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Patients have a right to privacy. When not essential, identifying information, patient names and photographs should not be published, unless the written informed consent of the patient (parent or guardian) has been given.

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Original Articles

Case Report

Original Article

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Comparison of the Diagnostic Accuracy of the Gamma-Glutamyl Transpeptidase to Platelet Ratio and Systemic Inflammation Response Index in Non-Alcoholic Fatty Liver Disease

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Abstract

Aim: The aim of this study was to evaluate the diagnostic usability of the systemic inflammation response index (SIRI) and the gamma-glutamyl transpeptidase to platelet ratio (GPR) in non-alcoholic fatty liver (NAFL).

Methods: This is a case-control study that was conducted with patients who came to a hospital for a check-up between July 2020 and July 2021, in the internal medicine outpatient clinic of a tertiary care university hospital. The existence and severity of NAFL were confirmed with ultrasonography, and patients were divided into two groups, mild and advanced, according to the severity of NAFL. Body mass index (BMI), alanine aminotranspherase (ALT), aspartate aminotranspherase (AST), gamma-glutamyl transpeptidase (GGT), complete blood count parameters, and erythrocyte sedimentation rates (ESR) were compared between groups.

Results: In total, 665 patients were enrolled in the study, and in 347 (52.3%) of them, the existence of NAFL was confirmed. Of the patients who had NAFL, 184 had mild (grade1), whereas 163 had advanced (grade 2 and 3) steatosis. The differences were significant in age and gender distribution, BMI, ESR, ALT, AST values, GPR, AST to platelet ratio (APRI), and fibrosis-4 (FIB-4) scores between the NAFL and control groups. Univariate regression analyses revealed an increased risk for the development of NAFL in BMI, ALT, AST, ESR, GPR, APRI, and FIB-4 variables. Age, BMI, GPR, and ALT were found to be independent risk factors for the development of NAFL in multivariate analyses. Gamma-glutamyl transpeptidase to platelet ratio was found to be the most effective parameter for predicting the existence of NAFL.

Conclusion: The gamma-glutamyl transpeptidase to platelet ratio is a new and simple marker for predicting the existence of NAFL.

Keywords: Gamma-glutamyl transpeptidase, inflammation, non-alcoholic fatty liver disease, platelet count

Introduction

Non-alcoholic fatty liver (NAFL) is a major reason for chronic liver disease and has a remarkable prevalence of 25-45% (1). In NAFL, chronic inflammation occurs, and it has an important role in the development of NAFL. Hepatocytes can store some fat, but when the amount increases above cell tolerance limits, inflammation starts (2). Non-alcoholic fatty liver has been linked to the severity of inflammation (3).

A liver biopsy result is the gold standard in the diagnosis of NAFL, but liver biopsy has its own risks and is an invasive procedure (4). Because of this, there is a need for novel, easily applicable, and non-invasive diagnostic approaches to NAFL. The relationship between NAFL and inflammatory markers was investigated previously; a fibrosis index score based on four factors fibrosis-4 (FIB-4), red cell diameter width (RDW) to platelet count ratio (RPR), and aspartate aminotransferase (AST) to platelet ratio index (APRI) were inspected (5-8).

The efficiency of the gamma-glutamyl transpeptidase to platelet ratio (GPR) to demonstrate the severity of fibrosis in the liver as a novel marker, was investigated in chronic hepatitis B, autoimmune hepatitis, cystic fibrosis, and drug-induced liver injury cases (9-13). A novel marker: systemic inflammation response index (SIRI), was reported to be effective in demonstrating the prognosis of the patients who had hepatocellular cancer (14). To our

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knowledge, the effectiveness of these novel markers in the diagnosis and demonstration of the severity of NAFL had not previously been reported in the literature.

The purpose of this study was to assess the diagnostic performance of GPR and SIRI in NAFL diagnosis and to demonstrate the severity of the disease. These two markers will also be compared with the previously reported markers used in the NAFL.

Materials and Methods

Compliance with Ethical Standards

This observational retrospective study was conducted with patients who came for check-ups between July 2020 and July 2021 to the internal medicine outpatient clinic of a tertiary care university hospital. This study was approved by the Lokman Hekim University Non-Invasive Clinical Research Ethics Committee (approval no: 2021154, date: 23.12.2021). All of the patients who took part in the study provided informed written consent. This study was conducted according to the Declaration of Helsinki directives.

Inclusion Criteria

Patients who had complete information about the inspected variables for the study-alanine aminotransferase (ALT), AST, gamma-glutamyl transpeptidase (GGT), complete blood count, and ultrasonography for the abdomen-in the hospital computer database were included.

Exclusion Criteria

Patients with liver diseases, malignancies, or who consumed more than 20 g of alcohol per day were excluded from the study, as were patients under the age of 18.

Patients were evaluated with hepatobiliary ultrasonography, which was performed by a 12-year-experienced radiologist with a GE Voluson 730 ultrasonography device (GE Medical Systems, Kretztechnik GmbH, Austria). Patients in whom fatty liver disease was detected were divided into two subgroups: mild (grade 1) and advanced (grade 2 and 3). Body mass index (BMI), AST, ALT, and erythrocyte sedimentation rate (ESR) data of all participants were recorded, and comparisons were made between groups according to the existence of NAFL and the severity of NAFL in patients with NAFL.

Criteria to determine the existence of fatty liver in an ultrasonographic evaluation

• Patients with no fatty liver; the liver's echogenicity is lower than that of the kidneys.

• Patients who have a fatty liver; In mild fatty liver, the echogenity of the liver is increased, periportal vascularity can be differentiated, and diaphragmatic echogenity is distinct compared with liver echogenity.

In advanced fatty liver, the echogenity of the liver is remarkably increased, and periportal vascularity and/or diaphragmatic echogenity cannot be distinguished from liver echogenity (15).

Calculations used in the study

Body mass index was calculated by dividing body weight in kilograms by the square of the height in meters. Calculations were made according to the following formulas;

RPR=RDW (%)/Platelet count ($\times 10^9$/L),

GPR=GGT (U/L)/Platelet count ($\times 10^9$/L),

FIB-4=age (years) ×AST (U/L)/[platelet count (10^9/L)×(ALT (U/L)1/2],

APRI=AST (U/L)/platelet count (10^9/L),

NLR=neutrophil count (10^9/L)/lymphocyte count (10^9/L)

SIRI=neutrophil count (10^9/L)×monocyte (10^9/L)/ lymphocyte count (10^9/L).

Laboratory Data

After a 12-hour fast, blood samples were collected. Whole blood counts were analyzed on a Sysmex XN-1000 (USA) device. Alanine aminotranspherase, GGT, and AST were analyzed by a Roche Hitachi Cobas 501 (Switzerland) device. Erythrocyte sedimentation rates were determined using a Biosed 100 (Italy) device.

Statistical Analysis

The SPSS for Windows 25.0 statistical software package (SPSS Inc., Armonk, NY, USA) was used for statistical analysis of the data. Data distributions or normality tests were evaluated by the Shapiro-Wilk test. Data for normally distributed variables were shown as the mean and standard deviation. The comparisons between groups were evaluated by a One-Way ANOVA and an independent t-test. P-values below 0.05 were considered significant. The risk factors for NAFL were investigated by univariate and multivariate logistic regression analyses. In the receiver operator characteristics (ROC) curve, the area under the curve was used to determine the diagnostic power in predicting NAFL.

Results

A total of 665 patients were included in the study, with 338 (50.8%) males and 327 (49.5%) females. The mean age of participants was 48.28±15.09 (males; 45.01±14.20, females; 51.67±15.26). Non-alcoholic fatty liver was confirmed in 347 (52.3%) participants. In the study group who had NAFL, age, gender, BMI, ESR, ALT, AST, GPR, APRI, and FIB-4 parameters were significantly different from those in the group without NAFL (Table 1).

Table 1. Demographic characteristics and laboratory data of participants with and without non-alcoholic fatty liver

Parameter	NAFL (+) (n=347)	NAFL (-) (n=318)	p-value
Age (years, mean±SD)	51.53±12.62	44.74±16.71	**<0.001**†
Gender (male/female ratio)	191/156	147/171	**0.023**‡
Body mass index (mean±SD)	29.12±4.48	25.41±3.88	**<0.001**†
Erythrocyte sedimentation rate (mm/hour)	18.41±13.66	15.80±12.83	**0.014**†
Red-cell diameter width (%)	13.58±1.86	13.36±1.72	0.119†
ALT (IU/L)	29.22±22.72	20.01±14.22	**<0.001**†
AST (IU/L)	22.15±17.48	18.04±6.39	**<0.001**†
Platelet count (×10^9/L)	273.66±71.92	264.56±66.44	0.092†
GPR	0.13±0.13	0.08±0.07	**<0.001**†
NLR	2.10±1.62	2.17±1.54	0.569†
APRI	8.86±8.04	7.22±3.20	**0.001**†
FIB-4	0.88±0.6	0.78±0.49	**0.016**†
SIRI	1.51±2.0	1.43±1.63	0.587†
RPR	0.05±0.02	0.05±0.02	0.485†

†Student's t-test, ‡Chi-square test SD: Standard deviation, NAFL: Non-alcoholic fatty liver, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GPR: Gamma-glutamyl transpeptidase to platelet ratio, NLR: Neutrophil to lymphocyte ratio, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis index score based on four factors, SIRI: Systemic inflammation response index, RPR: Red cell diameter width to platelet count ratio

Table 2. Comparison of demographic characteristics and laboratory parameters according to severity of non-alcoholic fatty liver

Parameter	Mild NAFL (n=184)	Advanced NAFL (n=163)	p-value
Age (years, mean±SD)	50.84±14.07	52.31±10.72	0.277†
Gender (male/female ratio)	97/87	94/69	0.388‡
Body mass index (mean±SD)	28.02±3.93	30.37±4.75	**<0.001**†
Erythrocyte sedimentation rate (mm/hour)	18.97±15.36	17.77±11.44	0.425†
Red-cell diameter width (%)	13.65±1.77	13.50±1.96	0.455†
ALT (IU/L)	24.27±19.71	34.80±24.59	**<0.001**†
AST (IU/L)	21.03±21.25	23.41±11.80	0.205†
Platelet count (×10^9/L)	275.09±74.95	272.05±68.54	0.695†
GPR	0.11±0.11	0.16±0.15	**0.001**†
NLR	2.29±1.99	1.88±1.0	**0.019**†
APRI	8.49±9.54	9.29±5.93	0.359†
FIB-4	0.92±0.74	0.85±0.40	0.268†
SIRI	1.62±2.37	1.38±1.47	0.263†
RPR	0.05±0.02	0.05±0.02	0.383†

†Student's t-test, ‡Chi-square test SD: Standard deviation, NAFL: Non-alcoholic fatty liver, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GPR: Gamma-glutamyl transpeptidase to platelet ratio, NLR: Neutrophil to lymphocyte ratio, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4, SIRI: Systemic inflammation response index, RPR: Red cell diameter width to platelet count ratio

Table 3. Univariate and multivariate regression analysis of risk factors for development for non-alcoholic fatty liver

Parameter	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
ESR	1.54 (1.48-1.61)	**<0.001**	1.01 (0.99-1.02)	0.483
Age	1.84 (1.71-1.96)	**<0.001**	0.95 (0.93-0.98)	**<0.001**
ALT	1.62 (1.57-1.68)	**<0.001**	0.97 (0.95-1.00)	**0.027**
AST	1.59 (1.52-1.66)	**<0.001**	1.00 (0.95-1.06)	0.979
BMI	2.68 (2.47-2.89)	**<0.001**	0.84 (0.80-0.89)	**<0.001**
GPR	1.59 (1.54-1.65)	**<0.001**	0.30 (0.00-0.59)	**0.021**
APRI	1.56 (1.50-1.62)	**0.001**	0.98 (0.85-1.13)	0.774
FIB-4	1.55 (1.48-1.62)	**0.016**	2.36 (0.84-6.60)	0.103

OR: Odd's ratio, CI: Confidence interval, ESR: Erythrocyte sedimentation rate, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BMI: Body mass index, GPR: Gamma-glutamyl transpeptidase to platelet ratio, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4

Of the patients who had NAFL, 184 had mild (grade 1) steatosis, whereas 163 had advanced (grade 2 and 3). Differences in ALT, BMI, GPR, and NLR parameters were significant between the groups who had mild and advanced NAFL (Table 2).

In univariate regression analysis, BMI, ALT, AST, ESR, GPR, APRI, and FIB-4 were found to be risk factors in the development of NAFL. Multivariate regression analysis of these parameters revealed that age, BMI, GPR, and ALT were independent risk factors for the development of NAFL (Table 3).

The ROC analysis was performed to determine the efficiency of inflammatory markers used to diagnose NAFL, and GPR was found to be the most effective marker (Figure 1). The optimal cut-off value for GPR in predicting the existence of NAFL was 0.9 (66% sensitivity, 62% specificity).

Discussion

This study documented that GPR values were the most effective markers for the diagnosis in people who had NAFL. Gamma-glutamyl transpeptidase has an important role in the metabolism of the main anti-oxidant in the human body known as glutathione. In the presence of conditions such as inflammation and increased oxidative stress, GGT levels are reported to be increased in the body (16,17). Increased fat deposition in the hepatocytes starts an inflammation and this results in an increase in GGT levels. Increased GGT activity reflects increased oxidative stress in NAFL (18,19). Decreased platelet counts are related to fibrosis of the liver (20). Gamma-glutamyl transpeptidase and platelet values, each also

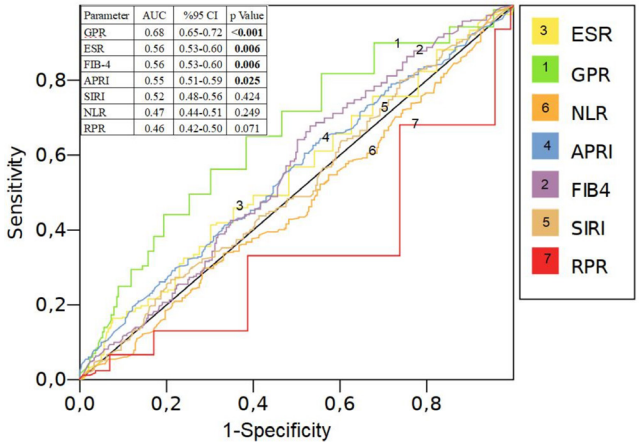

Figure 1. Receiver operating characteristic curve analysis to determine efficiency of markers used to diagnose NAFL
NAFL: Non-alcoholic fatty liver, ESR: Erythrocyte sedimentation rate, GPR: Gamma-glutamyl transpeptidase to platelet ratio, NLR: Neutrophil to lymphocyte ratio, APRI: Aspartate aminotranspherase to platelet ratio, FIB-4: Fibrosis-4, SIRI: Systemic inflammation response index, RPR: Red cell distribution width to platelet count

an inflammatory marker, were used to calculate GPR, a novel inflammatory predictor reported for the first time in 2016 in chronic hepatitis B virus (HBV) infections (21); GPR was also used in other studies inspecting autoimmune hepatitis, cystic fibrosis, and drug-induced liver injuries and was found to be superior to other inflammatory markers in demonstrating the existence of fibrosis (7-13). A study of 131 patients with chronic HBV infection who also had NAFL found that GPR was better than APRI at predicting liver fibrosis (12). The efficiency of GPR in patients who have NAFL but no chronic liver diseases has not been clearly evaluated before. The presented study showed that GPR was related to both the existence and severity of NAFL. The relationship between GPR and NAFL was preserved after multivariate regression analysis, considering the other parameters used in this study. The gamma-glutamyl transpeptidase to platelet ratio is becoming increasingly popular as a marker. Recently, in a new study, the normal reference ranges of GPR in the Chinese population were evaluated (22). This reference level will be useful for future research.

A study reported an association between age, BMI, and the existence of NAFL, independent of laboratory parameters (5). In a previous study, a positive correlation was found between ESR and obesity, and ESR was found to be increasing as BMI increased (23). Congruently, ESR is expected to be elevated in patients as their BMI increases. Obesity is a risk factor for NAFL, and the prevalence of NAFL is reported to be increased in obese individuals (24). Concordant with the aforementioned issues, this presented study reveals associations between age, BMI, ESR, and NAFL.

In one study, the FIB-4 and APRI markers were found to be effective in detecting NAFL (25); in another, the FIB-4 marker was found to be the most effective in demonstrating the presence of NAFL (5). In this study, although FIB-4 and APRI were associated with NAFL, GPR was found to be the most efficient marker in the diagnosis of NAFL.

Study Limitations

There are some limitations to this study. The diagnosis of NAFL was not confirmed with liver biopsies, but ultrasonography was used as a diagnostic tool. Since the study design was retrospective, detailed information about the concomitant diseases of patients and data about the measurement of waist circumference could not be found on every patient's record and thus could not be used. There are some strength parts in this study too. First, the number of participants was relatively high. Second,

participants who had no liver disease were evaluated. This group was not assessed before.

Conclusion

In the study, GPR and SIRI were evaluated in determining NAFL for the first time, but only GPR was found to be efficient. The gamma-glutamyl transpeptidase to platelet ratio is an easy, simple, and rapidly evaluated marker. Further studies, in which the existence of NAFL was confirmed with liver biopsies, are necessary to evaluate the efficiency of GPR in NAFL.

Ethics

Ethics Committee Approval: This study was approved by the Lokman Hekim University Non-Invasive Clinical Research Ethics Committee (approval no: 2021154, date: 23.12.2021).

Informed Consent: All of the patients who took part in the study provided informed written consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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Original Article

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The Impact of Hospitalization Time on Major Cardiovascular Event Frequency in Patients with ST-Elevation Myocardial Infarction Over a 6-Month Follow-up

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Abstract

Aim: The mortality rates related to acute myocardial infarction have significantly decreased recently due to early-period cardiovascular interventions. Some studies have shown that there is no difference in cardiovascular outcomes between the early discharge and the late one. In this study, we planned to investigate the effects of early and late discharge on the frequency of major events in patients treated for acute ST-segment elevation myocardial infarction (STEMI) in our clinic.

Methods: Angiography records, demographic characteristics, and laboratory parameters of the patients who were diagnosed with acute STEMI in our clinic between February 2020 and December 2021 were examined. Patients were classified as being in Group 1 (discharge within 48 h) or Group 2 (discharge after 48 h), and rates of recurrent hospitalization, heart failure attacks, cardiovascular events, and death were compared between the two groups.

Results: A total of 321 patients were included in our study. There were 129 patients in Group 1 and 192 patients in Group 2. There was no difference between the two Groups in terms of gender, age, or affected coronary vessels. The ejection fraction was lower in the late discharge group (p=0.004). The postoperative ventricular arrhythmia rate was found to be statistically significantly higher in the late discharge group (p=0.046). There was no difference in cardiovascular events between the first and sixth months in either group (p-values of 0.096 and 0.649, respectively).

Conclusion: Considering the positive economic and psychosocial effects of early discharge for the patient and physician, when planning the discharge of patients with STEMI, patients with low comorbidity, unaffected ejection fractions, no malignant arrhythmia in their follow-up, and appropriate laboratory parameters can be evaluated for early discharge.

Keywords: Angiography, coronary vessels, heart failure, patient discharge, ST-segment elevation myocardial infarction

Introduction

Atherosclerotic cardiovascular diseases are the ones that rank first with their mortality and morbidity rates worldwide (1). ST-segment elevation myocardial infarction (STEMI) continues to be the leading cause of cardiac emergency visits among atherosclerotic heart diseases. The goal of treating these diseases is to restore impaired myocardial blood flow. A reperfusion strategy is recommended as early as possible to minimize cardiac damage. Improvements in treatment options and hospital facilities, the adoption of guided medical treatments, and evidence-based preventive measures have all contributed to an improved prognosis for patients with STEMI. However, re-infarction, stent thrombosis, malignant arrhythmias, heart failure, and other mechanical complications are seen in a significant number of patient groups. These complications require monitoring of patients in the coronary care unit for at least 24-48 hours (2).

European Society of Cardiology (ESC) Guidelines recommend that low-risk patients be discharged within 72 hours with appropriate follow-up and early-term rehabilitation planning for patients with STEMI (3). Due to advances in management strategies and the use of evidence-based medical treatments, there is a trend toward shorter hospital stays for patients with STEMI. Different scoring systems [such as the Zwolle risk score (ZRS), the controlled abciximab and device investigation

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to lower late angioplasty complications (CADILLAC) risk score, and the primary angioplasty in myocardial infarction (PAMI) and Canadian assessment of myocardial infarction (CAMI)-STEMI risk scores] have been studied to calculate the risk of patients scheduled for early discharge, and the high patient safety and cost-effectiveness of reducing the length of hospital stay have been demonstrated by recent studies (4-6).

The feasibility of early discharge after primary percutaneous coronary intervention (PCI) in patients with STEMI varies according to the socioeconomic levels of the countries and the income levels of the individuals. Appropriate and evidence-based adoption of an early discharge strategy can have a significant financial impact for both the patient and the hospital (7,8). This study aims to evaluate the relationship between the discharge times of patients with STEMI in a tertiary heart center and the frequency of cardiovascular events in the first and sixth months after discharge, and to create a roadmap for the discharge process of patients considering the data to be obtained.

Materials and Methods

Compliance with Ethical Standards

This study was conducted in accordance with the principles of the Declaration of Helsinki. The ethics committee's approval was received at the meeting of the Ethics Committee of Necmettin Erbakan University, Non-Pharmaceutical and Medical Device Researches, dated March 4, 2022, and numbered 149 (decision no: 3681).

Study Design

This study was planned as an observational retrospective study, including patients with STEMI (n=321) who were admitted to our hospital between February 1, 2020, and December 31, 2021, underwent successful PCI, and were subsequently discharged.

Patient Evaluation and Follow-up

In our study, 321 patients were divided into two groups according to their discharge time: those who were discharged before 48 hours (n=129) and after 48 hours (n=192) (Figure 1). Those who died during hospitalization were excluded from the study. All patients within the specified period were included in the study and had no additional exclusion criteria. Demographic characteristics of the patients, cardiovascular risk factors, additional diseases, hemograms, biochemistry tests, and kidney and liver function tests were recorded. The Cockroft-Gault formula was used to calculate the patients' glomerular filtration rate, and the neutrophil x platelet, /lymphocyte formula was used to calculate the systemic immune inflammation index (9). Lipid profile values, troponin values, C-reactive protein (CRP) values, and HbA1c values in the blood collected during the hospitalization of the patients were recorded. During the hospitalization period, the blood values taken before discharge were compared with the values at the time of initial admission. All patients had coronary angiography performed via the femoral route. Coronary angiography images of the patients were examined, and the coronary artery with the lesion responsible for STEMI and the vessel with the additional severe lesion were recorded. After these records were scanned, other data were obtained from the hospital's automation system. Then, in the follow-up of the patients, it was learned whether they had a major cardiac event in the 1st and 6th months after discharge, by scanning on www.enabiz.gov.tr and by contacting the registered phone numbers in the hospital system for the patients whose information could not be accessed. Patients who were not treated in our clinic, patients whose information was missing in the file examination, and patients whose information could not be reached were excluded from the study.

Statistical Analysis

Evaluation of the research data was obtained using SPSS 20.0. In the results of the study, the mean values according to the distribution of the data were used for quantitative variables as descriptive statistics, and the number of cases (percentage) was given for qualitative variables. In the study, the normality assumptions of the data were checked by considering the Kolmogorov-Smirnov test, skewness, and kurtosis values. After checking the normality assumptions, cross tables and chi-square statistics were used to control the relationships, a t-test was used for the data showing normal distribution in comparisons for the two groups, and Mann-Whitney U statistics were used for the data that did not show normal distribution. A p-value of 0.05 or less was considered significant in all tests.

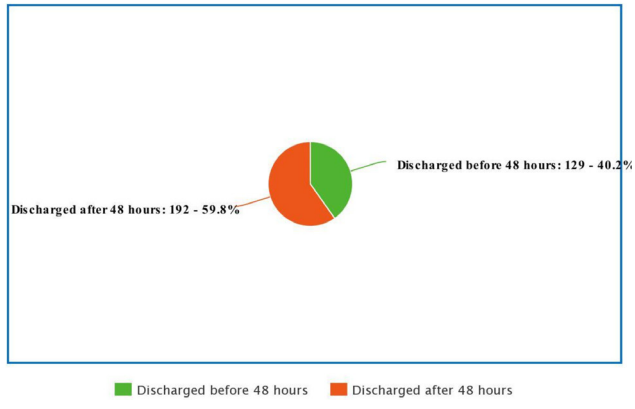

Figure 1. Distribution of groups

Results

The mean hospital stay of the patients included in Group 1 was found to be 37.2±8.9 h. The mean hospital stay of 192 patients in Group 2 was calculated as 110.1±88. There was no significant difference between the two groups in terms of gender or age. Although there was no statistically significant difference between the two groups in terms of comorbidities such as diabetes mellitus, hypertension, chronic renal failure, COPD (chronic obstructive pulmonary disease), and malignancy, these comorbidities were found to be more common in Group 2 (Table 1).

When the coronary angiographies of the patients in both groups were examined, it was seen that the left anterior descending artery was most affected, but no significant difference was observed between the coronary arteries responsible for the cardiovascular event. Serious lesions were detected in other coronary arteries, different from the main coronary artery responsible for the cardiovascular event in the groups (46.5%) and (44.7%), respectively. The mean ejection fraction in Group 2 was 45.1% and was found to be statistically significantly lower than the other group (p=0.004). In Group 2, the rate of atrial fibrillation was higher at the time of admission, and

Table 1. Comparison of demographic data and comorbidities of the patients

Discharge times	First 48 hour (n=129)	>48 hour (n=192)	p-value
Age (years, mean±SD)	60.26±11.02	61.38±13.37	0.482
Gender (male, n, %)	114 (88.37)	164 (85.41)	0.723
Diabetes mellitus (n, %)	39 (30.23)	53 (27.61)	0.617
Hypertension (n, %)	47 (36.43)	78 (40.62)	0.451
Chronic renal disease (n, %)	14 (10.85)	31 (16.14)	0.194
Hemodialysis (n, %)	2 (1.55)	1 (0.52)	0.461
COPD (n, %)	5 (3.87)	13 (6.77)	0.269
Malignancy (n, %)	6 (4.65)	13 (6.77)	0.481

Mann-Whitney U test, Student's t-test, chi-squared test, One-Way ANOVA tests were used in appropriate
COPD: Chronic Obstructive Pulmonary Disease, SD: Standard deviation

Table 2. Comparison of the perop and postoperative characteristics of the patients

Discharge times	First 48 hour (n=129)	>48 hour (n=192)	p-value
Culprit lesion - RCA (n, %) - CX (n, %) - LAD (n, %)	 46 (35.65) 28 (21.71) 55 (42.63)	 65 (33.85) 36 (18.75) 91 (47.39)	0.672
Another severe lesion (≥70%) (n, %) - None - RCA - CX - LAD - Multivessel	 60 (46.51) 43 (33.33) 7 (5.42) 10 (7.75) 9 (6.97)	 86 (44.79) 57 (29.68) 17 (8.85) 20 (10.41) 12 (6.25)	0.759
Heart rate (n, %)	69.30±23.87	67.63±24.64	0.551
Systolic blood pressure (mmHg, n, %)	131.41±24.95	132.18±28.06	0.801
Diastolic blood pressure (mmHg, n, %)	77.07±12.23	76.43±15.38	0.696
Ejection fraction (n, %)	48.08±7.61	45.14±9.09	**0.004**[1]
End-diastolic diameter (mm, n, %)	47.67±4.51	48.56±5.04	0.118
End-sysctolic diameter (mm, n, %)	30.44±5.17	31.96±6.84	**0.038**[1]
Left atrium (mm, n, %)	37.48±3.69	38.36±4.46	0.073
Sinus ryhtm (mm, n, %)	123 (95.34)	177 (92.18)	0.341
Atrial fibrillation (n, %)	6 (4.65)	15 (7.81)	0.421
Postoperative atrial fibrillation (n, %)	4 (0.311)	12 (6.25)	0.296
Postoperative ventricular arrhytmias (n, %)	1 (0.77)	7 (3.64)	**0.046**[1]
MACE for 1 months (n, %)	13 (10.07)	32 (16.66)	0.096
MACE for 6 months (n, %)	17 (13.17)	22 (11.45)	0.649

[1]: Chi-squared test Mann-Whitney U test, Student's t-test, Chi-squared test, One-Way ANOVA tests were used in appropriate,
RCA: Right coronary artery, CX: Circumflex artery, LAD: Left anterior desending artery, MACE: Major adverse cardiovascular events

atrial fibrillation was more common in the follow-up of the patients. The incidence of ventricular arrhythmia in the post-PCI period was also statistically higher in Group 2. Although the frequency of major cardiac events requiring hospitalization in the 1st and 6th months after discharge was numerically higher in Group 2, no statistically significant difference was found. In Group 1, 1 (0.7%) cardiovascular death occurred within 1 month and 2 (1.5%) within 6 months; in Group 2, 2 (1%) deaths in 1 month and 5 (2%) deaths in 6 months were observed (p≥0.05). Hospitalizations due to heart failure within 6 months were detected for 2 (1%) patients in Group 1 and for 4 (2%) patients in Group 2 (p≥0.05) (Table 2).

When the laboratory parameters of the patients were compared, the systemic immune inflammation index was lower in the early discharge group, although it was not statistically significant. However, the CRP value was higher in the early discharge group than in the late discharge group (Table 3).

Discussion

Ischemic heart disease presents as acute coronary syndrome in more than 50% of patients. Primary PCI is currently the most effective reperfusion method for patients presenting with acute STEMI. Patients presenting with STEMI are monitored for the first 24 hours in terms of risks such as re-infarction, heart failure, mechanical complications, and the development of malignant arrhythmias after revascularization; this period can be extended in high-risk patients (10). The patient's age, Killip class (determined at the time of admission to the hospital), the thrombolysis in myocardial infarction (TIMI) flow after PCI, the number of affected coronary vessels, the responsible lesion, and ejection fraction are predictors

Table 3. Comparison of the blood parameters of the patients at the time of admission and discharge

Discharge times	First 48 hour (n=129)	>48 hour (n=192)	p-value
Laboratory parameters during the first contact			
WBC (mean±SD)	11.22±3.36	11.28±3.52	0.869
NEU (mean±SD)	7.67±3.39	8.09±3.49	0.285
LYM (mean±SD)	2.54±1.54	2.31±1.39	0.142
HG (mean±SD)	15.93±13.43	15.78±15.91	0.930
PLT (mean±SD)	238±66.11	256±80.88	0.035
GFR (mean±SD)	77.47±24.63	73.75±25.22	0.196
CRE (mean±SD)	1.42±1.37	1.17±0.61	0.169
SGOT (mean±SD)	22.57±14.83	24.22±18.44	0.411
SGPT (mean±SD)	33.77±36.81	40.78±46.68	0.165
CRP	12.61 (9.8-34)	15.22 (11- 44)	0.482
LDL (mean±SD)	107.33±38.14	107.84±37.31	0.910
TROPONIN	2.79 (1.1-16)	2.74 (2-6.9)	0.952
HBA1C (mean±SD)	7.62±2.91	7.27±2.66	0.561
SII (mean±SD)	1054±998	1300±1163	0.051
Laboratory parameters during discharge			
WBC (mean±SD)	10.37±2.88	9.62±2.73	**0.023**[1]
NEU (mean±SD)	7.27±2.55	6.46±2.44	**0.006**[1]
LYM (mean±SD)	3.81±1.81	3.22±1.44	0.755
HG (mean±SD)	13.56±1.94	13.61±9.95	0.958
PLT (mean±SD)	218±55.97	234±92.8	0.108
GFR (mean±SD)	78.35±24.97	75.51±2466	0.328
CRE	2.54 (1.45-4.9)	1.46 (1.33-5.4)	0.277
SGOT (mean±SD)	110±14.5	34.18±17.89	**0.004**[1]
SGPT (mean±SD)	43.14±34.4	32.71±20.06	0.362
CRP (mean±SD)	115±65.5	51.94±38.43	**0.005**[1]
Mean hospital duration (mean±SD)	37.24±8.91	110.11±88	**0.001**[2]

[1]: Chi-squared test, [2]: Student's t-test Student's t-test, Chi-squared tests were used in appropriate.
SII: Systemic immun-inflammaton index, WBC: White blood cell, NEU: Neutrophil, LYM: Lymphocyte, PLT: Platelet, GFR: Glomerular filtration rate, CRE: Creatinin, CRP: C-reactive protein

of mortality, as are the other parameters used in clinical practice to identify high-risk patients.

Apart from these parameters, there are various scoring systems designed to identify high-risk patients and patients suitable for early discharge after STEMI. The ZRS, PAMI-II criteria, CAMI-STEMI score, CADILLAC risk score are some of them. Several studies have confirmed that the ZRS is a useful scale for risk stratification. The ZRS score is determined by whether the patient is 60 years old or older, whether the ischemia lasts more than 4 hours, whether there is an anterior wall infarction, TIMI flow after angioplasty, whether the patient has three-vessel disease, and the Killip class that the patient belongs to (11).

In the past years, percutaneous treatment methods were uncommon, and percutaneous techniques were not developed enough, causing delays in revascularization and incomplete reperfusion, which increased the possibility of heart failure, malignant arrhythmia, and mechanical complications. Accordingly, the length of hospital stay and the cost increased significantly, and long hospitalizations caused the patients to be affected psychologically. With the recent spread of percutaneous intervention centers, developments in the field of invasive cardiology have resulted in a shortening of revascularization times. In addition to the developments in this area, because of early rehabilitation and mobilization, the length of hospital stay of patients with STEMI has been significantly shortened, and significant reductions in mortality have been observed recently (12).

Many studies in the literature have examined the relationship between early or late discharge of patients and mortality. One of the earliest studies in this area, which shows the effectiveness of early discharge, is the study by Topol et al. (13) from 30 years ago. This study is among the first to demonstrate the safety of an early discharge strategy in 179 patients with uncomplicated STEMI (no angina, arrhythmia, or heart failure 72 hours after admission). A meta-analysis by Gong et al. (14) in 2018 investigating the safety of early discharge after primary angioplasty in low-risk patients with STEMI was as follows: In five randomized controlled trials involving 1575 patients with STEMI, patients were divided into an early discharge group and a standard discharge strategy group. There was no difference in mortality and readmission rates between the two groups (hazard ratio 0.78, 95% confidence interval 0.50 to 1.22, p=0.41) (14). Several randomized studies in this area have shown that a hospital stay of less than 72 hours is feasible. One of the largest studies conducted recently was by Satılmısoglu et al. (15) patients were divided into two groups in this prospective, randomized, multicenter study (which included 796 patients who underwent primary percutaneous intervention): those who received early discharge (48-56 hours) and those who received a standard discharge strategy. The primary endpoint was death from all causes and hospitalization at day 30. Compared with the standard discharge group, the early discharge group had a significantly shorter hospital stay (45.99±9.12 h vs 114.87±63.53 h; p<0.0001). There was no statistically significant difference between the two groups in the rates of all-cause mortality and readmission to the hospital (p=0.684 and p=0.061, respectively). It has been shown that discharge is feasible and safe 48-56 hours after successful PCI (15). The 2017 ESC STEMI guidelines have raised the recommended early discharge recommendations for low-risk patients with STEMI treated with primary angioplasty from class IIb to IIa (16).

In our study, it was again demonstrated that early discharge is safe. Recurrent hospitalization and death rates were similar in both groups. Additionally, the types and numbers of affected vessels in our patients were similar in both groups. The ejection fractions of the patients in Group 2 were found to be significantly lower than those in the other group, and the lack of a significant decrease in the EF values of the Group 1 patients may be due to early admission and rehabilitation. However, because the admission times of the patients cannot be clearly determined, this should be accepted as an assumption. Simultaneously, the prolonged hospital stay may be due to attacks of heart failure. Actually, although low EF alone does not explain this situation, acute low EF may cause this status and cause the discharge to be delayed by the physician who is following the patients. When the systemic immune inflammation indexes of the patients at the time of admission were compared, they were observed to be lower in the early discharge group, although it was not statistically significant. Recently, there have been many studies showing that inflammatory markers are associated with the severity of coronary artery disease and cardiovascular disease (17,18). At this point, the low inflammatory values of the patients in this period due to early admission may have caused such a result. The patients' high comorbidities, as well as the development of postoperative atrial fibrillation and ventricular arrhythmias, may have necessitated a longer hospital stay. Additionally, it was thought that the high CRP values at discharge of Group 1 patients might be due to hospital-acquired infections. But this finding may also be a coincidence. Furthermore, the femoral artery was the site of intervention in our patients. The length of hospital stay may be reduced if the radial route is used in these patient groups.

There is no clear consensus or guideline recommendation on the length of hospital stay for early discharge after STEMI. Current guidelines are based on

limited data from randomized controlled trials. Studies have shown that mechanical complications, malignant ventricular arrhythmias, large areas of myocardial necrosis, and heart failure often occur within the first 72 hours after admission. All these data support an early discharge strategy for eligible patients. Considering these data, with the widespread use of an early discharge strategy, significant reductions in health costs can be achieved, as can minimizing the psychological impact on patients traumatized by STEMI. Additionally, the possibility of developing disease-related complications in the early period in patients with acute myocardial infarction is still a problem in clinicians' minds at discharge. Especially in late admissions and advanced-age heart attacks, the high probability of complications may prolong the hospital stay. It is a fact that more comprehensive studies are needed, especially in this group of patients (19).

Similar to the existing studies, no statistically significant difference between the early and late discharge groups in low-risk patients observed in our study in terms of mortality and the incidence of undesirable major cardiac events in the first and sixth months.

Study Limitations

There are several limitations to our study. First, this was a retrospective, single-center study that may be subject to selection bias and statistical limitations due to sample size. Therefore, the findings may not reflect the patient population or healthcare performance in other centers. Additionally, the long-term results and cost-effectiveness of patients' follow-up were not evaluated. Additionally, the lack of participants in the young or old population to evaluate the results is another limitation. Despite these limitations, although it is a small-scale study, it can be considered a pioneering study in terms of showing the effectiveness of early discharge after STEMI in our country.

Conclusion

Our study formed an idea in terms of determining the length of hospital stay of patients with STEMI and the parameters that can be used in patients scheduled for early discharge in a tertiary center. However, larger prospective studies are needed to evaluate patient safety as well as the economic and psychological effects of early discharge of patients.

Ethics

Ethics Committee Approval: The ethics committee's approval was received at the meeting of the Ethics Committee of Necmettin Erbakan University, Non-Pharmaceutical and Medical Device Researches, dated March 4, 2022, and numbered 149 (decision no: 3681).

Informed Consent: This was a retrospective, single-center study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.T.S., Design: N.A., Data Collection or Processing: N.A., Analysis or Interpretation: Y.A., Literature Search: A.S.G., Writing: A.T.S.

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

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Original Article

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Nutritional Supplement Use Influencing by Cyberchondria and E-Health Literacy During the COVID-19 Outbreak in Turkey

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Abstract

Aim: "We're not just fighting an epidemic; we're fighting an infodemic," said World Health Organization Director-General Tedros Adhanom Ghebreyesus at the Munich Security Conference. In this context, we examined vitamin-mineral use frequency as influenced by cyberchondria, or E-health literacy level, and related factors during the coronavirus disease-2019 outbreak.

Methods: In this cross-sectional study, participants who were admitted to the outpatient clinics in a tertiary hospital between March 2021 and April 2021 were asked questions on socio-demographic data, the presence of vitamin and mineral use, and knowledge. The cyberchondria scores by the cyberchondria severity scale and the E-health literacy scores by the electronic health literacy scale were assessed based on nutrition type choice. The use of vitamins and minerals was compared between regular and non-regular supplement users. Factors related to the presence of nutritional supplement use were assessed through logistic regression analysis.

Results: A total of 417 participants, including those aged 39.3±12.09 years, were found to be regular nutritional supplement users at a rate of 52.99% during the outbreak. The most commonly used supplements were vitamin D (62.8%), vitamin C (54.4%), vitamin B12 (39.6%), zinc (37.9%), magnesium (35.7%), and iron (33.60%). The least used supplement was melatonin (5.30%). Iron, calcium, and vitamin A users had a higher cyberchondria score than non-users (p=0.002, p=0.044, and p=0.030, respectively). However, zinc, selenium, magnesium, calcium, vitamin B6, vitamin C, omega-3 fish oil, and probiotic users had a higher E-health literacy score than non-users (p<0.001, p=0.018, p<0.001, p=0.009, p=0.047, p=0.018, p=0.002, p=0.002, respectively). Logistic regression analyses identified higher E-health literacy [odds ratio (OR)=1.077; 95% confidence interval (CI): 1.042-1.115; p<0.001], female sex (OR=1,659; 95% CI: 1,005-2,737; p=0.048), graduated from university (OR=2,536; 95% CI: 1,009-6,374; p=0.048), presence of health professional's advice (OR=3,716; 95% CI: 2,260-6,119; p<0.001) and chronic disease presence (OR=2,755; 95% CI: 1,420-5,347; p=0.003) were predictors of supplement usage during the outbreak.

Conclusions: Higher E-health literate women with comorbidities were likely nutritional supplement users during the outbreak, regardless of cyberchondria severity or age generation differences.

Keywords: Vitamin C, vitamin D, minerals, health literacy, cyberchondria

Introduction

The immune system is a defense system consisting of various biological structures and activities and has a strong relationship with macro, micro, or other nutritional supplements (1). Vitamin supplements have previously been advised to reduce the severity of flu and acute respiratory distress syndrome and boost the immune system through their antioxidant properties (2). Additionally, based on some study results, such as analyses showing that patients with vitamin D and selenium deficiencies are more likely to experience coronavirus disease-2019 (COVID-19) mortality, it has been suggested to use some vitamins to suppress the adverse effects of COVID-19 (2).

Seasonal variation and COVID-19 influence the popularity of vitamins both worldwide and in Turkey (3). Public interest in vitamins can be investigated using Google Trends (3). Interest in vitamins has increased since the initiation of the COVID-19 pandemic. Especially, the largest online search related to all "vitamin" search terms was determined to be in March 2020 (3). Internet

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usage has become an important resource for research and informational health. This situation has caused the term "E-health literacy", which is an online form of health literacy, to gain importance. Electronic health literacy (E-health literacy) is a concept for health information in electronic resources. Many issues, such as which dose of a drug should be taken, what the test results mean, what the numbers in blood pressure and sugar measurement mean, and being aware of the risks brought by some habits, are closely related to health literacy (4). The concept of e-Health literacy is defined as the ability to seek, find, and understand health information from electronic sources and apply the knowledge to solve health problems (5). Cyberchondria is another concept that is described as exacerbated health anxiety because of repeated online searches for medical information. An interesting possible consequence of social media use during COVID-19, which may be connected to the spread of misinformation, is cyberchondria (6). It was concluded that the significant associations between impulsivity, fear of COVID-19, and cyberchondria were indirectly contributed by health-related cognition and metacognition (7).

"We're not just fighting an epidemic; we're fighting an infodemic," said World Health Organization Director-General Tedros Adhanom Ghebreyesus at the Munich Security Conference (8). In our study, the frequency and variety of nutritional supplement use, especially vitamin and mineral supplements, were questioned during the pandemic period. The effect of cyberchondria and E-health literacy was evaluated between those who regularly use supplements and those who do not. An answer was sought to the question of "whether exacerbated health anxiety or a conscious choice considering e-literacy were at the forefront of pandemic nutritional supplement use".

Materials and Methods

Compliance with Ethical Standards

This study was designed as an observational (cross-sectional) study between March 2021 and April 2021 at the University of Health Sciences Turkey, Gaziosmanpasa Training and Research Hospital. The Clinical Research Ethics Committee of University of Health Sciences Turkey, Gaziosmanpasa Training and Research Hospital accepted the study protocol by March 17, 2021, with approval number 241. Participants were informed about the procedure, and their written consent was obtained.

Sample Size

It was calculated that at least 317 people should be studied when the average frequency of use of vitamin and mineral supplements was taken as 29% and put into the formula $n=1.96^2* (0.29*0.81)/0.05^2$.

Participants

It was tried to determine the factors affecting the nutritional vitamin and mineral usage preferences of a sample group of 417 participants representing the outpatient clinics in a training hospital in Istanbul. The subjects participating in the study were selected by a random sampling method using a validated web-based "Research Randomizer" (https://www.randomizer.org/) based on the daily clinic application number list and were asked to answer questions about the topic through face-to-face interviews. Patients aged 18 years and older without any cognitive, psychological, or neurological problems were included. All participants were asked, "Did you intake any kind of nutritional supplements here in the last three months of the pandemic?" Responses were divided into two groups: those who received them regularly and those who received them occasionally or not. Additionally, respondents were asked, "How useful do you think the internet is when making decisions about your health?" and secondly, "How important is it to you to access health resources on the Internet?" Socio-demographic data were evaluated on the basis of age, generation, marriage, education, COVID-19 disease history, smoking presence, and additional diseases. Additionally, cyberchondria severity scale (CSS) scores and E-health literacy scale scores were calculated.

Scales in the Questionnaire

Cyberchondria is related to health anxiety, problematic Internet use, and symptoms of obsessive-compulsive disorder (9). The CSS is a 5-point Likert-type assessment tool that includes 33 items that can directly evaluate cyberchondria with a score range between minimum 33 and maximum 165 points. It was developed by McElroy and Shevlin (10) with university students. Fergus (11) and Norr et al. (12) have shown that the CSS is a valid and reliable scale for adults. In the Turkish validation of CSS by Utku et al. (13), the Cronbach alpha coefficient of CSS was 0.89 and had adequate psychometric properties of validity to assess cyberchondria.

The E-health literacy scale is an electronic health tool developed by Norman and Skinner to assess the information level of the users as an essential source of data (5). It was culturally adapted into Turkish by Tamer Gencer (14) with a 0.915 Cronbach alpha coefficient. It has a one-dimensional structure with 5-point Likert scales and eight items in the score range between minimum 8 and maximum 40 points (14).

Statistical Analysis

Normality control for the measurement variables was evaluated by drawing a single sample Kolmogorov-Smirnov test, histogram. Basic demographic details were

analyzed using descriptive statistics and expressed as mean, standard deviation, median, minimum, maximum, frequency, and percentage. The participants were divided into two clusters based on whether they were regular supplement users or non-users. The CSS and E-health literacy scores obtained were compared between the two clusters using Mann-Whitney tests according to the distribution of normality. A chi-square test was applied to compare groups. A p-value of <0.05 was considered statistically significant. Analyses were performed using the SPSS 22.0 software.

Results

A total of 417 participants, including those aged 39.3±12.09 years, were questioned about using 20 types of supplements in the last three months of the outbreak. In our results, 61.42% (n=256) of the participants found the internet useful for health searches, and accessing health information on the internet was important for 68.60% (n=286). Cyberchondria severity scale score and E-health literacy score scores were 73.91±21.13 and 28.01±7.17 indicating a low CSS level and moderate E-health literacy. The regular supplement use rate was 52.99%. As shown in Figure 1, the six most commonly used supplements were vitamin D (62.8%), vitamin C (54.4%), zinc (37.9%), vitamin B12 (39.6%), magnesium (35.7%), and iron (33.6%). The least used supplements were melatonin (5.3%) and Panax ginseng (5.5%). According to group differences, the use of nutritional supplements is presented in Table 1. In the age groups, 11.50% of the participants were baby boomers, 31.70% were X generation, 51.1% were Y generation, and 5.7% were Z generation. There was no statistically significant difference between the generations' supplement use rates (p=0.005). In terms of sex (p=0.026), presence of additional disease (p=0.006), and knowledge resource (p<0.001), regular supplement users differed significantly from occasional or non-users.

Table 2 compares nutritional supplement type intake differences between regular supplement users, occasional supplement users, and non-users. The use of all kinds of vitamins and minerals was observed at a higher rate in the regular supplement user group in the last three months of the outbreak compared with the occasional supplement user group.

Table 3 compared supplement users versus non-users based on CSS and E-health literacy scores. The CCS scores of supplement users (median=74) and non-users (median=74) were statistically similar (p=0.368). However, the E-health literacy score of regular supplement users (median=31) was significantly higher than that of the occasional or non-user group (median=26) (p<0.001).

An evaluation of cyberchondria and E-health literacy in the nutritional supplement type choice during the pandemic period is presented in Table 4. It was found that iron, calcium, and vitamin A users had a higher cyberchondria score than non-users (p=0.002, p=0.044, and p=0.030, respectively). However, zinc, selenium, magnesium, calcium, vitamin B6, vitamin C, omega-3 fish oil, and probiotic users had a higher E-health literacy score than non-users (p<0.001, p=0.018, p<0.001, p=0.009, p=0.047, p=0.018, p=0.002, p=0.002, respectively).

Table 5 shows the independent factors associated with regular supplement use. Logistic regression analyses revealed that higher E-health literacy [odds ratio (OR)=1.077; 95% confidence interval (CI): 1,042-1,115; p<0.001], female sex (OR=1,659; 95% CI: 1,005-2,737;

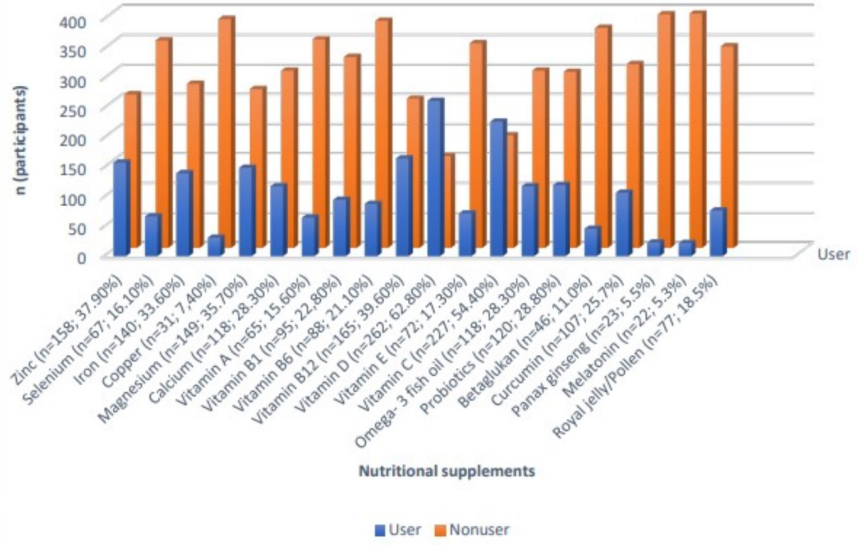

Figure 1. Distribution of vitamin-mineral use during outbreak

p=0.048), graduated from university (OR=2,536; 95% CI: 1,009-6,374; p=0.048), health professional's advice (OR=3,716; 95% CI: 2,260-6,119; p<0.001) and chronic disease presence (OR=2,755; 95% CI: 1,420-5,347; p=0.003) were predictors of pandemic supplement usage. Approximately, vitamin-mineral use was found to be 1.7 times higher in women, 2.5 times higher in university graduates, 2.8 times higher in those with comorbidities, and approximately 4 times higher if there was a recommendation from a healthcare professional.

Discussion

Considering this study, pandemic nutritional supplement use was observed as a conscious choice, with increased E-health literacy and health professionals' advice, especially in women and those with chronic disease, regardless of severity or age differences. Vitamin D (62.8%), vitamin C (54.4%), zinc (379.9%), vitamin B12 (39.5%), magnesium (35.7%), and iron (33.6%) were the most commonly used supplements, while melatonin (5.3%) was the least commonly used supplement.

Google Trends can be a beneficial tool for following public interest in identifying outbreak-related misinformation and scientific studies. For example, based on the relative search volumes for "coronavirus" and "COVID-19" in the USA and UK, there were strong correlations for the words "vitamin C" and "zinc" (15). In our study sample, the vitamin C, zinc, selenium, magnesium, calcium, vitamin B6, omega-3 fish oil, and probiotic users had a significantly higher E-health literacy score than the non-users of supplements.

It has been shown that the known anti-inflammatory and antiviral effects of serum levels of 25(OH)D, vitamin B12, and zinc at admission can affect clinical outcomes

Table 1. Evaluation of the characteristics of the participants according to their use of nutritional supplements

Details	Groups	Number of participants n (%)	Regular supplement users n (%)	Occasional or non-users n (%)	Test value* (p)
Generation	Babyboomers (1946-1964)	48 (11.50%)	33 (15.30%)	15 (7.40%)	**p=0.050**
	X generation (1965-1979)	132 (31.70%)	69 (32.10%)	63 (31.20%)	
	Y generation (1980-1999)	213 (51.10%)	104 (48.40%)	109 (54.00%)	
	Z generation (2000-2021)	24 (5.70%)	15 (7.40%)	9 (4.20%)	
Sex	Female	290 (69.5%)	160 (74.40%)	130 (64.40%)	**p=0.026**
	Male	127 (30.50%)	127 (25.60%)	72 (35.60%)	
Marital status	Married	259 (62.10%)	137 (63.70%)	122 (60.40%)	p=0.437
	Single	127 (30.50%)	60 (27.90%)	67 (33.20%)	
	Divorced	31 (7.40%)	18 (8.40%)	13 (6.40%)	
Education	Primary/secondary school	29 (7.00%)	11 (5.10%)	18 (8.90%)	p=0.118
	High school	83 (19.90%)	38 (17.70%)	45 (22.30%)	
	University	305 (73.10%)	166 (77.20%)	139 (68.80%)	
Occupation	Private sector/self-employed	174 (41.70%)	85 (39.50%)	89 (44.15%)	p=0.226
	Government sector	141 (33.80%)	81 (37.70%)	60 (29.7%)	
	Unemployed	102 (24.50%)	49 (22.80%)	53 (26.2%)	
Income	Low	98 (23.50%)	47 (21.20%)	51 (25.2%)	p=0.063
	Medium	215 (51.60%)	104 (48.40%)	111 (55.00%)	
	High	104 (24.90%)	64 (29.80%)	40 (19.80%)	
Additional disease	Positive	76 (18.20%)	50 (23.30%)	26 (12.90%)	**p=0.006**
	Negative	341 (81.80%)	165 (76.70%)	176 (87.10%)	
Smoking	Never use	197 (47.20%)	99 (46.00%)	98 (48.50%)	P=0.717
	Ex-smoker	81 (19.40%)	45 (20.9%)	36 (17.80%)	
	Smoker	139 (33.30%)	71 (33.0%)	68 (33.70%)	
Covid disease history	Positive	62 (14.90%)	34 (15.80%)	28 (13.90%)	0.575
	Negative	355 (85.10%)	181 (84.20%)	174 (86.10%)	
Resource of vitamin-mineral knowledge	Health professional	234 (56.10%)	159 (74.00%)	75 (37.10%)	**p<0.001**
	Friend/family	58 (13.90%)	15 (7.00%)	43 (21.30%)	
	Written/visual media	125 (30.00%)	41 (19.10%)	84 (41.60%)	

*Chi-square test

Table 2. Comparison of nutritional supplement type intake differences between regular supplement users versus occasional or non-users

Supplement type (n=total user; total use rate%) N=417	Supplement use	Regular users n (%)	Occasional or non-users n (%)	Test value* (p)
Zinc (n=158; 37.9%)	(+)	134 (62.30%)	24 (11.90%)	**p<0.001**
	(–)	81 (37.70%)	178 (88.10%)	
Selenium (n=67; 16.1%)	(+)	58 (27.00%)	9 (4.50%)	**p<0.001**
	(–)	157 (73.00%)	193 (95.50%)	
Iron (n=140; 33.6%)	(+)	108 (50.20%)	32 (15.80%)	**p<0.001**
	(–)	107 (49.80%)	170 (84.20%)	
Copper (n=31; 7.4%)	(+)	24 (11.20%)	7 (3.50%)	**p=0.003**
	(–)	191 (88.80%)	291 (96.50%)	
Magnesium (n=149; 35.7%)	(+)	124 (57.70%)	25 (12.40%)	**p<0.001**
	(–)	91 (42.30%)	177 (87.60%)	
Calcium (n=118; 28.3%)	(+)	95 (44.20%)	23 (11.40%)	**p<0.001**
	(–)	120 (55.80%)	179 (88.60%)	
Vitamin A (n=65; 15.6%)	(+)	47 (21.90%)	18 (8.90%)	**p<0.001**
	(–)	168 (78.10%)	184 (91.10%)	
Vitamin B1 (n=95; 22.8%)	(+)	79 (36.70%)	16 (7.90%)	**p<0.001**
	(–)	136 (63.30%)	186 (92.10%)	
Vitamin B6 (n=88; 21.1%)	(+)	74 (34.40%)	14 (6.90%)	**p<0.001**
	(–)	141 (65.60%)	188 (93.10%)	
Vitamin B12 (n=165; 39.6%)	(+)	136 (63.30%)	29 (14.40%)	**p<0.001**
	(–)	79 (36.70%)	173 (85.60%)	
Vitamin D (n=262; 62.8%)	(+)	190 (88.40%)	72 (35.60%)	**p<0.001**
	(–)	25 (11.60%)	130 (64.40%)	
Vitamin E (n=72; 17.3%)	(+)	60 (27.90%)	12 (5.90%)	**p<0.001**
	(–)	155 (72.10%)	190 (94.10%)	
Vitamin C (n=227; 54.4%)	(+)	174 (80.90%)	53 (26.20%)	**p<0.001**
	(–)	41 (19.10%)	149 (73.80%)	
Omega- 3 fish oil (n=118; 28.3%)	(+)	99 (46.00%)	19 (9.40%)	**p<0.001**
	(–)	116 (54.00%)	183 (90.60%)	
Probiotics (n=120; 28.8%)	(+)	89 (41.40%)	31 (15.30%)	**p<0.001**
	(–)	126 (58.60%)	171 (84.70%)	
Beta glucan (n=46; 11.0%)	(+)	37 (17.20%)	9 (4.50%)	**p<0.001**
	(–)	178 (82.80%)	193 (95.50%)	
Curcumin (n=107; 25.7%)	(+)	73 (34.00%)	34 (16.80%)	**p<0.001**
	(–)	142 (66.00%)	168 (83.20%)	
Panax ginseng (n=23; 5.5%)	(+)	19 (8.80%)	4 (2.00%)	**p=0.002**
	(–)	196 (91.20%)	198 (98.00%)	
Melatonin (n=22; 5.3%)	(+)	16 (7.40%)	6 (3.00%)	**p=0.041**
	(–)	199 (92.60%)	196 (97.00%)	
Royal jelly/pollen (n=77; 18.5%)	(+)	57 (26.50%)	20 (9.90%)	**p<0.001**
	(–)	158 (73.50%)	182 (90.10%)	

*Chi-square test

Table 3. Comparison of supplement users versus non-users based on cyberchondria score and E-health literacy score			
Scales	**Regular supplement users Mean±SD Median (min.-max.)**	**Occasional or non-users Mean±SD Median (min.-max.)**	**Test value***
CSS score	75.11±20.54 74 (33-148)	72.63±21.73 74 (33-151)	P=0.368 Z=-0.901
E-health literacy score	29.86±6.06 31 (8-40)	26.05±7.73 26 (8-40)	**P<0.001** Z=-3,895
*Mann-Whitney U test, CSS: Cyberchondria severity scale, min.-max.: Minimum-maximum, SD: Standard deviation			

Table 4. Evaluation of cyberchondria score versus E-health literacy score in the nutritional supplement use rates during the pandemic period					
Nutritional supplement types CSS score Mean±SD (Median)		**Scale scores**			
		p-value	**E-health literacy score Mean±SD (Median)**	**p-value***	
Zinc	(+)	75.39±29.73 (74.00)	p=0.368	29.74±6.36 (31.00)	**p<0.001**
	(–)	73.01±26.97 (74.00)		26.97±7.44 (27.00)	
Selenium	(+)	75.43±20.60 (73.00)	p=0.549	29.72±6.08 (32.00)	**p=0.018**
	(–)	73.62±21.25 (74.00)		27.69±7.32 (28.00)	
Iron	(+)	78.79±21.56 (77.00)	**p=0.002**	28.70±6.50 (29.00)	p=0.222
	(–)	71.44±20.52 (72.00)		27.67±7.47 (29.00)	
Copper	(+)	79.55±24.45 (73.00)	p=0.240	31.52±6.42 (32.00)	p=0.002
	(–)	73.46±20.81 (74.00)		27.73±7.16 (28.00)	
Magnesium	(+)	74.29±21.38 (73.00)	p=0.995	29.79±6.44 (31.00)	**p<0.001**
	(–)	73.69±21.03 (75.00)		27.03±7.38 (27.00)	
Calcium	(+)	78.25±22.91 (76.00)	**p=0.044**	29.35±6.76 (30.50)	**p=0.009**
	(–)	72.19±20.17 (76.00)		27.49±7.27 (28.00)	
Vitamin A	(+)	80.23±23.50 (77.00)	**p=0.030**	28.51±7.15 (30.00)	p=0.439
	(–)	72.74±20.49 (73.00)		27.92±7.18 (29.00)	
Vitamin B1	(+)	77.76±22.54 (77.00)	p=0.085	28.95±6.44 (29.00)	p=0.215
	(–)	72.77±20.60 (73.00)		27.74±7.36 (29.00)	
Vitamin B6	(+)	75.34±20.63 (73.50)	p=0.493	29.40±6.50 (30.50)	**p=0.047**
	(–)	73.53±21.28 (74.00)		27.64±7.30 (28.00)	
Vitamin B12	(+)	76.40±21.93 (76.00)	p=0.112	28.84±6.72 (30.00)	p=0.059
	(–)	72.29±20.48 (73.00)		27.47±7.41 (28.00)	
Vitamin D	(+)	73.52±21.35 (73.00)	p=0.455	28.66±7.01 (30.00)	p=0.007
	(–)	74.57±20.81 (76.00)		26.92±7.32 (26.00)	
Vitamin E	(+)	77.78±21.11 (76.00)	p=0.101	29.35±6.25 (31.00)	p=0.068
	(–)	73.10±21.07 (73.00)		27.74±7.32 (28.00)	
Vitamin C	(+)	74.90±21.03 (75.00)	p=0.393	28.69±7.02 (30.00)	**p=0.018**
	(–)	72.72±21.25 (73.00)		27.21±7.28 (27.00)	
Omega-3 fish oil	(+)	75.82±20.72 (74.50)	p=0.351	29.79±6.21 (30.00)	**p=0.002**
	(–)	73.16±21.28 (74.00)		27.31±7.41 (28.00)	
Probiotics	(+)	74.69±20.34 (72.50)	p=0.777	29.50±6.90 (31.00)	**p=0.002**
	(–)	73.59±21.47 (76.00)		27.41±7.19 (28.00)	
Beta glucan	(+)	77.94±21.68 (77.50)	p=0.174	29.54±6.51 (30.50)	p=0.134
	(–)	73.41±21.04 (73.00)		27.83±7.23 (29.00)	
Curcumin	(+)	76.25±21.69 (75.00)	p=0.223	28.88±7.04 (31.00)	p=0.075
	(–)	73.10±20.91 (73.50)		27.72±7.20 (28.00)	
Panax ginseng	(+)	75.35±27.79 (73.00)	p=0.889	29.04±5.68 (31.00)	p=0.552
	(–)	73.82±20.72 (74.00)		27.95±7.25 (29.00)	
Melatonin	(+)	75.55±18.22 (70.50)	p=0.725	28.95±8.28 (32.00)	p=0.295
	(–)	73.82±21.29 (75.00)		27.96±7.11 (29.00)	
Royal jelly/pollen	(+)	76.71±20.59 (77.00)	p=0.216	29.26±6.63 (31.00)	p=0.071
	(–)	73.27±21.23 (73.00)		27.73±7.27 (28.00)	
*Mann-Whitney U test, SD: Standard deviation					

in COVID-19 patients (16). It has been thought that vitamins D and C are central to determining the results of COVID-19 in many studies conducted to assess the efficacy of vitamins in the prognosis of COVID-19 (17,18). The fact that the most used supplements in our study were vitamin D and vitamin C shows that the health literacy of the patients and the physician's advice are followed.

Electronic health information seeking on the internet has many advantages, such as interaction with other patients, the amount of available information, social support, and cost-effectiveness (13,19). Cyberchondria was introduced in the context of the early days of the Internet, a revolutionary information and communication medium (9). In fact, cyberchondria was not taken seriously by academics for the first decade because it was considered a piece of magazine news (9,10). A report by the Microsoft company on health searches on the internet attracted the attention of medical academics. The main sign of cyberchondria is a repetitive pattern of problematic online health-related research (20). In 2014, the first instrument for assessing cyberchondria, the CSS, was introduced, as reflected in many research, review, and theoretical articles since then (9,20).

No conceptualization of cyberchondria includes a disease or diseases that drive online health searches. This is most likely due to the shifting focus of online search between individuals, and possibly even within a single individual, over time (9). A study examined how cyberchondria is related to changes in levels of COVID-19 concern and safety behaviors over two visits in Croatia (21). Results demonstrated that cyberchondria plays a moderating role in high levels of concern about COVID-19 and avoidance behaviors (21). According to another study, the people had practiced self-care measures like wearing a face mask, avoiding touching their faces, disinfecting the things they used as well as their home, and switching over to a healthy diet (22); Nutritional vitamin and mineral use as a part of a healthy diet is a self-care behavior; 85% of consumers seek relevant information before buying dietary supplements on the Internet as a primary source of information, and only a few consult with a health professional (23).

We do not know how healthy or necessary the use of electronic health resources is. Therefore, in our study, we determined a range between the E-health literacy score on the positive side and the CSS score on the negative side. We found that there is no difference in CSS scores between supplement users and non-users. However, some differences were observed for some vitamin and mineral supplement types. Calcium users had higher scores on both CSS and E-health literacy versus non-users in our study. Inadequate dietary calcium, particularly in a vitamin D-deficient environment, may predispose an individual to

Table 5. Presentation of effective factors in regular nutritional supplement use possibility in logistic regression

Details		Regular nutritional supplement use OR (95% CI)	p-value
E-health literacy	**Total score**	1,077 (1,042-1,115)	**<0.001**
Age generation	Babyboomer (1946-1964)	1,763 (0.506-6,146)	0.373
	X generation (1965-1979)	1,101 (0.377-3,218)	0.860
	Y generation (1980-1999)	0.797 (0.283-2,241)	0.667
	Z generation (2000-2021)	Ref	0.373
Sex	Female	1,659 (1,005-2,737)	**0.048**
	Male	Ref	-
Education	Primary/secondary school	Ref	-
	High school	2,075 (0.738-5,834)	0.166
	University	2,536 (1,009-6,374)	**0.048**
Income level	Low	Ref	-
	Moderate	1,120 (0.643-1,952)	0.688
	High	1,873 (0.983-3,571)	0.056
Supplement information source	Health professional	3,716 (2,260-6,119)	**<0.001**
	Friends/neighbours/family members	0.812 (0.381-1,729)	0.590
	Social media/internet	Ref	-
Additional chronic disease	Presence	2,755 (1,420-5,347)	**0.003**
	Absence	Ref	-

Cox & Snell R square: 0.220; Nagelkerke R square: 0.294; Model estimation percentage: 71.5%
OR: Odds ratio, CI: Confidence interval

osteoporosis (24). Another study revealed that, although they can easily access the most accurate information about health due to their occupation and working environment, healthcare professionals search for health information on the Internet. To ensure access to reliable health information, there is a need to create websites based on evidence-based, filtered sources (25). Calcium intake is important for bone structure, such as during growth, and for chronic diseases such as osteoporosis, renal disease, and dialysis patients. It is likely that there was more electronic searching for calcium in our study, as those with additional chronic diseases used nearly three times as much as others. The other CSS score differences were obtained for iron and vitamin A. The fear of calcium toxicity due to a higher cardiovascular risk (26), the fear of iron toxicity due to a higher risk of certain cancers, liver and heart disease, diabetes, and hormonal abnormalities (27), and the fear of vitamin A toxicity due to side effects such as elevated serum transaminases and skin irritation (28), may cause more health anxiety than other vitamin and mineral supplements. A higher CSS score may explore this fear of some vitamins and minerals that we mention.

Older age is typically associated with worse health, higher healthcare use, and increased healthcare costs (29). In a cross-sectional study, it was found that the point prevalence of E-Health literacy among older adults is moderate to high, which is a positive finding. However, there are differences among older adults based on factors such as being female, younger than 75 years, highly educated, in good health, and without psychological distress (30). Having adequate eHealth literacy will improve older adults' ability to manage their chronic conditions and minimize the negative effects on their health (31). Although baby boomers are often avid consumers of health information and are more willing to try new treatments than other generations (29,32), the boomers in our study are almost twice as likely to take nutritional supplements as those who don't. Studies on increased healthy life behaviors, such as healthy eating tendencies, have been observed in individuals over 50 years of age, those using vitamin supplements, and women (33). Older generations are more likely to develop multiple chronic additional diseases, necessitating more healthcare services and healthy lifestyles (29,34).

Study Limitations

The study's strengths are the use of each vitamin and mineral supplement and the comparison of E-health literacy and cyberchondria scores. Our study is the first to provide aggregated data specific to the supplement type. However, the use of supplements in the study was determined according to the patient declaration, so the lack of access to prescription information is a limitation of our study.

Conclusion

We found that women and those with additional chronic diseases had higher rates of using regular supplements than non-users. Regardless of the pandemic period, age generation, and cyberchondria level, it has been observed that one in every two people uses vitamin D or vitamin C based on higher E-health literacy. Using vitamin minerals may be a part of a longer life expectancy in triggering conditions.

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Ethics

Ethics Committee Approval: The Clinical Research Ethics Committee of University of Health Sciences Turkey, Gaziosmanpasa Training and Research Hospital accepted the study protocol by March 17, 2021, with approval number 241.

Informed Consent: Participants were informed about the procedure, and their written consent was obtained.

Peer-review: Externally and internally peer-reviewed.

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Evaluation of the Association between Multilobar Involvement and ACE Inhibitor Use in SARS-CoV-2 Patients

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Abstract

Aim: Angiotensin-converting enzyme 2 (ACE2) acts not only as an enzyme but also as a thought to be central receptor by which severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) enters host cells. Angiotensin-converting enzyme inhibitors (ACEIs) are thought to $1 are central to SARS-CoV-2 progression. However, its effect on clinical outcomes is still not fully explained. In this study, we investigated the effects of ACEIs use on pulmonary computed tomography findings.

Methods: The data of the patients who were hospitalized for SARS-CoV-2 pneumonia and were using medications for the diagnosis of hypertension from 20th March to 20th June 2020 were evaluated retrospectively. Patients were divided into 2 groups patients using ACEIs and not using ACEIs.

Results: The study was conducted with 107 patients. Mild cases without signs of pneumonia were excluded from this study. Moderate cases were accepted as patients with symptoms related to the respiratory system and pneumonia detected on imaging. SpO2≤93%, ≥30 breaths/min respiratory rate, and patients who developed respiratory failure, mechanical ventilator need, shock, or multiorgan failure were included in the severe and critically ill cases group. Severe and critical cases were evaluated as a single group. When the radiological images of the patients were examined, it was remarkable that multilobar findings were less common in the ACEIs using group ($p<0.001$). At the clinical end point, mortality rates in patients using ACEIs (12.7%) were significantly lower than patients without using ACEIs (32.7%).

Conclusion: In our study, we showed that SARS-CoV-2 progresses with less multilobar involvement in pulmonary computed tomography in patients using ACEI.

Keywords: Angiotensin-converting enzyme 2, angiotensin-converting enzyme 2 receptor, angiotensin-converting enzyme inhibitors, SARS-CoV-2, lung injury

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) continues to be a significant public health problem, affecting more than 50 million people worldwide. Although the mortality rate is below 5% (1), its mortality is significantly higher in individuals with a history of diabetes, hypertension, cardiovascular disease, or cerebrovascular disease, which has aroused considerable interest in the pathophysiological mechanisms triggered by this infection (2). Studies have shown that the novel-type coronavirus is from the betacoronavirus family, such as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), and is similar to the bat coronavirus with >95% homology (3). It has also been shown in genomic analyses that the SARS-CoV-2 genome sequence is more than 75% similar to the SARS-CoV genome (4). Concerning its clinical course, the novel type of coronavirus may lead to severe pneumonic involvement similar to SARS-CoV and MERS-CoV (5).

Severe acute respiratory syndrome coronavirus-2 acts through the angiotensin-converting enzyme 2 (ACE2) receptor (6,7). Angiotensin-converting enzyme 2 receptor, which is highly expressed in lung alveolar epithelial cells in the heart, kidney, and vascular endothelium tissues, is

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also considered to act as the receptor that initiates cellular infection of the new type of coronavirus (6). The efficacy of ACE inhibitors (ACEIs), which have been used safely for treating hypertension for many years, is supported by hard evidence in the treatment of heart failure, post-myocardial infarction, and diabetes-related kidney failure (8). Whether ACEIs use is effective against SARS-CoV infection remains a matter of debate yet. Although it is considered that the number of ACE2 receptors will be up-regulated because of the use of ACEIs it will be easier for the virus to infect the cell (1), this opinion has not been confirmed with clarity. In this study, we evaluated the epidemiological and clinical features of patients with coronavirus disease-2019 (COVID-19) who had taken ACEIs as well as, patients who had not taken ACEIs, before the diagnosis.

Materials and Methods

Compliance with Ethical Standards

Approval was obtained from the Ethics Committee of the University of Health Sciences Turkey, Haydarpasa Numune Training and Research Hospital (date: 29.06.2020, approval no: HNEAH-KAEK 2020/120). This was conducted in compliance with the principles of the Declaration of Helsinki. The hospital ethics committee waived written informed consent because the study was retrospective and evaluated only the clinical data of the patients and did not involve any potential risk.

Study Population and Data Collection

This study was approved by the University of Health Sciences Turkey, Haydarpasa Numune Training and Research Hospital's Ethical Committee. Written informed consent was waived by the local ethics committee due to the retrospective non-invasive nature of this study. In our study, electronic medical records and emergency department archives of COVID-19 patients hospitalized in University of Health Sciences Turkey, Haydarpasa Numune Training and Research Hospital from 20th March to 20th June 2020 were evaluated retrospectively. University of Health Sciences Turkey, Haydarpasa Numune Training and Research Hospital is a tertiary care center, and approximately 200000-250000 patients apply to the emergency clinic a year. By the literature, the COVID-19 clinical classification was classified as mild, moderate, severe, and critically ill cases (9). Mild cases without signs of pneumonia were excluded from this study. Moderated cases were accepted as patients with symptoms related to the respiratory system and pneumonia detected on imaging. SpO_2 ≤93%, ≥30 breaths/min. respiratory rate, and patients who developed respiratory failure, mechanical ventilator need, shock, or multiorgan failure were included in the severe and critically ill cases group. Severe and critical cases were evaluated as a single group.

Epicrisis information was obtained from 623 patients diagnosed with COVID-19 in 3-months period starting from March 2020, 453 of these patients were evaluated in the mild case group and were excluded from the study. Six patients using angiotensin-receptor blockers (ARBs) were excluded from the study. Patients (n=9) who were not diagnosed with hypertension but who used ACEIs due to congestive heart failure or diabetic nephropathy were excluded from this study. Two researchers reviewed the case report forms independently to double-check the collected data. Patients (n=48) whose epidemiological, laboratory, or symptomatic information could not be found in electronic medical records, emergency department archives, or nurse records were excluded from this study. Because of this study, 107 patients whose moderate or severe/critically ill COVID-19 pneumonia diagnoses were confirmed from their medical records and who were using antihypertensive drugs due to hypertension were included in this study.

The diagnosis of COVID-19 pneumonia was confirmed in patients presenting with respiratory symptoms in accordance with the literature by the presence of pulmonary computed tomography (CT) findings showing viral pneumonia and by the positive viral nucleic acid test (reverse transcription-polymerase chain reaction) performed on oropharyngeal and nasopharyngeal swab samples. Radiological findings suggesting COVID-19 pneumonia were accepted as parenchymal multilobar lung lesions, ground-glass opacities, crazy paving signs, and peripheral distribution detected in pulmonary CT (10-12).

By examining the medical and nursing records of the patients, their age, sex, comorbid diseases, complaints during admission, duration of symptoms, and vital signs at the time of admission to the emergency clinic (systolic blood pressure, body temperature, oxygen saturation, heart rate), D-dimer, ferritin, CRP, leukocyte, lymphocyte, and procalcitonin levels, medications used by the patient, ward or intensive care follow-up notes and clinical outcomes (mortality or discharge) were noted.

Pulmonary Computed Tomography Protocols

High-resolution transverse pulmonary CT images were obtained using a Canon CT Scanner (Model TSX-035A). The tube voltage was 120 or 135 kV, and the automatic tube current modulation was 10-300 mA. All images were reconstructed with a slice thickness of 1.0 mm. Images were acquired while holding a breath during full inspiration. Pulmonary CT data at hospital admission were collected retrospectively from the hospital archive system. Radiological evaluation was performed a retrospective review of radiological records. Radiological findings were classified as unilateral ground glass opacity/consolidation, bilateral ground glass opacity/consolidation, and multilobar lesions (13).

After the collected data were organized, the patients included in this study were divided into two groups: patients who used ACEIs and patients who did not use ACEIs. The epidemiological characteristics, vital signs, comorbid diseases, and mortality rates of the two groups were compared with each other.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). The normality assumptions were controlled by the Shapiro-Wilk test. Categorical data were analyzed by Fisher's Exact or Pearson chi-square test. Descriptive analyses were presented using mean±SD (range), median (range), or n (%), where appropriate. Mann-Whitney U test and Student's t-test were used for the analysis of normally and non-normally distributed numerical data, respectively. The 95 percent confidence interval was used to evaluate all analyses, and significance was determined at the $p<0.05$ level.

Results

In this study, the records of 107 patients who were diagnosed with COVID-19 pneumonia and who had been using antihypertensive drugs before this diagnosis was examined. Fifty-five patients included in this study were using ACEIs due to hypertension. Fifty-two patients were using calcium channel blockers (34.6%, n=37), β-blockers (31.8%, n=34), alpha-2 blockers (3.7%, n=4), or diuretics (28.9%, n=31) alone or in combination. The mean age of 107 patients included in this study was 68.49±11.95 years. 50.5% (n=54) of them were male. The mortality rate was 22.4% (n=24). When all patients were evaluated together, their comorbid diseases included diabetes (47.7%), coronary artery disease (CAD) (31.8%), chronic obstructive pulmonary disease (COPD) (10.3%), and chronic renal failure (CRF) (14%). The comparative demographic and clinical characteristics of the patient groups using ACEIs and not using ACEIs are given in Table 1. The comorbidity rates of diabetes, CAD, COPD, and CRF were similar in both patient groups (p=0.103, p=0.540, p=0.135, p=0.341, respectively). There was no difference between the two groups concerning symptom duration or complaint characteristics (Table 1). When the two groups were compared, no difference was found between the characteristics of the patients' ward or intensive care follow-up processes (p=0.161). When the CT findings of the patients were classified as the presence of unilateral or bilateral ground-glass appearance, or the dispersal of multilobar lung lesions, less multilobar involvement was found in the ACEIs using group ($p<0.001$).

There was a statistically significant difference in death rates between the ACEIs using and non-ACEIs using groups (12.7% vs. 32.7%, respectively, p=0.013). When vital signs (systolic blood pressure, body temperature, oxygen saturation, heart rate) and D-dimer, ferritin, CRP, creatinine, hemoglobin, leukocyte, lymphocyte, and procalcitonin levels were compared between the patient groups using ACEIs and not using ACEIs, no statistically significant difference was found ($p>0.05$) (Table 2).

For predicting mortality in univariate regression analysis; age [odds ratio (OR)=1,075; 95% confidence interval (CI): 1,026-1,126, p=0.002], CRF (OR=3.86; 95% CI: 1,231-12,105, p=0.021), ACEIs (OR=0.3; 95% CI: 0.112-0.802, p=0.016), multilobar lung lesions, (OR=3,385; 95% CI: 1,221-9,382, p=0.019), fever (OR=2,182; 95% CI: 1,339-3,556, p=0.002), D-Dimer (OR=17,942; 95% CI: 4.39-73,321, $p<0.001$), leukocytes (OR=1,113; 95% CI: 1,025-1,208, p=0.011), creatinine (OR=2,283; 95% CI: 1.49-3,498, $p<0.001$), hemoglobin (OR=1,113; 95% CI: 1,025-1,208, p=0.011) values' significant efficacy was observed (Table 3).

Discussion

In this study, we have shown that patients with COVID-19 who use ACEIs as antihypertensive have less multilobar involvement compared to patients who use drugs other than ACEIs as antihypertensive treatment and have a diagnosis of COVID-19. That multilobar involvement was less common in patients using ACEIs in our study suggests that viral replication is limited and viral load decreases in these patients. The significance of multilobar involvement and ACEIs in predicting mortality in the univariate regression analysis supports these results.

Angiotensin-converting enzyme inhibitors treatment reduces viral load and inhibit viral replication in previous studies (14,15). The renin-angiotensin system (RAAS) is critical in maintaining electrolyte balance and regulating blood pressure (8). Therefore, blockade of the RAAS pathway with ACEIs is considered among the leading treatment options for treating hypertension (8). When the literature is examined, there are different views about the results of ACEIs use in SARS-CoV cases. It has been reported that ACE2 receptors act as binding sites for virions of beta coronaviruses (1), and the RAAS pathway is considered to play a critical role in acute lung injury caused by viruses in blood pressure regulation (1,15,16). Therefore, a view has been proposed that patients using ACEIs may be at higher risk for SARS-CoV-2 infections, given that the number of ACE2 receptors will increase (1). However, sufficient evidence was not obtained to support or reject this view. The reason for this uncertainty is that there are not enough studies showing the ACE2 receptor levels in patients using ACEIs (17). When the previous studies were examined, it was seen that no significant

difference was found concerning ACE2 activity between the patient groups who were using ACEIs and were not using ACEIs for treating heart failure, atrial fibrillation, and CAD (17-20).

Angiotensin 2 has pro-inflammatory properties, cause endothelial and microvascular dysfunction, and play a role in maintaining vascular tone (15,21,22). Therefore, the RAAS blockade will also likely to decrease inflammatory cytokine release (15). Through this mechanism, the RAAS blockade can contribute to hemodynamic stabilization in the case of inflammation and will play a critical role in preventing sepsis-related adverse clinical outcomes (15,23). However, it is still unclear whether angiotensin II blockade that arises from ACEIs is associated with an improved clinical outcome in patients with COVID-19. In previous studies, it was reported that mostly bilateral or multilobar lung involvement was detected during the admission of COVID-19 patients (24). In a study conducted with 102 patients with a confirmed diagnosis of COVID-19, the findings showed that the number of lung lobes affected by COVID-19 was associated with mortality (25). Lung injury correlates with the viral load in patients infected with COVID-19 (14,15).

In the prospective study of Bauer et al. (26) with 204 patients using ACEIs or ARBs and diagnosed with COVID-19, the patients were randomly divided into two groups according to RAS inhibition therapy: discontinuation or continuation status. Although there

Table 1. Demographic and clinical characteristics of the patients

	Total (n=107)	Not using ACEIs (n=52)	Using ACEIs (n=55)	p-value
Age (years)	68.49±11.95 (38-97)	70.13±10.16 (43-91)	66.93±13.33 (38-97)	0.163
Gender				
Male (n, %)	54 (50.5)	27 (51.9)	27 (49.1)	0.770
Female (n, %)	53 (49.5)	25 (48.1)	28 (50.9)	
Past medical history (n, %)				
Diabetes mellitus	51 (47.7)	29 (55.8)	22 (40)	0.103
CAD	34 (31.8)	18 (34.6)	16 (29.1)	0.540
COPD	11 (10.3)	3 (5.8)	8 (14.5)	0.135
CRF	15 (14)	9 (17.3)	6 (10.9)	0.341
Prognosis (n, %)				
Discharged	83 (77.6)	35 (67.3)	48 (87.3)	**0.013**
Death	24 (22.4)	17 (32.7)	7 (12.7)	
No ICU care (n, %)	84 (78.5)	40 (76.9)	44 (80)	0.161
ICU care (n, %)	19 (17.8)	12 (23.1)	7 (12.7)	
Radiologic findings (n, %)				
Unilateral ground-glass opacity	13 (12.1)	7 (13.5)	6 (10.9)	0.686
Bilateral ground-glass opacity	90 (84.1)	45 (86.5)	45 (81.8)	0.504
Multiple lobe lesions	57 (53.3)	37 (71.2)	20 (36.4)	**<0.001**
Symptom duration (days)	4 (1-30)	4 (1-30)	5 (1-30)	0.406
Clinical symptoms (n, %)				
Fever	51 (47.7)	26 (50)	25 (45.5)	0.638
Cough and sputum	57 (53.8)	23 (44.2)	34 (63)	0.053
Dyspnea	49 (45.8)	23 (44.2)	26 (47.3)	0.752
Sore throat	4 (3.7)	1 (1.9)	3 (5.5)	0.618
Fatigue	30 (28)	14 (26.9)	16 (29.1)	0.803
Diarrhea	15 (14)	9 (17.3)	6 (10.9)	0.341
Chest pain	4 (3.7)	1 (1.9)	3 (5.5)	0.618
Myalgia or arthralgia	6 (5.6)	3 (5.8)	3 (5.5)	0.999
Anosmia	2 (1.9)	0 (0)	2 (3.6)	0.496

Mann-Whitney U test, Student's t-test, Fisher's Exact test, Pearson chi-square test used for analysis. Data are presented as mean±SD (range), median (range), or n (%). ACEI: Angiotensin-converting enzyme inhibitor, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure, ICU: Intensive care unit, SD: Standard deviation

Table 2. Clinical features and selected laboratory findings of the patients

	Total (n=107)	Not using ACEIs (n=52)	Using ACEIs (n=55)	p-value
Temperature °C	36.6 (36-40)	36.7 (36-40)	36.6 (36-39.5)	0.334
Heart rate, beats/min	85 (10-153)	85.5 (10-153)	84 (15-120)	0.638
SBP, mmHg	125.95±22.72 (60-176)	127.94±20.61 (80-170)	124.07±24.59 (60-176)	0.381
Oxygen saturation, %	96 (77-100)	95.5 (77-99)	96 (80-100)	0.508
D-dimer (ng/mL)	958 (198-9989)	1115 (250-9989)	920 (198-9440)	0.250
Ferritin (ng/L)	260 (9-5842)	253 (9-3952)	260 (18-5842)	0.311
Procalcitonin (ng/mL)	0.05 (0.05-50.64)	0.05 (0.05-50.64)	0.05 (0.05-23.63)	0.396
CRP (mg/L)	5.55 (0.2-38.8)	5.9 (0.2-38.8)	3.9 (0.2-31.2)	0.358
Leukocytes (10^3/μL)	6.89 (1.56-36.54)	6.84 (3.13-36.54)	6.89 (1.56-29.03)	0.594
Lymphocytes (10^3/μL)	1.33 (0.16-6.3)	1.28 (0.17-5.8)	1.48 (0.16-6.3)	0.566
Hemoglobin (g/dL)	12.3 (1.05-17.1)	12.25 (6.3-17.1)	12.3 (1.05-15.3)	0.874
Creatinine (mg/dL)	1.01 (0.39-7.54)	1.03 (0.59-7.54)	0.92 (0.39-3.76)	0.299

Mann-Whitney U test, Student's t-test used for analysis. Data are presented as mean±SD (range) or median (range).
CRP: C-reactive protein, SBP: Systolic blood pressure

Table 3. Univariate logistic regression analysis of factors affecting mortality

	Univariate regression analysis	
Variables	**OR (95% CI)**	**p-value**
Age	1.075 (1.026-1.126)	0.002
Male gender	2.368 (0.914-6.138)	0.076
Diabetes mellitus	1.4 (0.562-3.483)	0.470
CAD	1.096 (0.417-2.883)	0.852
COPD	1.833 (0.423-7.954)	0.418
CRF	3.86 (1.231-12.105)	**0.021**
ACEIs	0.3 (0.112-0.802)	**0.016**
CCBs	0.559 (0.201-1.559)	0.266
β-blockers	0.655 (0.234-1.834)	0.420
Alpha-2 blockers	1.159 (0.115-11.683)	0.900
Diuretics	2.164 (0.649-7.211)	0.209
Multilobar lung lesions	3.385 (1.221-9.382)	**0.019**
D-dimer (ng/mL)	17.942 (4.39-73.321)	**<0.001**
Leukocytes (10^3/μL)	1.113 (1.025-1.208)	0.011
Lymphocytes (10^3/μL)	0.986 (0.605-1.607)	0.955
Hemoglobin (g/dL)	0.788 (0.639-0.971)	**0.025**
Creatinine (mg/dL)	2.283 (1.49-3.498)	**<0.001**

ACEIs: Angiotensin-converting enzyme inhibitors, CAD: Coronary artery disease, CCBs: Calcium channel blockers, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure, OR: Odds ratio

was no significant difference between the groups in terms of 30-day mortality, it was emphasized that the discontinuation of the drug could accelerate the healing process. Azad and Kumar (27) meta-analysis with 1,566 subjects did not show a significant relationship between the use of ACEIs/ARB and death due to COVID-19. In another study conducted with 849 patients, a lower risk of death was observed in COVID-19 patients using ACEIs/ARBs for hypertension (28). In a meta-analysis examining 1321 COVID-19 patients, no association was found between the use of ACEIs/ARB and mortality and disease severity (29). In our study, baseline laboratory values and comorbidities of patients using and not using ACEIs were found to be similar. In the study by Aparisi et al. (28), the comorbidities and clinical features of COVID-19 patients using and not using ACEIs were found to be similar, and it was emphasized that the use of drugs in this group during COVID-19 would not adversely affect the prognosis of the patient.

In a cohort study in which 52,727 patients with a diagnosis of sepsis were included, it was shown that mortality rates were lower in patients using ACEIs or ARBs compared to the patients who did not use them regardless of the infectious agent and underlying comorbid diseases (23). Consistent with this study, other studies have also found an association between ACEI use and reduced mortality rates in patients hospitalized with a diagnosis of community-acquired pneumonia (23,30,31). In our study, the mortality rate was statistically different between the two groups. This difference may arise from the decreased viral load and multilobar involvement in patients using ACEIs.

Study Limitations

The most important limitations of our study are that it was single-centered and the sample size was small. Second, it was retrospective. However, in an ED with a high volume of pandemic patients, all consecutive patients meeting the criteria were included, thereby limiting patient selection bias. Prospective studies that would be conducted with a higher number of patients may reflect the effects of ACEIs use on mortality more accurately.

Conclusion

The findings obtained in this study suggest that COVID-19 progresses with less multilobar lung involvement in patients who have been using ACEIs before their diagnosis with infection. The positive effects of RAAS blockade on the radiological findings in patients with COVID-19 who also have hypertension suggest that the use of ACEIs as an antihypertensive treatment has clinical benefits during infection if there is no contraindication.

Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Committee of the University of Health Sciences Turkey, Haydarpasa Numune Training and Research Hospital (date: 29.06.2020, approval no: HNEAH-KAEK 2020/120).

Informed Consent: The hospital ethics committee waived written informed consent because the study was retrospective and evaluated only the clinical data of the patients and did not involve any potential risk.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.S., S.C., Design: D.S., B.G.Y., Data Collection or Processing: B.G.Y., S.C., Analysis or Interpretation: B.G.Y., S.C., Literature Search: D.S., B.G.Y., Writing: D.S., B.G.Y., S.C.

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

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Effects of Hypercaloric Enteral Feed on Malnutrition between Immigrants and Turkish Children

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Abstract

Aim: Malnutrition is a serious condition that causes many clinical consequences and causes diseases seen in adulthood. An early prevention of malnutrition is crucial and is widely applied via enteral or parenteral formula. Migration results in very low living standards that affect children more than adults and are considered a risk factor for malnutrition. This study separately investigates the effects of a hypercaloric enteral feed on malnourished immigrant and Turkish children in terms of body mass index (BMI), weight, and height scores alongside micronutrient deficiencies.

Methods: This case-control study was conducted in an outpatient clinic with patients who were diagnosed with malnutrition and aged 1-18 years, between January 1, 2019 and January 31, 2020. A total of 157 patients consisting of 111 Turkish and 47 immigrant children with primary malnutrition (<-2 SD) were included in the study. Anthropometric data recorded at baseline, 3rd and 6th months were retrospectively analyzed. All patient records were obtained from the Pediatric Outpatient Clinic of Esenler Children Hospital, Istanbul, Turkey.

Results: Both patient groups significantly benefited from the nutritional intervention in terms of weight for age or BMI, weight and height z-scores ($p<0.001$). Despite that improvement, baseline weight and BMI scores were lower in immigrant patients. The number of patients with iron deficiency anemia, B12 deficiency, and 25-hydroxy vitamin D3 was also diminished through enteral intervention ($p<0.001$).

Conclusion: The hypercaloric enteral intervention was well tolerated by both populations and has caused significant anthropometrical improvements during 6 months of duration alongside with the reduction in the number of patients with micronutrient deficiency.

Keywords: Malnutrition, body mass index, micronutrient deficiency, enteral feed

Introduction

Malnutrition is a serious condition that negatively influences the prognosis of other diseases (1). Malnutrition-based disturbed energy metabolism and immune system cause the body to be less responsive to medical care and more susceptible to side effects of the treatment, this is related to the poor clinical outcomes (2). Malnutrition occurs particularly in the case of highly stressful treatments like chemotherapy and radiotherapy. Additionally, malnourishment in children causes long-term effects that may appear in the future as various diseases (3). Moreover, even after adequate improvement in malnutrition status, they may still have persistent or long-lasting disturbances in metabolism that may adversely affect the clinical outcome (4). Nutritional interventions have developed rapidly because malnutrition is common and has severe clinical manifestations (1). The worldwide usage of enteral supplements is increasing alongside the personalized administration of these supplements according to patients' insufficiencies (5). Thus, all knowledge about tolerability, indications and side effects of these enteral supplements should be used to present the most beneficial intervention.

Studies have shown that malnutrition is affected by many factors and that some conditions are associated with malnutrition. In particular, sociodemographic

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characteristics such as family income, mother's education level, number of siblings, duration of breastfeeding, additional food intake and protein-rich food, and the number of members in the household are direct reasons for malnutrition (6-8). In addition to these, causes such as premature birth, neuromotor retardation, swallowing dysfunction, anatomical disorders, previous surgery and food allergies can be shown as patient-induced risk factors for malnutrition (9,10).

The migration causes very low living standards, which affects children more than adults. It has been observed that 20% of the immigrant refugees' children in Turkey have a chronic malnutrition disorder and %50 of the immigrant refugees who were involved in blood analysis have anemia (11). Additionally, it is known that the prevalence of malnutrition in the Middle East is more than 15% (12). Thus, comparing the efficiency of enteral supplementation among immigrants and native Turkish children diagnosed with malnutrition may present different baseline measurements such as initial blood biochemistry, metabolism, and initial weight for age (WFA) or body mass index (BMI) score. This may provide important knowledge about the effectiveness of nutritional interventions in different conditions.

This study compares the level of malnutrition among immigrant and Turkish children during their first admission to the hospital as well as to compare the effects of 1.5 kcal/mL enteral supplementation on weight, height, and BMI as well as iron, vitamin B12 and 25-25-hydroxy vitamin D3 levels (25D3).

Materials and Methods

Our study is a case-control study in which the malnutrition in Turkish and immigrant children aged 1-18 years who were followed and treated in the outpatient clinic between January 1, 2019 and January 31, 2020 was evaluated.

Compliance with Ethical Standards

The authors state that they obtained ethical approval, which was obtained from the Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital on 21/04/2021 with session number 06-2021. All patients and families were informed in detail about the study, and after giving consent enrolled on the study.

Sample

Our cohort includes 157 pediatric patients diagnosed with pediatric malnutrition by a pediatrician. Hypercaloric (1.5 kcal/mL) enteral supplementation was prescribed to the patients after diet adjustment was made at the first examination. Children with ages lower than 12 months and higher than 19 years were excluded from the study. The enteral nutrition product to be chosen for those younger than 12 months with malnutrition should not be hypercaloric (1.5 kcal/1 cc). Because the renal solute loads of hypercaloric enteral products may cause secondary conditions such as dehydration and prerenal acute renal failure in this age group (9). Therefore, children under 12 months were excluded from the study. Additionally, patients who were exposed to tube feeding as the nutritional intervention and patients with acute infections were also excluded from the study. All patient records were retrospectively obtained from the Pediatric Outpatient Clinic of Esenler Children Hospital, Istanbul, Turkey.

Observation

A retrospective analysis of the effects of nutritionally complete MF6-enriched hypercaloric (1.5 kcal/mL) enteral supplement, which contains 9% protein, 40% fat, 49% carbohydrates, and 2% dietary fiber. Our cohort included 157 pediatric patients aged 1-18 years who were diagnosed with malnutrition by a pediatrician, based on WFA <-2 SD under 2 years and BMI <-2 SD for over 2 years of age. The cohort included 47 immigrants and 111 Turkish children who were used to observe any probable variation of improvement provided by nutritional intervention. Patients with infectious diseases and patients undergoing tube feed were excluded from the study. Additionally, patients who were absent in follow-ups, as well as patients with irregular usage of the prescribed hypercaloric supplement, were also excluded from the study. Retrospective analyses were based on anthropometrical and biochemical data formed from the baseline dataset alongside the analysis made at the third month and six months followed by nutritional intervention. Each analysis includes the weight percentile, height percentile, related z-scores and WFA or BMI scores, which are calculated according to the traditional database of the World Health Organization, and deficient micronutrients of Turkish and immigrant children who are unable to gain weight or grow taller (13). Indications and contraindications were separately investigated among immigrant and Turkish children to observe any differences in incompatibility and tolerability between the two ethnicities.

Anthropometric measurements of all patients were taken with the same scale by 2 different observers (TBS model, scale and height meter, Tartımsan, Istanbul, Turkey). After the anthropometric measurements, weight percentile, height percentile, related z-scores and WFA or BMI scores were calculated using the auxology program developed by Turkish Pediatric Endocrinology and Diabetes Society.

Ferritin, vitamin B12, and vitamin D values, which evaluate micronutrients from the examinations taken at the time of arrival and 3rd and 6th months follow-up via the hospital information management system, and hemoglobin and hematocrit values for evaluating the presence of anemia were noted. Vitamin D deficiency was determined with levels of 25D3. A 25D3 level of 20 ng/mL indicated 25D3 deficiency (14). Iron deficiency anemia was defined as a hemoglobin value below -2SD, suitable for age groups, and a serum ferritin level below 12 microgram/L in children (15). Vitamin B12 deficiency was defined as a measured serum vitamin B12 level below 200 pg/mL (16).

Statistical Analysis

Statistical analysis of the data was maintained by IBM SPSS (Statistical Package for the Social Sciences) Statistics program (IBM Corporation, United States). The normality test was tested according to Shapiro-Wilk. In the case of the non-parametric dataset, the Friedman test was used, which was followed by the Wilcoxon signed-rank test to compare each layer of improvement. In the case of the parametric dataset, Repeated Measures ANOVA was used alongside the multivariate test of Wilks' lambda. During the Repeated Measures ANOVA analysis of pairwise significance, Bonferroni correction with significance $p<0.05$ was used. To analyze the probable difference in the effectiveness of 1.5 kcal/mL enteral supplement on immigrant and Turkish children via weight gain, height gain and BMI z-score improvement; the Mann-Whitney U test was used. In 2x2 categorical variable comparisons, when the expected result is below 5 in more than 20% of the cells with the chi-square test, Fisher's exact test was used. Otherwise, the chi-square test was preferred in all categorical comparisons. To analyze the number of patients who improved from micronutrient deficiency over 6 months of duration, the Cochran Q test was used. Significance was evaluated with $p<0.05$ level.

Results

From the total cohort of 157 malnourished outpatients, 70,3% (n=111) are Turkish and remaining 29.7% (n=47) are immigrants. The ages of the patients ranged from 1 year (12 months) to 17.3 years (208 months). There are 53 females (47.7%), 58 males (52.2%) in the Turkish group and 20 females (42.6%), and 27 males (57.5%) in the immigrant group. The major symptoms of our patients with malnutrition are 76.6% (n=121) not gaining weight and 23.4% (n=37) not gaining height.

As shown in Figure 1 and Table 1, a significant improvement in weight z-scores was seen in both immigrant and Turkish children with a feeding intervention of 1.5 kcal/mL ($p<0.001$). This overall improvement in weight z-scores of both malnourished immigrant and Turkish children was also observable during pairwise analysis between baseline, 3rd, and 6th months ($p<0.001$). Additionally, Turkish children had worse weight z-score status when they first applied to the hospital ($p=0.007$) (Table 2). The improvement trend of height z-scores was also similar to weight z-scores as significant overall and pairwise improvement was observed in both Turkish and immigrant children ($p<0.001$ and $p<0.001$ respectively). Moreover, there was no difference in the baseline height z-scores between the two groups ($p=0.681$) (Table 2). Similarly, significant overall and pairwise improvements in BMI z-scores were also observed in both populations ($p<0.001$). Like weight z-scores, the initial condition of BMI z-scores of Turkish children are worse than immigrant children ($p=0.036$) (Table 2). There was not a significant difference in the improvement rate of height, weight, and BMI z-scores between the two ethnic populations ($p=0.629$, 0.115, and 0.839 respectively). As seen in Table 3, the prevalence of iron deficiency anemia, B12 deficiency and 25-D3 deficiency in immigrant and Turkish patients decreased significantly to one-fifth of the initial prevalence. Thus, the number of patients without any micronutrient deficiency was significantly increased in both groups over 6 months of duration after 1.5 kcal/mL nutritional intervention ($p<0.001$).

Discussion

Our study is a retrospective observational study investigating the effects of oral nutritional supplements in children of two different ethnicities diagnosed with malnutrition according to a pediatrician, WFA or BMI <-2 SD for the appropriate age group. Malnutrition is a frequent condition affecting every population worldwide, with a prevalence of >900 million individuals worldwide (1). Malnutrition negatively affects energy metabolism, alters the wound-healing process and weakens the immune system. Early intervention is critical in children because of the serious consequences of malnutrition. Its negative effects on clinical prognosis cause complications such as the increased risk of infectious disease, slowing of mental development, delayed wound healing, decreased muscle strength, and impaired renal function (1,17). However, low-income countries suffer the consequences of undernourishment more often compared to high-income countries. Contrary to this, obesity and diabetes are more prevalent in high-income countries because of an unhealthy diet (18). Enteral nutrition interventions are preferred in patients with malnutrition but a normally functioning gastrointestinal tract. These interventions consist of artificially prepared formulas with different calorie amounts and additional ingredients (19).

Table 1. P-values of overall height, weight and BMI improvements along with patients with different ethnicity and different major symptoms over 6 months of nutritional intervention

Sub-groups	Height Z-scores			Weight Z-scores			BMI Z-scores		
	Baseline - 3rd Month	Baseline - 6th Month	3rd Month - 6th Month	Baseline - 3rd Month	Baseline - 6th Month	3rd Month - 6th Month	Baseline - 3rd Month	Baseline - 6th Month	3rd Month - 6th Month
Immigrant children n=47, 29.7% (Mean±SD)	<0.001* (-1.79±0.9) (-1.65±0.8)	0.001* (-1.79±0.9) (-1.35±1.0)	0.016* (-1.65±0.8) (-1.35±1.0)	<0.001* (-2.26±0.6) (-1.74±0.8)	<0.001* (-2.26±0.6) (-1.47±0.7)	<0.001* (-1.74±0.8) (-1.47±0.7)	<0.001† (-2.02±1.3) (-1.21±1.1)	<0.001† (-2.02±1.3) (-0.85±1.0)	<0.001† (-1.21±1.1) (-0.85±1.0)
Overall improvement (0-6 months)	<0.001**			<0.001**			<0.001†		
Turkish children n=111, 70.3% (Mean±SD)	0.004* (-1.91±0.9) (-1.77±0.9)	<0.001* (-1.91±0.9) (-1.59±0.8)	<0.001* (-1.77±0.9) (-1.59±0.8)	<0.001* (-2.02±0.6) (-1.49±0.6)	<0.001* (-2.02±0.6) (-1.06±0.7)	<0.001* (-1.49±0.6) (-1.06±0.7)	0.004† (-1.51±1.6) (-0.84±0.9)	<0.001† (-1.51±1.6) (-0.42±0.8)	<0.001† (-0.84±0.9) (-0.42±0.8)
Overall improvement (0-6 months)	<0.001**			<0.001**			<0.001†		
Inability to gain weight n=121, 76.6% (Mean±SD)	<0.001* (-2.43±0.6) (-2.18±0.6)	<0.001* (-2.43±0.6) (-1.82±0.9)	<0.001* (-2.18±0.6) (-1.82±0.9)	<0.001* (-1.96±0.6) (-1.45±1.0)	<0.001* (-1.96±0.6) (-1.28±08)	<0.001* (-1.45±1.0) (-1.28±08)	0.163† (-0.83±1.0) (-0.60±0.8)	<0.001† (-0.83±1.0) (-0.28±0.7)	0.098† (-0.60±0.8) (-0.28±0.7)
Overall improvement (0-6 months)	<0.001**			<0.001**			0.001†		
Inability to gain height n=37, 23.4% (Mean±SD)	<0.001* (-1.64±1.0) (-1.54±0.8)	<0.001* (-1.64±1.0) (-1.30±0.9)	<0.001* (-1.54±0.8) (-1.30±0.9)	<0.001* (-2.26±0.6) (-1.73±0.6)	<0.001* (-2.26±0.6) (-1.37±0.7)	<0.001* (-1.73±0.6) (-1.37±0.7)	<0.001† (-2.18±1.4) (-1.25±1.0)	<0.001† (-2.18±1.4) (-0.86±1.0)	<0.001† (-1.25±1.0) (-0.86±1.0)
Overall improvement (0-6 months)	<0.001**			<0.001**			<0.001†		
Total (Mean±SD)	<0.001* (-1.82±0.9) (-1.69±0.8)	<0.001* (-1.82±0.9) (-1.42±0.9)	<0.001* (-1.69±0.8) (-1.42±0.9)	<0.001* (-2.19±0.6) (-1.67±0.7)	<0.001* (-2.19±0.6) (-1.35±0.7)	<0.001* (-1.67±0.7) (-1.35±0.7)	<0.001† (-1.87±1.4) (1.10±1.0)	<0.001† (-1.87±1.4) (-0.7±0.9)	<0.001† (-1.10±1.0) (-0.7±0.9)
Overall improvement (0-6 months)	<0.001**			<0.001**			<0.001†		

*: Wilcoxon signed-rank test, **: Friedman test, †: Repeated measures ANOVA, SD: Standard deviation, Mean±SD values were written as two lines according to the order defined in the table [e.g. Baseline (0) - 3rd Month]

Oral nutritional interventions are widely used to treat malnutrition. Thus, the efficacy and compatibility of different ethnic populations should also be evaluated to choose the appropriate nutritional intervention and to prevent food insecurity (20). Despite many studies demonstrating the benefits of complementary feeding, information on the differentiating effects of oral nutrition supplements (ONS) is lacking. Compared with dietary advice (73%), ONS has shown a greater benefit (89%) upon regaining the disrupted energy metabolism in patients with malnutrition in a more cost-effective way. Despite numerous flavors of ONS products, the general downside of ONS intervention is adherence to the treatment, which has been found to be lower compared to dietary advice (21). Additionally, nausea and constipation may be encountered in ONS treatment, and it has been indicated that usage of ONS along with synbiotics prevents constipation compared to the group solely taking ONS. In our study, we selected our cohort based on patients who fully adhered to the given treatment to prevent results from irregular ONS usage and evaluated the sole effects of the intervention of two ethnic populations. Despite our hypercaloric intervention, none of our patients complained of nausea or constipation over 6 months of intervention. A greater number of patients may be required to test the compatibility of our ONS treatment.

Weight for age and BMI form the backbone of our study as they have been shown to be reliable and budget-friendly measurements in terms of evaluating the state of malnutrition (22,23). Our findings showed that 1.5 kcal/mL enteral intervention provided to both immigrant and Turkish children significantly restored weight and

height z-scores during 6 months of duration. Similarly, the number of patients with vitamin B12, 25-D3, and iron micronutrient deficiency was also diminished through enteral intervention. Our findings also showed that major symptoms of the inability to gain weight or height caused no significant difference in terms of anthropological improvement, which underlines the similar potential of hypercaloric ONS treatment on both wasted and stunted children due to undernourishment. Additionally, children from both ethnicities showed similar improvements in the case of weight, height, and BMI z-scores as well as micronutrient concentrations. This indicates that equal benefits were provided via hypercaloric intervention to both populations despite significantly different initial weight and BMI z-scores. Our study showed that treating malnutrition with hypercaloric ONS is a cost-effective choice with high tolerability in Turkish and immigrant children with the inability to gain weight or height as well as with micronutrient deficiencies.

Study Limitations

A longer period of treatment may be required to fully understand the long-term effectiveness of the hypercaloric treatment on both ethnic groups. Moreover, the immigrant cohort is limited in compared to our Turkish cohort, which may prevent healthy comparison. An equal number of participants with a higher total number may be required to demonstrate the side effects and efficacy of hypercaloric treatment on different ethnic groups. Lastly, the information about the regular dietary regimens in our patient's daily life is missing, which may pollute the exact effects of the selected nutritional intervention.

The strength of our study was that it was one of the few studies comparing and follow-up immigrant and local children's outcomes, reaching a high number of patients, and emphasizing micronutrient deficiencies in addition to anthropometric measurements.

Conclusion

Both immigrant and Turkish children tolerated the 1.5 kcal/mL enteral intervention well and significant improvements were observed in terms of BMI, weight, and height z-scores. No complaints were observed upon using hypercaloric ONS over 6 months. Additionally, nutritional intervention through hypercaloric formula has diminished the number of patients with deficient micronutrients. Rates of anthropometrical improvement were similar in both the immigrant and Turkish groups.

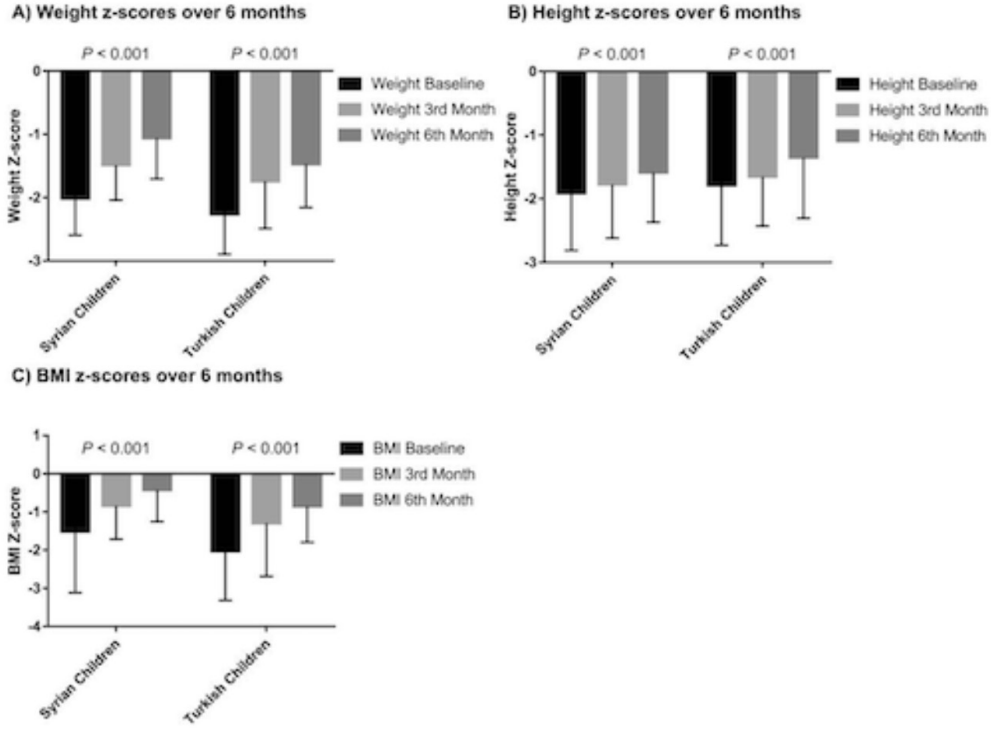

Figure 1. Weight, height and BMI z-score improvement in immigrant and Turkish children over 6 months of duration. Baseline **A)** weight, **B)** height and **C)** BMI z-scores were compared with the measurements done in the 3rd and 6th months separately in the Immigrant and Turkish cohorts. Related p-values were given inside the figure
BMI: Body mass index

Table 2. Differences of baseline anthropometrical measurements and number of micronutrient deficient between Turkish and Immigrant children along with male and female children

Categories	Baseline height Z-scores (Mean±SD)	Baseline weight Z-scores (Mean±SD)	Baseline BMI Z-scores (Mean±SD)	Baseline micronutrient status (N %)
P-values of immigrant (n=47, 29.7%) children vs Turkish (n=111, 70.3%) children	0.681* (-1.79±0.9) vs (-1.91±0.9)	0.007* (-2.26±0.6) vs (-2.02±0.6)	0.036† (-2.02±1.3) vs (-1.51±1.6)	0.699†† **Deficient:** (97, 87.4) vs (40, 85.1) **Non-deficient:** (14, 12.6) vs (7, 14.9)
P-values of female (n=73, 46.2%) vs male (n=85, 53.8%) children	0.792* (-1.83±0.9) vs (-1.82±0.9)	0.954* (-2.17±0.7) vs (-2.20±0.5)	0.610† (-1.81±1.4) vs (-1.92±1.5)	0.741†† **Deficient:** (64, 87.7) vs (73, 85.9) **Non-deficient:** (9, 12.3) vs (12, 14.1)
P-values of patients with the inability to gain weight (n=121, 76.6%) vs patients with the inability to gain height (n=37, 23.4%)	0.003* (-2.26±0.6) vs (-1.96±0.6)	0.000* (-1.64±1.0) vs (-2.43±0.6)	0.000† (-2.19±1.4) (-0.83±1.0)	0.165††† **Deficient:** (102, 84.3) vs (35, 94.6) **Non-deficient:** (19, 15.7) vs (2, 5.4)

*: Mann-Whitney U test, †: Student's t-test, ††: Chi-square, †††: Fisher's exact test, SD: Standard deviation, N: Number of patients, Mean and SD values were written according to the order given in "Categories" column; Percentage values were written based on sub-groups given in "Categories" column

Table 3. Number of Turkish and Immigrant patients with micronutrient deficiency over 6 months

	Number of Immigrant Children			Number of Turkish Children			Total		
	Baseline	3rd Month	6th Month	Baseline	3rd Month	6th Month	Baseline	3rd Month	6th Month
IDA N (%)	31 (66.0)	11 (23.4)	4 (8.5)	71 (64.0)	50 (45.0)	12 (10.8)	102 (64.6)	61 (38.6)	16 (10.1)
B12 deficiency, N (%)	12 (25.5)	1 (2.1)	1 (2.1)	33 (29.7)	5 (4.5)	1 (0.1)	45 (28.5)	6 (3.8)	2 (1.3)
25D3 deficiency, N (%)	17 (36.2)	7 (14.9)	4 (8.5)	46 (41.4)	18 (16.2)	3 (2.7)	63 (39.9)	25 (15.8)	7 (4.4)
Normal, N (%)	7 (14.9)	28 (59.6)	40 (85.1)	14 (12.6)	46 (41.4)	96 (86.5)	21 (13.3)	74 (46.8)	136 (86.1)
P-values according to the number of normal patients	Baseline vs 3rd Month: <0.001* Baseline vs 6th Month: <0.001* 3rd Month vs 6th Month: <0.001* Overall: <0.001**			Baseline vs 3rd Month: <0.001* Baseline vs 6th Month: <0.001* 3rd Month vs 6th Month: <0.001* Overall: <0.001**			Baseline vs 3rd Month: <0.001* Baseline vs 6th Month: <0.001* 3rd Month vs 6th Month: <0.001* Overall: <0.001**		
P-values of Turkish vs Immigrant patients in terms of elimination of micronutrient deficiency††	0.768† **Improved:** (82, 84.5) vs (33, 82.5) **Not improved:** (15, 15.5) vs (7, 17.5)								

*: McNemar test, **: Cohran's Q test, †: Chi-square, N: Number of patients, IDA: Iron deficiency anemia, 25D3: 25-Hydroxyvitamin D3, ††: N and percentage values were written according to the given order and percentage values were written based on Turkish and Immigrant sub-groups respectively after the exclusion of patients without baseline micronutrient deficiency

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital on 21/04/2021 with session number 06-2021.

Informed Consent: All patients and families were informed in detail about the study, and after giving consent enrolled on the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.A., M.C.U., Concept: E.A., M.C.U., Design: E.A., M.C.U., Data Collection or Processing: M.C.U., Analysis or Interpretation: E.A., Literature Search: E.A., M.C.U., Writing: E.A., M.C.U.

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Restless Leg Syndrome in Hidradenitis Suppurativa Patients: A Cross-Sectional Study with Current Literature Review

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Abstract

Aim: High frequencies of restless leg syndrome (RLS) have been reported in many dermatologic diseases like psoriasis and atopic dermatitis; however, its relationship with hidradenitis suppurativa (HS) is not clearly known. The aim of this study was to analyze the relationship between RLS and HS.

Methods: The cases of HS admitted to the dermatology clinic from February 2021 to May 2021 were included in this cross-sectional study. The study included HS patients as well as an age- and sex-matched healthy control group. The patients were evaluated with Hurley clinical staging. Body mass index (BMI) and waist circumference were noted. Laboratory tests were performed. A diagnosis and severity assessment of Restless legs syndrome were made using the International RLS Study Group (IRLSSG) criteria and the IRLSSG severity scale, respectively.

Results: A total of 40 patients with HS were enrolled in the study, with a control group of 99 healthy adults who were age and sex matched. The frequencies of RLS in the HS and control groups were 22.5% and 15.2%, respectively, and there was no statistically significant difference (p=0.43). Restless leg syndrome was rated as "very severe" in 55.6% of HS patients compared to 33.3% in the control group. There was no statistically significant difference in RLS severity among the groups (p=0.57).

Conclusion: There was no increase in the frequency of RLS in HS patients.

Keywords: Dermatology, hidradenitis suppurativa, restless leg syndrome

Introduction

Restless legs syndrome (RLS) is a common nervous system disorder that causes unpleasant leg feelings that are difficult to describe and an intense need to move them (1). Recent literature proposes possible conditions whereby patients with some defined diseases could also have RLS. The overall quality of this research, however, restricts the proven relationship of RLS to only a few diseases, such as uremia and iron deficiency anemia (2).

There is some evidence in the literature that RLS frequency is increased in a few dermatologic diseases such as psoriasis, atopic dermatitis (AD), and chronic spontaneous urticaria (CSU) (3-6). Sensory nerve cells in the skin respond to various stimuli, ranging from light touch to painful stimuli. The immune system and the neurological system share many characteristics. This has led to the discovery that nerve cells have some capabilities in common with innate immunity cells and can recognize infections and participate in innate immune responses. Soluble mediators from immune cells activate neurons, and soluble mediators from neurons can activate immune cells bidirectionally (7). The increased frequency of RLS in dermatologic diseases may be explained by this cutaneous neuro-immune interaction.

Although there are many studies pointing to sleep disturbance in hidradenitis suppurativa (HS) patients (8-

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10), there are no studies investigating the association of RLS in this patient group. The purpose of this study was to investigate the frequency and severity of RLS in HS patients, as well as the factors that influence it.

Methods

Compliance with Ethical Standards

The study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinical Research Ethics Committee (decision date: 23.12.2020, approval number: 2020-250), and all the patients who took part in it provided their written consent.

Study Design

Cases of HS admitted to the dermatology clinic from February 2021 to May 2021 were included in this cross-sectional study. The study included HS patients as well as an age- and sex-matched healthy control group. A clinical examination was performed after the patients' detailed histories were taken. Patients were evaluated with Hurley clinical staging. Body mass index (BMI) and waist circumferences were noted. Laboratory tests were performed. The International RLS Study Group (IRLSSG) criteria and IRLSSG severity scale were used to diagnose RLS and assess its severity.

Assessment of restless leg syndrome

All patients with HS, as well as an age- and sex-matched healthy control group, were requested to fill out an RLS symptom questionnaire, which included four cardinal criteria for RLS as defined by the IRLSSG:

- Uncomfortable leg sensations that lead to a desire to move them,
- Symptom onset or worsening during periods of rest,
- Symptom relief can be achieved by movement, such as walking or stretching, at least during the activity.
- Symptoms that are worse in the evening or at night than they are during the day, or that only happen in the evening or at night (11).

The symptoms were further divided into four categories: mild (1-10 points), moderate (11-20), severe RLS (21-30), and extremely severe according to the IRLSSG severity scale (31-40) (12).

Exclusion criteria were psychiatric illnesses, neurologic diseases such as MS and Parkinson disease, dermatologic diseases other than HS, rheumatologic diseases, end-stage renal disease, and pregnancy.

Results

A total of 40 HS patients and 99 age- and sex-matched healthy subjects were enrolled as a control group in the current study. The participants in the HS and control groups were 35.7±14.1 and 35.7±11.2 years old, respectively. The percentages of male patients in the HS and control groups were 77.5% and 76.5%, respectively. Between the HS and control groups, there was no statistically significant difference in terms of demographic values. The presence of additional diseases like hyperlipidemia, hypertension, hypothyroidism, asthma, etc., and drug usage were statistically significantly higher in the HS group, as expected (Table 1).

The Hurley stages were distributed as follows: stage 1 in 14 patients, stage 2 in 12 patients, and stage 3 in 14 patients. The study found no statistically significant link between the Hurley phases and the presence of RLS in HS patients. Some information about HS patients is demonstrated in Table 2.

There was no statistically significant increase in RLS frequency and severity between the HS and control groups (Figures 1, 2).

In a group analysis, there was no statistically significant difference in age, BMI, waist circumference, age at diagnosis, laboratory data, or accompanying diseases between HS patients with and without RLS (Tables 3, 4).

Discussion

Hidradenitis suppurativa is a chronic inflammatory illness marked by a range of skin lesions, such as deep nodules, draining tracts, abscesses, and fibrotic scars. These lesions are especially common in areas with a high concentration of apocrine glands, such as the axillary, groin, perianal, perineal, and inframammary regions (13).

Patients who are overweight or obese are more likely to get HS. Obesity results in a larger intertriginous surface area, which generates higher skin friction, increased sweat production and retention, and hormonal alterations that result in relative androgen excess, all of which are linked to HS. Obese people are more likely to develop metabolic syndrome, which is why it is more common in HS patients (14). The BMI and waist circumference of HS patients in this study were approximately 26 and 103, respectively, which are considered overweight.

There are publications showing that sex hormones may have an impact on the pathogenesis of HS. It's more common in women, and the age of onset is generally between puberty and menopause (14). In contrast to the literature, 77.5% of HS patients were male in our study, and the age range consisted of young patients, which did not comply with the above findings.

Hidradenitis suppurativa is one of the dermatological illnesses that has the most impact on one's quality of life (13). The severity of the disease, the number of flares, and the location of the lesion are the key factors that affect the quality of life. HS affects not only physical but also emotional and psychosocial beings (15).

The fact that it has such a negative impact on the quality of life could be attributed to its unpleasant symptoms. Patients' lives are made more difficult by HS lesions, which cause discomfort, itching, odor, and suppuration (16). Pain appears to be the most common and annoying symptom among HS patients, and it is mentioned more frequently than other skin conditions (17). As in neuropathic pain, the pain is primarily described as shooting, itching, and burning (18). Pruritus is another HS symptom that is frequently neglected in the literature, although HS is not generally recognized as a pruritic disease (19).

Table 1. Demographic variables of groups

		HS	Control	
		Mean±SD (median)	**Mean±SD (median)**	**p-value**
Age		35.7±14.1 (33)	35.7±11.2 (35)	[1]0.699
Children number		2.6±1.4 (2)	2.1±1.0 (2)	[1]0.170
		n (%)	**n (%)**	
Gender	Male	31 (77.5%)	76 (76.5%)	[2]0.8
	Female	9 (22.5%)	23 (23.5%)	
Marriage status	Married	18 (45%)	72 (72.7%)	[3]0.002*
	Single	22 (55%)	27 (27.3%)	
Having children	Yes	20 (100%)	68 (94.4%)	[4]0.573
	No	0 (0%)	4 (5.6%)	
Other diseases	Yes	22 (55%)	14 (14.1%)	[2]0.000*
	No	18 (45%)	85 (85.9%)	
Drug usage	Yes	38 (100%)	16 (16.2%)	[4]0.000*
	No	0 (0%)	83 (83.8%)	

In terms of demographic variables, there was no statistical difference between the groups (except marriage status). Additional diseases and drug usage were higher in the HS group than in the healthy controls, as expected.
[1]Mann-Whitney U test, [2]Continuity (yates), [3]Chi-square test, [4]Fisher's Exact test, *p<0.05, HS: Hydradenitis suppurativa, SD: Standard deviation, n: Number

Table 2. Some Information about the HS group

	Min.-Max.	Mean±SD	Median
BMI	15.8-36.1	26.08±4.03	26.0
Waist circumference	80-139	103.16±14.14	101.5
Disease duration (year)	1-55	10.25±10.79	6
Age at diagnosis	12-45	24.35±8.15	23

Some characteristics of HS patients were mentioned.
BMI: Body mass index, Min.-Max.: Minimum-Maximum, SD: Standard deviation, HS: Hydradenitis suppurativa

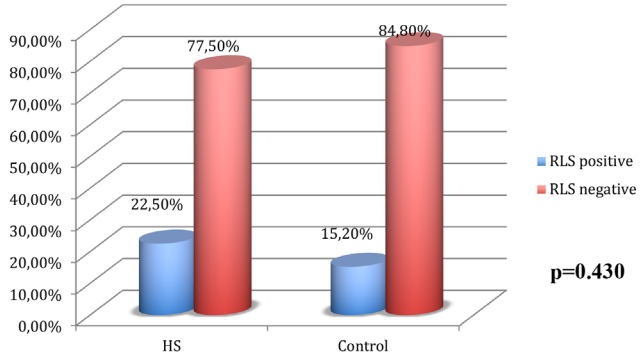

Figure 1. The frequency of RLS between groups. There was no statistically significant difference in the frequency of RLS between HS and control group
Continuity (yates), HS: Hydradenitis suppurativa, RLS: Restless leg syndrome

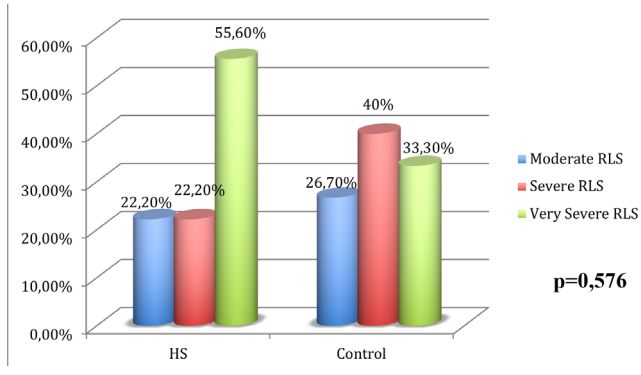

Figure 2. The severity of RLS between groups. There was no statistically significant difference in the severity of RLS between HS and control group
Fisher-Freeman-Halton test, HS: Hydradenitis suppurativa, RLS: Restless leg syndrome

Restless leg syndrome, which is among a group of neurological diseases, has increased in several dermatologic diseases such as psoriasis, AD, and CSU, as reported in recent publications (3-6).

The RLS incidence has been observed previously in patients with psoriasis, but there were discrepancies in the outcome of these studies. While some of these studies found an increase in the rate of RLS, some studies did not find any association (20,21).

Many theories have been proposed in the literature to explain the higher frequency of RLS in patients with psoriasis.

Approximately 90% of the diseases associated with RLS appear to be of inflammatory or infectious origin (22). Since psoriasis is also an inflammatory and autoimmune disease, increased RLS incidence seems logical from this perspective. Restless leg syndrome has also been linked to cardiovascular illness and diabetes mellitus, both of which are common among patients with psoriasis (23). Another possible link between RLS and psoriasis is iron deficiency, which is common in both disorders (24).

Restless leg syndrome is more common in patients with AD, especially in those with active disease (4). The reason for the high rate of RLS could not be explained precisely. But, there are some speculations in the literature about the pathogenesis of these disorders. According to some opinions, RLS symptoms may be confused with the symptoms of itching caused by AD. Clinical evaluation,

Table 3. Distribution of RLS according to some variables

	RLS		
	Positive (n=9)	**Negative (n=31)**	
HS group	**Mean±SD (median)**	**Mean±SD (median)**	**p-value**
Age	37.6±15.3 (40)	35.1±13.9 (32)	0.593
BMI	26.5±3.8 (26.3)	26.0±4.2 (26)	0.859
Waist circumference	101.3±11.7 (99)	103.7±15.0 (102)	0.823
Disease duration	9±6.7 (7)	10.6±11.7 (6)	0.897
Age at diagnosis	26.3±10.5 (25)	23.8±7.4 (22)	0.638
Hemoglobin	13.8±1.22 (12)	14.1±0.8 (13)	0.532
Neutrophil	14.3±21.1 (6.6)	6.7±3.2 (5.5)	0.317
Lymphocyte	3.2±0.6 (3.4)	3.0±1.1 (3)	0.342
CRP	18.4±18.7 (10)	17.9±38.7 (5.7)	0.064
HDL	38.6±9.1 (38)	45.5±12.5 (44)	0.149
LDL	109.6±35.9 (98)	120.2±40.1 (123)	0.391
Albumin	37.0±13.6 (43)	40.5±10.1 (43.9)	0.430
AST	52.7±104.2 (15)	20.3±7.8 (20)	0.744
ALT	21.1±13.9 (17)	24.6±16.7 (19)	0.492
Creatinin	0.72±0.1 (0.7)	0.63±0.2 (0.7)	0.924

In HS patients with and without RLS, there was no statistically significant difference in age, BMI, waist circumference, disease duration, blood values, chronic diseases, or anti-TNF use. Mann-Whitney U test, BMI: Body mass index, SD: Standard deviation, n: Number, HS: Hydradenitis suppurativa, RLS: Restless leg syndrome, CRP: C-reactive protein, HDL: High density lipoprotein, LDL: Low density lipoprotein, AST: Aspartate transaminase, ALT: Alanine aminotransferase

Table 4. Distribution of RLS according to presence of some chronic diseases and anti-TNF use

	RLS		
	Positive (n=9)	**Negative (n=31)**	
HS group	**n (%)**	**n (%)**	**p-value**
Diabetes mellitus	3 (33.3%)	4 (12.9%)	0.316
Hypertension	0 (0%)	4 (12.9%)	0.557
Anti-TNF use	2 (22.2%)	4 (12.9%)	0.602

In HS patients with and without RLS, there was no statistically significant difference in the presence of diabetes mellitus, hypertension and anti-TNF usage. Fisher's Exact test, n: Number, HS: Hydradenitis suppurativa, RLS: Restless leg syndrome

on the other hand, can easily distinguish this. Scratching relieves itching in AD. However, patients with RLS feel uncomfortable and unpleasant sensations in the legs that are relieved with movement (1,25). While the itching in AD can occur throughout the day, there may be a slight increase in the evening at rest. RLS symptoms, on the other hand, are usually felt in the evening or at night. Also, while AD symptoms can appear everywhere on the body or in a specific area, RLS symptoms are most commonly noticed in the legs (1,25).

There is evidence in the literature that the balance between the dopaminergic and noradrenergic systems in the brain is disturbed in patients with AD (25,26). Bupropion, a dopamine reuptake inhibitor, improves lesions of AD and psoriasis in individuals with severe and refractory disease, regardless of emotional circumstances. Although not fully clarified, the improvement of the balance in the dopaminergic system in the CNS may be a factor in the recovery of these lesions. However, other antidepressants may increase the symptoms of RLS by affecting the serotonin level in the nervous system (26,27). These theories may explain the increased frequency of RLS in patients with AD.

Crosstalk between the neurological and immune systems has been discovered in persistent AD, according to recent studies. Understanding the role of peripheral and central sensitization, as well as hypersensitization, in the chronicity and severity of itch in AD is important (28). The activation of central processes can also explain the higher incidence of RLS in active and long-term patients with AD.

Chronic spontaneous urticaria is another dermatological disorder associated with an increased prevalence of RLS. Urticarial pruritus can reduce the quality of sleep in people with RLS, as well as trigger and worsen the condition. Furthermore, RLS and CSU may share the same cause (5). Reports propose that CU may occur through interactions between the immune system and the central nervous system (29).

Pruritus has been discovered to be a possible risk factor for sleep disruption in various dermatoses (30,31). Pruritus was found to affect the quality of sleep in HS patients (8-10,32,33). The prevalence of RLS is estimated to be between 5% and 15% in the literature (34). In this study, 15.6% of healthy controls had RLS. Although the percentage was slightly higher in the HS group (22.5%), there was no statistically significant increase. Also, in patients with and without RLS, there was no difference in age, BMI, waist circumference, disease duration, blood values, chronic diseases, or anti-TNF use.

Study Limitations

Our research is significant since it is the first to look into the frequency of RLS in patients with HS. Although blood tests such as hemoglobin and renal function were performed in our study, the study's limitation is that iron, iron binding capacity, and ferritin values were not assessed. The study would have been more valuable if objective evaluation methods, such as polysomnographic studies of sleep disturbance in this patient group, had been used. The current study's other limitation could be attributed to the small number of participants. More research with a larger number of participants is needed to conclude if there is a link between HS and RLS.

Conclusion

There is no increased frequency of RLS in HS patients as there is in other dermatologic problems like psoriasis, AD, and CSU. In terms of concomitant conditions, there was no difference between HS cases with and without RLS.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinical Research Ethics Committee (decision date: 23.12.2020, approval number: 2020-250).

Informed Consent: All the patients who took part in it provided their written consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.S.O., T.O.A., Design: S.S.O., T.O.A., Data Collection or Processing: T.O.A., Analysis or Interpretation: S.S.O., T.O.A., Literature Search: S.S.O., Writing: S.S.O., T.O.A.

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

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Original Article

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Evaluation of the Parietal Foramen and its Surgical Importance in Dry Skulls: A Cross-Sectional Morphometric Study

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Abstract

Aim: Few studies have analyzed the possible association between parietal foramen (PF), sagittal suture (SS), and lambdoid suture (LS). The relationship between the SS, LS, and PF might play a role in identifying various ethnicities or essential in surgery. The study examined the location, type, incidence, diameter of PF, and the relationship between SS and LS in Turkish adult dry skulls.

Methods: A cross-sectional morphological and morphometrical study of PF was conducted with one hundred and sixty-six Turkish adult dry skulls in 2018-2020. The numbers, frequency, diameters, and types of PF were measured by a digital caliper. For morphometric analyses, the shortest distances between PF-SS, median PF (MPF), Lamba, and PF-LS were measured.

Results: The incidence of PF was 74.6% (right) and 74.7% (left). The incidence of PF was 63.3 in males, it was 36.7 in females. Bilateral PF was found in 74.65%, and unilateral PF was present in 55.75% of Turkish dry skulls. The MPF was found on the SS in 33.7% of the skull. The PF-LS was 39.88±1.99 mm (2.91-104.11 mm) on the left side and 40.69±1.67 mm (6.03-101.24 mm) on the right side. The PF-SS was 12.87±1.25 mm (0.26-85.03 mm) on the left side and it was 11.95±1.21 mm (0.40-83.36 mm) on the right side (p=0.01).

Conclusion: The significant differences in the PF-SS on the left side according to sex should be considered in surgery. Other findings of the study are the presence of more than one PF and its asymmetric distribution in the skull. This might be due to the delayed ossification process or differences in ethnicity.

Keywords: Parietal foramen, suture, incidence, ossification, ethnicity

Introduction

The parietal foramen (PF) is located on both sides of the sagittal suture (SS), near the juncture of the parietal bone's middle and posterior thirds (1). It transmits parietal emissary veins (EV), arteries to the superior sagittal sinus (SSS), one branch of the occipital artery, and an anastomotic artery from the scalp (2-4). Emissary veins connects the SSS to the veins of the scalp. The EV has no valves, allowing blood to flow in both directions and performing crucial tasks, including balancing the internal pressure and providing cerebral congestion (5). A skull's diploic veins have a significant association with PF, which may serve as a route for spreading infections from the superficial veins of the skull to the dural venous sinuses (1). The ossification of the parietal bone starts in the 7-8th fetal week at ossification centers and lasts until the seventh fetal month. The parietal notch forms as the ossification decelerates significantly along the midline, and the delayed closure of the parietal notch results in several abnormalities (6). The delayed or incomplete ossification process and closed the third fontanel, frequently leave behind variations like obeliac bones, PF, or parietal fissures (7). Therefore, the neurosurgeon must know the location, number, and size of the PF to avoid inadvertent hemorrhage from injury to the parietal EV (5).

However, few studies have analyzed the possible association between PF, SS, and LS (7). The relationship between the SS, LS, and PF might play a role in identifying various ethnicities or populations. Therefore, the current study examined the location, type incidence, diameter of PF, and the relationship between SS and LS in Turkish adult dry skulls.

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Materials and Methods

A cross-sectional morphological and morphometrical study of PF was conducted with 166 Turkish adult dry skulls in 2018-2020. The skulls were obtained from the Department of Anatomy, Akdeniz University Faculty of Medicine.

Compliance with Ethical Standards

The current study was approved by the Ethics Committee of the Akdeniz University Faculty of Medicine (approval date: 26.08.2020 and decision number: 596).

Study Design

The numbers (n), incidences (%), diameters (mm), and types of PF were measured bilaterally by an LCD digital caliper (0-150 mm) (Mitutoyo, Japan). The sex and morphology of the skulls were noted. Twenty-one deformed skulls with pathology and fractures were excluded from the study. The current study comprised skulls with precise SS and LS without parietal bone injury. For morphometric analyses, the shortest distances between the PF-SS, PF-LS, inferior border of median PF (MPF) and Lambda were measured (Figure 1). These measurements were repeated twice to provide a precision estimation. The three used precision estimates were calculated as follows to provide intraobserver precision.

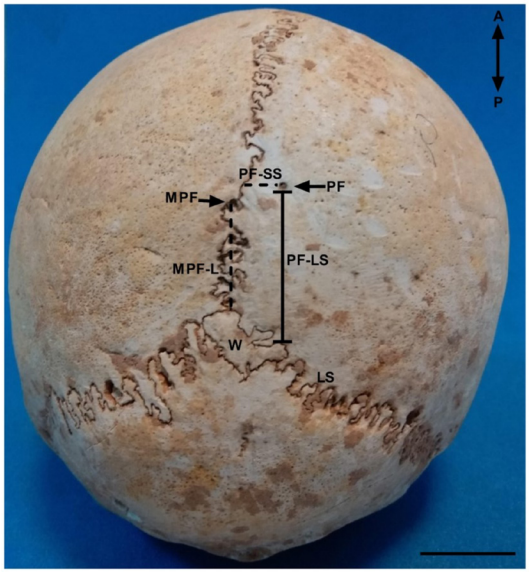

Figure 1. The morphometric measurements were taken as follows: the shortest transverse distance between the margin of the PF and the sagittal suture (PF-SS) (mm), the shortest vertical distance between the margin of the PF and the lambdoid suture (PF-LS) (mm), and the shortest vertical distance between the inferior margin of median PF (MPF) in the midline (over the SS) and Lambda (PF-L) (mm) were measured

A: Anterior, L: Lambda, LS: Lambdoid suture, MPF: Median parietal foramen, P: Posterior, PF: Parietal foramen, SS: Sagittal suture, W: Wormian bone

The technical error of measurement (TEM), the relative TEM (rTEM), and the coefficient of reliability (R) were all used in this research (8-11).

Statistical Analysis

SPSS 25 (IBM, United States) was used for analysis, and $p<0.05$ was deemed statistically significant for all comparisons. For continuous variables, descriptive statistics included mean standard deviation, standard error of the mean, minimum, and maximum, and for categorical variables, percentages (%). Multiple t-tests were used to compare groups with normal distributions.

Results

The R-values of the variables were close to one, indicating that measurements were achieved with an adequate degree of intra-observer accuracy.

Incidence

The incidence of PF was detected at a rate of 74.6% (right) and 74.7% (left). The incidence of PF was 63.3 in males, this rate was 36.7 in females. The incidences of PF on both sides are presented in Figure 2. Bilateral PF was found in 74.65%, and unilateral PF was present in 55.75% of Turkish dry skulls. The MPF was found on the SS in 33.7% of the skull. Five types of PF (absence, single, double, triple, quadruple, and quintet) were recorded (Figure 3).

Distance

The PF-LS was 39.88±1.99 mm (2.91-104.11 mm) on the left side, while the mean distance between PF-LS was 40.69±1.67 mm (6.03-101.24 mm) on the right side. The mean values of PF-LS and the differences between the sexes are presented in Table 1. Their differences were not significant on both sides ($p>0.05$). The PF-SS was 12.87±1.25 mm (0.26-85.03 mm) on the left side, and it was 11.95±1.21 mm (0.40-83.36 mm) on the right side. PF-SS values on the left side differ significantly according to sex. This value indicates that PF has an asymmetrical distribution ($p=0.010$, $p<0.05$). MPF-L was 45.64±3.34 mm. The MPF also differed significantly by sex ($p=0.04$, $p<0.05$). The number of PF and PF-LS values do not differ significantly according to the sex on both sides (Table 2).

Discussion

The incidence of bilateral PF (74.65%) was higher than unilateral PF (55.75%) in Turkish adult dry skulls. The incidence of the MPF (33.7%) was found to be higher than in other studies. A comparison of the findings of our study with other studies in the literature is presented in (Table 3). The incidence of PF varies from 50-80% in various populations (3,5,12). Several variants, including PF, may have a different occurrence according to the demographic, origin, and sex (13).

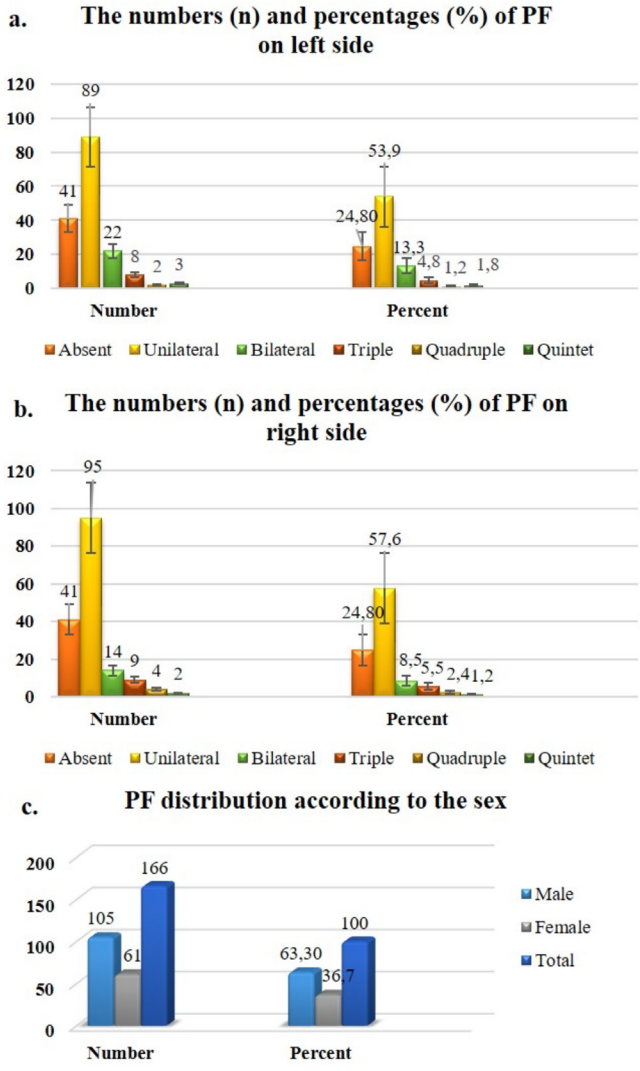

Figure 2. The numbers (n) and percentages (%) of the PF on both sides and PF distribution according to the sex. **a.** The incidence of PF on the left side was as follows; 24.8% were absent, 53.9% had a single PF, 13.3% had double, 4.8% had a triple, 1.2% had quadruple, and 1.8% had a quintet PF **b.** Incidence on the right side was absent in 24.8%, 57.6% had single PF, 8.5% had double, 5.5% had a triple, 2.4% had 4, and 1.2% had 5 PF **c.** The incidence of PF was 63.3 in males, this rate was 36.7 in females

The placement of the PF concerning the SS is crucial for neurosurgeons since the EV might rupture during surgery and result in spontaneous bleeding (5,14). The significant differences in the PF-SS on the left side according to sex should be considered in surgery. It was reported that 32% (calvaria) bilateral, and 35% (calvaria) of them unilateral (1). It has been reported that PF is more often unilateral than bilateral, and it was hardly ever multiple or MPF (15). PF was present on the SS in 5% calvaria (1). The mean incidence of bilateral PF was 41.2%, and unilateral PF was 29.9%, as reported in the literature (1). The data of our study was found to be lower than the de Souza et al. (16) (84.3%, Brazil), Mann et al. (7) (85%, Japan), Liu et al. (17) (82.86%, China), Shmarhalov et al. (18) (85.7%, Ukraine); however, it was higher than Boyd (13) (60%, Scotland), Wysocki et al. (12) (60%, Poland), Murlimanju et al. (19) (55.2%, India), Yoshioko et al. (3) (50%, USA) and Berge and Bergman (20) (30%, unilateral, USA). The incidence of MPF was noted by Mann et al. (7) (0.7%) and Naidoo et al. (1) (3.4%), which were conducted in Japanese, and South African populations. It has been reported that PF is greater in the Australian and New Zealand populations than in other ethnicities (13). There were no age or sex differences between the populations according to the distribution, frequency, and size of PF (13). However, this study revealed that the incidence of MPF was higher (33.7%) than in other studies. This difference between findings may be impacted by shifts in ethnicity, population, location, or intervariability in the same population, or by using criteria for determining the PF (18,20).

The relationship between the PF-SS is crucial for neurosurgical approaches because of the possibility of EV rupture during surgery (19). The shortest distance between PF and SS was 12.87±1.25 mm (0.26-85.03 mm) on the left side, and PF-SS was 11.95±1.21 mm (0.40-83.36 mm) on the right side in the current study. However, our findings were higher than those of Naidoo et al. (1) (4.44-18.2 mm; mean: 9.02 mm), Yoshioko et al. (3) (3-12 mm), and Murlimanju et al. (19) (0.5-15 mm), Halagatti and Sagar (2) (6.6 mm) and Shantharam and Manjunath (5) (2-36 mm). Piagkou et al. (21) asserted that PF-SS was 13.5 mm (right) and 14.6 mm (left) and PF-LS was 36.5 mm (right) and 40.8 mm (left). Similarly, it was found to be 39.88±1.99 mm on the left side and 40.69±1.67 mm on the right side in our study. Shantharam and Manjunath (5) reported that PF was located 7-56.1 mm from the Lambda. It was found to be 45.64±3.34 mm (range: 9-100.28 mm), and the MPF also differs significantly by sex ($p=0.04$, $p<0.05$). It might be due to the mechanical stresses in the vicinity of the PF over the SS and Lambda (7). The size and symmetry of the PF are significant because they may aid radiologists in diagnosing several pathological impairments (20). Safe radical surgery requires a thorough understanding of the morphological differences in the PF and skull vault (20). Failure to recognize this variance might injure the branches of EV and related arteries that have formed around the PF, leading to excessive intraoperative bleeding and sinus thrombosis (21). The mean size of PF was recorded by Yoshioka et al. (3) (0.4-4.3 mm), Shantharam and Manjunath (5) (0.86-5.57 mm), Mann et al. (7) (1.8-2 mm), Naidoo et al. (1) (0.74-3.08 mm), Berge and Bergman (20) (0.67 mm). Similarly, the mean diameter was 1.7 mm (0.6-2.9 mm) in our study. In the

literature, the size of the PF less than 0.5 mm or above 1.5 mm has been reported as a rare condition (7). Boyd (13) reported that PF was equal in size on both sides. In about half the cases mean diameter of PF was ≤0.5 mm, PF was >1-5 mm (7%), and their rest were 1 mm. A large PF was typically not linked to a larger EV and most likely resulted from an ossification deficiency in the parietal bones (13). Moreover, a large PF greater than 5 mm likely suggests an abnormal development of the fetal vascular system that may affect both skull and brain development (22).

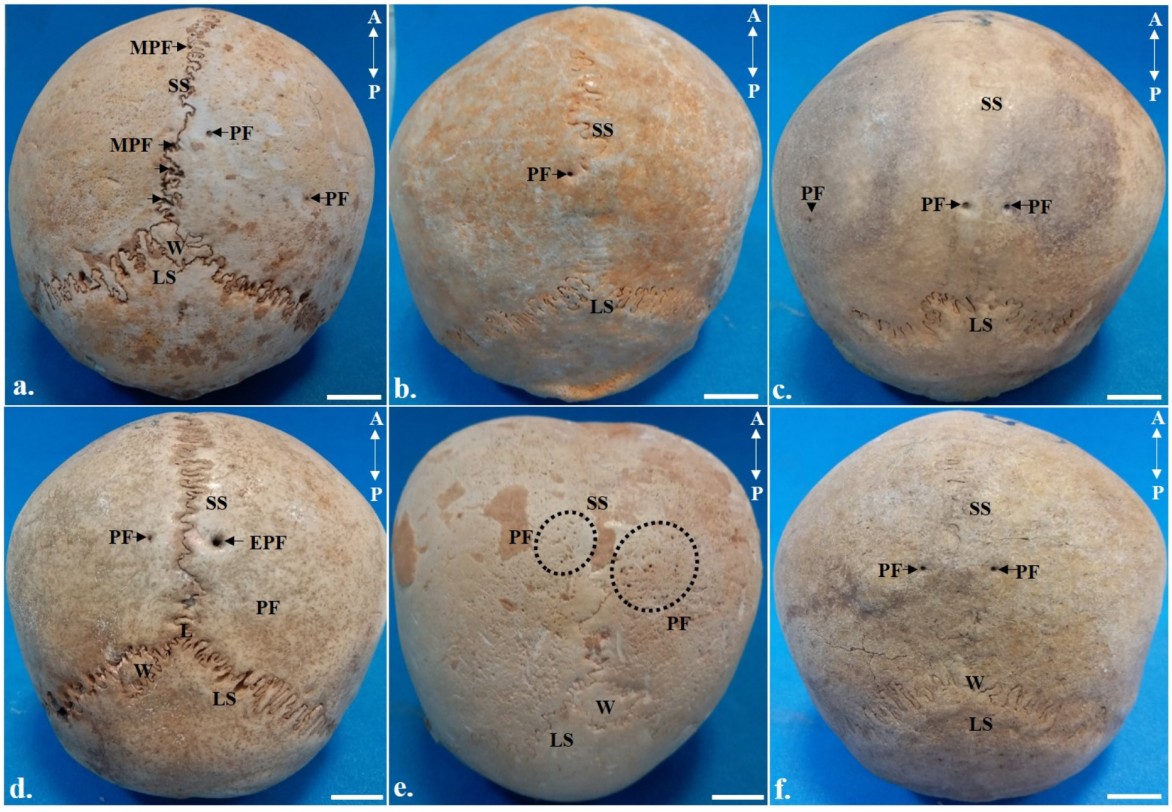

Figure 3. The types of PF according to the location and shape. **a.** Absent (on the left side), double round and oval PF (on the right side), median parietal foramen (MPF). Numerous MPFs were seen at the SS line along with Wormian bone (W) **b.** Unilateral single round PF (on the left side), **c.** A bilateral double round PF was detected on the left side and a single round PF on the right side **d.** Small round PF on the left side. Round Enlarged Parietal Foramen (EPF) on the right side along with W. **e.** There was more than one round, circle, oval, slit like PF on both sides; triple and quadruple (left), quintet (right). The PFs were located within the area indicated by the dashed lines. W was observed along with several PF, **f.** Bilateral single round PF was detected on either side of the SS

A: Anterior, EPF: Enlarged parietal foramen, L: Lambda, LS: Lambdoid suture, MPF: Median parietal foramen, P: Posterior, PF: Parietal foramen, SS: Sagittal suture, W: Wormian bone

Table 1. The descriptive statistics of PF

	Sex	PF-LS (Left)	PF-LS (Right)	PF-SS (Left)	PF-SS (Right)	MPF-L	PF (n) (Left)	PF (n) (Right)
Total number (n)*	166	123	116	123	117	56	165	165
Mean	1.3675	39.8890	40.6946	12.8705	11.9590	45.6430	1.0909	1.0667
Std. error of mean	0.03753	1.99672	1.67698	1.25931	1.21590	3.34121	0.07681	0.07648
Median	1.0000	35.0700	38.2950	9.1300	8.2500	41.9400	1.0000	1.0000
Std. deviation	0.48357	22.14467	18.06168	13.96642	13.15199	25.00333	0.98661	0.98236
Variance	0.234	490.386	326.224	195.061	172.975	625.166	0.973	0.965
Range	1.00	101.20	95.21	84.77	82.96	91.28	5.00	5.00
Minimum	1.00	2.91	6.03	0.26	0.40	9.00	-	-
Maximum	2.00	104.11	101.24	85.03	83.36	100.28	5.00	5.00

*The n numbers indicate the number of skulls observed in PF. L: Lambda, LS: Lambdoid suture, MPF: Median parietal foramen, PF: Parietal foramen, SS: Sagittal suture

Table 2. The p-values of parameters according to the PF on both sides

	F	Sig.	t	df	p-values	Mean	Std. error		
								Lower	Upper
PF-LS (Left)	0.230	0.632	1.388	121	0.168	5.59095	4.02667	2.38090	13.56279
		1.395	111.833	0.166	5.59095	4.00833	2.35117	13.53306	
PF-LS (Right)	0.727	0.396	0.318	114	0.751	1.09957	3.45506	5.74487	7.94401
			0.331	105.397	0.741	1.09957	3.32023	5.48355	7.68269
PF-SS (Left)	13.956	0.000	2.604	121	0.010	6.48566	2.49090	1.55427	11.41705
			2.911	98.593	0.004	6.48566	2.22825	2.06411	10.90721
PF-SS (Right)	7.148	0.009	1.627	115	0.106	4.03808	2.48170	0.87769	8.95385
			1.904	105.957	0.060	4.03808	2.12137	0.16775	8.24392
MPF-L	2.463	0.122	1.922	54	0.060	13.88088	7.22128	0.59693	28.35868
			2.134	35.174	0.040	13.88088	6.50392	0.67955	27.08220
PF (n) (Left)	0.013	0.910	0.580	163	0.562	0.09286	0.15999	0.40878	0.22307
			0.594	131.587	0.554	0.09286	0.15636	0.40217	0.21645
PF (n) (Right)	3.192	0.076	0.493	163	0.623	0.07857	0.15935	0.39323	0.23608
			0.528	148.412	0.598	0.07857	0.14881	0.37262	0.21548

Independent samples test was performed. L: Lambda, LS: Lambdoid suture, MPF: Median parietal foramen, PF: Parietal foramen, SS: Sagittal suture. PF-SS values on the left side differ significantly according to sex. This value indicates that PF has an asymmetrical distribution

Reddy et al. (14) claimed that aberrant vascular evolution with enlarged PF (>5 mm) during the fetal development might affect the development of the brain and skull. It has been reported that enlarged PF (foramina parietal permagna, Catlin marks) coexists with a benign calvarial deficiency with a prevalence of 1 in 15,000 to 1 in 50,000 individuals and numerous Wormian bones (14,21,23). Several reports of enlarged PF have been in conjunction with clinical diseases such as cerebral venous and cortical abnormalities, perineural tumors, and skull fractures (5,13,14). It has been reported that enlarged PF reveals a genetic background and carries an autosomal dominant inheritance (21). Although they are asymptomatic, they have been linked to nausea, multiple exostoses, mental retardation, cleft palate, headaches, encephaloceles, vomiting, myelomeningocele, Duane's syndrome, straight sinus hypoplasia, the persistence of the median prosencephalic vein and falcine sinus, a dilated vein, vascular or cortical malformations of the brain (14,21). In contrast, it has been claimed that small PF had only a minor hemodynamic role. Moreover, the persistence of the lateral margin of the parietal notch may cause a small PF during the development (21). Wysocki et al. (12) stated that sexual dimorphism in PF according to the size of the PF.

Halagatti and Sagar (2) reported that the frequency and situation of PF help in knowing the relationship between sinuses and extracranial veins. Their situation is essential for analyzing the injuries of the scalp and surgery (2). It has been reported that PF is positioned at the posterior one-third of the parietal bone (7). It is situated 83 mm anterior to the Inion, 2 cm in front of the Lambda in newborns, and 2-5 cm in front of the Lambda in adults (3,7). It has been reported that PF is found 3.5 cm anterior to the Lambda and on either side of the SS (2). In our study, similar to the others, PF was present on both sides of the SS or unilaterally and it was located in front of Lambda and LS. Yoshioka et al. (3) reported that PF occurred between the middle meningeal and scalp arteries. They reported scalp anastomosis that gives off a small artery via PF to communicate with the same branches of the middle meningeal artery (55%), and 45% had an anastomosis with pericranial artery through PF (3). It has been indicated that the PF and the skull's diploic veins had a direct relation (13). This association is likely to be crucial in transmitting the infection to the extracranial part of the skull (13). The risk of injury to the SSS or intraoperative blood loss can be reduced by precisely localizing the PF on radiological evaluation and then carefully obstructing the EV (24). The current findings may aid in safe movements around PF that transmit an arterial channel across the scalp and dura mater covering the SSS.

The PF can show variations concerning its type, number, size, and shape (2,3). Circular, oval, slit-like, and enlarged PFs have been described in the literature (7,15).

Table 3. The comparison of the PF by years

Author et al.	PF	Year	Study design	Total number	Incidence (%)	Place	Location	Average size (mm)	Clinical significance	Distance
Berge and Bergman (20)	Absent, Single, Double	2001	Dry skull	100	80% (bilaterally 50%; unilaterally 30%)	USA	Bilateral or unilateral side of the parietal bone	(0.30-1.67 mm) 0.67 mm	-The differences according to the incidence (unilateral, bilateral) may result from the populations or criteria used for determining if a foramen exists.	Unknown
Yoshioka et al. (3)	Absent, Single, Double, Triple	2006	Cadaver	Forty parietal regions from 20 adult cadavers	40 (Bilateral) 20 (Unilateral) Posterior 1/3 of the parietal bone.	Florida, USA	It lies 2 cm anterior to the Lambda in newborns and 20.5 cm anterior to the Lambda in adults	External 1.8 mm (range, 0.4-4.3 mm) internal 0.9 mm (range, 0.2-1.9 mm)	-The PF transmits an anastomosis between the middle meningeal and scalp arteries. -Anastomosis may be involved in several pathologies. -Symptoms include epidural hematoma, moyamoya disease, arteriovenous malfunctions	8 mm (3-12 mm) from the midline, 83 mm (range 55-95 mm) from the inion
Wysocki et al. (12)	Absent, Single, Double	2006	Dry skull	100 (50M, 50F)	60%	Poland The 13th century (Kielce)	Bilateral or unilateral side of the parietal bone	11.9 mm^2 (left), 16.8 mm^2 (right)	-There was a correlation between the total surface area of hypoglossal and condylar canals, oval foramen, mastoid and PF on both sides. -There was asymmetry among the PF	Unknown
Mann et al. (7)	Absent, Single, Double	2009	Dry skull	137 (79M, 58F)	67M (85%), 43F (74%) 47 unilateral (28M, 19F) 62 bilateral (39M, 23F)	Japan	2.05 cm anterior to the Lambda and Obelion	0.50-1.5 mm	-It reflects redirected bone stresses around a circular opening, resulting in reduced tensile stresses and increased compressive stresses adjacent to the PF.	PF-L: 3.8 cm
Collipal et al. (22)	Absent, Single, Double	2009	Dry skull	39	Bilaterally 23 (58.97%) Unilaterally 10 (10.25%) Right (15.38%) Left (10.25%)	Chile	The junction of the SS with the Lambda	0.37-2.65 mm	The contribution of these morphometric data of the PF allows increasing anatomical knowledge and serves as a basis for future anatomical clinical studies.	6.29 mm 33.25 mm PF-L
Murlimanju et al. (19)	Absent, Single, Double, Triple	2015	Dry skull	58	83 (71.5%)	South India	The junction of middle 1/3 and posterior 1/3 of the parietal bone.	Unknown	-It's critical to identify the parietal EV and accessory veins to reduce the loss of blood during surgery. -The most of the PF were situated about 4–8 mm from the sagittal suture.	PF-SS: 6.7±2.9 mm right 6.8±2.8 mm left
Tsutsumi et al. (24)	Absent, Single, Double, Triple	2016	MRI	104 (52M, 52F)	78/104 (75%) 116 PF (68% single, 30% double, 2% triple, 9.5% symetry)	Japan	Coursed above the SSS	Unknown	-EV demonstrated a relatively uniform sagittal path, despite perforating the skull at varying angles. -The PF and EV can be used as markers for the SSS that is directly below.	Unknown
Shantharam and Manjunath (5)	Absent, Single, Double	2018	Dry skull	78	87 (55.77%) (bilaterally 37.18%; unilaterally 18.59%)	South India	Middle and posterior 1/3 of parietal bones	01.99±0.78 (0.86-5.57)	-An important relationship between the emissary foramina and the diploic veins of the skull, which are involved in the spread of infection from the extra cranial veins to intracranial sinuses -The EV may be ruptured during the surgical procedure and cause spontaneous bleeding	PF-SS: 07.34±4.12 PF-L: 37.95±8.75

Table 3. Continued

Author et al.	PF	Year	Study design	Total number	Incidence (%)	Place	Location	Average size (mm)	Clinical significance	Distance
Halagatti and Sagar (2)	Absent, Single, Double, Triple	2018	Dry skull	215	326 (75.6%) Single 283, Double 35, Triple 8	India	The junction of the middle and posterior 1/3rd of the parietal bone.	N/A	-The number and location of PF helps in knowing the communications between dural venous sinuses and scalp veins. -Their location is also important for analysing the avulsion injuries of scalp and neurological surgeries.	PF-SS: 6.4±2.6 mm
Naidoo et al. (1)	Absent, Single, Double	2021	Dry skull	100	68% (bilaterally 32%; unilaterally 35%)	South Africa	Bilateral: 32 Unilateral: 35 SS: 5	1.55 mm (0.74 0 3.08 mm)	-The high incidence of the PF and EV of the cranium will be encountered by the Neurosurgeon, therefore knowledge of the anatomy of the emissary PF is imperative.	9.02 mm
De Souza et al. (16)	Absent, Single, Double, Triple, Quadruple	2021	Dry skull + MRI	89 dry skul 51 M 38 F 123 (MRI) 81 M, 42 F	Male: 43/51 (84.3%) Female: 32/38 (84.2%) Bilaterally 54.9% male 44.73% female Unilaterally M R 8/51 (16%) L 7/51 (14%) F R 8/38 (21%) L 7/38 (18%)	Brazil	The proximity of the SS and posterior part of the parietal bone	61 (75.3%) M, 26 (61.9%) F Bilaterally 45.9% M 53.8% F Unilaterally M R 21.3% L 32.7% F R 34.6% L 11.5%	-No major differences were encountered between the sexes regarding the anatomical features of PF	Male: 7.1±2.5 mm Female: 7.4±2.7 mm
Liu et al. (17)	Single	2021	Dry skull	280	82.86%	China	Most PFs were anteromedial direction	1.02±0.72 mm (left) 1.07±0.67 mm (right) 1.77±0.44 mm (on SS)	-The intracranial and extracranial communication was 39.97% and the incidence,location,diameter of PF were important for imaging diagnosis and neurosurgery	PF-SS: 5.90±2.78 mm (left), 5.85±2.75 mm (right)
Shmarhalov et al. (18)	Absent Single Double	2022	Fixed skull	42	85.7% (n=36) 54.8% (n=23) bilateral 30.9% (n=13) unilateral 14.3% (n=6) absence	Ukraine	The most frequent location of the PF was at the side of the SS, mid of the distance between the vertex and L	0.5-2.7 mm 1.7±0.6 mm (right) 2.7±0.5 (left)	To assist surgical and radiological procedures, it is essential to have in-depth knowledge of the anatomical differences of PF across various ethnicity	PF-L: 22.5-62.0 mm PF-bregma: 62.0-99.0 mm
Present study	Absent, Single, Double, Triple, Quadruple Quintet	2022	Dry skull	166	74.6% (right side) 74.7% (left side) M: 63.3 F: 36.7	Turkey	Bilateral or unilateral side of the parietal bone	Bilateral: 74.65%, unilateral: 55.75%, median: 33.7%	-Although the incidence of PF was 74% in our study, it was higher in males than in females -The significant differences in the PF-SS on the left side according to sex should be considered in surgery. -The current study revealed that PF has an asymmetrical distribution in the skull. -It may aid in safe movements around the PF during the surgery.	PF-LS: 39.88±1.99 (left) 40.69±1.67 mm (right). PF-SS:12.87±1.25 mm (left) 11.95±1.21 mm (right)

CN: Cranial nerve, EV: Emissary vein, F: Female, L: Lambda, LS: Lambdoid suture M: Male, MPF: Median parietal foramen, MRI: Magnetic resonance imaging, PF: Parietal foramen, SS: Sagittal suture, SSS: Superior sagittal sinus

Circular, oval, slit-like, and enlarged PFs were also detected in our study. The size of the PF and how far away it is from the midline affect the shape of the PF, and differences may be caused by alterations in the ossification process (18). A slit or V-shaped notch caused by a prolonged ossification process behind the parietal bone and especially in the obelion is known as the sub-sagittal suture or third fontonel (6). According to reports, heterozygous mutations of MSX2, an autosomal dominant gene, cause the enlarged PF and contiguous gene deletion syndrome (Potocki-Shaffer syndrome) with oval deformities of parietal bone (25). The PF often has a well-defined border, which aids the radiologist in distinguishing it from other clinical situations such as lytic lesions and burr holes during surgery (5,14). However, in a study, the margins of PF were not regular due to the presence of a small groove close to the PF (21). The variations in PF might be related to the changes in the embryological development of the parietal bone (3).

It has been revealed that knowledge about the prevalence and location of PF may help neurosurgeons modify the procedures to reduce the injury risk of EV and related arteries (1,26). The early fusion of the SS, excessive bone growth, and aberrant fibroblast growth factor (FGF) might cause craniofacial deformity and osteogenic differentiation (7). More than one PF could be explained by a delayed or incomplete ossification process of the parietal bone or third fontanel. In our study, the presence of more than one PF was detected (n=1-5), this indicates a delayed ossification process. PF has implications for bone biomechanics, suture development, reduced tensile stresses, increased compressive stresses, and transfer of infection to the cerebral cavity (2,7). The other hypothesis that ALX_4 is a specific gene for the formation of PF in the deletion syndrome is supported by individuals with 11p11.2 deletion who also have bilateral PF (25).

Additionally, enlarged PF has been recorded in Chinese populations; however, only 16% have a potential third locus on 4q21-q23, which are caused by these mutations (21). We can compare the allometric patterns in various populations thanks to epigenetic variants such as PF, which serve as indicators of embryological processes (4). The variations in PF might provide significant insights into the structure of the human genome and advance our knowledge of the causes of congenital diseases.

Study Limitations

The causes of death, pathology, and neurological or congenital disorders of the measured skulls were unclear. Therefore, we could not establish a correlation between our findings and clinical impairments. Despite these limitations, the study has strengths in emphasizing the possible association between PF, SS, and LS in dry skulls and the differences between the sexes. This relationship between them might play a role in identifying various ethnicities and reducing the surgical complications surrounding the PF.

Conclusion

The significant differences in the PF-SS on the left side according to sex should be considered in surgery. Other findings of the study are the presence of more than one PF and its asymmetric distribution in the skull. This might be due to the delayed ossification process or differences in ethnicity.

Ethics

Ethics Committee Approval: The current study was approved by the Ethics Committee of the Akdeniz University Faculty of Medicine (approval date: 26.08.2020 and decision number: 596).

Informed Consent: Not required.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: O.G., E.O., F.B.Y., Design: O.G., E.O., F.B.Y., Data Collection or Processing: O.G., E.O., Analysis or Interpretation: O.G., E.O., Literature Search: O.G., E.O., Writing: O.G., E.O.

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

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Original Article

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Impact of Subablative Erb:Yag Laser Applications on Vaginal Resting and Contraction Pressures

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Abstract

Aim: The existing data on vaginal laser treatment in pelvic floor dysfunction is encouraging and shows improvement in urinary incontinence (UI) and genital prolapsus symptoms. The aim of this study was to examine the effects of subablative Erb:Yag laser applications for incontinence and vaginal laxity (VL) in terms of changes in vaginal resting and contraction pressures.

Methods: This observational, assessor-blind study was conducted in the Women's Health Clinic of the American Hospital from 2015 to 2017. Data from 176 patients, aged 18 to 55, were analyzed. Each patient received a total of two laser applications, performed six weeks apart. The indications were UI or VL. The pre- and post-treatment vaginal pressures during resting and contraction were measured with a perineometer (Peritron 9300 Perineometer Laborie). All the laser procedures were performed by the same physician, and measurements were carried out by another physician. Laser applications were performed with an Er:YAG laser SMOOTH, Fotona SP Dynamis (Fotona, Slovenia).

Results: The age of patients showed a high correlation with the pre-treatment resting and contraction vaginal pressure values (r=-0.23, p=0.002, and r=-024, p=0.002, respectively). After evaluation of all cases, vaginal pressure values measured during rest and contraction showed a significant increase. The correlation coefficient was 0.67 for resting pressure values and 0.72 for contraction pressure values before and after treatment. There was no significant difference between the VL and UI groups in terms of the increase in pre- and post-treatment resting and contraction pressures (p=0.957 and p=0.743, respectively). After analyzing the effect of age, no difference was observed between the VL and UI groups in terms of pressure increase (p=0.515 and p=0.568, respectively). A total of 115 patients, or 61.8% of the cases, stated that they were "satisfied" or "very satisfied" with the treatment.

Conclusion: We observed significant improvements in intravaginal resting and contraction pressure values, which we interpreted as an objective strengthening effect of laser treatments on the pelvic floor.

Keywords: Vaginal laser, perineometer, pelvic pressure, vaginal pressure, vaginal laxity, urinary incontinence, pelvic floor

Introduction

Interest in non-invasive or minimally invasive treatment options in all areas of medicine and the frequency of their application are increasing. In gynecology, vaginal laser applications (CO_2 laser, Erb:Yag laser) are still controversial, but they continue to gain extreme popularity (1). The frequency of application is increasing in cases of all types of incontinence (mix, urge, or stress incontinence), vaginal laxity (VL), the genitourinary syndrome of menopause, and pelvic organ prolapse, although there is not enough evidence for the beneficial effect (2). The Er:YAG laser exerts a gradual thermal effect. After breaking the cross-connections of collagen in the subepithelial connective tissue-which is rich in water-and shortening the collagen fibrils, the thermomechanical interaction, which spreads to deeper tissues, causes tissue contraction and stretching, and then produces the formation of new collagen fiber. The effect of both mechanisms of action on the reshaping of connective tissue has been shown histologically (3).

A guideline has not yet been established regarding the place of laser applications for incontinence or pelvic organ prolapse in the treatment steps, as there is no FDA approval for these treatments. While informing the patient about possible treatment modalities, unless the patient's specific situation requires otherwise, the general tendency

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is to start with non-invasive or minimally invasive methods before requiring surgery. Thus, when recommending laser, it is possible to consider it as a minimally invasive application that can be offered to the patient after other non-invasive treatment modalities such as lifestyle modification, Kegel exercises, and pelvic floor exercises. Because of general practices, this ranking is more a reported opinion than a guideline.

Laser therapy can effectively improve trophism through a restorative reaction consisting of collagenesis, elastogenesis, and angiogenesis. This creates a warming process at the level of the lamina propria (3). Thus, without acting on the fascia, the collagen and elastin fibers in the mucosa are tightened and the support function is strengthened. In a recent prospective multicentric randomized placebo-controlled trial to evaluate the efficacy and safety of non-ablative Er:Yag laser for the treatment of stress urinary incontinence (SUI), O'Reilly describes the effect of laser as increasing the support of the connective tissue around the bladder neck, reducing urethral hypermobility, and contributing to pelvic floor support (4).

In our study, the effects of laser applications for UI and VL on vaginal resting and contraction pressures were examined. All participants reported experiencing discomfort due to incontinence or VL in their daily lives. Since the pelvic floor resistance of each patient was evaluated on its own before and after therapy, parity, body mass index (BMI), and additional pathologies were not considered.

Materials and Methods

Compliance with Ethical Standards

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and all its revisions. The data were generated, documented, and processed in accordance with good clinical practice (GCP). Extensive written informed consent for laser treatments was obtained from all subjects before every laser session. The patients also agreed to participate in the study and gave consent to publish their data. The study was approved by the Scientific Ethics Committee of Koç University (2022.273.IRB1.114).

Study Design

This observational, assessor-blind data analysis was conducted at the American Hospital. Data from 176 patients, aged between 18 and 55, treated between 2015 and 2017 were analyzed.

The patients complained of UI or VL. The pre- and post-treatment vaginal pressure values during resting and contraction were measured with a perineometer (Peritron 9300 Perineometer Laborie). The Peritron perineometer had a tapered vaginal probe with a measurable length of 55 mm and was connected to the main body by an 80 cm plastic tube, and when the vagina was compressed, the pressure sensor measured the vaginal pressure in cm H_2O. A medium-sized vaginal probe was used in this study.

Vaginal pressure measurements were performed in the supine lithotomy position. The probe -condom and gel-applied- was placed in the mid-part of the vagina, and the pressure values during rest and contraction were measured.

All the laser procedures were performed by the same physician, and measurements were carried out by another physician. Before laser applications, local anesthetic cream (EMLA 5% cream; 25 g lidocaine and 25 mg prilocaine) was applied to the introitus and distal 1/3 of the vagina and kept at a minimum for 10 min to take effect. Laser applications were performed with an Er:YAG laser SMOOTH, Fotona SP Dynamis (Fotona, Slovenia). The Er:YAG laser we used has a wavelength of 2940 nm (Er:YAG laser SMOOTH Fotona, Slovenia); it is the patented "SMOOTH MODE" that exerts a non-ablative effect on tissues and results in a controlled warm-up, creating a gradual thermal effect.

Two laser sessions, performed six weeks apart, were described as "treatment", and the data from patients who completed two sessions were included in the study. During rest and contractions, pre-treatment vaginal pressure measurements were taken with a perineometer. Then, two laser sessions six weeks apart were performed as per indication. The second measurement was carried out 6-8 weeks after the second laser application. None of the patients received pelvic floor muscle (PFM) exercises before or between laser sessions. Since each patient was its own control, parity, BMI, and concomitant diseases were not subject to evaluation.

In addition to the pre- and post-treatment pressure value comparison, the patients were asked to evaluate the treatment results using the 5-point Likert scale (1= very dissatisfied; 2= dissatisfied; 3= no change; 4= satisfied; 5= very satisfied). There was no separate symptom-based assessment.

The laser protocols used in the study were as follows:

For urinary incontinence, a total of three steps were applied as per the protocol determined on the device.

Step 1: Linear from proximal to distal, clockwise, by delivering energy to the entire anterior vaginal wall surface, 6 passes.

Step 2: Linear from proximal to distal, by delivering the energy with a 360°, 3 passes.

Step 3: Delivering energy, clockwise at the introitus with 3 passes.

For vaginal tightening: a total of two steps were applied according to the parameters determined in the device for that indication.

Step 1: Linear, by delivering energy to the entire vaginal wall, three passes.

Step 2: Introitus and the outer 1/3 of the vagina, delivering energy clockwise, three passes.

All laser parameters used are listed in Tables 1 and 2.

Statistical Analysis

Continuous variables were defined by means and standard deviations, and categorical variables were defined by numbers and ratios. Pre- and post-treatment measurements were compared using a Paired sample t-test, and categorical variables were compared using Fisher's exact test. The variance in measurements was evaluated using the Pitman-Morgan test.

The relationship between the measurements and the subject's age was evaluated by correlation analysis and expressed with Pearson r values. The change between pre- and post-procedure measurements was evaluated by the mean difference and correlation coefficient. Regression analysis was performed on a general linear model to control the female age variable. In the context of two-way hypothesis evaluation, $p<0.05$ was considered statistically significant. Statistical analysis and figures were performed with the Statistical Package for the Social Sciences (SPSS, 24.0) and GraphPad Prism (9.0.0) applications.

The primary outcome measure was the difference between rest and contraction pressures in the vagina, and the secondary outcome measure was the feedback received from the treatment.

Results

The laser procedures were held between March 2015 and February 2017. Vaginal laser applications were performed twice, six weeks apart, on 176 patients aged between 27 and 55.

Of the 176 patients involved, 94 (53.4%) and 82 (46.6%) were treated for VL and UI, respectively. The mean age of patients was 39.6±7.6 (27-55). VL cases were younger than UI cases (36.6±6.1 vs. 43.0±6.6, $p\leq0.0001$).

We observed that the age of patients showed a high correlation with the pre-treatment resting and contraction vaginal pressure values ($r=0.23$, $p=0.002$, and $r=-024$, $p=0.002$, respectively). The correlation persisted to a limited extent with the post-treatment values ($r=-0.15$, $p=0.046$, and $r=-0.16$, $p=0.033$, respectively).

The violin plot graph of the measurements made before and after the treatment is presented in Figure 1. When all cases were evaluated together, vaginal pressure values measured during rest and contraction showed a significant increase (Tables 3 and 4). The correlation coefficient was 0.67 for resting pressure values and 0.72 for contraction pressure values before and after treatment.

While there was a decrease in pressure values in 11 cases (6.2%) in pre- and post-treatment resting pressure measurements, no change was observed in 20 cases (11.4%). Again, in pre- and post-treatment contraction pressure measurements, a decrease in pressure values was observed in 6 cases (3.4%), while no change was observed in 17 cases (9.7%). The distribution of the calculated average changes between the measurements, as shown in Figure 2.

There was no significant difference between the VL and UI groups in terms of the increase in pre- and post-treatment resting and contraction pressures ($p=0.957$ and $p=0.743$, respectively). After analyzing the effect of age, no difference was observed between the VL and UI groups in terms of pressure increase ($p=0.515$ and $p=0.568$, respectively).

Patients' subjective perceptions were scored on a 5-point Likert scale, with 1 being the worst and 5 being the best. The results are shown in Figure 3. A total of 115 people, or 61.8% of the cases, stated that they were "satisfied" or "very satisfied" with the treatment.

Table 1. Laser parameters for urinary incontinence

Handpiece	Speculum	Mode	Spot	Fluence	Repetition	Stacking	Passes
PS03+ GAc	Glass	Smooth	7 mm	6 J/cm²	2 Hz	7	6
R11+ GCc	Glass	Smooth	7 mm	3 J/cm²	2 Hz	7	3
PS03		Smooth	7 mm	10 J/cm²	1.6 Hz	7	3

Table 2. Laser parameters for vaginal laxity

Handpiece	Speculum	Mode	Spot	Fluence	Repetition	Stacking	Passes
R11+ GCc	Glass	Smooth	7 mm	3 J/cm²	2 Hz	7	4
PS03		Smooth	7 mm	10 J/cm²	1.6 Hz	7	3

Table 3. Resting (vaginal pressure measurements pre and post treatment)						
	Number	Rest before treatment (cm H_2O)	Rest after treatment (cm H_2O)	Average difference	95% CI	p-value
Vaginal laxity	94	6.85±5.14	10.63±5.30	3.77	2.89-4.66	<0.0001
Incontinence	82	6.12±4.58	9.87±4.65	3.74	2.94-4.54	<0.0001
Total	176	6.51±4.89	10.27±5.01	3.76	3.16-4.36	<0.0001
Paired samples t-test, values represent mean -/+ 2SD and mean difference (95% confidence interval) CI: Confidence interval, SD: Standard deviation						

Table 4. Contraction (vaginal pressure measurements pre and post treatment)						
	Number	Pre-treatment contraction (cm H_2O)	Post-treatment post-treatment contraction (cm H_2O)	Average difference	95% CI	p-value
Vaginal laxity	94	23.04±11.40	33.47±13.32	10.42	8.49-12.36	<0.0001
Incontinence	82	17.83±10.45	27.78±13.17	9.95	7.82-12.08	<0.0001
Total	176	20.61±11.25	30.82±13.51	9.53	8.79-11.6	<0.0001
Paired samples t-test, values represent mean -/+ 2SD and mean difference (95% confidence interval) CI: Confidence interval, SD: Standard deviation						

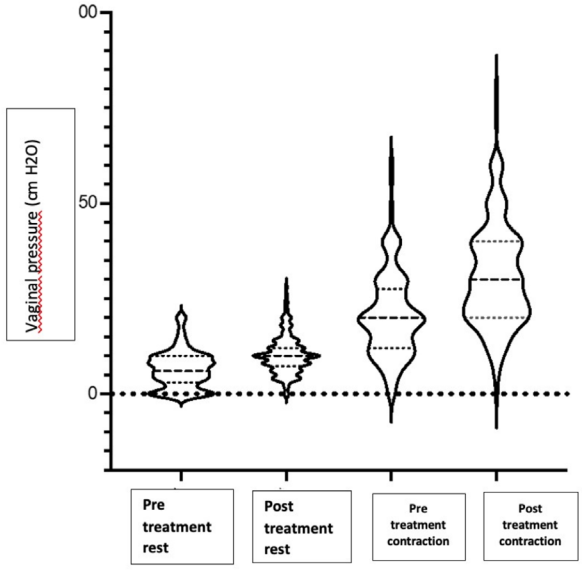

Figure 1. Violin plot chart pre-post treatment vaginal pressures mean and 25%-75%

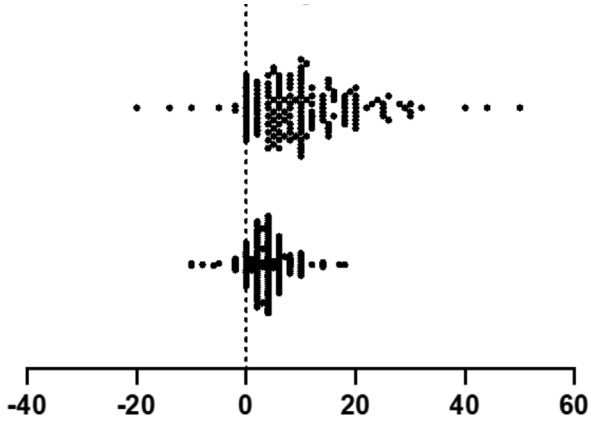

Figure 2. Distribution of pre and post treatment mean pressure differences (cm H_2O)

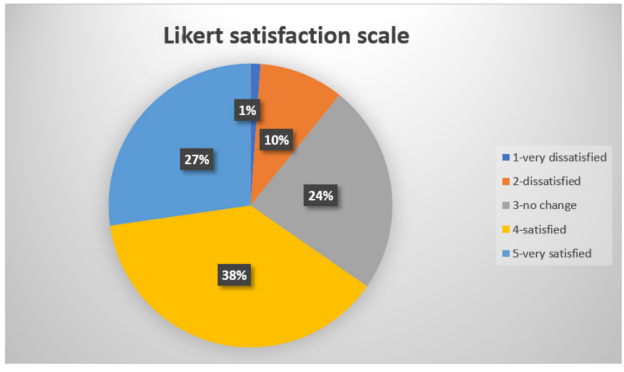

Figure 3. Likert 5-digit satisfaction scale options for patients (1- very dissatisfied, 2- dissatisfied, 3- no change, 4- satisfied, 5- very satisfied)

Discussion

This study differs from many other laser studies in that it uses a very simple method to show the effect of laser, which is applicable and affordable in every clinical setting. Our study is focusing on the changes in pelvic floor pressures after laser treatment, not only during contraction but during resting as well. Resting pelvic floor capacity is important for maintaining support for the pelvic organs. We observed a decline in pre-treatment resting and contraction vaginal pressure values with age, which can be interpreted as an age-related worsening in the contractile capacity of the tissue. But regardless of age, there was a significant increase in pre- and post-treatment pressure values in both groups.

Beside many observational and few randomized controlled trials (5-9), a recently published randomized, double-blind, sham-controlled study from Page used patient symptoms, validated screening tests, standard evaluation forms, and microscopy to demonstrate the effects of laser. There has been a lot of research done on the laser treatment of incontinence and genitourinary syndrome (10).

In PUBMED, there are a very limited number of publications "Lee (11), Fistonić et al. (12), Blaganje et al. (13)" on the use of perineometers for measuring pelvic floor pressures in laser applications. In Fistonić et al's. (12) study, they analyzed 42 women with SUI and reported a significant improvement in perineometry values after Er:YAG treatment. In another randomized, sham-controlled study by Blaganje et al. (13) in 2018, 114 cases of SUI and vaginal relaxation were evaluated. Patients were clinically examined at baseline and 3 months after treatment. They also answered questionnaires for SUI severity and sexual function assessment, and the PFM function was assessed with perineometry. Improvements in PFM strength and maximum pressure in the laser group were significantly better than those in the sham group (13).

Some recent studies used the vaginal tactile imager (VTI) technique to evaluate the vaginal elasticity and strength. Vaginal tactile imager allows biomechanical evaluation of soft tissue along the anterior, posterior, and lateral vaginal walls. The vaginal probe comprises a tactile sensor array, which is installed on the probe surface and is in contact with the vaginal wall during the examination procedure. The implemented VTI software allows real-time visualization of the pressure pattern on the probe head and stores the data in a digital format (14). An increase in vaginal pressures and elasticity has been reported in two recent studies using this measurement technique used by Gao et al. (15) and Lauterbach et al. (16) to evaluate the effects of CO_2 laser in SUI.

Of course, whether the significant difference in vaginal pressure levels observed after treatment is clinically reflected in the functions remains to be determined. The sole purpose of our study was to show vaginal pressure changes before and after the laser. Since the changes in symptom severity were not the main subject of this study, unlike many other laser studies, no distinction was made for the type of incontinence.

The study group consisted of a mixed group of patients with incontinence and VL, and as a single common evaluation criterion, patients were asked to subjectively evaluate the treatment outcomes and improvement in their complaints. To assess treatment success, we used a 5-digit Likert scale, which showed that 65% of patients were satisfied or very satisfied with the treatment. Even though there is no other screening test for symptom severity, this is an important outcome because it reflects patient satisfaction.

Simultaneously, additional applications to extend the duration of this positive effect should be determined. For example, it may be useful to teach patients regular Kegel exercises to get the maximum benefit from the pressure change obtained from the treatment. Combining physiotherapy practices with laser treatment in the patient's treatment program can be another option. Doing the pelvic floor exercises properly plays a crucial role, as the treatment will not bring any benefit if they are performed incorrectly. PFM training is shown as a Class A recommendation by the International Continence Society for treating stress, urinary incontinence, and pelvic organ prolapse (17-19).

However, the fact that patients must go to the hospital for the exercises several days a week is the biggest obstacle to compliance with the treatment. Hence, strengthening the supportive tissues of the pelvic fascia with laser applications that can be performed 4-8 weeks apart can provide us with satisfactory results that can be achieved in a shorter time interval. Laser treatments in gynecology are criticized for the superficial mucosal and submucosal effects, which do radiate to the pelvic fascia, but as an objective finding, the support in the connective tissue and the presence of the strengthening effect of laser, which means an increase in vaginal pressure values, were clearly observed in our study group. If the success and effectiveness of PFM training (the recommended treatment modality in pelvic organ prolapse) are objectively measured by the improvement in vaginal pressures, any other method resulting in an increase in vaginal pressures should be beneficial as well.

We know that pelvic relaxation is the weakness of the pelvic fascia, and this problem can manifest itself as pelvic organ prolapsus. Although the target areas of vaginal laser treatment are the mucosa and submucosa, we see the effect of treatment as a significant increase in vaginal resting and contraction pressures.

Effective measurement of vaginal pressure must assess the treatment's success. Physiotherapy and

biofeedback applications are important invasive treatment modalities for pelvic floor rehabilitation. The objective assessment of the success and effectiveness of these applications is based on the measurement of vaginal resting and contraction pressures. For this purpose, the Oxford scale, which provides a subjective evaluation, and validated perineometric measurements are frequently performed as well (20-22). In our study, we preferred perineometric measurements as an objective scale.

The measurement of PFM resistance depends on the size and location of the probe, the cooperation of the patient, and the experience and skills of the examiner assessing the vaginal pressures (22,23). This was not the case in our study, as the measurements were performed by a single examiner.

Study Limitations

The major limitation of the study can be seen in the lack of a control group with another treatment method and a validated questionnaire for symptom severity measurements before and after treatment. The study group consisted of a mixed group of patients with incontinence and VL, and as a single common evaluation criterion, patients were asked to subjectively evaluate the treatment outcomes and improvement in their complaints, and the patient's satisfaction was the benchmark of treatment success. Besides these limitations, there are certain strengths in our study. First, all vaginal pressure measurements were performed by a single examiner, who was blinded to the type and stage of the patient's treatment. All laser treatments were applied by another physician. The sample size is another study strength; the large sample size compared to similar studies and the easily applicable, objective measurement method for the laser effect make this study valuable for further research.

Conclusion

Our findings regarding the changes in vaginal pressure after laser irradiation are promising for the use of vaginal laser treatments, alone or along with pelvic floor physiotherapy, as a new treatment protocol in pelvic floor rehabilitation. The perineometer, as an assessment tool for pelvic pressure, is useful and easy to use. By increasing the support of the connective tissue around the bladder neck and contributing to pelvic floor support, non-ablative Er:YAG laser therapy is a promising option as a non-surgical treatment and should be offered to patients suffering from UI and VL.

Ethics

Ethics Committee Approval: The study was approved by the Scientific Ethics Committee of Koç University (2022.273.IRB1.114).

Informed Consent: Extensive written informed consent for laser treatments was obtained from all subjects before every laser session.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.A., S.A., Design: E.A., S.A., Data Collection or Processing: E.A., S.A., Analysis or Interpretation: E.A., S.A., Literature Search: E.A., Writing: E.A.

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

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Original Article

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Use of Complementary Therapy in Lung Cancer Patients Treated with Chemotherapy and its Effect on Survival: A Cross-sectional Study

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Abstract

Aim: Complementary therapies are being increasingly preferred in patients receiving anticancer therapy to strengthen the effect of chemotherapy and control cancer-related symptoms. In this study, we investigated the prevalence of complementary therapy (CT), the factors associated with its use, physician-patient information sharing about CT use, and the effect of CT on the survival and treatment process in lung cancer patients receiving chemotherapy.

Methods: This study was designed as a cross-sectional study including patients who underwent chemotherapy for lung cancer between November 2020 and March 2022 in the department of medical oncology at Tekirdag Namik Kemal University. A structured questionnaire with twenty questions was used. Fluor-18-fluorodeoxyglucose positron emission tomography/CT, and brain magnetic resonance imaging were used to stage the patients. The stages were grouped as early (stages 1B-3A) and advanced (stages 3B-4A).

Results: A total of 242 patients included in the study. One hundred and forty-seven (60.7%) patients reported using at least one type of CT since the first diagnosis. "Families/relatives" (n=128; 63.7%) and "other patients" (n=67; 33.3%) were the primary sources from which patients obtained CT information. The most widely used CT methods were recorded as phytotherapy (79.6%) and apitherapy (59.2%). 125 (85%) of the patients said that they used CT to support their existing anticancer treatments. Of the patients using CT, 94 (63.9%) stated that they did not disclose their use of CT to their physicians. The majority of patients stated that their physicians did not inquire about using CT. In the cox regression analysis performed to determine survival benefit, no survival benefit from the use of CT was determined (hazard ratio=0.86, p=0.495). In the subgroup analysis, the use of CT was associated with survival in early-stage patients, but no survival relationship was found in advanced-stage patients (log-rank p=0.027 and p=0.842, respectively).

Conclusion: The use of CT in conjunction with medical treatment is common among patients with lung cancer. The influence of the oncologist in guiding the use of CT in cancer patients is weak. Additionally, the use of CT does not provide benefits in terms of survival.

Keywords: Lung neoplasms, complementary therapies, phytotherapy, surveys and questionnaires

Introduction

According to the 2021 data, except for skin cancers, lung cancer is one of the most common cancers in the world, and it is the most common type of cancer that causes death in both men and women (1). Surgery, chemotherapy, and radiotherapy are included in the definitive treatment options in non-metastatic stages, while chemotherapy, immunotherapy, and other palliative treatments are among the main treatments in metastatic stages (2). Because the majority of patients are diagnosed in advanced stages, the high mortality rate of lung cancer persists despite constantly improving medical science and technological opportunities (1,3).

Due to both the disease and difficulties in the treatment process, cancer patients must experience many psychological and physical side effects during the chemotherapy period. This situation both negatively affects patients' compliance with treatment and reduces their quality of life (4). The difficulties experienced by the patients have raised interest in different treatment options, including supportive and complementary therapy (CT), over the years (4-6). As a matter of fact, it has been

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reported in previous studies that patients using CT during the treatment process benefited positively (7). However, there is a risk of drug interaction between anticancer and complementary therapies (8). Additionally, its benefit or harm to survival is not yet known (9).

In this study, we investigated the prevalence of CT, the factors associated with the use of CT, and the effect of CT on the survival and treatment processes in lung cancer patients receiving chemotherapy. Additionally, the effect of supplemental therapy on the treatment process and the situation of physician-patient information exchange were examined from the patient's perspective.

Materials and Methods

Compliance with Ethical Standards

This study was performed in line with the principles of the Declaration of Helsinki. The Tekirdag Namik Kemal University Ethics Committee granted formal approval for this study (date: 29.09.2020; approval number: 2020.224.09.11). All participants received information about the purpose of the study and were assured of anonymity and confidentiality before signing a consent form. Informed consent was obtained from all participants in the study.

Study Design and Participants

This study was designed as a cross-sectional study including patients who underwent chemotherapy for lung cancer between November 2020 and March 2022 in the department of medical oncology at Tekirdag Namik Kemal University. Archive files were scanned before distributing the questionnaire to the patients who accepted to participate in the study. According to the information scanned from the hospital archives, patients who were 18 years of age or older at the time of their cancer diagnosis, had an adenocarcinoma or squamous cell lung cancer subtype, received chemotherapy for at least 2 months, and used CT for at least 3 months were included in the study. At the time of diagnosis, patients with a life expectancy of <3 months, an Eastern Cooperative Oncology Group (ECOG) performance score of 4, and those diagnosed with different types of cancer together or sequentially were excluded from the study (Figure 1). Computed tomography, fluor-18-fluorodeoxyglucose positron emission tomography/computed tomography, and brain magnetic resonance imaging were used to stage the patients. The stages were grouped as early (stages 1B-3A) and advanced (stages 3B-4A).

Participants were assured that their answers would be kept confidential. Written and verbal consent was received from the patients who accepted to answer the questionnaire. The questionnaire, consisting of 20 questions, was completed by the oncologist through face-to-face interviews.

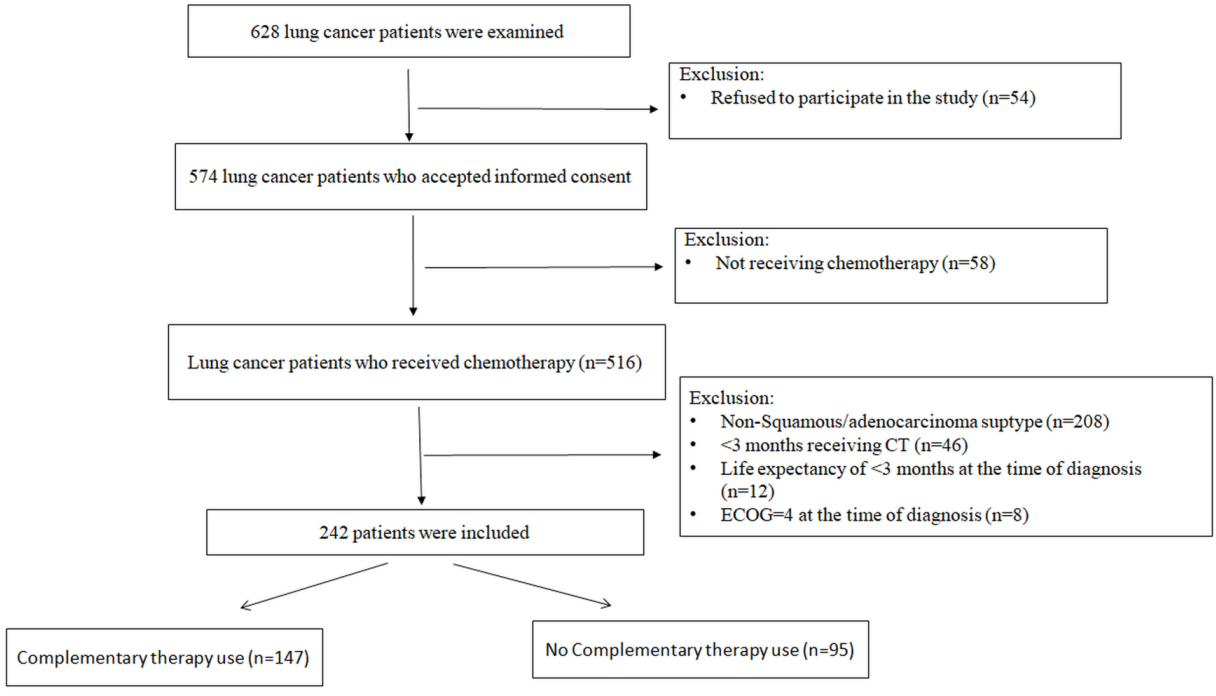

Figure 1. Algorithm for patients' inclusion and exclusion
ECOG: Eastern Cooperative Oncology Group

Study Questionnaire

To compare with the surveys in the literature, some of the survey questions were selected to be similar to the CT survey studies in the literature (6,10,11). The questionnaire was divided sequentially into four sections according to the areas of interest of the questions. In the first part (5 questions), the demographic attributes of patients and clinical characteristics were included. The histories of CT use before the disease, the level of knowledge of the patients about CT, and the sources from which they obtained CT information were questioned in the second section (6 questions). The questions in the third part (4 questions) were for determining the CT methods they used. CT methods (Phytotherapy, Apitherapy, Vitamin Supplements, Acupuncture, Homeopathy, Mushroom Supplements, and Cupping Therapy) were questioned in a manner similar to previous studies' questionnaires. In the fourth part (5 questions), the reasons given by the patients for applying for CT, their status in sharing it with their physicians, and the benefits and harms of CT for them were questioned. The questionnaire was designed in Turkish, and simple, clear expressions were used for the questions. In questions with multiple answers, the participants were instructed to select any or all appropriate responses. A pre-test including 10 people was conducted to see if the questions were clear, and some questions were changed at the end of these pre-tests. The survey study was started in its final form.

Statistical Analysis

Categorical measurements were summarized in numbers and percentage values, and continuous measurements were summarized as mean and standard deviation. The chi-square test or Fisher's exact test were used to assess the relationship between variables. Using retrospective data from the electronic record system, overall survival time (OS) was calculated as the time from the diagnosis time to the date of death or the patient's last follow-up. Survival analyses were performed using the Kaplan-Meier method, and the Log-Rank test was used for group comparison. A univariate analysis of factors affecting survival was performed with the Cox proportional-hazards model. All statistical analyses were performed using SPSS version 26.0 (IBM Corb, Armonk, NY). Statistical significance is defined as a p-value less than 0.05.

Results

Relationship between the characteristics of the patients and complementary therapy

The study was completed with 242 patients who agreed to complete the questionnaire. The median age was 64 years (range: 32-84 years). Ninety-two (38.2%) patients died during the follow-up period because of cancer-related reasons. Of the included patients, 147 (60.7%) reported that they used at least one type of CT. General characteristics of patients according to the status of CT use are demonstrated in Table 1.

Two hundred one (83.1%) patients had knowledge about CT. "Families/relatives (n=128; 63.7%)" and "other patients (n=67; 33.3%)" were the primary sources from which patients with CT knowledge obtained information (Table 2).

The number of patients who had knowledge about CT before the diagnosis of the disease was 99 (40.9%), and 42 (17.4%) patients stated that they used CT for different reasons before they were diagnosed with cancer. Additionally, the patients who had used CT for another reason before the diagnosis received CT more during the chemotherapy than the patients who had not used it before the diagnosis (p<0.001) (Table 1).

Reasons for and disclosures about using CT with a physician

Sixty-nine (28.5%) patients reported that they found the current treatments "insufficient" in providing recovery. 75.4% (n=52) of these patients said they used CT during the chemotherapy process. In the analysis, it was determined that the patients who reported the conventional treatment as "inadequate" used CT statistically significantly more than those who reported it as "adequate" (p=0.003).

Fifty-three (36.1%) patients told their doctors about their CT use. Age, gender, educational status, performance status, and disease stage were not determined to be associated with disclosing CT usage with physicians (p=0.282, p=0.607, p=0.284, p=0.632, p=0.092, respectively). The reasons for using CT, the answers of their physicians when they shared their CT usage with their physicians, and the reasons why patients avoided informing their doctor about CT are shown in Table 3.

Thirty-two (21.8%) patients using CT said that they greatly benefited from it, and 54 (36.7%) of them said that they partially benefited. Two (1.4%) patients said that they suffered from CT damage. Fifty-nine (40.1%) patients answered "neutral" about the CT they received. It was found that patients who reported a positive response to CT (beneficial or partially beneficial) strongly advised other patients to use CT more frequently (p<0.001).

Complementary therapy methods

While 44.9% (66) of the users stated that they used only one type of CT, the remaining reported that they used more than one type of CT. The most common CT methods used by the patients using CT were recorded as phytotherapy (79.6%) and apitherapy (59.2%). Detailed results are shown in Table 4.

Survival Analysis

The median OS (mOS) for all patients was 15.7 months (range, 5.1-181). The mOS of the patients using CT was 16.2 months, and the mOS of the patients not using CT was found to be 15.4 months, and there was no statistically significant difference between the two groups (log-rank p=0.494). The relationship between patient characteristics and CT types used and survival was examined using univariate Cox regression analysis. Complementary therapy use did not have any effect on survival [hazard ratio (HR)=0.86, 95% confidence interval (CI): 0.57-1.32, p=0.495]. In the analysis performed, poor ECOG performance status (HR=1.83, 95% CI: 1.05-3.21, p=0.034), the presence of metastases (HR=2.71, 95% CI: 1.73-4.24, p<0.001), advanced disease stage (HR=2.49, 95% CI: 1.28-4.84, p=0.007), and the absence of a surgical history (HR=0.51, 95% CI: 0.29-0.90, p=0.020) were associated with shorter survival time (Table 5).

Patients were divided into two subgroups: "early stage" and "advanced stage". It was found that the use of CT in early-stage patients was associated with survival (mOS=42.37 months, 95% CI: 18.30-66.44, log-rank p=0.027), while the use of CT in advanced-stage patients was not statistically significantly associated with survival (mOS=20.57 months, 95% CI: 16.48-24.66, log-rank p=0.842) (Figure 2).

Table 1. Distribution of the characteristics of the patients according to their status of complementary therapy use

		Complementary Medicine		
Variables	**Total N (%)**	**No N (%)**	**Yes N (%)**	**p-value***
Age				
<65	126 (52.1)	48 (38.1)	78 (61.9)	0.700
≥65	116 (47.9)	47 (40.5)	69 (59.5)	
Sex				
Male	213 (12.0)	88 (41.3)	125 (58.7)	0.076
Female	29 (88.0)	7 (24.1)	22 (75.9)	
Education				
Iliterate	14 (5.8)	5 (35.7)	9 (64.3)	0.540
Primary School	202 (83.5)	79 (39.1)	123 (60.9)	
High School	20 (8.3)	10 (50.0)	10 (50.0)	
University	6 (2.5)	1 (16.7)	5 (83.3)	
ECOG status				
0-1	200 (82.6)	81 (40.5)	119 (59.5)	0.387
≥2	42 (17.4)	14 (33.3)	28 (66.7)	
Histopathology				
Squamous	113 (53.3)	47 (41.6)	66 (58.4)	0.486
Adenocarcinom	129 (46.7)	48 (37.2)	81 (62.8)	
Metastatic status				
Metastatic	127 (52.5)	48 (37.8)	79 (62.2)	
Non-metastatic	115 (47.5)	47 (40.9)	68 (59.1)	0.625
Stage				
Early	37 (15.3)	16 (43.2)	21 (56.8)	0.589
Advanced	205 (84.7)	79 (38.5)	126 (61.5)	
Previous conventional treatments				
Radiotherapy	115 (100.0)	51 (44.3)	64 (55.7)	0.123
Surgery	57 (100.0)	24 (42.1)	33 (57.9)	0.614
Previous complementary therapy				
Yes	42 (17.4)	3 (7.1)	39 (92.9)	
No	200 (82.6)	92 (46.0)	108 (54.0)	**<0.001**

*Chi-square test or Fisher's exact test was performed. Significance level set at <0.05
ECOG: Eastern Cooperative Oncology Group

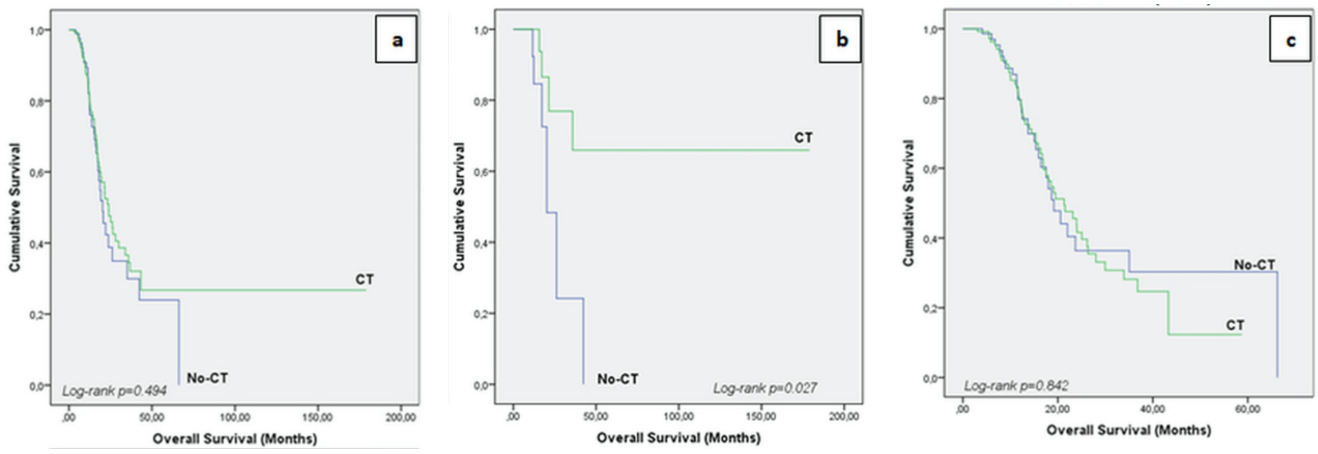

Figure 2. Kaplan-Meier survival curve by CT status, a) All patients, b) Early stage, c) Advanced stage
CT: Complementary therapy

Table 2. Sources of CT information of the patients		
	n	**%**
Friends/family	128	63.7
Internet/social media	70	34.8
Other patients	67	33.3
TV/radio	29	14.4
Health centers	17	8.5
Book/newspaper/magazine	9	4.5
Education centers	2	1.0
CT: Complementary therapy		

Table 3. The reasons of the patients for using complementary therapy and their status of sharing these with their physicians	
Why did you use CT? (n=147)	
	n (%)
To reduce the side effects of my treatments	51 (34.7)
To improve physical well-being	42 (28.6)
To support my treatments	125 (85.0)
To feel better and step up my hope	56 (38.1)
Desire to do everything possible to fight the disease	39 (26.5)
If you received CT and shared this with your doctor, how did your doctor react? (n=53)	
	n (%)
Suggested me to stop treatment	6 (11.3)
Encouraged me to continue treatment	26 (49.1)
Neither suggested nor recommended	21 (39.6)
If you have not shared this with your doctor despite having CT, what is the reason? (n=94)	
	n (%)
Because my doctor never asked me about this	82 (87.2)
I thought my doctor couldn't understand me	3 (3.2)
I thought my doctor wouldn't approve the use	9 (9.6)
CT: Complementary therapy	

Discussion

In this study, we investigated the prevalence of CT, CT types, the patients' sources of CT information, predictive factors for CT, and the effect of using CT on survival in lung cancer patients receiving chemotherapy. In our study, we found that the prevalence of using CT was 60.7%. In a study that has been conducted in 8 different European countries, including only lung cancer patients, the prevalence of use of CT has been reported to be 23.6% (10). The prevalence has been reported to be 45% in a study conducted in America and 41% in a study conducted in Asia (11,12). Dağtaş Gülgün and Kaya (13), in a previous study conducted in Turkey, reported the use of CT to be 56.5%, similar to the prevalence in our study, and Erbaycu et al. (14) reported the use of CT to be 27.4% in lung cancer patients receiving chemotherapy. These differences in CT usage rates may be related to differences in belief or culture, geographical differences between regions, or differences in confidence in conventional treatments (15,16). In our study, no relationship was found between

Table 4. CT preferences, phytotherapy and apitherapy products of the patients

	n (%)
Complementary therapy types	
Phytotherapy	117 (79.6)
Apitherapy	87 (59.2)
Vitamin supplements	12 (8.2)
Acupunctur	3 (2.0)
Homeopathy	3 (2.0)
Mushrooms supplements	3 (2.0)
Cupping therapy	2 (1.1)
Herbal supplements for phytotherapy (n=117)	
Green tea	38 (32.5)
Carob	24 (20.5)
Turmeric	24 (20.5)
Ginger	19 (16.2)
Linden tea	19 (16.2)
Black cumin	13 (11.1)
Grape seed/molasses	12 (10.3)
Sugar beet	11 (9.4)
Black mulberry	7 (6.0)
Thyme	6 (5.1)
Stinging nettle	6 (5.1)
Pistachio	4 (3.4)
Camomile tea	4 (3.4)
Pine cone	3 (2.6)
Garlic	3 (2.6)
Hypericumperforatum	3 (2.6)
Purslane	3 (2.6)
Juniper grass	2 (1.7)
Grapefruit	1 (0.9)
Carob molasses	1 (0.9)
Bee products for apitherapy (n=87)	
Honey	76 (87.4)
Propolis	21 (24.1)
Pollen	11 (12.6)
Royal jelly	3 (3.4)
Bee venom	1 (1.1)

CT: Complementary therapy

the use of CT and age, gender, education level, or disease characteristics. However, it was determined that the patients who found conventional treatments insufficient to provide a cure tended to use CT more.

In our study, the most common causes for the patients' using CT were to increase the effectiveness of anti-cancer treatments (85%), to feel better or raise hope (38.1%), and to reduce the side effects of chemotherapy (34.7%), in accordance with the most common reasons for using CT for cancer patients reported in previous studies (17-19). However, 41.5% of the patients stated that they did not benefit from CT treatment. Results similar to the results of our study have been reported as 46.8% in the study of Ceylan et al. (20) and 48% in the study of Samur et al. (21). Despite the high rate of patients stating that they did not benefit, and although the fact that only 2 (1.4%) of the CT users in our study stated that they were harmed by CT use shows that CT can be reliable, note that they may not be able to distinguish the side effects experienced by the patients receiving concurrent chemotherapy as chemotherapy-related or CT-related.

When the patients' information sources for CT were inquired about, families and close friends (63.7%) and the internet and social media (34.8%) were found to be the main sources. Physicians and health centers accounted for 8.5% of information sources. Similarly, in the study of Naja et al. (11), in which only lung cancer patients were included, friends (48%) and the media (40%) were reported to be the most common sources, while health professionals remained only 2%. The fact that social media and the internet are among the top sources of information is an acceptable result in a digitized world where access to the internet has become easier (22). However, the fact that healthcare professionals are not preferred as a source of information for CT usage may make it difficult for patients to access reliable CT information.

CT users and oncologists do not adequately discuss CT. Previous literature reports the percentage of patients who share their CT use with their physician as 12.5% to 58% (11,23-25). Consistent with the published studies, 37.3% of the patients in our study informed their physicians about CT usage. In our inquiry into the reasons lying

Table 5. Cox regression analyses of factors for overall survival

Variable	Category	HR (95% CI)	p-value*
Age	<65/≥65	0.93 (0.62-1.41)	0.746
ECOG PS	0-1/≥2	1.83 (1.05-3.21)	**0.034**
Histologic type	SCC/Adeno	1.24 (0.82-1.88)	0.300
Education	A/B**	0.74 (0.37-1.48)	0.399
Sex	Female/Male	0.66 (0.36-1.22)	0.184
Metastasis status	No/Yes	2.71 (1.73-4.24)	**<0.001**
Stage	Early/Advanced	2.49 (1.28-4.84)	**0.007**
History of radiotherapy	No/Yes	0.92 (0.61-1.39)	0.699
Surgical history	No/Yes	0.51 (0.29-0.90)	**0.020**
Complementary therapy	No/Yes	0.86 (0.57-1.32)	0.495
Phytotherapy	No/Yes	0.76 (0.50-1.14)	0.184
Green tea	No/Yes	1.19 (0.71-1.99)	0.520
Carob	No/Yes	0.94 (0.45-1.94)	0.865
Turmeric	No/Yes	0.98 (0.49-1.96)	0.963
Ginger	No/Yes	0.86 (0.39-1.86)	0.692
Linden tea	No/Yes	0.45 (0.14-1.44)	0.178
Black cumin	No/Yes	0.74 (0.23-1.70)	0.482
Grape seed/molasses	No/Yes	0.72 (0.26-1.95)	0.514
Sugar beet	No/Yes	1.38 (0.50-3.75)	0.535
Apitherapy	No/Yes	1.23 (0.81-1.88)	0.331
Honey	No/Yes	1.19 (0.77-1.84)	0.427
Propolis	No/Yes	1.64 (0.82-3.26)	0.161
Pollen	No/Yes	0.77 (0.28-2.09)	0.602
Vitamin supplements	No/Yes	0.75 (0.31-2.32)	0.748

[s]Significant values are indicated in bold. *The Cox Proportional-hazards model was used. Significance level set at <0.05. **A: Iliterate and primary school, B: High school and university
ECOG PS: Eastern Cooperative Oncology Group performance status, HR: Hazard ratio, CI: Confidence interval

behind this situation, 87.2% of the patients using CT attributed the reason for not sharing their CT status to the fact that the physicians did not ask any specific questions about this issue. In the study of Arıkan et al. (26), it has been reported that 92.5% of the patients attributed the reason for not sharing this situation with their physicians to the same cause. The main reason that patients are not sharing their use of CT could be their perception of CT methods as safe and unharmful instrumentation that can be used along with chemotherapy (27). However, hiding CT use from the treating physician raises the risk of life-threatening outcomes due to drug-CT interactions (8,28).

Consistent with the literature, the most common CT method used in our study was found to be herbal medicine/phytotherapy (79.6%) (10,29,30). The frequent use of phytotherapy in cancer patients is caused by the thought that it is natural and therefore not harmful (30). However, anti-cancer treatments have a narrow therapeutic range. The interaction of CT methods, especially herbal products, with antineoplastic drugs may change the serum levels of conventional treatments (28,31,32).

Although the patients have reported a high benefit from CT, there is no consensus among physicians and patients on the effectiveness of CT because of the limited evidence-based results (33). The studies with survival analysis are also limited. In the study of Pathak et al. (34) that included advanced-stage lung cancer patients, no contribution was determined to OS in the patients using vitamin and mineral supplements as CT. Chen et al. (35) reported that CT did not contribute to survival in their study with Chinese advanced-stage cancer patients. McCulloch et al. (36) reported that the use of CT improved OS in patients with localized lung cancer. In both studies conducted by Bae et al. (37) and Liu et al. (38), it was found that the use of CT-prolonged survival in advanced-stage lung cancer. Johnson et al. (39) reported in a study conducted in the USA, in which different cancer types were included, that the use of CT did not contribute to OS in early-stage patients. In our study, the use of CT did not have a statistically significant contribution to OS.

Study Limitations

Our study has several limitations. Firstly, it was a single-center study. Second, despite the researcher's physician informing the patients about confidentiality and safety, patients were able to conceal their true CT prevalence because the questionnaires were administered in a clinical setting. Third, the small number of early-stage patients and the division of the stages into early and advanced limited the generalizability of the findings. Lastly, depending on the chemotherapy chosen, the treatment effect or the adverse events that may result from the treatment may affect the results. The strengths of our study are that all the respondents were patients receiving active chemotherapy, that it was conducted with a comprehensive survey of a single cancer type, and that it included survival analysis.

Conclusion

Although the clinical utility of CT is questioned, its use along with medical treatment in lung cancer patients is common. For this reason, clinicians should question, follow, and guide their patients about complementary therapies that have a risk of interaction with anticancer therapies. Multicenter studies with more patients must generalize the results.

Ethics

Ethics Committee Approval: The Tekirdag Namik Kemal University Ethics Committee granted formal approval for this study (date: 29.09.2020; approval number: 2020.224.09.11).

Informed Consent: Informed consent was obtained from all participants in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.C., K.K., O.A., E.S.S., Design: E.C., K.K., Y.I., O.A., E.S.S., Data Collection or Processing: E.C., Y.I., Analysis or Interpretation: E.C., Y.I., O.A., Literature Search: E.C., Y.I., E.S.S., Writing: E.C., K.K., Y.I.

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

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Case Report

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Leuconostoc Lactis as an Early-onset Neonatal Sepsis Agent: A Case Report with the Current Literature Review

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Abstract

The patient, who was born spontaneously to a 22-year-old mother as $G_1P_1Y_1$ with a weight of 2605 g at 37 weeks of gestation, had an Activity, Pulse, Grimace, Appearance and Respiration (APGAR) of 8 and 5, respectively, at the first and fifth minutes APGAR 9. Physical examination revealed that the patient's general condition was moderate: body temperature was 36.7 °C, respiratory rate was 68 beats per minute, heart rate was 146 beats per minute, blood pressure was 59/33 mmHg, saturation was 92%, both hemithoraxes participated equally in respiration, consciousness was clear, and the sucking reflex was weak. Because the mother had a history of premature membrane rupture for 22 hours, ampicillin and gentamicin were given intravenously after a blood culture. *Leuconostoc lactis* was grown in a blood culture sent by the patient. On the 12th day of her hospitalization, the patient was discharged with full oral feeding, had started to weigh regularly, and had good general condition, oral intake, and activity. *Leuconostoc* species should be kept in mind in vancomycin-resistant gram-positive infections. It should be kept in mind that *Leuconostoc lactis* may be a cause of Early-onset neonatal sepsis, albeit very rarely.

Keywords: Newborn, *Leuconostoc lactis*, sepsis

Introduction

Early-onset neonatal sepsis (EONS) is an infection that occurs in the first 72 hours of life (1). The most common EONS agents are group B *Streptococci* and *Escherichia coli*. Less frequently: *Enterobacter*, *Enterococcus*, *Klebsiella*, *Listeria*, *non-typeable Haemophilus influenzae, other enteric Gram-negative bacilli, Staphylococcus aureus, and Streptococcus viridans* (2).

Leuconostoc is a Gram-positive cocci from the *Leuconostocaceae* family. It belongs to the *Streptococceae* family, is inherently glycopeptide-resistant, and has intrinsic or chromosomal resistance to vancomycin (3). Although *Leuconostoc* spp. were not considered pathogens for humans in the past, they have recently been accepted as an infectious agent, especially in immunosuppressed patients (4).

Infections due to *Leuconostoc* spp. in newborns were described in a few case reports in the literature. As far as we know, *Leuconostoc* spp. has not been reported as an EONS agent in the literature. Here, a term newborn case with *Leuconostoc lactis* growth in blood culture as an EONS agent is presented.

Case Report

The patient, who was born spontaneously to a 22-year-old mother as $G_1P_1Y_1$ with a weight of 2605 g at 37 weeks of gestation, was determined to be in the 1st minute 8 and 5 minutes for Activity, Pulse, Grimace, Appearance, and Respiration (APGAR) 9. Physical examination revealed that the patient's general condition was moderate: body temperature was 36.7 degrees Celsius, respiratory rate was 68 beats per minute, heart rate was 146 beats per minute, blood pressure was 59/33 (41) mmHg, saturation was 92%, both hemithorax participated equally in respiration, consciousness was clear, and the sucking reflex was weak. The patient with tachypnea was started

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on oxygen. Ampicillin and gentamicin intravenous (IV) were initiated after a blood culture was taken because the mother had a history of premature rupture of the membranes (PROM) for 22 hours. A bilateral infiltrative appearance was detected on the chest X-ray (Figure 1).

The C-reactive protein (CRP) was 0.54 mg/L, blood biochemistry was normal, hematocrit was 54.1%, platelet count was 114,000/mm^3, and leukocyte count was 9640/mm^3 in the complete blood count on the first day of the patient's stay. A peripheral smear examination revealed 5-6 platelets per 100 magnification field. It was learned that the mother's platelet count was normal. *Leuconostoc lactis* was grown in a blood culture sent by the patient. The antibiogram showed that the bacteria were sensitive to ampicillin, and the antibiotic treatment was continued. Enteral feeding with 8x5 cc of breast milk was started and increased gradually in the patient, whose general physical examination was normal, and no oxygen was needed on the fourth day. There was no growth in the blood cultures taken twice after the antibiotic treatment was started. The patient's IV fluid was gradually reduced and stopped as his sucking became more active. In the control blood tests taken on the 10^{th} day, blood biochemical parameters were normal, CRP 0.63 mg/L, hematocrit 52%, platelet count 250,000/mm^3, leukocyte count 9780/mm^3. On the 12^{th} day of her hospitalization, the patient was discharged with full oral feeding, had started to weigh regularly, and had good general condition, oral intake, and activity.

Discussion

Leuconostoc species were not considered pathogenic to humans until the early 1980s. For the first time, vancomycin-resistant Gram-positive cocci were produced in the blood cultures of two adult immunocompromised patients by Buu-Hoï et al. (5), and this bacterium was identified as *Leuconostoc* spp.

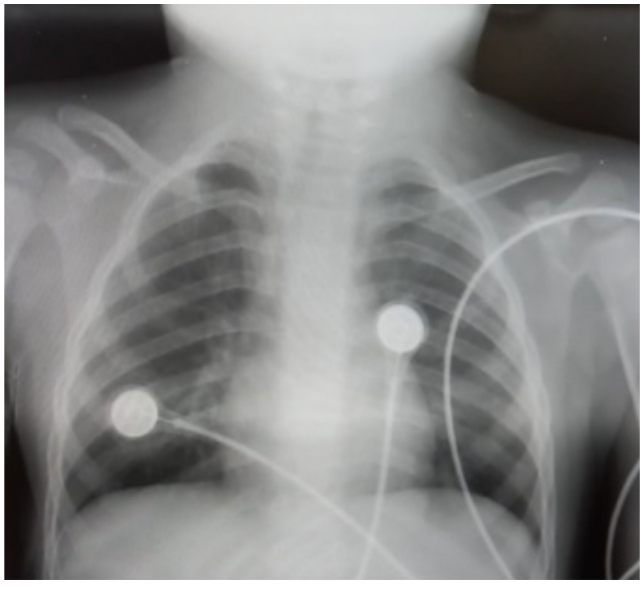

Figure 1. Bilateral infiltration and increased aeration on chest X-ray

Leuconostoc spp. it is a member of the *Streptococcaceae* family. Routine biochemistry and phenotypic identification are ineffective. Sheep agar can be confused with *Enterococcus* or *Streptococcus* because it contains non-hemolytic or alpha-hemolytic gram-positive cocci (6).

Leuconostoc species can grow in 6.5% NaCl and hydrolyze esculin in the presence of bile but cannot produce leucine aminopeptidase and pyrrolidonyl arylamidase, leading to the formation of glucose and CO_2. Antibiotic susceptibility tests are important for diagnosis. *Leuconostoc* strains are naturally glycopeptide-resistant (7). In our case, after BD Bactec-FX40 blood culture was incubated in an automated system, the material was inoculated onto blood agar and EMB (eosin methylene blue) agar after an automatic growth signal. Bacteria grown after incubation at 370 °C for 24 h in Oven Nuve 055 were stained by gram staining. Upon the detection of gram-positive cocci, BD Phoenix PMIC/ID-600 bacteria were inoculated into the identification and antibiogram kit. In October, the Phoenix Spec McFurlant 0.5 threshold was used. The test kit was placed in a Phoenix 100 instrument. Results were obtained after 12-24 hours. On the test kit Phoenix 100 instrument, the growth was identified as *Leuconostoc lactis*. Tigecycline, ampicilline, co-trimaxozol, ceftazidime, ceftriaxone, amoxicillin/clavulonic acid, erythromycin, tetracycline, penicillin, gentamicin, ciprofloxacin, rifampicin, and vancomycin were found to be susceptible and resistant, respectively.

Leuconostoc spp. are considered to have low pathogenic potential for healthy individuals; however, it has been reported recently that they cause fatal infections such as sepsis or meningitis, particularly in immunocompromised patients (8,9). Risk factors for *Leuconostoc lactis* infection include central venous catheters, parenteral nutrition, surgery, liver failure, chronic renal failure treated with hemodialysis, extensive burns, immunosuppression, and long-term vancomycin therapy (10).

Although pediatric patients who developed infections due to *Leuconostoc* species have been reported in the literature, there are few case reports in newborns. Janow et al. (11) found that a 26-day-old premature newborn with a gestational age of 24 weeks developed sepsis while receiving vancomycin, he was initially identified as vancomycin-resistant streptococcus in a blood culture, and later it was determined that the growing agent was *Leuconostoc* spp. They reported that it was fixed. Yossuck et al. (12) reported that three-week-old extremely low

birth weight newborn patients infected with vancomycin-resistant *Leuconostoc* spp. recovered with appropriate antibiotic therapy after removal of the central catheter. Hosoya et al. (13), *Leuconostoc lactis* is a glycopeptide-resistant, Gram-positive, facultative anaerobic coccus isolated from dairy products, whereas *Staphylococcus nepalensis* is a coagulase-negative coccus that has not been identified as a human pathogen. Additionally, there was an underlying risk factor in all three cases. The mother in our case had a 22-hour PROM history. In blood culture, the BD Phoenix PMIC/ID-600 bacterial identification system detected *Leuconostoc lactis* growth, which was vancomycin-resistant in the antibiogram. As far as we know, there are no EONS due to *Leuconostoc lactis* in the literature. They are often considered a source of entry for intravascular catheters and gastrointestinal tract bacteria (6). In our case, there was no catheter intervention; it was a baby who was given breast milk as soon as she was born.

Although *Leuconostoc lactis* is not found in the normal human flora, it has been reported to be isolated from the vagina in healthy women of reproductive age (14). A possible source of this in our patient was the vaginal flora of the mother. However, this is speculation since a vaginal culture cannot be obtained from the mother. Management of *Leuconostoc* infections consists of appropriate antibiotic therapy and removal of the source of infection (catheter removal, drainage of the abscess) (6). *Leuconostoc* strains are intrinsically glycopeptide-resistant. The most preferred antibiotic in treatment is penicillin with or without gentamicin. In our case, improvement was observed after 10 days of ampicillin treatment.

Conclusion

In conclusion, in vancomycin-resistant Gram-positive infections, it should be kept in mind that *Leuconostoc lactis* may be the cause of EONS, albeit very rarely. The most common EONS agents are group B *Streptococci* and *Escherichia coli.* Less frequently: *Enterobacter, Enterococcus, Klebsiella, Listeria, non-typeable Haemophilus influenzae,* other *enteric Gram-negative bacilli, Staphylococcus aureus, Streptococcus viridans*. However, it should be kept in mind that *Leuconostoc lactis* may be the cause of EONS.

Ethics

Informed Consent: Consent information was obtained from the patient's family.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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