Contributions

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

Conflict of Interest: No conflict of interest was declared by the authors.

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Massively enlarged wandering spleen with ruptured epidermoid cyst

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Keywords: Spleen, splenic cyst, wandering spleen, splenectomy

ABSTRACT

Wandering spleen is extremely uncommon, with a reported incidence of <0.5%. A cyst within the spleen is also uncommon. The majority of primary splenic cysts fall into the epithelial cyst category. The affected patients present with atypical symptoms, like feeling fullness in the left upper abdomen and a palpable mass. The treatment of a large wandering splenic cyst is an open splenectomy. This case presents a unique combination of a wandering spleen with a huge ruptured cyst, featuring an unusual right lower abdominal and pelvic location, a twisted pedicle, and a remnant of normal splenic parenchyma, collectively constituting an exceedingly rare clinical scenario.

Introduction

The wandering spleen lacks normal attachments, connected by a vascular pedicle. Twisting can cause ischemia. Rarely, a splenic cyst occurs even rarer in a wandering spleen (1). They can be parasitic (hydatid), brought on by the parasite *Echinococcus granulosus*. The two main types of nonparasitic cysts are primary (epithelial), which are covered by an epithelial layer (epidermoid, dermoid, and mesothelial) or endothelial layer (hemangioma, lymphangioma), and secondary (pseudocysts, non-epithelial), which are typically the result of trauma (2). We here report a unique combination of a wandering spleen and a splenic cyst, delving into the potential causes, diagnostic challenges, and surgical approach.

Case Presentation

A 39-year-old nulliparous female with no known medical illness was admitted with a chief complaint of abdominal mass and generalized abdominal discomfort for 4 months. She reported increasing abdominal pain during the past 2 months. The mass had been growing gradually and was associated with vomiting episodes. She had no constitutional symptoms like weight loss, reduced appetite, or fever. Physical examination revealed a huge, hard tumor of approximately 20.0 x 15.0 cm (Figure 1A). Ultrasonography revealed an enlarged spleen of 16.0 cm in diameter. Moreover, a well-defined, large, anechoic lesion was detected in the top and mid poles of the spleen, with a remnant of normal splenic parenchyma at the lower pole.

There was very little echogenic moving debris, and no solid components or calcification (Figure 2A). Contrasted computed tomography (CT) scan of the abdomen showed that the spleen was situated abnormally in the right lower abdomen and pelvis. There was a large, clearly defined cystic lesion in the spleen measuring 12.8 x 17.5 x 14.7 cm (AP x W x CC) in size. The cystic mass within the wandering spleen showed the features of a ruptured cyst (Figures 2B, 2C).

An exploratory laparotomy and splenectomy were performed. Intraoperatively, a huge wandering spleen was observed, which occupied the abdomen with a twisted pedicle. The patient was stable postoperatively and was discharged home after 5 days of admission. The patient received oral penicillin and pneumococcal vaccinations as per the protocol post-splenectomy. Upon follow-up at 4 weeks, she was well without any surgical complications or recurrence. Histopathological examination of the cyst revealed a thin fibrous wall partly lined by squamous, transitional, and flat cuboidal epithelium, consistent with an epidermoid cyst.

Discussion

A normal spleen maintains its anatomical position by a few ligaments, including the gastrosplenic, lienorenal, and phrenicocolic ligaments. A relatively uncommon disorder known as wandering spleen is characterized by the lack of all ligaments or the weakening of one or more of those ligaments (3). Echinococcus granulosus is a common type of parasitic splenic cyst.

The typical presentation of a wandering spleen is a mass with abdominal pain, but it may also present without any symptoms (4). The patient's primary concern was the presence of an abdominal mass. The patient described the mass as occupying a significant portion of her abdomen. In some patients, local inflammation of the left diaphragm may induce a chronic cough, and pressure in the cardiorespiratory system may cause pleuritic pain or dyspnea (5). Patients with acute torsion may exhibit acute severe abdominal pain, which often precedes fever and vomiting. In this instance, the patient could have experienced an acute-on-chronic presentation, given the gradual enlargement of the abdominal swelling over the preceding 4 months.

When examining chronic abdominal pain and the presence of an abdominal mass, it is important to include a splenic cyst as a possible consideration in the differential diagnosis. The unique features of splenic cysts on imaging help differentiate them from other conditions, such as ovarian cysts, gastrointestinal tumors, splenic tumors, or abdominal abscesses (6). For the acute abdomen, key biomarkers like whole blood count, serum lactate, lactate dehydrogenase, and blood urea nitrogen levels aid in early detection (7,8).

Ultrasonography is the preferred initial diagnostic method because it reveals the absence of the spleen in the left upper quadrant of the abdomen and indicates the presence of a solid mass in the abdomen or pelvis, consistent with our case. However, this method is operator-dependent, and bowel gas might obscure the findings (9). Typical CT findings for wandering spleen include the absence of the spleen anterior to the left

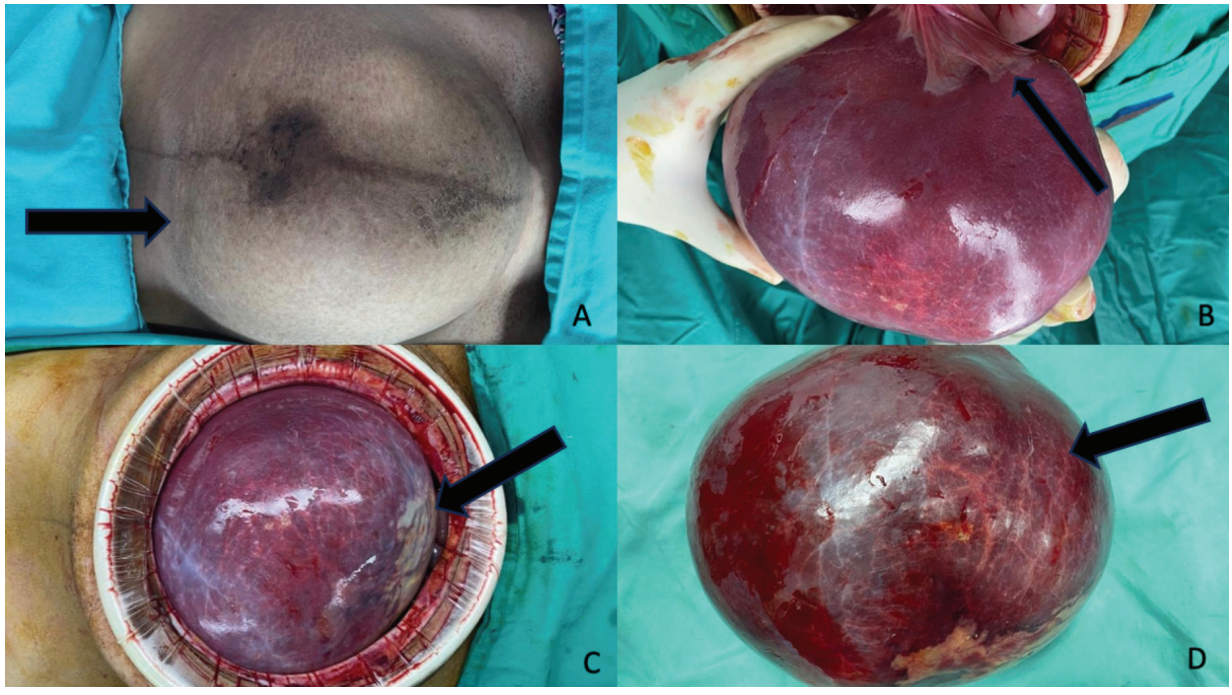

Figure 1. A) Abdominal examination revealed abdominal mass occupying the whole region of the abdomen and mimicking a termed size of the gravid uterus. B) A huge wandering splenic cyst with a twisted pedicle. However, the spleen was healthy and had no sign of ischemia/necrosis. C) A wandering spleen. D) Post-open splenectomy specimen showed wandering spleen with splenic cyst measuring 20 x 17 cm and weighed 2200 gm

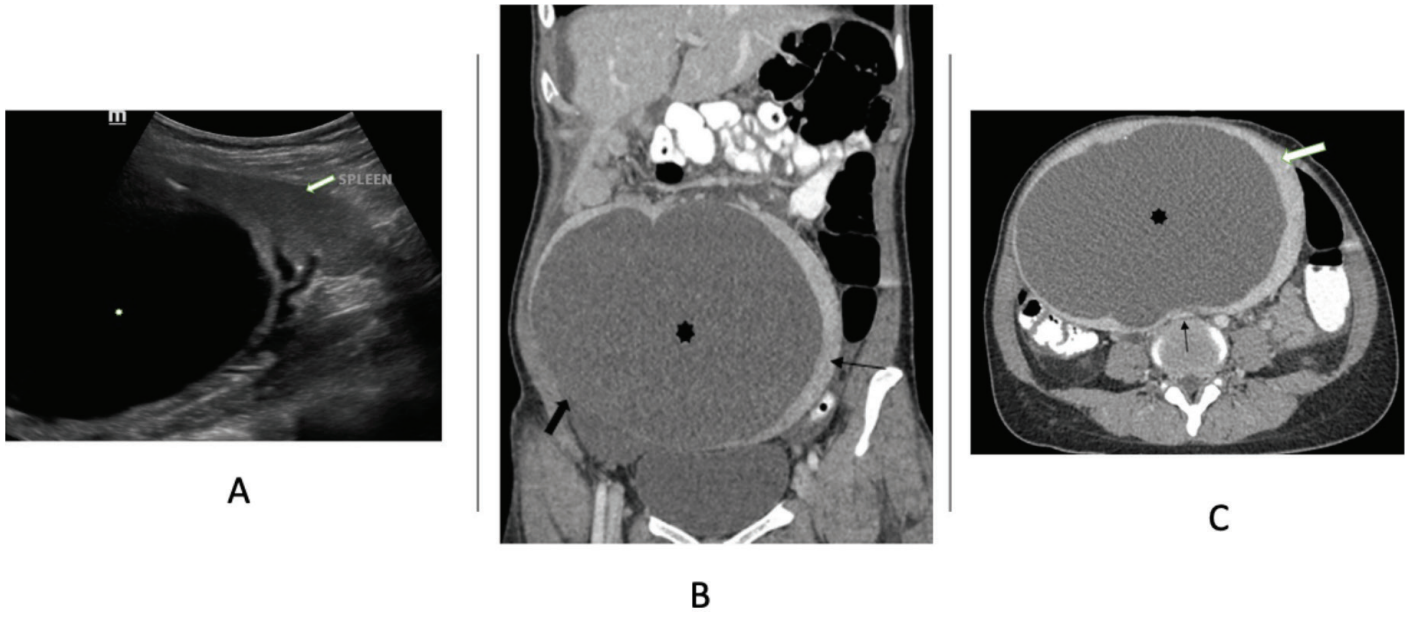

Figure 2. A) Ultrasound of the abdomen shows a large anechoic lesion (*) in keeping with the cyst occupying the spleen with remaining splenic parenchymal tissue (white arrow). B) Coronal view CT scan shows a large cyst (*) with the spleen (thin arrow). There is very thin remaining splenic parenchyma at the right lateral aspect with some areas showing focal discontinuity (big arrow) communicating with adjacent free fluid related to splenic rupture. C) Axial view CT scan shows spleen parenchymal tissue (big white arrow) at the lower abdomen with a large hypodense lesion (*) within in keeping with a cyst causing compression onto the left common iliac artery (thin black arrow). There is no solid component or septation within the cyst

CT: Computed tomography

kidney and posterior to the stomach with visualization of an abdominal or pelvic mass with homogenous or heterogenous splenic parenchyma enhancement (9). In this particular case, the spleen demonstrates regular enhancement without signs of splenic infarction. Nevertheless, a sizable cyst within the spleen exerts pressure on the splenic parenchyma and creates a mass effect on adjacent structures.

In the presented case, the cysts prompted clinical manifestations. Moreover, the CT image raises the suspicion of a ruptured cyst. As a result, surgical management was necessary. Treatment for a wandering spleen with a splenic cyst depends on cyst characteristics, patient health, and cyst size (10). Surgical options include open splenectomy or laparoscopic removal to preserve spleen function and manage associated risks. The laparoscopic approach is possible. Before the advent of laparoscopic surgery, primary splenic cysts are surgically managed with puncture, drainage, and marsupialization. However, splenic cysts can only be removed through laparoscopy if they are at the splenic poles or boundaries (11). Because of the risk of uncontrolled hemorrhages parenchymal cysts should not be drained. This is also applied for large splenic cysts where open splenectomy is the choice because of the possibility of significant complications (12). Considering our provisional diagnosis of a splenic cyst in a wandering spleen with a potential ruptured spleen, we opt for open splenectomy as the preferred surgical intervention (13).

Conclusion

In conclusion, this case emphasizes the need to consider rare conditions like wandering spleen with a cyst in patients with abdominal masses and pain. Accurate diagnosis, aided by advanced imaging, enables effective surgical intervention and enhances patient care and medical insights.

Ethics

Informed Consent: Informed consent was provided by the participant.

Authorship Contributions

Surgical and Medical Practices: M.N.S.C.J., W.Z.W.Z., S.B., Concept: W.Z.W.Z., Design: F.H., Analysis or Interpretation: A.D.Z., Literature Search: S.B., Writing: M.N.S.C.J., F.H.

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