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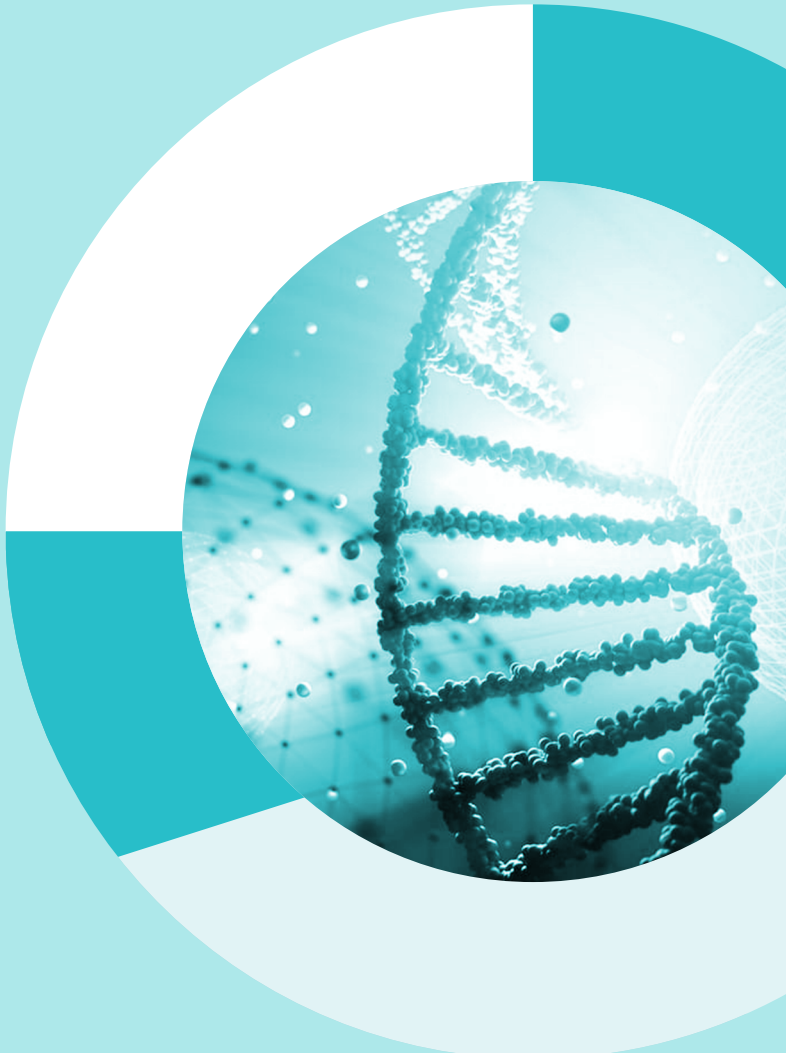

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LETTER TO EDITOR

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Revolutionizing Healthcare Practice: Unleashing the Potential of Interprofessional Education

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Keywords: Education, healthcare students, interprofessional education

Dear Editor,

I write to draw attention to the importance and impact of interprofessional education (IPE) within the complexity of today's healthcare settings. The aim of IPE is to improve healthcare professionals' teamwork and communication skills, prevent medical errors, maintain patient safety, and provide cost-effective quality healthcare services.[1]

IPE is an ideal teaching method that improves patient-centered care and effective teamwork.[2] Through this education, different professional roles and perspectives are better recognized,[3] the quality of care is promoted, patient safety is maintained, and the coordination between the members of the healthcare team is strengthened.[1] In addition, IPE contributes to the development of professional identity, the socialization of students, and learning to mutually respect each other's boundaries by being aware of the roles, authorities, and responsibilities of other healthcare professionals.[4]

Current curricula and practices result in insufficient opportunities for interprofessional collaboration to acquire the necessary knowledge and skills in basic communication and teamwork, thereby leading to stereotyped perceptions among future healthcare professionals.[1] Moreover, only after graduation do students have the opportunity to get to know other health professions in the clinical field. However, it is not easy to improve the perception and attitude of a healthcare professional who has not yet acquired competence in interprofessional collaboration within the healthcare system.[3] Therefore, IPE is essential for healthcare students to develop competence in interprofessional collaboration before graduation because it offers them the opportunity to prepare for the complex dynamics of healthcare that await them in their career.[2,4] Although IPE is an effective method, it is challenging to plan and implement.[3] These challenges include an insufficient number of health professionals, incompatible curricula, an imbalance in the number of students, and scarce resources.[4] Additionally, IPE is a new concept in Türkiye and is not included in the curriculum at the desired level. Therefore, there is a need to integrate IPE into educational programs in Türkiye and to measure its results through research.

The main cause of many medical errors and health accidents is communication problems between healthcare professionals.[5] Traditional unprofessional education focuses solely on the development of collaboration and communication skills between patient- nurse or patient- physician, and does not focus on communication among healthcare professionals, resulting in the exacerbation of these medical errors.[1] Therefore, IPE, which focuses on interaction and communication between healthcare professionals, should be integrated into nursing curriculum and theoretical and clinical education at all levels.[4]

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REVIEW

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Intermittent Fasting and Its Potential Effects on Health

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Abstract

This compilation study explains intermittent fasting, ways to practice it, and discusses its potential health effects, studies on intermittent fasting, and when to avoid practicing it. For many years, people have applied various diet models to lose weight, prevent nutrition-related diseases, and maintain high quality of life. Intermittent fasting has recently become a popular nutrition model, and it has been shown to have positive effects on several metabolic processes, particularly on the loss of body weight. Intermittent fasting is the restriction of energy or food intake on certain days of the week, day, or specific time, and there are different ways to perform it. Alternative day fasting is a method in which around 25% of the energy needs are met and then the other meal is consumed after a 24-hour fasting period. In the modified fasting regime, around 20-25% of the daily energy needs are met on non-successful two days of the week. The time-restricted eating model is the most common regime in which the daily energy intake is compacted into 8 hours with 16-hour abstinence. Ramadan fasting is an act of abstinence from all food in İslam from dawn until sunset. Unlike other fasting methods, fasting is conducted for religious purposes only, where no food or drink is allowed regardless of the energy content. Alternative day fasting, modified fasting regime, time-restricted eating, and Ramadan fasting are some of the intermittent fasting methods. Although intermittent fasting seems like an alternative diet model for losing body weight, it has many positive effects on heart health, insulin resistance, brain health, cancer, metabolic health, inflammation, and aging, all of which can be explained by the various effects of intermittent fasting. Ketone bodies, which are the fuel of the brain and body during fasting and long-term exercise, increase during hunger. They are not only a source of energy but also facilitate many metabolic events in tissues and cells. It also affects the circadian rhythm when intermittent fasting is associated with the circadian rhythm because it limits food intake at certain times. Eating late at night disturbs circadian rhythm and may cause chronic diseases like obesity, diabetes etc. the intermittent fasting also has effects on the microbiota, and studies revealed that intermittent fasting improves the gut microbiota diversity and good gut bacteria with benefits on gut health. Similar to any other diet, intermittent fasting may vary with age, sex, and special condition (pregnancy, breast feeding, adolescents etc., or it is not recommended for specific circumstances.

Keywords: Intermittent fasting, time restricted fasting, fasting, metabolic diseases

INTRODUCTION

Fasting is the voluntary abstinence from food for a limited time, which people practice for centuries due to various reasons. A diet model is used for therapeutic purposes with varying ways of practice according to religion and ethnic origin.[1,2] Intermittent fasting is a nutrition model that differs from religious fasting that aims to attain spiritual satisfaction. Unlike religious fasting, consumption of non-energy beverages is forbidden.[3,4] Intermittent fasting is effective for weight loss because it causes less energy intake or hunger for a certain period. Fasting lowers insulin levels in the body. Low insulin levels allow the use of stored fat. In addition, autophagy is triggered when cells are hungry, whichcleans the damaged cells. Fasting also influences growth hormone levels, increasing growth hormone levels, leading to fat burn and muscle increase.[5]

Obesity, which has become increasingly common worldwide, causes the incidence and progression of many diseases, particularly cardiovascular

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diseases, cancer, and hypertension[I]. Intermittent fasting may help with weight loss, metabolic health, decreasing inflammation, advanced immunity, decreasing cholesterol, protection against neurodegenerative diseases, better cognitive performance and mental status, aging, and improving sleep quality[II].

Methods

This study is a compilation of previous studies. This study has not been applied to any animals or humans. No patient informed consent form was obtained.

The Types of Intermittent Fasting

Alternative Day Fasting: A Short Form

Alternative day fasting includes meeting 25% of energy intake on the days of fasting and eatingas desired on the other days. One has a meal at their preferred time and then stops eating for the next 24 hours; they may consume no-energy drinks. For instance, an individual who has the first meal at 06.00 p.m. does not eat until 06.00 p.m. the next evening but may drink energy-free beverages (tea - coffee - herbal tea without sugar, sparkling water, etc.) alternative day fastingmay have a positive influence on weight loss and treatment of vascular health.[4]

Short-term studies on the effect of alternative day fasting covering 2-3-week period revealed that triglyceride levels and consequently body mass decreased by 3%, while long-term studies reflected that weight loss was higher by 8% when compared with the initial weight; visceral fat rate reduced and low-density lipoprotein (LDL) cholesterol and triglyceride levels improved, respectively.[6] However, studies on pessimist mood, low attention span, and low work performance.

[I]https://hsgm.saglik.gov.tr/tr/obezite/dunyada-obezitenin-gorulme-sikligi.html

[II]https://www.sleepfoundation.org/physical-health/intermittent-fasting-sleep

On days of fasting[2,7] while While studies conducted on animals have concluded that alternative day fasting reduces cardiovascular diseases, type 2 diabetes, and cancer risk, yet there are not sufficient data for human.[8]

Modified Fasting

This model is not about the total restriction on energy intake on fasting days but 20-25% of energy intake on 2 non-successive days in a week. On days of fasting, women consumed approximately 500 kcal/day and men 600 kcal/day, and they continued their regular diet on the other days. Modified fasting is also known as the 5:2 diet.[9]

Pursuant to the studies conducted to identify the influence of modified fasting on humans with a sample size between 10-107 pre-obese or obese adults, the control group practicing modified fasting experienced weight loss and a decrease in fasting insulin and glucose with improvements in LDL and triglyceride levels. Some individuals may find it challenging to adhere to certain fasting patterns, and there may be social or psychological implications worth considering. In terms of the effect on mood, very few participants showed several side-effects like feeling chill, uneasiness, low energy levels, and hunger, but positive effects like lesstension, aggression, exhaustion, and confidence.[4,10,11]

Time Restricted Eating

This is a type of intermittent fasting in which one eats at certain time intervals. This model particularly focuses on when food is consumed rather than what is consumed at all. The most common models are 16:8, 18:6, 20:4. The effect mechanism was based on adjusting metabolic times by affecting circadian rhythm. The most widely used model is 16:8, and the day is planned as around 8 hours for eating and drinking and 16 hours for fasting. This model generally plans 2 main meals and where necessary snacks in 8-hour periodd determined based on lifestyle. For instance, the first meal would be at 12.00 p.m. and the latestmeal would be at 8:00 p.m.[12,13]

In consideration of the results from animal trials, timetime restricted eating reduced body mass, total cholesterol, triglyceride, glucose, insulin, interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) concentrations.[14]

The meta-analysis study regarding the effect of time-restricted eating on body composition and other parameters revealed that participants practicing time-restricted eating had lower body weight, fat mass while restoring lean mass, blood pressure, fasting glucose concentration, cholesterol and triglyceride.[15]

Ramadan Fasting

Ramadan fasting is the act of not consuming any food, beverage, medicine, cigarette, etc. in Islam for almost a month from dawn until sunset. Other than intermittent fasting, the patient is not allowed to consume any energy-free liquid or food during fasting.[14]

A cross-sectional study conducted with 1,780 participants with diabetes to evaluate the impact of Ramadan fasting on patients with type 2 diabetes concluded that Ramadan fasting reduces blood pressure, blood sugar, hemoglobin A1C (HbA1c), and body mass index (BMI); hence, it has a positive effecton type 2 diabetes.[14]

Studies have revealed that Ramadan fasting affects the loss of body weight, particularly more weight loss as BMI increases; however, people with regular weight are not affected by such circumstances. Various studies have indicated that people gain the weight that they lose during the Ramadan fasting.[16,17]

Intermittent Fasting and Circadian Rhythm

The benefits of intermittent fasting originate from its metabolic effects, which arise from its effects on circadian rhythm. Circadian rhythm is the repetition of effects that the world has on individuals due to its 24-hour rotation like sleep-wakefulness, blood pressure, heart rate, hormone release, mood adjustment, etc. Several factors like light, melatonin, temperature, jet lag, shift work, etc. influence the circadian rhythm. The distortion of circadian rhythm may lead to many pathological events like obesity, metabolic syndrome, sleep disorders, diabetes, and cardiovascular diseases. Limiting food intake is effective in adjusting circadian rhythm.[18]

A large-scale randomized controlled isocaloric study covering gene expression analysis revealed that time-restricted eating affects the expression of 6 genes related to circadian rhythms. Another study noted that time-restricted eating provides significant and permanent improvement on the quality of sleep.[19] Intermittent fasting may improve the quality of sleep by affecting circadian rhythms and may increase

growth hormone levels. This hormone generated while sleeping repairs the muscle cells, making one feel quite vigorous and relaxed[II].

A one-week study performed on healthy adults concluded that individuals practicing intermittent fasting wake up and move less at night and experience an increase in REM sleep, leading to better leading better quality sleep[II].

A study conducted via a mobile application to analyze the eating habits of a group of healthy adults showed that many individuals have frequently and irregular eating patterns, where individuals eating more than 14 hours lose body weight when they eat 10-11 hours for 16 weeks while they become much energetic with better sleep.[20]

Intermittent fasting may improve the quality of sleep; however, there may be an opposite situation based on the practice method, particularly eating just before bedtime, which may negatively affect sleep quality. For instance, studies have concluded that waking up at night and eating during Ramadan fasting reduce melatonin levels (known as sleep hormone) and REM sleep. Moreover, leptin and ghrelin hormones affected by meal plan, food intake, sleep, etc. during Ramadan fasting may also affect circadian rhythms[II].[21]

Intermittent Fasting and Microbiota

Intermittent fasting may directly affect the gut biota, which comprises complex, diverse, and wide-ranging microbial groups in the gut. Karakan[22] reflected that intermittent fasting encourages browning of white adipose tissue and reduces obesity by changing the gut microbiota.

Fecal samples were collected, and genomic DNA sequencing was performed within the scope of a 7-month animal study conducted with alternative day fasting. The data noted that the composition of gut microbiota and the phyla *Bacteroidetes, Firmicutes, Verrucomicrobia, Tenericutes, Actinobacteria,* and *Proteobacteria* may change with long-term intermittent fasting.[23] A study on 17 pre-diabetes patients regarding the effect of long-term fasting on the microbiota compared pre- and post-Ramadan stool and indicated an increase in *Eubacterium hallii*, *Firmucutes* bacteria.[24]

Moreover, the consumption of fermented foods such as yoghurt, matured cheese, kefir, kimchi, kambucha, and sauerkraut with probiotics; plant-origin products with probiotics like onion, leeks, asparagus, garlic, and whole-wheat food; lentils, beans, nuts, and quinoa with high fiber and protein; and avoiding processed foods (fizzy drinks, cereals, hot-dogs etc.) would have a positive effect on gut microbiota as well as support during intermittent fasting. However, it is important to note that the gut microbiome is unique to individuals, and each person has a different reaction to food[III].

[II]https://www.sleepfoundation.org/physical-health/intermittent-fasting-sleep

[III]https://joinzoe.com/learn/intermittent-fasting-gut-health (E.T.09.09.2022)

Intermittent Fasting and COVID-19

People continue to live amid the COVID-19 pandemic around the world. Many diseases like obesity, cardiovascular diseases, diabetes, and cancer, increase the morbidity and mortality of COVID-19. Hyperglycemia, weak immunity, inflammation, and metabolic dysfunction in obese individuals with diabetes cause severe COVID-19 symptoms.[25]

The strategies like lockdown during the peak of cases triggered unhealthy eating habits and a sedentary life. Intermittent fasting is considered to have an impact on COVID-19 because it prevents unhealthy eating habits, improves metabolic health and immunity, reduces inflammation, and has further effects on autophagia.[18]

Intermittent Fasting and Obesity

Intermittent fasting is considered an effective method with various benefits against obesity. A systematic compilation study analyzing intermittent fasting and energy-restricted nutrition models for periods ranging from 14 to 48 weeks revealed that both models have similar effects on weight loss; hence, intermittent fasting may be effective in the treatment of obesity.[26]

In addition to decreasing weight gain, intermittent fasting minimizes visceral adiposity, cardiometabolic risk, metabolism, muscle function, and glucose homeostasis.[23]

Various studies have noted that intermittent fasting ensures weight loss mainly from fat.[27-29] A study conducted with obese individuals in which individuals practicing 8-hour time-restricted eating for 12 weeks and individuals practicing 6-hour time-restricted eating for 8 weeks were compared with the control group observed that the intervention group had higher weight loss levels than the control group.[30] A clinical study on obese abdominal participants concluded that 40 participants lost around 5.3±3.1 cm from their waistlines after a 3-month TRF intervention.

The meta-analysis study by Park et al.[31] reflected that alternative day fasting minimizes BMI, body weight, and total cholesterol in overweight and obese adults.

When combined with physical activity, intermittent fasting has a greater effect on weight loss.[17]

Intermittent Fasting and Heart Health

Intermittent fasting limits many risk factors associated with cardiovascular diseases and consequently the occurrence of cardiovascular diseases. It reduces the concentration of inflammatory markers like IL-6, homocysteine and C-reactive protein (CRP) help the development of atherosclerotic plaque. It prevents the occurrence of heart diseases by reducing blood sugar, triglyceride, LDL levels, insulin resistence.[32]

A study regarding the effect of intermittent fasting on coronary heart disease performed for 12 weeks in 32 individuals revealed that body weight and stored fat decreased but no change in lean mass was observed among participants practicing alternative day fasting.[33]

Pursuant to the results of a study conducted with 60 overweight and obese adult participants, the group practicing alternative day fasting by limiting 75% of calories had lower LDL and triglyceride levels by 10±4% and 17±5%, respectively, at the end of 12 weeks.[34] Similarly, a study of 83 obese individuals concluded that high-density lipoprotein and LDL levels improved with alternative day fasting and exercise.[6]

Clinical trials have indicated that intermittent fasting lowers systolic and diastolic blood pressure. A study with pre-diabetic male participants reported that an 18 h fast lowers diastolic blood pressure by 11±4 mmHg and 10±4 mmHg at the end of 5 weeks.[35]

Intermittent Fasting and Insulin Resistance

During fasting, insulin sensitivity increases and insulin levels decrease, leading to the recovery of fasting and postprandial glucose levels. Insulin resistance is associated with increased CRP, lower adiponectin, LDL particle size, atherosclerosis, and increased inflammatory events with other metabolic factors that contribute to or are related to the development of coronary artery disease.[36]

A comprehensive randomized controlled study was conducted to assess fasting glucose, insulin, HbA1c, and HOMA-IR levels to identify the effect of intermittent fasting on glucose metabolism. Consequently, the fasting glucose level decreased by 0.15 mmol/L after intermittent fasting. Glycated hemoglobin level decreased by 0.08%, but no significant change was observed in HbA1c levels. While the insulin level decreased by approximately 13.25 mU/L, the HOMA-IR decreased by 0.31.[37]

A study regarding the effect of alternative day fasting on calorie restriction, body weight, and glycoregulatory factors in obese adults with insulin resistance revealed that the net energy intake of participants practicing alternative day fasting and a calorie-restricted diet for 6 months was reduced by approximately 25% daily. Participants following alternative day fasting consumed 25% of their daily energy needs on fasting days as lunch (between, 12.00-14.00). while they consumed 25% of their daily energy need in 3 meals while participants following a calorie-restricted diet consumed around 75% of their energy needs in 3 meals during the day. The participants were asked to restore their existing weights until the end of 12 months. At the end of 12 months, the fasting glucose of participants who practiced intermittent fasting had a higher decrease, whereas insulin resistance decreased more than that of individuals who practiced calorie-restricted diet. The decrease in body weight was similar between the groups. These findings indicate that intermittent fasting is much more beneficial than a calorie-restricted diet in reducing insulin resistance among adults with diabetes risk.[30]

Intermittent Fasting and Brain Health

The liver is where glucose is stored as glycogen. Based on the physical activity levels of individuals, a 12-24 h fasting reduces serum glucose levels by approximately 20% or more, causing glycogen exhaustion in the liver. Because glycogen runs out during fasting, the liver transforms free fatty acids into ketone bodies and uses them as energy sources. Many tissues use fatty acids for energy, whereas while in long-term fasting, the brain uses glycose together with beta (β)-hydroxybutyrate and acetoacetate as ketone bodies. These ketone bodies stimulate brain-derived neurotrophic factor that is effective in the formation and repair of brain nerve cells. Moreover, mouse clinical trialshave revealed that people practicing intermittent fasting exhibit fewer symptoms of neurodegenerative diseases (Alzheimer, Parkinson, Huntington).[1,38]

Although the root of Alzheimer disease is not yet known, the disease is characterized by beta-amyloid plaques and neurofibrillary tangles. Intermittent fasting may diminish amyloid plaque accumulation and slow cognitive decline.[39]

A 2-week study conducted with 90 adults between the ages of 18 and 65 identified depression symptoms in 63.2% of females (n=57) and 30.3% of males (n=33), reflecting the anxiety among individuals about losing weight.[40] In contrast to this study, a study performed for 8 weeks with 36 health volunteers concluded that intermittent fasting remedies the headspace of participants, as measured by the Hospital Anxiety and Depression Scale and World Health Organization Well-Being Index.[41]

Consequently, there is not sufficient data on the direct effects of intermittent fasting on the mechanisms that support the development of brain-related diseases in humans. Therefore, there is a need for further studies.

Intermittent Fasting and Cancer

The effects of intermittent fasting on the prevalence and prognosis of cancer are not certainly known due to the lack of clinical studies. Some studies have indicated that long-term fasting may diminish chemotherapy-related toxicity and tumor growth. However, further studies are required to recommend intermittent fasting for active cancer patients.[42]

There is not any human clinical trials on the effect of intermittent fasting on cancer, yet it is considered to have the potential to prevent cancer by decreasing DNA damage and carcinogenesis due to its impact on insulin like growth factor (IGF-1), insulin, glycose, insulin like growth factor binding protein 1, and ketone bodies.[38]

Some studies on animals have noted that intermittent fasting may stop cancer development and progression. A mouse clinical trial concluded that individuals following intermittent fasting have 40-80% less breast tumor formation than those following ad libitum feeding.[43]

Intermittent Fasting and Metabolic Health

Intermittent fasting may provide many metabolic benefits like the treatment of glycose homeostasis, in addition to helping to lose body fat and weight.

A study, which was conducted to identify the benefits of intermittent fasting other than weight loss, concluded that a 6-hour restricted nutrition model in males with pre-diabetes for 5 weeks improved insulin levels and sensitivity, beta cell response, blood pressure, and oxidative stress levels. Time-restricted eating as an intermittent fasting method with an effect on the harmony of eating by circadian rhythm is considered to be effective against pre-diabetes and pre-hypertension.[35]

A meta-analysis study was performed with 335 participants with the aim of evaluating the effects of intermittent fasting and calorie-restricted diet on glycemic control and weight loss among pre-obese or obese patients and patients with type 2 diabetes and metabolic syndrome. This study revealed that intermittent fasting and a calorie-restricted diet had similar effects on glycemic control based on HbA1c and fasting plasma glycose levels. The patients experienced similar hypoglycemic events in both diet models, with improvements in fasting insulin and lipid profile. However, intermittent fasting was associated with greater weight loss.[44]

Metabolic syndrome is a clinical state related to advanced cardiovascular disease and diabetes mellitus risk. Metabolic syndrome is also defined as the collective existence of risk factors, such as obesity, high fasting plasma glucose, dyslipidemia, and high blood pressure.

In consideration of the literature review, there is not any study on the direct effect of intermittent fasting on metabolic syndrome, but scientific evidence regarding the improvement of cardiometabolic parameters indicates a possible effect.[15]

Intermittent Fasting and Inflammation

With the development of glycose homeostasis, some studies have reported that inflammatory cytokines decrease with intermittent fasting. Moreover, TNF-α, IL- 1β, and IL-6 levels in the circulation system decrease, and weight loss and glycose metabolism are improved.[45,46]

Similarly, intermittent fasting in rodents showed significant decreases in the circulation and fat tissue levels of IL-6, TNF-a and IGF-1 and leptin compared with ad libitum feeding mice.[47]

Fasting and intermittent fasting methods reduce leptin levels and eliminate any immunity disorders related to leptin disorders, including aging, obesity, metabolic syndrome, and auto immunity.[48]

A study conducted on mice with chronic inflammatory disease revealed that alternative day fasting reduced proinflammatory monocyte levels and expression of TNF-α, IL-1β as proinflammatory genes.[25]

Intermittent Fasting and Aging

There are several positive effects of intermittent fasting on the delay of aging, such as decreasing oxidative stress and inflammation, stimulating autophagy and inhibiting mTOR (the mammalian target of rapamycin protein complex) and decreasing insulin and glycose levels in the circulation and insulin-like growth factor.[49] Studies performed on rodents to analyze the impact of fasting on rodents indicated that the life expectancy of mice that practice alternative fasting for two days weekly is increased. Studies have shown that intermittent fasting is effective in preventing aging and age-related diseases.[1,49] More human studies are needed to examine its effects on aging.

A randomized 4-day study conducted with 11 pre-obese adults where one group had time- restricted eating between 8 a.m. and 2 p.m. and the control group had a normal eating regime between 8 a.m. and 8 p.m. revealed that the time-restricted eating group showed a decrease in glycose levels and oxidative stress with an increase in LC3A as an autophagy gene and SIRT1 as an aging gene.[50]

CONCLUSION

In particular, with an effect on weight loss, intermittent fasting has positive effects on the cardiovascular system, decreases inflammation, strengthens immunity, protects brain health, improves sleep quality, delays aging, and has potential effects on the elimination of insulin resistance and prevention of cancer. Such effects are mainly caused by the decrease in insulin levels, formation of ketone bodies, stimulation of autophagy, and decrease in oxidative stress with effects on circadian rhythm and gut microbiota. Although intermittent fasting improves many biochemicals, not everyone experiences the same benefit, and individual factors such as age, gender, and current health status may play an important role. Intermittent fasting is a type of nutrition that should be adopted as a lifestyle rather than a diet model. However, this may not be applicable to everyone because nutrition should be unique to each individual based on their needs. Intermittent fasting is not recommended during adolesce, including infancy and puberty, pregnancy, and breast feeding, for underweight individuals or individuals with eating disorders since they require more energy and nutrients. During such periods, the weight should be kept under control and sufficient protein, quality carbohydrates, healthy fat, and fruits and vegetables should be consumed based on the individual needs. In this case, it would be appropriate for the person to consult an expert and obtain appropriate advice for their current situation. Sustainability is the key to diet modification. Intermittent fasting should be stopped when the menstrual cycle stops or becomes irregular; difficulties in sleeping occur; one starts experiencing hair loss, dry skin, and acne; any delays in wound recovery; stress; and negative effects on mental status. Many studies on intermittent fasting cover the short period; hence, a much wider scope clinical study is required to assess its long-term effects.

MAIN POINTS

- The mechanism of action of intermittent fasting is the reduction of insulin levels, formation of ketone bodies, stimulation of autophagy, reduction of oxidative stress, and circadian rhythm.
- Intermittent fasting has been shown to promote weight loss, reduce insulin resistance, and positively change leptin and adiponectin levels.
- Preclinical and clinical studies have shown that intermittent fasting has a wide range of benefits for improving cardiovascular risk factors and many diseases, including obesity, T2DM, and hypertension.

ETHICS

Authorship Contributions

Concept: S.Ç.S., Design: S.Ç.S., Literature Search: S.Ç.S., S.N.T., Writing: S.Ç.S., S.N.T.

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RESEARCH ARTICLE

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Investigation of Heavy Metal Levels in Hematology Analyzer Wastewater in March-April 2021

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Abstract

BACKGROUND/AIMS: Micropollutants are an important environmental problem that can be found in wastewater at very low concentrations. Heavy metals classified as micro-pollutant are the most common and toxic substances found in wastewater. Exposure to heavy metals exceeds the concentration allowed by the World Health Organization can cause serious health problems.

MATERIALS AND METHODS: In this study, our aim was to determine heavy metal contents in samples taken from hematology analyzer wastewater on 7 different days using inductively coupled plasma - mass spectrometer (ICP-MS). Quantitative analysis of 10 different heavy metals was made with ICP-MS and the results were obtained in ppb. Statistically minimum-maximum, median, and average values were obtained.

RESULTS: Aluminum (135.9 µg/L), chromium (29.5 µg/L), manganese (41.8 µg/L), nickel (103.4 µg/L), copper (2776.1 µg/L), zinc (9662.9 µg/L), arsenic (1.3 µg/L), cadmium (0.2 µg/L), and lead (202 µg/L) were detected. Vanadium was not detected in any of the measurements. Aluminum, arsenic, chromium, and cadmium were below the micro-pollutant levels, while the amounts of manganese and nickel were above the micro-pollutant levels. The amounts of copper, zinc, and lead, which have serious toxic effects on human and environmental health, were much higher than the micro-pollutant levels.

CONCLUSION: It is considered appropriate not to discharge the wastewater of the hemogram device directly into groundwater but to pass it through appropriate treatment systems beforehand.

Keywords: Heavy metal, hematology analyzer, wastewater

INTRODUCTION

The existence of the micropollutants in wastewater is one of the most important environmental problems. Micropollutants are chemical compound groups that exist at significantly low concentrations (ngL^{-1}) in the environment.[1] Synthetic organic materials such as pharmaceuticals, personal care products, industrial chemicals, pesticides, polycyclic aromatic hydrocarbons, food additives, detergents, and natural compounds like estrogen and heavy metals are microparticle pollutants.[2]

Micropollutants are organic and inorganic compounds resulting from human activities. These compounds cause endocrine failure, and they are mostly toxic to the environment and people. Decreased entry of micro pollutants into the environment and protection of water sources have become important cases for public health. Heavy metals such as Cd, Zn, Pb, Fe, Cu, Hg, Ni, Mn, Co, etc. are classified as micro pollutants and exist only in trace amounts under normal conditions; however, it is accepted that they are the most toxic compounds and common in wastewater.[3] Heavy metals can be pumped into living organisms

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because of their high concentrations in aquatic environments. When heavy metals enter the food chain, they accumulate in the human body at high concentrations. Higher concentrations of heavy metals than the World Health Organization (WHO) guidelines can cause severe health problems.[4] These heavy metal accumulate in soft tissues and harm the body because they cannot be metabolized by the human body. The maximum acceptable micropollutant concentrations of the human body have been determined.[5] Excessive accumulation of copper is toxic to cell membranes, DNA, and proteins, as a result of which copper is affected by bone health, immune function, increased infection frequency, cardiovascular risk, changes in cholesterol metabolism, liver disease, and severe neurological defects.[6-8] Long-term and high-dose zinc supplementation prevents copper uptake. Therefore, the toxic effects of zinc are mostly caused by copper deficiency.[9-11] Excessive exposure or intake of manganese can lead to dopaminergic neuronal death and manganism, a neurodegenerative disorder with parkinsonian-like symptoms.[12-14] Exposure to arsenic, skin, lung, liver, and bladder cancer, nausea and vomiting, decreased erythrocyte/leukocyte production, abnormal heart rhythm, skin lesions, circulatory disorders, neurological complications, diabetes, respiratory complications, and deaths due to chronic diseases may occur.[15-17] Kidney, bone, and lung damage are observed in cadmium toxicity,[15-19] neurological disorders, osteomalacia, accumulation in the liver, development of cholestasis, normo- or microcytic anemia, and impaired erythropoiesis are observed in aluminum toxicity.[20] Inhalation of high levels of chromium can cause respiratory problems, such as nasal ulcers, runny nose, asthma, cough, shortness of breath, skin contact can cause skin ulcers, and long-term exposure can cause damage to the liver, kidney circulatory, and nerve tissues, as well as skin irritation.[21-23] Lead exposure causes neurological, cardiovascular, and hematological disorders, encephalopathy, and edema.[24,25] The toxic effects of nickel include Allergy, cardiovascular and kidney diseases, lung fibrosis, lung cancer, mitochondrial dysfunction, and oxidative stress.[26-28]

Trace elements with an atomic density greater than 4±1 g/cm^3 are known as heavy metals, and they are persistent in wastewater resulting from natural and anthropogenic factors. The main natural sources of heavy metal pollutants are soil erosion, urban waste, aerosol particles, volcanic activities, dumps, metal plating and electroplating, and extraction processes.[3] Hospitals are important sources of these micropollutants. Diagnosis, laboratory, and research activities, as well as drug excretion from patients, cause a wide variety of microcontaminants.[29] Most micro pollutants are insufficiently removed in traditional wastewater treatment plants. These micropollutants are emitted into the aquatic environment at low concentrations (ng/L-µg/L). Even at very low concentrations, these compounds can affect sensitive organisms living in water because most are biologically active. Therefore, they are referred to as micropollutants.[30,31] Until now, many technologies have been used to remove heavy metals from wastewater. Common refinement technologies are shown in Figure 1.

The aim of this study is to investigate the levels of some heavy metals in the hematology analyzer effluent, which is formed after the necessary tests are performed on the hematology analyzer using blood samples from patients admitted to different polyclinics due to different diseases.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of Selçuk University Faculty of Medicine (approval number: 2019/194, date: 26.06.2019).

The most important heavy metals, the permitted concentrations of these heavy metals in tap water and wastewater by WHO, and their toxic effects are summarized in Table 1.

Collection of Hematology Analyzer Wastewater

This study was performed at the exit of the hematology analyzer, where routine examinations are performed, without contact with any patient. Accumulated wastewater samples were collected from the wastewater tank of the Beckman Colter DHX850 hematology analyzer placed in the Biochemistry Laboratory of Selçuk University Faculty of Medicine, in 4 replicate 15 mL metal-free tubes on 7 different days for 45 days. Approximately 35 L of wastewater was collected every 7 days on average. The wastewater tank was manually mixed to homogenize the samples before sampling. Samples were stored at 4 °C until analysis.

ICP-MS Analyze

The hematology analyzer wastewater samples were filtered separately using 0.45 µm pore cellulose membrane filters at Selçuk University

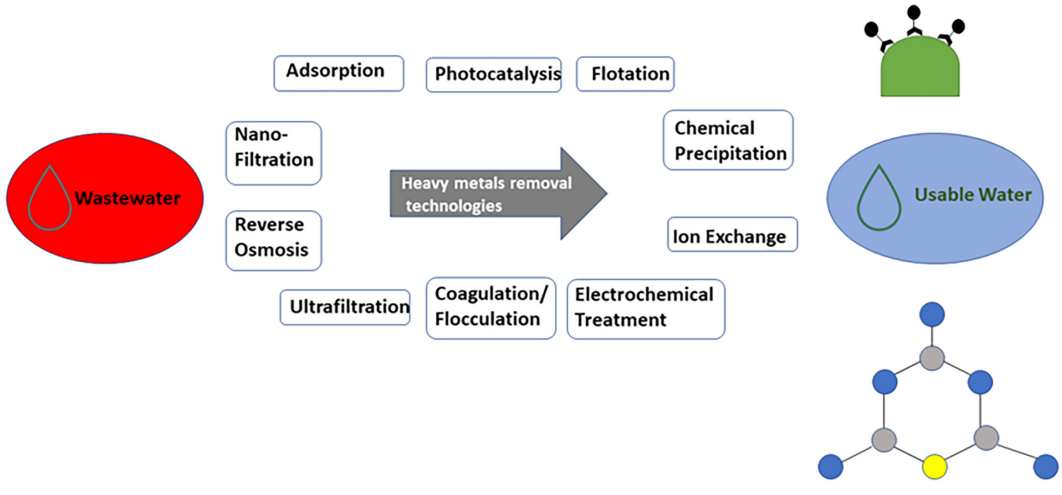

Figure 1. Commonly used refinement technologies for heavy metals from wastewater.

Advanced Technology Research Center. To prevent any metal precipitation, the filtered samples were acidified to a 0.1 mol L1 nitric acid concentration, and heavy metal contents were determined by inductively coupled plasma - mass spectrometer (ICP-MS) device.

A tuning solution containing 10 µg L-1 of lithium (Li), cobalt (Co), yttrium (Y), cerium (Ce), and thallium (Tl) for the optimization of the resolution, mass calibration, and sensitivity data required for the pre-measurement calibration of ICP-MS was used. The required operating and optimization parameters for the ICP-MS device are listed in Table 2.

Statistical Analysis

All statistical analyses were performed using the IBM SPSS 21.0 package program. Descriptive statistics for numerical variables are presented as median and minimum-maximum. In addition, measurement averages are presented as mean and standard deviation (SD) graphs.

RESULTS

ICP-MS Results

Wastewater samples were collected from the Medical Biochemistry Laboratory of Selçuk University Faculty of Medicine. Heavy metal analysis was performed with ICP-MS in Selçuk University Advanced Technology Research Center. Result of the analysis are shown in ppb in Table 3. According to the obtained results, aluminum was found above the maximum pollutant level (MPL) in the fourth measurement. Vanadium was not determined in any of the measurements. Chrome was detected below the MPL in all measurements. Manganese, nickel, lead, copper, and zinc levels were detected above the MPL in all measurements. Arsenic and cadmium levels were below the MPL in all measurements.

According to the data in Table 3, aluminum was not determined in the fifth and seventh measurements (M5 and M7), and higher results were observed in the fourth measurement (M4). Although arsenic was found only in the first four measurements (M1, M2, M3, M4), it was not found in the last three measurements (M5, M6, M7). Cadmium was detected only in the first measurement (M1), not more than MPL. Levels of chromium, copper, manganese, nickel, lead, and zinc were close to the average values for each measurement.

Hospital Information System

The data containing patient numbers and polyclinics for which hemogram analysis was applied to patients according to the day and hour when the samples were collected are shown in Table 4. Hemogram test samples were collected at seven different times with four repetitions. It is thought that heavy metal contents differ for each measurement due to differences in the numbers of patients who underwent hemogram analysis on the day of measurement. For example, while there were 26 patients coming from the dermatology

Table 1. Permitted boundaries for heavy metal toxicities and toxic effects on human health

Heavy metals	Micro pollutants concentrations that are tolerated by the human body at max (MKS)[8]	Secure limits on tap water suggested by WHO	Secure limits on wastewater suggested by WHO	Toxic effects
Cupper (Cu)	25 µg/L	<2 mg/L	1 mg/L	It affects bone health and immune function, increases the frequency of infections, cardiovascular risk, changes in cholesterol metabolism, liver disease, and serious neurological defects, and its excessive accumulation is toxic to cell membranes, DNA, and proteins.
Zinc (Zn)	800 µg/L	<3 mg/L	2-5 mg/L	Long-term high-dose zinc supplementation inhibits copper uptake. Therefore, most toxic effects are due to copper deficiency.
Manganese (Mn)	20 µg/L	<0.12 mg/L	<0.2 mg/L	Excessive exposure or ingestion can lead to dopaminergic neuronal death and manganism, a neurodegenerative disorder with parkinsonian-like symptoms.
Arsenic (As)	50 µg/L	<0.01 mg/L	None	Skin, lung, liver, and bladder cancer, nausea and vomiting, decreased erythrocyte/leukocyte production, abnormal heart rhythm, skin lesions, circulatory disorders, neurological complications, diabetes, respiratory complications, and death due to chronic diseases may occur.
Cadmium (Cd)	5 µg/L	0.003-0.005 mg/L	0.003 mg/L	Kidney, bone and lung damage.
Krom (Cr)	50 µg/L	<0.05 mg/L	0.05 mg/L	With high inhalation levels, respiratory problems, such as nasal ulcers, runny nose, asthma, cough, shortness of breath, and skin contact can cause skin ulcers. Long-term exposure can cause damage to liver, kidney circulatory, and nerve tissues, as well as skin irritation.
Nikel (Ni)	20 µg/L	0.02-0.07 mg/L	0.02 mg/L	Allergy, cardiovascular and kidney diseases, lung fibrosis, lung and nose cancer, mitochondrial dysfunction, and oxidative stress.
Lead (Pb)	6 µg/L	<0.01 mg/L	0.01 mg/L	Impairment of body function, which can be neurological, cardiovascular, hematological, or reproductive, leads to malfunction of the central nervous system and ultimately encephalopathy and edema, which mainly affect the cerebellum.
Aluminum (Al)	200 µg/L	<0.2 mg/L	0.2 mg/L	Post-dialysis encephalopathy, neurological disorders, osteomalacia, liver accumulation, cholestasis, normo- or microcytic anemia, impaired erythropoiesis.

WHO: World Health Organization.

polyclinic in the first measurement (M1), there were 2 patients coming from the dermatology polyclinic in the fourth measurement (M4). Since there are differences in the drugs used and body reactions, it is thought that blood samples of patients who come from different polyclinics and who undergo hemogram analysis affect heavy metal contents found in water.

Statistical Analysis

The mean, median, maximum, and minimum values of each heavy metal were calculated from seven measurements. In addition, the MPL values and percentage deviation from the MPL values are shown in Table 5. SD graphs of the data are shown in Figure 2. According to these results, it is observed that Al, As, Cr, and Cd elements were below their MPL and they were not harmful to human health. On the other hand, Mn and Ni were detected above their MPLs, especially Cu, Zn, and Pb, which were much higher above their MPLs.

DISCUSSION

Because it is very difficult to obtain permission to conduct analytical research on hospital wastewater (HWW), the literature on this topic is also scarce. In their review, Verlicchi et al.[29] reported mean concentrations for different classes of compounds using all data from previous studies on HWW and urban wastewater (UWW). According to these data, average HWW concentrations were determined to be approximately 2-150 times higher than average concentrations in UWWs.[29]

In the research conducted, wastewater originating from Konya province, state hydraulic works, has been stated that it reaches Tuz Lake (Salt Lake) through irrigation channels and that heavy metal concentrations in the water cause heavy metal pollution in Tuz Lake. In this study, Heavy metals in the water were analyzed along the Konya Main Drainage Channel, and the results were evaluated seasonally.[32]

Table 2. Perkin Elmer ELAN DRC-e ICP-MS maintenance and optimization parameters

Parameter	Value, unit
ICP RF power	1300 watt (W)
Plasma gas flow	18.0 L/min
Nebulization gas flow	0.76 L/min
Omega lens	10.75 V
Auxiliary gas flow	1.40/min

ICP-MS: Inductively coupled plasma - mass spectrometer.

Within the scope of the study, 7 measurement stations were used in 2014; In a total of 28 samples taken in 4 seasons: spring, summer, autumn and winter, 20 heavy metals (silver, aluminum, arsenic, barium, chromium, copper, iron, potassium, lithium, magnesium, manganese, sodium, nickel, lead, selenium, tin, zinc boron, mercury, phosphorus) parameters were examined. When the analysis results are examined; It was determined that, in particular, arsenic, barium, chromium, copper, nickel, lead, tin, and boron parameters were at higher values in the autumn period, unlike other seasons. It was determined that heavy metal concentrations in spring, summer, and winter were generally close to each other.[32]

In a study conducted in Giresun, cadmium, arsenic, lead, nickel, and chromium metals in the wastewater of different car wash centers were determined by ICP-MS. The highest metal concentrations in the analyzed wastewater samples were; As (15.2±0.3 µg L-1), Pb (26.9±0.4 µg L-1), Ni (31.5±1.1 µg L-1) and Cr (9.8 It was determined as ±0.4 µg L-1).[33]

In a similar study, Agbere et al.[34] investigated the physicochemical properties of wastewater obtained from various laboratory equipment. According to their results, some trace element concentrations detected by atomic absorption spectrometry in the Mindray hematology analyzer wastewater were as follows; arsenic: 105.80±0.96, cadmium: 6.53±0.49, lead: 61.98±5.15, mercury: 10.63±1.17. Trace-element concentrations were found to be below WHO standards.[34]

The aim of this study is to investigate the levels of some heavy metals in the hematology analyzer wastewater, which is formed after the necessary tests are performed on the hematology analyzer with blood samples from patients who apply to different outpatient clinics due to different diseases. Since the medications used and treatments received by patients who apply to different outpatient clinics for different diseases will differ, their body metabolites and therefore the microelements found in their blood samples will also differ. According to the results, the amounts of each element differed on the day of analysis. The reason for this was thought to be the different outpatient variations of the patients compared with the hemogram, but the concentrations of trace elements released from clinical laboratory vending machines were mainly due to chemicals and test kits. The heavy metal content of the standard solutions used in the relevant devices for hematology analyses is unknown. If we look at the general picture, according to the MKS values we obtained as a result of the literature review, in the average values of 7 measurement days, Al, Cr, Cd, and As were detected below

Table 3. Average amounts of measurements (M1, M2, M3, M4, M5, M6, M7) which are measure four times in ppb (µg/L)

Element	Unit	MPL	M1	M2	M3	M4	M5	M6	M7
Al	ppb	200	129.1	117.8	1.9	361.8	0	114.8	0
V	ppb	-	0	0	0	0	0	0	0
Cr	ppb	50	40.6	33.9	26.8	31.2	27.7	24.4	21.9
Mn	ppb	20	42.9	36.8	51.3	42.2	30.6	42.5	46.5
Ni	ppb	20	141.5	102.4	106	101.4	96.9	89.8	85.6
Cu	ppb	25	3205.3	2853.5	2684	2816.1	2628.7	2655.6	2589.7
Zn	ppb	800	12900.8	12511.5	10815.4	9215.9	8438.4	7002.2	6755.9
As	ppb	50	2.42	0.87	0.15	0.95	0	0	0
Cd	ppb	5	0.2	0	0	0	0	0	0
Pb	ppb	6	223.2	205.2	197.9	209	195.3	194.2	189.3

Table 4. Polyclinics where patients who underwent hemogram tests were examined and the number of patients

Polyclinic	M1	M2	M3	M4	M5	M6	M7
Emergency medicine	6	9	11	13	7	10	9
Family medicine	4	7	5	1	7	2	3
Anesthesiology	2	1	3	4	5	2	0
Brain and nerve surgery	5	6	5	5	5	15	5
Pediatric emergency	2	3	4	5	1	3	6
Paediatric allergy	2	1	3	4	5	0	2
Pediatric surgery	3	0	3	2	3	0	2
Paediatric endocrinology	1	1	1	2	1	1	2
Pediatric infection	4	2	5	4	4	2	0
Paediatric gastroenterology	13	11	5	10	15	7	16
Paediatric cardiology	7	2	8	0	6	4	3
Paediatric nephrology	12	10	13	11	9	7	5
Pediatric neurology	6	3	5	1	5	3	2
Paediatric oncology	9	2	2	3	4	5	1
Pediatric rheumatology	4	9	6	8	17	10	7
Dermatology	26	16	5	2	8	6	13
Endocrinology and metabolism	19	21	11	11	17	16	15
Infection diseases	7	11	12	25	30	10	8
Physiotherapy	13	10	4	6	11	7	7
Gastroenterology	13	15	13	18	5	10	6
General surgery	21	5	7	11	11	15	6
Chest diseases	10	15	7	25	9	26	10
Ophthalmology	6	3	1	2	4	4	5
Hematology	14	9	18	10	10	14	9
Internal medicine	19	6	4	12	3	9	10
Gynaecology and oncology	2	2	1	0	1	1	0
Obstetrics and gynecology	28	25	28	34	26	25	21
Cardiology	16	16	11	13	11	11	6
Nephrology	10	12	10	9	9	5	7
Neurology	12	10	11	14	9	10	8
Orthopedics	13	19	15	9	10	7	11
Plastic surgery	3	2	7	2	2	2	1
Rheumatology	30	21	21	22	34	23	20
Medical oncology	17	14	20	17	13	14	12
Urology	9	6	8	3	7	7	6

Table 5. Statistical values for whole measurements

Element	Median	Min.	Max.	Mean	MPL (ppb)	(%) deviation from MPL
Al	117,825	1.9	361.85	115.69	200	↓ 32%
Cr	27,725	18.85	43.1	32.08	50	↓ 41%
Mn	37.6	26.05	73.55	39.11	20	↑ 109%
Ni	98.9	82.15	180.35	92.96	20	↑ 417%
Cu	2738.75	2519.9	3365.6	2432.23	25	↑↑ 11,000%
Zn	9319.375	4852.7	17823.15	8555.04	800	↑↑ 1,108%
As	1.1	0.1	2.9	6.80	50	↓ 2,528%
Cd	0.2	0.2	0.2	0.65	5	↓ %96%
Pb	197.35	187.45	243.05	177.52	6	↑↑ 3,267%

Min.: Minimum, max: Maximum.

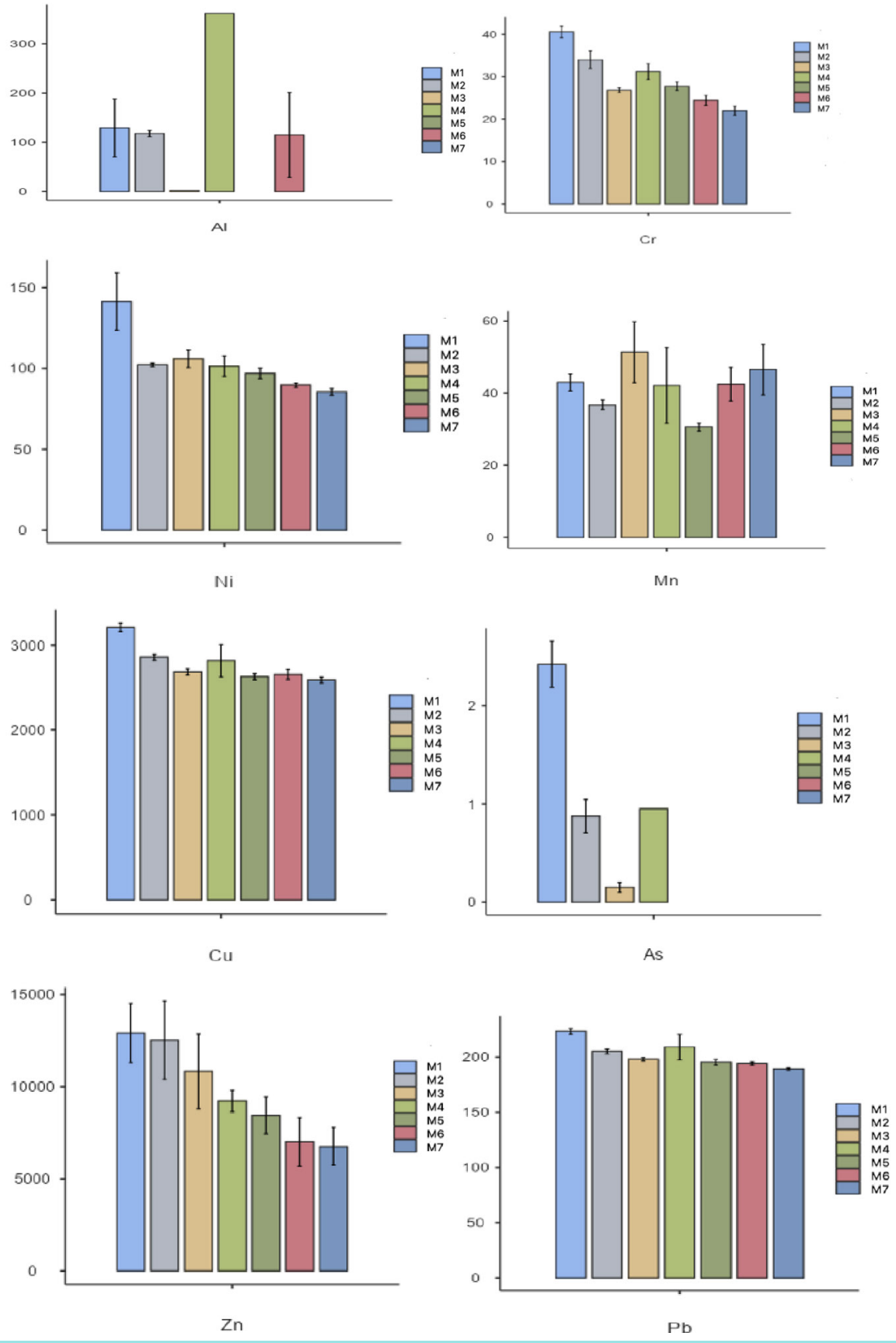

Figure 2. Standard deviation graphs of the data.

these levels, and it is estimated that they will not have a toxic effect. While Mn and Ni were detected above the MKS, Cu, Zn, and Pb were detected at values much higher than the MKS. Detection that is much higher than the MKS value poses a serious risk. In addition, heavy metal levels may change daily during analysis due to the lack of continuous mixing equipment and manual mixing before sampling. This can cause the precipitation of heavy metals. Domestic, industrial, and agricultural activities increase the concentration of heavy metals in wastewater. Heavy metals with serious toxic effects should be treated in HWW using appropriate treatment systems and then discharged. The disposal of micropollutants requires important processes, and the most appropriate process should be selected. Advanced purification processes such as activated carbon adsorption, oxidation, nanofiltration, reverse osmosis, and membrane bioreactors can provide higher and more consistent removal of micropollutant. However, regardless of the technology, the removal of micropollutants depends on the physicochemical properties and treatment conditions. Assessing the removal of micropollutants from wastewater should cover a range of aspects, from sources to end use. After the release of micropollutants, a better understanding and modeling of their fate in surface waters is essential for effectively predicting their impacts on the receiving environment.

CONCLUSION

Currently, preferred systems can be recommended for the proper disposal of HWW. It is generally known that HWW is mixed with UWW at some point. It is recommended that separate treatment plants be established to prevent micropollutants from mixing with UWW. In addition, because other physicochemical parameters such as total dissolved salts, electrical conductivity, pH, total suspended solids, and temperature are strongly related to trace elements in hematology wastes, it is important to examine these parameters in further studies. Further studies and experimental research are needed to evaluate the removal capacity of micropollutants from hemogram device wastewater and to provide information on the most technically and economically efficient methods.

MAIN POINTS

- Laboratory equipment wastewater contains heavy metals.
- Appropriate processes should be selected for wastewater treatment in hospitals.
- Exposure to heavy metals at concentrations above permissible limits is dangerous for living things.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of Selçuk University Faculty of Medicine (approval number: 2019/194, date: 26.06.2019).

Informed Consent: It wasn't obtained.

Authorship Contributions

Surgical and Medical Practices: İ.Ç., F.K., F.O., H.V., Concept: İ.Ç., F.K., F.O., H.V., Design: İ.Ç., F.K., F.O., H.V., Data Collection and/or Processing: İ.Ç., F.K., F.O., H.V., Analysis and/or Interpretation: İ.Ç., F.K., F.O., H.V., Literature Search: İ.Ç., F.K., F.O., H.V., Writing: İ.Ç., F.K., F.O., H.V.

DISCLOSURES

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

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RESEARCH ARTICLE

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Comparison of Primary Repair Techniques for MPFL Ruptures: Is Anchor Use Essential?

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Abstract

BACKGROUND/AIMS: To compare the effects of suture-anchored and unanchored repairs on clinical outcomes in primary medial patellofemoral ligament (MPFL) repair techniques.

MATERIALS AND METHODS: A total of 16 patients who underwent surgery between 2021 and 2023 were retrospectively analyzed. Postoperative assessments included range of motion, apprehension tests, pain with squatting, Tegner-Lysholm Knee Scoring Scale, Kujala Anterior Knee Pain Score, recurrence, Q Angle, Sulcus angle and Insall-Salvati Index.

RESULTS: Among the 16 patients assessed, eight patients (50%) underwent primary repair with a suture anchor, while the remaining eight patients (50%) underwent repair without a suture anchor. The range of motion of the lower extremity was symmetrical to that of the contralateral side at the last follow-up in all patients. No implant-related complications were observed in any patient. Statistical analysis showed no significant differences between the two groups regarding functional scores, physical examination findings, radiological findings, and recurrence ($p>0.05$).

CONCLUSION: Primary repair of the MPFL with or without suturing can effectively prevent the recurrence of patellar dislocation and instability and provide satisfactory clinical and radiological outcomes. Although the successful primary repair results question the necessity of anchor use, anchor use should not be avoided in primary repair cases if necessary.

Keywords: Medial patella-femoral ligament, patellar redislocation, primary repair, suture anchor

INTRODUCTION

Patellar dislocation is a relatively common injury accounting for 3.3% of all knee injuries.[1] It most commonly occurs in 2nd-3rd decades of life, and its incidence rate varies from 7 to 77 per 100,000 person-years in various studies.[2-4] After proper treatment, recurrence rates after primary dislocation can be relatively high, reaching up to 40%.[5]

The injury mechanism is usually a non-contact twisting injury with the knee extended and the foot externally rotated. Risk factors for patellar dislocation include malalignment syndrome, increased Q angle (femoral anteversion, genu valgum and external tibial torsion), patella alta, trochlear, and lateral femoral dysplasia, dysplastic vastus medialis obliquus muscle and iliotibial band, and excessive tension in the vastus lateralis. Osteochondral lesions commonly develop after patellar dislocations.[1-5]

In the treatment of patellar dislocations, conservative management is mostly preferred for initial dislocations, whereas primary repair of the medial patellofemoral ligament (MPFL) is preferred in the presence of bony fractures. On the other hand, Le et al.[6] reported that acute repair of first-time MPFL ruptures had clinical results similar to those of conservative treatment, with a lower redislocation rate.

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Two main surgical techniques have been described in MPFL repair; primary suturing with and without the use of a suture anchor. In 2008, Christiansen et al.[7] reported the results of primary MPFL repair using suture anchors. Results showed that primary repair with suture anchors did not change the redislocation rate or functional outcomes compared to conservative treatment.[7] On the other hand, to our knowledge, there is a lack of studies in the literature that compare the efficacy of the use of suture anchors (5.0 mm Excalibur Screw Anchor Titanium, Tulpar Medical Solutions®, Ankara, Türkiye) for primary MPFL repair.[8,9]

Our objective was to determine the effect of suture-anchored and unanchored repair on clinical outcomes in primary MPFL repair for patients with first-time patellar dislocations. Our hypothesis was that unless there is a clear superiority of the use of suture anchors, their use should be avoided to reduce implant burden, implant-related complications, and cost.

MATERIALS AND METHODS

Study Design and Variables

After obtaining approval from the University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (approval number: 94, date: 14.06.2023), all patients who underwent MPFL rupture surgery with a diagnosis of first-time patellar dislocation between 2021 and 2023 were included in this retrospective study. Patients who received alternative surgical methods, underwent reconstruction, were treated conservatively, failed to adhere to the prescribed physical therapy protocol, missed their final control and functional evaluation, and declined to participate in the study were excluded from the study. A total of 7 patients were excluded based on our criteria, and a total of 16 patients were analyzed while adhering to the specified inclusion and exclusion criteria.

Surgical Technique

Patients were operated according to the techniques described in the literature[6-9] and were grouped and compared accordingly; in group 1, the primary repair without a suture anchor group, the damaged MPFL was sutured with absorbable sutures, while in group 2, the suture anchor group, repair was performed with the help of a suture anchor (5.0 mm Excalibur Screw Anchor Titanium, Tulpar Medical Solutions®, Ankara, Türkiye) placed on the medial aspect of the patella. All surgeries were conducted by the same surgical team with similar incision lengths, and intraoperative examinations performed after primary repair of the patella were not required. Regardless of the surgical technique used, all patients underwent the same postoperative medical and physical therapy protocols.

Functional Outcomes

All patients were called to our clinic in August 2023 using the information registered in the system, and postoperative final control evaluations were completed. Assessments consisted of measurements of range of motion, apprehension tests, and existence of pain with squatting, as well as evaluations of the Tegner-Lysholm Knee Scoring Scale, Kujala Anterior Knee Pain Score, and recurrence. The Tegner-Lysholm Knee Scoring Scale is a numerical patient-reported assessment tool used to assess the outcomes of knee ligament surgery. This scale provides an objective evaluation of a patient's performance in activities of daily living and sport, under the subheadings of pain, instability, locking, swelling, limp, stair climbing, squatting, and the need for support, with scores ranging from 0 (severe disability) to 100 (minimal disability).[10] The Turkish validated version of the Kujala Anterior Knee Pain Score, which consisted of 13 questions, evaluated patients' patellofemoral function and knee stability, with scores ranging from 0 to 100.[11,12]

Radiological Outcomes

Preoperative and final control radiographs were obtained for all patients, and radiological measurements were performed on these radiographs. The Q angle, Sulcus Angle, and Insall-Salvati Index values were measured according to the literature. To determine the Q angle, we drew two lines: One from the center of the patella to the anterior superior iliac spine and another from the tibial tubercle through the center of the patella. We then measured the angle between them. The Insall-Salvati index compares the length of the patellar tendon with that of the patella. We measured the patellar tendon length as the distance between the lower patellar pole and the tuberosita tibia, while the patella length was measured as the distance between the upper and lower patellar poles. Additionally, the sulcus angle was determined by drawing two lines from the highest points of the medial and lateral condyles, which meet at the lowest point of the intercondylar groove.[10,13,14]

Statistical Analysis

Statistical analysis was performed using IBM® SPSS® version 26.0.0.0. 7. Because the number of patients is very limited, the data was assumed to be skewed distributed, and descriptive statistics were expressed using median, interquartile range and minimum-maximum values for all parameters. The percentage frequency values were used to define categorical data. For intergroup comparisons, non-parametric tests were preferred considering the skewed distribution and limited number of patients; and all numerical data were analyzed by Mann-Whitney U test, and categorical data were compared using the chi-square test. Fisher's exact test was used when the chi-square assumption was not met. Statistical significance was considered significant when the "p" value was below 0.05.

RESULTS

A total of 16 patients were analyzed, and of the 16 patients assessed, eight patients (50%) underwent primary repair with a suture anchor, while the remaining eight patients (50%) underwent repair without a suture anchor. The mean follow-up period was 16.7 months (range; 8-25 months). Statistical analysis showed no significant difference between the two groups regarding demographic characteristics ($p>0.05$) (Table 1).

The range of motion of the lower extremity was symmetrical to that of the contralateral side at the last follow-up in all patients. No implant-related complications were observed in any patient. In the primary repair group without suture anchors, only one patient (12.5%) experienced recurrent dislocation, whereas no recurrence was observed in any patient repaired with anchor ($p=0.317$). Functional scores and physical examination findings at the last follow-up did not significantly differ between the groups ($p>0.05$) (Table 2, Figure 1).

DISCUSSION

There is no consensus in the literature regarding the treatment of acute first-time patellar dislocation (APD). Various studies have emphasized the superiority of conservative treatment, MPFL primary repair and

Table 1. Demographic profile of the patients

		Primary repair (n=8)	Anchor repair, (n=8)	Total, (n=16)	p
Age		16.5 (18) (13-37)	14 (5) (9-23)	15 (5) (9-37)	0.234
Gender	Female	2 (25%)	5 (62.5%)	7 (43.8%)	0.315
	Male	6 (75%)	3 (37.5%)	9 (56.3%)	
Side	Right	3 (37.5%)	3 (37.5%)	6 (37.5%)	1,000
	Left	5 (62.5%)	5 (62.5%)	10 (62.5%)	
Follow-up period (month)		18.5 (3) (8-25)	14 (8) (10-22)	18 (8) (8-25)	0.130

N: number of the patients. P: statistical significance.

Table 2. Analyzing functional and radiological outcomes of the patients

		Primary repair, (n=8)	Anchor repair, (n=8)	Total, (n=16)	p
Range of motion	Symmetrical	8 (100%)	8 (100%)	16 (100%)	N/A
	Defective	0	0	0	
Apprehension test	Negative	7 (87.5%)	7 (87.5%)	14 (87.5%)	1,000
	Positive	1 (12.5%)	1 (12.5%)	2 (12.5%)	
Pain with squat	None	4 (50%)	6 (75%)	10 (62.5%)	0.608
	Yes	4 (50%)	2 (25%)	6 (37.5%)	
Recurrence	None	7 (87.5%)	8 (100%)	15 (93.8%)	0.317
	Yes	1 (12.5%)	0	1 (6.3%)	
The Tegner-Lysholm Knee Scoring Scale		70.5 (10) (41-82)	70.5 (56) (10-92)	70.5 (30) (10-92)	0.958
Kujala Anterior Knee Pain Score		85.5 (20) (106-140)	76 (29) (56-99)	80.5 (31) (45-100)	0.574
Q angle		8° (5) (6-14)	11° (3) (7-14)	9.5° (5) (6-14)	0.130
Sulcus angle		120° (20) (106-140)	120° (3) (113-134)	120° (15) (106-140)	0.798
Insall-Salvati Index		1.25 (0.3) (0.9-1.6)	1.25 (0.5) (0.6-1.6)	1.25 (0.4) (0.6-1.6)	0.645

N: Number of the patients. P: Statistical significance value. N/A: Not applicable.

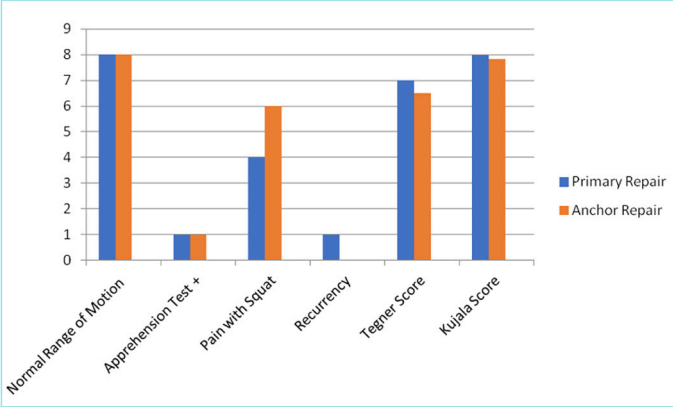

Figure 1. Graphical comparison of the functional and clinical outcomes of two techniques.

reconstruction on each other.[6-9] On the other hand, few studies have investigated the superiority of different primary repair techniques over one another. This is the most important aspect of our study. Our hypothesis was that unless a clear superiority of anchor use is established, avoiding its use will reduce implant burden, implant-related complications, and cost. The main finding of this study was that we confirmed that primary repair of MPFL achieved satisfactory results in terms of clinical, functional, and radiological outcomes, regardless of anchor use (p>0.05 for each).

Available evidence indicates that surgery is more effective than conservative treatment in reducing short-term recurrence. However, surgery is associated with worse functional outcomes in the short term. However, it appears that neither treatment maintained long-term superiority.[8,14] Moreover, previous studies have reported that MPFL reconstruction may result in significantly lower rates of redislocation and reoperation compared with primary repair and medial reefing following APD.[15] On the contrary, there was insufficient evidence to suggest that MPFL reconstruction yielded enhanced functional outcomes compared with MPFL repair and medial reefing.[6-9,14,15] With this study, with an average follow-up period of 18 months, we observed notable ameliorations in the motion range, Tegner-Lysholm Scale score, and Kujala anterior knee pain score after primary MPFL repair, with no difference between groups (p>0.05 for each). Furthermore,

no significant difference was detected in relation to recurrence among the groups (p=0.317). The similar clinical and functional results and recurrence rates in patients with anchors and those without anchors led us to question the necessity of suture anchors. As long as similar clinical and functional results are obtained, avoiding the use of implants as much as possible can prevent unnecessary implant load in patients and prevent future implant-related complications. Moreover, although an economic analysis was not performed in this study, it is obvious that not using implants is more cost effective.

Measurements of the Q angle and sulcus angle are powerful diagnostic tools for evaluating patellofemoral issues, particularly in cases of patellar instability and patellofemoral problems.[10,13,14] Additionally, patellar height plays a crucial role in knee stability, and height-related pathologies have been associated with cartilage defects and instability-related issues.[17] The Insall-Salvati Index is the most reliable method for assessing patellar height.[17] Our study evaluated the radiological stability of patients using these three parameters, and no differences were observed between the groups (p>0.05 for each). These findings indicate that the use of suture anchors for primary MPFL repair does not provide any radiological advantages. The similar radiological results and the absence of clinical and functional superiority of the use of suture anchors in primary MPFL repair, as mentioned before, lead us to question the necessity of suture anchor use in primary MPFL repair once again.

Study Limitations

There are several limitations in our study. First and foremost, the retrospective design and the limited number of patients are important limitations. Second, given the limited number of patients, it was not possible for us to conduct subgroup analysis according to age. Furthermore, the relatively short follow-up period]18 months (minimum of 8 months)] was another important limitation in our study. Finally, the lack of economic analysis is a significant limitation. Prospective studies with long-term follow-up and sufficient numbers of patients, including radiological and economic analyses, may yield different results.

CONCLUSION

This study demonstrated that primary repair of the MPFL with or without suturing anchors can effectively prevent the recurrence of patellar dislocation and instability after first-time APD and provide satisfactory clinical outcomes. Although the successful primary repair results question the necessity of anchor use, anchor use should not be avoided in primary repair cases if necessary.

MAIN POINTS

- Primary repair of MPFL achieves satisfactory clinical and functional outcomes, regardless of the anchor use.
- Primary repair of the MPFL with or without the use of a suture anchor can effectively prevent the recurrence of patellar dislocation and instability during mid-term follow-up.
- Considering that similar clinical, functional, and radiological results can be obtained, avoiding the use of implants as much as possible can both prevent unnecessary implant load in patients and prevent future implant-related complications.

ETHICS

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (approval number: 94, date: 14.06.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: O.G., H.E., T.A., Concept: O.G., B.G., S.E.İ., H.E., T.A., Design: O.G., B.G., S.E.İ., H.E., T.A., Data Collection and/or Processing: O.G., B.G., S.E.İ., H.E., T.A., Analysis and/or Interpretation: O.G., B.G., S.E.İ., H.E., T.A., Literature Search: B.G., S.E.İ., T.A., Writing: O.G., B.G., S.E.İ., H.E.

DISCLOSURES

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RESEARCH ARTICLE

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Internet Addiction of School-Age Children and the Effects of Daily Habits

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Abstract

BACKGROUND/AIMS: Internet use among school-age children has increased, and the age at first contact with a mobile device has decreased. Although the elucidation of the risks and health problems due to excessive internet usage by parents and health professionals has led to children developing a perspective on and normalized the comprehension of classes that are accessed through the internet at home. All previous studies focused only on limited age groups, such as preschool, adolescents, and adults (university students).

MATERIALS AND METHODS: This study was conducted at a tertiary research hospital in April-October 2019 with the participation of parents of 320 children who were given a questionnaire in addition to the Young Internet Addiction Test-Short Form.

RESULTS: The data revealed that 33% of children had first contact with mobile devices between the age of 5 and 9. It was found that 18.4% of respondents had problematic internet use and 7.2% had internet addiction. Moreover, while 26% of the children postponed toilet use while engaged with mobile devices, 6% experienced digestion problems, 31% encountered eye-related complaints, 6% had urinary problems, and 22% had musculoskeletal problems due to internet usage. When parents considered their children's daily self-hygiene or self-needs, 11% indicated that their children tended to postpone these issues significantly in terms of IA.

CONCLUSION: To the best of our knowledge, this study is the first to include a school-age population aged 7-18 years. Therefore, our objective was not only to research the sociodemographic features, the duration spent on the virtual environment, the frequency and type of virtual media use, but also to evaluate the current situation of IA among children, raising awareness due to the health and security risks that IA may cause and to highlight the prevention of those risks, Internet usage must be examined on healthy child visits to identify the effects on children's and adolescents' physical and mental health.

Keywords: Children, game addiction, internet addiction, social media, self-care

INTRODUCTION

The virtual environment has gradually become widespread due to tablet use in schools as the age of children who have access to mobile devices decreases. It is considered that internet use causes physical, sentimental, material, and sexual abuse, especially due to inappropriate content, and causes postponement in sleep and toilet use as well as self-care routines in addition to affecting eating habits, social activities, eye-related health, and musculoskeletal health in children's lives.[1] Not only is the body mass index (BMI) affected, but daily activities are also lessened as habits of snacking in front of the monitors develop, and the risk of obesity due to exposure to food advertisements increases accordingly.[2,3]

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In sleep, the brain engages new ideas and sustains their permanent existence in memory. The common use of portable electronic devices and lack of sleep due to placing monitors in children's bedrooms has appeared to affect 30% of children aged between 1 and 3 years and most school-age children and adolescents in the United States.[4] It is known that 72% of the population is an active internet user and spends approximately 7 hours and 15 minutes on the internet daily, with 2 hours and 46 minutes on social media through a device such as a mobile phone/tablet, etc.[5]

Game addiction, on the other hand, is identified as an attached behavior that draws attention when gaming is prioritized and could cause traumatic indications in the absence of gaming in ICD-11. It is also classified as slight, medium, and heavy in case it lasts for a year depending on its effects on daily life.[6] At the latest status of the world due to the COVID-19 pandemic, children have developed a perspective on and normalized the comprehension of classes that are accessed through the internet at home. Although the elucidation of the risks and health problems due to excessive internet usage by parents and health professionals is crucial, unfortunately, there are major efficiencies in the pediatric literature on this topic. All previous studies have focused only on a limited age group, such as preschool or adolescents, and even have focused on the adult group (university students) over the age of 18. In addition, only one study mentioned problems related to internet addiction. All studies regarding IA have focused on adolescents and university-age young adults, and no similar study is not found concentrating on children aged 7-18 years.[7-9] Therefore, to raise awareness of the health and security risks that IA may cause and highlight the prevention of those risks, our objective was not only to research the sociodemographic features, the duration spent on the virtual environment, the frequency and type of virtual media use, including the effects on children aged 7-18 years but also to evaluate the current situation of IA among children.

MATERIALS AND METHODS

Voluntarily applied at a tertiary research hospital between April and October 2019, 320 parents of children— of whom made their applications with the company of one or both parents—are included within the study based on the approval of the ethical boards. This study was approved by the University of Health Sciences Türkiye, Ankara Children's Hematology Oncology Training and Research Hospital Clinical Research Ethics Committee (approval number: 2019-078). Informed consent was obtained. Following the literature scan, the attendants conducted a face-to-face interview technique, which was supported by a 63-step questionnaire with multiple choices and questions about how internet use is actualized.[4,10,11] In the first part of the questionnaire, the socio-demographic features, educational level of the family, level of income, employment status of the parents, ages at first contact with mobile devices, technological means of the attendants, social media use features and contents of the shares of children, internet usage and features, and the level of knowledge of the parents regarding the risks of internet use were observed. In the second part, the problems they encountered due to the internet and their reactions, the effects of internet use on toilet-use routine, eating habits, musculoskeletal problems, deprivation symptoms and characteristics (if any), sleep orders and duration, the effects of internet use on sleep disorders, eye-related problems due to internet use, weight perceptions, academic success, social activities and relations, and the effects of internet use on daily hygiene activities and self-care routine were observed. Finally, a 12-question Young Internet Addiction Test—Short Form (YIAT-SF) was applied to identify the internet addiction level by summing the total points at the end of the test to score the level. Ones who had a total score of below 30 were classified among "normal internet use," while the ones between 30 and 37 were classified among "problematic internet use" whereas values above 37 were classified among "internet addiction" levels.[10,12] This study did not include any person who was not a volunteer, was below 7 years old and above 18 years old, had neuromotor or growth retardation, was visually or hearing impaired, or had any chronic illnesses.

Statistical Analysis

Throughout the statistical analysis, descriptive features of the variables were identified and checked for normality. In the comparison of the two groups, the Student's t-test was used for normally distributed numeric variables, whereas the Mann-Whitney U test was used for non-normally distributed numeric variables. In cases in which more than two variables were compared, ANOVA was conducted on normally distributed variables, and the Kruskal-Wallis test was conducted on non-normally distributed variables. The chi-square test was used to evaluate categorical variables. The analysis was completed using the SPSS 20 software, and $p<0.05$ was considered significant.

RESULTS

The children in our study were 53% girls and 48% boys. The age average was remarked as 12 ± 3.2 and 36.6% of the children continued in primary school, 30% in secondary school, and 33.1% in high school. We classified the participants according to age groups; three groups: primary school (age 7-10), middle school (age 11-14) and high school (age 15-18) to understand their different habits and attitudes according to age. 36.6% of the children continued to primary school, 30% in secondary school, and 33.1% in high school. There was no statistical significance regarding age.

According to the YIAT-SF test, the data showed that 74.4%, 238 of the children had normal internet use; 18.4%, 59, had problematic internet use; and 7.2%, 23, had internet addiction. In other words, 25.6% of children, that is every one child in four, have either problematic internet use or IA.

87.4% of families had a low monthly income. The academic levels, employment status, and family incomes of the participating families are summarized in Table 1. A significant relationship was not found between educational levels, employment status, parental income, and IA ($p>0.05$). The results indicated that 33% of the children had their first contact with mobile devices at ages varying between 5 and 9 years, and a significant relationship was found between the age at first contact and IA ($p<0.001$). The results indicate that 81% of the participants had internet connections at home and 53% had social media accounts. A significant relationship was observed between YouTube accounts and IA was present ($p<0.001$). Participating children had not made any shares by 38% (n=114), shared photographs [14% (n=41)], videos [11% (n=34)], or other posts [4% (n=12)]. A significant relationship was found between the frequency of posting through social media accounts, sharing videos and IA was found ($p<0.001$). Internet usage and sharing features of school-age children are indicated in Table 2.

There was a significant relationship between having a mobile phone or tablet for their own home and Internet access at home and IA ($p<0.05$).

Table 1. The academic levels, employment status, and family incomes of the participating families			
Educational status of the participating parent			
	Illiterate	1	0.4%
	Literate	3	1.3%
	Primary education	33	13.9%
	Secondary school education	38	16%
	High school	73	30.7%
	University undergraduate	68	28.6%
	University	22	9.2%
Employment status of the participating parent			
	Employed	126	52.9%
	Unemployed	112	47.1%
Other parent's educational status			
	Illiterate	2	0.8%
	Literate	2	0.8%
	Primary school	44	18.5%
	Secondary school	38	16%
	High school	54	22.7%
	University undergraduate	77	32.4%
	University	21	8.8%
The other parent's employment status			
	Employed	184	77.3%
	Unemployed	54	22.7%
Monthly average income ($)			
	Low	104	43.7%
	Middle	107	44.9%
	High	27	11.3%

Table 2. Internet usage and sharing of school-age features		
The place of internet connection:	**Number**	**Percentage**
Home	204	85.70%
Internet cafe	3	1.30%
Cafe/mall/restaurant etc.	6	2.50%
Visit	11	4.60%
Other	28	11.80%
Use of computer, tablet and internet without permission:		
Yes	97	40.70%
No	141	59.20%
Use of internet outside of house:		
Yes	103	43.30%
No	135	56.70%
If the answer is yes; where?		
Home visit	55	23.10%
Internet cafe	6	2.50%
Shopping	22	9.20%
School	41	17.20%
Other	39	16.40%

Table 2. Continued		
The place of internet connection:	**Number**	**Percentage**
The device connected to the internet		
His/her own computer	23	9.70%
His/her own laptop	27	11.30%
Smart TV	25	10.50%
Family computer	13	5.50%
Family laptop	31	13.00%
Tablet	75	31.50%
Game console (playstation, X-box etc.)	14	5.90%
Phone	187	78.60%
Accompanying the child while using the internet:		
Yes	189	79.40%
No	49	20.60%
Location of the device connected to the internet:		
Hall	121	50.80%
Living room	47	19.70%
Bedroom	7	2.90%
Child's room	31	13.00%
Other	32	13.40%
Child protection program on the device		
Yes	103	43.30%
No	106	44.50%
Age of first connection to the internet:		
Within the first 1 year	3	1.30%
2nd age	1	0.40%
Between 2-5 years	31	13.00%
In Kindergarden	14	5.90%
Primary school	145	60.90%
Secondary school	38	16.00%
High school	6	2.50%
The time the child spends on a mobile device during the day:		
Less than 1 hour	82	34.50%
1 hour	43	18.10%
2 hours	54	22.70%
3 hours	33	13.90%
4 hours and more	26	10.90%
The time the child spends on a mobile device during the night:		
Less than 1 hour	172	72.30%
1 hour	43	18.10%
2 hours	15	6.30%
3 hours	4	1.70%
4 hours and more	4	1.70%
The aim of internet connection:		
Making homework and studying	180	75.60%
Watching videos	159	66.80%
Playing games	135	56.70%
Chatting (WhatsApp, messenger etc.	73	30.70%
Visiting social networking site	35	14.70%
Sending mails	7	2.90%

Table 2. Continued		
The place of internet connection:	**Number**	**Percentage**
Setting up an information program to the link in the e-mail	4	1.70%
Sending SMS	13	5.50%
Downloading or watching music or movies	98	41.20%
Shopping	16	6.70%
Using credit card information	4	1.70%
Sharing address and phone information	1	0.40%
Sharing own photos	29	12.20%
Posting a photo that is not his/her own	5	2.10%
Meeting and talking with the chatted people outside	9	3.80%
Sharing game or social media account passwords with friends	9	3.80%
Sharing a special family situation	2	0.80%
Other	6	2.50%
Her/his gamefriends from internet:		
Alone	135	56.70%
Friends	118	49.60%
Siblings	21	8.80%
Online game players	11	4.60%
Unknown	15	6.30%

On the other hand, a significant relationship was found between children using the internet without permission and sharing information at places other than home ($p<0.05$) and internet use duration ($p<0.001$). Additionally, a significant relationship was found between connecting to the internet for playing games, sharing credit card information, self-images, game and social account passwords, sharing the private status of the family, address and phone information, and IA ($p<0.001$).

It was found that 40% of the parents had not guided their children on what to do when they encountered a serious problem on the internet. The questionnaire indicated a significant relationship between advertisement exposure, encountering a negative situation online ($p<0.001$), and IA ($p<0.05$). Furthermore, there was a significant relationship between exposure to inappropriate content, gossiping, and humiliation, and IA ($p<0.05$). In addition, 7 children were abused, 5 were financially damaged, 3 were emotionally abused, and one was sexually harassed. The children shared the negative situation or asked for help from an older brother, sister, or friend, which was significant for IA ($p<0.05$). Making friends over the internet and IA were also related ($p<0.001$).

When parents were questioned regarding their perception of weight, 68.1% (n=162) stated as normal, 16.8% (n=40) as overweight, and 15.1% (n=36) as slim. When children's height and weight were evaluated according to the percentile by age; it was classified that 35.9% (n=115) were slim, 55% (n=176) were normal, 5.9% (n=19) were overweight/pre-obese, and 3.1% (n=10) were obese. Hence, BMI calculations were not significantly related to IA ($p>0.05$). However, there was a significant relationship between junk food consumption during internet use and IA ($p<0.001$).

Moreover, 26% of the parents reported that their children postponed toilet use when occupied by mobile devices, while 8% reported digestive problems. Depending on internet use, 31% of the children experienced eye-related problems, such as eye inflammation, burning, and pain, and these problems were significantly related to IA ($p<0.001$). According to the answer of the parents, 11% of the children tended to postpone their daily hygiene/self-care routines and 6% experienced urinary problems. A crucially significant relationship between postponing toilet use and digestive problems while using mobile devices and IA was found ($p<0.001$). Moreover, a significant relationship was found between urinary incontinence while using mobile devices and IA ($p<0.05$).

It was found that low academic success of the child, encountering problems in social relationships due to the internet, a tendency to postpone social activities due to the internet, and encountering problems among family members, school friends, and other people were significantly related to IA ($p<0.001$). Also, it was found that 46% of children were bored, 12% were upset, 11% were upset, 10% were anxious, 5% felt lonely, and 4% behaved aggressively in the absence of mobile devices. This study revealed a significant relationship between deprivation symptoms and IA ($p<0.001$).

22% of the parents indicated that their children had musculoskeletal problems following the use of the internet, which affected their sleep routines ($p<0.001$). The effects of internet use on daily activities, the eye and musculoskeletal systems, and sleep orders are summarized in Table 3.

DISCUSSION

Our study aims to raise awareness regarding the risks of using the internet and possible health problems among school-age children. There are major deficiencies in the pediatric literature regarding this issue. Studies previously conducted were focused only on limited age groups, such as preschool or adolescent, or on the adult group (university students) over the age of 18. In addition, only one study mentioned problems related to internet addiction. In this context, our study is the most comprehensive in this regard.

When the internet usage habits of the study volunteers were analyzed in terms of IA, it was found that 25.6% of the participating children had problematic use of the internet or internet addiction, as in every one child in four. Similar findings were reported in a similar study of adolescents.[1] When assessing the ages of children regarding their first contact with a mobile device, 16% interacted with a mobile device at age 1. Similar results were obtained for children younger than 7 years old.[7,13] Research has indicated the positive effects of dialog on language skills; however, internet users depend on passive listening or unidirectional interaction through a monitor.[14] Therefore, experts do not recommend interaction with mobile devices until a child is one year old. Similar to the literature, our study indicated that the younger the children interacted with the mobile phone, the higher their risk of IA.[7] It was found that 68% of the participating children had a mobile phone of their own, 78% had Internet access at home, and 50% had a personal social media account. IA was very common among these children. A study indicated that one in every three children has a smartphone, and 24% of those are online constantly.[13] Moreover, another study suggested that the exposure of social media users in adolescence is highly triggered to be depressed by the idealized images of higher-standard possessing young adults; moreover, they develop less self-respect in a period when their self-confidence is still improving and cause negative body perception.[15] Deprivation symptoms enlisted within the diagnostic criteria of IA, were also questioned in the questionnaire. In addition,

Table 3. The effects of internet use on daily activities, the eye and musculoskeletal systems, and sleep orders		
Child's self-perception of his/her body:		
Underweight	36	15%
Normal	162	68%
Overweight	40	17%
Academic success of the child:		
Weak	2	1%
Average	29	12%
Good	99	42%
Very good	108	45%
Social problems the child experienced due to the internet:		
Yes	16	7%
No	222	93%
People that the child had problems with due to the internet:		
Family members (mother, father, brother, sister etc.)	21	9%
School friends	8	3%
Not having problems	1	0%
Other	209	88%
Postponing social activities via the internet:		
Yes	21	9%
No	217	91%
Postponing active sports activities due to the internet:		
Yes	50	21%
No	209	88%
Daily active sports time of the child:		
Less than 1 hour	97	41%
1-2 hours	113	48%
2-3 hours	18	8%
3-4 hours	4	2%
4 hours or more	6	3%
Postponing toilet necessities due to internet access:		
Yes	90	30%
No	207	70%
Digestion problems that the child experienced due to the internet:		
Yes	33	11%
No	264	89%
The type of digestion problem:		
Constipation	13	6%
Gas	4	2%
Fecal incontinence	5	3%
Other	7	3%
Urinary problems caused by mobile devices and internet use:		
Yes	14	6%
No	224	94%
The type of urinary problem:		
Urinary retention	11	5%
Urinary incontinence	4	2%
Urinary tract infection	4	2%
Not having complained	1	0%
Child's self-perception of his/her body:		
Eye-related complaints based on mobile device and internet use:		
Yes	74	31%
Not having complained	164	69%
Eye-related complaints following internet use:		
Tearing	16	7%
Blushing	37	16%
Burning	20	8%
Pain	17	7%
Eyeglasses:		
Yes	56	24%
No	182	77%
Musculoskeletal problems following internet use:		
Yes	53	22%
No	185	78%
Musculoskeletal problems experienced by the child:		
Headache	30	13%
Neck pain	25	11%
Back pain	21	9%
Shoulder pain	8	3%
Arm pain	4	2%
Wrist pain	11	5%
The feelings of the child when not using a mobile device:		
Unhappiness	27	11%
Loneliness	12	5%
Tension	24	10%
Anxiety	28	12%
Aggression	10	4%
Boredom	110	46%
The effect of internet use on sleep patterns:		
Yes	72	30%
No	166	70%
The child's daily sleeping time:		
Under 6 hours	11	5%
7-8 hours	150	63%
Over 9 hours	77	32%

individuals experiencing problems with family members or other people surrounding them and postponing daily sports activities due to long-duration internet use were affected at high levels, and this infinite loop continues as long as internet use is maintained.

Currently, posts including advertisements can be seen very intensely on YouTube and similar social media platforms. Most advertising companies assist brands with marketing purposes by targeting social media users. The food sector conducts its advertisements and marketing strategies for young adults using social media. In a period when healthy and proper dietary habits are achieved, posts regarding unhealthy junk food and fast food adversely affect children's dietary habits adversely. Among the participants, 81% indicated that they have been exposed to advertisements while using the internet, 11% skip meals, 35% eat

while using the Internet, and 60% consume junk food. There has been a significant relationship between meal skipping, eating while using the internet, consuming junk food, and IA. In a previously conducted study on adolescents in our country, significant relationships were found among IA, eating habits, BMI, and obesity.[1] Our study, on the other hand, did not indicate this relationship between obesity and IA; and this may be because fewer obese patients were found in general pediatric outpatient clinics since obese patients in particular apply directly to endocrine polyclinics.

Among children, 47% had a YouTube account, 67% watched videos, 23% shared content through social media once a month, and 14% shared videos. A crucially significant relation was found between video watching, having a YouTube account, and sharing videos with the IA. A similar study conducted over 9 to 19 years researched internet activity risks and parental behaviors that can cause IA risks.[16] Children in the developmental period are highly affected by comments and likes and think they are accepted by society through these. This directs them to connect to the internet outside their houses and share content during visits, malls, etc. without asking for permission. Our study indicated a significant relation between frequency and increase in sharing and IA. Studies conducted also suggest that shares cause stimulation at the pleasure centers on the brain through the number of likes, especially during adolescence, and lead individuals to develop an addiction through directing the individual to share more, which was likewise the case in our study.[17]

Peer victimization can be identified as intentional harming and mobbing the powerless in terms of physical, verbal or psychological levels. However, peer victimization at schools has surrendered to cyber mobbing.[18] Cyber mobbing is emerging as one of the most dangerous features of our times because bullies can camouflage their identities. Our study indicates that 14% of the participants have a virtual friend, and this situation is significantly related to IA. Although virtually adopted friends provide socialization for children, on the one hand, it can allow individuals to open up for abuse on the other hand. Each parent has been informed regarding the abuse to which they were exposed. The literature requires additional studies in this area. Media literacy lessons should be adapted to the syllabus to teach children what behavior can be comprehended as a crime and which actions to take when encountering a sort of abuse; informative public service announcements should be published on TV and social media to contribute to raising awareness. Experimental studies have indicated that video games decrease children's public behaviors and benevolence, but increase violence and aggressive thoughts.[19] When exposed to violence on TV, a child watches it only; however, on video games, the child participates in the violence. In this context, rather than TV, the internet, media, and video games affect children's physical and mental health more adversely.[19] Moreover, 6.7% of the participants stated exposure to inappropriate content. As with TV, some signings that define the appropriate audience regarding the content of the published material as well as publishing the objectionable content at hours, when most children are expected to be sleeping, can prevent this; if a child-protection program is not set up on a mobile device, this cannot be prevented. As 43% of the participants had set a child-protection program on their mobile devices, 29% of the parents were observed not to have any idea about this. To raise public awareness, training should be provided, media literacy should be added to the syllabus, TV programs should be prepared for parent awareness and educational public service advertisements should be developed.

Studies by experts indicate that environmental stimuli should be reduced and a dark and peaceful environment should be prepared for children to sleep well in high quality. Reading, sleeping friends, and sleeping routines are recommended, but dynamic activities, food, and visual stimuli are not recommended.[4] In studies on sleep physiology, it has been determined that melatonin is a hormone released by the pineal gland that provides circadian rhythm. Through melatonin release, during the sleep cycle, the release of anterior hypophysial hormones, such as prolactin, thyroid-stimulating hormone, sex steroids, and growth hormones, are regulated.[20] Exposure to light causes delayed and decreased melatonin release, thereby affecting anterior hypophysial hormone levels in the blood. This condition has effects not only on cognitive functions such as language development but also on growth and development and causes low academic achievement due to drowsiness during the daytime.[1,20] Similarly, our study suggests that 30% of the parent's sleep patterns of their children are affected by internet use, and a significant relationship was found with IA. The recommendations for digital media and sleep quality are frequently mentioned in the American Academy of Pediatrics protocols developed before or during sleep.[21] Likewise, long exposure to monitors, the flash-blue may cause dry eye and redness; long video-watching periods cause lazy eyes because the individual is affected by exciting graphics.[22,23] 31% of the participants are seen to experience eye-related complaints similar in literature, and a significant relationship is found with IA.

Repetitive game-playing actions enlisted within the internet and game addiction diagnosis criteria harm the time that an individual spends on their affairs and increase the duration of internet use. Therefore, daily hygiene, self-care, toilet use, and sports activities are limited because the child is never satisfied by the time that is spent.[1] It was found that 26% of children postponed their toilet activities due to IA. Changes in bowel habits, the consequence of this issue, cause digestive problems in 8% of children, mostly with obstruction. Similarly, 6% of children are found to be experiencing urinary continence and incontinence problems. A significant relationship was found between IA use and delayed toilet use. Literature has not concentrated on this issue, as only one study has been conducted in our country. Our study is a type of secondary work in these terms, in which the findings of the two works have similarities that support each other.[1]

Looking toward a monitor or touching the keys for a long time are among the mere physical activities while an individual is on the internet or playing video games. Therefore, musculoskeletal problems are likely to occur. Japan and the United States take ergonomic measures for long-duration employees working at desks in front of a computer.[24] Computer applications automatically go to sleep more for 20 seconds every 20 minutes and allow users to relax their eyes; as mouse-pad pillows are used to prevent wrist and back pain. In addition, employees are allowed to benefit from fitness saloons or massage units within their offices.[25] The participating children experienced musculoskeletal problems by 22%, and a significant relationship was found with the IA. Some studies have reported similar findings.[20] The monitor should be placed 30 or 45 centigrade below the child's eye: which would enable protection for spinal health.[11] The monitor can be easily positioned where applicable cover cases are sold for tablets and phones. Ergonomic measures should be taken by parents at home. Additionally, children should participate in physical activity for at least an hour daily to support muscle development as well as regular pauses for long periods of computer use. AAP recommends that computer use for longer than 2 hours may cause risks of obesity and IA.

IA is a severe problem that is gradually increasing among school-age children, and the risks should be acknowledged by the public. Families, teachers, and adolescents should be aware of the positive and negative effects of social media devices. Families and teachers encourage students to share problems they may experience offline and online.[2] When encountering children who have intense media interaction, appropriate measures should be taken while considering possible problems. The results of this study suggest that children who spend a lot of time on the internet are at increased risk of secondary disabilities. Health applicators, teachers, and parents are accountable for taking necessary actions that would jeopardize children's health while providing Internet access.

CONCLUSION

The IA must be interrogated while evaluating its effects on the physical and mental health of children and adolescents. Primary care physicians, nurses, psychologists, pediatricians, and child and adolescent psychiatrists should provide training for the correct use of the internet and pioneer the dissemination of protective measures. IA diagnostic criteria should be explained children, families, and teachers to increase awareness. Guidelines, which include information on how mobile media equipment is to be used, should be developed accordingly.

MAIN POINTS

- Our study is the most comprehensive research on internet addiction and its effect on daily habits that focused on a wide age range.
- The risk of internet addiction increases with screen exposure, particularly at a younger age, especially under the age of 1. Our study indicated that the younger the children interacted with the mobile phone, the higher their risk of IA.
- Starting to be exposed to screens at a younger age causes an increase in internet addiction and unhealthy eating behaviors, neglect of daily self-care, sedentary life, and related health problems in later ages.
- There is a need for guides containing information on how families' mobile media devices can be used by children. General practitioners, nurses and psychologists, child health and disease specialists and child and adolescent psychiatrists should provide training on the correct use of the media, inform families and young people and lead media education .
- Physicians should be aware of the impact of media on the physical and mental health of children and adolescents, and their relationship with the media should be questioned during follow-up examinations of children.

ETHICS

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, Ankara Children's Hematology Oncology Training and Research Hospital Clinical Research Ethics Committee (approval number: 2019-078).

Informed Consent: It was obtained.

Authorship Contributions

Surgical and Medical Practices: S.O., Ş.Ş., M.A., E.A.A., M.M.O., H.Y., E.P., Concept: S.O., Ş.Ş., M.A., E.A.A., M.M.O., H.Y., E.P., F.Z.Ö.Ç., S.Ş., Design: S.O., Ş.Ş., M.A., E.A.A., M.M.O., H.Y., E.P., F.Z.Ö.Ç., S.Ş., Data Collection and/or Processing: S.O., Ş.Ş., M.A., E.A.A., M.M.O., S.Ş., Analysis and/or Interpretation: S.O., Ş.Ş., M.A., M.M.O., F.Z.Ö.Ç., Literature Search: S.O., Ş.Ş., E.A.A., H.Y., E.P., F.Z.Ö.Ç., Writing: S.O., Ş.Ş., H.Y., F.Z.Ö.Ç.

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RESEARCH ARTICLE

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Pulmonary, Hepatic, and Renal Fibrosis due to Nitrofurantoin in Rat Pups

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Abstract

BACKGROUND/AIMS: Nitrofurantoin is a commonly used antimicrobial drug for treating and prophylaxis of uncomplicated urinary tract infections in both children and adults. Mild and severe adverse reactions to nitrofurantoin may occur with its acute and chronic use. We aimed to investigate nitrofurantoin-induced fibrosis in lung, kidney, and liver tissue.

MATERIALS AND METHODS: We investigated the fibrosis-causing effect of nitrofurantoin in a rat pup experiment designed as 3 groups taking water, 60 mg/kg nitrofurantoin and 120 mg/kg nitrofurantoin for 60, 90, and 120 days. Histopathological evaluation was performed to detect fibrosis in lung, liver, and kidney tissues.

RESULTS: Fibrosis was detected in lung, liver, and kidney tissues and increased with increasing drug dose and duration. The degree of fibrosis ranged from none to abundant in lung and kidney tissues, whereas there were none to mild fibrosis in liver tissues. Surviving rat pups were asymptomatic, but fibrosis was continuously increasing.

CONCLUSION: Pediatric patients receiving nitrofurantoin should be regularly monitored for systemic side effects, particularly pulmonary, renal, and hepatic fibrosis.

Keywords: Nitrofurantoin, fibrosis, lung, liver, kidney

INTRODUCTION

Nitrofurantoin, an antibacterial, has been commonly used for the treatment and prophylaxis of uncomplicated urinary tract infections (UTIs) for more than half a century. Although pulmonary and hepatic fibrosis are more common potential serious adverse reactions, renal, neural, and hematological side effects may also be seen in adults.[1-3] These side effects have also been reported as less common than in adults in the pediatric population.[4]

We aimed to investigate the fibrosis-causing effect of nitrofurantoin on the lung, kidney, and liver tissues of 3-19 weeks aged rat pups for 4 months starting 21 days after birth following weaning.

MATERIALS AND METHODS

Study Design, Sample Collection and Ethical Consideration

Sixty-four Wistar Albino rat pups were enrolled in the study after obtaining approval from the Near East University Institutional Ethics

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All rats were kept without food and water limitation in 21±3 °C temperature and 50±5% humidity.

Study groups were designed as three groups of rats containing both female and male genders mixed randomly. The control group consisted of 18 rats that were only given drinking water (group 1), the second group consisted of 24 rats that were given 60 mg/kg nitrofurantoin dissolved with 1:5 diluted dimethylsulfoxide (DMSO) (group 2), and the third group consisted of 22 rats that were given 120 mg/kg nitrofurantoin dissolved in 1:5 DMSO (group 3). Nitrofurantoin and drinking water were all administered at the same time daily to all gavage groups. All rats were 3 weeks old at the beginning of the study period and were weighed weekly until the end of the study. Each group was divided into three as 1/3 received medications for 60 days, 1/3 for 90 days and 1/3 for 120 days. Each 1/3 of all groups was dissected at the end of 60., 90. and 120. days (Figure 1). Serum samples were obtained and stored at -80 °C on 60., 90. and 120. days to measure blood nitrofurantoin levels by ELISA. Experiments were carried out at the Laboratory of Animal Experiments, Faculty of Veterinary Medicine.

Histopathological Evaluation

The lung, liver, and kidney were surgically removed and fixed in 10% neutral-buffered formalin solution. All materials were processed at the Medical Pathology Laboratory of the Faculty of Medicine. Approximately 3 mm thick incisions were made parallel to the specimens. Each group was sampled from different areas. Samples were routinely embedded in paraffin. Paraffin blocks were serially sectioned with an average thickness of 3-4 micrometers. Sections were stained with hematoxylin and eosin and examined under light microscopy. Two histological slides (4 fields in each) were evaluated for each block. We used a 0-4 scoring system for the histopathological evaluation of fibrosis (0: None, 1: Rare, mild, 2: Moderate, 3: Frequent, 4: Abundant).

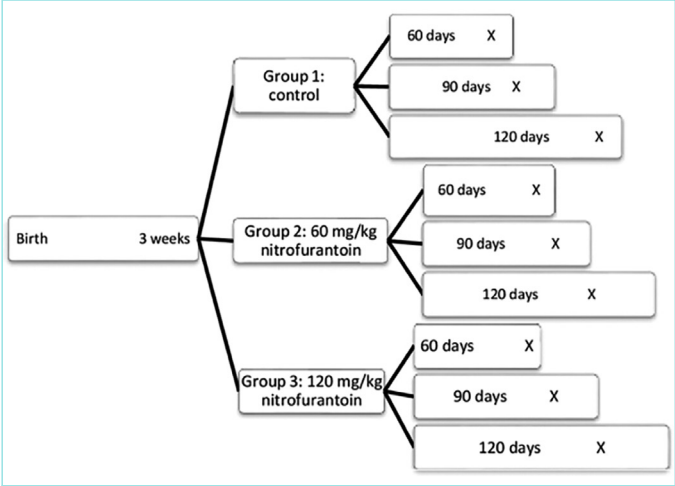

Figure 1. Study design.
X: Serum sample and lung, liver, kidney histopathology.

Statistical Analysis

The obtained data were tabulated in an Excel sheet, and statistical analysis was performed at the 95% confidence level. Descriptive statistics for the study variables were calculated (arithmetic mean and standard deviation). A two-way repeated measures ANOVA test was applied to assess the significance of differences. In cases of significance, Tukey's multiple comparison test was used to assess pairwise differences. GraphPad Prism (version 9.00 for Mac) was used for statistical calculations. The significance level was set as 0.05.

RESULTS

Comparison of the mean fibrosis scores of the lung, liver, and kidney tissue samples is presented on (Figure 2A-C). Histopathology of the lungs, liver, and kidney tissue is shown on (Figures 3-5).

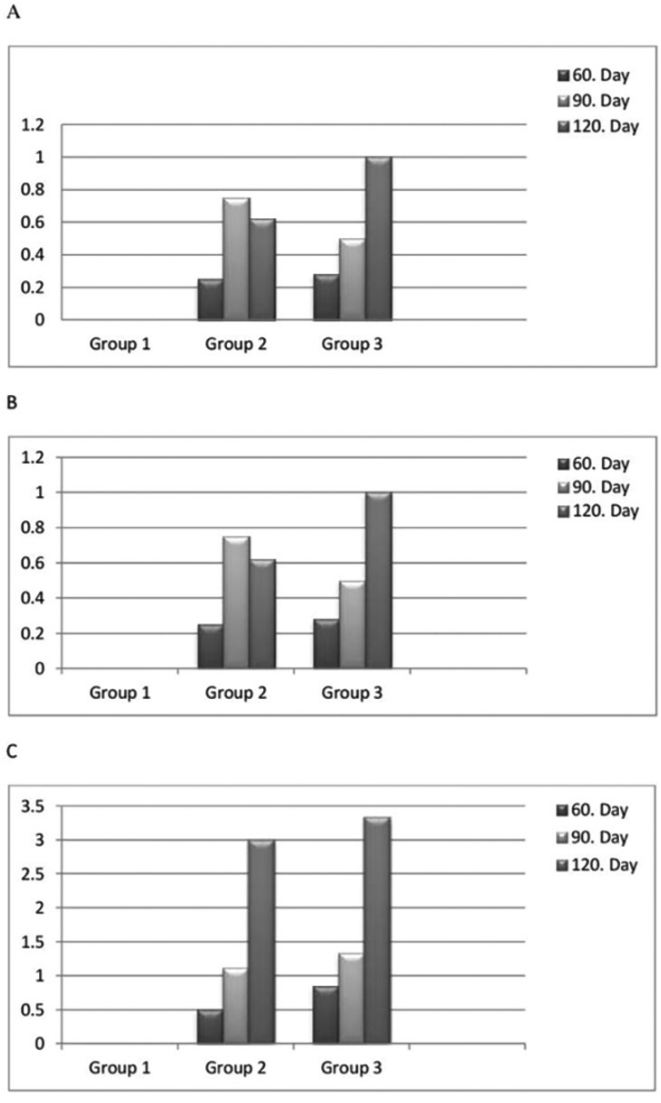

Figure 2. Relationship between nitrofurantoin exposure dose and duration with fibrosis scores in the (A) lung, (B) liver, and (C) kidney tissues.

Lung Tissues

Pathological examination of lung tissues from the first dissected group on day 60 of study revealed no fibrosis in group 1. There were mild fibrosis in 4/8 rats in group 2, although the result was not statistically significant when compared with group 1 (p=0.072). There were mild fibrosis in 7/7 rats in group 3, and this was higher than that in group 2 (p=0.05). Fibrosis in group 3 was much higher than group 1 with a statistically significant result (p<0.0001).

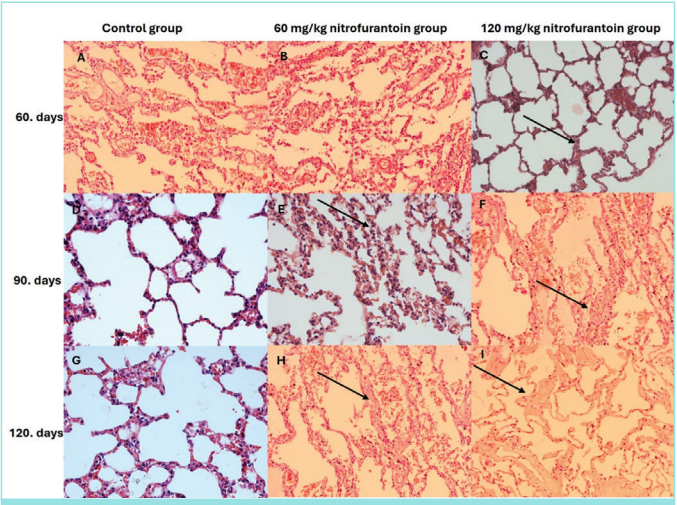

Figure 3. Histopathological lung tissue findings of control, 60 mg/kg and 120 mg/kg nitrofurantoin groups. Fibrosis areas are shown by arrowheads (100x hematoxylin eosin stain). (A) Normal lung tissue, (B) lung tissue without fibrosis, (C) mild fibrosis, (D) normal lung tissue, (E) mild fibrosis, (F) moderate fibrosis, (G) lung tissue without fibrosis, (H) moderate fibrosis, (I) abundant fibrosis in alveolar wall.

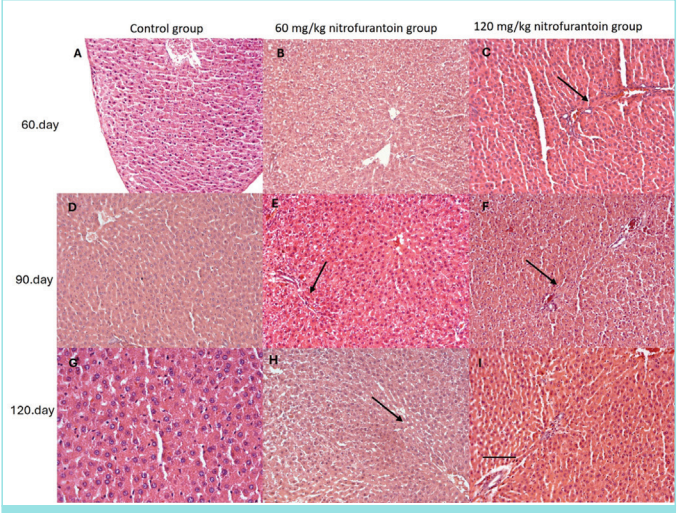

Figure 4. Histopathological liver tissue findings of control, 60 mg/kg and 120 mg/kg nitrofurantoin groups. Fibrosis areas are shown by arrowheads (100x hematoxylin eosin stain). (A) Liver without fibrosis, (B) normal liver parenchyma, (C) mild fibrosis in portal region, (D) normal liver parenchyma, (E) mild fibrosis, (F) moderate fibrosis, (G) normal liver parenchyma, (H) moderate fibrosis, (I) moderate fibrosis.

On day 90, there was no pulmonary fibrosis in group 1. In group 2, 7/8 rats had mild fibrosis, which was significantly higher than in group 1 (p=0.0003). In group 3, there were mild fibrosis in 3/6 rats and moderate fibrosis in 3/6 rats, which were statistically significantly higher than in group 1 (p<0.0001) and group 2 (p=0.014).

On day 120, no fibrosis was detected in group 1. In group 2, 5/8 rats had moderate fibrosis, and 3/8 rats had frequent fibrosis and results were was statistically significantly higher than in group 1 (p<0.0001). In group 3, there were frequent fibrosis in 4/6 rats and abundant fibrosis was observed in 2/6 rats, and the results were statistically significantly higher than in group 1 (p<0.0001) and group 2 (p<0.0001).

In group 2, fibrosis on day 90 (mean; 0.87) was higher than that on day 60 (mean=0.5) (p=0.11). Fibrosis detected on day 120 (mean; 2.3) was higher than that detected on day 90 (p<0.0001) and much higher than day 60 results (p<0.0001).

In group 3, fibrosis on day 90 (mean; 1.5) was higher than that on day 60 (mean; 1) (p=0.04). Fibrosis on day 120 (mean; 3.3) was higher than that on day 90 (p<0.0001) and much higher than that on day 60 (p<0.0001).

Liver Tissues

On day 60, no liver tissue fibrosis was observed in group 1. In group 2, there was mild fibrosis in 2/8 of the rats, and the result was not statistically significant compared with group 1 (p=0.579). There was mild fibrosis in 2/7 of the rats in group 3, but the results were not statistically significant compared with group 2 (p=0.99) and group 1 (p=0.49).

Results obtained on day 90 revealed that all 6 rats had no fibrosis in group 1. In group 2, 6/8 rats had mild fibrosis, which was more than in group 1 (p=0.001). Three/six rats of group 3 had mild fibrosis, and the results were not statistically significant compared with group 1 (p=0.08) and group 2 (p=0.59).

On day 120, there were no fibrosis in 6 rats in group 1 (p>0.99). Five/eight rats had mild fibrosis in group 2, and the results were statistically significant compared with group 1 (p=0.017). In group 3, 6/6 of the rats had mild fibrosis. Group 3 had higher fibrosis rates compared to group 1 (p=0.0001) and group 2 (p=0.22).

In group 2, hepatic fibrosis on day 90 (mean; 0.75) was higher than that on day 60 (mean; 0.25) (p=0.01). Fibrosis on day 120 (mean; 0.62) was more than that on day 60 (p=0.1) and less than that on day 90 (p=0.76).

Regarding group 3, fibrosis on day 90 (mean; 0.5) was higher than that on day 60 (mean; 0.28) (p=0.53). Fibrosis on day 120 (mean; 1) was higher than that on day 90 (p=0.05) and much higher than that on day 60 (p=0.002).

Kidney Tissues

On day 60, no kidney tissue fibrosis was observed in group 1. In group 2, 4/8 rats had mild fibrosis, which was higher than in group 1, but the result was not statistically significant (p=0.1). In group 3, 6/7 rats had mild fibrosis, which was higher than in group 1 (p=0.001) and group 2 (p=0.31).

On day 90, there were no signs of renal fibrosis in 6 rats in group 1. In group 2, 7/8 rats had mild fibrosis, and 1/8 rats had moderate fibrosis.

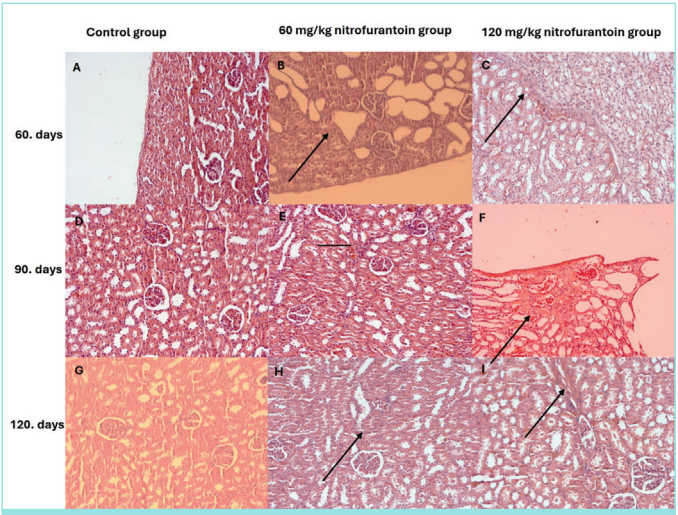

Figure 5. Histopathological renal tissue findings of control, 60 mg/kg and 120 mg/kg nitrofurantoin groups. Fibrosis areas are shown by arrowheads (100x hematoxylin eosin stain). (A) Kidney without fibrosis, (B) mild fibrosis, (C) mild fibrosis, (D) normal kidney parenchyma, (E) mild fibrosis, (F) moderate fibrosis, (G) Normal kidney parenchyma, (H) moderate fibrosis, (I) abundant fibrosis in parenchyma.

Results of group 2 were higher than those of group 1 ($p<0.0001$). In group 3, 4/6 rats had mild fibrosis and 2/6 rats had moderate fibrosis. This was higher than group 1 ($p<0.0001$) and group 2 ($p=0.76$).

Results of day 120 showed that 6 rats in group 1 had no fibrosis. In group 2, 4/8 rats had more frequent fibrosis, whereas 4/8 rats had more abundant fibrosis, and the results were higher than those in group 1 ($p<0.001$). In group 3, 4/6 rats had frequent fibrosis and 2/6 rats had abundant fibrosis. This was higher than in group 1 ($p<0.0001$) and group 2 ($p=0.0014$).

In group 2, fibrosis on day 90 (mean; 1,125) was higher than that on day 60 (mean; 0.5) ($p=0.007$). Fibrosis on day 120 (mean; 2.5) was more than that on days 60 ($p<0.0001$) and day 90 ($p<0.0001$).

In group 3, fibrosis on day 90 (mean; 1.33) was higher than that on day 60 (mean; 0.85) ($p=0.08$). Fibrosis on day 120 (mean; 3.33) was higher than that on days 60 ($p<0.0001$) and day 90 ($p<0.0001$).

There were three rat deaths (4.6%) in group 3, one on day 12, one on day 21, and one on day 26 of nitrofurantoin intake.

DISCUSSION

Nitrofurantoin, an old antibacterial, has regained interest in recent decades due to its efficient treatment results and almost no resistance rates, leading to its increased utilization for treating lower UTIs and prophylaxis of recurrent UTIs.[5]

Nitrofurantoin can lead to adverse reactions both in acute and chronic course. Adverse reactions reported in pediatric patients are mild gastrointestinal complaints beginning in the first week of nitrofurantoin treatment, including abdominal discomfort, nausea, and vomiting (4.4% risk per year). Pulmonary side effects detected in 0.7% of children were mild acute pulmonary reactions or chronic interstitial pneumonitis that subsided after nitrofurantoin discontinuation. Hepatic side effects in 12 cases, 3 of whom died, were the most lethal side effects and occurred after 4 months of therapy, suggesting a dose-dependent mechanism with equal incidence in both genders.[4,6] One was a 16-year-old boy who developed and recovered from cholestatic hepatitis detected on biopsy 1 week after consuming the milk of a cow treated with parenteral nitrofurantoin.[7]

A 16-year-old girl with a history of thoracic laminectomy, paraplegia, and recurrent UTI died of fatal cholestatic hepatitis and acute respiratory distress syndrome 11 years after intermittent nitrofurantoin use.[8]

Pulmonary fibrosis was recently reported in a 6-year-old female patient who was on nitrofurantoin prophylaxis for 2 years. Fibrosis was detected by chest computed tomography (CT) and lung biopsy. The use of nitrofurantoin was stopped, and 35 mg/kg methylprednisolone for 3 days was continued with oral prednisolone for 2 months. Total resolution of the fibrosis was detected by CT and lung function tests after 17 months.[9]

A 7-year-old girl was administered nitrofurantoin for recurrent urinary incontinence for 30 months and developed respiratory failure and liver dysfunction. She was thought to have asthma and had been treated for asthma for a long time. Restrictive lung function test results, desquamative interstitial pneumonitis on lung biopsy, and severe hepatitis with portal fibrosis on liver biopsy were detected. After nitrofurantoin withdrawal and the initiation of 2 mg/kg prednisolone, liver test results normalized in 10 days. Prednisolone was tapered every 2 weeks. Chest CT scan and lung function were normal after 3 months.[10]

Renal fibrosis due to nitrofurantoin is not reported in children. However, adult cases of acute granulomatous and acute interstitial nephritis have been reported. A 76-year-old man who was administered nitrofurantoin for 2 weeks developed acute granulomatous interstitial nephritis. Renal function improved 6 weeks after withdrawal of nitrofurantoin.[11] Another adult patient developed acute renal failure due to nitrofurantoin-associated acute granulomatous interstitial nephritis. Renal function recovered after nitrofurantoin administration without the need for corticosteroids.[12] Acute interstitial nephritis related to nitrofurantoin was reported in a 57-year-old female patient after receiving nitrofurantoin for 5 days for UTI. She developed fever, eosinophilia, eosinophiluria, and hepatic and renal dysfunction. Fever subsided 1 day after nitrofurantoin withdrawal. Elevated urea, creatinine, and liver enzyme levels gradually normalized in 5 weeks. An allergic or immune mechanism was suspected.[13] A 68-year-old man who was given nitrofurantoin for prostatitis for 14 days was hospitalized with fever, hypertension, rash, leucocytosis, eosinophilia, microscopic hematuria, proteinuria, sterile pyuria, and increased blood urea nitrogen and creatinine. Three days after the nitrofurantoin withdrawal fever resolved, the rash faded. After 6 weeks, he was well, and all findings were normal. Acute interstitial nephritis is the most likely diagnosis.[14] We detected renal fibrosis in several rats, but we did not observe granuloma formation in our study. It may be useful to question previous nitrofurantoin use in chronic renal failure without an obvious cause.

Bioactivation and oxidative stress caused by nitrofurantoin play roles in hepatic and pulmonary adverse reactions shown by animal experiments. Antinuclear antibody and anti-smooth muscle antibody positivities in hepatic and lung tissue also suggest immune-mediated

reactions. The dramatic disappearance of findings associated with drug cessation and the onset of side effects associated with drug rechallenge also support an immunological mechanism. However, long-term adverse reactions suggest a dose-dependent phenomenon. Multiple mechanisms seem to be responsible for the adverse effects of nitrofurantoin.[3,15]

The majority of patients in the literature recovered after supportive treatment and cessation of nitrofurantoin, while some required corticostreoid administration, liver transplantation and some died.[3,6] Pulmonary, hepatic, and renal fibrosis are serious problems, especially in the chronic course of nitrofurantoin used for prophylaxis of UTIs.[1-3,13,14] A recent adult study reported not only hepatocellular injury due to short term (<7 days) nitrofurantoin use, but also hepatic fibrosis, nodularity and cirrhosis in long term use (>1 year) of the medication. Autoantibody production resembling autoimmune hepatitis, steroid requirement, liver transplantation, and mortality were also observed recommending periodical ALT monitorisation for those receiving nitrofurantoin.[16]

The relationship between renal and pulmonary fibrosis due to nitrofurantoin was not confirmed with tissue diagnosis before the current study. We obtained significant fibrosis despite the protective effect of DMSO, which is found to prevent drug-induced hepatic fibrosis in rats by blocking inflammation.[17] Fibrosis in lung, liver, and kidney tissues increased parallel to increased dose and prolonged duration of nitrofurantoin use. Pulmonary and renal fibrosis were more severe than hepatic fibrosis in the current study. Three rat deaths possibly due to toxicity were also observed in group 3. There were no symptoms of the surviving rat pups, but significant fibrosis was present. There were no deaths in group 2 however fibrosis was again continuing to increase in tissues. This may also be similar in children too. We do not detect fibrosis in asymptomatic patients because tissue biopsy is not routine for children receiving nitrofurantoin.

Study Limitations

Although we had planned, we could not measure serum nitrofurantoin concentrations to correlate with pathological severity because the ELISA kits could not be obtained at that time due to COVID-19 restrictions and lockdown of Cyprus island. On the other hand, serum nitrofurantoin levels were almost undetectable, with a maximum concentration of 1 mg/L, except in patients with renal failure. Therapeutic drug levels were observed mainly in the lower urinary tract.[5] Therefore, histopathological evaluation is of major importance for the detection of fibrosis and may not always be correlated with serum nitrofurantoin levels. Lack of gender comparison is another lack of the study; however, we did not expect a significant difference related to genders, as not reported in the literature. Fibrosis is more common in females, probably because of higher UTI rates in females.[13,18]

CONCLUSION

As a result, monitoring of pulmonary, hepatic, and renal functions is necessary in patients receiving both short-term and long-term nitrofurantoin prophylaxis or treatment to prevent severe adverse outcomes as early as possible. Nitrofurantoin use should be kept in mind as a potential cause of several systemic complications to be able to take advantage of symptom resolution by early withdrawal of the medication.

MAIN POINTS

- Nitrofurantoin is commonly preferred in recent years for the treatment and prophylaxis of UTIs as an efficient treatment option without resistance.
- Increased dose and duration of nitrofurantoin increased fibrosis in the lung, liver, and kidney tissue samples of rat pups.
- Although rarely observed, systemic side effects should not be missed in patients receiving nitrofurantoin.

ETHICS

Ethics Committee Approval: Sixty-four Wistar Albino rat pups were enrolled in the study after obtaining approval from the Near East University Institutional Ethics Committee of Animal Experiments (approval number: 2017/13-22, date: 03.05.2017).

Informed Consent: Patient approval has not been obtained as it is performed on animals.

Authorship Contributions

Surgical and Medical Practices: B.B., A.A., H.Ö., S.K., Concept: İ.B., A.S., S.K., Design: İ.B., A.S., N.B., S.K., Data Collection and/or Processing: İ.B., B.B., Analysis and/or Interpretation: İ.B., B.B., N.B., S.K., Literature Search: İ.B., Writing: İ.B.

DISCLOSURES

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

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RESEARCH ARTICLE

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Daytime Sleepiness, Body Mass Index, and Physical Activity Levels Among University Undergraduate Students: Do They Affect Sleep Quality?

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Abstract

BACKGROUND/AIMS: This study aimed to determine the relationship between sleep quality and body mass index (BMI), physical activity level, and daytime sleepiness among university students.

MATERIALS AND METHODS: This study was conducted with 299 undergraduate students. Data were collected using a sociodemographic questionnaire, the International Physical Activity Questionnaire Short Form, the Epworth Sleepiness Scale, and the Pittsburgh Sleep Quality Index. All participants underwent anthropometric measurements.

RESULTS: 55.9% of the students had good sleep quality and 44.1% had poor sleep quality. Sleep quality was not significantly associated with BMI. Poor sleep quality was correlated with excessive daytime sleepiness. Physical activity level was significantly associated with BMI, sleep latency, subjective sleep quality, and sleep disorders.

CONCLUSION: Sleep quality was found to affect daytime sleepiness, with excessive daytime sleepiness observed in students with poor sleep habits. Physical activity and BMI did not affect sleep quality.

Keywords: Body mass index, daytime sleepiness, physical activity level, sleep quality

INTRODUCTION

Sleep is an essential physiological need of humans. A state of physical and mental rest is characterized by reduced body movements and decreased awareness of one's surroundings. Sleep allows the body and brain to slow down and engage in recovery processes. Sleep pattern, duration, and quality are crucial for the overall health and quality of life of individuals.[1] Persons with good sleep quality feel rested and energetic upon waking up in the morning and do not experience excessive sleepiness during the day.[1,2] Excessive daytime sleepiness is characterized by an irresistible urge to sleep and a tendency to drowsiness during the daytime.[3] Excessive daytime sleepiness largely results from poor sleep quality, leading to distraction and poor performance during activities of daily living.[4] Sleep quality is correlated with daytime sleepiness as well as physical activity. Physical activity is defined as any movement produced by skeletal muscle that requires energy expenditure.[5] The need, duration, and depth of sleep are increased after physical activity to allow for tissue regeneration.[6]

Regular physical activity improves sleep quality through its positive effects on total sleep time, sleep latency, slow-wave sleep, and rapid eye movement (REM) sleep.[7] In a study examining the association between physical activity and sleep quality, improved sleep quality and longer time spent in the first and second stages of sleep were reported in

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individuals with increased exercise levels.[6] Persons with a low level of physical activity carry a higher risk of chronic diseases such as obesity.[8] Poor sleep quality can also cause weight gain, which increases the risk of developing chronic conditions due to reduced physical activity levels during the day.[9-11]

The aim of the current study was to examine the association between sleep quality and body mass index (BMI), physical activity level, and daytime sleepiness. The three hypotheses tested in the study were as follows: 1) poor sleep quality leads to excessive daytime sleepiness, 2) increased physical activity improves sleep quality, and 3) increased BMI decreases sleep quality.

MATERIALS AND METHODS

This was a cross-sectional study. The study sample consisted of undergraduate students in all years of undergraduate education at the Department of Nutrition and Dietetics, Near East University Faculty of Health Sciences. Eight students could not be reached because of their absence from school. Overall, the study was conducted with a total of 299 students. All students participated in the study on a voluntary basis and provided informed consent. Ethics committee approval for the study was obtained from the Near East University Scientific Research Ethics and Review Board (approval number: YDU/2016/39-321, date: 22.09.2016).

General Characteristics

Sociodemographic data (e.g., age, gender, health status) were collected through face-to-face interviews using a study-specific questionnaire developed by the study investigators. All participants underwent anthropometric measurements. The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality, the Epworth Sleepiness Scale (ESS) to evaluate sleepiness, and the International Physical Activity Questionnaire-Short Form (IPAQ-SF) to determine physical activity levels. of the subjects.

Anthropometric Measurements

Hip circumference (HC), waist circumference (WC), body weight, and height measurements were obtained for all subjects. Body weight was measured after a 1-day rest (avoiding physical activity) using a portable weighing scale (HAMIDI) with the individual wearing light clothes and shoes taken off. Height measurements were taken using a stadiometer with the head positioned in the Frankfort plane. WC was measured under the midline of the subject's armpit at the midpoint between the lower part of the last rib and the iliac crest using non-stretch measuring tape. WC values were categorized into three health risk groups according to the World Health Organization (WHO) classification: normal, <80 cm for female and <94 cm for male; increased risk, 80-88 cm for female and 94-102 cm for male, and high risk, >88 cm for female and >102 cm for male.[12,13] HC measurements were obtained while standing to the right side of the subject using a non-stretch measuring tape at the level of the maximum protrusion of the buttocks. WC and HC were used to calculate the waist-to-hip ratio. Calculated waist/hip ratios were divided into two groups according to the WHO classification: normal, <0.85 for female and <0.90 for male, and increased risk, ≥0.85 for female and ≥0.90 for male.[12] The subjects were divided into three groups based on waist-to-height ratio: increased risk, <0.4; normal, ≥0.4 to <0.5; and high risk, ≥0.5.[14] BMI values were categorized according to the WHO classification as follows: underweight (<18.5 kg/m^2); normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥30.0 kg/m^2).[15]

Assessment of Sleep Quality

Pittsburgh Sleep Quality Index

The PSQI was developed with the aim of determining sleep quality, assessing various sleep disorders that may affect sleep quality, and distinguishing good from poor sleep. The PSQI is a self-reported questionnaire that evaluates sleep quality during the previous month.[16] The reliability and validity of the Turkish version of the PSQI were demonstrated by Ağargün et al.[17] The PSQI consists of a total of 24 questions and seven subscales, including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, daytime dysfunction, and use of sleep medication. The scores for each of the 7 subscales range from 0 to 3, with a maximum score of 21 points. An overall score ranging from 0 to 5 points indicates good sleep quality, whereas a score ranging from 6 to 21 point denotes poor sleep quality.[16]

Epworth Sleepiness Scale

The ESS is a self-administered questionnaire with 8 items to assess daytime sleepiness in adults. It is widely used to evaluate sleepiness in sleep disorder research. The ESS measured daytime sleepiness in eight different situations over a 1-month interval. Respondents were asked to rate their sleepiness on a 4-point Likert scale (0=would never doze, 1=slight chance of dozing, 2=moderate chance of dozing and 3=higher chance of dozing). The scores for the eight items were summed to obtain an overall score ranging from 0 to 24. Higher ESS scores indicate greater daytime sleepiness. Individuals with a score >10 are considered to have increased daytime sleepiness. The validity and reliability of the Turkish version of ESS were demonstrated by Izci et al.[18]

Assessment of Physical Activity

The IPAQ is available in both short and long forms. The IPAQ long form evaluates physical activity in several contexts: recreation, work, transport, home, and gardening. The short form consists of 7 questions that assess walking, moderate- and vigorous physical activities, and time spent sitting within the last 7 days.[19,20] Total physical activity is measured in metabolic equivalent (MET), which indicates the intensity of physical activity and energy efficiency.[21] Physical activity is categorized into three levels: Health-enhancing physical activity (HEPA)-active, inactive, and minimally active.[19,20] The reliability and validity of the Turkish version of IPAQ have been demonstrated by Saglam et al.[22]

Statistical Analysis

Quantitative study data are presented as the arithmetic mean ($\bar{x}$), standard deviation, median and minimum-maximum values. Descriptive statistics are summarized as numbers (n) and percentages (%) for qualitative data. The normality of data distribution was checked using Kolmogorov-Smirnov and Shapiro-Wilk tests. The Independent samples t-test (Student's t-test) was used to compare continuous variables between two independent groups, and the One-Way analysis of variance (ANOVA) was used to compare multiple groups. Pearson's chi-square (χ^2) and Fisher's exact (χ^2) tests were employed for the analysis of qualitative and categorical variables. The significance of the relationships between quantitative variables was assessed using Pearson correlation (r). Multiple binary logistic regression analysis was used to evaluate the relationships among sleep quality, daytime sleepiness,

BMI, and physical activity. For the regression analysis, sleep quality was considered the dependent variable. Daytime sleepiness, BMI, and physical activity were independent variables. The SPSS (Statistical Package for Social Sciences), version 20.0 (IBM Corp., Armonk, NY) was used for all statistical analyses. The significance level was set at $p<0.05$.

RESULTS

A total of 299 subjects were included in the study, of whom 223 (74.6%) were female and 76 (25.4%) were male. The mean age of the subjects was 21.1±2.6 years. 84.6% of the students did not have any illness, and 15.4% were diagnosed with at least one disease. Among the students with health conditions, 13.9% had respiratory diseases, 12.6% had gastrointestinal problems, and 10.2% had cardiovascular diseases. Thyroid disease, neurological disorders, or anemia were present with a frequency of 8.5% each. 5.5% were diabetic, and 32.3% had other health problems.

According to the BMI values of the students, 13.7% were underweight, 68.9% were normal, 12.7% were overweight, and 4.7% were obese. A waist/height ratio of <0.4 or >0.5 poses health risk and requires action, which was observed in 16.1% and 18.4% of the subjects, respectively. Furthermore, 65.6% of the subjects had a normal waist/height ratio. Waist/hip ratios were normal in 94.6% and high in 5.4% of the subjects. WC was classified as normal in 82.2%, increased risk (11.4%) and high risk (6.4%) in the subjects (Table 1).

Regarding students' sleep habits, 20.1% reported having a consistent bedtime, 51.5% did not follow a regular sleep schedule, and 28.4% were occasionally going to sleep at the same time every night. Furthermore, 29.5% of the students reported waking up feeling rested, 33.4% reported waking up feeling tired, and 37.1% reported that they sometimes felt rested in the morning. There were no significant differences between genders or among students in different academic years ($p>0.05$). When asked about dozing while studying, 45.2% of the students answered "yes", 24.7% answered "no" and 30.1% answered "sometimes". With respect to dozing while studying, a non-significant difference was found among students in different academic years ($p=0.282$), but the difference between genders was significant ($p=0.029$). Male students were less likely to doze off while studying than female students. In addition, 37.5% of the students reported feeling sleepy, 23.1% reported not feeling sleepy, and 39.5% reported occasionally feeling sleepy in class. The difference between genders was significant ($p=0.022$) but the difference among academic years was non-significant ($p=0.210$) (Figure 1).

The mean ESS scores were 4.9±3.3 for the study population, 4.9±3.2 for the females and 4.9±3.6 for the males. Based on the ESS scores, 93.0% of students exhibited normal daytime sleepiness, whereas 7.0% exhibited increased daytime sleepiness. The difference in total ESS scores among academic years ($p=0.608$) and between genders ($p=0.731$) was not significant (Table 2).

The mean PSQI scores were 5.6±2.9 for the study population, 5.6±3.0 for the males and 5.6±2.9 for the females. Regarding the overall sleep quality of the students, 55.9% of them had good sleep quality and 44.1% had poor sleep quality. However, no significant difference was observed in the total PSQI scores among students in different academic years and between genders (Table 2).

The mean IPAQ-SF scores were 1923.0±1792.4 METs (minutes/week) for the study population, 1539.0±1173.0 METs for the females and 2631.0±2535.9 METs for the males. Regarding the physical activity level of the students, 18.6% were inactive, 35.0% were minimally active, and 46.4% were HEPA-active. The difference in the global IPAQ-SF scores was non-significant among academic years ($p=0.102$) but significant between the genders ($p=0.013$). Male students were found to be physically more active than female students (Table 2).

The relationships of the PSQI subscales with IPAQ-SF, ESS, PSQI scores, and BMI values are presented in Table 3. Although total IPAQ-SF scores were positively correlated with subjective sleep quality, sleep latency, and sleep disorders, no significant correlation was found with other subscales. BMI was not significantly correlated with PSQI subscale scores, but total ESS scores were positively correlated with subjective sleep quality, daytime dysfunction, sleep disorders, and use of sleep medication (Table 3).

When the relationships among IPAQ-SF, ESS, PSQI scores, and BMI values were analyzed, no significant correlation was observed between PSQI and IPAQ-SF scores or BMI; however, total PSQI scores were positively correlated with ESS scores. As the total PSQI scores of the students increased, their total ESS scores also increased. Because higher PSQI scores indicate poor sleep quality and higher ESS scores denote increased daytime sleepiness, students with poor sleep quality experience increased daytime sleepiness. Total ESS scores were not significantly correlated with BMI or total IPAQ-SF scores. A positive correlation was found between total IPAQ-SF scores and the students' BMI. Thus, as the students' physical activity increased, their BMI also increased (Figure 2).

The established regression model is significant. The coefficient of the independent variable X1 (BMI) was not significant ($p>0.05$). On the other hand, the explanatory variable X2 (daytime sleepiness) was statistically significant ($p=0.001$). The regression coefficient of variable X3 (physical activity level) was also significant ($p<0.05$). Consequently, the established regression model was expressed as $y=4.893 + 0.018x1 + 0.178x2 - 0.225x3$. In summary, daytime sleepiness was significantly associated with sleep quality.

Among the students with good sleep quality, 46.9% engaged in HEPA, while 33.3% were minimally active and 19.8% were inactive. In comparison, among students with poor sleep quality, the corresponding figures were 45.7%, 37.1%, and 17.2%, respectively. No significant difference in physical activity levels was observed between the groups ($p=0.781$). Regarding daytime sleepiness, 95.8% of the students with good sleep quality had normal daytime sleepiness, whereas 89.4% of the students with poor sleep quality reported increased daytime sleepiness. The difference between the groups was significant ($p<0.05$), indicating that the students with good sleep quality experienced normal daytime sleepiness. In terms of BMI, 15.0% of the students were underweight, 67.7% were normal, 12.5% were overweight, and 4.8% were obese. For the students with poor sleep quality, the corresponding figures were 12.1%, 70.5%, 12.9%, and 4.5%, respectively. The differences among the groups were not significant (Table 4).

DISCUSSION

Determining students' sleep quality and the factors involved is crucial for improving their sleep quality and well-being in adulthood. Therefore, sleep disorders that may be caused by insufficient or poor-quality sleep can be prevented. Therefore, this study is important for evaluating

Table 1. Distribution of BMI, waist-to-height ratio, waist-to-hip ratio, and waist circumference values of students by gender

	Female		Male		Total	
	n	%	n	%	n	%
BMI classification						
Underweight	34	15.2	7	9.2	41	13.7
Normal	160	71.7	46	60.5	206	68.9
Overweight	20	9.0	16	23.7	38	12.7
Obese	9	4.0	5	6.6	14	4.7
Total	223	100.0	76	100.0	299	100.0
p	0.005[1*]					
Waist/height ratio						
Increased risk of disease requires action	42	18.8	6	7.9	48	16.1
Normal	150	67.3	46	60.5	196	65.6
Increased risk of disease requires action	31	13.9	24	31.6	55	18.4
Total	223	100.0	76	100.0	299	100.0
p	0.001[1*]					
Waist/hip ratio						
Normal	216	96.6	67	88.2	283	94.6
Increased risk	7	3.1	9	11.8	16	5.4
Total	223	100.0	76	100.0	299	100.0
p	0.007[2*]					
Waist circumference						
Normal	183	82.1	63	82.9	246	82.2
Increased risk	26	11.7	8	10.5	34	11.4
High risk	14	6.3	5	6.6	19	6.4
Total	223	100.0	76	100.0	299	100.0
p	0.962[1]					

[1]Pearson's chi-square test (c^2); *p<0.05, [2]Fisher's exact test (c^2); *p<0.05, n: Number of subjects, %: Percentage, BMI: Body mass index.

the sleep quality of university students and the factors affecting sleep quality.

The sleep habits of the students aligned with findings from previous studies. In a study investigating sleep disorders and sleep quality among Gülhane Military Medical Academy students, 42.5% reported going to bed at the same time every night and 37.6% reported waking up feeling refreshed in the morning. Dozing at school was also questioned, and dozing in almost all classes was found in 15.2%, frequent dozing in 31.9%, occasional dozing in 37.9%, infrequent dozing in 12.6%, and no dozing in 1.9% of the students.[23] Similarly, in a study involving 558 university students, 16.3% reported having a consistent bedtime, 43.2% occasionally went to bed at the same time every night, and 40.5% did not follow a routine sleep schedule.[24] Another study on university students found that 57.3% did not have a regular bedtime and 73.0% did not wake up feeling rested in the morning.[25] In a study involving adolescent students, 60.3% reported experiencing sleepiness while studying and 49.3% reported dozing in class.[26]

Individuals with ESS scores above 10 points are typically considered to have increased daytime sleepiness.[18] In this study, both female (4.9±3.2) and male students (4.9±3.6) had ESS scores below 10 points, indicating minimal daytime sleepiness. These findings are consistent with previous reports.[4,24,27,28] Increased daytime sleepiness was found in only 7.0% of the students in the present study. Contrarily, a study from Malaysia involving 201 university students reported increased daytime sleepiness in 64.6% of the students.[29] Likewise, a study among nursing students found that 57.4% were found to have increased daytime sleepiness.[3]

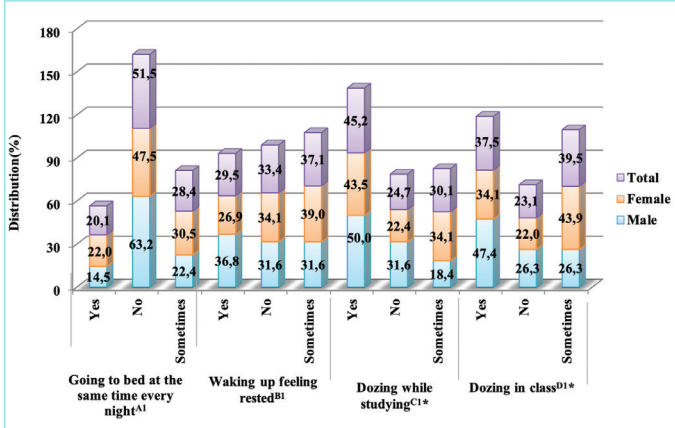

Figure 1. Distribution of sleep habits among students by academic year and gender (%).

[1]Pearson's chi-square test (χ^2); *p<0.05, A1: year (p=0.876[1]), gender (p=0.061[1]); B1: year (p=0.088[1]), gender (p=0.240[1]); C1: year (p=0.282[1]), gender (p=0.029[1*]); D1: year (p=0.210[1]), gender, p=0.022[1*].

Table 2. Distribution of total ESS, PSQI, and IPAQ-SF scores by academic year and gender

			Female		Male		Total		p
			n	%	n	%	n	%	
ESS score	Year 1	Normal daytime sleepiness	61	93.8	28	96.6	89	94.7	0.608[1]
		Increased daytime sleepiness	4	6.2	1	3.4	5	5.3	
	Year 2	Normal daytime sleepiness	73	92.4	24	92.3	97	92.4	
		Increased daytime sleepiness	6	7.6	2	7.7	8	7.6	
	Year 3	Normal daytime sleepiness	44	97.8	8	80.0	52	94.5	
		Increased daytime sleepiness	1	2.2	2	20.0	3	5.5	
	Year 4	Normal daytime sleepiness	30	88.2	10	90.9	40	88.9	
		Increased daytime sleepiness	4	11.8	1	9.1	5	11.1	
	Total	Normal daytime sleepiness	208	93.3	70	92.1	278	93.0	
		Increased daytime sleepiness	15	6.7	6	7.9	21	7.0	
	p		0.731[2]						
PSQI score	Year 1	Good sleep quality	30	46.2	17	58.6	47	50.0	0.557[1]
		Poor sleep quality	35	53.8	12	41.4	47	50.0	
	Year 2	Good sleep quality	46	58.2	14	53.8	60	57.1	
		Poor sleep quality	33	41.8	12	46.2	45	42.9	
	Year 3	Good sleep quality	27	60.0	6	60.0	33	60.0	
		Poor sleep quality	18	40.0	4	40.0	22	40.0	
	Year 4	Good sleep quality	21	61.8	6	54.5	27	60.0	
		Poor sleep quality	13	38.2	5	45.5	18	40.0	
	Total	Good sleep quality	124	55.6	43	56.6	167	55.9	
		Poor sleep quality	99	44.4	33	43.4	132	44.1	
	p		0.883[2]						
IPAQ-SF score	Year 1	Inactive	15	27.8	3	10.3	18	21.7	0.102[1]
		Minimally active	12	22.2	10	34.5	22	26.5	
		HEPA-active	27	50.0	16	55.2	43	51.8	
	Year 2	Inactive	9	13.4	1	4.8	10	11.4	
		Minimally active	29	43.3	11	52.4	40	45.5	
		HEPA-active	29	43.3	9	42.9	38	43.2	
	Year 3	Inactive	11	26.8	0	0.0	11	22.0	
		Minimally active	13	31.7	1	11.1	14	28.0	
		HEPA-active	17	41.5	8	88.9	25	50.0	
	Year 4	Inactive	9	29.0	1	9.1	10	23.8	
		Minimally active	12	38.7	4	36.4	16	38.1	
		HEPA-active	10	32.3	6	54.5	16	38.1	
	Total	Inactive	44	22.8	5	7.1	49	18.6	
		Minimally active	66	34.2	26	37.1	92	35.0	
		HEPA-active	83	43.0	39	55.7	122	46.4	
	p		0.013[2*]						

[1]Pearson's chi-square test (c^2), [2]Fisher's exact test (c^2), n: Number of subjects, %: Percentage, ESS: Epworth Sleepiness Scale, PSQI: Pittsburgh Sleep Quality Index, HEPA: Health-enhancing physical activity, IPAQ-SF: International Physical Activity Questionnaire-Short Form.

A study of 273 medical students reported that 22.3% experienced increased daytime sleepiness.[30] In another study, increased daytime sleepiness was found in 58.1% of dental students.[31] In a study by Muhammad et al.[32] involving individuals aged 18-74 years, 55.3% were identified as experiencing increased daytime sleepiness. In a study involving only male participants, 12.7% reported increased daytime sleepiness.[27] In the present study, a lower prevalence of daytime sleepiness was observed than in previous studies. This may be attributed to a number of factors, including students' adherence to early bedtime routines, getting the recommended amount of sleep daily, and the low prevalence of factors associated with increased daytime sleepiness, such as stress, smoking, alcohol consumption, and unhealthy eating habits.

PSQI score of ≥6 indicates poor sleep quality.[16] In this study, the mean PSQI score of the students was 5.6±2.9, and 44.1% of them were found

Table 3. Relationships of the PSQI subscale scores with BMI, IPAQ-SF, ESS, and PSQI scores

PSQI subscales	IPAQ-SF		ESS		PSQI		BMI	
	r	p	r	p	r	p	r	p
Subjective sleep quality	0.229	0.000[1**]	0.173	0.003[1*]	0.660	0.000[1**]	0.062	0.289
Sleep latency	0.181	0.002[1*]	0.078	0.177	0.640	0.000[1**]	-0.064	0.273
Sleep duration	0.088	0.129	0.006	0.921	0.551	0.000[1**]	0.009	0.874
Sleep efficiency	0.077	0.185	-0.083	0.155	0.431	0.000[1**]	-0.074	0.200
Sleep disorders	0.256	0.000[1**]	0.205	0.000[1**]	0.475	0.000[1**]	0.003	0.963
Use of sleep medication	0.071	0.219	0.118	0.042[1*]	0.324	0.000[1**]	0.083	0.153
Daytime dysfunction	-0.069	0.238	0.153	0.008[1*]	0.586	0.000[1**]	0.078	0.180

[1]Pearson's correlation test, *p<0.05, **p<0.001, IPAQ-SF: International Physical Activity Questionnaire Short Form, ESS: Epworth Sleepiness Scale, PSQI: Pittsburgh Sleep Quality Index, BMI: Body mass index.

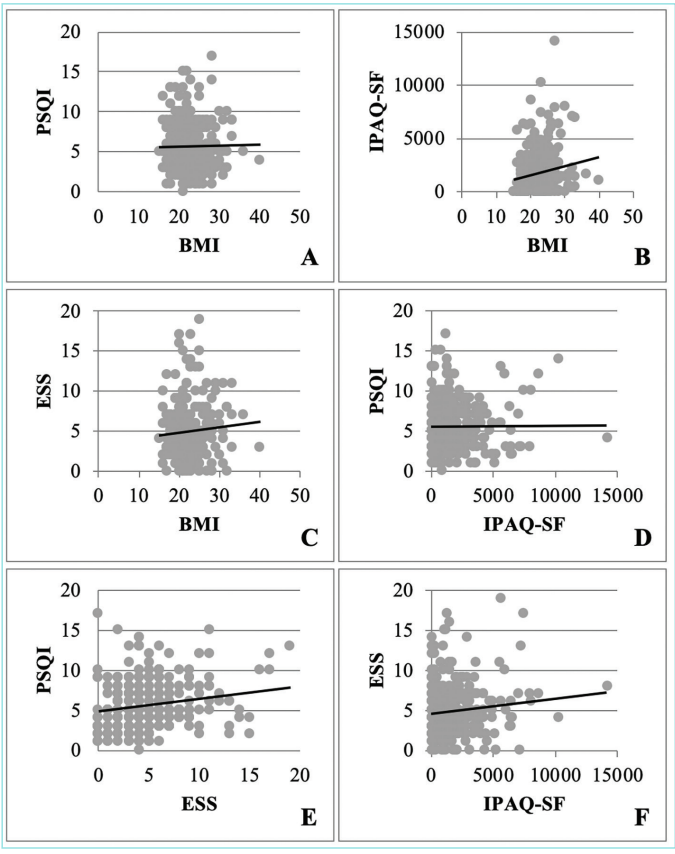

Figure 2. Relationships among IPAQ-SF score, ESS score, PSQI score, and BMI.

(A) r=0.024, p=0.676[1]; (B) r=0.157, p=0.006[1*]; (C) r=0.082, p=0.156[1]; (D) r=0.003, p=0.958[1]; (E) r=0.174, p=0.003[1*]; (F) r=0.109, p=0.061[1].

[1]Pearson's correlation test; *p<0.05, IPAQ-SF: International Physical Activity Questionnaire Short Form, ESS: Epworth Sleepiness Scale, PSQI: Pittsburgh Sleep Quality Index, BMI: Body mass index.

to have poor sleep quality. The difference in sleep quality between genders was not significant. A study conducted at Stanford University with 628 athletes from 29 varsity teams reported average PSQI scores of 5.3±2.4 among the athletes, with 42.4% experiencing sleep disturbances.[33] Similarly, another study involving university students reported average PSQI scores of 6.3±3.0, with 58.2% having poor sleep quality. No significant difference was found between genders in terms of sleep quality.[4] In a separate study of university students, 71.1% had poor sleep quality. In that study, the average PSQI scores were 8.3±2.9 for females and 8.1±3.1 for males, with no significant difference between genders.[31] A previous study investigating sleep quality reported mean PSQI scores of 9.1±4.5 in the study population, 9.2±4.4 among females and 9.1±5.1 among males, with no significant difference between genders.[28] The recommended average sleep duration for adults is approximately 7-8 hours daily.[34] The sleep quality of the university students included in this study may have been influenced by various factors, including being away from home, disruptions to their sleep routines, long hours of studying due to demanding curricula, high academic stress, and changes in dietary patterns.

When analyzing the distribution of the IPAQ-SF scores, 18.6% were found to be inactive, 35.0% were minimally active, and 46.4% engaged in HEPA. There was a significant difference between female and male students, with male students exhibiting higher levels of physical activity than female students. Similarly, in a study of university students, lower physical activity levels were observed among female students than male students.[8] In a study involving 87 medical students aged 18 to 25 years, 40% were inactive, 47% were minimally active, and 13% reported HEPA.[21] In a separate study of 831 university students, 9% were found to be inactive, 32.1% were minimally active, and 58.9% reported performing HEPA. A significant difference was observed between genders in that study (p<0.001), with female students being physically less active than male students.[5] Another study in 255 university students, 11.4% were inactive, 73.7% were minimally active, and 14.9% engaged in HEPA. The difference between genders was significant (p=0.005), with male students having higher levels of physical activity.[35] Collectively, the aforementioned findings are consistent with our results. The higher levels of physical activity observed among male students in our study may be attributed to anorexia or muscle dysmorphia, which are more prevalent among males. A survey conducted by the Turkish Ministry of Health in 2011, titled Chronic Diseases and Risk Factors, revealed inadequate physical activity in 87% of women and 77% of men. According to the survey, individuals with inadequate physical activity face a 20-30% increased risk of death compared with individuals engaging in moderate or vigorous physical activity for at least 30 minutes daily, 4-5 days a week. In adults, 150 min of physical activity per week is associated with a 30% reduction in the risk of ischemic heart disease, 27% reduction in the risk of type 2 diabetes and 20-25% reduction in the risk of breast and colon cancer. Regular physical activity is essential for improving health, preventing the development of chronic diseases, and maintaining body weight.[36]

Table 4. Distribution of physical activity level, sleepiness, and BMI according to sleep quality

	Good sleep quality		Poor sleep quality		Total		p
	n	%	n	%	n	%	
Physical activity level							
Inactive	29	19.8	20	17.2	49	18.6	0.781[1]
Minimally active	49	33.3	43	37.1	92	35.0	
HEPA-active	69	46.9	53	45.7	122	46.4	
Sleepiness							
Normal daytime sleepiness	160	95.8	118	89.4	278	93.0	0.040[2*]
Increased daytime sleepiness	7	4.2	14	10.6	21	7.0	
BMI classification							
Underweight	25	15.0	16	12.1	41	13.7	0.911[1]
Normal weight	113	67.7	93	70.5	206	68.9	
Overweight	21	12.5	17	12.9	38	12.7	
Obese	8	4.8	6	4.5	14	4.7	

[1]Pearson's chi-square test (χ^2), [2]Fisher's exact test (χ^2); *p<0.05, n: Number of subjects, %: Percentage, HEPA: Health-enhancing physical activity, BMI: Body mass index.

In the present study, a significant relationship was observed between physical activity and BMI (p<0.05) (Figure 2). The students' physical activity levels increased in a direct correlation with their BMI values. Despite engaging in physical activity, the students showed increased BMI values, which may be explained by a number of factors such as irregular meal times, altered eating habits, increased prevalence of muscle dysmorphia, increased consumption of fast food due to convenience, accessibility, and affordability, impaired sleep quality, and excessive daytime sleepiness. A study on undergraduate students reported a decrease in physical activity levels with increasing BMI values.[37] Similarly, another study found that reduced physical activity was associated with an increased risk of obesity among students.[38] In a study involving university students (age range, 18-30 years), a significant association was demonstrated between BMI values and physical activity levels (p=0.001).[35] In a study by Gangwisch et al.[39] analyzing NHANES I follow-up studies, a significant relationship was observed between physical activity level and BMI. Additionally, a study on medical students also found a positive correlation between physical activity levels and BMI values (r=0.192, p=0.013), with lower physical activity levels observed in females than in males.[8] However, another study on medical students did not find a significant association between BMI and physical activity levels (p=0.133).[40] The 2020 WHO physical activity guidelines recommend at least 150 minutes of moderate-intensity physical activity per week for adults. Engaging in physical activity improves quality of life and well-being by promoting the prevention of chronic diseases.[41]

The present study revealed a non-significant association between sleep quality and BMI (Figure 2). Consistent with our findings, several studies in the literature have reported no significant relationship between sleep quality and BMI.[28,42,43] Sleep quality and sleep duration are factors that both influence and are influenced by BMI. Many studies have described the association between sleep quality and BMI.[44-49] Poor sleep quality has been shown to contribute to a sedentary lifestyle, inadequate physical activity, unhealthy eating habits, and poor nutrition. Moreover, it can lead to the activation of the sympathetic nervous system and increase hunger hormone levels while decreasing insulin sensitivity, glycolysis efficiency, voluntary muscle contractions, and satiety hormone levels. Through its negative effects on health, poor sleep quality is associated with an elevated risk of chronic diseases, particularly obesity.[50]

This study did not find a significant relationship between physical activity and sleep quality (Figure 2), a finding consistent with that of previous studies. A study on university students also found no significant correlation between physical activity and sleep quality.[51] In a randomized, controlled study involving healthy young adults (n=12) and older adults (n=21), physical activity was non-significantly associated with sleep efficiency in both young adults (r=-0.162, p=0.62) and older adults (r=-0.014, p=0.95).[52] Regular physical activity is known to increase the need for slow- wave sleep and REM sleep, as it promotes tissue regeneration. This increased need, in turn, results in reduced sleep latency, increased total sleep time, and improved sleep quality.[6,7] The lack of regular physical activity observed among the students in this study may, therefore, explain the non-significant association between their sleep quality and physical activity levels.

A positive correlation was found between sleep quality and daytime sleepiness (Figure 2), which is in line with findings reported in previous studies.[3,27,28,33] Increased daytime sleepiness was the most common sleep deprivation problem observed among the students. This finding may be attributed to a number of important factors affecting daytime sleepiness, including demographic characteristics (e.g., gender), sleep patterns, dietary habits, demanding curriculum, and exam stress. Notably, the ESS and PSQI daytime dysfunction scores were positively correlated. Thus, as PSQI daytime dysfunction scores increased, ESS scores also increased, indicating that the ability to perform daily activities decreased as sleepiness increased. Similar results were also reported by Buysse et al.[53] The increased daytime sleepiness observed among university students may be explained by several factors, including living in student accommodation with roommates having different sleep schedules, environmental stimuli (e.g., light, noise), diminished sleep quality in smokers due to the stimulating effects of nicotine, long study hours and demanding curriculum, and increased consumption of caffeinated beverages to stay awake during examination periods.

Study Limitations

A number of limitations should be noted for this study. First, the study included only students from the department of nutrition and dietetics, potentially limiting the generalizability of the findings to a broader population. Second, assessments of sleepiness, sleep, and

physical activity levels relied on patient self-reports. The unequal gender distribution was the third limitation of the study, particularly considering that the study aimed to draw conclusions applicable to the general population. Despite these limitations, the results of this study are consistent with those of previous studies.

CONCLUSION

The results of this study revealed that the majority of the students had normal BMI and daytime sleepiness levels. Female students were physically less active than male students. The students with poor sleep quality experienced increased daytime sleepiness compared to those with good sleep quality. No significant correlations were found between physical activity, BMI, and sleep quality. This study provides important data for future research aimed at understanding factors associated with sleep problems. Further comprehensive studies are warranted to elucidate the risk factors that influence sleep quality more definitively.

MAIN POINTS

- There was a significant relationship between daytime sleepiness and sleep quality. Increased daytime sleepiness decreased sleep quality.
- There was a significant relationship between subjective sleep quality, sleep latency, and sleep disorders and physical activity level.
- There was a significant relationship between physical activity level and body mass index, but no significant relationship was found between sleep quality and body mass index.

ETHICS

Ethics Committee Approval: Ethics committee approval for the study was obtained from the Near East University Scientific Research Ethics and Review Board (approval number: YDU/2016/39-321, date: 22.09.2016).

Informed Consent: All students participated in the study on a voluntary basis and provided informed consent.

Authorship Contributions

Concept: G.Ö., S.Y., Design: G.Ö., S.Y., Data Collection and/or Processing: G.Ö., Analysis and/or Interpretation: G.Ö., Literature Search: G.Ö., S.Y., Writing: G.Ö.

DISCLOSURES

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

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RESEARCH ARTICLE

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Psychometric Properties of Turkish Versions of Post-Intensive Care Syndrome Questionnaire and Healthy Aging Brain Care Monitor Self-Report for Evaluating Post-Intensive Care Syndrome

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Abstract

BACKGROUND/AIMS: Post-intensive care syndrome (PICS) is frequently undertreated because of the complexity of its three domains and the need for different assessment tools. There is a need for clinical tools that can assess all PICS domains simultaneously and within a short period of time. This study aimed to determine the psychometric properties of the Turkish versions of the Post-Intensive Care Syndrome Questionnaire (PICSQ-T) and Healthy Aging Brain Care Monitor Self-Report (HABC-M-T).

MATERIALS AND METHODS: This methodological study included 157 intensive care unit patients. The data were collected via telephone two weeks after patient discharge. Data collection tools included the Patient Characteristic Form, the PICSQ-T, the HABC-M-T, and the standardized external scales Pfeiffer's Short Portable Mental Status Questionnaire (cognitive domain), the Barthel Index (physical domain), and the Hospital Anxiety and Depression Scale (mental domain).

RESULTS: The content validity indices of both scales were greater than 0.80 at the item and scale levels. According to confirmatory factor analysis, the 18-item PICSQ-T and 27-item HABC-M-T had good fit indices, and the factor loadings of the items of these scales were above 0.30. The scales showed a significant correlation with the standard scales corresponding to the three domains of PICS. Cronbach's alpha values were 0.94 for the PICSQ-T and 0.96 for the HABC-M-T. Test-retest analysis results were 0.84 for the PICSQ-T and 0.89 for the HABC-M-T.

CONCLUSION: The results show that the PICSQ-T and HABC-M-T, which are highly valid and reliable, may be easily used to screen for PICS.

Keywords: Post-intensive care syndrome, critical care, validity, reliability

INTRODUCTION

Intensive care medicine has advanced dramatically over the last quarter of a century through technological innovations, the development of organ support systems, and the standardization and refinement of training programs.[1,2] These developments have led to significant improvements in mortality. However, such promising improvements in quality of care have also created a population of intensive care patients who are likely to face a variety of challenges that can last for years after hospital discharge.[2,3]

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The challenges faced by the survivors of intensive care units (ICUs), particularly in the physical, cognitive, and mental domains, are termed post-intensive care syndrome (PICS).[4] Over the past 20 years, studies have shown that critical illnesses can have widespread and devastating long-term consequences, which can severely affect the patients themselves as well as their family members.[5] In the United States, 5.7 million patients are admitted to ICUs annually, of whom approximately 4.8 million survive.[6] It is estimated that up to 80% of critically ill patients discharged from the hospital will have symptoms of PICS, and although PICS may improve over time, more than half of them will continue to experience symptoms for a year.[7] In an observational cohort study of ICU-treated survivors, a significant proportion of the patients were found to have newly acquired cognitive impairment, depression, and/or inability to perform activities of daily life in the three-month (64%) or twelve-month (56%) period after their discharge.[8]

To detect and treat the consequences of critical illnesses experienced by patients, healthcare professionals providing intensive care services must assess patients after discharge. Valid and reliable scales are required for this purpose. There are two scales in the literature that currently assess PICS: The Post-Intensive Care Syndrome Questionnaire (PICSQ) and the Healthy Aging Brain Care Monitor Self-Report version (HABC-M).[9,10] Adaptation studies on these scales are being conducted in many countries and languages (Chinese, Japanese, Spanish, French) but their adaptation into Turkish has not yet been performed. This study aimed to adapt the PICQ and HABC-M scales to Turkish and test their psychometric properties.

MATERIALS AND METHODS

Design, Setting, and Sample

This cross-sectional and methodological study was conducted between April 2022 and April 2023 in four ICUs of a hospital in the fourth largest city of Türkiye. The inclusion criteria were (a) age 18 years or older, (b) staying in ICU for 48 hours or more, (c) being on mechanical ventilation (MV) for 48 hours or more, (d) having consciousness on the day of transfer, and (e) being discharged from the ICU after more than 2 weeks.[10-13] Patients with problems in reading, writing, or comprehension in Turkish, patients with neurological diseases that may affect cognition, patients with a history of dementia or cognitive impairment, patients who were readmitted to the ICU within the study period, and patients who were referred from an external ICU were excluded from the study.

In the validity and reliability studies, the sample size was based on the number of items in the measuring instruments, with a minimum of 5 times that number.[14] Since the PICSQ comprises 18 items and the HABC-M comprises 27 items, it was planned to reach at least 135 patients, considering the scale with the highest number of items.

Data Collection Procedures and Instruments

The data collection was performed by two researchers who identified potential ICU patients who met the inclusion criteria. During the discharge of these patients, the patients and their relatives were given detailed information about the study and were invited to participate in the study. Informed consent and contact information were obtained from patients or their relatives who agreed to participate. The participants were informed that they would be contacted via telephone two weeks after their discharge[10] because the hospital did not have an outpatient clinic for post-intensive care follow-up. Participants were handed copies of the study's data collection tools so that they would be familiar with these tools and could follow during the interview if they wished when they were called by phone (except for the patients included in the test-retest phase). Two weeks later, in line with the contact information received, the patient or his/her relatives were contacted by telephone, and the items for each data collection tool were read one by one, and their answers were recorded by the researchers. On average, the interviews lasted approximately 18-25 minutes per participant.

The data collection tools included the Patient Characteristic Form, the PICSQ, and the HABC-M, as well as the standardized external scales selected to represent the three domains of PICS to assess the concurrent validity of the scales: Pfeiffer's Short Portable Mental Status Questionnaire (SPMSQ) (for the cognitive domain), the 10-item Barthel Index (BI) (for the physical domain), and the Hospital Anxiety and Depression Scale (HADS) (for the mental domain). For the three domain-specific standardized scales, we considered the most commonly used instruments in studies reporting the use of PICS in the literature.[12-14]

Patient Characteristic Form: This form was prepared by the investigators and included questions regarding the socio-demographic characteristics (age, gender, etc.) and health status of the patients (comorbidities, APACHE-II score, duration of MV monitoring, presence of delirium with CAM-ICU, duration of ICU stay, etc.).[9,10,12,13]

PICSQ: This 18-item self-report scale was developed by Jeong and Kang[9] and consists of three subscales (six items each) covering the cognitive, physical, and mental domains of PICS. Items are rated using a four-point Likert scale (0= "never," 1= "sometimes," 2= "most often," 3= "always") and the total score ranges from 0 to 54. Higher scores indicate more severe PICS.[9] The validity and reliability of the scale were tested through exploratory factor analysis (EFA), confirmatory factor analysis (CFA), and internal consistency. The three-factor structured PICSQ demonstrated high internal consistency reliability, with a Cronbach's alpha of 0.93 for the overall scale and 0.84-0.90 for the sub-scales.[9]

HABC-M: Although this scale was originally developed for patients with dementia, its content similar to the PICS has led to its validation for assessing PICS in ICU patients.[10] The scale consists of a total of 27 items that examine the cognitive, functional, and behavioral/mood domains. The cognitive subscale consists of 6 questions related to memory, orientation, and judgment; the functional subscale consists of 11 questions related to activities of daily life; and the behavioral subscale consists of 10 questions related to depression, psychotic symptoms, and anxiety symptoms.[10] Each item was graded according to the patient's perceived frequency of the symptom within the last 2 weeks: 0= Not at all (0-1 day), 1= Several days (2-6 days), 2= More than half the days (7-11 days), 3= Almost daily (12-14 days). The maximum total score across the scale was 81, and higher scores were associated with higher symptom severity.[10] Psychometric properties of the scale were tested concurrently, in known group validity; and internal consistency reliability. The total scale and all subscales demonstrated good to excellent internal consistency, with Cronbach's values ranging from 0.83 to 0.92.[10]

Standard scales in the three domains of PICS: The SPMSQ is a brief, 10-item cognitive screening tool with a score range of 0-10. Scoring is based on the number of incorrect responses: 0-2 incorrect responses indicate normal cognitive function and 3-4 incorrect responses indicate mild, 5-7 incorrect responses indicate moderate, ≥8 incorrect responses indicate high cognitive impairment.[15] The 10-item BI is commonly

used in functional disability to measure an individual's performance in activities of daily living. The total score ranged from 0 to 100, where low scores indicate low functional status.[16] The HADS was developed by Zigmond and Snaith and consists of 14 items: seven for anxiety symptoms and seven for depression symptoms. The maximum score for each subscale is 21; the cut-off is ≥8; and higher scores indicate higher levels of anxiety or depression.[17]

Translation of Scales

The five recommended steps were followed for the translation and cross-cultural adaptation procedures of the scales:[18]

1) Translation from English to Turkish: The scales were translated from English to Turkish by two independent sworn translators (T1 and T2) who are native Turkish speakers and have good knowledge of both languages.

2) Synthesis of the translations: The two first translators synthesized the translations of the scales and summarized them into a single version (T1.2).

3) Back translation: Two native and bilingual translators (BT1 and BT2) who were not familiar with the original version of the scales independently translated the T1.2 version of the scales into English.

4) Expert Committee: An expert committee of T1, BT1, two specialist physicians with at least five years of experience and research studies in the field of intensive care, one physiotherapist, one psychiatrist, one neurologist, and two nursing faculty members who have research experience in the field of intensive care and scale development/adaptation evaluated the accepted versions of the scales in terms of semantic, idiomatic, experiential, and conceptual equivalence and created the preliminary final versions of the scales in Turkish.

5) Pilot testing of the pre-final version: Finally, two groups of five (a total of 10) ICU survivors were excluded from the overall sample and invited to participate in a pilot test (face validity) of the PICSQ and HABC-M. They assessed the clarity and understanding of the items of the PICSQ and HABC-M on a four-point Likert scale (1= not clear/understandable, 2= somewhat clear/understandable, 3= quite clear/understandable, and 4= highly clear/understandable). Since all items had at least a 90% level of clarity and understandability (a score of three or higher), the final Turkish versions of the scales were created without additional revision.

A second panel of 10 experts was formed and asked to assess the content validity of the scales using item-level content validity index (I-CVI) and scale-level content validity index (S-CVI/Ave) within two weeks. Accordingly, experts rated each item on a 4-point Likert-type CVI scale according to its clearness, relevance, and important an item was.[19] Panel members were also asked to provide additional comments or feedback on the sections they considered necessary. The I-CVI was calculated as the number of experts scoring 3 or 4 divided by the total number of experts (minimum acceptability ≥0.78); the S-CVI/Ave was calculated as the sum of the I-CVIs divided by the total number of items (minimum acceptability ≥0.80).[19]

Ethical Considerations

The research was conducted in accordance with the Declaration of Helsinki. Permissions were obtained from the Ethics Committee for Clinical Research at Bursa City Hospital (approval number: 2022-5/1, date: 06.04.2022) and the hospital. Prior to data collection, each patient or their relatives was informed about the study, and written consent was obtained. Participants were informed that they had the right to withdraw from the study at any time without any impact on their treatment or services. For the adaptation of the PICSQ, under the guidance of Dr. Jiyeon Kang, a request for permission to use the questionnaire was made via https://www.thepersoncenteredcare.org/picsq-1, and the request was approved. Permission to adapt HABC-M was obtained from Dr. Malaz A. Boustani via e-mail. Permission was also obtained via e-mail from the authors who performed the Turkish validation of the standard scales used for the PICS.

Statistical Analysis

The data were analyzed using the SPSS (Statistical Package for Social Sciences for Windows version 28.0) and AMOS (Analysis of Moment Structures version 28) software packages. Results from each scale were analyzed independently. The normal distribution was assessed using skewness/kurtosis and the Shapiro-Wilk test. Descriptive statistics were used to summarize the participants' characteristics and outcome variables. CFA was used to test the construct validity of the scales, and the existing structure was examined with the following acceptance criteria for goodness-of-fit indices: chi-square/degree of freedom (χ^2/df) <5, goodness-of-fit index (GFI) >0.85, comparative fit index (CFI) >0.90, root mean square error of approximation (RMSEA) <0.08, Tucker-Lewis Index (TLI) ≥0.90, and Standardized Root Mean Residual (SRMR) ≤0.06.[20,21] Item factor loadings were expected to be ≥0.30.[21] For concurrent validity, the relationship between each domain level of the PICS and the validated instruments was assessed via correlation analysis. The interpretation of correlation coefficients was as follows: negligible relationship (<0.20); low correlation, (0.20-0.40); moderate correlation (0.40-0.70); high correlation (0.70-0.90); and very high correlation (0.90-1.00).[22] Cronbach's alpha coefficient and item-total correlation (ITC) were used to measure internal consistency reliability. Cronbach's alpha results were assessed as follows: $\alpha \geq 0.9$ is excellent, $0.9 > \alpha \geq 0.8$ is good, $0.8 > \alpha \geq 0.7$ is acceptable, $0.7 > \alpha \geq 0.6$ is questionable, $0.6 > \alpha \geq 0.5$ is poor, $0.5 > \alpha$ is unacceptable.[23] For the ITC, a value greater than 0.30 indicated that the item was correlated with the overall scale.[23] The intraclass correlation coefficient (ICC) was used to determine test-retest reliability (stability), and the acceptable value was ≥0.70.[24] The significance level was accepted at $p<0.05$.

RESULTS

Characteristics of Patients

Of the 332 patients reached during the study, 175 were excluded from the study for the following reasons: 36 patients died during the study period, 85 patients did not meet the inclusion criteria, 24 patients wanted to drop out of the study or did not respond to follow-up phone calls, and 20 patients were excluded because they were involved in the test-retest (10 patients for each scale) and face validity (5 patients for each scale) phases of the study. Therefore, the overall sample consisted of 157 ICU patients.

The mean age of the patients was 62.13±11.47 years; 66.2% were male, and more than half (65.0%) had at least a high school education. Comorbidities were present in 73.9% of patients, most of whom were medical patients (62.4%), and 22.3% developed delirium. Participants had a median APACHE II score of 16 [interquartile range (IQR): 13-20], median number of MV days of 5 (IQR: 2-11), and median ICU stay of 8 days (IQR: 2-15) (Table 1).

Validity

Content Validity

According to the expert panel, the items of both scales were highly acceptable in terms of clarity, relevance, and importance. I-CVIs were within the range of 0.80-1.00 for both PICSQ-T and HABC-M-T; S-CVIs were within 0.91-0.95 for PICSQ-T and 0.93-0.96 for HABC-M-T.

Table 1. Characteristics of ICU patients

Variables	(n=157)
Age (years), mean ± SD	62.13±11.47
Males, n (%)	104 (66.2)
Education level, n (%)	
Less than high school	55 (35.0)
High school and more	102 (65.0)
Comorbidities, n (%)	116 (73.9)
Type of patient, n (%)	
Medical	98 (62.4)
Surgical/trauma	59 (37.6)
Delirium positive[a], n (%)	35 (22.3)
APACHE II, median (IQR)	16 (13-20)
MV days, median (IQR)	5 (2-11)
Length of ICU stay (days), median (IQR)	8 (2-15)

SD: Standard deviation, IQR: Interquartile range, APACHE: Acute Physiology and Chronic Health Evaluation, MV: Mechanical ventilation, ICU: Intensive care unit, [a]Delirium is evaluated by CAM-ICU.

Construct Validity

CFA with maximum likelihood was performed to test whether the factor structures of the adapted scales were compatible with those of the original scales (Figure 1). As a result, the fit indices of PICSQ-T and HABC-M-T were found to be χ^2/df=2,017 and 2.043, respectively; GFI=0.863 and 0.876, respectively; CFI=0.930 and 0.945, respectively; RMSEA=0.071 and 0.062, respectively; TLI=0.915 and 0.923, respectively; and SRMR=0.053 and 0.049, respectively (Table 2). As a result of CFA, the factor loadings of the PICSQ-T items ranged from 0.54 to 0.88, and for the HABC-M-T items, they ranged from 0.64 to 0.82, and the critical ratio and p-values of the items were significant (p<0.05) (Table 2).

Concurrent Validity

As shown in Table 3, all three domains in the PICSQ-T and HABC-M-T scales showed a close and significant correlation with the corresponding standard scales (p<0.05).

Reliability

Internal Reliability

Cronbach's alpha value was between 0.852 and 0.903 for the subdimensions of the PICSQ-T and 0.945 for the total scale; it was between 0.865 and 0.933 for the subdimensions of the HABC-M-T and 0.963 for the total scale (Table 4). ITC values were between 0.530 and 0.806 for the PICSQ-T and between 0.517 and 0.824 for the HABC-M-T.

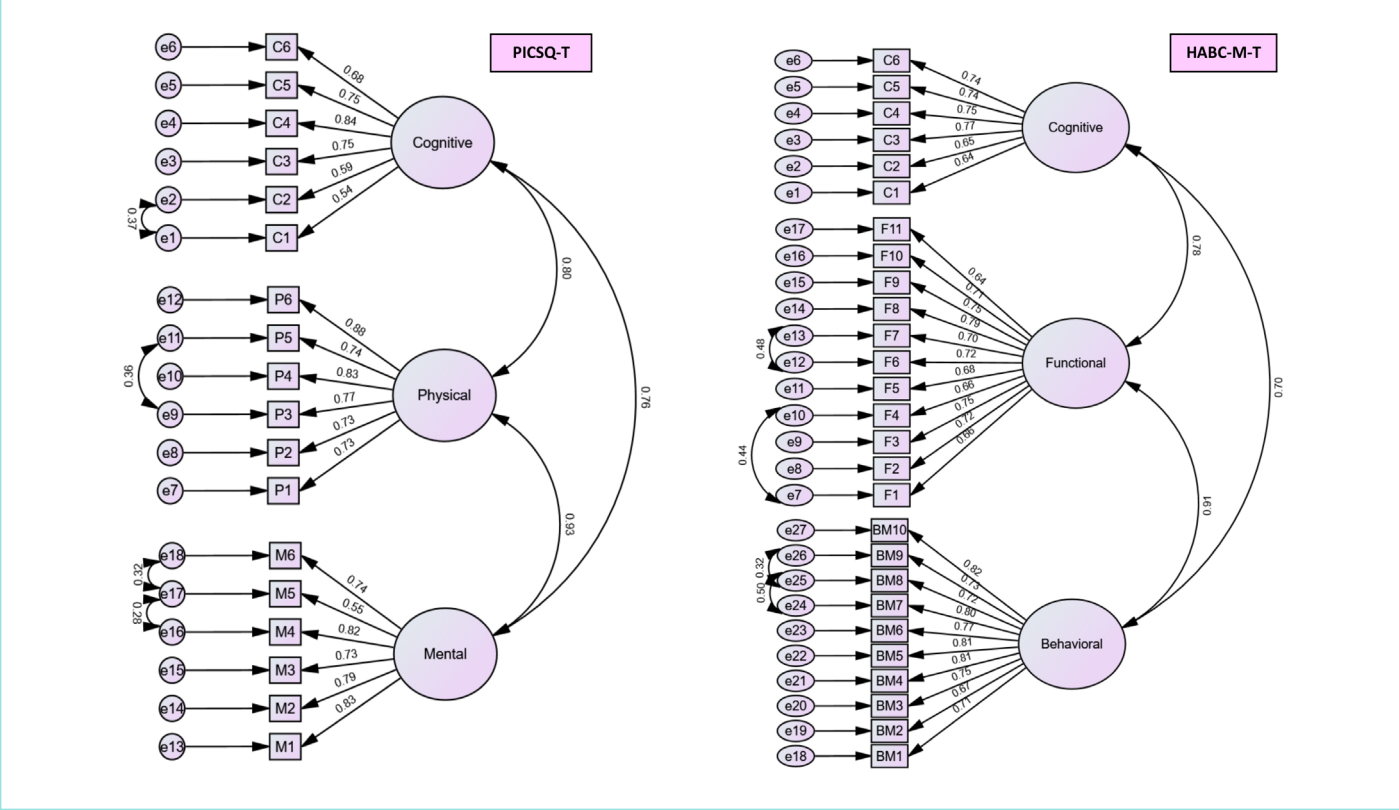

Figure 1. Factor structure of the PICSQ-T and HABC-M-T.

PICSQ-T: Turkish version of the Post-Intensive Care Syndrome Questionnaire, HABC-M-T: Turkish version of the Healthy Aging Brain Care Monitor.

Table 2. Model goodness of fit indices and factor loadings of the PICSQ-T and HABC-M-T based on CFA

PICSQ-T						**Model goodness-of-fit indices**		
Factors	**Items**	**SE**	**CR**	**p-value**	**Factor loadings**	**Goodness-of-fit index**	**Criteria**	**Results**
Cognitive	C1				0.537	χ^2/df	<5	**2.017**
	C2	0.169	7,028	<0.001	0.587	GFI	>0.85	**0.863**
	C3	0.235	6,458	<0.001	0.751	CFI	>0.90	**0.930**
	C4	0.244	6,816	<0.001	0.841	RMSEA	<0.08	**0.071**
	C5	0.256	6,463	<0.001	0.752	TLI	>0.90	**0.915**
	C6	0.229	6,129		0.683	SRMR	≤0.06	**0.053**
Physical	P1				0.730			
	P2	0.140	9,070	<0.001	0.730			
	P3	0.148	9,623	<0.001	0.773			
	P4	0.123	10,431	<0.001	0.833			
	P5	0.159	9,127	<0.001	0.735			
	P6	0.137	11,114		0.885			
Mental	M1				0.834			
	M2	0.087	11,646	<0.001	0.793			
	M3	0.090	10,416	<0.001	0.734			
	M4	0.075	12,140	<0.001	0.815			
	M5	0.101	7,195	<0.001	0.553			
	M6	0.079	10,611	<0.001	0.743			
HABC-M-T						**Model goodness-of-fit indices**		
Factors	**Items**	**SE**	**CR**	**p-value**	**Factor loadings**	**Goodness-of-fit index**	**Criteria**	**Results**
Cognitive	C1				0.636	χ^2/df	<5	**2.043**
	C2	0.157	6,884	<0.001	0.648	GFI	>0.85	**0.876**
	C3	0.168	7,873	<0.001	0.770	CFI	>0.90	**0.945**
	C4	0.174	7,737	<0.001	0.752	RMSEA	<0.08	**0.062**
	C5	0.162	7,637	<0.001	0.739	TLI	>0.90	**0.923**
	C6	0.159	7,666	<0.001	0.743	SRMR	≤0.06	**0.049**
Functional	F1				0.665			
	F2	0.146	8,109	<0.001	0.718			
	F3	0.135	8,443	<0.001	0.752			
	F4	0.097	10,108	<0.001	0.659			
	F5	0.154	7,773	<0.001	0.684			
	F6	0.126	8,075	<0.001	0.715			
	F7	0.135	7,881	<0.001	0.696			
	F8	0.138	8,841	<0.001	0.794			
	F9	0.146	8,436	<0.001	0.752			
	F10	0.127	8,010	<0.001	0.708			
	F11	0.138	7,328	<0.001	0.640			
Behavioral	BM1				0.711			
& Mood	BM2	0.124	8,093	<0.001	0.667			
	BM3	0.118	9,055	<0.001	0.746			
	BM4	0.122	9,852	<0.001	0.811			
	BM5	0.106	9,824	<0.001	0.809			
	BM6	0.127	9,343	<0.001	0.770			
	BM7	0.113	9,731	<0.001	0.801			
	BM8	0.112	8,685	<0.001	0.716			
	BM9	0.112	8,811	<0.001	0.726			
	BM10	0.104	9,949	<0.001	0.819			

PICSQ-T: Turkish version of the Post-Intensive Care Syndrome Questionnaire, HABC-M-T: Turkish version of the Healthy Aging Brain Care Monitor, SE: Standard error, CR: Critical ratio, χ^2/df: Chi-square divided by the degrees of freedom, GFI: Goodness-of-fit index, CFI: Comparative Fit Index, RMSEA: Root Mean Square Error of Approximation, TLI: Tucker-Lewis Index, SRMR: Standardized Root Mean Square Residual.

Table 3. Concurrent validity of the PICSQ-T and HABC-M-T

Domains	Standard scales			
PICSQ-T	**SPMSQ**	**BI**	**HADS-A**	**HADS-D**
Cognitive	0.45*			
Physical		-0.80*		
Mental			0.74*	0.72*
HABC-M-T	**SPMSQ**	**BI**	**HADS-A**	**HADS-D**
Cognitive	0.47*			
Functional		-0.89*		
Behavioral			0.83*	0.80*

PICSQ-T: Turkish version of the Post-Intensive Care Syndrome Questionnaire, HABC-M-T: Turkish version of the Healthy Aging Brain Care Monitor, SPMSQ: Pfeiffer's Short Portable Mental Status Questionnaire, BI: Barthel Index, HADS-A: Hospital Anxiety and Depression Scale-Anxiety, HADS-D: Hospital Anxiety and Depression Scale-Depression, *p<0.05.

Test-Retest Reliability

In the test and retest measurements, ICCs were between 0.842 and 0.875 for the subscales of the PICSQ-T and 0.840 overall and between 0.712 and 0.877 for the subscales of the HABC-M-T and 0.892 overall (Table 4).

DISCUSSION

Despite its high prevalence and numerous adverse patient outcomes, PICS remains underrecognized, undertreated, and ignored. This is also true for Turkey, and to our knowledge, no study has been conducted on PICS in ICU patients in Turkey. One of the most important reasons for this situation is that the syndrome affects all three domains; there is a complex relationship between these domains, and different assessment tools should be used for each domain.[3,7] A systematic review of 18 studies investigating the characteristics of existing instruments used to measure PICS in adults reported that there were 41 different instruments in the studies, with two or more instruments used in each study.[25] It is clear that there is a need for clinical tools that evaluate all PICS domains together and within a short period of time. The HABC-M and PICSQ are two tools available to identify PICS in current studies.[9,10] In this study, we aimed to adapt both scales to Turkish and examine their psychometric properties. Our results showed that the Turkish versions of the scales were highly appropriate and acceptable properties.

CFA was performed to validate the subfactors of the scales. In the validation study of the Chinese version of the HABC-M, EFA was utilized, and factor loadings of the 19-item scale were reported to be >0.45.[26] In the study of the Spanish version of the HABC-M, the three-factor model structure of the scale was examined with CFA, and it was reported that the model showed a good to excellent fit with RMSE=0.073, CFI=0.99, and TLI=0.98, similar to our study.[27] In the original study on the development of the PICSQ, the CFA analysis for the three-factor and 18-item structure resulted in a χ^2/df of 3.08, CFI of 0.90, RMSEA of 0.090, TLI of 0.90, and SRMR of 0.06.[9] In light of these results, the model fit indices of the PICSQ-T in our study seem to be higher than those in the original study. This suggests that the translated items are better adapted to the Turkish language and culture and potentially better represent the underlying constructs.

The PICS domains of both scales showed moderate to high correlation with standardized scales, with the highest correlation found for the physical/functional domain and the lowest for the cognitive domain. This may have been due to the SPMSQ, which allowed us to assess the cognitive domain based on the data collection method used in the study. In studies reporting on PICS, the scales used to assess the cognitive domain are varied and include the MMSE, MoCa, and SPMSQ.[12-14] The SPMSQ has been reported to have high specificity but low sensitivity in identifying cognitive impairment, whereas the MoCA shows higher agreement and sensitivity than the other tests.[28]

In the analysis of the internal consistency of the scales, Cronbach's alpha values for the PICSQ-T and HABC-M-T were 0.94 (0.85-0.90 across subscales) and 0.96 (0.86-0.93 across subscales), respectively. In addition, the ITC values were >0.30 for both scales (lowest 0.525 for PICSQ-T and lowest 0.517 for HABC-M-T); therefore, no items were removed from the scales. In the original study for the development of the PICSQ, Cronbach's alpha was reported to be 0.93 for the overall scale and 0.84-0.90 for the subscales, which are very similar to those in our study.[9] In the first study for the validation of the HABC-M for PICS, its internal consistency was found to be 0.92 (0.83-0.84 for sub-dimensions).[10] In the studies adapting the HABC-M to other cultures, the internal consistency was reported as 0.92 (0.82-0.92) for the Chinese version,[26] 0.94 (0.87-0.90) for the Spanish version,[27] 0.80-0.91 for sub-dimensions of the Japanese version,[29] and 0.79 for the overall scale in French.[30] These results indicate that the HABC-M-T has higher internal consistency for both the overall scale and its subdimensions than other cross-cultural adaptations. This result reflects the impact of careful language and cultural adaptation, sample homogeneity, cultural sensitivity, and high-quality translation that we used throughout the study.

To assess the stability of the scales, a test-retest was performed with a group of 10 patients for each scale at a 2-week interval. The ICC values were acceptable (>0.70) for both scales at the subscale level and overall. In the original study for the PICSQ, a test-retest was performed with a 1-week interval, and the ICC values for each factor were within the range of 0.82-0.88 (p<0.001) and 0.90 (p<0.001) for total scores.[15] In the French version of the HABC-M, ICC values were reported to be higher than those reported here (0.98-0.99).[30] However, that study was conducted with patients in the post-intensive care follow-up clinic, and all patients were instructed to answer the questionnaire for the second time a day after the first administration. The high test-retest results in that study may have been due to the very short interval between the two tests.

Although various tools have been applied to assess the symptoms of PICS, ICU nurses and physicians may need additional training to use these tools, and the assessment process may be time-consuming. Our study showed that the Turkish versions of the HABC-M and PICSQ have

Table 4. Results of the reliability analysis of the PICSQ-T and HABC-M-T

PICSQ-T subscales	Items	Mean ± SD	Item-total correlation	Cronbach's α if item deleted	Cronbach's α	ICC
Cognitive	1	2.48±0.70	0.553	0.944	**0.852***	**0.859****
	2	2.17±0.76	0.530	0.944		
	3	1.95±0.76	0.636	0.942		
	4	1.96±0.74	0.703	0.941		
	5	1.97±0.83	0.639	0.942		
	6	2.31±0.77	0.632	0.942		
Physical	7	2.71±0.58	0.655	0.942	**0.903***	**0.842****
	8	2.38±0.74	0.723	0.941		
	9	2.24±0.78	0.745	0.940		
	10	2.55±0.66	0.767	0.940		
	11	2.05±0.84	0.720	0.941		
	12	2.43±0.73	0.806	0.939		
Mental	13	2.38±0.77	0.759	0.940	**0.890***	**0.875****
	14	2.29±0.81	0.737	0.940		
	15	2.22±0.82	0.658	0.942		
	16	2.40±0.72	0.773	0.940		
	17	2.22±0.85	0.525	0.945		
	18	2.39±0.72	0.705	0.941		
Total scale		41.20±9.85			**0.945***	**0.840****
HABC-M-T subscales	**Items**	**Mean ± SD**	**Item-total correlation**	**Cronbach's α if item deleted**	**Cronbach's α**	**ICC**
Cognitive	1	2.08±0.78	0.517	0.963	**0.865***	**0.846****
	2	1.90±0.77	0.587	0.963		
	3	1.90±0.79	0.644	0.962		
	4	1.93±0.79	0.651	0.962		
	5	2.25±0.76	0.678	0.962		
	6	2.54±0.70	0.647	0.962		
Functional	7	2.25±0.77	0.713	0.962	**0.928***	**0.877****
	8	2.20±0.77	0.723	0.962		
	9	2.43±0.71	0.715	0.962		
	10	2.03±0.85	0.705	0.962		
	11	2.38±0.69	0.739	0.962		
	12	2.31±0.75	0.694	0.962		
	13	2.20±0.79	0.766	0.961		
	14	2.17±0.78	0.672	0.962		
	15	2.36±0.72	0.770	0.961		
	16	2.22±0.81	0.571	0.963		
	17	2.35±0.74	0.724	0.962		
Behavioral	18	2.18±0.79	0.683	0.962	**0.933***	**0.712****
	19	2.19±0.77	0.743	0.962		
	20	2.10±0.75	0.704	0.962		
	21	2.26±0.71	0.735	0.962		
	22	2.14±0.77	0.714	0.962		
	23	2.26±0.71	0.711	0.962		
	24	2.27±0.72	0.723	0.962		
	25	2.36±0.70	0.754	0.961		
	26	2.34±0.66	0.824	0.961		
	27	2.36±0.68	0.577	0.963		
Total scale		60.10±14.59			**0.963***	**0.892****

SD: Standard deviation, ICC: Intraclass correlation coefficient, PICSQ-T: Turkish version of the Post-Intensive Care Syndrome Questionnaire, HABC-M-T: Turkish version of the Healthy Aging Brain Care Monitor, ICC: Intraclass correlation coefficient, *p<0.001, **p<0.05.

significant potential as standardized, user-friendly clinical tools that enable the screening and assessment of PICS symptoms across the three domains. Therefore, we believe that PICS measurement tools can be used by ICU nurses and physicians to assess all domains quickly and easily without resorting to different assessment tools for each domain when screening for PICS. They can also be used in a wide variety of healthcare settings (e.g., primary care and outpatient care) and applied in patient follow-up via phone calls or the internet, in addition to face-to-face examinations. Rapid screening of ICU survivors for cognitive, physical, and mental impairments may help identify where they need additional support and treatment and referral them to appropriate subspecialty care. In addition, we believe that the introduction and validation of these two PICS-related scales in the Turkish language will lead to the emergence and acceleration of epidemiological studies on PICS in Turkey. Although the patients in our study were in the early period after their discharge, their mean scores on the scales indicated severe PICS (41.20±9.85 points for PICSQ-T and 60.10±14.59 points for HABC-M-T), which is remarkable and illustrative for future studies to urgently address the cognitive, physical, and mental problems of intensive care survivors in Türkiye.

Study Limitations

This study has some limitations. First, since the study was conducted on patients within 2 weeks of their discharge from the ICU, the results reflected the observations of early ICU survivors. Second, the results cannot be generalized because the study was conducted at a single center, and the sample size was 157. Third, we excluded patients with diseases that may affect cognition because self-report scales are not suitable for these patients. Fourth, we used the Pfeiffer test, which has a lower performance than the MMSE or MoCA in assessing cognitive impairment, because the data were collected via phone calls. Finally, the disadvantages of the phone survey include the inability to make an objective face-to-face assessment while collecting data about the patient; the interview may take more than 15 minutes due to the number of questionnaires; calls may be interrupted; and the interview may have to be postponed as individuals are sometimes unavailable to answer the call.

CONCLUSION

Our results showed that the Turkish versions of the HABC-M and PICSQ had high validity and reliability and could be easily used to screen for PICS. Routine adoption of these tools to screen for PICS will enable healthcare professionals to recognize PICS symptoms in patients and ensure timely referral to appropriate subspecialties and post-ICU follow-up clinics, if available.

MAIN POINTS

- This study showed that the Turkish versions of the PICSQ and HABC-M had high validity and reliability and could be easily used to screen for PICS.
- These PICS assessment tools can be used by ICU nurses and other healthcare professionals to quickly assess all domains together, without having to resort to different assessment tools for each domain when screening for PICS.
- By using these scales, ICU survivors can be rapidly screened by healthcare professionals for PICS to identify which area of PICS they need additional support and treatments and can thus be referred to appropriate subspecialty care.

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ETHICS

Ethics Committee Approval: Permissions were obtained from the Ethics Committee for Clinical Research at Bursa City Hospital (approval number: 2022-5/1, date: 06.04.2022) and the hospital.

Informed Consent: Informed consent and contact information were obtained from patients or their relatives who agreed to participate.

Authorship Contributions

Surgical and Medical Practices: Ö.E.D., G.Ç., N.K.G., Concept: Ö.E.D., G.Ç., N.K.G., Design: Ö.E.D., G.Ç., N.K.G., Data Collection and/or Processing: Ö.E.D., G.Ç., Analysis and/or Interpretation: Ö.E.D., G.Ç., Literature Search: Ö.E.D., Writing: Ö.E.D., G.Ç., N.K.G.

DISCLOSURES

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

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RESEARCH ARTICLE

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Patient Safety Culture Scale in Medication Administration: A Scale Development Study

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Abstract

BACKGROUND/AIMS: Patient safety is an essential concept in all stages of patient care. The aim of this study was to develop the "Patient Safety Culture Scale in Medication Administration" as an assessment tool for safe drug administration, which is a very important concept in patient safety culture.

MATERIALS AND METHODS: This scale-development study was conducted with nurses working in a research hospital in Turkey. An item pool of 45 items was created by the researchers and presented to the experts. In line with expert opinions, an initial scale with 36 items was obtained by excluding 9 items. Exploratory and confirmatory factor analyses, test-retest reliability, and internal consistency analyses were used as the statistical methods.

RESULTS: In this study, a scale was developed to determine the importance that nurses attach to patient safety during drug administration. The final version of the scale comprises 14 items under 3 subscales. The subscales were chosen as "importance, caution, dedication" in order to help define the culture.

CONCLUSION: It can be asserted that the "Patient Safety Culture Scale in Medication Administration" has strong levels of validity and reliability in the assessment. It was observed that the developed scale model is theoretically and statistically appropriate and a valid and reliable assessment tool.

Keywords: Patient safety, medication management, medication mistakes, health care quality, nursing care management

INTRODUCTION

Medical mistakes are among the most important factors that threaten patient safety, and drug administration mistakes are the most common ones.[1] The National Coordinating Council for Medication Error Reporting and Prevention defines a medication mistake as "any preventable event that may lead to inappropriate medication use or patient harm while the medication is administered under the control of the health care professional, patient, or consumer.[2]

The American Food and Drug Administration reports that it receives over 100,000 reports of medication mistakes every year in the United States.[3] Medication mistakes can result in death or a life-threatening situation, infirmity or disability, hospitalization, and congenital anomaly.[4] Medication mistakes, which have such serious effects on human life, must be reported, and preventive developmental activities must be planned. These mistakes are related to the extent to which the patient safety culture has developed in institutions.

In healthcare systems, medication mistakes can occur at any stage of taking drugs to the pharmacy, storing them, administering them, and the disposing wastes.[5] One of these stages is the period that includes the request, acceptance, and administration of drugs.[6] At this stage, nurses

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should have direct contact with patients, should have a good command of all the practices in the care and treatment process, and assume an important role and responsibility in safe drug practices. The principle of non-maleficence is one of the basic principles in nursing care, and in this context, safe medicine practices are among the important responsibilities of the nurses.[7,8]

When the literature is examined, numerous studies have been conducted on patient safety, ranging from scale development on patient safety culture,[9] to system development for patient safety[10] and model/program development.[11] When analyzing from the nursing point of view, national and international studies have been conducted on attitudes and behaviors related to patient safety.[12-14] Studies on safe drug use and drug mistakes often cover incorrect drug administration, factors causing mistakes, and the level of knowledge and attitude of nurses.[15,16]

In these studies, it was observed that there was no scale for patient safety culture specifically designed for safe drug practices. In this sense, this research is a scale-development study on safe drug administration, which is a very important area in terms of patient safety culture, unlike studies on patient safety culture in the literature. This study is original because it focused on a specific area of patient safety. Future studies using this scale can identify cultural concerns related to safe drug administration and can then be investigated in more detail using interventional or pre-post designs.

MATERIALS AND METHODS

The methods used for this study were designed by Kartal and Bardakçı.[17] The following steps were followed in order in the development of the "Patient Safety Culture Scale in Medication Administration". The stages followed in the research are explained below;

- Stage 1: Creation of Draft Scale;

 - Establish an item pool for the draft scale by scanning the literature).

- Stage 2: Ensuring the Content Validity of the Draft Scale;

 - Submitting the item pool to experts for content validity and,

 - Submitting the initial scale to language experts to evaluate the intelligibility of the expressions in the item pool and their compliance with the language rules.

- Stage 3: Evaluation of construct validity of scale;

 - Determining the sample and applying the initial scale,

 - Exploratory factor analysis (EFA) and Confirmatory Factor Analysis (CFA) were applied to evaluate the construct validity of the scale,

 - Making item analysis of the scale.

- Stage 4: Evaluation of Scale Reliability;

 - Evaluating the reliability of the scale with test-retest reliability,

 - The reliability of the scale was calculated using Cronbach's Alpha internal consistency coefficient.

Sample

The population consisted of 650 nurses working in training and research hospitals in Türkiye. A simple random sampling method was used to determine the sample group. According to the method of sample size calculation for a finite population, the sample size was calculated as 242 with a power of 95%, margin of error of 5%, and effect size of 0.05.[18] Data were collected from 637 nurses in the sample group who were voluntary to participate in the study and filled out the online questionnaires. Links to the prepared forms were sent to the nurses via email, and they were asked to fill them out. 13 nurses did not participate in the study because they declined to participate in the study or were on leave. As suggested by Kartal and Bardakçı,[17] different sample groups should be selected for EFA, CFA, and test-retest. In this context, the nurses were divided into 3 groups. Data were collected from 387 nurses for EFA, 200 nurses for CFA, item analysis, and calculation of Cronbach's alpha coefficient, and 50 nurses for test-retest reliability. Nurses were assigned to the groups using an online randomization program.[19] The data were collected between September 1 and November 1, 2021. Nurses who were not specifically trained in drug safety, worked in clinics where treatments were intensive, had high patient circulation, and who filled out the research form completely were included in the study. Nurses who received drug safety training and completed the forms incompletely were excluded from the study.

Structure of the Scale

A 7-point likert type structure is safer because it is more sensitive than 5-point likert one.[17] For this reason, a 7-point Likert type structure was chosen for the developed scale. The items in the scale are rated as "7= Strongly agree", "6= Agree", "5= Partially agree", "4= Undecided", "3= Partially disagree", "2= Disagree", and "1= Strongly disagree". The scale scores were close to seven, it means that the level of agreement with the statement in that item was high. It approaches one, it signifies low level of agreement.

Establishing an Item Pool

The researchers established the initial pool of items based on a literature review[15,16,20-22] and their expertise. The initial item pool for the scale consisted of 42 positive items and 3 negative items.

Seeking Expert Opinion on Content Validity

To ensure content validity on a scale, all items included in the assessment tool should assess the targeted feature, and all details of the targeted feature should be questioned by the items in the scale. Thus, the assessment tool should have content validity at the level that it assesses the conceptual infrastructure of the quantity it aims to assess.[17] The experts were asked to evaluate each item and the overall scale using a rating scale. The items of the first draft scale were submitted to the opinion of 13 academic experts. These academics also have strong nursing backgrounds. The fields of these experts are surgical diseases nursing, pediatric nursing, internal medicine nursing, obstetrics and gynecology nursing, public health nursing, nursing management, and psychiatric nursing. The experts were reached via a corporate email, and their opinions were obtained. All experts evaluated all questions. After obtaining expert opinions, 9 items were not included in the item pool and were removed from the scale by content validity (CVI, Content Validity Index) analysis. Lawshe's method was used to calculate the CVI. As a result of the analysis, the CVI was 0.95 for the overall scale

and ranged from 0.90 to 0.97 for the items. The significance of the content validity index exceeded 0.80 and was accepted as acceptable.[23] The initial scale was also submitted to translation and grammatical structure experts for review of the 36 items.

Ethical Considerations

Ethics committee approval was obtained from the Adıyaman University Social and Human Sciences Ethics Committee (approval number: 125, date: 29.07.2021) and the permission was obtained from the Ministry of Health of the Republic of Turkey (date: 23.06.2021, form no: 2021-06-23T14_23_07).

Assessment tools were sent to the participants online, and they were asked to respond at a convenient time for them to ensure that their business plans did not disrupt. In addition, they were informed that they could withdraw from the study at any time without being subjected to any negative situations in their work life.

Statistical Analysis

The SPSS v.23.0 and SPSS AMOS Graphics v23.0 programs were used for statistical analysis. Exploratory and CFA, test-retest method, and internal consistency analysis were used as statistical methods. The reliability of the scale was examined by test-retest method and internal consistency analysis.

RESULTS

Sociodemographic Characteristics of the Participants

The majority of nurses participating in the study were female, in the same age range, married, had a bachelor's degree, and worked in internal medicine units. Moreover, 36.4% of them stated that they made a mistake in administering drugs at least once, 33.8% did not consider themselves competent in patient safety, and 87.4% wanted to receive up-to-date training on patient safety (Table 1). Considering the distribution of nurses based on their sociodemographic data, it was observed that the number in each group was sufficient. Nurses were categorized according to their demographic variables. The homogeneity test for these variables is presented in Table 2. Levene's test was used for homogeneity testing; $p>0.05$ indicates that the groups are homogeneous.[24] According to Levene's test, which was performed to check whether the groups were homogeneously distributed, the p-value was calculated as 0.05 <0.867, indicating that the group variances were homogeneously distributed (Table 2).

Findings on Construct Validity

In scale development studies, factor analysis is the most frequently used method to reveal the assessment structure of the scale. As a result of factor analysis, information about the general factor, subscales, and number of subscales was obtained.[17] Using data from the participants, we primarily aimed to determine the assessment structure of the scale. EFA was used on the data. In general, the sample size is requested to be 5-10 times the number of items in the scale. The most important criterion for applying EFA to a dataset is whether the sample is adequate or not. In EFA, Kaiser-Meyer-Olkin (KMO) statistics are considered to determine the adequacy of the sample and the rate of variance among the variables. The KMO test on the initial scale data was calculated as 0.810. In this context, it was determined that the sample adequacy was sufficiently good for EFA. Another important test to apply EFA to a dataset is Bartlett's test of sphericity. A high correlation between variables was sought in the factor analysis. This study aims to determine whether or not the scale is not an identity matrix. As a result of the analysis, it was determined that there was a high and significant correlation between the variables on the initial scale. Furthermore, the sphericity assumption was satisfied (χ^2=1844.160; $p<0.001$).

In order to determine the factor structure of the scale, EFA was applied to 36 items in the initial scale using Principal Component analysis and Varimax Rotation methods. Cross-loading items that did not fit into any factor were determined and removed from the scale. After removing 10

Table 1. Socio-demographic characteristics of the nurses (n=637)

Socio-demographic characteristics	n	%
Gender		
Female	412	64.7
Male	225	35.3
Age		
20-25 years	223	35.0
26-30 years	190	29.8
31 years and above	224	35.2
Marital status		
Married	405	63.5
Single	232	36.5
Educational background		
High school	85	13.4
Associate degree	146	22.9
Bachelor's degree	348	54.6
Postgraduate	58	9.1
Unit		
Internal medicine units	309	48.5
Surgical units	234	36.8
Outpatient clinic	94	14.7
Tenure in the profession		
0-5 years	367	57.6
6-10 years	118	18.6
11-15 years	58	9.1
16 years and above	94	14.7
Have you ever made a medication mistake?		
Yes	232	36.4
No	405	63.6
Do you find yourself sufficient in terms of patient safety?		
Yes	422	66.2
No	215	33.8
Do you want to receive up-to-date patient safety training?		
Yes	557	87.4
No	80	12.6

Table 2. Homogeneity test results according to the demographic variables of nurses

Levene's test	df1	df2	p
0.028	1	184.62	0.867

p>0.05.

items from the scale, EFA was applied to the remaining 26 items, and the results shown in Table 3 were obtained.

The eigenvalue is an important coefficient used to determine the number of factors. An eigenvalue of >1 is used to determine the number of factors to be extracted. This criterion is known as the Kaiser criterion in the literature.[17] According to the EFA result, 3 subscales with an eigenvalue of >1 were obtained within the scope of the Kaiser criterion. The total explained variance is an important criterion for determining the number of subscales and ensuring construct validity. The EFA results revealed that the total variance of the 3 factor initial scale structure was 46.943%. The variance rates explained by the factors were 28.20% for factor 1, 38.073% for factor 2, and 46.943% for factor 3 (Table 3). It is stated that the rate of variance explained by the assessment tool should be at least 40%.[17] In this context, the scale has an explained total variance rate above the lowest explained total variance rate reported in the literature.

In the literature, factor load values of ≥0.45 for items have been reported to be sufficient criteria for item selection.[17] When the factor loadings of the items were evaluated, it was determined that the factor loadings were in the range of 0.602-0.783. In this context, the factor loading levels of the items in the 3 factor model were high and sufficient.

In order to examine the validity of the assessment structure of the scale consisting of 3 subscales and 14 items after EFA, a CFA was conducted using data obtained from an independent sample of 200 nurses using the AMOS 23 program. Fit indices are used to determine whether or not the measurement model designed after CFA is compatible with the data. χ^2/SD, GFI, CFI, TLI, IFI, and Root Mean Square Error of Approximation (RMSEA) are fit indices commonly used in the literature.[25] Table 4 shows the reference intervals of the fit indices and scale values.[26] When the fit indices of the scale were examined as a result of CFA, it can be asserted that χ^2/SD and GFI values showed a good level of fit, wherease IFI, TLI, CF, andd RMSEA values showed an acceptable level of fit. Therefore, the validity of the 3-dimensional assessment structure determined by EFA was verified using an independent sample. Additionally, CFA findings are presented in Figure 1.

It is important that the regression coefficients in CFA are significant. Regression values express the predictive power of the items, namely, the factor loadings. A standard factor load value of >0.40 in CFA is necessary for construct validity.[25] In this context, the regression coefficients obtained by CFA are presented in Table 5.

According to the CFA results, the factor loadings were greater than 0.40 and acceptable in terms of the structure and validity of the scale (Table 5). Another important indicator of construct validity is average variance extracted (AVE) values. If the AVE value, which gives important information about whether items under the factor are in harmony or not, is greater than 0.5, the factor has concordance validity. If the AVE value is less than 0.5, then there is a measurement error; that is, there is no concordance validity.[17] It was determined that the AVE exceeded 0.5 in all factors of the scale (Table 5). Accordingly, it can be concluded that the scale has constructed validity.

Table 3. Results of exploratory factor analysis (n=387)

Subscales	Items	Factor load value	Eigenvalue	Variance (%)	Cumulative variance (%)
Importance	14. I know the absorption time of the drug to be administered.	0.602	6,486	28,201	28,201
	15. I know the importance of recording medication administration errors immediately.	0.769			
	18. I know the importance of reporting medication administration errors.	0.762			
	20. I report when medication administration errors occur.	0.702			
	30. I take precautions to prevent the mixing up of drugs that look and sound (by name) similar to one another.	0.704			
	32. I pay attention to intra-team communication to prevent medication administration errors.	0.618			
Precaution	5. I know the precautions to be taken to prevent medication administration errors.	0.693	2,270	9,871	38,073
	6. I participate in in-service training sessions to prevent medication administration errors.	0.712			
	7. I pay attention to the necessary precautions to prevent medication administration errors.	0.741			
	8. I take the necessary precautions to prevent the development of drug-induced allergy.	0.644			
	9. In the administration of narcotic drugs, I pay attention to practices within the scope of the institution's "Narcotic drug administration procedure".	0.609			
Devotion	11. When the clinic is busy, if the doctor has not written down the medicine/prescription in the patient's file, I follow what was requested the day before. Thus, patients receive their medication on time.*	0.783	2,040	9,871	46,943
	13. I will keep frequently used/difficult-to-find drugs in reserve.*	0.761			
	16. It is more appropriate to keep the medicines brought by patients with them.*	0.777			

*Negative items.

Item Analysis Findings

The item analysis process of the scale, which consists of 3 subscales and 14 items and was determined to have construct validity, was carried out using data collected from 200 nurses. Therefore, item analyses based on both item-total score correlations and lower-upper groups were used. Each of these analyses is used to evaluate whether or not items should be retained.

Item Analysis Based on Item-Total Score Correlation

This analysis was used to examine the correlation between the scores for each item in the scale and the total score of the scale. Items with an item-total correlation coefficient of <0.20 are excluded from the scale. Items with 0.20-0.30 can remain on the scale after evaluation of their remaining on the scale. Items with a coefficient of >0.30 were included in the scale because they were similar to the scale in general.[17]

The item-total correlation coefficient was greater than 0.30 for all 14 items of the scale. Accordingly, since all items on the scale were in the same direction as the entire scale, no item was removed from the scale (Table 6).

Table 4. References of fit indices and scale values

Fit indices	Good fit	Acceptable fit	Scale values
χ^2/SD	≤3	≤5	1.974
GFI	≥0.90	≥0.85	0.911
IFI	≥0.95	≥0.90	0.922
TLI	≥0.95	≥0.90	0.900
CFI	≥0.97	≥0.95	0.958
RMSEA	≤0.05	≤0.08	0.070

GFI: Goodness of fit index, IFI: Incremental fit index, TLI: Tucker-lewis index, CFI: Comparative fit index, RMSEA: Root Mean Square Error of Approximation.

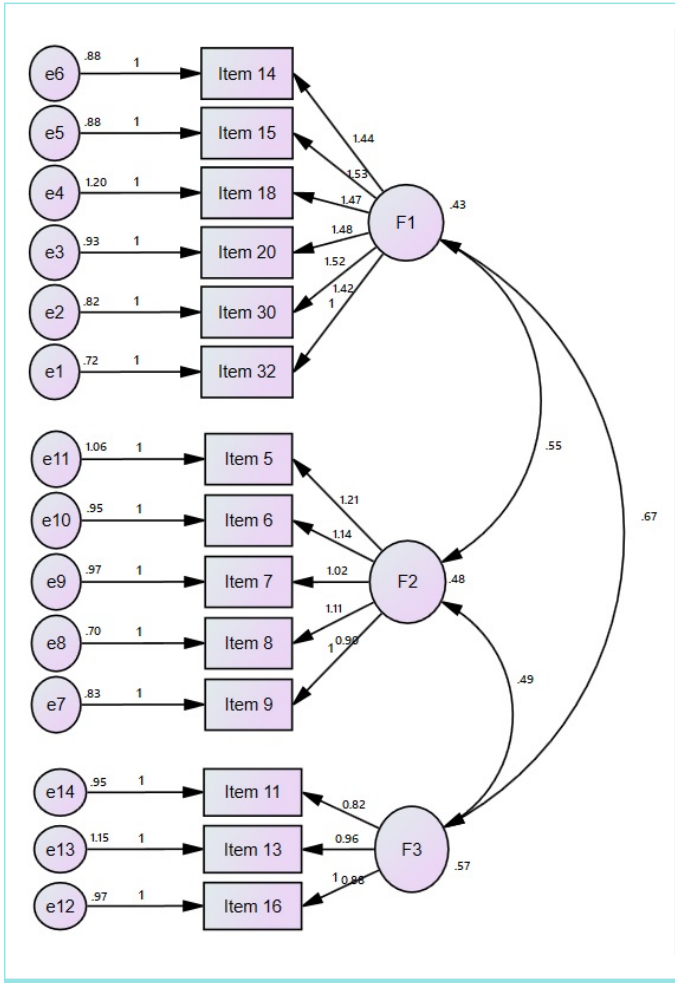

Figure 1. Confirmatory factor analysis results of the patient safety culture scale for the medication administration factor structure.

Table 5. Standard regression coefficients of items as a result of CFA (n=200)

Items	Importance	Precaution	Devotion
14. I know the absorption time of the drug to be administered.	**0.702**	0.553	0.578
15. I know the importance of recording medication administration errors immediately.	**0.819**	0.612	0.542
18. I know the importance of reporting medication administration errors.	**0.801**	0.428	0.603
20. I report when medication administration errors occur.	**0.775**	0.455	0.559
30. I take precautions to prevent the mixing up of drugs that look and sound (by name) similar to one another.	**0.796**	0.632	0.591
32. I pay attention to intra-team communication to prevent medication administration errors.	**0.689**	0.429	0.501
5. I know the precautions to be taken to prevent medication administration errors.	0.482	**0.703**	0.529
6. I participate in in-service training sessions to prevent medication administration errors.	0.379	**0.712**	0.598
7. I pay attention to the necessary precautions to prevent medication administration errors.	0.561	**0.741**	0.497
8. I take the necessary precautions to prevent the development of drug-induced allergy.	0.389	**0.721**	0.566
9. In the administration of narcotic drugs, I pay attention to practices within the scope of the institution's "Narcotic drug administration procedure".	0.474	**0.681**	0.512
11. When the clinic is busy, if the doctor has not written down the medicine/prescription in the patient's file, I follow what was requested the day before. Thus, patients receive their medication on time.*	0.601	0.558	**0.743**
13. I will keep frequently used/difficult-to-find drugs in reserve.*	0.485	0.597	**0.731**
16. It is more appropriate to keep the medicines brought by patients with themselves.*	0.563	0.643	**0.807**
AVE	0.585	0.503	0.579

*Negative items. CFA: Confirmatory factor analysis, AVE: Average variance extracted.

Table 6. Total score correlations							
Item	**Item 5**	**Item 6**	**Item 7**	**Item 8**	**Item 9**	**Item 11**	**Item 13**
Item-total	0.332	0.455	0.370	0.453	0.530	0.368	0.432
Item	**Item 14**	**Item 15**	**Item 16**	**Item 18**	**Item 20**	**Item 30**	**Item 32**
Item-total	0.552	0.484	0.544	0.512	0.609	0.514	0.589

Item Analysis Based on Lower-Upper Groups

In order to select items that have the capacity to discriminate, item total correlation calculation and significance of differences between 27% upper-lower group item averages are used in likert-type scale development studies.[27] The total scale scores obtained with the participation of 200 nurses were ordered from largest to smallest. To examine the discrimination capacities of the 14 items in the scale. The total mean scores of 57 nurses in the 27% upper-lower groups were determined using the independent samples t-test (Table 7). In addition, the overall scale and each item were compared separately (Table 8). When the mean scores of the lower and upper groups were compared, the difference was statistically significant ($p<0.05$).

When the mean scores of the 14 items in the scale were compared between the upper and lower groups, it was determined that there was a significant difference ($p<0.05$). According to the findings, all 14 items in the scale were distinctive and should be retained.

Table 7. Comparison of the mean scores of the lower and upper groups on the scale					
Groups	**n**	**x̄**	**SD**	**t**	**p***
Lower	54	66.72	10.65	28,385	0.002
Upper	54	95.9	3.27		
*p<0.01, SD: Standard deviation.					

Findings on the Reliability of the Scale

Test-Retest Reliability of the Scale

In the test-retest reliability, the scale was administered twice with an interval of 15 days. During this phase, we matched the participants by giving them nicknames. The absence of a significant difference between the mean scores obtained from the scale as a result of the application indicates the similarity of the two measurement results. Consistency, on the other hand, is among the well-known reliability criteria in assessment tools, which include measurement in the target, whose continuity is similar to attitudes and whose change feature is limited.[17] In this context, the stability of the scale was evaluated with the test-retest reliability on data obtained with the participation of all 50 randomly selected nurses.

There was no significant difference between the results of the 1st and 2nd application of the scale and its subscales ($p>0.05$). However, the test-retest stability coefficients of the scale and its subscales were found to be quite high and significant ($p<0.01$) (Table 9).

Internal Consistency Analysis

In scale development, there should be a correlation between the items in the scale and the characteristics that are aimed to be measured using Likert-type scales, and each item in the scale should assess a similar attitude.[28] In the literature, the Cronbach's α coefficient is generally used to control this hypothesis and determine its reliability level. It can be asserted that the higher the α coefficient, the more consistent are the items on the scale with each other. A Cronbach's α coefficient of >0.70 indicates that the scale is reliable.[17] Cronbach's α coefficients for the scale and its subscales were calculated using data obtained from 200 nurses who participated in the internal consistency reliability and item analysis stage (Table 10). The obtained data indicated that the reliability of the scale was sufficient, as evidenced by the Cronbach's α coefficient was greater than 0.70 (Table 10).

Table 8. Comparison of mean scores for item discrimination						
Item	**Groups**	**n**	**x̄**	**SD**	**t**	**p***
Item 1	Upper	54	6.87	0.52	10,031	**0.001**
	Lower	54	3.25	0.39		
Item 2	Upper	54	6.77	1.09	12,735	**0.001**
	Lower	54	2.99	1.07		
Item 3	Upper	54	6.03	0.35	11,843	**0.001**
	Lower	54	2.77	0.33		
Item 4	Upper	54	6.51	0.70	10,220	**0.001**
	Lower	54	3.12	0.68		
Item 5	Upper	54	6.21	0.45	9,888	**0.001**
	Lower	54	3.11	0.47		
Item 6	Upper	54	6.37	2.17	15,421	**0.001**
	Lower	54	2.57	2.43		
Item 7	Upper	54	5.96	1.18	11,553	**0.001**
	Lower	54	2.88	1.08		
Item 8	Upper	54	5.63	1.28	7,521	**0.001**
	Lower	54	2.85	1.16		
Item 9	Upper	54	6.66	0.63	6,591	**0.001**
	Lower	54	3.57	0.80		
Item 10	Upper	54	6.31	0.71	14,523	**0.001**
	Lower	54	2.79	0.87		
Item 11	Upper	54	6.81	0.74	13,728	**0.001**
	Lower	54	2.75	0.83		
Item 12	Upper	54	5.88	0.80	7,567	**0.001**
	Lower	54	2.96	0.57		
Item 13	Upper	54	5.87	0.64	8,312	**0.001**
	Lower	54	2.59	0.56		
Item 14	Upper	54	6.08	0.72	5,428	**0.001**
	Lower	54	3.44	0.61		
*p<0.01. SD: Standard deviation.						

Table 9. Results of test-retest (n=50)

	Application	n	x̄	SD	t	p	r	p*
Importance	1.	50	31.42	4.01	0.884	0.421	0.921	**0.001**
	2.	50	31.58	3.96				
Precaution	1.	50	28.77	11.28	0.781	0.394	0.901	**0.001**
	2.	50	28.96	11.33				
Devotion	1.	50	17.23	13.29	0.326	0.567	0.945	**0.001**
	2.	50	17.39	13.17				
Total	1.	50	76.25	14.23	1,253	0.183	0.936	**0.001**
	2.	50	76.39	14.31				

*p<0.01. SD: Standard deviation.

Table 10. Cronbach's α coefficients of the overall scale and its subscales (n=50)

	Number of Items	Cronbach's α
Importance	6	0.796
Precaution	5	0.810
Devotion	3	0.756
Total	14	0.814

DISCUSSION

Scale Validity and Reliability

This study aimed to develop a Likert-type scale to measure patient safety culture in nurses' medication administration practices and to evaluate the scale's validity and reliability by performing necessary analyses. The 45-item item pool created by the researchers was examined in line with expert opinions and 9 items were removed. The expert opinion was then taken in terms of language and meaning. After EFA was performed to determine the factor structure, items that could not be placed on any factor and cross-loaded were removed from the scale. After the analysis, a scale structure consisting of 3 subscales and 14 items was obtained, which accounted for 46,943% of the total variance. It has been reported in the literature that the total variance limits should be between 40% and 60%.[25] It has been reported that factor loadings of items obtained as a result of EFA above 0.45 are sufficient.[17] The factor loadings of the scale developed in this study were in the range of 0.602-0.783. It can be concluded that the factor load values were high and sufficient.

After EFA, the scale structure was subjected to CFA with an independent sample. CFA revealed that the scale model consisting of 3 subscales and 14 items was compatible, and the scale structure created by EFA was valid for another sample. The factor loadings of all items were high and significant after CFA. In addition, the AVE values of the factors were higher than 0.50. These findings confirmed the construct validity of the 14-Item scale with 3 subscales.[17]

In medication administration, item analysis was performed within the scope of item-total correlation of items included in the patient safety culture scale. The correlation coefficient should be greater than 0.30, and the correlation coefficients of all the items in the present study were found to be higher than the lower limit.[25] As a result of the item analysis based on the lower and upper groups, which is a different item analysis, it was determined that the overall scale and all items were distinctive.

The reliability analyses of the scale were performed in terms of stability and internal consistency. To determine the stability of the scale with the test-retest reliability, it was determined that the scores determined by applying the scale and its subscales in the same sample with an interval of 15 days were similar, and the stability coefficients were greater than 0.70. It can be asserted that the assessment results of the scale developed with these findings were invariant, stable, and reliable. The internal consistency of the scale was examined by calculating the Cronbach's α coefficients of the overall scale and its subscales. As a result of the calculations, it was determined that the Cronbach's α coefficients of the overall scale and its subscales were greater than 0.70. Turkmen et al.[29], reported that the Cronbach's α internal reliability coefficient of the "Patient Safety Culture Scale" they developed in this area was 0.97 for the overall scale and ranged between 0.83 and 0.92 for its subscales. Likewise, Baykal et al.[30], and Sexton et al.[31], reported that the item-total score correlation values of the patient safety attitude scale, of which a Turkish validity and reliability study was conducted, ranged between 0.35 and 0.58, and the Cronbach's α value was 0.93. The Cronbach's α values for the subscales of the related scale were 0.85 for job satisfaction, 0.86 for teamwork, 0.83 for safety climate, 0.77 for management mentality, 0.74 for defining stress, and 0.72 for working conditions.

Contributions to the Nursing field

It is known that patients in many countries and healthcare institutions are harmed due to medical mistakes and malpractices.[32,33] Adopting safety practices for patients is essential to prevent deaths and other adverse events caused by medical mistakes. Ensuring patient safety is important for enhancing the quality of nursing care as well as providing the basis for the delivery of high-quality care. In order to achieve sufficient patient safety practices, first, the perception of a patient safety culture must be established among healthcare professionals.[34]

Medication mistakes, one of the subdimensions of patient safety, include misadministration that threatens patients' lives. It is important to administer drugs by nurses in many countries and health institutions

by paying attention to patient safety principles. In the literature, many studies have reported that a great majority of nurses make medication mistakes.[35,36] Therefore, assessment tools are designed to assess knowledge levels or improve safe drug administration. However, to ensure drug safety, it is not sufficient to identify and correct mistakes at the stage of application. The research findings and remedial studies are insufficient in terms of defining culture and planning remedial activities in this field. Individual and institutional culture should be established to prevent mistakes in drug administration. Developing a safety culture for drug administration will contribute to the development of nurses' perceptions of their practices, the determination and improvement of the importance they attach to their work, and the maintenance of safe practices principles and patient safety.

Therefore, to prevent medication mistakes and ensure patient safety, a safety culture for drug administration should be established among nurses. Evaluation of the safety culture for drug administration in institutions will contribute to the preparation of education plans for the personnel of the institution, to create a joint decision-making mechanism, and to enhance the quality of patient care.

When the literature was reviewed, it was observed that there were scales evaluating the patient safety culture, but these scales did not make separate measurements for the subdimensions of patient safety. This is valid for drug administration. The scale developed in the present study consists of items that mention all stages of drug administration. It is considered an adequate tool in terms of evaluating patient safety culture in nurses' medication administration because it includes all stages. The use of this scale can help eliminate medication mistakes.

Study Limitations

One of the important limitations of our study is that the scale developed specifically was designed for nurses. It does not include members of other professions who play a role in medication administration and delivery of health care services. The second limitation is that it contains limited data on nurses working in a certain geographical area in Turkey. It cannot be generalized to all nurses.

CONCLUSION

In this study, a scale was developed to determine the importance that nurses attach to patient safety during drug administration. The final version of the scale comprises 14 items under 3 subscales. The subscales were chosen as "importance, caution, dedication" in order to help define the culture. According to the results, the "Patient Safety Culture Scale in Medication Administration" has strong validity and reliability in the assessment.

The use of this scale in the field will contribute to the definition of drug-administration culture at the institutional level in the relevant institutions. Thus, it will allow the planning of remedial development activities to ensure the development of a safe drug-administration culture, which is the first step in preventing malpractise. Validity and reliability studies of the developed scale in other languages may also contribute to the definition of intercultural differences.

MAIN POINTS

- Medication administration mistakes are the most common medical mistakes that threaten patient safety.
- The use of this scale in the field will contribute to the definition of drug-administration culture at the institutional level in the relevant institutions.
- This will allow the planning of remedial development activities to ensure the development of a safe drug-administration culture, which is the first step in preventing malpractise.

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ETHICS

Ethics Committee Approval: This study was approved by the Adıyaman University Social and Human Sciences Ethics Committee (approval number: 125, date: 29.07.2021).

Informed Consent: It wasn't obtained.

Authorship Contributions

Surgical and Medical Practices: A.T.Ö., Y.Ç., Concept: A.T.Ö., Y.Ç., Design: A.T.Ö., Y.Ç., Data Collection and/or Processing: A.T.Ö., Y.Ç., Analysis and/or Interpretation: A.T.Ö., Y.Ç., Literature Search: A.T.Ö., Y.Ç., Writing: A.T.Ö., Y.Ç.

DISCLOSURES

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

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RESEARCH ARTICLE

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Determination of Death Anxiety in Individuals with Chronic Obstructive Pulmonary Disease

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Abstract

BACKGROUND/AIMS: Chronic obstructive pulmonary disease (COPD) causes patients to experience a number of disturbing physical and psychological symptoms. One of these disorders is death anxiety. The purpose of this study was to determine death anxiety in patients with COPD.

MATERIALS AND METHODS: The study was conducted as a cross-sectional descriptive study. The study included 100 patients with COPD at a government hospital in the Turkish Republic of North Cyprus (TRNC) between January and May 2021. A Descriptive Information Form and the Templer Death Anxiety Scale were used to collect data. The t-test in independent groups and ANOVA analysis were used in the analysis of data that showed normal distribution, and the Mann-Whitney U test and the Kruskal-Wallis H test were used for data that did not show normal distribution.

RESULTS: The patients' mean scores on the Templer Death Anxiety Scale was high. A significant difference was found between mean scores for death anxiety according to patients' ages, duration of illness, meeting physical needs, and presence of another illness.

CONCLUSION: Death anxiety among individuals with COPD was high in the TRNC. The death anxiety level of patients should be determined during hospitalization, and support should be provided. It is also recommended that a study on death anxiety in individuals with COPD and related factors be conducted in the TRNC with a wider sample.

Keywords: Chronic obstructive pulmonary disease, death anxiety, COPD patients

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a significant and increasing cause of morbidity and mortality worldwide. According to World Health Organization data, COPD caused the death of 3.17 million people in 2015 and was the cause of 5% of all deaths.[1] According to the Turkish Chronic Diseases and Risk Factors Study, the prevalence of COPD in Türkiye is 5.3%.[2] According to 2017 data from the Turkish Statistical Institute (TURKSTAT), chronic respiratory system diseases are in third place among diseases that are the cause of death.[3] In the Turkish Republic of North Cyprus, there are insufficient records and spirometric measurements, so there are no studies or official data.

COPD causes patients to experience a series of physically and psychologically disturbing symptoms. As the disease progresses, patients experience changes in both functional and cognitive performance.[4] The clearest physical signs of COPD are shortness of breath, coughing, and

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the production of phlegm. Shortness of breath results in a restriction in patients' daily activities, a decline in their quality of life, and anxiety.[5-8]

It has been stated that the incidence of signs of anxiety in patients with COPD varies from 2 to 50%.[9] Many studies conducted in Türkiye and around the world, show that COPD patients experience anxiety.[4,8,10-12] Shortness of breath is the basic cause of anxiety in individuals with COPD.[13] In a study by Kapısız and Eker[14] it was stated that severe shortness of breath was an important predictor of anxiety in patients with COPD. In particular, air hunger occurring with shortness of breath caused anxiety that approached panic in patients, and with it, a "fear of death".[15]

Death is defined in the Turkish Language Society's Dictionary of Biological Terms as "the end of all life events in living things, not starting again". The Large Turkish Dictionary defines it as "the complete and definite end of life of a person, animal or plant, the journey to the afterlife, eternal sleep". Death anxiety does not have a universal definition that is accepted by everyone.[16]

It has been reported that the anxiety experienced along with difficulty breathing causes death anxiety in COPD patients.[8] In studies by İnce[17], Güçlü[18], Demir-Gökmen and Fırat[19] it is stated that patients with COPD experienced death anxiety to a medium level. In another study, it was emphasized that patients with COPD experienced death anxiety at a high level.[11] In a qualitative study, it was revealed that patients with COPD experience death anxiety. The patients stated that the inability to get enough air caused death anxiety and that this anxiety limited their daily lives.[8]

Studies relating to COPD have shown that in patients with anxiety, the risk of widespread anxiety disorder,[20,21] exacerbation of the illness,[22] and death are high.[23] Therefore, it is important to evaluate the death anxiety of these patients to provide support in coping with death anxiety and to protect their psychological well-being and quality of life. Nurses play an important role in supporting patients in coping with death anxiety and protecting their psychological well-being. Understanding patients' death anxiety will help nurses plan patient care. No scientific data on this topic have been found in the Turkish Republic of North Cyprus. Therefore, the purpose of this study was to determine death anxiety in patients with COPD. It is considered that the results of this study will contribute to the literature on the topic in the country and will serve as a guide for further studies on COPD and death anxiety. This study is also considered important in terms of raising awareness among nurses who are responsible for managing the death anxiety experienced by patients with COPD and using the data obtained in nursing care.

Research questions

- What is the level of death anxiety in patients with COPD?

- Does death anxiety differ according to sociodemographic and illness-related characteristics of patients with COPD?

MATERIALS AND METHODS

The type of Study

This was a cross-sectional study.

Setting

The study was conducted between January and May 2021 in the lung disease department of a government hospital in the TRNC.

Sample

The sample of the study was made up of patients with COPD who visited the lung disease service of the hospital. Because the number of patients in the study population was unknown, hospital records were examined, and it was found that 137 patients were admitted to the hospital for treatment in 2018 and 2019. This was taken as a reference for determining the sample number, and the sample calculation formula for a known population was used. The sample was determined using a simple random sampling method. According to this, it was found that out of the 137 people in the population, only 100 had to be interviewed for a confidence interval (CI) of 95% and a 5% sampling error. As a result of the post hoc power analysis performed with a 95% CI and a 5% sampling error, it was found to be 99%.

Data Collection Instruments

A Descriptive Information Instrument made up by the researcher in line with the literature[11,17,18,25,26] and the Templer Death Anxiety Scale were used to collect data. There are 20 questions in the Descriptive Information Instrument, including the patients' sociodemographic characteristics and illness information.

The Death Anxiety Scale was developed by Templer[24], and Turkish validity-reliability work was conducted by Akça and Köse.[25] The model comprises 15 items with true-false responses. Those with a total score of 7 are considered to have high death anxiety. In the adaptation study, the Cronbach's alpha value of the scale was 0.75, whereas in the present study, it was 0.84.

Data Collection

Data were collected from patients in the lung disease service who volunteered to participate. The data were collected by one of the researchers between January and May 2021. This researcher works as a clinical nurse in a similar service. The researcher collected data face-to-face from the inpatients. The researcher asked questions and the patient answered.

Ethical Considerations

Regarding the ethical aspects of the study, consent to carry out the study was obtained from the Scientific Research Ethics Committee of the European University of Lefke (approval number: ÜEK/56/01/12/2021/04, date: 02.12.2020), and institutional permission was obtained from the hospital. Verbal and written informed consent was obtained from patients who volunteered to participate.

Statistical Analysis

The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess whether the data conformed to normal distribution. In the analysis of data with normal distribution, the t-test in independent groups and ANOVA analysis were used, whereas the Mann-Whitney U test and the Kruskal-Wallis H test were used in the analysis of data that did not show normal distribution. The Statistical Package for Social Sciences (SPSS) 25.0 software was used for data analysis.

RESULTS

Table 1 shows the distribution of patients who agreed to participate in the study according to their sociodemographic characteristics.

Table 1 shows that 37% of the participants were aged between 66 and 75 years, 64% were male, 74% were married, 37% lived in a village, 86% were not working, 57% were retired, 60% did not smoke, and 78% had another chronic illness.

Table 2 presents the distribution of patients according to certain characteristics related to their illness.

It is seen that the starting age of the illness of 39% of the patients included in the study was 59 years, 42% had had the illness for 6-14 years, 92% had received information on the illness, and of those (n=92), 83.75% had received information from a doctor, 31.5% from a nurse, 22.8% from television, a magazine or a book, and 9.8% from the internet. It is also seen that 36% of those participating in the study could partially meet their physical needs, 65% were able to comply with treatment, 38% had been admitted to hospital four times or more, 72% had a history of COPD in their family, and 90% had received help or support regarding the illness, 63.3% from their partners and 71.1% from their children (Table 2).

Table 1. Distribution of participants by socio-demographic characteristics (n=100)

	n	Percentage (%)
Age group		
65 years or less	35	35.0
66-75 years	37	**37.0**
76 years	28	28.0
Gender		
Female	36	36.0
Male	64	**64.0**
Marital status		
Single	13	13.0
Married	74	**74.0**
Divorced/separated/widowed	13	13.0
Place of residence		
City	34	34.0
Town	29	29.0
Village	37	**37.0**
Work status		
Working	14	14.0
Not working	86	**86.0**
Profession		
Office worker	3	3.0
Manual worker	10	10.0
Tradesman	3	3.0
Retired	57	**57.0**
Other	27	27.0
Smoking status		
Smoking	40	40.0
Not smoking	60	**60.0**
Other chronic illnesses		
Yes	78	78.0
No	22	22.0
Illness (n=78)*		
Hypertension	56	71.8
Diabetes	39	50.0
Heart disease	30	38.5
Other	13	16.7

*More than one was selected.

Table 2. Distribution of participants according to various illness-related characteristics (n=100)

	n	Percentage (%)
Age at onset of illness		
59 years or less	39	**39.0**
60-69 years	31	31.0
70 years or more	30	30.0
Duration of illness (years)		
5 years or less	41	41.0
6-14 years	42	**42.0**
15 years or more	17	17.0
Receipt of information about an illness		
Yes	92	**92.0**
No	8	8.0
Source of information (n=92)*		
Doctor	77	**83.7**
Nurse	29	31.5
TV/magazine/book	21	22.8
Internet	9	9.8
Ability to meet physical needs		
Not at all.	31	31.0
Partially	36	**36.0**
Completely	33	33.0
Compliance with treatment		
Yes	65	**65.0**
No	35	35.0
Number of hospital admissions		
This is the first time	28	28.0
This is the second time	18	18.0
This is the third time	16	16.0
Four times or more	38	**38.0**
Family history of COPD		
No	28	28.0
Yes	72	**72.0**
Receipt of illness-related help or support		
Yes	90	**90.0**
No	10	10.0
Person providing illness-related help or support*		
Partner	57	63.3
Children	64	**71.1**
Sibling	10	11.1
Friend	5	5.6
Psychologist/psychiatrist	8	8.9
Mother/father	2	2.2
Other	2	2.2

*More than one was selected. COPD: Chronic obstructive pulmonary disease.

The patients' mean Templer Death Anxiety Scale was found to be 10.31±3.66. Table 3 shows the participants' median Templer Death Anxiety Score according to their characteristics. A significant difference was found between the patients' median Templer Death Anxiety Scale scores according to age, duration of their illness, status of meeting physical needs, and whether they had another chronic disease. The difference relating to age is derived from the 65 years and below age group. The median death anxiety scores of individuals who had been ill for 15 years or more were significantly higher than those of the other two groups. The median death anxiety scores of patients who were completely unable to meet their physical needs were significantly higher than those of patients who were able to meet their physical needs partially or completely. Furthermore, the median death anxiety scale scores of patients who were able to partially meet their physical needs were significantly higher than those of patients who were able to meet their physical needs completely. No difference was found between the median death anxiety scale scores of the patients according to other characteristics.

Table 3. Comparison of Templer Death Anxiety Scale scores according to participants' characteristics (n=100)

			Templer Death Anxiety Scale Scores			
Variable	**Category**	**n**	**Median**	**Mean rank**	**Significance**	**Difference**
Age	65 years or less	35	8.00	38.66	X^2=9,097 **p=0.011***	**1-2** **1-3**
	66-75 years	37	12.00	56.32		
	76 years	28	12.00	57.61		
Gender	Female	36	11.00	53.29	Z=-0.725 p=0.468	
	Male	64	11.00	48.93		
Marital status	Single	13	9.00	38.31	X^2=2.666 p=0.264	
	Married	74	11.00	52.32		
	Divorced/separated/widowed	13	11.00	52.35		
Place of residence	City	34	11.00	53.28	X^2=1.347 p=0.510	
	Town	29	10.00	45.33		
	Village	37	11.00	52.00		
Work status	Working	14	8.00	44.96	Z=-0.774 p=0.439	
	Not working	86	11.00	51.40		
Smoking status	Smoking	40	10.50	49.83	X^2=-0.191 p=0.849	
	Not smoking	60	11.00	50.95		
Age at onset of illness	59 years or less	39	8.00	42.46	X^2=5.442 p=0.066	
	60-69 years	31	12.00	53.11		
	70 years or more	30	12.00	58.25		
Duration of illness	5 years or less	41	9.00	46.00	X^2=8.594 **p=0.014***	**1-3** **2-3**
	6-14 years	42	11.00	47.35		
	15 years or more	17	14.00	69.15		
Receipt of information	Yes	92	11.00	49.65	Z=-0.996 p=0.319	
	No	8	13.00	60.25		
Ability to meet physical needs	Not at all	31	13.00	60.89	X^2=7,626 **p=0.022***	**1-2** **1-3** **2-3**
	Partly	36	10.50	50.31		
	Completely	33	8.00	40.95		
Compliance with treatment	Yes	65	10.00	48.47	Z=-0.959 p=0.338	
	No	35	12.00	54.27		
No. of hospital admissions	One	28	10.50	49.02	X^2=2,127 p=0.547	
	Two	18	11.50	57.75		
	Three	16	11.00	54.06		
	Four or more	38	9.00	46.66		
Family history of COPD	No	28	9.00	46.55	Z=-0.853 p=0.394	
	Yes	72	11.00	52.03		
The presence of another chronic illness	Yes	78	12.00	56.47	Z=-3,893 **p=0.001***	
	No	22	7.00	29.34		
Receipt of support for illness	Yes	90	11.00	52.28	X^2=-1,854 p=0.064	
	No	10	7.00	34.45		

*p<0.05.

DISCUSSION

The purpose of this study was to determine death anxiety in patients with COPD, and the results are discussed in line with this.

The patients in this study had high death anxiety scores (10.31±3.66). There are studies that support our findings and show that patients with COPD have a high level of death anxiety.[11,17-19,26,29,30] In patients with COPD, severe difficulty in breathing is generally accompanied by anxiety. In addition, problems such as chronic coughing, loss of appetite, weight, insomnia, and fatigue diminish quality of life and increase death anxiety.[27] Additionally, it is stated in the literature that anxieties specific to disease are indicators of a fear of death,[28] that patients report that the symptoms they experience are related to their illness, and that as symptoms increase, death anxiety also increases.[19] It is known that COPD causes physical and psychosocial problems. Individuals are negatively affected by these problems. This condition causes the development of death anxiety.[29]

Some studies in the literature have shown that death anxiety increases with age, but others have shown that it is higher in the young. In a study by Güçlü[18], no difference was found between the mean death anxiety scores of patients with COPD according to their age. İnce[17] also, in a study with patients with COPD, found no correlation between age and death anxiety. In a study by Toğluk and Çuhadar[26], no difference was found between mean death anxiety scores according to age, and the greatest age in this group was 65 years old. In our study, a significant difference was found between the mean death anxiety scores of patients according to age. Death anxiety was significantly lower among those aged below 65 than among the other two groups. Thus, it can be concluded that death anxiety increased with advancing age in our study. Different results concerning death anxiety showed that death anxiety is related to many factors and cannot be explained by age alone.

When the patients' death anxiety was examined according to sex in our study; it was found that there were no differences between the mean scores of death anxiety. Other studies conducted with patients with COPD have found that the death anxiety of women was significantly higher than that of men.[11,17,18,25,31] These results can be supported by the fact that females express their feelings more easily than males. In addition, in some cultures, social roles require men to give an image of being strong and not afraid of anything. The lack of gender difference may be explained by cultural, role, and social life differences in the TRNC, where this study was conducted. More data on this topic are needed from the TRNC.

There are different results in the literature regarding the effect of marital status on death anxiety. Some studies, similar to our study, have shown that there is no difference between the mean death anxiety scores of patients according to marital status.[11,18] On the other hand İnce[17] reported that death anxiety was higher in those who were married than in those who were single. The reason why married individuals have higher death anxiety than single individuals may be that married individuals have more responsibilities toward their spouses and children. In our study, it can be said that variables that were significant, such as age, the presence of another disease, and ability to meet individual needs, may be more effective.

When elderly people living in villages have serious health problems, reaching hospitals or units where they can obtain help is more difficult than in other settlements. When they encounter such a problem, the anxiety they feel due to not being able to help may increase their death anxiety. Some study results also showed that the death anxiety of those living in a village was significantly higher than that of people living in a town or city.[26,32] The present study was conducted in the TRNC, where even the furthest parts of the island can be reached within 90 minutes from the hospital in Lefkoşa. This may explain the lack of difference in mean death anxiety scores according to place of residence. There were no regional differences in receipt of medical assistance or access to 112 emergency services.

It has been observed that studies examining death anxiety according to working status are limited.[17,26] Working life can make an individual feel valuable by creating an environment where they can take responsibility and produce. Leaving behind a legacy or effort can be an important factor in alleviating death anxiety. Conversely, working life may increase death anxiety by preventing individuals from receiving regular treatments. In the present study, there were no differences in mean death anxiety scale scores according to the patients' working status. It is thought that qualitative and quantitative studies examining this variable are needed.

Lengthening the illness duration, increasing symptoms, and increasing additional chronic illnesses may cause death anxiety. In addition, as the duration of illness increases, patients may experience more difficulties in managing symptoms, which may trigger death anxiety. The finding that death anxiety was higher in patients with longer disease durations in our study can be explained in this way. Death anxiety also increased as the illness duration increased. The findings of our study are similar to those of Nal et al.[11], Genç[30], Görpüz and Kıssal.[31] The longer the disease duration, the higher the number of hospitalizations. Increased hospitalization may increase mortality anxiety. In our study, there was no difference in the mean death anxiety scores of patients according to the number of hospitalizations. This can be explained by patients adapting to the disease by admission to hospitals, and admission to hospitals gives them confidence.

Lack of information is a factor that causes patients to experience death anxiety. It is thought that informing patients about the disease will be effective in managing the disease and anxiety. Güçlü[18] reported that patients who had COPD and received information on self-care had a significantly lower level of death anxiety. In our study, the mean death anxiety scores of patients who had not received information on their illness were high, but there was no difference between the mean scores of the groups that had or had not received information. It can be concluded that the quality of the received information is important.

Dyspnea, one of the most prominent symptoms of COPD, may increase over time and limit the individual's ability to meet physical needs.[19] These limitations affect the patient psychologically over time and may cause anxiety and death. This can be explained by increased dependence on factors such as oxygen treatment as the disease advances, triggering death anxiety. Meeting patients' physical needs gives them confidence and decreases their stress and death anxiety levels. Similarly, in our study, we found that death anxiety was significantly higher in those whose physical needs were not met than in those whose physical needs were partially or completely met. The findings of İnce[17] support our findings.

Death anxiety is a subjective feeling. It is believed that there may be many individual and environmental factors affecting this anxiety. The lack of difference between the mean death anxiety scores of the patients according to the presence of a person with COPD in the family can be explained in this way. Toğluk and Çuhadar[26] support our findings.

Chronic diseases do not fully heal, progress slowly, and often cause permanent damage. Studies have shown that death anxiety is high in patients with chronic diseases.[33] It has been stated that the presence of another chronic disease is an important determinant of stress in patients with COPD and that perceived stress has a positive and significant relationship with death anxiety.[30] The emergence of symptoms of another chronic disease in addition to COPD and patients' insufficient coping skills regarding these symptoms may be a factor that increases death anxiety. Every symptom can be perceived by patients as a life-threatening factor. Therefore, the presence of another chronic disease may increase death anxiety. Similarly, in our study, a significant difference was found between the patients' mean death anxiety scores according to the presence of another chronic illness. Güçlü[18] reached similar conclusions.

Study Limitations

The limitations of the study are that it was conducted in a hospital, and the scales used were self-reported. This study can only be generalized to this sample group.

CONCLUSION

The results of the study revealed that the mortality anxiety of patients with COPD was high. A significant difference was found between the mean death anxiety scores of patients according to age, duration of illness, whether physical needs were met, and presence of another chronic disease. It is thought that this study will contribute important data to the literature because it was conducted with this sample from the TRNC. These results will guide TRCN nurses about the psychosocial needs of patients with COPD. Nurses will have awareness of the evaluation of patients with COPD, not only physically but also psychosocially. It is recommended that the death anxiety of patients with COPD and related factors be studied with a wider sample from the TRNC. At the same time, it is recommended that patients with COPD be assessed for death anxiety and that suitable nursing approaches be planned for those with death anxiety.

MAIN POINTS

- Chronic obstructive pulmonary disease (COPD) causes patients to experience a number of physical and psychological symptoms. One of these disorders is death anxiety.
- There are no scientific data on this topic in the Turkish Republic of North Cyprus (TRNC).
- Death anxiety is high among patients with COPD in the TRNC.
- Death anxiety among patients with COPD and related factors should be studied with a wider sample from the TRNC.

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ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of European University of Lefke (approval number: ÜEK/56/01/12/2021/04, date: 02.12.2020).

Informed Consent: Verbal and written informed consent was obtained from patients who volunteered to participate.

Authorship Contributions

Concept: M.Ç., P.T., Design: M.Ç., D.B., P.T., Data Collection and/or Processing: M.Ç., Analysis and/or Interpretation: M.Ç., D.B., Literature Search: D.B., P.T., Writing: M.Ç., D.B., P.T.

DISCLOSURES

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

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RESEARCH ARTICLE

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Early Detection of Endocervical Adenocarcinoma and Adenocarcinoma in Situ: Role of PAP Smear and HPV Screening Test

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Abstract

BACKGROUND/AIMS: Endocervical adenocarcinoma (ECA) accounts for 25% of cervical cancers and is clinically more aggressive than squamous cell carcinoma (SCC). Similarly, SCC and ECA can be treated without the formation of invasive tumors if precursor lesions are identified and treated accordingly. The objective of this study is to analyze the effectiveness of screening tests in the detection of endocervical adenocarcinoma in situ (AIS), which represents a precursor lesion of ECA.

MATERIALS AND METHODS: The study comprised a total of 121 cases, including 83 cases of ECA and 38 cases of AIS, diagnosed through histopathologically examination between 2020 and 2023 at our center. The clinical history, cytological findings, results of the high-risk human papillomavirus (hrHPV) test, and other pathological findings from the pathology reports of the patients aged 26 to 84 years were subjected to analysis.

RESULTS: A total of 22.2% of the cervical carcinoma cases diagnosed histopathologically at our center during the study period were ECA. The mean age of the ECA cases was 48.6 years while that of the AIS cases was 39 years. A positive association was observed between HPV and 94% of ECA cases. Among the 83 ECA cases, 56.6% had not undergone screening, and 88% had not undergone an hrHPV test. A total of 33 patients with AIS underwent a screening test, and 31 cases exhibited abnormalities in the smear. All 13 AIS cases that underwent hrHPV screening tested positive for hrHPV. A biopsy was performed in 33 of the 38 AIS cases based on the combined evaluation of the PAP smear and the hrHPV test results.

CONCLUSION: Our study emphasizes the effectiveness of the combined PAP smear and hrHPV screening tests in the early detection of ECA at the AIS stage, achieving a success rate of 96.9%.

Keywords: Adenocarcinoma in situ, endocervical adenocarcinoma, HPV screening test, PAP smear

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INTRODUCTION

Endocervical adenocarcinoma (ECA) accounts for a smaller proportion of cervical carcinoma cases comparing to squamous cell carcinoma (SCC); however, it still represents a significant portion, approximately 25%.[1-3] An aggressive tumor, it is particularly common in women aged 40-50.[4-6]

Although there was a remarkable reduction in SCC rates by up to 80% due to the human papillomavirus (HPV) vaccine and papanicolaou (PAP) smear test, the incidence of ECA showed a significant increase.[5,7] This increase may be attributed to differences in the etiology, morphology, and molecular characteristics of ECA and SCC.[5,8] Research indicates that adenocarcinoma in situ (AIS), the precursor lesion of ECA, can progress to invasive carcinoma over a span of at least 5 years.[9] Similar to the identification of precursor lesions of SCC, the detection of AIS through screening tests, such as PAP smears and high-risk human papillomavirus (hrHPV), can enable timely intervention before invasive tumors develop.[9]

The effectiveness of the PAP smear and HPV tests for detecting cervical squamous intraepithelial lesions (SIL) is well established. However, their efficacy in detecting ECA and its precursor lesions is limited by several factors.[9-11]

One of the main challenges in the diagnosis of ECA and AIS is the difficulty in obtaining an adequate sample.[12] Unlike squamous lesions, which are more easily accessible, ECAs may not be adequately sampled on PAP smears, leading to false-negative results. In addition, the cytological features of ECA and its precursor lesions can be difficult to interpret, leading to observer misinterpretation. Benign lesions may have characteristics similar to those of ECA or its precursors, further complicating the diagnostic process.[12]

Furthermore, because ECA and its precursor lesions frequently lack clinical symptoms, they are frequently identified incidentally during biopsy or hysterectomy procedures performed for other indications.[11]

In summary, although PAP smear and HPV tests are effective in detecting cervical SIL, their sensitivity and specificity for ECA and its precursor lesions are limited by sampling challenges, observer misinterpretation, and the asymptomatic nature of these lesions.

HPV plays a significant role in the diagnosis and classification of ECAs. Approximately 85% of ECAs are associated with HPV infection, whereas 15% do not.[7,13,14] Among HPV-associated ECAs, types 18, 16, and 45 are the most implicated.[7,13,14] Clinical features, P-16 expression, and HPV status play a main role in determining prognosis and treatment response.[3,7] Since 2020, the classification of ECAs has evolved to incorporate the HPV status, with tumors being categorized into HPV- associated and HPV-independent subtypes.[6,14] The incidence of ECA is higher in younger women, particularly around the age of 30, whereas the less common type, accounting for 15% of cases, is more prevalent in older individuals and tends to be more aggressive.[5] Precancerous lesions that precede ECA by 10-15 years provide a crucial window for detection and intervention.[5,11,14] Although the PAP test has relatively low sensitivity and specificity for the detection of ECA and precancerous lesions, approximately 90% of cases exhibit abnormal cytological findings.[9]

In the clinical approach, colposcopy examination and biopsy are recommended when encountering a high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells cannot be excluded, atypical glandular cells that are not otherwise specified (AGC, NOS), atypical endocervical cells that are neoplastic (AEC, FN), AIS smear results, and/or hrHPV positivity.[15,16]

Currently, few comprehensive studies have included both clinical and pathological analyses of ECA and its precursor lesion AIS, particularly in large case series. Although limited research is available, the World Health Organization predicts an increase in the incidence of these tumors in the future. Consequently, conducting clinical and pathological analyses of ECA and AIS in large case series is increasingly crucial to inform future research and clinical practice. Such studies can illuminate the difficulties encountered in the detection of ECA and facilitate the development of effective detection strategies.

The objective of this study was to investigate the efficacy of early diagnostic methods for ECA at the AIS stage. The aim of this study was to determine the benefit of using a PAP smear and high-risk HPV screening tests together in detecting AIS cases. Additionally, the study will identify the clinical features of ECA and AIS cases.

MATERIALS AND METHODS

Study Population and Ethics Approval

This retrospective study was approved on 28.03.2024 by Acıbadem University and Acıbadem Healthcare Institutions Medical Research Ethics Committee (ATADEK) under study number 2024-5/178.

The study included a total of 121 patients histopathologically diagnosed with AIS or ECA who presented to our laboratory with surgical specimens between January 2020 and January 2024. In this study, we evaluated whether PAP smears and HPV screening tests were performed before histopathological diagnosis, and the results of cases in which screening tests were performed were included in the analysis. The patients exhibited a wide age range, from 26 to 84 years, with a mean age of 46.6. Each case was analyzed for clinical history, clinical symptoms, biopsy type, smear results, HPV co-test results, HPV subtypes, and additional immunohistochemical studies utilized during the diagnostic phase before reaching a histopathological diagnosis.

Histopathological Samples and Immunohistochemistry

The specimens were fixed in 10% neutral-buffered formalin solution and processed using Tissue-Tek Vip® 6 AI (Sakura Finetek Japan Co., Ltd., Tokyo, Japan) to generate paraffin blocks. Subsequently, 3 µm-thick sections were from all blocks and subjected to hematoxylin and eosin (H&E) staining using a Shandon Gemini stainer (Epredia, USA). Immunohistochemical staining was then conducted using a Ventana Benchmark XT (Roche Diagnostics, Basel, Switzerland).[17]

Cytopathological Sampling and HPV Co-Test

The Thin Prep process used PreservCyt and CytoLyt solutions (Aptima, Canada) for specimen collection. Cytological preparations were performed using the ThinPrep technique (Cytyc Corp., Boxborough, MA, USA) with a ThinPrep 5000 automated processor utilized for processing. Any surplus materials were preserved in ThinPrep solution (Cytyc's ThinPrep PreservCyt medium). For hrHPV co-testing, the Aptima Panther test, which covers 14 hrHPV types (31, 33, 35, 39, 51, 52, 56, 58, 59, 66, 68) with type 16 detected individually, types 18/45 in combination, and the remaining 11 types collectively,[18] was employed.

All slides were examined and interpreted by experienced cytopathologists using a light microscope (Olympus BX51). PAP smears were evaluated in accordance with The Bethesda System for Reporting Cervical Cytology, 2016.[1,19,20]

In this study, specimens prepared and reported using the methods described above were used. The histological sections stained with H&E and immunohistochemical preparations of the cases were reviewed and analyzed along with the information provided in the pathology reports (SE). All images were captured using the latest version of Viracenter Digital Pathology's latest version.[21]

Statistical Analysis

Statistical analyses were conducted using the SPSS 21.0 software (IBM Corp., Armonk, NY, USA; licensed from Istanbul University, Türkiye). Results are presented as frequencies and percentages.

RESULTS

Biopsy Results

A total of 83 cases of ECAs were included in the study, representing 22.3% of the 372 cases of invasive cervical carcinoma diagnosed at our laboratory between January 2020 and January 2024. In addition, all 38 cases of AIS within this period (38 cases) were included.

The patients in our study cohort ranged in age from 26 to 84 years (mean 46.6). Among the patients, 31.4% (n=38) were diagnosed with AIS, with a mean age of 39 years, whereas 68.6% (n=83) were diagnosed with ECA, with a mean age of 48.6 years. Of the AIS cases, 92.1% were younger than 50 years old, with only 3 patients (7.9%) age of 50 years or older. For the ECA cases, 65% were younger than 50 years old, and 35% (n=29) were 50 years or older.

Diagnosis was made by cervical biopsy in 61.4%, endometrial curettage in 9.6%, hysterectomy 9.6% and loop electrosurgical excision procedure (LEEP) in 2.4% of ECA cases. ECA diagnosis was made in metastatic tissue in 14 cases (17%), of which 3 cases represented the first presentation. The procedures which AIS was diagnosed on were as follows: cervical biopsy (71.1%), LEEP (15.7%), hysterectomy (7.9%), and endometrial curettage (5.3%).

In 5% (n=6) of the 121 cases, non-ECA malignancy was also present. Additionally; endometrial polyps were observed in seven cases, leiomyomas in two cases, and pregnancy in two cases. Among the cases, 24% (n=29) exhibited accompanying SIL, with HSIL being the most common. One case of AIS was detected in a patient with SCC, and one case of ECA was accompanied by SCC.

In all cases, the primary clinical indication for biopsy was PAP smear abnormality and/or hrHPV positivity, which accounted for 45.5% (n=55). The other common clinical indications for biopsy, excluding cases in which biopsy was performed due to metastasis, smear, and HPV test results, were cervical hemorrhagic lesion (n=30), postmenopausal bleeding (n=12), abnormal uterine hemorrhage (n=5) and cervical polyp (n=5).

In ECA cases, the most common clinical indication for biopsy was cervical hemorrhagic lesions (accounting for 31.3%), followed by abnormal smears and/or HPV positivity (at a rate of 27.7%). In AIS cases, abnormal smears and/or HPV positivity were the primary clinical findings leading to sampling in 84.2% of cases.

In one patient with age of 51, hysterectomy was performed due to postmenopausal bleeding attributed to multiple leiomyomas, and AIS was an incidental finding (Figure 1). Graphic 1 displays the age, clinical complaint, and cytological findings following biopsy in patients with ECA and AIS. cases.

Of the 83 cases, of ECA, 94% (78 cases) were associated with HPV infection. Among these, 68 were of the usual type and 10 were of the mucinous type (Figure 2, 3). In contrast, 6% (n=5) of the ECA cases were independent of HPV infection, with four cases of gastric type and one case of clear cell type.

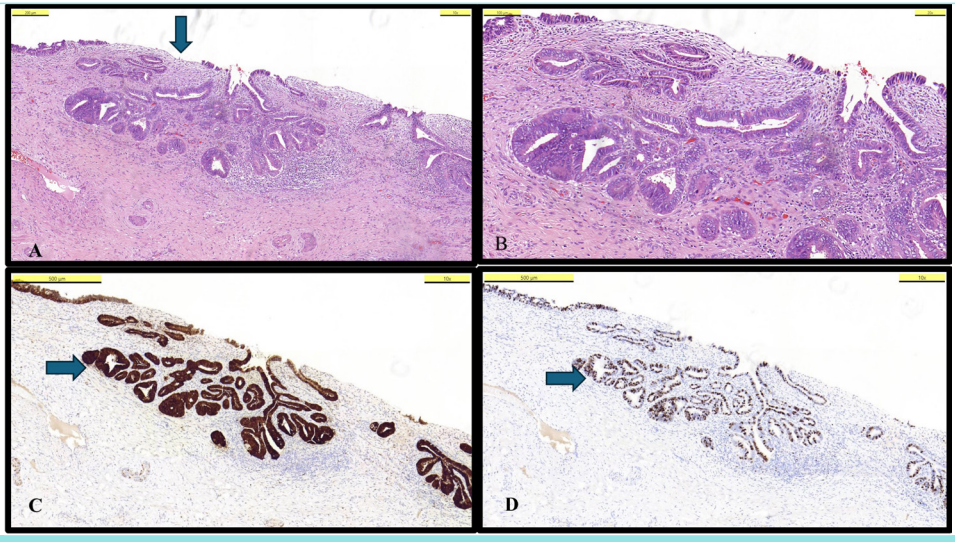


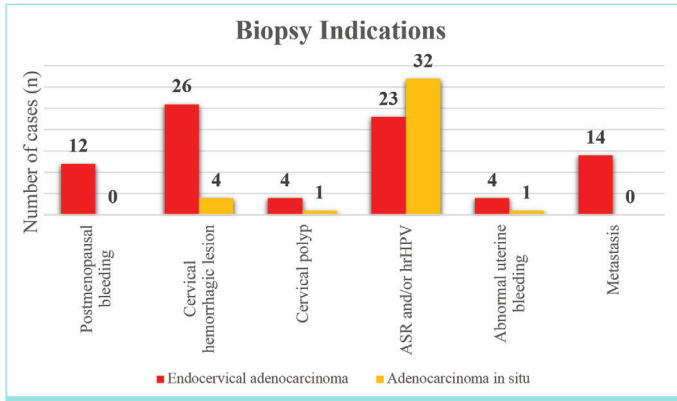
Figure 1. A 52-year-old patient with incidentally detected adenocarcinoma in situ (AIS) in hysterectomy material. (A) AIS area hematoxylin and eosin (H&E), (B) magnified view of the area marked by the arrows in A (H&E) and (C) diffuse strong positive expression in the AIS area with P-16 antibody (indicated by an arrow, (D) high positivity in the AIS area with Ki-67 antibody indicated by an arrow. The patient did not have a papanicolaou smear and human papillomavirus screening test.

Smear Test Results

Periodic smear tests were conducted in 24.8% of the cases (n=30). Among these, cytological abnormalities were also present in 33.3% (n=10) of the previous smear tests, with atypical squamous cells of undetermined significance (ASCUS) being the most common abnormality (n=7). In one patient aged 59 years and diagnosed with ECA, the previous smear result indicated ASCUS, whereas the latest smear test was negative for intraepithelial lesion or malignancy and negative for hrHPV.

Pre-sampling smear tests were conducted in 57% of the cases. Among these, smear tests were performed in 86.8% (n=33) of AIS cases and 43.4% (n=36) of ECA cases prior to biopsy. Distribution of PAP-smear and hrHPV test results according to final diagnoses are presented in Tables 1, 2, respectively.

The most common smear result observed before biopsy was HSIL (18.8%), followed by ASC-H (17.4%) in all cases in which a smear test



Graphic 1. Biopsy indications by diagnosis.

ASR: Abnormal smear results, hrHPV: High risk human papillomavirus.

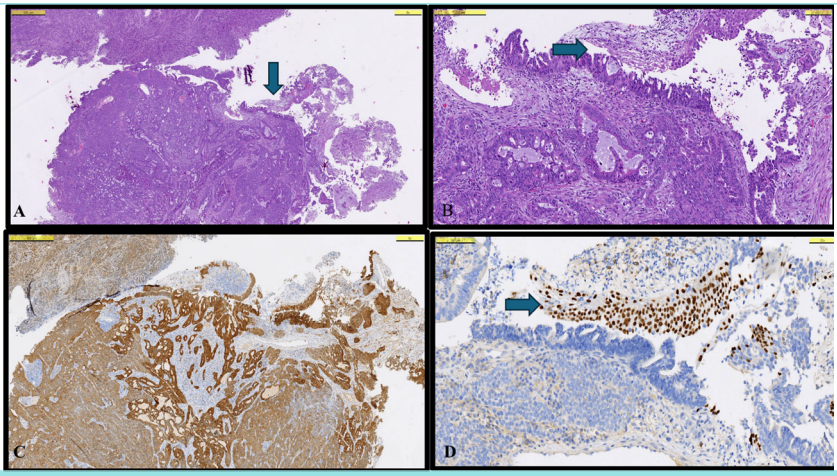


Figure 2. Cervical biopsy material from a 75-year-old patient with postmenopausal bleeding. (A) Endocervical adenocarcinoma (ECA) hematoxylin and eosin (H&E), (B) Magnified view of the area marked by the arrows in A (H&E) and (C) Diffuse strong positive staining in tumor with P-16 antibody, (D) Negative staining of the ECA area with P40 antibody, positive staining in high-grade squamous intraepithelial lesion area. The patient did not have a papanicolaou smear and human papillomavirus screening test.

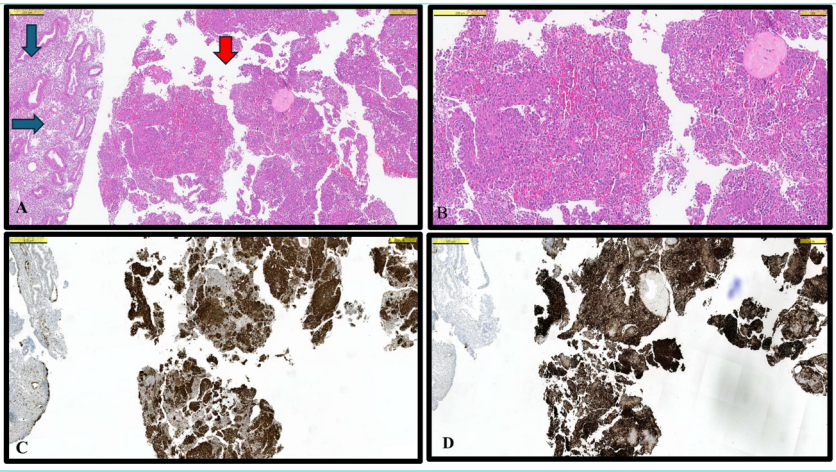


Figure 3. Histories of abnormal uterine bleeding in a 47-year-old woman who underwent hysteroscopic polypectomy material. (A) Blue arrows indicate endometrial polyp areas, and red arrows indicate ECA areas hematoxylin and eosin (H&E). (B) Magnified view of the red arrows in A (H&E). (C) Diffuse strong positive staining of tumors with P-16 antibody. (D) Diffuse strong positive staining of the tumor with CEAm antibody. The tumor location in the patient was ER (-), PR (-). The patient did not have a papanicolaou smear and human papillomavirus screening test.

was performed prior to biopsy. ASCUS (27.3%) was the most common smear result in AIS cases, whereas HSIL and NLIM (22.2%) were the most common smear results in ECA cases. The distribution of the smear results based on biopsy results is shown in Table 3.

Another notable finding was the absence of SILs in the biopsy results of AIS or ECA, despite the presence of squamous cell abnormalities on the smear in 16 cases. In seven AIS cases with ASCUS on smear, only AIS was identified on biopsy. Similarly, in nine ECA cases with smear results indicating ASC-H (n=5), HSIL (n=3), and ASCUS (n=1), no SIL was observed in the biopsy specimens.

HPV Test Results

HPV testing was performed in 23 (19%) of all cases. Of the 10 ECA cases that underwent HPV testing (12% of all ECA cases), half tested positive for HPV. The mean ages of patients who underwent HPV testing were 37 years in AIS cases and 47.8 years in ECA cases. The distribution of HPV test results according to the final biopsy diagnosis is shown in Table 2. All 13 AIS cases that underwent HPV screening (34.2% of all AIS cases) tested positive for hrHPV.

The most common subtype detected in the 23 cases that underwent HPV testing was HPV type 16, present in 12 cases (52.2%).

Cervical biopsy was performed in a total of nine cases because of hrHPV positivity, including two cases with NLIM smear results (one ECA, one AIS), five cases with ASCUS (one ECA, four AIS), and two cases with LSIL (one ECA, one AIS).

DISCUSSION

A total of 372 cases were diagnosed with cervical carcinoma in our laboratory during the period when the study cases were selected. The prevalence of ECA cases was 22.2%, with 83 cases identified. This prevalence rate was consistent with the 25% prevalence rate reported in the literature.[1,3,7]

The age range for ECA is typically reported to be between 40 and 50 years.[4,5] In our study cohort, the mean ages were 48.6 years for ECA cases and 39 years for AIS. Considering the recognized progression of AIS to invasive tumors over a period of at least 5 years, the mean age of our AIS cases was also consistent with the literature.[9] Only 3 cases of ECA were under the age of 30 years. Among them, two cases (aged 26 and 29) were diagnosed with HPV-associated usual-type ECA based on metastatic tissue. The third case (aged 29) was diagnosed using LEEP material obtained from an HSIL smear result. In these patients, HPV-associated usual-type ECA and accompanying HSIL were detected. Unfortunately, all three of these young patients did not undergo HPV

Table 1. Distribution of PAP-smear results according to final diagnosis

	Abnormal, n (%)	Negative, n (%)	N/A, n (%)	Total, n (%)
Endocervical adenocarcinoma	28 (33.8)	8 (9.6)	47 (56.6)	83 (68.6)
Adenocarcinoma in situ	31 (81.6)	2 (5.3)	5 (13.1)	38 (31.4)
Total	59 (48.7)	10 (8.3)	52 (43)	**121 (100)**

N/A: Non-applicable.

Table 2. Distribution of hrHPV results according to the final diagnosis

	Positive, n (%)	Negative, n (%)	N/A, n (%)	Total, n (%)
Endocervical adenocarcinoma	6 (7.2)	4 (4.8)	73 (88)	83 (68.6)
Adenocarcinoma in situ	13 (34.2)	0	25 (65.8)	38 (31.4)
Total	19 (15.7)	4 (3.3)	98 (81)	**121 (100)**

N/A: Non-applicable, hrHPV: High-risk human papillomavirus.

Table 3. Biopsy correlations between PAP-smear tests

	AIS, n (%)	ECA, n (%)	Total, n (%)
NILM	2 (6)	8 (22.2)	10 (14.5)
ASCUS	9 (27.3)	1 (2.8)	10 (14.5)
LSIL	2 (6)	1 (2.8)	3 (4.4)
HSIL	5 (15.2)	8 (22.2)	13 (18.8)
ASC-H	6 (18.2)	6 (16.6)	12 (17.4)
AGC, NOS	6 (18.2)	3 (8.3)	9 (13)
AEC, FN	0	6 (16.7)	6 (8.7)
AIS	3 (9.1)	1 (2.8)	4 (5.8)
ECA	0	2 (5.6)	2 (2.9)
Total	33 (47.8)	36 (52.2)	100 (69)

NILM: Negative for intraepithelial lesion or malignancy, ASCUS: Atypical squamous cells of undetermined significance, LSIL: Low grade squamous intraepithelial lesion, HSIL: High grade squamous intraepithelial lesion, ASC-H: Atypical squamous cells - cannot exclude high grade squamous intraepithelial lesion, AGC: Atypical glandular cell, NOS: Not otherwise specified, AEC: Atypical endocervical cell, FN: Favor neoplastic, AIS: Adenocarcinoma in situ, ECA: Endocervical adenocarcinoma.

testing or undergo a prior smear test. In the review by Rivera-Colón and Zheng[5], it was mentioned that typical AIS can present around the age of 15, and these patients may develop ECA at a young age.

Although the sensitivity and specificity of the PAP smear test for the detection of AIS and ECA are known to be low, smear abnormalities have been reported in up to 90% of cases, as demonstrated in a study by Niu et al.[9]. In our study, smear abnormalities were observed in 94% (31/33) of AIS cases, 77.8% (28/36) of ECA cases, and 85.5% (59/69) of all cases. Unfortunately, 42.1% of our patients did not undergo a pre-biopsy smear test, and 75.2% did not undergo periodic smear tests in previous years.

A notable observation in the smear results was the presence of squamous epithelial abnormalities in 16 cases, despite the absence of SIL on biopsy. These abnormal smear results included ASCUS in patients with AIS and ASC-H and HSIL in patients with ECA.

Research by Liu et al.[22] suggests that ASCUS results, especially when accompanied by hrHPV positivity, may indicate an increased risk of carcinoma or precancerous lesions. Similarly, in a study by Bamanikar et al.[23], ASCUS was found to be the most common abnormal smear result in cervical cancer cases.

The absence of SILs accompanying AIS and ECA in our cases may be attributed to the difficulty in accurately characterizing the abnormal cellular changes observed in ASCUS and ASC-H. It is plausible that the HSIL results indicated glandular involvement in squamous epithelial lesions. However, it is important to note that our study included a limited number of ECA and AIS cases, which limits the depth of our analysis on this issue. Further research with a larger sample size is warranted to explore this issue comprehensively.

A similar result was observed for the hrHPV test. In 81% of all cases and 88% of ECA cases, hrHPV testing was not performed. In cases where hrHPV testing was performed, 82.6% of 23 cases and 100% of 13 AIS cases tested positive for hrHPV. This positivity rate is similar to that reported by Bruehl et al.[24], who reported a positivity rate of 92.7%. However, it is important to note that our study may not reflect the true prevalence rates because of the limited number of patients tested.

In contrast, the low number of hrHPV tests performed (n=23), biopsies were performed and in 9 cases the diagnosis was made based on hrHPV positivity, even in cases in which the smear results did not require a cervical biopsy. In one case of HPV-associated usual-type ECA (58 years old), periodic smear tests, the most recent smear test, and the hrHPV test were negative. However, biopsy was performed in this case due to the clinical finding of a cervical hemorrhagic lesion. The negative result of the periodic smear test in this case could be attributed to the difficulty in sampling the lesion because of its deep location. Nevertheless, the negativity of the hrHPV test is interesting because the tumor was associated with HPV.

Giannella et al.[25] and Tjalma and Depuydt[26] reported that cancer rates are higher in association with HPV infection and that hrHPV testing may yield negative results in cases of HPV infection. Tjalma and Depuydt[26] showed that 8.3% of HPV 16 and 27.9% of HPV 18 genotypes could not be detected by hrHPV testing. In addition, some studies have suggested that test negativity may occur due to low viral load in latent infections and the presence of low-risk HPV types that are undetectable by testing but still have oncogenic potential.[27,28]

Although HPV 18 is the subtype most commonly associated with ECA in the literature, we found that HPV 16 was the causative type in 57.9% (11/19) of our HPV-positive cases.[7,15,23]

Among patients with AIS, 86.4% (n=33) had undergone periodic smear tests, and 34.2% (n=13) had hrHPV screening tests. Of the 31 AIS cases with smear abnormalities, 25 had smear results indicating the need for biopsy. The smear results of the other seven patients did not contain biopsy indications, including ASCUS (n=5), LSIL (n=1), and NLIM (n=1). Nevertheless, these cases were hrHPV-positive, and therefore biopsy was indicated. The HPV test was not performed on an AIS case whose smear result of NLIM. This patient was diagnosed with AIS with a prediagnosis of endocervical polyp. Among the five AIS cases without periodic screening tests, two were detected incidentally in hysterectomy specimens obtained for other reasons. In the remaining three cases, cervical sampling was performed because of the presence of cervical hemorrhagic lesions.

Mitchell et al.[29] showed that increasing the frequency of smear screenings can reduce the incidence of ECA. Zhao et al.[30] demonstrated that long-term and periodic screenings can detect abnormal findings and be effective in the early detection of curable lesions, even in cases with negative smear and negative hrHPV test results. Unfortunately, in our study, only 24.8% of the 121 patients had periodic smear results in the last 5 years.

Study Limitations

In this study, the number of patients with AIS was limited. Nonetheless, the interpretation of the AIS results is consistent with the existing literature. It is known that the number of AIS cases is limited in many studies in the literature. Therefore, the results from more comprehensive studies with a higher case count may provide further insight into elucidating and preventing the development of ECA.

CONCLUSION

Our study highlights the potential for early detection of ECA at the AIS stage through the combined use of PAP smear and hrHPV screening tests. The use of both screening methods demonstrated a success rate of 96.9% in detecting AIS cases in our study cohort. In addition, consideration of deep sampling of endocervical tissue in cases with cervical hemorrhagic lesions (such as postcoital bleeding) and a history of postmenopausal bleeding may aid in early diagnosis.

We recommend the use of PAP smear and HPV screening tests according to guidelines starting from the onset of sexual activity. Furthermore, we advocate for the inclusion of HPV vaccinations in routine immunization programs, administered to the young population, without gender discrimination, ideally before the age of 25 years. We expect that these proactive measures will significantly contribute to the prevention and early detection of cervical cancer, ultimately improving patient outcomes.

MAIN POINTS

- It is evident from our study that screening tests are not employed to the fullest extent in the clinical histories of patients with ECA. A combined approach using both smear and HPV screening tests was effective in detecting 84.6% of AIS cases.
- In our cases, the smear results demonstrated a high prevalence of cytological abnormalities in both ECA and AIS although these were not specific.
- High-risk HPV positivity, particularly HPV 16 positivity, was significantly elevated in our cases.
- The combined use of both screening tests enabled the detection of AIS cases prior to the development of invasive tumors.

ETHICS

Ethics Committee Approval: This study was approved by the Acıbadem University and Acıbadem Healthcare Institutions Medical Research Ethics Committee (ATADEK) (approval number: 2024-5/178, date: 28.03.2024).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: S.E., S.E., Concept: S.E., Design: S.E., S.E., Data Collection and/or Processing: S.E., S.E., Analysis and/or Interpretation: S.E., S.E., Literature Search: S.E., Writing: S.E.

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DISCLOSURES

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

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