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Evaluation of Gastric Emptying Time in Patients with Subclinical Hypothyroidism and Euthyroid Goiter

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ABSTRACT

Objective: Upper gastrointestinal complaints are common in patients with euthyroid goiter and subclinical hypothyroidism for whom follow-ups are performed without treatment. This study evaluated gastroparesis using radionuclide imaging in patients with dyspepsia.

Methods: A total of 56 adult patients were included in this retrospective study. The average age of the patients was calculated as 70.88±2.33 years. Euthyroid goiter was observed in 29 patients and subclinical hypothyroidism in 27 patients. A liquid gastric emptying scintigraphy test was performed on all patients, and thyroid function tests, thyroid ultrasonography, and body mass index evaluations were performed. Regions of interest, including the antrum and fundus, were drawn from anterior images. A time activity curve was obtained.

Results: The gastric emptying half-time was calculated using liquid gastric emptying scintigraphy. This value was found to be significantly higher in patients with subclinical hypothyroidism than in those with euthyroid goiter (p=0.033). Gastric emptying was prolonged in 17 subclinical hypothyroidism patients (63%) and 10 (34.5%) patients diagnosed with euthyroid goiter.

Conclusion: Liquid gastric emptying scintigraphy may be preferred in elderly patients with suspected gastroparesis because of its easy application and short duration. Detecting the prolongation of gastric emptying time due to the presence of gastroparesis in subclinical hypothyroidism and euthyroid goiter cases followed up without treatment may guide the prescription of treatment.

Keywords: Gastric emptying, goiter, dyspepsia, thyroid function tests, radionuclide imaging

INTRODUCTION

The presence of gastroparesis in patients with dyspepsia can be evaluated by gastric emptying scintigraphy. Gastric emptying scintigraphy can be applied to solid or liquid food (1). Solid gastric emptying scintigraphy (SGES) is considered to be the optimal test because it is a shorter study lasting for a bout 4 hours. There is a correlation between the results obtained by liquid gastric emptying scintigraphy (LGES) and those obtained by solid gastric scintigraphy (2). Upper gastrointestinal complaints are frequently encountered in patients with euthyroid goiter (EG) and subclinical hypothyroidism (SH) with whom follow-ups are held in thyroid outpatient clinics without treatment. Treatment is controversial in patients with EG if there is no suspicion of malignancy or signs of compression (3). Goiter is an enlargement of the thyroid gland and is common in the elderly (4). Ultrasonography (USG) and thyroid function tests (TFTs) are primarily used for diagnosis and follow-up. If necessary, scintigraphy and biopsy can be performed (5). SH describes conditions in which free T4 (fT4) and fT3 values are normal but the thyroid-stimulating hormone (TSH) value is above the upper limit. In these patients, treatment does not begin before TSH reaches a certain level or without obvious clinical symptoms, such as recurrent hypothyroidism symptoms (6,7). The present study evaluated gastric emptying time with LGES in elderly patients with a diagnosis of EG or SH with no use of thyroid hormone preparations and who suffered dyspeptic complaints. This study is expected to contribute to the literature to optimize treatment initiation in these patients.

METHODS

This retrospective study included 56 adult patients. The median age of the patients was 72 years (minimum 68, maximum 74). Of these, 49 (87.5%) were women. A total of 29 patients were diagnosed with EG and 27 with SH. LGES testing was performed on all patients. In addition, TFT, thyroid USG, and body mass index (BMI) evaluations were performed. Indigestion complaints were observed in all patients. Not included in the study were

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very underweight or obese patients, those with a thyroid volume of more than 40 mL, those with the presence of chronic disease and thyroid preparation, prokinetic drug use, chronic drug use, diabetes mellitus, smoking, stomach or bowel operation anamnesis, hiatal hernia, gastroesophageal reflux, or a diagnosed esophageal motility disorder. Those with 20 to 30 mL of thyroid volume were accepted as mild goiter, and those with 30 to 40 mL were accepted as moderate goiter. According to their BMI, the patients were evaluated as normal or overweight. Four to six hours of fasting were required before scintigraphy. Imaging was performed early in the morning when gastric emptying was faster. The study did not include patients with blood glucose levels of <40 mg/dL or >275 mg/dL. When liquid food enters the stomach, the fundus relaxes. The fluid takes approximately 30 min to empty from the relaxed stomach. For the test, 18.5-37 MBq (0.5-1 mCi) Tc-99m nanocolloid was added to 300 mL of water, which the patient was asked to swallow immediately. A low-energy multi-purpose collimator was used in a 128x128 matrix. The patient was seated at a 30-to 45-degree angle. Imaging started immediately after the patient drank the liquid. Late images were acquired at 30 min and 1 h. The patient was kept in a sitting position to reduce physical activity between the images. Regions of interest containing the antrum and fundus were drawn from the anterior images (Figure 1), and a time activity curve was obtained. LGES half-time was accepted as 23±3 normal gastric emptying time (8). Our study was retrospective, and informed consent was obtained from all patients. Our study was approved by the University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee on 01.03.2023 with 28 decision numbers.

Statistical Analysis

SPSS version 21 software was used for statistical analysis. Normally distributed continuous variables were expressed as mean ± standard deviation, non-normally distributed continuous variables were expressed as median (minimum and maximum values), and categorical variables were expressed as number of cases and percentage. Whether continuous variables were normally distributed or not was determined by visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov test) methods. Patients with SH and patients with EG were tested for categorical variables (gender, excess goiter volume, obesity, and length of gastric emptying time) using the chi-square test and for normally distributed continuous variables (TSH and fT4) using Student's t-test. It was compared with the Mann-Whitney U test for age and fT3, which is a non-normally distributed continuous variable. P<0.05 value was considered statistically significant. The tests were evaluated as two-sided.

RESULTS

A total of 29 patients were diagnosed with EG. Of these, 25 (86.2%) were female. The thyroid gland size was between 30 and 40 mL in 16 of these patients (55.2%) and between 20 and 30 mL in 13 patients (44.8%). TFT was within normal limits in these patients. In the 27 patients diagnosed with SH, TSH levels were higher than normal (7.47±0.20 mIU/L). fT4 (1.09±0.02 ng/dL) and fT3 [2.42 (2.17-2.73) pg/mL] values were within normal limits. These patients did not have any presence of goiter. The data for the patients are summarized in Table 1. The patients' upper gastrointestinal complaints were examined (patient assessment of upper gastrointestinal disorders-symptom severity index) (9,10). All patients complained of fullness of the stomach, early satiety, postprandial bloating, and frequent belching. Gastric emptying half-time (GEHT) was calculated using LGES. GEHT in SH cases was found to be significantly longer than that in EG cases (p=0.033). GEHT was prolonged in 17 of the SH patients (63%). Of the 10 patients whose GEHT was calculated as normal, three were male. TSH levels in these 10 patients ranged from 7.12 to 7.35 mIU/L. GEHT was prolonged in only 10 (34.5%) patients with a diagnosis of EG; all 10 were female. Goiter volume was between 30 and 40 mL in eight patients. BMI was within normal limits for seven of the 10 patients. TSH values were between 3.47 and 3.69 mIU/L in these 10 patients (Table 1).

DISCUSSION

Hypothyroidism and gastroparesis commonly coexist. Thyroid hormones play an important role in the regulation of metabolism (11). Gastroparesis is a disease in which gastric emptying is delayed in the absence of mechanical obstruction. Patient quality of life decreases because of upper gastrointestinal complaints (12,13). Levothyroxine (LT4) tablets are preferred for treating hypothyroidism. However, in patients with EG and SH, LT4 is prescribed in selected patients only if necessary (14). Approximately 10% of patients receiving LT4 therapy are euthyroid. Treatment is initiated for these patients because of

Figure 1. Region of interest drawing in functional gastric emptying scintigraphy

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recurrent hypothyroidism symptoms (15). Hormone therapy can be used in patients with EG and SH in the presence of clinical conditions such as unexplained fatigue, resistant obesity despite a low-calorie diet, severe hypercholesterolemia, depression resistant to antidepressant drugs, infertility in women with high TPO, and simple goiter that grows over time (16). There was no history of LT4 in the patients included in this study. Among the surveyed patients, gastric emptying delay was more pronounced in patients with SH. These findings may be due to the relative hypothyroid state of the patients. Insufficient production of peripheral LT4 and LT3 may have occurred because of intracellular hypothyroidism and variations in LT4 transfer (17). TSH suppression can cause osteoporosis and cardiac mortality. As such, some studies caution against prescribing LT4 therapy to elderly patients with EG or SH (18). Although the use of LT4 to treat goiter is still preferred, additional treatments, such as selenium and iodine, are not recommended (19). EG and SH are quite common in the general population. In the Pomeranian Population-Based Health Study, which included 4310 participants without known thyroid disease, 5.9% had goiter and 20.2% had thyroid nodules (20). Goiter is usually asymptomatic until the thyroid volume is 40 mL (19). In 85% of asymptomatic goiter cases, compression occurs on the trachea or esophagus at a rate of 30% (19). The patients surveyed in this study had a goiter volume between 20 and 40 mL. Patients with goiter exhibited less GEHT prolongation than patients without goiter. If patients with goiter present signs of malignancy, such as a hypoechoic nodule, microcalcification, intra-nodular vascularization, or a lesion with irregular borders, a biopsy should be performed (21). Thyroid USG was performed in all patients in this study. The sensitivity and specificity of USG were 83-99% and 85-56%, respectively. None of the patients had any signs of malignancy. Currently, there is no generally accepted approach to the drug treatment of goiter in euthyroid patients (22). Some large-scale studies have indicated goiter volume reduction after treatment with levothyroxine iodide (22). These studies report that with radioactive iodine treatment, a 35-40% reduction in thyroid volume can be achieved in the first year (22). Even large goiters (100-300 mL) have been reported to reduce in volume by 40-60% in two years (23). None of the 56 patients in this study received radioactive iodine treatment before the study. Many studies do not recommend LT4 treatment for SH and EG disease until certain clinical findings occur. In elderly patients, this is due to TSH suppression, which can put the patients at risk of atrial fibrillation and metabolic bone disorder (3). If the aim is to reduce the euthyroid nodular goiter size, surgery or radioactive iodine treatment can be applied (3). Surgery is mandatory in the presence of cancer. A single measurement is not sufficient to diagnose TFT at follow-up. The present study's patients were followed up from 6 months to one year, at least three months apart. Thyroid disease is generally more common in women (11). Female gender was also more common in the present study's patients. Some male patients were excluded from the study because of smoking, which is more common among males in the country of study. Dyspeptic complaints in patients who received follow-ups without treatment may have resulted from gastroparesis. To evaluate gastroparesis, LGES and SGES results are correlated (2). SGES testing is lengthy and complex; therefore, it can be difficult to apply in the elderly population. LGES, in contrast, is very easy to apply and to obtain cooperation from elderly patients. Existing studies indicate that the correlation between GEHT and dyspeptic complaints lack statistical power (2). The present study, which evaluated GEHT by scintigraphy, found that more than one-third of the patients had normal gastric emptying (9). GEHT was within the normal limits for 29 patients with dyspeptic complaints. However, scintigraphic GEHT calculations may not fully represent the digestive process and gastrointestinal neuroendocrine events (9). A meta-analysis study that examined 25 studies in which GEHT was calculated using scintigraphy reported a relationship between delayed gastric emptying and dyspepsia complaints (24). In this study, prolonged GEHT was more common in patients with SH. Another study using wireless motility reported a relationship between gastroparesis and duodenal contractility severity (24), and a further study reported that gastroparesis symptoms are associated with small bowel dysmotility (25). In this study, LGES testing was completed within 1 h, and the standard method was used for all patients (9). As stated, there is no reliable method to evaluate mixed solid-liquid food and liquid gastric emptying (9). LGES may be preferred over SGES in the elderly population to evaluate gastroparesis apart from specific diseases. LGES, unlike

Table 1. Data on subclinical hypothyroidism and euthyroid goiter cases

	Subclinical hypotiroidism (n=27)	Euthyroid goiter (n=29)	p-value
Age [med (min-max)]	72 (68-74)	72 (68-74)	0.584
Gender (female/male)	24 (88.9%)	25 (86.2%)	1
TSH (mIU/L) (mean ± standard deviation)	7.47±0.20	3.30±0.24	<0.001
fT4 (ng/dL) (mean ± standard deviation)	1.09±0.02	1.28±0.08	<0.001
fT3 (pg/mL) [med (min-max)]	2.42 (2.17-2.73)	3.15 (2.53-3.29)	<0.001
Liquid gastric emptying T1/2 (prolonged/normal)	17 (63%)	10 (34.5%)	0.033
BMI (overweight/normal)	9 (33.3%)	10 (34.5%)	0.928
Goiter size (mild/moderate/normal)	0/0/27 (0/0/100%)	13/16/0 (44.8%/55.2%/0)	0.005

min-max: minimum-maximum, med: median, TSH: thyroid-stimulating hormone, fT4: free T4, BMI: body mass index

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SGES, is an easy and short-term test. Solid foods are broken down into small pieces by enzymes and gastric juice. While solid food must be broken down to pass through the pyloric sphincter, liquids pass directly. No cause is found in 50% of patients with dyspeptic complaints (9). Patients with upper gastrointestinal symptoms may have anthropyloriduodenal contraction disorder (24). Scintigraphic GEHT calculation is superior to barium studies because LGES is a physiological test (24). Small intestinal dysmotility may be associated with gastroparesis symptoms. Normally, 12% of antral contractions cause duodenal spread (25). Gastroparesis is common in diabetic patients. The prevalence of gastroparesis in diabetic patients is 64% (25). Some studies involving diabetic patients have reported a correlation between dyspeptic complaints and prolonged GEHT. Furthermore, acute changes in blood sugar affect gastric emptying (24). Diabetic patients were not included in this study; the included patients did not have hypoglycemia or hyperglycemia. Rapid gastric emptying may also be a consequence of autonomic dysfunction (25). There was no evidence of rapid gastric emptying in the present study. Although SGES is the gold standard method for calculating GEHT, dynamic imaging for 90 min and imaging late at 4 h make it difficult to apply, especially in the elderly population. Dynamic imaging places significant strain on the SPECT system; therefore, static imaging is more advantageous. In this study, GEHT was calculated using LGES and static images. The radiation dose required for LGES imaging is very low and the test time is short; therefore, it fulfilled the requirement of a practical test. Dyspepsia complaints may accompany many chronic diseases, such as diabetes, neuromuscular disorders, and endocrine disorders. However, with appropriate precautions, dyspeptic complaints can be prevented. In cases of SH, minor changes in thyroid hormone levels may delay gastric emptying. In this study, patients with gastroparesis who were prolonged in GEHT were referred to the endocrinology outpatient clinic for treatment prescription.

Study Limitations

A retrospective approach is a weakness of our study.

CONCLUSION

LGES may be preferred in elderly patients with suspected gastroparesis because of its easy application and short duration. Detecting the prolongation of gastric emptying time due to the presence of gastroparesis in SH and EG cases followed up without treatment may guide the prescription of treatment.

Ethics Committee Approval: Our study was approved by University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee on 01.03.2023 with 28 decision numbers.

Informed Consent: Informed consent was obtained from all participants of this study.

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Adherence to Prophylaxis in Patients with Chronic Headaches and Effect of Internet/Social Media Use

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ABSTRACT

Objective: To determine the medication adherence rates of patients with chronic headaches to prophylaxis and the factors affecting this rate, including internet and social media use.

Methods: This study was conducted in two hospitals between May and September 2021. Adult patients with chronic headaches requiring prophylaxis were recruited for this study. Demographic data, headache types/features, prophylactic drugs, Hospital Anxiety and Depression scale scores, and duration of internet/social media use (hours/day) were recorded. Medication Adherence Report scale scores, changes in headache characteristics, and drug-related adverse effects were assessed during the first month.

Results: In total, 113 patients were recruited. Most patients had migraines (69%). The medication adherence rate in the first month was 72.6%. Patients with a longer duration of internet/social media use and adverse drug effects were more likely to show poor adherence (p=0.005). Decreasing baseline maximum headache severity increased the likelihood of medication non-adherence (p=0.005). Public hospital patients (p=0.036) and married patients (p=0.048) were more prone to non-adherence.

Conclusion: Internet/social media use, headache severity, and medication-related side effects are the most important factors associated with medication adherence. Non-profit healthcare professionals/organizations should use the internet and social media as communication channels to increase medication adherence. Health policies need to be adjusted to allow more time for the healthcare worker-patient communication.

Keywords: Medication adherence, chronic headache, internet/social media

INTRODUCTION

Medication adherence is a crucial factor in treating chronic diseases, and non-adherence to treatment is an important problem affecting treatment success. Non-adherence is observed in 25-65% of patients with headaches requiring prophylaxis (1,2). Similar to many studies conducted in different fields of headache, migraine is the most investigated type in terms of adherence to prophylaxis (3-5).

Factors influencing adherence to treatment in headache prophylaxis are unclear and remain controversial. Poor efficacy or adverse effects of drugs are among the most cited reasons (2,6-9). In this context, the impact of the internet/social media (I/SM), which has become an important source of health information in the last few decades and can affect patients' medication adherence, has not been sufficiently investigated (10-14). This study was conducted when the coronavirus disease-2019 pandemic had largely lost momentum but had not yet been fully controlled. During the pandemic, the use of I/SM as a source of information has increased worldwide, especially among people staying at home, in isolation, or quarantined (14,15). Media/SM misinformation regarding health issues and medical treatments has significantly increased, and the pandemic has highlighted the key role of SM misinformation (14,16). To the best of our knowledge, there are limited studies in the literature investigating the effect of I/SM use on medication adherence.

This study aimed to determine the level of adherence to prophylaxis in patients with chronic headaches and the factors that may influence adherence, including I/SM use.

METHODS

Study Population and Data

This study included adult patients with chronic headaches (aged ≥18 years) requiring prophylaxis who consented to participate. The study was conducted in two different hospitals (one private

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and one public) between May and September 2021. Demographic data of the patients (age, sex, marital status, education, and economic level), duration of I/SM use (hours/day), headache type (according to the third edition of the International Classification of Headache Disorders-3), features of the headache (frequency, duration, severity), number of emergency room visits due to headache (per year), analgesic type and number per month taken by patients, comorbidities, number of other drugs taken by patients chronically, status of previous headache prophylaxis drug use, and newly prescribed headache prophylaxis drugs were recorded (17).

Measures and Procedures

At the beginning of the study, all patients were asked to complete the Hospital Anxiety and Depression scale (HADS), a self-assessment test including 14 items and divided into an anxiety subscale (HADS-A) and a depression subscale (HADS-D) (18,19). The answer format offers four response options, which are scored with values ranging from 0 to 3. This resulted in scale values between 0 and 21 for each scale. The authors of the original test defined three ranges for both scales: 0-7 (non-cases), 8-10 (doubtful cases), and 11-21 (cases). The HADS total score was calculated by summing the anxiety and depression items.

After initiating prophylactic drug treatment, a face-to-face visit was planned in the first month. Adherence rate was measured in the first month using the Medication Adherence Report scale (MARS-5). In addition, changes in headache frequency and severity [based on a visual analog scale (VAS) score between 0 and 10], percentage of improvement in headache according to the patient, and adverse effects of prophylactic drugs were recorded by asking the patients.

MARS-5 is a self-report medication adherence scale used to assess medication adherence in many chronic diseases (20). Translation of MARS-5 into Turkish and Turkish validation studies has been conducted previously (21). MARS-5 consists of five general statements about non-adherent behavior (I forget to take my medicines, I alter the dose of my medicines, I stop taking my medicines for a while, I decide to miss out on a dose, I take less than instructed) answered on a 5-point Likert scale (1= always, 2= often, 3= sometimes, 4= rarely, 5= never). The outcome variable was calculated as the total score on the MARS-5 (maximum, 25), and a score <23 was considered non-adherent (6).

Ethics Approval and Consent to Participate

This study was approved by the Clinical Research Ethics Committee of Demiroğlu Bilim University (decision no: 22.12.2020/2020-24-03). The study was conducted in accordance with the Good Clinical Practice and the Declaration of Helsinki ethical standards. Written informed consent was obtained from all participants.

Statistical Analysis

The normality of the distribution was examined using the Kolmogorov-Smirnov test. Normally distributed data are presented as mean ± standard deviation, whereas skewed data are presented as median (25-75%). Univariate and multivariate binary logistic regression analyses were performed to investigate the possible predictors of medication adherence. In the multivariate model, the backward Wald method was used to include independent variables. Pearson's chi-square test with Yates correction was used to compare categorical data between the adherent and non-adherent groups, and the Z test with Bonferroni correction was performed for multiple comparisons. Statistical calculations were performed using the IBM SPSS V.23 software. Statistical significance was defined as $p<0.05$.

RESULTS

A total of 113 patients were included in this study. The demographic characteristics, comorbidities, total number of medications (per day), HADS scores, duration of I/SM use (hours/day), and the type of hospital in which the patients were recruited (private-public) are presented in Table 1.

Headache characteristics, previous prophylaxis status, number of annual admissions to the emergency room due to headache, number of analgesics taken per month, type of headache prophylaxis drug initiated, and first-month MARS scores are shown in Table 2. Most patients had migraine without aura (64.6%), followed by tension-type headaches (41.6%) and cervicogenic headaches (23%). Approximately 60.2% of the patients had more than one type of headache. The medication adherence rate in the first month was 72.6%. The most common statement was, "I forget to take it" (38.9%). The statements "I'm quitting for a while," "I've decided to skip the dose" and "I'm changing the dose" were reported by the patients at the rates of 22.1%, 10.6%, and 2.7%, respectively.

The independent variables predicting adherence in the first month were analyzed by binary logistic regression analysis, and the backward Wald method was used to include the independent variables in the model. When the model was analyzed univariately, increasing the daily I/SM usage time of the participants increased the probability of non-adherence by 1.37 times ($p=0.016$). Decreasing the maximum initial VAS score increased the probability of non-adherence (1/0.66) by 1.51 times ($p=0.024$). The probability of non-adherence was 3.82 times higher in patients with prophylaxis side effects than in those without side effects ($p=0.005$). Multivariate analysis found that the probability of medication non-adherence of those treated in public hospitals was 3.71 times higher than that of those treated in private hospitals ($p=0.036$). The probability of non-adherence of married patients was 4.28 times higher than that of unmarried patients ($p=0.048$). Increasing the duration of daily SM use increased the probability of non-adherence by 1.68 times ($p=0.005$). A decrease in the initial maximum VAS score increased the probability of non-adherence (1/0.5) 2-fold ($p=0.005$). The probability of non-adherence was 4.68 times higher in patients with prophylaxis side effects than in those without side effects ($p=0.005$). Other variables did not have a statistically significant effect on the risk of treatment non-adherence ($p>0.05$) (Table 3).

Table 1. Patient demographics, medical history, and Hospital Anxiety and Depression scale (HADS) scores at baseline

Type of hospital - n (%)	
Private hospital	60 (53.1)
Public hospital	53 (46.9)
Age - mean ± SD	42.35±10.9
Sex - n (%)	
Male	89 (78.8)
Female	24 (21.2)
Marital status - n (%)	
Single	26 (23.0)
Married	81 (71.7)
Divorced/widowed	6 (5.3)
Educational status - n (%)	
Unable to read and write	5 (4.4)
Primary school and below	39 (34.5)
Secondary and high school	30 (26.5)
College/university completed	39 (34.5)
Economic status - n (%)	
Low	20 (17.7)
Middle	84 (74.3)
High	9 (8.0)
Duration of internet/social media use (hour/day) - median (Q1-Q3)*	2 (1-4)
Total number of diseases other than headache - n (%)	
0	19 (16.8)
1	29 (25.7)
2	41 (36.3)
3	11 (9.7)
≥4	13 (11.5)
Types of diseases other than headache - n (%)	
Fibromiyalgia/myofascial pain	27 (23.9)
Cervical hernia	17 (15.0)
Hypertension	20 (17.7)
Bruxism	11 (9.7)
Psychiatric diseases	11 (9.7)
OSAS - insomnia	12 (10.6)
Other diseases	71 (62.8)
Total number of medication types (per day) - n (%)	
0	45 (39.8)
1	37 (32.7)
2	11 (9.7)
3	11 (9.7)
4	3 (2.7)
≥5	6 (5.4)
HADS scores	
Anxiety score - median (Q1-Q3)	9 (6-10)
0-10 - n (%)	87 (77)
≥11 - n (%)	26 (23)
Depression score - median (Q1-Q3)	6 (3-8)
0-10 - n (%)	97 (85.8)
≥11 - n (%)	16 (14.2)

*Median (25-75%)
SD: standard deviation, OSAS: obstructive sleep apnea syndrome, HADS: Hospital Anxiety and Depression scale

There was no significant difference in the distribution of the type of prophylaxis drug (p=0.342) or type of headache according to medication adherence (p=0.173) (Supplementary Table 1).

DISCUSSION

This study, in which most participants had migraines, showed that 27.4% of patients with headaches were non-adherent to prophylaxis in the first month. This rate was not substantially different from the rates reported in previous studies (4,6,7,22,23). It was determined that the probability of adherence was negatively affected by an increase in the duration of I/SM use, a decrease in the maximum headache VAS score at baseline, and the presence of drug side effects. In addition, this probability was lower in patients from public hospitals and in married patients.

Previous studies have shown different medication adherence rates in patients with headaches (1). These differences may have resulted from the study methods, patient populations, or other factors (1). In an early prospective study assessing self-reported adherence to prophylaxis of patients with different types of headaches, 48% were reported to be adherent to their medication, and adherence rates decreased to 34% in the third month (24). In another 1-year observational study that included patients with migraine and tension headaches, it was determined that 9% of patients showed an adherence problem from the beginning, 16% changed their medication, and only 35% fully complied with the instructions until the next visit (2).

It should be noted that most drug adherence studies in patients with headaches have been conducted on migraineurs (1). A prospective study on adults with chronic migraine found that 78.4% of patients reported adherence to preventive medication (25). A different longitudinal study on children and adolescents (age 8-17 years) with migraine found that self-report and pill number adherence rates were high (over 90%); however, the adherence rates of serum drug levels were lower and showed a decrease (from 84% to 76%) during the study period (26). A retrospective study by Dozza and Krymchantowski (4) also showed similar results (overall adherence of 79.6%). However, other studies found much lower adherence rates of patients with migraine to prophylaxis drugs (26.2-37%) (3,22,23,27,28).

In this study, one of the most influential factors affecting adherence was the duration of I/SM use. The decrease in the probability of drug adherence as the duration of I/SM use increases may be explained by the fact that patients who have used I/SM for a long time are affected by misinformation. The Internet and SM are among the most popular and accessible sources of information for every subject. However, misinformation and conspiracy theories creating panic/anxiety about various diseases and drug use on I/SM have increased during the pandemic (14,29-31). Arguably, the uncertainty arising from science-based decision-making processes during the pandemic has significantly increased pre-existing public suspicion and mistrust of scientific communities, experts, and public institutions (32,33). Studies suggest that frequent and conflicting information

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Table 2. Headache characteristics, previous prophylaxis status, initiated prophylaxis drugs, number of annual admissions to the emergency and Medication Adherence Report scale-5 (first-month) scores	
Duration of headache (years) - median (Q1-Q3)*	9 (2-18)
Total number of headache types - n (%)	
1	45 (39.8)
2	48 (42.5)
≥3	20 (17.7)
Type of headache - n (%)	
Primary headache	
Migraine without aura	73 (64.6)
Migraine with aura	5 (4.4)
Tension headache	47 (41.6)
Trigeminal autonomic cephalgias	4 (3.5)
Secondary headache	
Cervicogenic headache	26 (23.0)
Headache attributed to hypertension	14 (12.39)
Headache attributed to sinusitis	2 (1.77)
Headache attributed to TMD* (e.g. bruxism)	13 (11.5)
Medication-overuse headache	19 (16.8)
Number of emergency room visits for headache acute attack (per year) - n (%)	
0-5	98 (86.7)
6-10	5 (4.4)
≥10	10 (8.8)
Type of analgesic used by patients (on admission) - n (%)	
No analgesic use	3 (2.7)
Triptans	14 (12.4)
NSAID	59 (52.2)
Paracetamol ± caffeine	35 (31)
Ergots	2 (1.8)
Previous prophylaxis status - n (%)	
Never been on prophylaxis	74 (65.5)
Stopped prophylaxis	33 (29.2)
On regular prophylaxis	6 (5.3)
Headache frequency (per month) - median (Q1-Q3)	
On admission	10 (8-15)
1 month	5 (3-9)
Average VAS score - median (Q1-Q3)	
On admission	6 (5-7)
1 month	5 (4-5)
Maximum VAS score - median (Q1-Q3)	
On admission	9 (8-10)
1 month	7 (6-8)
Type of headache prophylaxis drug initiated - n (%)	
Beta blocker	
Propranolol/metoprolol	21 (18.6)
Antidepressant	
TCA	14 (12.4)
SSRI/SNRI	44 (38.9)

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Table 2. Continued

Antiepileptic	
Topiramate	14 (12.4)
Gabapentinoid	23 (20.4)
Others (valproic acid, lamotrigine)	10 (8.9)
Percent benefit of prophylaxis in the first-month - median (Q1-Q3)	0.6 (0.5-0.8)
Number of analgesics taken per month - median (Q1-Q3)	
On admission	8 (6-13)
1 month	4 (3-7)

*Median (25-75%)
NSAID: non-steroidal anti-inflammatory drug, SNRI: serotonin-norepinephrine reuptake inhibitor, SSRI: selective serotonin reuptake inhibitor, TCA: tricyclic antidepressant, TMD: temporomandibular disorder, VAS: visual analog scale

Table 3. Univariate and multivariate binary logistic regression analyses for predictors for first-month adherence

	Univariate		Multivariate¶	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Type of hospital*	0.76 (0.33-1.75)	0.516	3.71 (1.09-12.64)	**0.036**
Sex**	1.83 (0.7-4.76)	0.217	-	-
Age	1.01 (0.97-1.05)	0.775	-	-
Marital status***	1.59 (0.61-4.17)	0.343	4.28 (1.02-18.01)	**0.048**
Education†	0.71 (0.29-1.74)	0.452	-	-
Economic status††	0.61 (0.19-2)	0.415	-	-
Daily duration of internet/social media use	1.37 (1.06-1.76)	**0.016**	1.68 (1.17-2.42)	**0.005**
Total number of other diseases	0.93 (0.67-1.3)	0.667	-	-
Total number of medication types (per day)	0.93 (0.71-1.22)	0.610	-	-
Total number of headache types	0.58 (0.32-1.05)	0.074	-	-
Duration of headache (years)	0.99 (0.94-1.03)	0.504	-	-
Previous use of prophylaxis†††	0.71 (0.29-1.74)	0.452	-	-
0 month/headache frequency (per month)	0.95 (0.87-1.03)	0.197	-	-
0 month/average VAS score	0.89 (0.68-1.17)	0.403	-	-
0 month/maximum VAS score	0.66 (0.47-0.95)	**0.024**	0.5 (0.31-0.81)	**0.005**
Number of ER visits due to headache (per year)	0.92 (0.82-1.04)	0.166	-	-
HADS-A	0.94 (0.85-1.05)	0.266	-	-
HADS-D	0.99 (0.89-1.11)	0.920	-	-
Total HADS score	0.98 (0.92-1.04)	0.481	-	-
Number of headache prophylaxis drug initiated	0.56 (0.11-2.75)	0.474	-	-
Side effects of prophylaxis††††	3.82 (1.5-9.75)	**0.005**	4.68 (1.52-14.41)	**0.005**
1 month/percent benefit from prophylaxis	0.38 (0.03-4.44)	0.440	-	-
1 month/headache frequency (per month)	1.03 (0.92-1.15)	0.571	-	-
1 month/average VAS score	1.32 (0.95-1.84)	0.101	-	-
1 month/maximum VAS score	1.04 (0.84-1.29)	0.733	-	-

ER: emergency room, HADS-A: Hospital Anxiety and Depression scale-anxiety sub-score, HADS-D: Hospital Anxiety and Depression scale-depression sub-score, OR: odds ratio, CI: confidence interval, VAS: visual analog scale. Reference groups: *private hospital; **female; ***not married); †0-8 years of education; ††middle and high income; †††no previous prophylaxis; ††††no side effect; (¶Backward Wald method)

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provided by the mass media can negatively affect patients' beliefs about the benefits of drugs and lead to negative health behaviors (12). A study evaluating the accuracy of some claims on SM, where drug-related information was also shared, revealed that the most frequently shared messages were "possibly misleading" (34). Another example of the influence of mass media is the discontinuation of statin therapy by thousands of patients in Australia following a misinformative media program (35).

The Internet and SM provide opportunities to disseminate information about diseases and their treatments to benefit patients. International headache associations, such as the European Headache Federation, American Headache Society, and International Headache Society, strive to promote their organizations' expertise and disseminate research findings (32). However, recent studies have shown that the most popular online content on migraine management is not evidence-based and is driven by for-profit organizations (32). The content about headache management in popular sources, such as Google, YouTube, Instagram, and Facebook, reaches millions of people, and the potential impact cannot be ignored (32,36,37). Non-pharmacological approaches and complementary alternative medicine attract more attention from healthcare consumers (36-39). Additionally, only a small fraction of the popular videos on the I/SM are provided by non-profit health professionals in this field (for example, less than one-tenth of the most popular migraine-related videos on YouTube) (36). I/SM users of health community members with the same diagnosis and health status tend to trust each other more than professionals (40). Patients' treatment decisions may be affected by anecdotal information rather than evidence-based statistical information from experts in the field (32,41). Although different social networking sites show some differences, established health communities are more likely to reach a large audience regardless of their socioeconomic background and health status (16,40,42).

Patients' concerns about possible side effects of medications, refusal to take daily medication, no further need for improvement, preference for non-pharmacologic approaches, and recommendations from other people are among the reasons that may cause or contribute to non-adherence to prophylaxis (2,6).

Regarding VAS scores, Acikgoz et al. (43) found that VAS scores were negatively correlated with understanding the disease in patients with headaches but not with treatment control. There are also other studies showing that there is no difference between the pain intensity of patients who are adherent and non-adherent (6).

The higher medication adherence among patients attending private hospitals may be related to the higher health literacy of the patients in these hospitals, the longer time allocated per patient in the hospital, and the easier access of the patient to their physicians (44,45). In public hospitals in Türkiye, the examination time physicians can allocate to a patient is 2.5-10 min, and it is difficult for patients to reach their physicians (45-47).

It has been suggested that the most preferred prophylactic drug groups, such as beta-blockers, antidepressants, and antiepileptics, may cause low adherence because they are not specific to migraine and have frequent side effects (22). Social prejudices and beliefs about these medicines, especially against antidepressants and antiepileptics, may affect drug adherence (6,48-50). However, we found no effect of prophylactic drug groups on medication adherence, as shown in some previous studies. Other studies have reported that beta-blockers (followed by topiramate) are advantageous for drug adherence (1,27).

Study Limitations

One of the main limitations of this study is the use of a patient-reported scale to measure adherence. In addition, the amount of time patients spent on health news compared with the total time they spent on I/SM and the content of these health news items were not questioned. However, an advantage of this study is that it was conducted in two different hospitals, reflecting different patient populations.

CONCLUSION

This study emphasizes that the duration of I/SM use, headache severity, and drug-related side effects are among the factors that most affect medication adherence in patients with chronic headaches. In addition, the probability of adherence decreased among patients who visited public hospitals. Therefore, preventing the spread of misinformation on SM and improving health literacy and conditions in public hospitals should be among the goals of clinicians and researchers to improve medication adherence.

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Demiroğlu Bilim University (decision no: 22.12.2020/2020-24-03). The study was conducted in accordance with the Good Clinical Practice and the Declaration of Helsinki ethical standards.

Informed Consent: Written informed consent was obtained from all participants.

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Supplementary Table 1. Chi-square tests of association between type of prophylaxis drug, type of headache and medication adherence

	Medication adherence		Test stat.	p-value*
	Non-adherent	Adherent		
Type of prophylaxis drug				
Duloxetine	4 (12.9)	9 (11)	8,999	0.342
Gabapentin	2 (6.5)	8 (9.8)		
Beta blockers	5 (16.1)	15 (18.3)		
Topiramate	4 (12.9)	10 (12.2)		
Pregabalin	5 (16.1)	4 (4.9)		
Valproic acid	2 (6.5)	2 (2.4)		
Lamotrigine	0 (0)	2 (2.4)		
SSRIs	4 (12.9)	24 (29.3)		
Amitriptyline	5 (16.1)	8 (9.8)		
Type of headache				
Common migraine	20 (64.5)	53 (64.6)	14,002	0.173
Migraine with aura	2 (6.5)	3 (3.7)		
Cervicogenic headache	4 (12.9)	21 (25.6)		
Tension type headache	9 (29)	38 (46.3)		
Headache attributed to HT	3 (9.7)	11 (13.4)		
Medication-overuse headache	4 (12.9)	15 (18.3)		
Headache attributed to TMD	4 (12.9)	9 (11)		
Others	3 (9.7)	3 (3.6)		

HT: hypertension, TMD: temporomandibular disorder
*Pearson's chi-square test
Pearson's chi-square test with Yates correction was used to compare categorical data between the adherent and non-adherent groups, and the Z test with Bonferroni correction was performed for multiple comparisons

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Factors Associated with Prolonged Length of Stay in the Emergency Department Prior to Hospitalization

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ABSTRACT

Objective: The aim of this study was to investigate the factors associated with prolonged emergency department (ED) length of stay (LOS) in inpatients.

Methods: This was a retrospective and cross-sectional study conducted in the adult ED of a tertiary care hospital where approximately half a million patients are examined annually. Between August 1, 2022 and August 1, 2023, patients hospitalized from the adult ED were included in the study. Prolonged LOS was defined as patients who stayed in the ED for at least 8 hours. The relationship between prolonged LOS and patient-related and hospital-related factors was investigated. Mann-Whitney U and chi-square tests were performed statistically.

Results: The median LOS of all patients in the ED was 4.4 h. Prolonged LOS (>8 hours) was independently significantly associated with older age (p=0.009), refugee status (p=0.004), non-urgent triage category (p<0.001), diagnostic tests and imaging (p<0.01), internal ward admission, and night shift arrival (p<0.01).

Conclusion: Several factors were significantly associated with prolonged LOS in the ED. Prolonged LOS can be reduced through the implementation of these strategies designed to address these contributing factors.

Keywords: Emergency department, length of stay, prolonged length of stay, overcrowding

INTRODUCTION

It has been reported that emergency room admissions have increased (1). Emergency department (ED) crowding is an important phenomenon that negatively affects emergency health services (2-4). This phenomenon leads to delayed treatment of emergency patients, decreased service quality, increased costs, and mortality (5-9). Prolonged ED length of stay (LOS) is an important factor that increases ED crowding (10,11). LOS in the ED includes the time between patient registration and discharge from the ED or hospitalization (12,13). At the same time, ED LOS is associated with patient satisfaction (14). It is thought that determining the factors affecting LOS in the ED and making improvements accordingly will increase the quality of emergency health services.

The aim of this study was to evaluate the relationship between prolonged LOS in the ED and factors related to patients and hospitals.

METHODS

Study Design and Settings

This was a retrospective single-center cross-sectional study. University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital is a tertiary care university hospital with 650 beds. Provides healthcare services to a population of approximately one million in its region. In the Adult ED, healthcare services are provided to an average of 1500 patients daily. Three-level triage is used and patients are classified as nonurgent (green), urgent (yellow), and emergent (red) according to their urgency. Emergency laboratory, radiography, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are available 24/7. One associate professor, one assistant professor, 13 emergency medicine specialists, 25 emergency medicine assistants, and 10 general practitioners work in the ED.

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Study Population

Between August 1, 2022 and August 1, 2023, 5568 adult patients (age>17 years) admitted to the inpatient ward from the adult ED of University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital were included in the study. Data were obtained anonymously from the Hospital Information Management System. After excluding patients with missing data, patients hospitalized in obstetrics and pediatrics wards, and coronavirus disease-2019 patients, 5240 patients were included in the study.

Methods

ED LOS was determined by calculating the time in minutes between the time of registration and hospitalization. According to the legislation in Türkiye, patients who need hospitalization should not wait more than 8 h in the ED (15). Therefore, prolonged LOS was defined as an ED stay of 8 h. In our study, we focused on patient-related factors such as age, gender, social security, citizenship, and time of arrival, and hospital-related factors such as triage category, urine and blood tests, ultrasound, CT and MRI, and hospitalization.

Approval for the research protocol was obtained from the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital (decision no: 388, date: 22.12.2021). Because our study was a retrospective study based on anonymous data, patient consent was not obtained.

Statistical Analysis

The data evaluation and analysis were conducted using IBM Corp.'s Statistical Package for the Social Sciences version 29.0.2.0 software on Windows. Descriptive characteristics were presented using frequencies (n) and percentages (%), while numerical variables were expressed as median (interquartile range). The normal distribution of the data was assessed using descriptive techniques, including the coefficient of variation, skewness, and kurtosis, along with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare variables that exhibited a non-normal distribution between the two groups. Distribution among categorical variables was assessed using the chi-square test. The findings are presented in the form of a 95% confidence interval. A p-value <0.05 was considered the threshold for statistical significance.

RESULTS

The characteristics of the groups with and without prolonged ED stay and the statistical results between the groups are shown in Table 1. Of the 5240 patients included in the study, 1060 (20.2%) had prolonged LOS and 4180 (79.2%) did not. The median LOS was 4.43 (4.83) hours. A significant relationship was found between older age and prolonged LOS in the ED (p=0.009). Sex distribution was similar between the groups (p=0.099). Almost all patients had insurance (98%) and there was no significant correlation between the presence of insurance and prolonged LOS (p=0.131). It was found that most of the patients were Turkish citizens (94.7%), 3.8% were Syrian refugees, 1.5% were from other countries, and the LOS of Syrian refugees was significantly longer (p=0.004).

It was observed that 35.6% of the patients had a triage category of nonurgent, 43.9% urgent, and 20.4% emergent at the first presentation, and those with a triage category of nonurgent had a significantly prolonged LOS (p<0.001). Urine test was ordered in 38.2%, blood test in 77.7%, ultrasound in 21.2%, CT in 76.3%, and MRI in 15.4% of the patients, and all of them were significantly associated with prolonged LOS (p<0.001). In addition, 56.2% of the patients were hospitalized in surgical wards, 28.1% in internal medicine wards, and 15.8% in intensive care unit, and those hospitalized in internal medicine wards were significantly associated with prolonged LOS (p<0.01). However, although 19.8% of the patients arrived at night, LOS was significantly prolonged (p<0.001).

DISCUSSION

Prolonged LOS in the ED is important in terms of service quality, patient satisfaction, and evaluation of the administrative processes of the ED (16). It has also been shown that ED LOS over 6 h increases in-hospital mortality and is associated with poor prognosis (17-20). However, according to the study by Richardson (21), the LOS of patients with an ED stay of more than 8 h is also significantly prolonged, which limits the bed utilization capacity.

According to the legislation in Türkiye, it is recommended that emergency patients be hospitalized within 8 h (15). In our study, it was determined that the average LOS was 5.5 h and 20.8% of the patients hospitalized from the ED stayed in the ED for more than 8 h. Targeted LOS varies between studies. In some studies, the cut-off value is not specified, but 4 h, 6 h, 8 h, 12 h, etc. different values were used (22-25). The average LOS in crowded EDs has been reported as 5.8 h (26). However, we obtained a result similar to this in our study.

The initial triage of 35.6% of patients was stated as nonurgent. However, patients admitted to nonurgent triage were found to have significantly longer LOS. First, the fact that a significant proportion of hospitalized patients are triaged as nonurgent shows that triage is not done effectively. For this reason, we observe that the LOS is prolonged. It is thought that this problem can be solved by effective triage.

According to the United Nations, there are approximately 3.6 million registered Syrian refugees in Türkiye (27). Previous studies have shown that language and communication barriers are associated with prolonged LOS (28). In this study as well, a significant association was identified between Syrian refugees and prolonged LOS. Similar results have been reported in previous studies on refugees (29,30). More widespread use of interpreters can reduce prolonged LOS.

Patients hospitalized for internal medicine and older age have prolonged LOS due to having more comorbidities and special needs such as isolation (31,32). Previous studies have also demonstrated that comorbidities prolong LOS in the ED (33-35).

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Table 1. Characteristics of patients admitted from the ED to the inpatient ward (n=5240)

Presenting characteristics	All n (%)	LOS n (%)		p-value
		Not prolonged 4180 (79.8)	Prolonged 1060 (20.2)	
Patient-related				
Age				
Median (IQR)	56 (37)	56 (17.104)	58 (34)	0.009[1]
Sex				
Female	2329 (44.4)	1834 (43.9)	495 (46.7)	0.099[2]
Male	2911 (55.6)	2346 (56.1)	565 (53.3)	
Social security				
Secured	5128 (97.9)	4097 (98)	1031 (97.3)	0.131[2]
Not secured	112 (2.1)	83 (2)	29 (2.7)	
Citizenship				
Turkish citizen	4960 (94.7)	3976 (95.1)	984 (92.8)	**0.004[2]**
Syrian	200 (3.8)	141 (3.4)	59 (5.6)	
Other	80 (1.5)	63 (1.5)	17 (1.6)	
Time of arrival				
Night shift	1040 (19.8)	725 (17.3)	315 (29.7)	**<0.01[2]**
Day shift	2377 (45.4)	932 (46.2)	445 (42)	
Evening shift	1823 (34.8)	1523 (36.4)	300 (28.3)	
Hospital-related				
Triage				
Non-urgent	1867 (35.6)	1304 (31.2)	563 (53.1)	**<0.01[2]**
Urgent	2302 (43.9)	2002 (47.9)	300 (28.3)	
Emergent	1071 (20.4)	874 (20.9)	197 (18.6)	
Urine test				
Yes	2004 (38.2)	1341 (32.1)	663 (62.5)	**<0.01[2]**
No	3236 (61.8)	2839 (67.9)	397 (37.5)	
Blood test				
Yes	4073 (77.7)	3042 (72.8)	1031 (97.3)	**<0.01[2]**
No	1167 (22.3)	1138 (27.2)	29 (2.7)	
Ultrasonography				
Yes	1110 (21.2)	724 (17.3)	386 (36.4)	**<0.01[2]**
No	4130 (78.8)	3456 (82.7)	674 (63.6)	
Computed tomography				
Yes	3996 (76.3)	3079 (73.7)	917 (86.5)	**<0.01[2]**
No	1244 (23.7)	1101 (26.3)	143 (13.6)	
Magnetic resonance imaging				
Yes	808 (15.4)	606 (14.5)	202 (19.1)	**<0.01[2]**
No	4432 (84.6)	3574 (85.5)	858 (80.9)	
Inpatient ward				
Surgery	2943 (56.2)	2510 (60)	433 (40.8)	**<0.01[2]**
Medicine	1470 (28.1)	1031 (24.7)	439 (41.4)	
İntensive care unit	827 (15.8)	639 (15.3)	188 (17.7)	
Time of arrival				
Night shift	1040 (19.8)	725 (17.3)	315 (29.7)	**<0.01[2]**
Day shift	2377 (45.4)	1932 (46.2)	445 (42)	
Evening shift	1823 (34.8)	1523 (36.4)	300 (28.3)	

[1]Mann-Whitney U test was applied. [2]Chi-square test was applied. ED: emergency department, LOS: length of stay, IQR: interquartile range

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In this study, elderly patients and patients hospitalized in the internal medicine department were significantly associated with prolonged LOS in the ED. Effectively assessing elderly and comorbid patients in the ED, in line with guidelines, and increasing awareness among clinicians and hospital management regarding admission care may contribute to reducing prolonged LOS.

It was found that 19.8% of patients were admitted during the night shift, and these patients were significantly associated with prolonged LOS. Previous studies have reported that access to consultations, investigations, and treatment is more limited during the night shift than during the day (25). Although night shift was found to be associated with prolonged LOS in some studies, there are also studies showing the association of day shift with prolonged LOS (25). This may vary according to population characteristics, region, and hospital and institutional preferences. It is thought that accelerating the health service processes during the night shift will contribute to the solution of the problem.

Study Limitations

Our study has some limitations. First, the fact that our study is a single-center, retrospective study covering only one year weakens its generalisability. In addition, factors that may have a possible effect on prolonged LOS, such as the number of consultations, presence of comorbid diseases, treatments applied, and clinical diagnosis, were not investigated.

CONCLUSION

We identified both patient-related and hospital-related factors associated with prolonged LOS in the ED, including older age, Syrian refugee status, diagnostic tests, admission to internal medicine units, and nighttime arrivals. Prolonged LOS can be reduced through the implementation of these strategies designed to address these contributing factors. Furthermore, multicenter, prospective studies investigating the factors affecting prolonged LOS in the ED should be conducted in the future.

Ethics Committee Approval: This study protocol was approved by Clinical Research Ethical Committee of University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital (decision no: 388 date: 22.12.2021). The study was conducted in accordance with the Good Clinical Practice and the Declaration of Helsinki ethical standards.

Informed Consent: This study was a retrospective study based on anonymous data, patient consent was not obtained.

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Perceived Stress in Life and Smoking

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ABSTRACT

Objective: We believe that it is very important to identify the factors that increase smoking, which is known to be the cause of many chronic diseases in the family medicine practice. In this study, we aimed to investigate the effect of stress perceived by people on cigarette smoking.

Methods: The study was conducted with 384 participants out of 1150 people who met the inclusion criteria, who were followed in the University of Health Sciences Türkiye, İstanbul Bağcılar Training and Research Hospital, Clinic of Family Medicine, Güneşli Educational Family Health Center between 01.02.2022 and 28.02.2022. Sociodemographic data form, Perceived Stress scale-14 and Fagerström test for Nicotine Dependence (to current smokers only) were responded by the participants. The study was analyzed by SPSS version 23.0 statistical program and cut-off value of statistical significance was accepted as $p<0.05$.

Results: According to our study, it was determined that perceived stress levels are higher in young people, women, those who have never worked, those who use 2 or more regular medications, those who do not exercise regularly, and those who do not have a regular sleep pattern. In this study, we found that elders and men have higher nicotine addiction levels. Additionally, men's risk of smoking was found to be approximately twice that of women.

Conclusion: In our study, no significant relationship was found between high perceived stress and nicotine addiction level, cigarette consumption amount and smoking status. However, various factors such as age, gender and regular physical activity have been found to be significantly related to perceived stress. Additionally, gender, insufficient self-efficacy and perceived stress/discomfort were found to be effective on smoking.

Keywords: Perceived stress, smoking, family medicine, nicotine addiction, perception of self-efficacy, holistic approach

INTRODUCTION

According to World Health Organization (WHO) 2021 data, approximately 1.3 billion people around the world use tobacco, and more than 80% of them live in low- and middle-income countries (1). Türkiye ranks tenth among the countries that use the most tobacco in the world. In Türkiye, 18 million people (28%) aged 15 and overuse tobacco every day (41.3% of men and 14.9% of women) (2). For this reason, smoking is considered an important public health problem in our country.

Smoking is the most important preventable cause of premature death in the world and in our country. Smoking is a leading cause of many diseases, including lung cancer, stroke, transient ischemic attacks, cardiovascular diseases, and chronic obstructive pulmonary disease (3). WHO estimates that tobacco use causes the death of 8.7 million people worldwide every year. More than 1.2 million of these deaths are caused by passive smoking. Almost half of children regularly breathe air polluted with tobacco smoke in public places, and 65 thousand children die from diseases related to passive smoking every year (4).

Pharmacological research has found that the main addictive agent in tobacco smoke is nicotine. Nicotine, which has been believed to cause milder addiction than other substance addictions for many years, has been shown to be one of the most powerful addictive substances in epidemiological and animal studies (5). Nicotine exposure activates the mesocorticolimbic pathway, also known as the reward pathway, and increases dopamine release from dopaminergic neurons in the ventral tegmental area and nucleus accumbens. It has also been demonstrated that nicotine, unlike other addictive substances, increases sensitivity to subsequent exposure in the reward circuit (6).

Stress is a state of emotional and physical tension felt by a person. Many different situations or life events can cause stress. It is usually triggered when we experience something new, unexpected, threatening to our sense of self, or when we feel like we have little control over a situation. The same situation or event can cause different stress levels in individuals depending on their previous experiences, personal characteristics, educational background and beliefs. This reveals the concept of perceived stress, which is a

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subjective experience. Perceived stress is the feelings or thoughts an individual has about how stressed they are during a certain period of time. It has been shown that the excess of negative thoughts about a situation or event is significantly related to the high level of stress perceived by the person (7).

We believe that in family medicine practice, where preventive health services are a priority, it is very important to reveal the factors that increase smoking, which is known to be the cause of many chronic diseases, and to approach the individual holistically, considering factors that are not questioned at first, such as perceived stress in life. Based on this idea, this study aims to investigate the effect of stress perceived by people in life on smoking.

METHODS

This study was an observational, descriptive and cross-sectional study. It was conducted between 01.02.2022-28.02.2022 at Güneşli Education Family Health Center (EASM) affiliated with the Family Medicine Clinic of Health Sciences University Türkiye, İstanbul Bağcılar Training and Research Hospital. The sociodemographic data form and the Perceived Stress scale (PSS-14), prepared by examining similar studies, were responded by 384 participants who met the inclusion criteria out of 1150 patients who were admitted within a month, and the Fagerström test for Nicotine Dependence (FTND) was applied to current smokers using face-to-face interview technique. Informed written consent was obtained from those who participated in the study. Our study was reviewed at the meeting of the İstanbul Medipol University Non-invasive Clinical Research Ethics Committee on 23.12.2021 and was found ethically appropriate according to decision no 1297.

Those who filled out the survey forms incompletely, those who were not registered in Güneşli EASM, those who were mentally unstable, those under the age of 18, and pregnant women were not included in the study.

The PSS-14 was developed by Cohen et al. (8) in 1983. Turkish validity and reliability study was conducted by Eskin et al. (9). It is an easily applicable scale that measures how stressful life events in a person's life are perceived (8,9). In the scale, participants are asked a total of 14 questions about their personal experiences in the last month. Participants evaluate each item on a 5-point Likert-type scale ranging from "Never (0)" to "Very often (4)". Seven of the items containing positive statements are reverse scored. The first of the two sub-dimensions obtained by factor analysis using the principal components method is called the perception of insufficient self-efficacy, consisting of 7 questions with positive statements, and the other is called the perception of stress/discomfort, consisting of 7 questions with negative statements. The total score obtained as a result varies between 0 and 56. A high score indicates a person's perception of stress is high.

The FTND was developed by Heatherton et al. (10) in 1991. Turkish validity and reliability study was conducted by Uysal et al. (11) published. It is a short and practical scale that measures nicotine addiction in smokers and is used as a basis in smoking cessation clinics (10,11). In the scale, participants are asked a total of 6 questions about their smoking habits. The total score obtained as a result of the answers given to the test varies between 0 and 10. Depending on the score the person receives from FTND, the degree of nicotine addiction is classified as very low (0-2 points), low (3-4 points), medium (5 points), high (6-7 points) and very high (8-10 points) (12).

Statistical Analysis

The SPSS version 23.0 program was used for statistical analysis. When evaluating study data, descriptive statistics were shown as mean ± standard deviation, median (interquartile range), frequency or percentage. The suitability of quantitative data for normal distribution was tested using the Shapiro-Wilk test and graphical analysis. Student's t-test was used for two-group comparisons of normally distributed quantitative variables, and Mann-Whitney U test was used for non-normally distributed variables. One-Way ANOVA test was used for more than two group comparisons of normally distributed quantitative variables, and Bonferroni test was used for post-hoc evaluations. Kruskal-Wallis test and post-hoc Dunn-Bonferroni test were used for variables that did not show normal distribution. Spearman correlation analysis was used to evaluate the relationships between quantitative variables. Logistic regression analysis was used in multivariate evaluations. Statistical significance was accepted as $p<0.05$.

RESULTS

The study was conducted with a total of 384 participants, 44.5% of whom (n=171) were female and 55.5% (n=213) were male. The ages of the participants ranged from 18 to 67 and the average was 33.23±10.94. The distribution of the descriptive characteristics of the participants is given in detail (Table 1).

It was observed that 37.8% (n=145) of the participants smoked, 6.8% (n=26) had quit, and 55.4% (n=213) did not smoke. Participants' cigarette use varied between 1 and 60 cigarettes per day and average daily usage was 15.00±9.00 cigarettes. Duration of smoking varied between 1 and 50 years, and the average duration was 12.56±9.51 years. The total cigarette smoking amount of the participants varied between 0.10 and 100 packs/year, and the average amount was 10.57±13.03 packs/year. The relationship between the participants' scores from the total and sub-dimensions of the PSS-14 and sociodemographic data is shown (Table 2).

Perceived stress levels of individuals who were young, female, had never worked, used 2 or more regular medications, did not exercise regularly and had no regular sleep pattern were found to be higher than other groups (p=0.001, p=0.007, p=0.028, p=0.014, p=0.008 and p=0.001, respectively). In addition, individuals who were young, female, single, high school or undergraduate graduates, never worked or quitted their jobs, did not have children, and had poor sleep quality were found to have higher stress/discomfort perceptions than other groups (p<0.001, p=0.001, p=0.020, p=0.003, p=0.014, p=0.015 and p=0.001, respectively). In addition, individuals who were obese,

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whose total family income was at or below the minimum wage, who used 2 or more regular medications, who did not exercise regularly, who exercised a small number of times per week, who did not have a regular sleep pattern, who did not drink alcohol and who did not smoke, were found to have higher inadequate self-efficacy perceptions compared to other groups (p=0.031, p=0.001, p=0.012, p=0.012, p=0.007, p=0.001, p=0.031 and p=0.009, respectively).

Table 1. Distribution of descriptive characteristics

		n	%
Gender	Female	171	44.5
	Male	213	55.5
Age	Mean ± SD	33.23±10.94	
BMI	Underweight	18	4.7
	Normal	171	44.5
	Overweight	141	36.7
	Obese	49	12.8
	Morbidly obese	5	1.3
Marital status	Single	194	50.5
	Married	177	46.1
	Divorced	13	3.4
Educational status	Primary school	34	8.9
	Middle school	36	9.4
	High school	70	18.2
	Associate degree	54	14.1
	Bachelor's degree	153	39.8
	Master's degree and Above	37	9.6
Working status	Never worked	27	7
	Housewife	23	6
	Working	285	74.2
	Quitted the job	21	5.5
	Retired	14	3.6
	Student	14	3.6
Having child/children	No	232	60.4
	Yes	152	39.6
Income	Below the minimum wage	24	6.3
	Minimum wage	81	21.1
	Between the minimum wage and 2 times of the minimum wage	148	38.5
	2 times of the minimum wage and above	131	34.1
Chronic disease		77	20.1
Drug use		63	16.4
Exercise		151	39.3
Sleep		231	60.2
Alcohol	No	270	70.3
	Yes	109	28.4
	Quitted	5	1.3
Smoking	No	213	55.5
	Yes	145	37.8
	Quitted	26	6.8

BMI: body mass index, SD: standard deviation

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Table 2. Comparison of descriptive characteristics according to the Perceived Stress scale

		Insufficient perception of self-efficacy		Perception of stress/discomfort		Total score of Perceived Stress scale	
		Mean ± SD/ median (IQR)	p-value	Mean ± SD/ median (IQR)	p-value	Mean ± SD/ median (IQR)	p-value
Gender	Female	12.00±4.55	[b]**0.312**	15.75±5.27	[b]**0.001****	27.75±8.50	[b]**0.007****
	Male	11.55±4.66		13.94±4.86		25.49±7.74	
BMI	Underweight	12.7 (3)	[c]**0.031***	18 (7)	[d]**0.083**	30.7 (8)	[d]**0.166**
	Normal	11.6 (6)		14.6 (6)		26.2 (10)	
	Overweight	11.6 (5)		14.8 (6)		26.3 (10)	
	Obese	12.8 (5)		14.1 (5)		26.9 (9)	
	Morbidly obese	7.6 (1)		14.8 (7)		23 (8)	
Marital status	Single	11.9 (6)	[c]**0.850**	15.5 (7)	[d]**0.020***	27.3 (10)	[d]**0.118**
	Married	11.6 (6)		14 (6)		25.6 (9)	
	Divorced	11.8 (5)		14.4 (4)		26.2 (4)	
Educational status	Primary school	12.1 (7)	[c]**0.815**	12.7 (3)	[d]**0.003****	24.8 (9)	[d]**0.591**
	Middle school	12.6 (7.5)		12.3 (6)		24.9 (10)	
	High school	11.9 (5)		15.4 (7)		27.3 (9)	
	Associate degree	12.3 (6)		14.4 (7)		26.7 (13)	
	Bachelor's degree	11.4 (4)		15.4 (6)		26.8 (8)	
	Master's degree and above	11 (5)		15.5 (6)		26.4 (9)	
Working status	Never worked	13.6 (6)	[c]**0.259**	16.7 (6)	[c]**0.014***	30.3 (12)	[c]**0.028***
	Housewife	12.1 (7)		14.4 (6)		26.5 (12)	
	Working	11.5 (6)		14.6 (6)		26.1 (10)	
	Quitted the job	12.6 (7)		16.4 (8)		29 (12)	
	Retired	11 (6)		11.1 (6)		22.1 (7)	
	Student	12.8 (4)		16.3 (5)		29.1 (7)	
Child	No	11.67±4.54	[b]**0.823**	15.26±5.05	[b]**0.015***	26.93±8.26	[b]**0.200**
	Yes	11.88±4.73		13.96±5.15		25.84±7.97	
Family income	Below the minimum wage	13.2 (4)	[c]**0.001****	16 (3)	[d]**0.510**	29.2 (4)	[d]**0.076**
	Minimum wage	12.8 (5)		14.3 (8)		27.1 (7)	
	Between the minimum wage and 2 times of the minimum wage	11.9 (5)		14.9 (6)		26.9 (10)	
	2 times of the minimum wage and above	10.6 (7)		14.6 (6)		25.2 (9)	
Chronic diseases	No	11.91±4.62	[b]**0.604**	14.80±5.01	[b]**0.625**	26.70±7.96	[b]**0.756**
	Yes	10.95±4.51		14.48±5.70		25.43±9.10	
	1	12 (5)	[a]**0.604**	15 (6)	[a]**0.880**	27 (10)	[a]**0.727**
	≥2	14 (7)		14.6 (6)		27 (11)	

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Table 2. Continued

		Insufficient perception of self-efficacy		Perception of stress/discomfort		Total score of Perceived Stress scale	
		Mean ± SD/ median (IQR)	p-value	Mean ± SD/ median (IQR)	p-value	Mean ± SD/ median (IQR)	p-value
Drug use	No	11.91±4.62	[b]**0.281**	14.80±5.01	[b]**0.649**	26.70±7.96	[b]**0.257**
	Yes	10.95±4.51		14.48±5.70		25.43±9.10	
	1	10.5 (5)	[a]**0.012***	14 (7)	[a]**0.067**	25.5 (10)	[a]**0.014***
	≥2	14 (5)		16 (8)		29 (11)	
Regular exercise	No	12.22±4.65	[b]**0.012***	15.16±5.14	[b]**0.057**	27.38±7.94	[b]**0.008****
	Yes	11.03±4.46		14.10±5.04		25.13±8.31	
	1-2 days a week	11.98±4.44	[c]**0.007****	14.60±5.05	[d]**0.226**	26.57±8.05	[d]**0.055**
	3-4 days a week	9.91±4.61		12.86±5.65		22.77±9.38	
	More than 4 days a week	9.52±3.67		14.10±4.04		23.62±6.95	
Regular sleep	No	12.78±4.93	[b]**0.001****	16.09±5.54	[b]**0.001****	28.88±8.79	[b]**0.001****
	Yes	11.06±4.26		13.85±4.62		24.92±7.31	
	1-2 days a week	11.42±3.91	[d]**0.508**	14.02±4.47	[d]**0.497**	25.44±7.15	[d]**0.391**
	3-4 days a week	11.26±3.94		14.24±4.28		25.50±6.33	
	More than 4 days a week	10.70±4.70		13.44±4.98		24.14±8.09	
Alcohol	No	12.1 (5)	[c]**0.031***	14.5 (7)	[c]**0.155**	26.5 (10)	[c]**0.737**
	Yes	10.8 (6)		15.5 (7)		26.3 (8)	
	Quitted	15.6 (5)		13.6 (6)		29.2 (4)	
Smoking	No	12.42±4.50	[d]**0.009****	14.61±4.80	[d]**0.795**	27.03±7.59	[d]**0.320**
	Yes	10.99±4.68		14.97±5.67		25.96±8.98	
	Quitted	10.54±4.36		14.58±4.54		25.12±7.71	

The variables tested with [a]Mann-Whitney U test, [c]Kruskal-Wallis test and Dunn-Bonferroni test are shown as median (Q1-Q3) in the table. The variables tested with [b]Student's t-test, [d]One-Way ANOVA test and Dunn-Bonferroni are shown as mean ± standard deviation (SD), *p<0.05, **p<0.01
IQR: interquartile range

Perceived stress levels and perceptions of stress/discomfort of the participants according to smoking did not show a statistically significant difference (p>0.05). The insufficient self-efficacy perceptions of smokers were found to be significantly lower than those of non-smokers (p=0.022).

A weak, statistically significant relationship was detected between the participants' ages and the PSS-14 total score and stress/discomfort perception sub-dimension score (PSS-14 and stress/discomfort perception scores decreased as age increased) (r=-0.166, p=0.001 and r=-0.213, p<0.001). There was no correlation between the total amount of cigarettes consumed (pack/year) by smoker and ex-smoker participants and total score and sub-dimensions scores of PSS-14 (p>0.05). There was no correlation between the number of cigarettes consumed by smoker participants daily and the total score and sub-dimensions scores of the PSS-14 (p>0.05).

When the FTND scores of the smokers were examined; 38.4% (n=56) had very low score, 32.2% (n=47) low score, 7.5% (n=11) moderate score, 14.4% (n=21) high score and 7.5% (n=11) very high score.

The total scores of the FTND of male participants were found to be statistically significantly higher than female participants (p=0.015). A weak and positive (as age increased, FTND score increased) statistically significant correlation was detected between the participants' ages and their total FTND scores (r=-0.189, p=0.022).

The relationship between the participants' total scores and sub-dimensions scores of the PSS-14 and their age, total cigarette use, number of cigarettes per day and FTND is shown (Table 3).

Backward stepwise logistic regression was evaluated by including age, body mass index (BMI), gender, chronic disease, PSS-14 total score and sub-dimensions scores, which were thought to be effective on smoking, and the model was found to be significant

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Table 3. Relationship between Perceived Stress scale and age, total cigarette use, number of cigarettes used per day and Fagerström test for nicotine dependence

		Insufficient perception of self-efficacy	Perception of stress/ discomfort	Total score of Perceived Stress scale
Age	r	-0.061	-0.213	-0.166
	p	**0.230**	**0.001****	**0.001****
Total smoking (packs/years)	r	-0.114	-0.144	-0.147
	p	**0.137**	**0.061**	**0.055**
Daily smoking (pieces)	r	-0.078	-0.018	-0.038
	p	**0.350**	**0.830**	**0.649**
Total score of Fagerström test for nicotine dependence	r	0.024	0.013	0.018
	p	**0.773**	**0.877**	**0.825**

r: Spearman correlation test, **p<0.01

Table 4. Logistic regression analysis of risk factors effective on smoking

		B	SE	p-value	Odds	95% CI for odds	
						Lower	Upper
Step 4	Gender (M)	0.737	0.230	**0.001****	2.091	1.332	3.282
	Insufficient perception of self-efficacy	-0.101	0.029	**0.001****	1.107	1.044	1.172
	Perception of stress/discomfort	0.067	0.026	**0.009****	1.070	1.017	1.126

**p<0.01, B: beta coefficient, SE: standard error, CI: confidence interval

(F=23.438; p<0.001). The explanatory coefficient of the model was 71.5%.

In the evaluation made with the Backward stepwise method, at the end of the 4th step, gender, insufficient self-efficacy perception and stress/discomfort perception measurements were included in the model (p<0.01) (Table 4). When female gender was taken as reference, the risk of smoking in men was higher [odds ratio (OR): 2.091, 95% confidence interval (CI): 1.33-3.28]. The OR of the effect of a unit decrease in the perception of insufficient self-efficacy in smokers was 1.107 (95% CI: 1.044-1.172). The OR of the effect of a unit increase in the perception of stress/discomfort on smoking was 1.070 (95% CI: 1.017-1.126).

While the univariate effects of age, BMI, chronic disease and PSS-14 total score were significant, their effects on smoking were not found to be significant in the multivariate evaluation (p>0.05).

DISCUSSION

In our study, no statistically significant relationship was found between smokers' total and subdimensions scores of the PSS-14 and FTND score. In the study by Warner et al. (13), the mean total score of the smokers with a high or higher addiction level was found to be significantly higher than those with a medium or lower addiction level. In a study conducted by Banazadeh et al. (14) among students of Kerman University of Medical Sciences in Iran, it was found that there was a positive and significant correlation between perceived stress and nicotine addiction level. In Białożyt's (15) thesis study, which included 216 participants, no significant relationship was found between perceived stress and nicotine addiction level, and this result was attributed to the limitations of the study. People with high perceived stress have high nicotine addiction levels in the literature. We think that it is effective for people to see smoking as a tool that suppresses the perception of stress and to associate the feeling of happiness and relaxation that comes with the effect of dopamine secreted as a result of nicotine's activation of the reward pathway, with its stress-reducing effect.

In our study, no statistically significant relationship was found between the total amount of cigarettes consumed (pack/year) and the PSS-14 total subdimensions scores in smokers and ex-smokers. In addition, no statistically significant relationship was found between the number of cigarettes consumed per day and the PSS-14 total and subdimensions scores in smokers. In the study of Stubbs et al. (16) which included 217, 561 participants from 41 countries, increased perceived stress level was associated with heavy smoking (≥30 cigarettes per day) among daily smokers.

In Ng and Jeffery's (17) study, which included 12,110 participants in 26 workplaces, the number of cigarettes consumed per day among smokers was not found to be related to perceived stress. There is no one-to-one relationship between high perceived stress and the amount of cigarette consumption in the literature. The main reason why cigarettes are consumed in increasing amounts over time can be explained by the physiological addiction it creates in the person.

In our study, while there was no statistically significant relationship between the smoking status of the participants and their

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PSS-14 mean total score and stress/discomfort perceptions; the perception of insufficient self-efficacy of smokers was found to be significantly lower than that of non-smokers. In Tüfekçi and Türktemiz's (18) study, which included 443 participants between the ages of 18-65 in Konya, no statistically significant difference was found between smoking status, PSS-14 mean total score and stress/discomfort perceptions, consistent with our study. In the same study, contrary to our study, the perception of insufficient self-efficacy of smokers was found to be significantly higher than that of non-smokers (18). In Koçak's (19) study conducted with students of the school of physical education and sports, no significant difference was found in the PSS-14 total score and its subdimensions scores according to smoking status. In the study conducted by Naquin and Gilbert (20) on university students, the PSS-14 mean total score of current smokers was found to be significantly higher than that of those who had never smoked. These different results in various studies can be explained by the fact that perceived stress alone is not effective in smoking status, but various factors such as age, gender, and working status may also be effective.

Study Limitations

The most important limitation of our study was that it was a single-center study. Our results may not be valid for the whole population. Therefore, studies with larger populations are needed.

CONCLUSION

In our study, no significant relationship was found between high perceived stress and nicotine addiction level, cigarette consumption amount and smoking status. However, various factors such as age, gender, and regular exercise were found to be significantly related to perceived stress. Additionally, gender, insufficient self-efficacy perception and perception of stress/discomfort were found to be effective on smoking.

Perceived stress may be a facilitating factor in starting to smoke. It is predicted that one of the important reasons why cigarettes are consumed in increasing amounts over time may be the physiological addiction it creates in the person as a result of the increased number of nicotine receptors due to smoking. In conclusion, in addition to motivational interviews in smoking cessation clinics, treatments aimed at reducing physiological addiction, especially nicotine replacement therapy, should also be planned for suitable patients.

Ethics Committee Approval: This study was approved by the Non-Interventional Clinical Research Ethics Committee of İstanbul Medipol University (decision no: 1297, date: 23.12.2021).

Informed Consent: From those who participated in the research informed written consent was obtained.

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The Role of Health Literacy in Adult Immunization

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ABSTRACT

Objective: This study investigated how health literacy (HL) affects adult immunization (AI) knowledge and behavior in individuals aged 18 years.

Methods: This cross-sectional observational study was conducted with adults who presented to an educational family health center. study data were collected using a 28-item questionnaire inquiring about the sociodemographic characteristics, knowledge, attitudes, and behaviors of AI and the 32-item Turkish Health Literacy Survey Questionnaire (HLS-TR-Q32) administered face-to-face interviews.

Results: The study included 312 participants. The mean age of the participants was 38.3±13.6 years (minimum-maximum: 18-83). Of participants, 73.1% (n=228) reported knowing about AI. Approximately 71.4% (n=223) of the respondents had received at least one adult vaccination, the most common being the tetanus vaccine (41.0%, n=128). The most common justification for not getting adult vaccination was "vaccination not being recommended by the doctor" (42.1%, n=37). Additionally, 47.4%, 16.1%, 25.8%, and 10.6% of the respondents had limited, inadequate, sufficient, and excellent HL, respectively. Knowledge of AI and receiving adult vaccination positively correlated with the HLS-TR-Q32 subdomain scores for "Treatment and Service-Appraising Health-Related Information" (p=0.014, p=0.037).

Conclusion: The HL level was found to be mostly inadequate or limited among the participants, and this was found to influence knowledge and behaviors. AI rates can be significantly increased by improving HL as well as by physicians advising adults to get vaccinated.

Keywords: Immunization, knowledge, attitude, health literacy, primary health care

INTRODUCTION

Lifelong immunization is recommended for protection against vaccine-preventable diseases (1). Adults at risk of illness, hospitalization, disability, and, in some cases, death from vaccine-preventable diseases are advised to be vaccinated based on age, medical condition, lifestyle, and previous vaccination status (2). Despite many studies on childhood immunization and the inclusion of childhood immunization in the Expanded Program on Immunization, data on adult immunization (AI) and related factors remain limited, especially in developing countries (3).

Health literacy (HL) is the ability of individuals to access, understand, and use information needed to protect and maintain health (4). HL affects an individual's ability to read and understand written health information, act on this information, communicate needs to health care providers when necessary, and understand health warnings. A low level of HL results in poorer medication adherence and affects individuals' knowledge of diseases and self-care skills (5). HL is significantly associated with general health status, use of resources, hospitalization, and access to care (6).

This study examined the relationship between HL, knowledge of AI, and vaccination uptake among adults. Determination of factors affecting AI, particularly the relationship between AI and the level of HL as an improvable factor, is hypothesized to enhance social awareness and develop relevant family medicine strategies.

METHODS

The study was designed as a cross-sectional, face-to-face survey, and its population consisted of 312 individuals aged 18 years who presented to an educational family health center in May-June 2022 and agreed to participate in the study.

The study was conducted using a 28-item data collection form, which was developed based on the literature and inquiries about sociodemographic characteristics, knowledge, attitudes, and behaviors about adult vaccines, and the 32-item Turkish Health Literacy Survey Questionnaire (HLS-TR-Q32) (7), which was developed by Abacıgil et al. (7) in 2016 and built on the European Health Literacy Research Consortium (HLS-EU CONSORTIUM, 2012) study. The questionnaire was administered through face-to-face surveys.

The HLS-TR-Q32 survey was developed based on the experiences from the Health Literacy Survey Development Workshop and the HLS-EU-TR (European Health Literacy Scale Turkish Adaptation)

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Study. Unlike the original survey (HLS-EU), it combined the domains of "disease prevention" and "health promotion" into one domain. It consists of 32 questions categorized into two domains instead of three ("Treatment and Service" and "Disease Prevention/Health Promotion") and four processes (accessing, understanding, appraising, and applying health-related information) (Table 1) (7).

The scale was scored in the range of 0-50 points, as in the original formula. The index calculated is classified into four categories as in the HLS-EU study:

(0-25): Inadequate HL,

(>25-33): Problematic or limited HL,

(>33-42): Sufficient HL,

(>42-50): Excellent HL.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0. variables were assessed for normality of distribution using histograms and the Kolmogorov-Smirnov test. Descriptive analyses are given in mean, standard deviation, median, interquartile range, and minimum-maximum values. Categorical variables were compared using Pearson's chi-square test. Non-normally distributed (non-parametric) variables were compared between the two groups using the Mann-Whitney U test. Factors influencing knowledge of adult vaccination and vaccination uptake were analyzed using binary logistic regression analysis. Statistical significance was set at $p<0.05$.

Ethical Considerations

Ethical approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital (decision no: HNEAH-KAEK 2022/96, date: 18.04.2022). This research complies with the Helsinki Declaration and Good Clinical Practice principles and does not conflict with the ethical rules of human research. An informed consent form was obtained from the research participants.

RESULTS

Of the 312 respondents, 199 (63.7%) were female and 113 (36.2%) were male, with a mean age of 38.3 years; 202 (64.7%) were university graduates and 44 (14.1%) were healthcare workers. There were 171 (54.8%) respondents whose income was equal to their expenditures, 85 (27.2%) participants had an income less than their expenditures, and 56 (17.9%) respondents had an income greater than their expenditures. Approximately 84 (26.9%) participants had at least one chronic disease and were on continuous medication (Table 2).

The HL level was found to be limited among 47.4% of the participants, sufficient among 25.8%, inadequate among 16.1%, and excellent among 10.6% of them (Table 3).

Of the respondents, 228 (73.1%), including 42 (13.4%) healthcare workers, reported knowing about AI. The participants were most familiar with vaccines for influenza (n=208, 66.6%), tetanus (n=161, 51.6%), and rabies (n=143, 45.8%); they were the least familiar with vaccines for yellow fever (n=34, 10.9%) and shingles (n=45, 14.4%). A few answered "other vaccines" (n=15, 4.8%). On the other hand, 84 (26.9%) respondents reported not knowing about AI (Figure 1).

Among respondents who reported knowing about AI, the source of information was television or the Internet (105, 45.4%), physicians (81, 35.1%), immediate circle (81; 35.1%), training received (72, 31.1%), and books or newspapers (43, 18.6%).

The proportion of individuals who reported knowing about AI was significantly higher among healthcare workers (95.5%) than among non-healthcare workers (69.4%) ($p<0.001$). Likewise, the proportion of individuals who reported knowing about AI was significantly higher among individuals with chronic diseases (86.9%) than among those without chronic diseases (67.9%) ($p=0.001$). The mean age of those who reported knowing about AI was 40.4 years versus 32.6 years for those who reported not knowing about AI ($p<0.001$). Respondents who reported knowing about AI scored 29.0 on the HLS-TR-Q32 subdomain of Treatment and Service-Appraising Health-Related Information, whereas those who reported not knowing scored 26.1 on the same subdomain ($p=0.01$) (Table 4).

Being a healthcare worker increases knowledge of AI by 10.5 times, having a chronic disease by 2.2 times, and increasing each one-unit age by 1.04 times. A one-unit increase in the score from the HLS-TR-Q32 subdomain "Treatment and Service-Appraising Health-Related Information" increased immunization knowledge by 1.04 times (Table 5).

When the respondents were asked whether they had received any vaccination during adulthood, 223 (71.4%) reported receiving at least one vaccination, whereas 89 (28.5%) reported receiving no adult vaccination. Of the participants, 128 (41.0%) reported receipt of tetanus vaccination, 102 (32.6%) influenza vaccination, and 56 (17.9%) hepatitis B vaccination. Approximately 58 respondents (18.5%) who reported receipt of "other vaccines"

Table 1. 2x4 matrix components of the HLS-TR-Q32 and item numbers corresponding to these components (7)

	Access to health-related information	Understanding health-related information	Appraising health-related information	Using/applying health-related information
Treatment and service	1,4,5,7	2,8,11,13	3,9,12,15	6,10,14,16
Disease prevention/ health promotion	18,20,22,27	19,21,23,25	24,26,28,32	17,29,30,31

HLS-TR-Q32: 32-item Turkish Health Literacy Survey Questionnaire

said they received the coronavirus disease-2019 (COVID-19) vaccine and other vaccines. Because COVID-19 vaccination is not included in the routine vaccination schedule, respondents were not questioned separately about that vaccination. However, most participants who selected the option "other vaccines" reported receiving COVID-19 vaccination. Because we did not directly inquire respondents about the "COVID-19 vaccine" as an option, the rate turned out to be low (Figure 1).

Among 58 women aged 19-26 years, only one (1.7%) reported having received human papillomavirus (HPV) vaccination (cervical cancer) recommended for this age group, whereas none of the 18 men reported having received HPV vaccination. Four of nine respondents aged 65 years and over (44.4%) reported receipt of pneumococcal vaccination recommended for this age group. None of the 22 respondents aged 60 years had received the shingle vaccine recommended for this age group.

Of the healthcare workers involved in the study, 39 (88.6%) had received at least one adult vaccination; 30 (68.1%) had received vaccination for tetanus, 26 (59.1%) for hepatitis B, 24 (54.5%) for influenza, 6 (13.6%) for hepatitis A, and 2 (4.5%) for HPV.

Of the respondents with chronic diseases, 63 (75.0%) had received adult vaccinations. Of the 17 participants with diabetes, 10 (58.8%) received vaccination for influenza, 9 (52.9%) for tetanus, and 9 (52.9%) for pneumococcal. Of the 28 subjects with cardiovascular disease, 13 (46.4%) reported receipt of vaccination for seasonal influenza, 12 (42.8%) for tetanus, and 7 (25.0%) for pneumococcal. Of the respondents with chronic lung disease, six reported receipt of flu vaccination, and three reported receipt of pneumococcal vaccination. Finally, two respondents with cancer reported having received flu vaccination.

The uptake of adult vaccination was 88.6% among healthcare workers, 74.4% among other professional groups, and 59.6% among the unemployed/pensioner group (p=0.001). The HLS-TR-Q32 subdomain Treatment and Service-Appraising Health-Related Information score was 29.0 for those who received adult vaccinations and 26.2 for those who did not (p=0.02). The uptake of adult vaccination differs significantly by educational level (p=0.001). Vaccination uptake was higher among university graduates than among primary and high school graduates (77.2% and 59.0%, respectively) (Table 6).

Table 2. Sociodemographic characteristics and chronic disease status

		n	%
Age (range), years (mean ± SD)	38.3±13.6 years (18-83)		
Gender	Male	113	(36.22)
	Female	199	(63.78)
Marital status	Single	107	(34.29)
	Divorced	10	(3.21)
	Married	195	(62.50)
Education level	Illiterate	3	(.96)
	Literate	7	(2.24)
	Primary school	40	(12.82)
	High school	60	(19.23)
	University	202	(64.74)
Is a healthcare worker?	No	268	(85.90)
	Yes	44	(14.10)
Occupation	Civil servant	76	(28.36)
	Worker	29	(10.82)
	Retired/unemployed	22	(8.21)
	Self-employed/trader	59	(22.01)
	Housewife	38	(14.18)
	Student	44	(16.42)
Income level	Income exceeds expenses	56	(17.95)
	Income equals expenses	171	(54.81)
	Income is less than expenses	85	(27.24)
Chronic illness	Yes	84	(26.92)
	No	228	(73.08)

SD: standard deviation

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Compared with being unemployed and pensioner, being a healthcare worker increases the uptake of adult vaccinations by 3.6 times. Each one-unit increase in the score from the HLS-TR-Q32 subdomain Treatment and Service-Appraising Health-Related Information increases adult vaccination by 1.03 times (Table 7).

When inquired about the reasons for vaccination, 130 (58.0%) of the respondents reported having received vaccination for "protection against diseases," 87 (38.8%) upon "recommendation by physician," 43 (19.2%) for "exposure to sharps injuries," 33 (14.7%) due to "pregnancy," 17 (7.6%) due to "living in crowded environments," 16 (7.1%) because of "animal bites," 15 (6.7%) upon "recommendation by other health personnel and pharmacists," 12 (5.3%) for "traveling abroad," and 11 (4.9%) due to "having a chronic disease".

When asked about the reasons for not having received any adult vaccination, 37 (42.1%) of the participants replied "it was not recommended by the physician," 32 (36.3%) stated "I believe my knowledge of vaccines is inadequate," 9 (10.2%) cited "fear of side effects," 7 (7.9%) said "I believe vaccines are not protective," and 4 (4.5%) mentioned "fear of injection." Approximately 13 (14.7%) participants stated other reasons for not getting vaccinated, the most common answer being "I have found it unnecessary."

DISCUSSION

This study found that knowledge of AI and vaccination uptake were positively correlated with HL. Other salient findings were low levels of AI and "inadequate" or "limited" levels of HL in more than half of the participants. "Being a healthcare worker", "having a chronic disease," "age" and "HL level" emerged as factors influencing vaccination knowledge, whereas "being a healthcare worker" and "HL level" influenced vaccination uptake.

A large proportion (73.1%) of the individuals who participated in this study reported knowing about AI. This rate is similar to the rate reported by Uzuner et al. (8) (64.8%) and higher than 47.2% reported by Uragan et al. (9) and 43.5% reported by Baran Aksakal et al. (10).

In our study, the best-known vaccines were influenza (66.6%) and tetanus vaccines (51.6%), while the least-known vaccines were yellow fever (10.9%) and shingles vaccines (14.4%). Some studies

Table 3. Participants' mean scores on HLS-TR-Q32

	Mean ± ss	Median (IQR)
Total scores on HLS-TR-Q32	31.45±7.17	30.21 (7.81)
"Treatment and service" total score	32.27±7.51	31.25 (8.33)
Access to health-related information	33.57±9.44	33.33 (8.33)
Understanding health-related information	33.58±8.45	33.33 (8.33)
Appraising health-related information	28.24±9.13	29.17 (12.5)
Using/applying health-related information	33.69±9.12	33.33 (12.5)
"Disease prevention/ Health promotion" total score	30.66±7.66	30.21 (7.63)
Access to health-related information	32.94±8.56	33.33 (8.33)
Understanding health-related information	32.32±8.67	33.33 (5.55)
Appraising health-related information	29.28±9.05	29.17 (8.33)
Using/applying health-related information	28.08±9.36	29.17 (12.5)

HLS-TR-Q32: 32-item Turkish Health Literacy Survey Questionnaire, IQR: interquartile range, ss: sum of squares

Table 4. Univariate analysis results in knowledge of adult immunization

		Do you know about adult immunization?				p-value
		No		Yes		
		n	%	n	%	
Healthcare worker	No	82	(30.60)	186	(69.40)	**<0.001***
	Yes	2	(4.55)	42	(95.45)	
Chronic illness	No	73	(86.90)	155	(67.98)	**0.001****
	Yes	11	(13.10)	73	(32.02)	
		Mean ± ss	**Median (IQR)**	**Mean ± ss**	**Median (IQR)**	
Age		32.61±12.13	28 (19)	40.44±13.55	40 (22)	**<0.001¹**
Treatment and Service-Appraising Health-Related Information		26.11±9.04	25 (12.5)	29.03±9.05	29.17(12.5)	**0.010¹**

**Chi-square test, *Fisher's Exact test, ¹Mann Whitney-U test, IQR: interquartile range ss: sum of squares

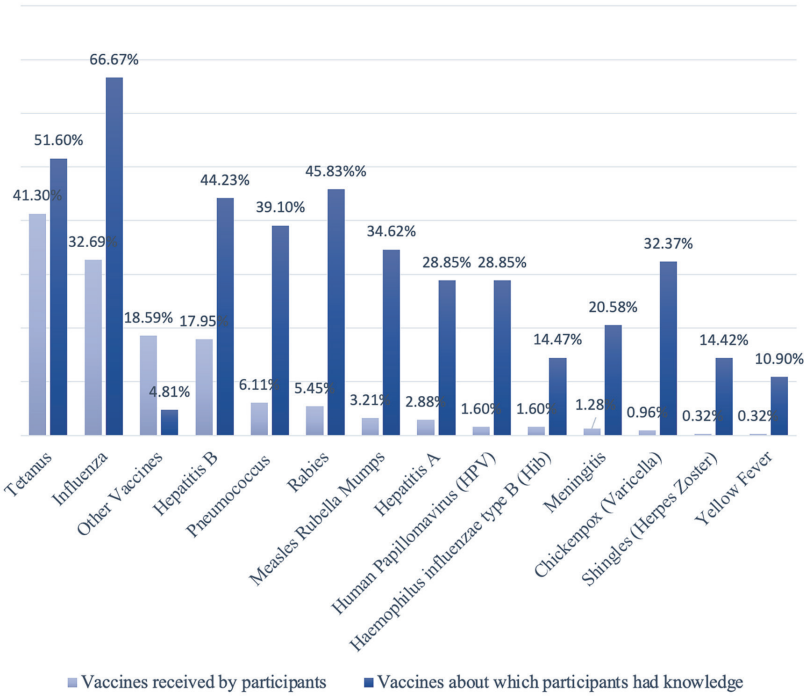

Figure 1. The rates of adult vaccines received during adulthood and vaccines about which participants had knowledge (%)

Table 5. Analysis of factors influencing knowledge of adult immunization

		B	SE	p	Exp(B)	95% CI for Exp(B)	
						Lower	Upper
Step 1[a]	Healthcare worker (yes)	2.357	0.746	**0.002**	10.561	2.447	45.571
	Chronic illness (yes)	0.824	0.386	**0.033**	2.279	1.070	4.852
	Age	0.047	0.012	**0.000**	1.048	1.024	1.074
	Treatment and Service-Appraising Health-Related Information	0.040	0.016	**0.014**	1.040	1.008	1.074

Binary logistic regression, omnibus test p<0.001, Nagelkerke r square =23.3%, Hosmer and Lemeshow test chi-square: 2.838 p=0.944. Step 1a regression analysis refers to a first step in which all independent variables are included in the model at the same time. B: coefficients of the independent variables, SE: standard error, Exp: exponentiation, CI: confidence interval

Table 6. Univariate analysis results for adult vaccination uptake

		Have you had an adult vaccination?				
		No		Yes		p-value
		n	%	n	%	
Education level	Primary school+ high school	41	(47.13)	59	(27.44)	**0.001****
	University	46	(52.87)	156	(72.56)	
Employment status	Retired/unemployed	42	(47.19)	62	(27.80)	**0.001****
	Healthcare worker	5	(5.62)	39	(17.49)	
	Other	42	(47.19)	122	(54.71)	
		Mean ± ss	**Median (IQR)**	**Mean ± ss**	**Median (IQR)**	
Treatment and Service-Appraising Health-Related Information		26.29±8.83	25.00(12.5)	29.02±9.15	29.17(12.5)	**0.020[1]**

**Chi-square test, [1]Mann Whitney-U test, IQR: interquartile range, ss: sum of squares

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have reported that the best-known vaccines are influenza, tetanus, and hepatitis B vaccines (8,11).

According to the results of this study, the most common sources of information about AI were television or the Internet (45.4%) and physicians (35.1%). Previous studies have identified "media, family health centers, doctors, friends, and neighbors" as sources of information (8,10,12).

The factor that most influenced knowledge about AI was "being a healthcare worker." This result was expected given the training received by healthcare workers and their being at risk of contracting diseases. The second factor that most influenced knowledge about AI was "having a chronic disease." This may be attributed to this group of individuals being a risk group, recommendations given to them by physicians, and frequent media reports urging individuals with chronic diseases to receive adult vaccinations. Another factor that influenced knowledge about AI was found to be "age;" increasing age led to greater knowledge of AI. More regular doctor visits by older people and the opportunity to receive information on AI from doctors during these visits may lead them to prioritize vaccinations (13).

The HLS-TR-Q32 subdomain Treatment and Service-Appraising Health-Related Information' was also found to influence knowledge about AI. This result agrees with some previous studies that found HL to be positively correlated with the level of knowledge and awareness of AI (14,15).

Of the individuals who participated in the study, 71.4% reported having received at least one vaccination during adulthood, whereas 28.5% reported having received none. Previous studies have reported different rates of adult vaccination uptake (60.5%, 57.9%, and 47.4%) (8,9,16). The vaccine most commonly received by the individuals who participated in our study was the tetanus vaccine (41.03%). This result is supported by many previous studies that have reported the tetanus vaccine as the most commonly received vaccination (9,10,16). This is probably because the tetanus vaccine is administered on numerous occasions, such as before employment, in military service, in case of pregnancy, and in the emergency department when indicated in case of injuries.

The current study found that "being a healthcare worker" was the factor that most influenced the knowledge and uptake of adult vaccination. The second most influential factor was the score from the HLS-TR-Q32 subdomain, Treatment and Service-Appraising Health-Related Information. A meta-analysis identified studies that reported a positive and negative correlation between HL and vaccination behavior and studies that found no correlation. Inconsistent results on the correlation between HL and vaccination behavior may be due to the different methods used to assess HL (17). Limited HL has been associated with reduced immunization and lower cancer screening rates, greater use of the emergency room, and higher rates of medication errors (18).

This study also found that adult vaccination uptake among the participants differed significantly by educational level. The vaccination rate was 77.2% among university graduates and 59.0% among primary and high school graduates (p=0.001). This result agrees with previous studies that found that vaccination rates increase significantly with higher educational levels (9,10,16).

The presence of chronic diseases was found to influence knowledge about AI but not its uptake. Previous studies have reported that vaccination uptake is higher among individuals with chronic diseases than among those without chronic diseases (9,16), whereas others have found no association (8,19).

When asked, "If you have ever been vaccinated during adulthood, what was the reason for getting vaccinated?" the participants replied "protection against diseases, doctor's recommendation, sharps injury, and pregnancy" in order of frequency. These answers were found to be consistent with those of previous studies (10,12). On the other hand, when asked, "If you have never been vaccinated during adulthood, what was the reason for not getting vaccinated?" the participants replied "My doctor has not recommended vaccination" and "lack of information," in line with the literature (20,21).

The level of HL in the present study was found to be limited for 47.4% of the respondents, sufficient for 25.8%, inadequate for 16.1%, and excellent for 10.6% of the participants. Tanröver et al. (22) found 40.1% of the population to have problematic and 24.5% to have inadequate HL levels. In contrast, only one-third of the population was categorized as having adequate or excellent

Table 7. Analysis of factors affecting adult vaccination uptake

		B	SE	Sig.	Exp(B)	95% CI for Exp(B)	
						Lower	Upper
Step 1[a]	Education level	0.549	0.308	0.074	1.731	0.947	3.162
	Employment status (retired/unemployed)			**0.048**			
	Employment status (healthcare worker)	1.304	0.551	**0.018**	3.683	1.250	10.855
	Employment status (other)	0.493	0.315	0.117	1.638	0.884	3.035
	Treatment and Service-Appraising Health-Related Information	0.033	0.016	**0.037**	1.033	1.002	1.066

Binary logistic regression, Omnibus test p<0.001, Nagelkerke r square =10.6%, Hosmer and Lemeshow test chi-square: 11.007 p=0.201. Step 1a regression analysis refers to a first step in which all independent variables are included in the model at the same time. B: coefficients of the independent variables, SE: standard error, Sig.: significance, Exp: exponentiation, CI: confidence interval

HL. According to HL data from the USA, 53% of more than 19,000 adults had intermediate levels of HL, 22% had basic HL, 14% had below-basic HL, and 12% had adequate HL (23). Sørensen et al. (24), on the other hand, found that more than 10% of the population had inadequate HL, and between 29% and 62% had limited HL. These rates show that much remains to be done about HL, which is a modifiable factor.

The uptake of the influenza vaccine in any influenza season was found to be 32.6% among the adult population in our study. Other studies have reported 24.0% and 29.6% influenza vaccination rates (8,11). The influenza vaccine coverage rate was reported to be 41.8% according to a 2019 study from Canada and 46.1% among adults according to 2018 data from the United States of America (USA). The World Health Organization's (WHO) "Healthy People 2020" initiative set a target influenza vaccination goal of 70% (25-27).

The pneumococcal vaccine uptake in this study was found to be 6.1% for the adult population and 44.4% among participants aged 65 years. Other studies from Türkiye have found coverage rates of 4.7% and 3.4% for the pneumococcal vaccine (8,11). According to a study from Canada, pneumococcal vaccine uptake was 25.4% among individuals aged 19-64 years and 58.1% among individuals aged 65 years. On the other hand, 2018 data from the USA showed that 23.3% of people aged 19-64 years and 69% of people aged 65 years and over had received at least one dose of pneumococcal vaccine. The WHO set its "Healthy People 2020" target for pneumococcal vaccination at 60% for people aged 19-64 years and 90% for people in the age group 65 and over (25-27). The coverage rates found in our study for both vaccines were well below the target rates, which is in line with other studies from Türkiye.

The WHO's "Healthy People 2020" target for the shingles vaccine was 30% for the group over 60 years of age. However, our study found that shingles vaccination was received by none of the participants over 60 years of age. This result is in line with other studies from Türkiye, which have found the shingles vaccination uptake to be very low (0.9%, 3.2%) (8,9). Coverage rates in the USA and Canada have approached the target, whereas the rates found in our study remain well below the target (25-28). Such low vaccination rates may be attributed to the shingles vaccine not being reimbursable in Türkiye and the lack of information about it.

The rate of tetanus vaccination uptake at any time was found to be 41% among the adult population in this study. Only 13.7% of the participants reported receiving a regular tetanus vaccination every 10 years. Other studies from Türkiye have reported similar results, while a study from Canada reported a rate of 69%, and 2018 data from the USA reported a rate of 62.9% (8,11,25,26).

In our study, the uptake of HPV vaccination among women aged 19-26 years was 1.7%, whereas men had never received this vaccine, a result in line with other studies from Türkiye. According to 2018 data from the USA, 52.8% of women aged 19-26 years and 34.4% of men aged 19-21 years have received HPV vaccination (8,9,26). The high vaccination rate in the USA may be attributed to the HPV vaccine being reimbursable and its inclusion in the routine vaccination schedule. In contrast, in Türkiye, this vaccine is not reimbursable, is not included in the vaccination schedule, and is not sufficiently known among the population, which may explain why it is rarely administered.

Study Limitations

The fact that the study is a cross-sectional study and was conducted in a training family health center affiliated with our hospital prevents generalization of the results. Other limitations include the lack of a standard measurement tool to determine AI knowledge and attitudes. The fact that the study was conducted under pandemic conditions may have affected the results.

CONCLUSION

At a time when the elderly population is growing, increasing rates of AI could contribute to healthy aging. Therefore, it is essential that family physicians provide recipients of preventive health services with counseling about AI. According to our study, the most prominent reasons for not receiving adult vaccines were physicians not sufficiently advising patients on AI and individuals' lack of knowledge. In contrast, the most common reasons for receiving adult vaccines were "protection against diseases" and "physicians' advice." A more effective use of preventive health services, particularly immunization, requires access to accurate information and improvement of HL. Therefore, HL can be improved through several actions, including cross-sectoral cooperation and effective use of communication tools, as well as communication of accurate messages to service users by healthcare personnel, especially physicians.

It is essential that physicians inquire about individuals' adult vaccination status, no matter for what reason they present, and recommend adult vaccines appropriate for individuals' health status and age. Further information and awareness-raising activities on AI can help increase vaccination uptake in the community. It is also recommended that vaccination units be established in hospitals and family health centers where people with chronic diseases can receive vaccines.

Ethics Committee Approval: Approval was obtained from the Clinical Researches Ethics Committee of University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital (decision no: HNEAH-KAEK 2022/96, date: 18.04.2022). The study was conducted in accordance with the Good Clinical Practice and the Declaration of Helsinki ethical standards.

Informed Consent: Written informed consent was obtained from all participants.

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The Effects of *Prunus Laurocerasus* Fruit Extract on Oxidative and Endoplasmic Reticulum Stress Responses in Doxorubicin-induced Cardiac Damage

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ABSTRACT

Objective: In this study, the effects of *Prunus laurocerasus* fruit extract (PLE), which is known for its high levels of phenolic compounds and antioxidant efficiency, on doxorubicin (DXR)-induced cardiotoxicity were examined.

Methods: Male Sprague-Dawley rats were randomly assigned to the Control, DXR, PLE_{500}+DXR, and PLE_{1000}+DXR groups (n=6). PLE was orally administered to the animals in the PLE_{500}+DXR (500 mg/kg) and PLE_{1000}+DXR (1000 mg/kg) groups for 2 weeks. DXR was injected (15 mg/kg, intraperitoneally) 2 days before sacrification in the DXR, PLE_{500}+DXR, and PLE_{1000}+DXR groups. At the end of the study period, serum troponin I levels, myocardial superoxide dismutase (SOD) and catalase (CAT) activities, malondialdehyde (MDA), glutathione (GSH), glucose-regulated protein (GRP)78, and pro-caspase 12 levels were measured.

Results: In the DXR group, serum troponin I concentration significantly increased ($p<0.001$), however PLE treatment significantly reduced this DXR-induced increment ($p<0.001$ and $p<0.05$ in the PLE_{500}+DXR and PLE_{1000}+DXR groups, respectively). DXR-induced increase in myocardial MDA ($p<0.001$) significantly reduced in the PLE_{500}+DXR ($p<0.001$) and PLE_{1000}+DXR ($p<0.001$) groups. However, DXR-induced changes, such as GSH depletion ($p<0.001$), reduced CAT ($p<0.001$) and SOD ($p<0.001$) activities, increased GRP78 ($p<0.01$) and decreased pro-caspase 12 ($p<0.001$) levels, were not significantly affected by PLE treatment.

Conclusion: The present results indicate that pretreatment with PLE reduced, but not completely prevented, cardiac damage induced by DXR. While a reduction in oxidative stress appears to play a role in the partial protective effect of PLE treatment, endoplasmic reticulum stress appears to have no role. Further research is necessary to understand the mechanisms of action underlying PLE treatment.

Keywords: MDA, GSH, CAT, SOD, GRP78, pro-caspase 12, troponin

INTRODUCTION

Doxorubicin (DXR) belongs to the anthracycline group of chemotherapy drugs and is widely used for treating various cancer types, including sarcoma, lymphoma, and breast cancer. Nonetheless, its substantial efficacy is frequently overshadowed by cardiotoxic side effects, which often constrain the clinical application of DXR (1-3). Different molecular mechanisms have been suggested to underlie the development of DXR-induced cardiotoxicity, including topoisomerase II inhibition, oxidative stress, mitochondrial dysfunction, disturbances in calcium balance, and cell death (4). Among these, oxidative stress is a notable mechanism of DXR-induced cardiotoxicity. DXR increases the generation of reactive oxygen species (ROS) and weakens enzymatic and non-enzymatic antioxidant defense systems (5). Contemporary studies have demonstrated the involvement of endoplasmic reticulum (ER) stress in DXR-induced cardiotoxicity (6). ER stress is a condition arising from disruptions in ER functions due to various stressors, including adenosine triphosphate deficiency, oxidative stress, drugs, or toxins, and if it persists for a prolonged period, it can lead to cell death (7). In DXR-induced cardiotoxicity, the upregulation of ER stress proteins, including glucose-regulated protein (GRP)78, as well as caspase-12 activation have been reported previously (8,9).

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To reduce the cardiotoxic effects of DXR, various strategies have been discussed, including combination therapies with different bioactive compounds (10). Phenolic compounds, including rutin, caffeic acid, chlorogenic acid, vanillic acid, quercetin, naringenin, and resvarotrol, have been reported to exhibit protective effects by mitigating damage mechanisms, including oxidative stress, ER stress, or apoptosis, in DXR-induced cardiotoxicity (10-16). *Prunus laurocerasus* (*P. laurocerasus*) (synonym *Laurocerasus officinalis*), a perennial plant rich in bioactive compounds, is primarily found on the Black Sea coast of Türkiye and throughout southeastern Europe and southwestern Asia (17,18). In experimental studies using *P. laurocerasus* fruit, leaf, or seed, the protective effects of extracts have been reported in conditions such as kidney and liver damage induced by paracetamol, gastric damage stimulated by indomethacin, and diabetes (17,19-23). In most cases, treatment with the extract resulted in a reduction of oxidative stress, leading to alleviation of tissue damage. Although it has the potential to be protective against DXR-induced cardiotoxicity because of its bioactive components, the possible protective effect of *P. laurocerasus* against the systemic side effects of DXR has not been investigated until now. The objective of this research was to evaluate the impact of *P. laurocerasus* fruit extract (PLE) on DXR-induced cardiotoxicity through two important mechanisms in its pathophysiology: oxidative stress and ER stress responses.

METHODS

Extraction of *P. laurocerasus* Fruits

Freshly collected *P. laurocerasus* fruits were first dried and then ground into a powder. The ground fruits were mixed with 80% ethanol (1:5), and the mixture was agitated for 2 days at room temperature in a shaking water bath. The mixture was filtered through the filter paper at the end of the second day, and the fruit extract was obtained by evaporating the solvent using an evaporator at 50 °C. The concentrated extracts were diluted with tap water and administered to the treatment groups as described below.

Animals and Their Grouping

In this study, 24 male Sprague-Dawley rats weighing between 280 and 320 g were used. The Ordu University Animal Experiments Local Ethics Committee approved all the experimental procedures (decision no: 12, date: 22.10.2020). The 24 rats were randomly separated into 4 groups, namely Control, DXR, PLE_{500}+DXR, and PLE_{1000}+DXR, with 6 rats in each group.

Control group (n=6): For 2 weeks, the animals received drinking water via intragastric gavage (ig).

DXR group (n=6): The rats were administered drinking water (ig) for 2 weeks, and DXR (15 mg/kg, single dose) was injected intraperitoneally (IP) 2 days before the end of the experimental period (24).

PLE_{500}+DXR group (n=6): The animals received a daily administration of PLE (500 mg/kg, ig) for 2 weeks, and DXR (15 mg/kg, IP) was administered on the 13th day of the experimental period.

PLE_{1000}+DXR group (n=6): For a duration of 2 weeks, the rats orally received a daily administration of PLE (1000 mg/kg, ig), and DXR (15 mg/kg, IP) was injected on the 13th day of the study.

On the 15th day of the study, the rats were anesthetized with ketamine and xylazine (80 mg/kg: 10 mg/kg, IP). Blood samples were collected from the abdominal aorta and allowed to coagulate at ambient temperature. Subsequently, serum samples were obtained by centrifugation at 1000 g for 20 min. Heart tissue and serum samples were kept in a 80 °C deep freezer until these parameters were analyzed:

Serum troponin I: The level of cardiac troponin I in the serum samples was measured using a commercial enzyme-linked immunosorbent assay kit (Elabscience, E-EL-R1253, China). The analysis was performed in accordance with the guidelines provided by the manufacturer, and the outcomes were evaluated by comparing the optical density of the samples against the standard curve.

Malondialdehyde (MDA): Myocardial MDA levels were determined using Buege and Aust's (25) thiobarbituric acid reactive substance formation method. The pink color formed by the reaction of MDA with thiobarbituric acid was detected at 535 nm using a spectrophotometer (25).

Glutathione (GSH): GSH levels in cardiac homogenates were measured by the method of Aykaç et al. (26). The yellow color formed by the interaction of GSH and 5,5-dithio-bis (2-nitrobenzoic acid) was detected using a spectrophotometer at 412 nm.

Catalase (CAT) activity: CAT activity in cardiac tissue was assessed by measuring absorbance at 240 nm, reflecting the rate of hydrogen peroxide (H_2O_2) decomposition catalyzed by CAT per unit of time (27).

Superoxide dismutase (SOD) activity: SOD activity in cardiac tissue was measured by determining the red color created by superoxide radicals, which are formed using xanthine and xanthine oxidase by reducing nitroblue tetrazolium at 505 nm (28).

GRP78: GRP78 levels were measured using commercial ELISA kits (Bioassay Technology Laboratory BT-E1255Ra, China) in cardiac tissue homogenates. The assay protocol was performed in accordance with the manufacturer's guidelines. The results were computed using a standard curve and conveyed as ng/mg of protein.

Pro-caspase 12: Myocardial pro-caspase 12 concentrations were assayed using a commercial ELISA kit (Bioassay Technology Laboratory BT-E2111Ra, China) according to the manufacturer's instructions. The pro-caspase 12 concentration in tissue homogenates was determined by contrasting the optical density of the samples with the standard curve, and the findings were expressed in relation to the total protein content.

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Statistical Analysis

The findings are presented as mean ± standard deviation. Normality and homogeneity of the data were assessed using the Kolmogorov-Smirnov and Levene's tests, respectively. Normally distributed and homogeneous data were then tested by One-Way analysis of variance, followed by the Tukey test as a post hoc analysis. Significance was assigned to values with $p<0.05$

RESULTS

Serum troponin I: The serum troponin I level was 806.75±52.72 pg/mL in the control group. This value was significantly higher in the DXR (1813.68±142.36 pg/mL, $p<0.001$), PLE_{500}+DXR (1554.34±174.63 pg/mL, $p<0.001$) and PLE_{1000}+DXR (1514.03±141.74 pg/mL, $p<0.001$) groups. Compared with the DXR group, PLE_{500}+DXR ($p<0.05$) and PLE_{1000}+DXR ($p<0.01$) groups had higher levels of troponin I. No statistical difference was observed between the two extract treatment groups (Figure 1).

Oxidative Stress Parameters

In the control group, the MDA level was measured as 188.28±45.85 nmol/g wet tissue (wt). Increased concentrations of MDA were observed in the DXR (527.67±64.68 nmol/g wt, $p<0.001$), PLE_{500}+DXR (343.245±47.99 nmol/g wt, $p<0.001$) and PLE_{1000}+DXR (368.71±72.26 nmol/g wt, $p<0.001$) groups. In the PLE_{500}+DXR and PLE_{1000}+DXR groups, MDA levels were significantly lower than those in the DXR group ($p<0.001$ and $p<0.001$, respectively) (Figure 2A).

GSH levels were significantly lower in the DXR (1.13±0.26 µmol/g wt, $p<0.001$), PLE_{500}+DXR (1.42±0.32 µmol/g wt, $p<0.001$) and PLE_{1000}+DXR (1.25±0.34 µmol/g wt, $p<0.001$) groups than in the control values (3.82±0.59 µmol/g wt). Treatment with two different doses of PLE did not significantly change cardiac GSH levels, and the results were not different from the DXR group or each other (Figure 2B).

Cardiac CAT activity was 3.7±0.36 µmol/H_2O_2/min/mg wt in the control group. The value significantly reduced to 1.412±0.41 µmol/H_2O_2/min/mg wt in the DXR group ($p<0.001$). CAT activities were significantly lower in the PLE_{500}+DXR (1.79±0.38 µmol/H_2O_2/min/mg wt) and PLE_{1000}+DXR (1.62±0.47 µmol/H_2O_2/min/mg wt) groups compared with the control ($p<0.001$ and $p<0.001$, respectively), and the values were not significantly different from the DXR group or each other (Figure 2C).

SOD activity was measured as 4.24±0.53 U/mg wt in the control group and was significantly reduced in the DXR (1.37±0.50 U/mg wt, $p<0.001$), PLE_{500}+DXR (1.64±0.57 U/mg wt, $p<0.001$) and PLE_{1000}+DXR (1.82±0.539 /mg wt, $p<0.001$) groups. Compared with the DXR group, no significant alterations were noted in the PLE_{500}+DXR and PLE_{1000}+DXR groups (Figure 2D).

ER Stress Parameters

The GRP78 level was 0.59±0.07 ng/mg prot in the control group and significantly increased to 0.79±0.08 ng/mg prot in the DXR group ($p<0.01$). Although the GRP78 levels were lower in the PLE_{500}+DXR (0.68±0.13 ng/mg prot) and PLE_{1000}+DXR (0.64±0.11 ng/mg prot) groups, the results were not significantly different from the control or DXR groups (Figure 3A).

The pro-caspase 12 level in the DXR-injected group (10.14±1.57 ng/mg prot) was found to be significantly lower ($p<0.01$), than that in the control group (16.32±3.43 ng/mg prot). In the PLE_{500}+DXR and PLE_{1000}+DXR groups, pro-caspase 12 levels did not significantly change (12.91±1.82 and 13.19±2.93 ng/mg prot, respectively) (Figure 3B).

DISCUSSION

Cancer remains a major global health challenge, with a growing number of individuals being diagnosed due to rising life expectancy and population growth. Therefore, research is ongoing to reduce the cardiotoxic side effects of DXR, a widely used anticancer drug. This study investigated the effectiveness of PLE in reducing the cardiotoxic side effects of DXR.

Myocardial damage induced by DXR can be monitored using various circulating biomarkers, including cardiac troponins. The cardiac-specific troponin proteins (troponin I, troponin T) are located in the myocardium, enabling their use as specific biomarkers to identify alterations in cardiac muscle. Because troponin I is accepted as a sensitive and specific indicator of DXR-induced myocardial injury, its serum concentrations were evaluated in the present study (29,30). Increased troponin I levels in the DXR group were considered an indicator of cardiac damage. Oxidative stress is a conspicuous mechanism in the pathophysiology of DXR-induced cardiotoxicity (5,31). Elevated ROS levels lead to modifications in the functional and structural components of the cell, resulting in myocardial damage and functional loss. Previous studies have reported that a decrease in cardiac antioxidant enzymes such as CAT, SOD, and GSH peroxidase and a reduction in the level of the non-enzymatic antioxidant molecule GSH are important factors in the development of oxidative damage of the myocardium during DXR treatment (5,31,32). In the current study,

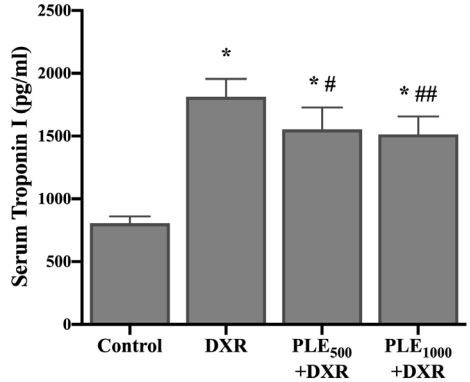

Figure 1. Circulating troponin I concentrations in the control, DXR, PLE_{500}+DXR and PLE_{1000}+DXR groups (n=6). The results were presented as the mean ± standard deviation. Comparing to the control group *$p<0.001$, comparing to the DXR group #$p<0.05$, ##$p<0.01$.
PLE: Prunus laurocerasus fruit extract, DXR: doxorubicin

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the increase in lipid peroxidation, along with GSH depletion and decreased SOD and CAT activities, suggested the presence of DXR-induced cardiac oxidative stress.

The *P. laurocerasus* fruit used in this study is rich in phenolic compounds such as chlorogenic, caffeic, gallic, vanillic, benzoic, and coumaric acids, rutin, and quercetin. This high phenolic content largely contributes to the pharmaceutical significance of the plant (33,34). In studies using different experimental damage models, it has been shown that pretreatment with *P. laurocerasus* extracts successfully reduces injury-related oxidative stress in stomach, kidney, and liver tissues (17-22). Not only fruit extract but also seed and leaf extracts of *P. laurocerasus* have been used in previous studies. For example, Uslu and Uslu (23) demonstrated a significant improvement in oxidative stress parameters (MDA, GSH peroxidase, GSH) in diabetic rats treated with leaf, fruit, or seed extracts of *P. laurocerasus* (21 days, 500 mg/kg) and reported that the effectiveness of these different extracts was at the similar level. To date, it has not been shown whether *P. laurocerasus* extracts affect cardiac oxidative stress in any injury model. Our study is the first to demonstrate that treatment with fruit extracts of *P. laurocerasus* can reduce oxidative stress in cardiac tissue. According to the present results, lipid peroxidation induced by DXR significantly decreased in the extract treatment groups; however, it did not return to control values. Similar changes observed in serum troponin levels indicate that the treatment could

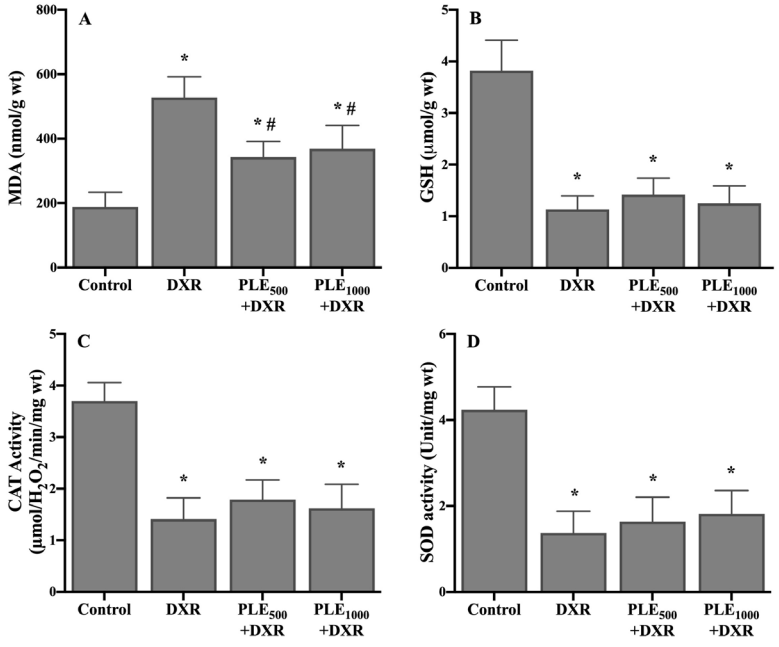

Figure 2. Oxidative stress parameters measured in myocardial tissue of the control, DXR, PLE_{500}+DXR and PLE_{1000}+DXR groups (n=6). Myocardial MDA levels (A), GSH levels (B), CAT activity (C) and SOD activity (D). The results were presented as the mean ± standard deviation. Comparing to the control group *p<0.001, comparing to the DXR group #p<0.001.
PLE: Prunus laurocerasus fruit extract, DXR: doxorubicin, CAT: catalase, GSH: glutathione, MDA: malondialdehyde, SOD: superoxide dismutase

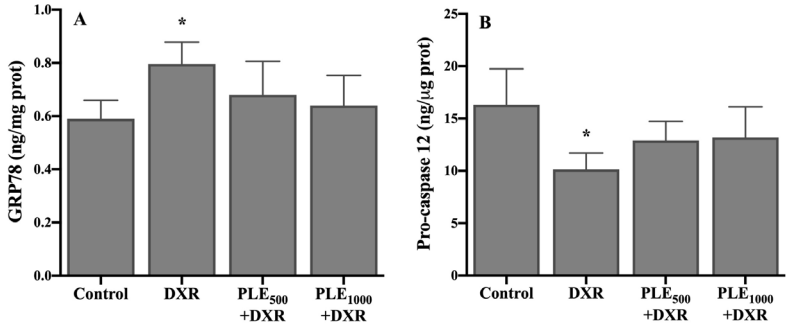

Figure 3. ER stress parameters measured in myocardial tissue of the control, DXR, PLE_{500}+DXR and PLE_{1000}+DXR groups (n=6). Myocardial GRP78 levels (A), pro-caspase 12 levels (B). Comparing to the control group *p<0.01.
PLE: Prunus laurocerasus fruit extract, DXR: doxorubicin, GRP78: glucose-regulated protein78

not completely prevent oxidative damage of the myocardium but was successful in reducing it. Decreased lipid peroxidation after *P. laurocerasus* treatment appeared to be related to the free radical scavenging properties of the extract because there was no improvement in endogenous GSH levels or antioxidant enzyme activities (CAT, SOD). This finding contradicts previous studies demonstrating elevated GSH levels and increased SOD and CAT activities in renal, gastric, and hepatic tissues following *P. laurocerasus* treatment (17-22), indicating that the efficacy of *P. laurocerasus* might vary depending on the tissue, as increasing the dose of the extract did not alter its efficiency for the heart.

The ER plays a crucial role in eukaryotic cells, being responsible for tasks such as the synthesis, folding, and secretion of proteins and maintaining calcium homeostasis. ER stress is a cellular response aimed at restoring ER functions and generally involves a slowing down of protein synthesis, accelerated proteasomal degradation of unfolded or misfolded proteins, and increased synthesis of ER chaperone proteins involved in the protein folding process, such as GRP78 (7). In the current study, the increased GRP78 level in the DXR group indicated the presence of cardiac ER stress, which is consistent with previous studies demonstrating the role of ER stress in DXR-induced cardiotoxicity (8,9,35). Although restoration of cellular homeostasis is aimed, severe or prolonged ER stress triggers cell death through apoptotic signaling pathways, namely caspase-12, c-JUN NH2-terminal kinase, and C/EBP homologous protein pathways. In the present study, a significant decrease in pro-caspase 12 levels was interpreted as an increase in caspase 12 activation, a result that is consistent with previous literature findings indicating the role of ER stress-mediated apoptosis in DXR-induced cardiotoxicity (8,9,35). While the effect of PLE on oxidative stress has been previously studied for different tissues, excluding the heart, its effect on ER stress in the heart was examined for the first time in this study. Our results showed a trend for GRP78 and pro-caspase 12 levels to return to the control levels, but these changes caused by extract pretreatment were not statistically significant in the DXR group. Although individual bioactive components within *P. laurocerasus* have been reported to reduce DXR-induced ER stress (10-16), it appears that their levels within the extract may not be sufficient to produce the same response even at higher doses. Because oxidative stress is one of the ER stress triggering factors, reduced oxidative stress would be expected to be accompanied by decreased ER stress in the extract-treated groups. However, it should be noted that oxidative stress was not completely prevented in the extract groups. Ongoing oxidative stress may play a significant role in the persistence of both ER stress and cardiac damage.

Study Limitations

One of the most significant shortcomings of this study is that cardiac damage was assessed only through serum troponin I measurement without histopathological evaluation. Demonstrating the histological evidence of both DOX-induced damage and partial recovery after treatment could have supported the current findings.

CONCLUSION

In this study, the effects of PLE on DOX-induced cardiotoxicity were investigated for the first time. Although histopathological evaluation was not conducted, which is a limitation of the current study, the results indicated that pretreatment with PLE partially prevented myocardial damage in DXR-induced cardiotoxicity. We suggested that PLE treatment decreased cardiac lipid peroxidation, possibly due to its endogenous radical scavenging property, without causing any changes in the tissue levels of enzymatic (SOD and CAT) or non-enzymatic antioxidants (GSH). While a reduction in oxidative stress appears to play a role in the partial protection of PLE treatment, it seems that the ER stress response plays no role. The incomplete prevention of DXR-induced cardiac damage does not appear to be related to dose insufficiency; however, future studies with longer treatment durations can be planned.

Ethics Committee Approval: The Ordu University Animal Experiments Local Ethics Committee approved all the experimental procedures (decision no: 12, date: 22.10.2020).

Informed Consent: Animal experiment study.

Author Contributions: Surgical and Medical Practices - S.C., E.K., G.H.; Concept - S.C.; Design - S.C.; Data Collection and/or Processing - S.C., E.K., G.H., E.G.G.P.; Analysis and/or Interpretation - S.C., E.K., G.H., E.G.G.P.; Literature Search - S.C., E.K.; Writing - S.C.

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

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Utility of Relative ADC in Discriminating the Benign and Malign Liver Masses: Diagnostic Potential in Comparison to ADC

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ABSTRACT

Objective: The aim of this study was to compare the utility of apparent diffusion coefficient (ADC) and relative ADC (rADC) values in differentiating benign and malignant liver masses and retrospectively evaluate the diagnostic contribution of rADC values.

Methods: We evaluated 92 focal liver lesions in 56 patients (27 females and 29 males) who were histopathologically diagnosed or did not increase in size on follow-up imaging. Diffusion-weighted images were acquired at two different b values (b=0 and b=800 s/mm^2) and mean ADC values and rADC values obtained from ADC maps with renal cortex as the reference organ were measured. Receiver operating characteristic curve analysis was performed to determine the ADC and rADC cut-off values. Diagnostic values and confidence intervals were obtained. P<0.05 was accepted as the level of statistical significance.

Results: The mean ADC values of benign and malignant lesions were 1.66±0.49x10^{-3} mm^2/s and 1.04±0.24x10^{-3} mm^2/s, respectively. The sensitivity and specificity of ADC at a cut-off value of 1.149x10^{-3} mm^2/s were 88% and 77%, respectively. The mean rADC was 0.88±0.25 for benign lesions and 0.57±0.15 for malignant lesions. The sensitivity and specificity of the rADC at a cut-off value of 0.62 were 95% and 72%, respectively.

Conclusion: rADC was not significantly superior to ADC in the differentiation of benign and malignant lesions. Both ADC and rADC values show high sensitivity and specificity for the differentiation of benign and malignant liver lesions. They are recommended to be used together in cases of suspected malignancy.

Keywords: Apparent diffusion coefficient, hemangioma, hepatic metastasis, hepatocellular carcinoma, magnetic resonance imaging

INTRODUCTION

Accurate detection of malignant liver lesions such as hepatocellular carcinoma (HCC) and metastases is of critical importance in optimal patient management (1,2).

Magnetic resonance imaging (MRI) is often used to characterize liver masses detected by ultrasonography or computed tomography. In the characterization of liver lesions, mass morphology; signal intensity, and enhancement patterns are evaluated on conventional MRI sequences. Diffusion-weighted imaging (DWI) has recently been added to the abdominal MRI protocol (3). DWI is an advanced imaging method that provides important information about the diagnosis of the mass, prognosis, treatment planning, and response to treatment. Its benefits have also been demonstrated in patients with contraindications to gadolinium contrast agents (4). The diffusion imaging technique is based on the evaluation of random movements of water molecules in the environment driven by kinetic energy and is quantitatively evaluated by measuring the ADC value. In most malignant lesions, diffusion is restricted due to increased

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cellularity and disruption of the extracellular space, resulting in low ADC values (5). Different ADC values have been reported for different cancer tissues in previous studies (6,7). These differences in ADC values may be due to patient-related factors, such as age and body temperature, or technical differences, such as variations in the region of interest (ROI) area measurement and the use of different b values during the formation of ADC maps (8-12). The use of relative ADC is recommended to minimize variability and optimize the ADC value. The relative ADC is calculated using the formula $ADC_{mass}/ADC_{reference\ organ}$.

In previous studies, adjacent parenchymal tissue, contralateral tissue, or different organs have been used as reference organs for rADC, and the contribution of rADC to the diagnosis has been reported (13-17). The spleen and renal cortex have been used as reference organs in liver MRI (18-20). As it is associated with the most distinctive anatomical borders in the ADC map and the lowest coefficient of variation, the renal cortex has been considered to be the most suitable reference organ in the abdomen for the calculation of relative ADC (21).

We aimed to evaluate the diagnostic utility of rADC in discriminating the benign and malignant liver masses on DWI by comparing the ADC values with the rADC values obtained by considering the renal cortex as the reference organ.

METHODS

This retrospective single-center study was approved by the University of Health Sciences Türkiye, Taksim Training and Research Hospital Ethics Committee (decision no: 7, date: 13. 05.2015). Informed consent forms were obtained from all.During a 24-month period (January 2013 to February 2015), 80 patients were referred to our center for liver MRIs. Patients with severe motion artifacts (n=9) and renal parenchymal disease (n=3) or those who had received chemotherapy within the last 12 months (n=12) were excluded from the study. The inclusion criteria were as follows: lesions larger than 1 cm; histopathologically proven malignant liver masses; benign masses with typical MRI signal characteristics, no size change on follow-up imaging, or histopathologically proven. Histopathological was examined for 43 lesions (46.7%), while the remaining were followed up throughout the 3-year period at 12-month intervals. Consequently, 92 lesions in 56 patients (27 women and 29 men) were included in the study.

Benign lesions involved simple liver cyst (n=5), hemangioma (n=25), focal nodular hyperplasia (FNH) (n=8), hydatid cyst (n=2), adenoma (n=3) and angiomyolipoma (n=1) while malignant lesions were metastases (colorectal cancer n=19, gastric cancer n=2, pancreatic cancer n=4, breast cancer n=5), HCC (n=14), FHCC (n=1) and cholangiocarcinoma (n=3).

Simple liver cysts and hemangiomas were diagnosed based on typical MRI findings (3). Two cases of hydatid cysts were diagnosed with typical radiological features [cystic echinococcosis (CE3a)] (22). The diagnoses of FNHs were confirmed by biopsy and imaging features on T1-T2W images and contrast enhancement patterns on dynamic MRI (16). One patient with FNH had undergone surgical resection because of the increased lesion size during the follow-up period. Other FNHs remained stable in size at follow-up. The diagnosis of other benign solid liver masses was confirmed either by biopsy or surgery. Adenomas showed heterogeneous signal intensity on T1-T2W images and intense contrast enhancement in dynamic post-contrast sequences. Hepatic angiomyolipoma was observed as signal drop out on out-of-phase imaging due to the presence of fat.

Malignant masses were histopathologically confirmed. In metastatic lesions, the pathological diagnosis of the largest lesion was confirmed. HCCs were enhanced early after intravenous contrast administration and became hypointense on delayed images, except for five lesions. These lesions exhibited an atypical enhancement pattern. Alpha-fetoprotein levels were high in patients diagnosed with HCC. All patients who had HCC, except one, had chronic liver disease. Four patients had single masses and the others had multifocal masses. Follow-ups of patients with known primary malignancies detected 30 metastases that showed pathologic tracer uptake on positron emission tomography/computed tomography. Fibrolamellar hepatocellular carcinoma (FHCC) was a large mass with a central scar and calcifications. Cholangiocarcinomas showed peripheral and delayed contrast enhancement. These masses were located peripherally, and two of them showed capsular retraction.

MRI Protocol

All was examined using 1.5-T systems (Magnetom Avanto, Siemens Healthcare, Germany). DWI was performed using a single-shot echo-planar imaging fat-suppressed sequence in the axial plane during a single end-expiratory breath-hold using the following parameters: TR/TE, 6000-72; slice thickness, 7 mm; interslice gap, 1.4 mm; field of view, 485x379 mm; matrix, 192x120 and bidirectional gradients in x, y, and z directions were acquired using the following b values: 0, 800 s/mm^2. ADC maps were prepared using these images. The routine MR sequences also included coronal T2W turbo spin-echo with fat suppression half-Fourier acquisition single-shot turbo spin-echo, axial fat-suppressed T2W turbo spin-echo with the BLADE technique, gradient-recalled echo T1W in-phase and out-of-phase, and unenhanced and contrast-enhanced 3D T1W gradient-echo [volumetric interpolated breath-hold examination VIBE)]. After contrast agent administration, VIBE T1W sequences were acquired in different phases. As a nonspecific agent, Gd-BT-DO3A (Gadovist, Bayer Schering Pharma, Germany) and as a liver-specific agent, EOB-Gd-BPTA (Primovist, Bayer Schering Pharma, Germany) were employed. The liver-specific agent was used in 38 patients.

Apparent Diffusion Coefficient Analysis

The DWI data were transferred to a workstation (syngo. via; Siemens Healthcare, Erlangen, Germany), and the average ADC values of all lesions were measured using these maps. The ADC is calculated according to the equation ADC =-1/(b2-b1)ln(S2/S1); S1 and S2 are the signal intensities in the regions of interest with

two different b values (b1=0 s/mm^2 and b2=800 s/mm^2). Circular ROIs of at least 20 mm^2 were inserted by one radiologist (N.U.) to measure ADC and rADC values. Normal liver parenchymal tissue and necrotic areas were not included in the T2W and post-gadolinium T1W images in ADC measurements. Three measurements were performed, and the lowest mean ADC value was set. In the calculation of the relative ADC, the ADC value obtained from the right renal cortex was used. The ratio of the ADC value of the liver lesion to the ADC value of the renal cortex was considered as the rADC value.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA) and MedCalc® Statistical Software version 19.6 (MedCalc Software Ltd, Ostend, Belgium) statistical package programs. Descriptive statistics are given as the number of units (n), percentage (%), mean (X), standard deviation, median, minimum, and maximum values.

In addition, Kolmogorov-Smirnov normality test results showed that the data conformed to a normal distribution (p=0.053 for ADC, p=0.200 for rADC). In the comparison of lesion groups, independent sample t-test was used for normally distributed variables and Mann-Whitney U test was used for non-normally distributed variables. Pearson's chi-square test was used to compare lesion groups by gender. The performance of ADC and rADC in predicting lesion groups was evaluated by receiver operating characteristic curve analysis. The optimum cut-off value was determined as the value with the maximization of the sum of the sensitivity and specificity values. P<0.05 was considered statistically significant.

RESULTS

A total of 56 patients, 28 in the benign group and 28 in the malignant group, were included in the study. The median age of the patients in the benign group was 45 years and 50 years in the malignant group. The number of male patients was 14 (50%) in the benign group and 15 (53.6%) in the malignant group. The number of female patients was 14 (50%) in the benign group and 13 (46.4%) in the malignant group. The descriptive characteristics of the patients in the lesion groups had a similar (homogeneous) distribution (p>0.05) (Table 1). A total of 92 lesions were evaluated in patients, 44 in the benign group and 48 in the malignant group. The median number of lesions in the benign and malignant groups was 1. In the benign group, 25 (56.8%) hemangiomas, 8 (18.2%) FNHs, 7 (15.9%) cystic lesions, and 4 (9.1%) other solid benign lesions were observed. In the malignant group, there were 15 (31.3%) HCC, 3 (6.3%) cholangiocarcinomas, and 30 (62.5%) metastatic lesions. While the number of lesions in the groups had a similar (homogeneous) distribution (p>0.05), the types of lesions were different in the two groups (p<0.05) (Table 2).

The mean ADC was 1.66±0.49x10^{-3} mm^2/s for benign lesions and 1.04±0.24 02x10^{-3} mm^2/s for malignant lesions. Mean ADC was statistically higher in the benign group than in the malignant group (p<0.001). The mean rADC was 0.88±0.25 and 0.57±0.15 for the benign and malignant groups, respectively. The mean ADC was statistically higher in the benign group than in the malignant group (p<0.001). The mean ADC of all lesions was 1.34±0.49x10^{-3} mm^2/s and the mean rADC was 0.72±0.25 (Table 3).

The area under the curve (AUC) value for ADC was 0.898 (p<0.001). The optimum cut-off value for the ADC value was obtained as 1.149x10^{-3} mm^2/s. According to this value, the sensitivity was 88.65% and the specificity was 77.08%. The AUC value for rADC was 0.890 (p<0.001). Sensitivity was 95.45% and specificity was 72.92%, using an optimum cut-off value of 0.62 for rADC. When the confidence intervals for AUC are analyzed, the AUC confidence intervals for ADC and rADC intersect. Accordingly, while ADC and rADC values showed similar effects in differentiating benign and malignant groups, they were not significantly superior to each other (Table 4) (Figure 1).

Cystic lesions showed the highest mean ADC and rADC values in the benign lesions group. The mean ADC and rADC values of liver hemangiomas were higher than those of other benign solid lesions (Figure 2,3). Mean ADC and rADC values of FNHs and other solid benign lesions were higher than those of malignant lesions (Figure 4). The mean ADC and rADC values of HCCs were higher than those of other malignant lesions (Figure 5). There were overlaps between the ADC values of solid benign and solid malignant subtype lesions.

Table 1. Comparison of demographic characteristics of patients according to lesion groups

	Group		All patients	Test (p)
	Benign	Malign		
	n=28	n=28	n=56	
Age, (year)				z=-1.617 p=0.106
M (IQR)	45 (13)	50 (11)	49 (13)	
Gender, n (%)				χ^2=0.072 p=0.789
Male	14 (50%)	15 (53.6%)	29 (51.8%)	
Female	14 (50%)	13 (46.4%)	27 (48.2%)	

Mann-Whitney U test (z); chi-square test (Pearson chi-square) (χ^2); M: median, IQR: interquartile range, n: number of patients, %: percentage

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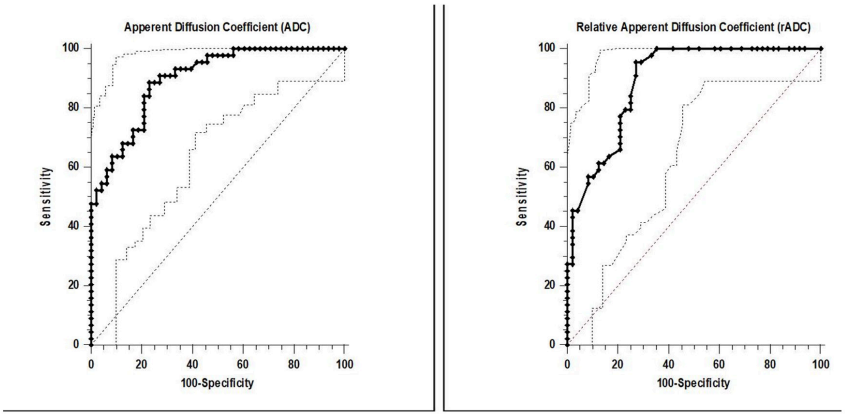

Figure 1. ROC curve for ADC and rADC
ROC: receiver operating characteristic

Table 2. Comparison of types of lesions of patients according to lesion groups

	Group		All lesions	Test (p)
	Benign	Malign		
Number of lesions, n	48	44	92	z=-0.834 p=0.404
M (IQR)	1 (1)	1 (2)	1 (1)	
Type of lesions, n (%)				-
Hemangioma	25 (56.8%)	0 (0%)	25 (27.2%)	
FNH	8 (18.2%)	0 (0%)	8 (8.7%)	
Cystic lesions*	7 (15.9%)	0 (0%)	7 (7.6%)	
Other solid benign lesions**	4 (9.1%)	0 (0%)	4 (4.3%)	
HCC	0 (0%)	15 (31.3%)	15 (16.3%)	
Cholangiocarcinoma	0 (0%)	3 (6.3%)	3 (3.3%)	
Metastasis	0 (0%)	30 (62.5%)	30 (32.6%)	

Mann-Whitney U test (z); M: median, IQR: interquartile range, n: number of patients, %: percentage
*Cystic lesions refer simple cyst and hydatid cyst. **Other solid benign lesions refer adenoma and angiomyolipoma

Table 3. Comparison of mean ADC and rADC values between benign and malignant groups

	Group		All of lesions	Test (p)
	Benign	Malign		
	n=44	n=48	n=92	
ADC (10^{-3} mm^2/s)				**t=7.710 p<0.001**
X ± SD	1.66±0.49	1.04±0.24	1.34±0.49	
rADC				**t=7.294 p<0.001**
X ± SD	0.88±0.25	0.57±0.15	0.72±0.25	

Independent sample t-test (t); descriptive statistics are given as mean (X) and standard deviation (SD) values. ADC: apparent diffusion coefficient, rADC: relative ADC

Table 4. ROC curve analysis findings for ADC and rADC values

	Cut-off	Sensitivity	Specificity	AUC	p-value
		(95% CI)	(95% CI)	(95% CI)	
ADC (10^{-3} mm^2/s)	>1.149	88.64	77.08	0.898	**<0.001**
		(75.4-96.2)	(62.7-88.0)	(0.817-0.951)	
rADC	>0.62	95.45	7.92	0.890	**<0.001**
		(84.5-99.4)	(58.2-84.7)	(0.808-0.946)	

ROC: receiver operating characteristic, ADC: apparent diffusion coefficient, rADC: relative ADC, AUC: area under the curve, CI: confidence interval

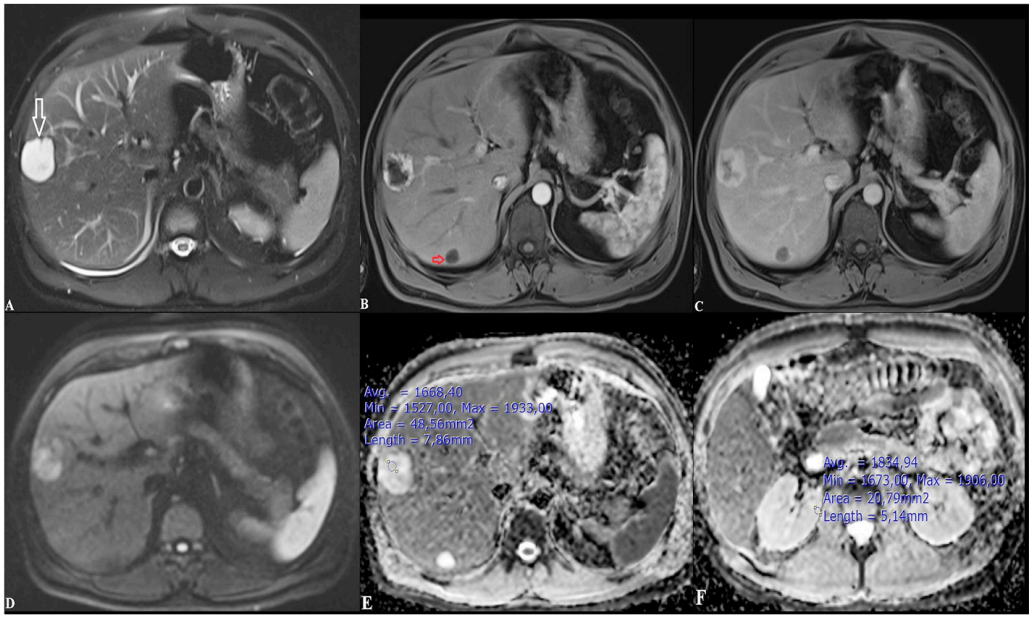

Figure 2. 53-year-old male patient with rapidly enhancing hemangioma. A. T2W fat-saturated image demonstrates a well-defined hyperintense lesion (white arrow). B. In arterial phase of dynamic MRI, a typical peripheral nodular contrast-enhancement pattern is observed. Also, a simple cyst can be seen (small arrow). C. In portal phase, rapidly contrast enhancement is seen. D. DWI (b-value of 800 s/mm2) shows hyperintensity. E-F. On the corresponding ADC map, the hemangioma shows high ADC and rADC values

ADC: apparent diffusion coefficient, rADC: relative ADC, MRI: magnetic resonance imaging, DWI: diffusion-weighted imaging

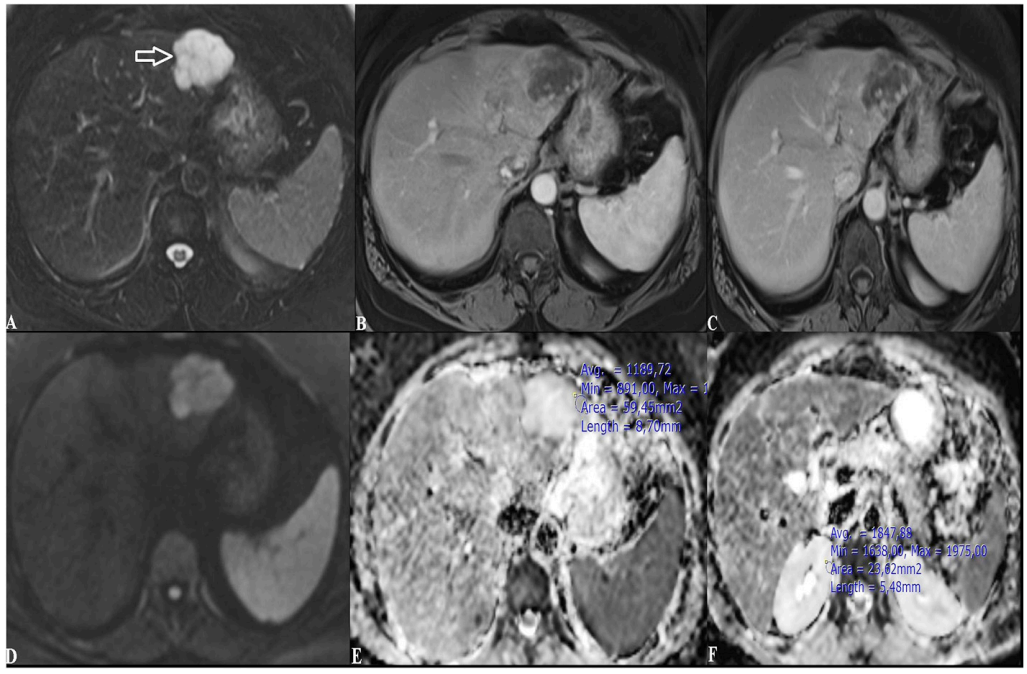

Figure 3. 52-year-old female patient with slowly enhancing hemangioma. A. T2W fat-saturated image shows hyperintense lesion (white arrow). B-C. On dynamic contrast-enhanced MRI images are observed peripheral nodular discontinuous enhancement which slowly progresses centripetally. D. DWI (b-value of 800 s/mm^2) shows heterogeneous hyperintensity. E-F. The ADC value of the lesion was below the cut-off value, and rADC was above the cut-off value

ADC: apparent diffusion coefficient, rADC: relative ADC, MRI: magnetic resonance imaging, DWI: diffusion-weighted imaging

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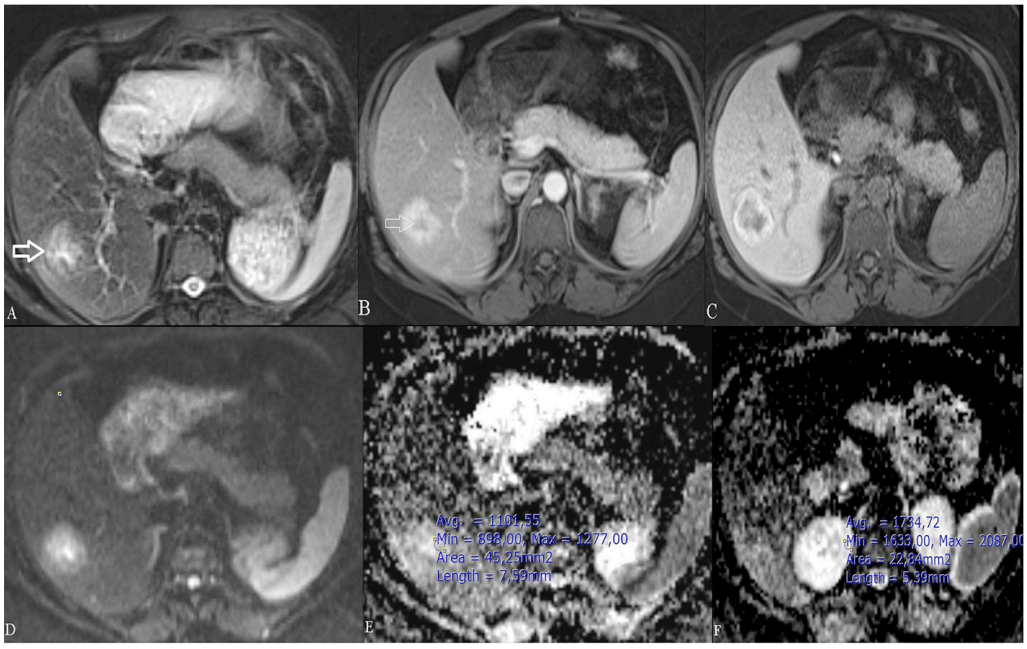

Figure 4. 29-year-old female patient with FNH. A. T2W fat-saturated image shows heterogeneous hyperintense lesion (white arrow). B. In a portal phase of dynamic MRI, Intense enhancement and central fibrotic scar are seen (thin white arrow). C. Hepatobiliary phase on contrast-enhanced MRI demonstrates hyperintensity on the outer layer. D. DWI (b-value of 800 s/mm^2) shows hyperintensity. E-F. The FNH shows low ADC and rADC values

FNH: focal nodular hyperplasia, ADC: apparent diffusion coefficient, rADC: relative ADC, MRI: magnetic resonance imaging, DWI: diffusion-weighted imaging

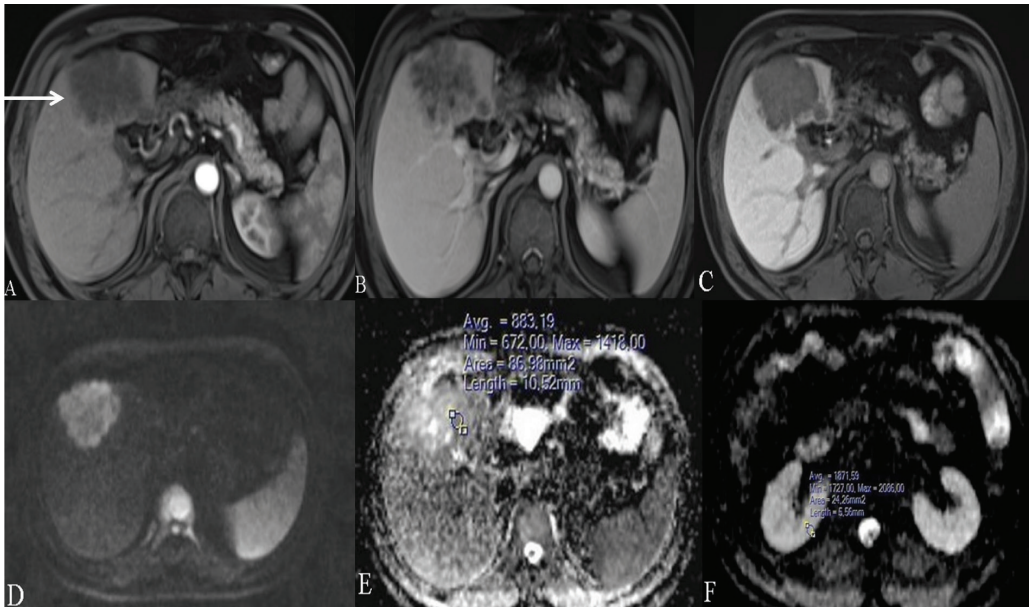

Figure 5. 50-year-old male with HCC. A-B. On dynamic contrast-enhanced MRI images show peripheral progressive enhancement (white arrow). These enhancement patterns are atypical radiologic findings of HCC. DWI shows hyperintensity. C. No contrast enhancement is observed in the hepatobiliary phase image of contrast-enhanced MRI. D. DWI (b-value of 800 s/mm^2) shows hyperintensity. E-F. ADC and rADC values were below the cut-off values

HCC: hepatocellular carcinoma, ADC: apparent diffusion coefficient, rADC: relative ADC, MRI: magnetic resonance imaging, DWI: diffusion-weighted imaging

DISCUSSION

DWI is an advanced imaging method that aids in the differential diagnosis of focal liver lesions when used together with routine sequences in MRI. ADC values of benign and malignant focal liver lesions have been compared in prior publications (23-25). Several studies have shown that the ADCs of benign hepatic lesions may overlap with those of malignant lesions (26,27).

As mentioned above, technical differences and patient-related factors may cause variability in ADC values. The primary purpose of using the relative ADC value is to establish a threshold value independent of technical limitations and patient factors. It was stated that the renal medulla of the kidney showed anisotropic diffusion because of the radial orientation of its structures (10). Therefore, the ADC value obtained from the right renal cortex, avoiding the renal medulla as the reference organ, was used to calculate the relative ADC. Our findings regarding the potential utility of the rADC value in the diagnosis of liver lesions revealed that both ADC ($p<0.001$) and rADC ($p<0.001$) values can be used in the discriminating the benign and malignant liver lesions, with no significant superiority of rADC over ADC.

The contribution of the rADC value to diagnosis has been investigated in various studies. Do et al. (18) calculated the rADC values using the spleen as a reference organ in the evaluation of liver fibrosis and demonstrated that the rADC value increased the diagnostic accuracy in the detection of liver fibrosis. Park et al. (21) determined the renal cortex as the reference organ with the highest reproducibility in the first series of their studies, and then in the second series by comparing the ADC and rADC values of metastatic and non-metastatic lymph nodes in 130 patients with uterine cervical cancer, they reported the likelihood of the rADC value to increase the accuracy of the diagnosis of metastatic lymph nodes.

Hong et al. (20) compared liver ADC and rADC values to evaluate liver fibrosis via 3 Tesla MRI in chronic hepatitis B patients. Liver ADC and rADC values (specifically, S-rADC and R-rADC values, defined as the ratio of the liver ADC to the spleen and renal cortex ADC values, respectively) were measured and compared with METAVIR liver fibrosis scores. The results showed that R-rADC at b=600 s/mm^2 was more accurate in predicting the stages of hepatic fibrosis. The renal cortex has been suggested as a reference organ (20).

In this study, all simple cysts, two hydatid cysts, and one angiomyolipoma showed higher ADC and rADC values consistent with benignity. In addition, while FNHs showed the lowest ADC and rADC values in the benign group, they overlapped with malignant lesions. Previous studies have reported that the ADC values of some benign lesions, such as FNH and adenoma, overlap with the ADCs of malignant lesions (26,27). These findings were attributed to the hypercellularity of FNHs, which resulted in restricted diffusion. However, in our study, the ADC and rADC values of adenomas were in the benign group. The reason for this could be explained by the lower number of cysts in our study and the relatively higher mean ADC values of adenomas because of the decrease in our cut-off value due to solid lesions.

Wu et al. (28) stated that the difficulty in distinguishing atypical hemangiomas from colorectal cancer metastases might lead to misdiagnosis and unnecessary surgical resection. Nam et al. (29) divided 69 hemangiomas into three groups to evaluate the ratio of total tumor volume to the visually estimated contrast increase in portal phase images, and contrast enhancement of >75% was classified as group 1, those with 25-75% as group 2, and those with 25% as group 3. The lowest ADC values were calculated in group 3, and a significant difference was observed between groups 1 and 3. They reported that restricted diffusion may be due to structural differences in hemangiomas (29). In this study, we observed that the ADC values were below the cut-off value in four of the 25 hemangiomas. These lesions were above the cut-off value determined for the rADC values. The enhancement features of these lesions with low ADC values and suspected malignancy were compatible with group 3. This result suggested that the rADC value may be superior to the ADC value in terms of contribution to diagnosis. We then evaluated the contribution of rADC to the differentiation of hemangiomas and malignant masses. However, no statistical difference was observed.

Evaluation of the malignant lesions included in our study revealed that the ADC and rADC values of five colorectal cancer metastases were above the cut-off value. In a study by Cui et al. (30), 87 colorectal and gastric hepatic metastases were divided into two groups as lesions responsive to and non-responsive to chemotherapy according to ADC values before and during treatment. The authors reported that nonresponsive lesions had higher pretreatment mean ADC values than responding lesions and stated that high ADC values may be associated with necrotic areas (30). In our study, in contrast to the study by Cui et al. (30), measurements were performed from ROI areas that did not cover the entire tumor but included the peripheral parts with the most restricted diffusion and with exclusion of the cystic or necrotic components. It has been reported that metastatic liver lesions may be perfused by vessels originating from the lower oxygenated portal venous system, leading to the formation of hypoxic tissue in the tumor (31). In addition, the presence of viable hypoxic cells around the necrotic areas developing in the tumor causes the development of hypoxia-related treatment resistance (32). A moderate correlation between ADC values and tumor hypoxia levels was reported in an animal model study (33). Accordingly, in the current study, the identification of high ADC values in all five lesions and concomitantly high rADC values in all lesions may be related to the ADC variability of the hypoxic areas resulting from decreased perfusion of the tumor.

Study Limitations

There are several limitations to this study, such as the small sample size, particularly in the benign group, and the inability to include lesions 1 cm because of limited spatial resolution in diffusion sequences. In addition, the images were analyzed by

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one radiologist in our study; therefore, the intra- and interobserver variability of ADC measurements could not be tested. It would be better to include a larger-scale study population in future studies.

CONCLUSION

Both ADC and rADC values can be used to differentiate benign and malignant lesions with high sensitivity and specificity. The combined use of ADC and rADC values for lesions with suspected malignancy is recommended because of their advantages in different cases.

Ethics Committee Approval: Study was approved by the University of Health Sciences Türkiye, Taksim Training and Research Hospital Ethics Committee (decision no: 7, date: 13. 05.2015).

Informed Consent: Informed consent forms were obtained from all.

Author Contributions: Surgical and Medical Practices - N.U., E.Y., E.E.E.; Concept - H.Ö.; Design - N.U., H.Ö.; Data Collection and/or Processing - N.U., L.K.; Analysis and/or Interpretation - L.K., A.H.B.; Literature Search - N.U., A.H.B.; Writing - N.U., E.E.E.

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