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Message from the Editor-in-Chief

Message from the Editor-in-Chief,

Vaccination programs for the COVID-19 pandemic are progressing on a global scale. With the help of basic and clinical science, we will soon reach our more active, social days. We will never forget the healthcare professionals who carry the heaviest burden of admissions and hospitalizations.

We are launching the fifth issue of the Gülhane Medical Journal since the beginning of the pandemic in 2020. Meanwhile, the increase in the number of submissions and publications on COVID-19 continues.

In the current issue of the Gülhane Medical Journal, we have interesting original articles, review articles, case reports, and editorials. As always, this latest issue covers a wide range of articles from different disciplines.

I would like to express my gratitude to all submitting authors, reviewers, and editors for their contributions.

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

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Interaction of local and systemic renin angiotensin aldosteron system with COVID-19

Zehra Çiçek

University of Health Sciences Turkey, Gülhane Faculty of Medicine, Department of Physiology, Ankara, Turkey

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Corresponding Author:
Zehra Çiçek, M.D., University of Health Sciences Turkey, Gülhane Faculty of Medicine, Department of Physiology, Ankara, Turkey

ORCID:
orcid.org/0000-0003-3205-5463

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ABSTRACT

Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) passes into cells through binding the angiotensin-converting enzyme-2 (ACE-2). While many scientists worldwide are trying to understand the physiopathological mechanisms of the disease and its relationship with other diseases, they are trying to find drugs that can treat Coronavirus disease-2019 (COVID-19). It is reported that the incidence of COVID-19 increases in cardiovascular diseases and associated conditions such as diabetes mellitus and hypertension in studies. That is why a large number of scientists are now questioning the use of renin-angiotensin-aldosterone system (RAS) antagonists, angiotensin-2 (Ang-2) receptor antagonists (angiotensin receptor blockers), and ACEs in COVID-19 patients. When all these facts are considered together, their potential effects may be more significant. Some researchers stated that RAS inhibitors might amplify COVID-19 severity. Per the classical knowledge, ACE-2 regulates RAS by converting Ang-2 to angiotensin-(1-7), which has antioxidant, vasodilatory, anti-inflammatory, and protective effects on many cell types, especially cardiomyocytes and vascular cells. Local and systemic RAS components such as ACE-2, ACE, and Ang-2 and their interactions are pretty complex. However, numerous reported RAS substrates and enzymes are synthesized intracellularly in many cell types. This review highlights that the intracellular RAS may have prominent roles in developing potential treatment strategies for COVID-19.

Introduction

Coronavirus disease-2019 (COVID-19) pandemic is currently the most critical health problem threatening the world. The relation of COVID-19 with renin-angiotensin-aldosterone system (RAS), especially with angiotensin-converting enzyme-2 (ACE-2), has been suggested (1). There are many pathways in the physiopathological and biochemical mechanisms of RAS that are still not understood. It is well-known that RAS plays a leading role in the initiation and progression of cardiovascular diseases. At the same time, RAS is a regulator of blood volume, pressure, and systemic vascular resistance that plays a pivotal role in the physiological and pathological responses in the cardiovascular system, such as regulating blood pressure, maintaining water and electrolyte homeostasis, vascular permeability, cellular proliferation, migration, apoptosis, intracellular signaling, angiogenesis and fibrosis (2,3). RAS contains renin, angiotensin-2 (Ang-2), Ang-2 receptors (ATRs), ACE, and ACE-2. The most potent molecule of this system is Ang-2. As such, ACE inhibitors or ATR blockers are used to treat hypertension (HT) and chronic cardiovascular diseases. Inhibition or decrease in Ang-2 levels reduces blood pressure and causes arteriolar vasodilation by decreasing sodium and water reabsorption. Systemic endocrine effects occur when the components are produced in specific organs with enzymes and substrates and released into the bloodstream (4). However, in recent years, it has been shown that the effects of this system are not only systemic but RAS components are synthesized intracellularly in various organs and tissues. It is regulated independently from systemic RAS and has local paracrine and autocrine effects (5,6). Notably, the synthesis of Ang-2 and other substrates and enzymes of RAS [angiotensinogen, Angiotensin-1 (Ang-1), renin, ACE] occurs locally (intracellular) by many cells such as neurons, cardiomyocytes, fibroblasts, endothelium, and vascular smooth muscle cell (7). In addition,

it has been emphasized in many scientific studies that local RAS induces the acute defects and progression of various cardiovascular diseases. An increase in Ang-2 synthesis is observed in HT. Therefore, drugs to inhibit the components of this system have been developed to treat RAS-associated cardiovascular and renal diseases. Especially, ACE, AT1R (8), and renin antagonists are among the current drug therapies used in HT, heart failure, and diabetic nephropathy patients (9).

Effects of Renin-Angiotensin System

RAS components have detrimental effects on the cardiovascular system. The main components of classical RAS are:

1. Angiotensinogen, a massive globular protein,

2. Renin, which converts angiotensinogen to Ang-1 molecule,

3. ACE, an enzyme that converts Ang-1 to Ang-2, an octapeptide, membrane-dependent metalloproteinase,

4. Ang-2, basic effector peptide,

5. ATR, responsible for the cellular effects of Ang-2.

These essential components information about RAS is gradually increasing. Different ATRs (AT1R, AT2R, AT3R, AT4R) and signaling pathways arising from the activation of these receptors are defined. Ang-2 contacts with well-defined cell membrane receptors, AT1R and AT2R, and additional intracellular receptors (cytoplasmic and nucleus) (4,10). However, while rodents have two types of AT1R, humans have only one form. Conformational change occurs when it binds to the AT1R that mediates Ang-2 signal transduction. It activates phospholipase C with AT1R receptor stimulation and increment of inositol 1, 4, 5 triphosphates (IP3) and cytoplasmic (intracellular) calcium and diacylglycerol activate mitogen activator protein kinases (MAPK), extracellular signal-regulating kinases (ERK), and JAK/STAT pathway, increases protein phosphorylation. AT1R activation leads to cardiovascular remodeling (11). Binding of Ang-2 to AT1R, while Ang-2-AT1R passes quickly into the cell cytoplasm, desensitization takes place by stimulation with the agonist. As the receptor turns back to the plasma membrane, Ang-2 settles down intracellular localizations such as lysosome and cell nucleus (12). However, internalization and desensitization in AT2R do not occur. It is believed that Ang-2 has less relationship with AT2R on acute cardiovascular effects (13). These two receptor types have also been shown to have functionally opposite effects.

Meanwhile, Ang-2 shows its effects through cell proliferation, growth, formation of new vascular structures and vasoconstriction through AT1R, and the inhibition of cell proliferation and growth via AT2R. Its activation causes vasodilation and antiangiogenesis with the formation of NO and cGMP. RAS includes peptides consisting of Angiotensin-2-8 (Ang-3), Angiotensin-3-8 (Ang-4), Ang-(1-7), and Ang-(1–12) (5). The degradation of Ang-2 synthesizes Ang-(1–7) by catalytic reactions via ACE-2. It is thought that responses such as vasodilation and cytoprotective effects increased by promoting antagonist effects and thus stabilizing RAS. ACE is ordinarily a cell surface protein and is found in serum, lung, seminal fluid, and plasma (14,15). The majority of this enzyme that provides the formation of Ang-2 is found in endothelial cells. Although most of the transformation occurs during blood flow through the lungs, it is stated that this transformation occurs in many parts of the body (16). Discussions continue about the increase of vascular ACE in experimental hypertension. Vascular ACE has been shown to increase in two kidney single clip hypertensive rats, but this increase could not be confirmed in spontaneously hypertensive rats (17). It has been shown that ACE production in many living species (human, dog, and rabbit) is also in the endothelial and adventitia layer (5). After all, it has been reported that ACE concentration is high in the vascular smooth muscle cell and endothelial cell cultures. In addition to membrane-attached forms, secreted and local forms of ACE have been characterized in mesangial cells. ACE also inactivates bradykinin, a potent vasodilatory (14,18). Increased bradykinin level due to ACE inhibitors in HT causes cough in more than 20% of patients (19). ACE inhibitors have been primary care therapy for HT for years (8,20).

Coronavirus and RAS Affinity

COVID-19 is a pandemic affecting countries and millions of people that causes severe pneumonia and cardiovascular damage. Accordingly, understanding the tissue damage and underlying mechanisms caused by severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) is crucial. COVID-19 spreads over cells through one of the RAS components, ACE-2 (21). Although RAS is a complex set of mechanisms, it plays essential roles in many physiological processes involving vascular structure and remodeling. Spike protein of SARS-CoV-2 is transmitted to cells by connecting with ACE-2 membrane receptor. SARS-CoV-2 mediates tissue injury and causes an imbalanced ACE/ACE-2 ratio. In addition, ACE-2 adversely affects RAS and functions as the binding receptor for the coronavirus (2,22).

The incidence of SARS-CoV-2 increases in older people with cardiac diseases, hypertension, and diabetes mellitus (23-25). Studies have reported that the target of SARS-CoV-2 is ACE-2 in cells, which is expressed excessively in lung epithelia, small intestine, heart, and kidney in humans (14,26). ACE-2 is a membrane-involved enzyme that converts Ang-1 to Ang-(1–9) and Ang-2 to Ang-(1–7) (27), a peptide with vasodilator and antiproliferative properties (28,29). Ang-(1–7) levels were associated with several diseases, including hypertension, hypertrophic myocardial disease, myocardial infarction, chronic kidney disease. Ang-(1-7) has anti-growth and antiproliferative effects in cardiomyocytes, fibroblasts, and vascular smooth muscle cells (26,30). Thus, ACE-2 regulates RAS in the

negative direction by inhibiting Ang-2 and competing with ACE for Ang-1. ACE-2 knockout mice developed cardiomyopathy with increased pathological hypertrophy, collagenase levels, oxidative stress, inflammatory cytokines, and MAPK activation, and these signaling pathways were inhibited by angiotensin receptor blockers (ARB) (9). The expression of ACE-2 is increased in type 1 or type 2 diabetes mellitus and HT patients. These data indicate that ATRs and ACE inhibitors increase ACE-2 expression (31).

In another cohort study, it was reported that people using ACE inhibitors and ARBs had less severe disease (32). ACE-2 protein expression and activity in the heart and kidney are augmented by treatment with ACE inhibitors and ARBs differently (26). This leads to an organ-specific augmentation of local production of Ang-(1–7), as demonstrated in rats (14,31,33). As a result, the increase in ACE-2 expression would facilitate infection with COVID-19. It was hypothesized that the increase of ACE-2 synthesis augments the risk of COVID-19 infection.

Notwithstanding, although not shown in human studies or the setting of COVID-19, such potential upregulation of ACE-2 by ARBs or ACE inhibitors have caused speculation of contingently increased risk for COVID-19 course in the users of RAS blockers. However, no clinical or experimental data have demonstrated adverse or beneficial outcomes with background use of ATR blockers and ACE inhibitors or other RAS antagonists in COVID-19 patients. A recent study determined an increase in serum Ang-2 levels of COVID-19 patients. Based on this, ACE/ACE-2 balance appears to be critical inside and outside in many cell types, particularly the lung cells (34). As ACE-2 level increases following treatment with ARBs and ACE inhibitors (31,35), it is thought that the use of soluble ACE-2 in therapy may prevent the coronavirus from binding to its receptors (36). However, ACE inhibitors in practice did not inhibit ACE-2 (37). ACE-2 deficient mice do not develop lung injury following exposure to SARS-CoV-2 (38). Although these evaluations may seem to be correct on the systemic RAS, another issue to be considered is the intracellular ACE-2 production and COVID-19 connection.

Interestingly, in vitro works in cell lines suggested that ACE-2 is the physiological receptor for coronavirus associated with SARS-CoV-2 and acute respiratory distress syndrome (39). It is known that in diabetic conditions, cardiomyopathic hamsters show an increased intracellular ACE synthesis in cardiomyocytes (40,41). From this point of view, ACE inhibitors used today can provide ACE inhibition outside the cell. For this reason, it seems more appropriate to try drugs that can be effective by entering through the cell membrane for inhibition of ACE and ACE-2 produced into the cell. At the same time, it can be thought that intracellular RAS, which is present in many cell types other than the vascular cells, may facilitate the spread of COVID-19 in the human body. However, it may be considered that the coronavirus binding to ACE-2 increases the penetration into the cell. After internalizing the receptor, intracellular ACE-2 level may increase when the receptor exposes to the membrane again.

Conclusion

The intracellular RAS has hidden substantial therapeutic implications and generally not inhibited by classical ARBs and ACEs. Since they do not pass into the cell and inhibit ACE and angiotensin receptors outside of the cell. Drugs that can inhibit ACE-2 internalization can be developed. Recent findings show that blockage of the local RAS might provide significant additional clinical implications in COVID-19 patients. This is consistent with recent reports that 'classical' therapeutic protocols of RAS inhibition (ARBs and ACEs blockers) might not have as much cardiovascular efficacy as anticipated. High doses of ACE inhibitors are often necessary to inhibit the RAS completely. Another issue that should be mentioned is that renin is contained in the synthesis of both local and extracellular RAS components. Thus, a renin inhibitor therapy might be an attractive therapeutic modality for conditions with intracellular RAS activation. Consequently, with the increase of molecular studies on RAS and its components, their roles in organ pathologies and the mechanisms of RAS activation at the tissue level will be revealed. In this manner, as the number of experimental practices increases, we may learn more about COVID-19 and related consequences.

Ethics

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The relationship between computer game addiction and obesity in third and fourth grade elementary school students

Umut Kocakoğlu, Nazan Karaoğlu, Ruhuşen Kutlu

Necmettin Erbakan University, Meram Faculty of Medicine, Department of Family Medicine, Konya, Turkey

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Corresponding Author:
Nazan Karaoğlu, Prof. M.D., Necmettin Erbakan University, Meram Faculty of Medicine, Department of Family Medicine, Konya, Turkey

ORCID:
orcid.org/0000-0002-3057-2988

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ABSTRACT

Aims: Childhood obesity has been defined as a very serious public health issue. It was aimed to investigate the relationship between computer game addiction and obesity in 3rd and 4th grade elementary school students.

Methods: In this cross-sectional study, two separate questionnaires including demographic characteristics, physical activity, nutrition and computer game habits were applied to students and their parents. The students were also asked to fill the Computer Game Addiction Scale.

Results: This study included 491 children and parents. Above the half (51.5%) were female and 69% were at normal weight. The body mass index (BMI) percentile values of children in the 8-9-year-old group were higher than those in the 10-11-year-old group (t=3.044; p=0.002). When children's computer game addiction was evaluated, it was found that while 86.9% of them were at low level of addiction, 12.7% were at moderate level of addiction. Having an overweight brother/sister, high paternal BMI, increase in time spent on screen, and low maternal education status increased BMI percentile values in children (p<0.05). As long as the time of playing computer game increased, it was observed that BMI percentile values also increased significantly (p=0.033).

Conclusions: This study shows that the level of computer game addiction and the time spent on screen are factors that increase obesity. In addition, the high level of frequency of snack in children is supportive of this result. If the ways to fight obesity are to promote physical activity and to move away from sedentary life style in children, it is clear that measures should be taken regarding the time that they spend in front of the screen.

Introduction

Childhood obesity has been defined as a very serious public health issue because it paves the way for the development of many chronic diseases. According to the 2016 report of World Health Organization (WHO), 340 million children in the age range of 5-19 years are either overweight or obese. The upsetting point is the prevalence of overweight. Obesity rate was 4% in the same age group in 1975, while it exceeded 18% in 2016 (1). According to a nationally comprehensive obesity study conducted on elementary school 2nd grade students with the support of WHO, the rates of obesity and overweight were 9.9% and 14.6%, respectively (2). In a review investigating the studies in 2000-2010 all around Turkey, the prevalence of overweight and obesity in children at the age of 6-16 years was reported as 10.3-17.6% and 1.9-7.8%, respectively (3).

There are many factors influencing childhood obesity. WHO has stated that the likelihood of a child being obese is 80% if both parents are obese, 40% if one parent is obese, and 14% if none of the parents are obese (4). This does not solely depend on genetic factors, nutritional habits of the family can also be effective along with cultural factors.

Various reasons leading to a child's being less active, decreased sports events and increased immobile activities can lead to a positive energy balance in children with similar nutrition. Activities with less physical demand such as watching TV, playing video games, and using the computer are closely

related to obesity. AAP states that daily TV and computer use of children should be limited to a maximum of two hours (5). In a study performed on a thousand cases, 17% of adolescents who watched TV more than two hours a day during the week were overweight when they reached the age of 26 years (6). Socioeconomic status by itself is a risk factor for obesity; if it is low, there is imbalanced and erroneous nutrition and if it is high, there is over nutrition (7). Although the educational and occupational statuses of parents have been related to obesity in various manners, children grown in challenging life settings and bad conditions carry higher risk for obesity (8).

Although computer games have positive cognitive, emotional and social effects on children and adolescents, there are some negative physical effects, including obesity, as well as psychological and social negative effects. Similar to other behavioral addictions, game addiction is an extreme, compulsive, uncontrollable desire for playing game, resulting in psychological or physical harm (9). In a study performed in Australia, the relationship between obesity and watching TV and game addiction was stronger than the relationship between obesity and physical inactivity (10). A recent study from Afyon, Turkey, states that among 297 healthy students, 245 (82.5%) were video game players. The rate of video game addiction was 1.6% in the whole sample, 3.1% aming the male students, and significantly high in obese children (9).

There have been various studies investigating the relationship between watching TV and obesity; nonetheless, studies on the relationship between computer game addiction and obesity are very limited. The present study aimed to analyze the relationship between computer game addiction and obesity in primary schools of Konya, which is a city with a high frequency of obesity.

Methods

This study was a cross-sectional study and its universe consisted of students attending the 3rd and 4th grades of elementary school in the center of Konya Province and their parents. The sample of the study was randomly formed by the three schools representing the students in Selcuklu, Meram and Karatay districts in accordance with the permission of the Provincial Directorate of National Education. The target sampling group consisted of at least 377 children and parents with 5% error margin and 95% confidence interval between February and May 2018. However, keeping the possibility of empty or incomplete questionnaires in mind, all data belonging to volunteering participants during the study period were included in the analyses. Inclusion criteria were as follows; being a student/student's parent of a school given permission by the Provincial Directorate of National Education, volunteering, being present at the school during the study period, having no chronic disease, no mental or physical impediments, having opportunity to reach computer games at home, at school, or outside, and having language, writing and expression skills sufficient enough to read, understand, and answer the questions.

Ethics Committee approval (no: 2018/1196, date: 09.02.2018) was taken from Necmettin Erbakan University Meram Faculty of Medicine and written permission was taken from the Provincial Directorate of National Education of Konya. Principals of the schools where the study was to be conducted were contacted and the study was performed with the consent of these principals and the support of school counselors.

Two separate questionnaires were prepared for children and parents. Both forms were given at the same number so that children and their parents were matched. The survey form prepared was first performed on 10 students and 10 parents as a pilot to assess possible problems regarding comprehensibility and practicality with the aim of making corrections accordingly and these data were not included in the main study.

The questionnaire form for children included questions about date of birth, gender, and status of playing computer games, along with Computer Games Addiction Scale for Children. The questionnaire form for parents included questions about familial educational status, family structure, height and body weight, socioeconomic status, along with questions about their children (nutrition, physical activity, sleep, time spent by technologic products like the television and computer).

Computer Game Addiction Scale (CGAS): It is developed by Horzum et al. (11) as a 5-point Likert scale consisting of 21 questions. There are 4 factors in the scale; 1) Not being able to quit/stop playing computer games, 2) Associating computer games with real life, 3) Disruption of tasks because of playing computer games, and 4) Opt for computer games over other activities. The scale is coded as 1 to 5 scores being "never", "rarely", "sometimes", "often", and "always". All questions in the scale are positive. The minimum and maximum scores to be taken from the scale are 21 and 105, respectively. While 21 to 49 scores indicate low levels of addiction, 50-77 shows moderate levels, and 78-105 shows high levels of computer game addiction (11).

Anthropometric measurements: For the evaluation of childhood obesity, the most frequent and practical method, the body mass index (BMI), was used. BMI is calculated by dividing body weight (kg) by square of height (in meters) (BMI=kg/m^2). However, as parameters change with age in children, BMI standards for age are used in school age children and adolescents, and percentiles and z scores should also be taken into account (12). Thus, every child's BMI percentiles for age and gender were determined in accordance with the reference values of Neyzi et al. (13) standards while defining obesity categories. Accordingly, children under 5 percentiles were

grouped as slim, 5-85 percentiles as normal, 85-95 percentiles as overweight, and over 95 percentiles as obese. In the present study, body weight and height measurements of the children were performed by the researcher. Height was calculated when the shoes were off, and the tape measure was attached to the wall while the child was looking forward in the most upright position possible. Body weight was determined by a digital scale sensitive to 100 grams, while facing forward in an upright position without shoes.

Statistical Analysis

The Statistical Package for Social Sciences for Windows 20.0 program was used for statistical analyses and evaluation of study findings. Definitive statistics of continuous variables were defined as mean and standard deviation while definitive statistics of categorical data were defined as frequency and percentage. Comparison of quantitative data with normal distribution was performed with the Independent Samples-t-test and one-way variance analysis (one-way ANOVA) test, while the Mann-Whitney U and Kruskal-Wallis analyses were used for data with abnormal distribution. The chi-square test was used for comparison of categorical data and $p<0.05$ was considered statistically significant. Relationships between parameters were inquired with the Pearson's correlation analysis and the correlation coefficient (r) was considered weak, moderate, strong, or very strong when between 0.00-0.24, 0.25-0.49, 0.50-0.74, or 0.75-1.00, respectively.

Results

A total of 491 children and parents were included in the study. School distribution of the participants was as follows: 32% (n=157) from Karaarslan Cumhuriyet Primary School, 39.5% (n=194) from Zeliha Lutfi Kulluk Primary School, and 28.5% (n=140) from Mehmet Hasan Sert Primary School.

Gender and age distribution was as follows: 51.5% (n=253) were girls and 54.2% (n=266) were 9 years old. Normal body weight was encountered in 69% (n=339) and in this subgroup, more than half the mothers (51.1%; n=251) were educated at primary school level or less. More than half (62.1%; n=305) of patients defined their economic status as moderate level. Sociodemographic features are given in Table 1.

Children's weekly physical activity time was 7.3±6.2 hours, weekly number of breakfasts was 5.7±2.0, number of regular consumption of 3 main courses per week was 5.2±2.3, number of weekly take-home foods was 0.9±1.0, and daily sleep time was 9.0±1.0 hours. Snacking between main courses was a habit for 66% (n=326) of children while in 34% (n=99) of them, this habit was more frequent when they were facing electronic media devices. Physical activity and nutritional status are given in Table 2.

Table 1. Demographic features in accordance with parent forms

Parameters	Number (n)	Percentage (%)
Age groups		
8 years old	23	4.6
9 years old	266	54.2
10 years old	188	38.3
11 years old	14	2.9
Gender		
Female	253	51.5
Male	238	48.5
School		
Karaarslan Cumhuriyet Primary School	157	32.0
Zeliha Lutfi Kulluk Primary School	194	39.5
Mehmet Hasan Sert Primary School	140	28.5
BMI classification of children		
0-5 percentile (slim)	8	1.6
5-85 percentile (normal)	339	69.0
85-95 percentile (overweight)	70	14.3
Over 95 percentile (obese)	74	15.1
Maternal BMI classification		
<18.5 (slim)	5	1.0
18.5-24.99 (normal weight)	218	44.4
25.00-29.99 (overweight)	195	39.7
30 and more (obese)	73	14.9
Paternal BMI classification		
18.5-24.99 (normal weight)	162	33.0
25.00-29.99 (overweight)	240	48.9
30 and more (obese)	89	18.1
Presence of overweight siblings		
Yes	53	10.8
No	438	89.2
Birth time of children		
Term	441	89.8
Preterm	50	10.2
Maternal educational status		
Illiterate	16	3.3
Elementary school	235	47.8
Secondary school	170	34.6
High education	70	14.3
Paternal educational status		
Illiterate	8	1.7
Elementary school	174	35.4
Secondary school	177	36.0
High education	132	26.9
Economic status		
Very good	17	3.5
Good	155	31.6
Moderate	305	62.1
Bad	12	2.4
Very bad	2	0.4

BMI: Body mass index

Table 2. Features regarding children's physical activity and nutrition in accordance with parent forms

Parameters	Mean±SD	
Weekly physical activity time of children (hours)	7.3±6.2	
Weekly number of breakfasts of children	5.7±2.0	
Number of weekly consumption of regular 3 main courses of children	5.2±2.3	
Number of weekly consumption of take-home food of children	0.9±1.0	
Daily sleeping time of children (hours)	9.0±1.0	
Parameters	**Yes**	**No**
Snacking status of children between courses	326 (66%)	165 (29%)
In children, snacking between courses. Whether or not they snacked more frequently when facing electronic media devices	92 (34%)	399 (71%)

SD: Standard deviation

While 22% (n=108) had a computer and 2.9% (n=14) had a game console, the mean age for starting to play computer games was 7.0±1.4 years and more than half (57.9%; n=260) played computer games both during the week and at the weekends. Children's use of electronic media devices in accordance with parent and children questionnaires are given in Table 3.

Before analyzing the relationship between age groups and BMI percentiles, some age groups were combined because there were a scarce number of children who were 8 and 11 years old, so 2 groups were formed for evaluation as those at the age of 8-9 years and those at the age of 10-11 years. The BMI percentile values of children in the 8-9-year-old group were higher than those in the 10-11-year-old group (t=3.044; p=0.002). There was no statistically significant relationship between gender and BMI percentiles (t=0.598; p=0.550). Similarly, educational levels of parents were classified as 'primary school or less' and 'secondary school or more. Maternal educational level was significantly related to BMI percentiles (t=0.389; p=0.038). Familial economic groups were defined as 'good' and 'moderate or bad'. Economic status was not significantly related to BMI percentiles (t=-0.263; p=0.793). Although time of birth had no significant relationship with BMI percentiles (t=0.767; p=0.443), having overweight siblings had (t=2.872; p=0.004). The relationship between BMI percentiles and sociodemographic features is demonstrated in Table 4.

Grouping for obesity classification was defined as 'slim and normal', 'overweight', and 'obese'. Children's obesity status had no significant relationship with physical activity, eating weekly regular three course meals, weekly number of breakfasts, weekly consumption of take-home foods, daily sleeping hours,

Table 3. Demographic features regarding children's use of electronic media devices in accordance with parent and children forms

Parameters	n	%
Owning a computer*		
Yes	108	22.0
No	383	78.0
Owning a tablet*		
Yes	227	46.2
No	264	53.8
Owning a telephone*		
Yes	35	7.1
No	456	92.9
Owning a game console*		
Yes	14	2.9
No	477	97.1
Total	491	100.0
Parameters	**Mean±SD (hours)**	
Mean daily time spent across the television*	2.1±1.2	
Mean daily time for playing computer games*	0.8±0.9	
Mean daily time spent facing the computer other than playing games*	0.7±0.8	
Mean daily time for playing tablet games*	0.5±0.7	
Mean daily time spent facing the tablet other than playing games*	0.5±0.7	
Mean daily time spent playing telephone games*	0.4±0.6	
Mean daily time spent facing the telephone other than playing games*	0.2±0.5	
Mean daily time spent playing games with the game console*	0.1±0.3	
Parameters	**Mean±SD (years old)**	
Mean age for starting to play computer games**	7.0±1.4	
Parameters	**n**	**%**
Status of playing computer games during the week and at the weekends**		
Only during the week	21	4.7
Only weekends	168	37.4
Both during the week and at the weekends	260	57.9
Total	449***	100
Parameters	**Mean±SD (hours)**	
Mean daily time for playing computer games during the week**	0.9±1.0	
Mean daily time for playing computer games at the weekends**	1.4±1.0	
Parameters	**n**	**%**
Place where computer games are mostly played**		
Home	422	94.0
School	26	5.8
Other	1	0.2
Total	449***	100

*Evaluated in accordance with parent forms.
**Evaluated in accordance with children's forms.
***A total of 42 cases that did not play computer games were not taken into account.
SD: Standard deviation

Table 4. The relationship between body mass index percentiles and demographic features

Parameters		BMI percentile Mean±SD	t	p*
Age group	8-9 years old (n=289)	65.4±27.2	3.044	0.002
	10-11 years old (n=202)	57.6±28.5		
Gender	Female (n=258)	62.9±26.3	0.598	0.550
	Male (n=253)	61.4±29.7		
Maternal educational level	Primary school or lower (n=251)	64.7±27.4	0.389	0.038
	Secondary school or higher (n=240)	59.5±28.4		
Paternal educational level	Primary school or lower (n=182)	63.5±28.4	0.770	0.442
	Secondary school or higher (n=309)	61.4±27.6		
Economic status	Good (n=172)	61.7±28.8	-0.263	0.793
	Moderate or bad (n=319)	62.4±27.6		
Birth time	Term (n=441)	62.5±27.9	0.767	0.443
	Preterm (n=50)	59.3±28.6		
Presence of overweight siblings	Yes (n=53)	72.5±26.6	2.872	0.004
	No (n=438)	60.9±27.9		
Snacking between courses	Yes (n=326)	62.8±28.3	0.673	0.501
	No (n=165)	61.0±27.3		
Snacking status while using electronic media	Yes (n=92)	66.2±28.2	1.528	0.127
	No (n=399)	61.3±27.9		

*The independent samples t-test was used for analyses.
SD: Standard deviation, BMI: Body mass index

and daily time for watching TV (p>0.05). On the other hand, obesity had a significant relationship with daily computer playing times (p=0.005). Obesity was significantly related to CGAS scores (p=0.049). The relationship between childhood obesity classification and some factors influencing obesity is given in Table 5.

Children's level of addiction was divided into 3 groups according to their CGAS scores as low (21-49 scores), moderate (50-77 scores), and high (78 and higher scores). A total of 42 cases that did not play computer games were not taken into account. Most of the children (86.9%; n=390) had low levels of addiction. While 12.7 (n=57) were moderately addicted, there were only 2 cases (0.4%) who were found to be at high addiction level.

Between BMI percentile and daily total screen time (r=0.122; p=0.007) and total CGAS scores (r=0.126; p=0.008), a weak but positive correlation was determined. In addition, there was a weak but positive correlation between daily total screen time and total CGAS scores (r=0.219; p<0.001).

Discussion

The present study is important, as it is the first study performed in Konya in this field and it has a wide sampling size with high numbers of students and parents. This study showed that 14.3% of the study group was overweight and 15.1% was obese as the Turkish Project of Monitoring Growth in School Children saying that 20.8% was overweight or obese in 6-10-year-old age group (14). Nonetheless, this means almost one in every five children is overweight or obese and this finding supports the serious risk of obesity that our Turkish Ministry of health has been warning about.

Studies performed abroad have revealed that the rate of computer game addiction in children and adolescents using computers is 9.3% in Singapore and 11.9% in Germany (15,16). The present study revealed that levels of addiction were moderate in 12.7% of the children and high in 0.4%. The increased ratios in our study suggest that computer game addiction has increased among children over the years.

In the literature, it is accepted that obesity in the family is one of the strongest risk factors for childhood obesity. In the present study, increased paternal BMI values were associated with increased childhood obesity. Maternal BMI values showed no statistically significant relationship with childhood obesity. In the study of Ohlund et al. (17), paternal obesity was defined as an independent risk factor for childhood obesity. The outcome for maternal BMI may be related to mothers reporting less than their actual weight, as data on parental weights are collected based on their report.

In the present study, when the relationship between paternal educational levels and BMI percentiles was investigated, maternal educational levels were found to be significantly associated while paternal levels showed no significant relationship. Huerta et al. (18) reported that similar low levels of parental education could misdirect children in terms of healthy nutrition and induce obesity by unbalanced and erroneous nutrition.

The presence of obese individuals within the family is thought to be a risk factor for childhood obesity and it is believed to be related to the genetic and environmental basis of obesity (4). Similarly, the present study found that BMI percentile values were related to the possibility of having an obese sibling.

Table 5. The relationship between obesity classification and some factors influencing obesity

	0-85 percentile Slim-normal (a)	85-95 percentile Overweight (b)	>95 percentile Obese (c)	F	p
	Mean±SD Min-max	Mean±SD Min-max	Mean±SD Min-max		
Weekly physical activity time	7.3±6.1	7.6±6.6	7.1±5.9	0.116	0.944*
	0-30	1-28	0-28		
Weekly number of eating regular 3 course meals	5.3±2.2	4.8±2.4	5.2±2.3	2.143	0.342*
	0-7	0-7	0-7		
Weekly number of breakfasts	5.8±1.9	5.4±2.2	5.5±2.1	3.983	0.137*
	0-7	0-7	0-7		
Weekly frequency of consumption of take-home food	0.9±1.0	1.2±1.3	0.9±1.1	3.368	0.186*
	0-6	0-7	0-5		
Sleep time	9.0±1.0	8.8±0.9	9.0±0.9	2.445	0.295*
	7-12	7-11	7-12		
Daily time spent watching TV	2.1±1.2	2.3±1.1	2.1±1.3	1.873	0.392*
	0-6	0-5	0-5		
Daily time spent playing computer games	0.7±0.8	1.1±1.1	1.0±1.2	11.864	0.005[ab*]
	0-5	0-4	0-5		
Daily computer activity time other than game playing	0.6±0.8	0.7±0.9	0.7±0.8	1.757	0.415*
	0-5	0-4	0-3		
Daily time spent playing tablet games	0.6±0.8	0.5±0.7	0.5±0.7	0.096	0.953*
	0-5	0-3	0-3		
Daily tablet activity time other than game playing	0.5±0.7	0.4±0.8	0.5±0.8	2.325	0.313*
	0-5	0-3	0-4		
Daily time spent playing telephone games	0.4±0.6	0.5±0.6	0.4±0.6	3.825	0.148*
	0-4	0-2	0-3		
Daily telephone activity time other than game playing	0.2±0.4	0.3±0.6	0.2±0.4	3.794	0.150*
	0-3	0-2	0-1		
Daily time spent playing games on the game console	0.1±0.3	0.1±0.4	0.1±0.3	0.481	0.786*
	0-2	0-2	0-1		
Maternal BMI (kg/m^2)	25.7±4.2	26.0±4.4	26.5±4.0	1.180	0.308**
Paternal BMI (kg/m^2)	26.4±3.4	27.2±3.4	28.3±4.1	10.227	<0.001[ac**]
Total daily time spent facing the screen (hours)	5.2±2.6	6.0±2.7	5.7±2.9	3.834	0.033[ab**]
Total CGAS scores	35.6±11.0	39.3±12.7	38.3±11.5	3.489	0.049[ab**]

*The Kruskal-Wallis test was used for analyses and in cases of differences between the groups, the non-parametric post-hoc (Dunn) test was used.
**One-way ANOVA test was used and in cases of differences between groups, the post-hoc (Tukey) test was used.
[a]Slim-normal.
[b]Overweight.
[c]Obese.
CGAS: Computer Game Addiction Scale, SD: Standard deviation, BMI: Body mass index, Min-max: Minimum-maximum

In the present study, BMI percentile values were higher in children who were snacking frequently between main courses; however, the difference was not statistically significant. Similarly, Özilbey and Ergör (19) found no significant relationship between snacking between main courses and BMI percentile values in elementary school students and snacking between main courses is a variable that affects obesity in adults. Yet, it can be thought that despite the influence, it is not a prominent factor in childhood period.

BMI percentiles of children showed no significant relationship with physical activity. The studies performed by Öztora (20) in 2005 and Koçoğlu et al. (21) in 2003 showed that the duration of weekly sports activities was not related to obesity. However, individuals who do not sufficiently engage in physical activities

are known to be more obese when compared to individuals who engage in high levels of physical activity. In addition, it is a well-known fact that obese individuals engage in lower levels of physical activity. In the present study, the results can be because the activity presented could not objectively be evaluated in accordance with the suggestions of the American Academy of Pediatrics (5).

In the literature, there are various studies supported and unsupported by the claims that weekly regular three course main meals and weekly number of breakfasts are interrelated with obesity. The present study, similar to the study performed by Özilbey and Ergör (19), found that having breakfast was not related to obesity. Contrary to this, another study reported that obesity was more frequent in students who skipped main courses (22). These different results can depend on the content of breakfast. As a matter of fact, a breakfast including plenty of carbohydrates and fats can increase the risk of obesity. This situation shows that regular courses by themselves do nott mean much as their content should also be questioned in details.

The present study could not reveal a significant relationship between BMI percentiles and weekly consumption of take-home foods. This finding was similar to the studies of Özilbey and Ergör (19) and Savaşhan et al. (23) in which no significant relationship between obesity and frequency of consumption of fat food could be revealed. Miller (24), on the other hand, remarked that limiting consumption of fast food/quick bites, sweetened beverages, and snacks was an important step in preventing obesity. Children who skip main courses can turn to high calorie fast food at the school or outside and this in turn can lead to obesity. The reason for this variable not being significantly related to obesity in the present study can be generally low frequency of fast food consumption in the studied population.

Some studies indicate a positive relationship between screen time across the television and obesity while others state that there is no significant relationship (20,21). A study performed in United States in 2008 revealed that screen time and BMI was not related but prolonged high attention and orientation to the television led to increased BMI values. Same researchers reported that consuming energy-loaded food during the time when primary attention was concentrated on the television was related to obesity (25). Similarly, in the present study, there was no significant relationship between daily time of watching TV and BMI percentiles and the reason of this could be the relationship of appetite and obesity with attention and concentration on the television rather than screen watching time.

In the present study, the increase in daily time of playing computer games led to increased BMI percentile values in children. Goldfield et al. (26) performed a study in 2011 and stated that playing computer games was significantly related to blood pressure and blood lipid levels. Researchers reported that video game playing, which was investigated in well-controlled laboratory research, could lead to high blood pressure and high blood lipid levels because of its leading to spontaneous food and energy-loaded snack consumption. In addition, this same study showed that the stress, concentration, and other acute reasons resulting from the wish to play an effective game during video gaming increased heart rate, blood pressure, and sympathetic tonus, along with increased mental activity when compared to resting. Other authors depending on this above-mentioned conclusion stated that computer games leading to increased sympathetic activity could lead to the consumption of high calorie food and thus affect obesity.

The BMI percentile values and total daily screen time of our children were interrelated. In a study performed in the US, it was stated that this relationship led to exposure to encouraging ads to eat and was associated with unwitting consumption of food with high calorie and high sugar content (27). In the present study, levels of computer game addiction increased along with BMI percentile values. Turel et al. (28) also found that computer game addiction and obesity were interrelated and explained this relationship with computer games encouraging sleep deprivation and direction to snacks by using ads. Karimi and Ghorbani (29) performed a study on a total of 2,195 children in the age group of 6-12 years in 2015 and concluded that computer games led to obesity by decreasing physical activity.

The present study revealed that total daily screen time and computer game addiction were significantly related. Another similar study suggested that pathological game addicts spent twice longer screen time when compared to non-addicts (30). Nevertheless, electronic media devices like the television, computer, tablet, telephone, and the game console reinforce the relationship between each other by acting as a supporting infrastructure and it can be thought that the brain activates its dopamine-related reward system, hence game addiction.

This study has some limitations. First of all, its cross sectional design and getting information from this age group with a questionnaire may create biases. For controlling age bias, we also got information from parents. Schools were selected with the permission of the Provincial Directorate of National Education. So, different school students might give different results but because of randomly selection, we thought that this study group might represent the whole. Accessing data, especially getting their weight and height, may have bias but in the present study, body weight and height measurements of the children were performed by the same researcher.

Conclusions

In this study, in addition to other obesity studies in the literature, obesity-related factors in children were investigated extensively in Konya, a city with a high obesity rate. The presence of overweight siblings, increased paternal BMI, increased total screen time, and low maternal educational status were found to increase the risk of obesity.

Childhood obesity is known to develop as a result of genetic and environmental factors. One of the important factors due to its interchangeability is inactivity. Children addicted to computer games have decreased physical activity, decreased sleep time and quality, direct to high calorie food because of the ads they are exposed to and thus their obesity risk becomes suggestive. Nowadays, due to increased access to computers in every home, the relationship between computer games and obesity becomes more important. When investigating the relationship between computer games and obesity, the levels of addiction should also be taken into account along with screen times. In our country, while there are studies involving the relationship between obesity and the duration of playing games, it is important to note that more studies are needed to investigate the relationship between obesity and computer game addiction. Computer game addiction is essential in terms of the possible future results of obesity. There is a need to raise awareness of families, schools and the whole community on this issue. Ensuring a safe environment and green spaces for children should be a national policy.

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Ethics

Ethics Committee Approval: Ethics Committee Approval (no: 2018/1196, date: 09.02.2018) was taken from Necmettin Erbakan University Meram Faculty of Medicine and written permission was taken from the Provincial Directorate of National Education of Konya.

Informed Consent: Principals of the schools where the study was to be conducted were contacted and the study was performed with the consent of these principals and the support of school counselors.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: U.K., R.K., Concept: U.K., N.K., R.K., Design: U.K., N.K., Data Collection or Processing: U.K., Analysis or Interpretation: N.K., R.K., Literature Search: U.K., N.K., Writing: U.K., N.K., R.K.

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Opinions of parents concerning childhood vaccine refusal and factors affecting vaccination in Konya

Hüseyin İlter[1], Lütfi Saltuk Demir[2]

[1]*Ministry of Health General Directorate of Public Health, Ankara, Turkey*

[2]*Necmettin Erbakan University Faculty Meram of Medicine, Department of Public Health, Konya, Turkey*

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Corresponding Author:
Hüseyin İlter, M.D., Ministry of Health General Directorate of Public Health, Ankara, Turkey

ORCID:
orcid.org/0000-0002-4452-8902

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ABSTRACT

Aims: The purpose of this study was to reveal the opinions, knowledge, and attitudes of parents in Konya, who refuse vaccination, concerning vaccine refusal.

Methods: The study has a cross-sectional design. The research data were collected in 2019 using a survey form developed by the researchers. The survey form was filled out by the parents of children in the 0-4 age group who had not been vaccinated in Konya and its districts in 2017. We were able to reach 801 out of 923 children who had not been vaccinated and still living in Konya. The parents of 590 children (73.7%) who agreed to participate in the study were interviewed.

Results: The most commonly refused type of vaccination was hepatitis A, whereas the least was hepatitis B. The most common reasons for vaccine refusal were believing that vaccines were not safe (63.9%), not believing that vaccines were useful and necessary (57.6%), and not trusting vaccines because they were produced overseas (47.3%). While 65.9% of the families reported that a family health worker tried to convince them to have their children vaccinated, 32.4% reported that a family physician tried to convince them. 48.8% of the parents believed that vaccines caused autism. 70.0% of the parents named their family physician as their source of information, 65.4% named internet/social media.

Conclusions: The families had difficulty with trusting health workers and disregarded the information provided by health workers. Additionally, it was found that gynecologists did not sufficiently inform pregnant women regarding vaccination during the follow-up process.

Introduction

Immunization is a very important and cost effective primary health care service for the protection of individual and public health (1). For this reason, it is regarded as the most significant public health achievement of the 20th century (2,3).

Vaccines are quite safe and effective in developing the immunity of the individual and the society. However, they are not 100% effective and safe (4). Vaccination does not provide immunity in 1-5% of cases. There is also a group that cannot get vaccinated consisting of, for example, those who are unable to access health care services, those who have certain diseases, or those whose immunity is impaired due to medication. The addition of vaccination refusers to this group who cannot develop an immunity against vaccine-preventable diseases creates a non-vaccinated, and therefore unprotected segment in the society. This is a significant risk in terms of collective immunity. Failure to reach an adequate level of vaccination as a society leads to increased risk and paves the way for disease outbreaks.

Reservations concerning vaccines have emerged with the introduction of vaccination. In parallel with the developments around the world, the anti-vaccination movement has emerged in Turkey as well. However, after the decision of the Constitutional Court on 2015, the number of families refusing to vaccinate their children increased rapidly, reaching from 183 in 2011 and 980 in 2013 to 5.400 in 2015, 12,000 in 2016, and exceeding 23,000 in 2017 (5).

Increasing number of vaccine hesitation or refusal cases poses a serious risk not only for the individual, but also for the society due to the loss of gains related to children's health in

particular. Due to the risk of re-emergence of diseases that are no longer seen or rarely seen, World Health Organization (WHO) designated vaccine hesitancy as one of the ten leading threats to global health in 2019.

The Konya province of Turkey is one of the leading cities in terms of vaccine refusal, which is a growing problem in the entire world as well as Turkey. According to TurkStat birth statistics, the vaccine refusal rate in the province of Konya in 2017 was found to be 2.6% (6). The purpose of this study was to identify the facts by reaching the parents living in Konya who had refused or hesitated to have their children vaccinated in 2017, to compare findings with similar studies conducted in Turkey, and to suggest possible solutions.

Methods

The study has a cross-sectional design. The research data were collected in March-August 2019 using a 4-section and 26-item survey form developed by the Necmettin Erbakan University Faculty of Medicine Public Health Department researchers. For the purposes of the study, the parents of children in the 0-4 age group living in Konya and its districts who were registered by family physicians and not vaccinated in 2017 due to vaccine refusal or other various reasons were reached through family health centers and the survey was administered electronically.

No sample selection was performed. In Konya, there were 923 children, who were not vaccinated in 2017 due to vaccine refusal or hesitancy. The parents of 122 of these children were excluded from the study since they could not be reached. The parents of 211 of the remaining 801 children refused to respond to the survey and therefore did not participate in the study. The study was completed by interviewing the parents of 590 (73.7%) children living in Konya, who we were able to reach.

Statistical Analysis

The data obtained from the survey administration were imported to the database created in Statistical Package for Social Sciences version 23.0 to perform the statistical analysis. Mean±standard deviation was used for numerical data, frequency and percentage were used for categorical data, and the chi-square test was used for comparisons between categorical variables. The statistical significance level was set at $p<0.05$.

Results

The distribution of non-vaccinated children by district is shown in Figure 1, and the density map obtained by comparing the district populations with the number of vaccine refusal cases is shown in Figure 2. 61.9% of the families with vaccine refusal or hesitancy were living in the central districts (Karatay, Meram, Selcuk), whereas 38.1% were living in the districts out of the center.

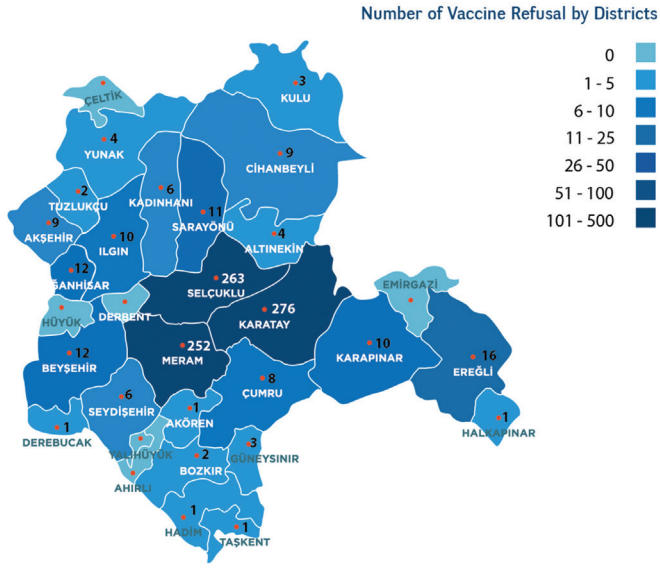

Figure 1. Distribution map of families refusing vaccination by district, Konya-2019

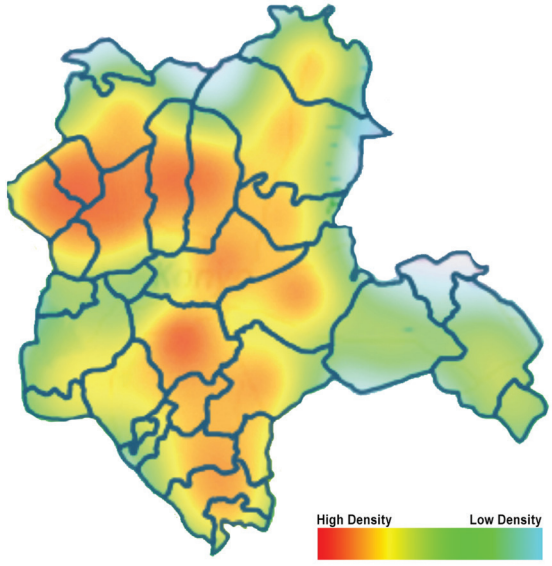

Figure 2. Density map based on the ratio of families refusing vaccination to district population, Konya-2019

Four hundred seventy-eight (81.0%) mothers and 112 (19.0%) fathers were interviewed in the study. The mean age of the mothers was 30.84±5.59 years and the age interval was found to be from 21 to 47 years. The mean age of the fathers was 33.81±5.62 years and the youngest was 21 years old, while the oldest was 51 years old. The age distribution, education and employment status of the parents are shown in Table 1. 28.3% of the employed mothers and 7.6% of the employed fathers stated that they were working in the health industry.

37.9% of families with multiple children stated that they refused to have their other children vaccinated as well. The vaccine refusal was the most common for hepatitis A,

measles, mumps, and rubella (MMR) combination vaccine, and chickenpox vaccine, and the least common for hepatitis B, Bacillus Calmette-Guérin, and Td vaccines (Table 2).

The most common reason for vaccine refusal was found to be believing that vaccines were not safe, followed by not believing that vaccines were useful and necessary, not trusting vaccines because they were produced overseas, believing that vaccines contained religiously forbidden ingredients such as pork products, and being influenced by negative news stories in the media about vaccines (Table 3). The majority of the participants stated that they decided against vaccination jointly with their partners (67.5%). All of the vaccine refusers reported that a health worker tried to convince them otherwise. It was a family health worker for 65.9%, a family physician for 32.4%, and pediatrician for 1.7%.

Opinions of parents regarding vaccination are summarized in Table 4 and information sources on childhood vaccines are seen in Table 5.

4.2% of participants reported that they were not informed about vaccines by their family physicians or family health workers during pregnancy, 24.2% reported that they were not informed by their gynecologist during pregnancy follow-ups, and 19.0% reported that they were not informed by health workers in the hospital where they gave birth.

There were some differences of opinion between the mothers and fathers participating in the study. 74.1% of the fathers believed that recommended vaccines served the economic interests of drug companies compared to 68.8% of the mothers (p=0.016). Similarly, more fathers than mothers believed that vaccines contained religiously forbidden ingredients such as pork products (p=0.023). Additionally, more fathers (18.8%) than mothers stated that they were not accurately informed when they decided not to have their children vaccinated (p=0.020).

It was found that more parents with undergraduate and postgraduate education believed that vaccines caused autism than the parents with middle school/high school and primary school education (p=0.003). Parents with middle school and high school education stated that personnel that performed the vaccination allocated sufficient time to clear their doubts concerning vaccination (p=0.003). More parents with undergraduate and postgraduate education agreed with the statement, “Personnel that perform the vaccination have sufficient knowledge about vaccines” (p=0.001).

Table 1. Socio-demographic characteristics of parents, Konya-2019

	Mother		Father	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)
Educational status				
Literate	11	1.9	1	0.2
Primary school	118	20.0	54	9.2
Middle school	89	15.1	59	10.0
High school	167	28.3	117	19.8
Undergraduate	187	31.7	331	56.1
Postgraduate	18	3.1	28	4.7
Total	590	100.0	590	100.0
Employment status				
Full-time	128	21.7	556	94.2
Part-time	39	6.6	20	3.4
Unemployed	423	71.7	14	2.4
Total	590	100.0	590	100.0

Table 2. Status of children whose families refuse vaccination according to Extended Immunization Program, Konya-2019

	Vaccinated on time	Not vaccinated, but will be	Will not be vaccinated/I am not sure	I do not know/ I do not remember	No response	Total
Vaccine	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hepatitis B	146 (24.7)	121 (20.5)	183 (31.0)	15 (2.5)	125 (21.2)	590 (100.0)
BCG	152 (25.8)	21 (3.6)	230 (39.0)	11 (1.9)	176 (29.8)	590 (100.0)
DTaP-IPV-Hib	69 (11.7)	105 (17.8)	261 (44.2)	9 (1.5)	146 (24.7)	590 (100.0)
PCV	84 (14.2)	83 (14.1)	273 (46.3)	8 (1.4)	142 (24.1)	590 (100.0)
MMR	81 (13.7)	26 (4.4)	295 (50.0)	7 (1.2)	181 (30.7)	590 (100.0)
DTaP-IPV	41 (6.9)	40 (6.8)	265 (44.9)	15 (2.5)	229 (38.8)	590 (100.0)
OPV	55 (9.3)	63 (10.7)	286 (48.5)	12 (2.0)	174 (29.5)	590 (100.0)
Td	24 (4.1)	21 (3.6)	237 (40.2)	18 (3.1)	290 (49.2)	590 (100.0)
Hepatitis A	22 (3.7)	57 (9.7)	301 (51.0)	16 (2.7)	194 (32.9)	590 (100.0)
Chickenpox	72 (12.2)	23 (3.9)	294 (49.8)	9 (1.5)	192 (32.5)	590 (100.0)

DTaP-IPV: Acellular pertussis, diphtheria, tetanus, inactive poliovirus vaccines, DTaP-IPV-Hib: Acellular pertussis, diphtheria, tetanus, inactive poliovirus, haemophilus influenzae type B vaccines, BCG: Bacillus Calmette-Guérin (tuberculosis) vaccine, PCV: Conjugated pneumococcal vaccine, OPV: Oral polio vaccine, Td: Adult diphtheria, tetanus vaccine, MMR: Measles, mumps, and rubella combination vaccine

It was observed that as the educational level increased, more parents agreed with the statement, "Recommended vaccines serve the interests of drug companies" (p=0.002), "Health workers provide information about the benefits of vaccination, but not about risks" (p=0.001), "Mixed-combined vaccines limit the freedom to choose acceptable vaccines" (p=0.001) and "Mixed-combined vaccines wear the immune system excessively" (p=0.044). It was more common among the parents with undergraduate and postgraduate education to agree with the statements mentioned above. More parents with middle school/high school education agreed with the statement, "My pediatrician has sufficient knowledge about vaccines and allocates sufficient time for me" (p=0.040).

It was more common among the parents with undergraduate and postgraduate education to use print sources and anti-vaccination groups compared to the parents with high school or lower education (p<0.001, <0.001, respectively).

Discussion

Although the level of anti-vaccination sentiment varies from country to country, 182 out of 194 WHO member countries reported at least one case of vaccine hesitancy in 2014 (7). National and international studies indicate that vaccine refusal will continue to be a significant problem in terms of preventing infectious diseases around the world. The growing anti-vaccination movement may destroy the gains made in relation to vaccine-preventable diseases.

Studies around the world have revealed that some socio-demographic characteristics such as age, gender, education level, income level, and number of children may be associated with the anti-vaccination sentiment. In our study, a large portion of the parents who refused vaccination were found to be in the 25-34 age group and the vaccine refusal rate increased with increasing number of children. However, considering that vaccine refusal has rapidly grown after the Constitutional Court decision, we need comprehensive studies to reveal whether the growth in vaccine refusal is related to number of children or the decision of the Constitutional Court.

Vaccine refusal can be seen at all educational levels. 63.1% of the mothers and 80.6% of the fathers in our study had high school or higher education. The fact that some of the employed parents were working in the health care industry shows that the problem is not directly associated with education and profession and that knowledgeable families working the health care industry can also have concerns related to vaccines.

In some studies conducted in Turkey, a relationship was found between low educational level and incomplete vaccination (8,9), and the vaccine refusal rate was found to be higher among families with two or more children (10). Knowing these associations well will be beneficial in terms of determining effective strategies in the fight against anti-vaccination movement.

In our study, the three most common vaccine refusal reasons were believing that vaccines were not safe, not believing that vaccines were useful and necessary, and not trusting vaccines because they were produced overseas. One study conducted in Croatia, France, Greece and Romania based on the views of health professionals revealed that vaccine hesitancy was present in all four countries, but there were differences in terms of ranking, and the most common concern was related to the

Table 3. Distribution of reasons behind vaccine rejection of the parents, Konya-2019*

	Number (n)	Percentage (%)
I do not believe that vaccines are safe.	377	63.9
I do not believe that vaccines are useful and necessary.	340	57.6
I do not trust vaccines because they are produced overseas.	279	47.3
I believe that vaccines contain religiously forbidden ingredients (pork products, etc.).	229	38.5
Negative news stories influence my decision.	129	21.9
I admire anti-vaccination groups.	93	15.8
I have observed negative experiences in my social circle or with my other children after vaccination.	90	15.3
I thought my child was too young.	72	12.2
My child had a disease that prevented vaccination.	53	9.0
I forgot the visit date/failed to show up for visit due to personal reasons.	39	6.6
I did not know the vaccination date; I learned about it too late.	11	1.9
I do not believe that school is an appropriate place for vaccination.	8	1.4
Health workers did not inform me sufficiently and did not allocate enough time.	4	0.7
Health workers did not recommend me to participate in the vaccination program.	3	0.5
Other**	16	2.7

*The participants marked more than one option.
**Other family members like uncle did not want it, the vaccination schedule abroad is being applied, I do not want my opinion clear.

Table 4. Opinions of parents regarding vaccination, Konya-2019

	Strongly agree n (%)	Agree n (%)	Disagree n (%)	Strongly disagree n (%)	I do not know n (%)
If we stop vaccination, diseases that have become very uncommon will return.	50 (8.5)	154 (26.1)	245 (41.5)	62 (10.5%)	79 (13.4)
Childhood vaccinations are for the benefit of the entire society.	124 (21)	88 (14.9)	264 (44.7)	60 (10.2%)	54 (9.2)
Mandatory vaccines (e.g. measles) are more important than non-mandatory vaccines (e.g. influenza).	50 (8.5)	169 (28.6)	232 (39.3)	54 (9.2%)	85 (14.4)
I am scared of negative outcomes that may occur right after vaccination.	132 (22.4)	218 (36.9)	162 (27.5)	38 (6.4)	40 (6.8)
I am scared of possible damages that may occur years after vaccination.	147 (24.9)	226 (38.3)	158 (26.8)	33 (5.6)	26 (4.4)
I believe that vaccines cause autism.	104 (17.6)	184 (31.2)	159 (26.9)	36 (6.1)	107 (18.1)
I believe that vaccines cause sterility.	100 (16.9)	179 (30.3)	181(30.7)	34 (5.8)	96 (16.3)
I believe that vaccines weaken the immune system.	104 (17.6)	270 (45.8)	113 (19.2)	31 (5.3)	72 (12.2)
If you lead a healthy lifestyle or use natural medicines, vaccination is not necessary.	134 (22.7)	252 (42.7)	75 (12.7)	41 (6.9)	88 (14.9)
It is too early to vaccinate a child right after birth and it would be better to wait until the child older.	131 (22.2)	185 (31.4)	125 (21.2)	45 (7.6)	104 (17.6)
I believe that some vaccines are more dangerous than infections that they prevent.	100 (16.9)	238 (40.3)	136 (23.1)	32 (5.4)	84 (14.2)
Recommended vaccines serve the interests of drug companies.	179 (30.3)	233 (39.5)	55 (9.3)	27 (4.6)	96 (16.3)
I believe that numerous vaccines contain hazardous substances (thiomersal, mercury).	150 (25.4)	233 (39.5)	113 (19.2)	21 (3.6)	73 (12.4)
I believe that vaccines contain religiously forbidden ingredients such as pork products.	127 (21.5)	201 (34.1)	116 (19.7)	48 (8.1)	98 (16.6)
When I decided against the vaccination of my child, I was not accurately informed.	23 (3.9)	43 (7.3)	299 (50.7)	183 (31)	42 (7.1)
Health workers provide information about the benefits of vaccination, but not about risks.	82 (13.9)	60 (27.1)	217 (36.8)	75 (12.7)	56 (9.5)
I believe that free vaccines offered by health authorities are too much.	80 (13.6)	199 (33.7)	144 (24.4)	33 (5.6)	134 (22.7)
I would prefer avoiding multiple vaccines in one session.	73 (12.4)	197 (33.4)	201 (34.1)	32 (5.4)	87 (14.7)
I do not believe vaccines are useful; the diseases that they prevent are not very serious.	142 (24.1)	264 (44.7)	100 (16.9)	30 (5.1)	54 (9.2)
A vaccine recommended by the family physician is safe.	32 (5.4)	82 (13.9)	269 (45.6)	110 (18.6)	97 (16.4)
A vaccine recommended by health authorities is safe.	34 (5.8)	79 (13.4)	294 (49.8)	93 (15.8)	90 (15.3)
Personnel that perform the vaccination allocate sufficient time to dispel my doubts concerning vaccination.	142 (24.1)	305 (51.7)	107 (18.1)	20 (3.4)	16 (2.7)
Personnel that perform the vaccination have sufficient knowledge about vaccines.	139 (23.6)	313 (53.1)	90 (15.3)	18 (3.1)	30 (5.1)
My pediatrician has sufficient knowledge about vaccines and allocates sufficient time for me.	115 (19.5)	297 (50.3)	81 (13.7)	24 (4.1)	73 (12.4)
My pediatrician has sufficient knowledge about vaccines and allocates sufficient time for me.	165 (28.0)	337 (57.1)	47 (8.0)	16 (2.7)	25 (4.2)
My pediatrician's opinion is very important in my decision about vaccination.	46 (7.8)	196 (33.2)	226 (38.3)	46 (7.8)	76 (12.9)
My family physician's opinion is very important in my decision about vaccination.	44 (7.5)	133 (22.5)	305 (51.7)	49 (8.3)	59 (10)
Mixed-combined vaccines (multiple vaccines in a single syringe such as DTaP-IPV-Hib) limit the freedom to choose acceptable vaccines.	53 (9.0)	216 (36.6)	122 (20.7)	36 (6.1)	163 (27.6)
Mixed-combined vaccines (multiple vaccines in a single syringe such as DTaP-IPV-Hib) wear the immune system excessively.	67 (11.4)	213 (36.1)	86 (14.6)	30 (5.1)	194 (32.9)

DTaP-IPV-Hib: Acellular pertussis, diphtheria, tetanus, inactive poliovirus, haemophilus influenzae type B vaccines

Table 5. Information sources on childhood vaccines, Konya-2019*

	Number* (n)	Percentage (%)
Family physician	413	70.0
Internet, social media	386	65.4
Religious sources	229	38.8
Friends/family	227	38.5
Pediatrician	189	32.0
Anti-vaccination groups	189	32.0
Religious opinion leaders	188	31.9
Print sources (book, magazine, newspaper, etc.)	187	31.7
Television	116	19.7
Another trusted physician	115	19.5
Public Health Center	34	5.8
Other**	11	1.9

*The participants marked more than one option.
**Aidin Salih (MD), uncle, dentist

side effects of vaccines (11). In one review based on data from 194 WHO Member States, vaccine safety concerns and fear of side effects, one of the most common reasons for vaccine hesitancy increased from 22.0% to 23.0%, lack of knowledge of parent on benefit of immunization increased from 10.0% to 15.0%, and religion, culture, gender and socioeconomic issues regarding vaccines increased from 9.0% to 12.0% over the three-year period from 2014 to 2016 (12).

Moreover, many studies show that families believe that although vaccines are beneficial, they also contain possibly harmful ingredients; families believe that vaccines may be more harmful than the diseases that they prevent; there are concerns about MMR in particular, families find multiple vaccines in one session to be risky; and families believe that health workers hide some negative aspects of vaccines (13-15).

Researchers concluded that the lack of information provided to mothers during pregnancy was effective in the emergence of these sentiments (13). In our study, one fourth of the parents stated that they were not sufficiently informed about vaccines by their gynecologist during pregnancy. The lack of knowledge of parents on vaccines is a problem that needs to be solved urgently to prevent vaccine refusal. The fact that vaccination is not seen as a priority issue in some specialties is a significant problem.

Every year, vaccines prevent 2.7 million measles, 2 million neonatal tetanus, and 1 million pertussis cases around the world. In 2017, WHO reported 14,000 measles cases in Europe, which increased to 83,000 cases in 2018. Although the idea that vaccine-preventable diseases would not be seen again in the absence of vaccination was common among the respondents in our study, 87.0% of the measles cases in Europe were non-vaccinated individuals (16).

56.0% of the families in our study refused vaccination due to religious reasons. Although it was not one of the top three reasons of vaccine refusal, religious reasons are still a matter of concern in terms of preventing vaccine refusal since they influence certain groups. In one study conducted in 13 countries from 6 WHO regions including Muslim countries such as Saudi Arabia and Yemen, religious concerns were among the most significant reasons of vaccine refusal in most of the countries (17). Similarly, the fact that vaccines did not have halal certificate was found to be a reason for vaccine refusal in a study conducted by WHO and UNICEF with participants from 154 countries (18). Vaccine refusal due to religious reasons is a problem experienced not only in Muslim countries, but in countries where other religions are dominant as well. Failure to eliminate concerns of the society may be due to failure to involve civil society organizations and religious opinion leaders in decision mechanisms related to vaccination and exclusion of politicians or health professionals from the decision-making process of families refusing to have their children vaccinated due to religious incompatibility. This matter needs to be studied in more detail.

The vaccine-autism association continues to be a concern for parents. Thiomersal, which contains ethyl mercury, has been used as a preservative in some vaccines since the 1930s. However, the claims that the increase in the number of vaccines in the childhood vaccination schedule and the fact that some of these vaccines contain thiomersal increase the cumulative exposure of infants; and therefore, cause an increased number of nervous system development disorders such as autism, attention deficit/hyperactivity disorder, and delayed speech have been debated more and more in recent years (19-21).

In our study, one third of the families believed that vaccines cause autism. Studies from various countries showed no association between mixed vaccines, MMR in particular, and vaccines containing or not containing thiomersal in terms of spectrum disorders (19-21). Many scientific studies such as those mentioned above showed no difference between vaccinated and non-vaccinated children in terms of autism spectrum disorder prevalence, regardless of whether multiple vaccines are given together or each vaccine group is given within a vaccination schedule.

Similar to the results of other studies (15), 63.4% of the families in our study believed that vaccines weakened their children's immune system. Similarly, numerous studies show that the most significant concerns of vaccine refusers are related to the safety and side effects of vaccines (14,22,23). There are also studies which reveal that families believe that side effects of vaccines are not as rare as claimed (24), a natural diet and healthy lifestyle provides better protection than vaccines (25), and undergoing the disease strengthens the immune system

more than vaccines (24). It is believed that a significant lack of knowledge is behind concerns related to vaccines. This lack of knowledge maybe a result of insufficient number of scientific studies, insufficient understanding of existing studies or ineffective use of communication tools and techniques.

47.0% of the families in our study were concerned about vaccines being produced overseas. Other studies also found that the belief that domestically produced vaccines would be safer was common (15,26).

One study conducted in a hospital in Turkey revealed that 73.0% of health workers had concerns related to commercial activities and inducements of vaccine companies (27). In our study, about two third of the families believed that recommended vaccines served commercial benefits of pharmaceutical companies. It is believed that domestic and national vaccine production efforts in Turkey will be beneficial in terms of eliminating such concerns and increasing acceptance of vaccine by the society.

What really shapes the opinions of families regarding vaccines is their source of information. The most common sources of information in our study were health workers, family physicians in particular, followed by internet and social media. In one study from the US, parents were found to get their information about vaccines from health workers, followed by print materials such as books and magazines, and friends and relatives, and it was revealed that about half of families used the internet as their source of information (28). Although television, radio, and newspapers were mentioned as the sources of information in some studies, internet and social media are becoming more and more popular as an source of information on vaccines (13,29). On the other hand, only 3.0% of the content about vaccines on the internet was found to be created by health professional (30).

In our study, religious opinion leaders and anti-vaccination groups were mentioned as sources of information by one third of the families. While families should be able to obtain accurate and reliable information from health workers such as family physicians, they get their information from other sources such as the internet, social media, friend circle, or religious opinion leaders, which is noteworthy.

Although the majority of the families reported that they were informed by health workers, 41.0% stated that health workers provided incomplete information about vaccines and did not mention negative aspects of vaccines. Although health workers were found to try to convince families to change their vaccine refusal decision, it was also found that their efforts to eliminate families' concerns fell short. Detailed studies are needed to reveal whether this is a result of a lack of confidence in health professionals or a lack of communication.

This study has some limitations. The study was conducted in family health centers. This led to the difficulty in persuasion of families who had to meet family health centers staff about vaccine refusal repeatedly. This was a limitation that negatively affected participation in the study.

Conclusion

In conclusion, although it is not representative of the entire country, the fact that vaccine refusal is so common in a large city reveals the extent of the danger. Particularly reasons behind families' distrust in vaccines should be studied in more detail. The families' lack of knowledge on vaccines needs to be eliminated. Parents need to be informed about the contents of vaccines using appropriate communication channels. Interventions aiming at vaccine refuser families need to be in line with cultural, historical, and religious values of the target group. In this context, detailed, long-term, multi-directional, well-planned, proactive communication strategies which use appropriate tools to reach the target group in cooperation with communication experts, opinion leaders, and civil society organizations are required. It is important to prefer vaccines that do not contain porcine gelatin in order to eliminate concerns of families who display religious incompatibility. Halal certification could be considered for vaccines.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethical Committee (Drug and Non-Medical Device Research Ethical Committee of Necmettin Erbakan University Faculty of Meram Medicine, approval number: 05.10.2018/1514). The procedures were in line with the Helsinki Declaration.

Informed Consent: Informed consent was obtained from all participants at the time of survey application.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: L.S.D., Concept: H.İ., L.S.D., Design: H.İ., L.S.D., Data Collection or Processing: H.İ., L.S.D., Analysis or Interpretation: H.İ., L.S.D., Literature Search: H.İ., Writing: H.İ.

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Evaluation of serum interleukin-33 and gene polymorphisms in patients with bronchial asthma

Kadir Canoğlu[1], Oğuzhan Okutan[1], Dilaver Taş[2], İsmail Yılmaz[3], Soner Yeşilbaş[4], Tayfun Çalışkan[1], Ayşe Filiz Arpaçağ Koşar[5], Zafer Kartaloğlu[1], Ömer Ayten[1], Yasin Uyar[6]

[1]University of Health Sciences Turkey, Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Chest Diseases, Istanbul, Turkey

[2]Baskent University, Health Application and Research Center, Department of Chest Diseases, Istanbul, Turkey

[3]University of Health Sciences Turkey, Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Pathology, Istanbul, Turkey

[4]University of Health Sciences Turkey, Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Biochemistry, Istanbul, Turkey

[5]University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Chest Diseases, Istanbul, Turkey

[6]Merzifon Kara Mustafapasa State Hospital, Amasya, Turkey

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Corresponding Author:
Kadir Canoğlu, M.D., University of Health Sciences Turkey, Istanbul Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Chest Diseases, Istanbul, Turkey

ORCID:
orcid.org/0000-0003-1579-3392

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Keywords: Asthma, IL-33, cytokine

ABSTRACT

Aims: Asthma is a chronic inflammatory disease of the airways. The aim of the study was to investigate the association between serum interleukin (IL)-33 level and IL-33 gene rs1342326, rs1929992 and rs3939286 polymorphisms in patients with asthma.

Methods: Ninety patients aged 18 years and older, who were diagnosed with asthma, and 90 healthy control subjects were included in the study. Serum IL-33 levels were measured by enzyme-linked immunosorbent assay; and IL-33 gene polymorphisms were studied by real-time polymerase chain reaction.

Results: IL-33 level was higher in patients with asthma (4.16±0.88 pg/mL) compared to the control subjects (1.28±0.37 pg/mL) ($p<0.001$). The frequencies of AA, CC and AC alleles for the rs1342326 polymorphism were 52 (57.8%), 5 (5.6%) and 33 (36.7%) in the patient group, and 53 (58.9%), 7 (7.8%) and 30 (33.3%) in the control group, respectively. The frequencies of CC, TT and CT alleles for the rs1929992 polymorphism were 17 (18.9%), 31 (34.4%), and 42 (46.7%) in the patient group and 13 (14.4%), 41 (45.6%), and 36 (40%) in the control group, respectively. The frequencies of CC, TT and CT alleles for the rs3939286 polymorphism were 46 (51.1%), 7 (7.8%), and 37 (41.1%) in the patient group and 44 (48.9%), 9 (10%), and 37 (41.1%) in the control group, respectively. There was no statistically significant difference between the groups in terms of IL-33 gene polymorphisms (rs1342326, rs1929992 and rs3939286) ($p=0.784$, $p=0.304$, $p=0.863$, respectively).

Conclusions: The current study showed increased serum IL-33 levels in patients with asthma compared to healthy controls but gene polymorphism studies did not show any significant difference.

Introduction

Asthma is a major public health problem that affects approximately 300 million people worldwide. Current evidence suggests asthma is a disease in which genetic origins are important and which has complex inheritance characteristics (1). Interleukin (IL)-33 is a new member of the IL-1 cytokine family (2) and is generally released from epithelial cells (eye, skin, intestine, airway, lymphoid organs, keratinocytes, smooth muscle cells), fibroblasts and endothelial cells that are associated with the external environment (3). IL-33 is known to activate both hereditary and acquired immunity. In hereditary immunity, IL-33 activates group 2 innate lymphoid cells (ILC2s), leading to the release of IL-4, IL-5 and IL-13. In addition to ILC2s, it stimulates macrophages, eosinophils, masts and basophils. IL-33-activated dendritic cells increase IL-5 and IL-13 secretion by stimulating Th2 cells (4). Th2 cells promote B cell proliferation and increases secretion of immunoglobulin (Ig) M, IgG1, IgA and IgE antibodies (4) and they also play a critical role in allergic immune response including airway eosinophilia and mucus hyperplasia (5). IL-33 plays a role in the pathogenesis of many diseases, and studies of the entire genome have implicated IL-33 in the pathogenesis of asthma (6). There is a need for new drugs in patients with asthma. IL-33 can be an important target for potential new treatment studies in asthma treatment and biological treatments that are able to control IL-33 levels in patients with asthma may be a potential new approach (7).

The aim of the study was to investigate the association between serum IL-33 level and IL-33 gene rs1929992 (6.251.588. C/T genotype), rs3939286 (6.210.099. C/T genotype) and rs1342326 (6.190.076. A/C genotype) polymorphisms in patients with asthma.

Methods

The study was designed as a single-center, prospective case-control study. In the study, 90 patients diagnosed with asthma according to the GINA 2015 criteria were recruited in the pulmonary outpatient clinic of our hospital between March 2016 and June 2017. Ninety healthy control subjects were recruited in the study. Exclusion criteria were age under 18 years and presence of conditions other than asthma. Written informed consent was obtained from all participants. The study was approved by the Local Ethical Committee (Gülhane Military Medical Academy Haydarpasa Training and Research Hospital, approval number: 26.02.2016/1491-46-16/1539). The procedures were in line with the Helsinki Declaration.

Serum IL-33 Levels

The Serum IL-33 level was measured by an enzyme-linked immunosorbent assay (ELISA) using a Biotek elx-800 device, Gen5 software and the appropriate commercial kits (Human IL-33 Coated ELISA Kit BMS2048, Bender MedSystems GmbH, Wien, Austria), as per the manufacturer's instructions.

IL-33 Gene Polymorphisms

A 2-mL blood sample was collected in ethylenediaminetetraacetic acid tubes from both the patient and control group subjects. The blood samples were stored in a freezer at -80 °C until the day of analysis, when the blood samples were taken out of freezer and left to thaw at room temperature. VIC and FAM probes were used for polymorphism detection. VIC adenine (A) and FAM cytosine (C) allele was determined for the rs1342326 polymorphism, VIC C, FAM thymine (T) for the rs1929992 polymorphism, and VIC C, FAM T allele for the rs3939286 polymorphism.

Reverse Transcription-polymerase Chain Reaction

Genomic DNA was prepared from peripheral blood samples, using standard protocols. All DNA samples were diluted to a final concentration of 50 ng/µL. DNA samples, 2X master mix (TaqMan Genotyping Master Mix, Applied Biosystems, California, USA) and 20X assays [TaqMan single nucleotide polymorphism (SNP) Genotyping Assays, Applied Biosystems, California, USA] were vortexed and centrifuged for 1 minute. A 96-microwell plate was prepared. Each well was filled with 1.25 µL assay, 12.5 µL of master mix and 11.25 µL of DNA sample (20 ng) to yield a final total reaction volume of 25 µL. No DNA was added to at least two wells for no template control.

Statistical Analysis

The study data were uploaded into IBM SPSS Statistics 23 software. In the analysis of the study data, descriptive statistics were presented as mean and standard deviation for numerical variables, and as a frequency distribution for categorical variables. A chi-square test was used to evaluate the relationship between two independent categorical variables. An independent samples t-test was used to evaluate the significance of differences between the two groups. The Hardy-Weinberg equilibrium for the two groups showed no disequilibrium in genotype distribution

Results

Evaluation of Demographic and Clinical Findings

The study included a total of 180 participants, including 90 patients (53 male/37 female) and 90 control subjects (27 male/63 female). The mean age was 36.6±17.2 years in the patient group and 34.9±8.8 years in the control group. There was no statistically significant difference in the age distribution between the two groups ($p=0.406$), although a significant difference was noted in gender distribution ($p<0.001$). The mean serum IL-33 level was 4.16±0.88 pg/mL in the patient group and was 1.28±0.37 pg/mL in the control group. An independent samples t-test showed a statistically significant difference between the groups in terms of the mean IL-33 levels ($p<0.001$). The mean IL-33 level was significantly higher in the patient group than in the control group. The mean age of asthma onset was 25.54±15.05

years in the patient group. The mean asthma control test (ACT) score was 12.98±4.93 in the patient group. The mean forced expiratory volume in the first second (FEV1) % was 77.53±21.80 and the mean total IgE level was 366.71±817.13 IU/mL in the patient group (Table 1).

The age of asthma onset was <18 years in 24 (26.7%) patients, between 18 and 39 years in 50 (55.5%) patients, between 40 and 59 years in 14 (15.6%) patients, and ≥60 years in two (2.2%) patients. The ACT score was ≥20 points (good asthma control) in 11 (12.2%) patients and <20 points (poor asthma control) in 79 (87.8%) patients. The total IgE level was ≤165 IU/mL in 61 (67.8%) patients and >165 IU/mL in 29 (32.2%) patients (Table 2).

Allele and Genotype Analyses

The rs1342326, rs1929992 and rs3939286 variants of the IL-33 gene polymorphism were studied in 90 patients in the asthma group and in the 90 healthy control subjects. In the patient group, 52 (57.8%) patients were VIC homozygous (AA), five (5.6%) patients were FAM homozygous (CC), and 33 (36.7%) patients were heterozygous (AC) for the rs1342326 polymorphism. The frequencies of AA, CC and AC alleles for the same polymorphism in the control group were 53 (58.9%), 7 (7.8%), and 30 (33.3%), respectively.

In the patient group, 17 (18.9%) patients were VIC homozygous (CC), 31 patients (34.4%) were FAM homozygous (TT), and 42 (46.7%) patients were heterozygous (CT) for the rs1929992 polymorphism. The frequencies of CC, TT, and CT alleles for the same polymorphism in the control group were 13 (14.4%), 41 (45.6%) and 36 (40%), respectively.

In the patient group, 46 (51.1%) patients were VIC homozygous (CC), 7 (7.8%) patients were FAM homozygous (TT), and 37 (41.1%) patients were heterozygous (CT) for the rs3939286 polymorphism. The frequencies of CC, TT and CT alleles of the same polymorphism in the control group were 44 (48.9%), 9 (10%), and 37 (41.1%), respectively. A chi-square test showed no statistically significant difference in the genotype distribution of the three polymorphisms among the three groups (p=0.784, p=0.304, p=0.863, respectively) (Table 3).

In the alleles for the rs1342326 polymorphism in the patient group, 137 (76.1%) A alleles and 43 (23.9%) C alleles were identified. The numbers of A and C alleles for the same polymorphism in the control group were 136 (75.6%) and 44

Table 1. Demographic data, IL-33 levels, asthma control test scores, FEV1% and total IgE levels in the patient and control groups

		Control group (n=90)	Patient group (n=90)	p
Age		34.9±8.8	36.6±17.2	0.406
Gender	**Male**	27 (30%)	53 (58.9%)	<0.001
	Female	63 (70%)	37 (41.1%)	
IL-33 (pg/mL)		1.28±0.37	4.16±0.88	<0.001
Age of asthma onset (years)		-	25.54±15.05	-
ACT score		-	12.98±4.93	-
FEV1 (%)		-	77.53±21.8	-
Total IgE		-	366.71±817.13	-

IL-33: Interleukin-33, IgE: Immunoglobulin E, ACT: Asthma control test, FEV1: Forced expiratory volume in one second

Table 2. Distribution of age at asthma onset and asthma control test scores

		n	%
Age of asthma onset (years)	<18	24	26.7
	18-39	50	55.5
	40-59	14	15.6
	≥60	2	2.2
ACT score	Poor asthma control	79	87.8
	Good asthma control	11	12.2
Total IgE	Negative	61	67.8
	Positive	29	32.2

ACT: Asthma control test, IgE: Immunoglobulin E

Table 3. Evaluation of interleukin-33 gene polymorphisms in the patient and control groups

			Groups		Total	p
			Control group	Patient group		
rs1342326	AA	n	53	52	105	0.784
		%	58.9	57.8	58.3	
	AC	n	30	33	63	
		%	33.3	36.7	35.0	
	CC	n	7	5	12	
		%	7.8	5.6	6.7	
rs1929992	CC	n	13	17	30	0.304
		%	14.4	18.9	16.7	
	CT	n	36	42	78	
		%	40.0	46.7	43.3	
	TT	n	41	31	72	
		%	45.6	34.4	40.0	
rs3939286	CC	n	44	46	90	0.863
		%	48.9	51.1	50.0	
	CT	n	37	37	74	
		%	41.1	41.1	41.1	
	TT	n	9	7	16	
		%	10.0	7.8	8.9	

A: adenine, C: cytosine, T: thymine
rs1342326: AA: VIC homozygous, CC: FAM homozygous, AC: heterozygous
rs1929992: CC: VIC homozygous, TT: FAM homozygous, CT: heterozygous
rs3939286: CC: VIC homozygous, TT: FAM homozygous, CT: heterozygous

(24.4%), respectively, The number of C alleles was 76 (42.2%) and the number of T alleles was 104 (57.8%) in the rs1929992 polymorphism. The numbers of C and T alleles for the same polymorphism in the control group were 62 (34.4%) and 118 (65.6%), respectively. In the rs3939286 polymorphism, the number of C alleles was 129 (71.7%) and the number of T alleles was 51 (28.3%). The numbers of C and T alleles for the same polymorphism in the control group were 125 (69.4%) and 55 (30.6%), respectively. A chi-square test showed no statistically significant difference in the allele distribution of the three polymorphisms among the three groups (p=0.902, p=0.129, p=0.644, respectively) (Table 4).

Table 4. Evaluation of allele distribution in the patient and control groups

			Groups		Total	p
			Control group	Patient group		
rs1342326	A	n	136	137	273	0.902
		%	75.6	76.1	75.8	
	C	n	44	43	87	
		%	24.4	23.9	24.2	
rs1929992	C	n	62	76	138	0.129
		%	34.4	42.2	38.3	
	T	n	118	104	222	
		%	65.6	57.8	61.7	
rs3939286	C	n	125	129	254	0.644
		%	69.4	71.7	70.6	
	T	n	55	51	106	
		%	30.6	28.3	29.4	

A: Adenine, C: Cytosine, T: Thymine

Discussion

The present study investigated serum IL-33 levels and the rs1342326, rs1929992 and rs3939286 variants of the IL-33 gene polymorphisms in patients with asthma and healthy controls. The study revealed that there was a significant difference in serum IL-33 levels between the patient group and the healthy controls, while there was no statistically significant difference between the groups in terms of the studied rs1342326, rs1929992 and rs3939286 polymorphisms.

Koca et al. (8) reported that there was no significant difference in serum IL-33 levels between the patients with Behçet's disease and controls and IL-33 may be related to an increase in Th2 cytokine, while Behçet's disease is known to be related to an increase in Th1 cytokine. They also concluded that there was no significant relationship between the development of Behcet's disease and the rs1929992 and rs7044343 SNPs (8). IL-33 levels were higher in patients with systemic sclerosis than in the control group in the study by Yanaba et al. (9). In a study on patients with systemic lupus erythematosus (SLE), Xu et al. (10) studied the rs1929992 and rs7044343 variants of the IL-33 gene polymorphisms. They showed a significant relationship between the rs1929992 polymorphism and SLE and concluded that this polymorphism could serve as a potential biomarker for SLE (10). Higher IL-33 levels in patients with ankylosing spondylitis than in the control group were reported by Han et al. (11). In a study on patients with rheumatoid arthritis (RA), Li et al. (12) found that the rs7044343 polymorphism reduced IL-33 expression and suggested that this variant was a protective genotype against RA. These studies indicated that IL-33 had both pro-inflammatory and anti-inflammatory effects. The protective effect of IL-33 against myocardial infarction and the development of atherogenesis has been demonstrated (13). High IL-33 levels have been also reported in allergic diseases as asthma and anaphylactic shock (14). The intraperitoneal administration of anti-IL-33 prior to sensitization with ovalbumin administration reduced serum IgE levels, eosinophils and lymphocytes and the IL-4, IL-5 and IL-13 levels in bronchoalveolar lavage fluid, and caused a significant reduction in eosinophilic inflammation and mucus secretion in the lung tissue (15). IL-33 levels were significantly higher in the asthma group than in the control group in the present study. IL-33 blockade may be investigated as a new therapeutic target in patients with asthma.

Sakashita et al. (16) reported a significant correlation between the rs1929992 SNP on the IL-33 gene region and Japanese cedar pollinosis (Odds ratio: 1.82; 95% confidence interval: 1.00-3.31; p=0.048). The rs1929992 gene polymorphism was found to be a risk factor for SLE (17). The present study revealed no correlation between the rs1929992 SNP and asthma.

Charrad et al. (18) reported significantly higher IL-33 levels in the asthma group than in the control group in consistence with the present study. They concluded that the rs1342326 polymorphism reduced the risk of asthma and the rs1342326 C allele reduced the risk of development of atopic asthma (18). Schröder et al. (19) showed a positive correlation between rs1342326 SNP and seasonal allergic rhinitis. There was a significant relationship between rs1342326 SNP in the IL-33 gene region and asthma in a study by Moffatt et al. (20). In contrast, the present study found no correlation between rs1342326 SNP and asthma.

In previous studies, there was no significant relationship between the rs3939286 variant of the IL-33 gene polymorphism and preeclampsia (21) and gout (22). López-Mejías et al. (23) suggested that the rs3939286 gene polymorphism had a protective role against the development of subclinical atherosclerosis. Latiano et al. (24) revealed a statistically significant relationship between achalasia and rs3939286 SNP. There was a significant correlation between nasal polyps and the presence of rs3939286 SNP in the IL-33 gene region in another study (25). The present study found no statistically significant relationship between rs3939286 SNP and asthma.

Predisposing genes for asthma were reported to be transferred to the children from their mothers with atopic asthma (26). There was a significant relationship between the defensin β-1 polymorphism and asthma in female patients, whereas no such relationship was reported in males and this gender difference was considered to be linked to hormone-dependent processes in females (27). The lack of an association between the studied IL-33 gene polymorphisms and asthma may be caused by gender difference, because there were significant gender differences between the patient and control groups in the present study.

The strength of this study was its being a prospective case control study. The patients and controls were unmatched, so chi-square test and unconditional logistic regression analysis were used for statistical analysis. Since Hosmer and Lemeshow test showed that goodness of fit test of the model was not found to be statistically compatible ($p>0.05$) in the study, odds ratio value could not be calculated. The limitation of this study was that the patients with asthma had different asthma phenotypes such as eosinophilic asthma, non-eosinophilic asthma, asthma in elderly, refractory atopic asthma, and asthma with allergic rhinitis. We did not classify and compare them according to phenotypes.

Conclusion

In conclusion, IL-33 levels were significantly higher in the asthma group than in the control group. There was no significant difference between patient and control groups in terms of IL-33 gene polymorphisms (rs1929992, rs1342326 and rs3939286). Our findings demonstrated that asthma patients had a higher level of IL-33, and that IL-33 may be considered as a potential therapeutic target in the future. Further molecular studies and clinical studies addressing therapeutic agents that would reduce IL-33 levels are required.

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Ethics

Ethics Committee Approval: The study was approved by the Local Ethical Committee (Ethical Committee of Gülhane Military Medical Academy Haydarpasa Training Hospital, approval number: 26.02.2016/1491-46-16/1539).

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: K.C., D.T., T.Ç., Design: K.C., A.F.A.K., Z.K., Data Collection or Processing: K.C., Y.U., Analysis or Interpretation: K.C., O.O., İ.Y., S.Y., Literature Search: K.C., Ö.A., Writing: K.C., D.T.

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

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Investigating the in-hospital mortality rate of stroke and its related factors at Ali-Ibn-Abi Talib Hospital of Rafsanjan

Alireza Vakilian[1], Zahra Kamiab[2], Sakineh Afzal[3], Amir Moghadam-Ahmadi[1], Nazanin Jalali[1]

[1]Department of Neurology, Faculty of Medicine, Non-communicable Diseases Research Center, Rafsanjan University of Medical sciences, Rafsanjan, Iran

[2]Department of Family Medicine, Faculty of Medicine; Clinical Research Development Unit, Ali-Ibn Abi-Talib Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

[3]General physician, Clinical Research Development Unit, Ali-Ibn Abi-Talib Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

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Corresponding Author:
Zahra Kamiab, Asst. M.D., Prof., Department of Family Medicine, Faculty of Medicine; Clinical Research Development Unit, Ali-Ibn Abi-Talib Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
ORCID:
orcid.org/0000-0001-6670-1828

Keywords: Mortality, stroke, risk factors, Rafsanjan

ABSTRACT

Aims: Stroke is the third leading cause of disability and the second leading cause of death worldwide. Due to the effects of different factors on stroke mortality, the present study aims to determine the in-hospital mortality rate of stroke and its related factors at Ali-Ibn-Abi Talib Hospital of Rafsanjan.

Methods: In this cross-sectional descriptive study, the records of all dead patients with the diagnosis of stroke at Ali-Ibn-Abi Talib Hospital of Rafsanjan were studied for the period of 2012-2017. The inclusion criteria were the definite diagnosis of stroke not longer than 72 hours from the onset of symptoms and being older than 18 years at the time of stroke. The exclusion criteria included other fatal cerebral lesions, having incomplete information for the records, death at the time of admission, and having an indefinite cause of death.

Results: From among 2,199 stroke patients (the mean age was 68.46±15.67, 46% male, 54% female) who were hospitalized, 9.04% (199 patients) died during the hospitalization period. The in-hospital mortality rate was 7.54% (n=142) and 17.98% (n=57) in ischemic stroke and cerebral hemorrhage, respectively. The major risk factor percentages in died patients were 68.3% hypertension, 35.7% diabetes mellitus, 18.6% cholesterolemia. The most common fatal complications in died patients included neurological complications (48.7%, n=97), infections (23.1%, n=46), cardiac complications (18.1%, n=36), and thromboembolism (5.5%).

Conclusions: Our findings are consistent with other studies about risk factors and complications of a stroke. We should focus on the prevention of complications in stroke patients by controlling important risk factors.

Introduction

Stroke is a syndrome characterized by the acute onset of neurological symptoms for at least 24 hours, which is caused by a central nervous system condition resulting from a disorder in the cerebral blood flow. Thus, the syndrome is characterized by the four main manifestations of acute onset, the duration of disorder, vascular origin, and the local complication (1). Stroke is the third leading cause of disability and the second leading cause of death after heart diseases worldwide (2,3). About 70% of stroke cases and 87% of its related deaths and disabilities occur in low- and middle-income countries (3). The prevalence of risk factors for stroke and the related deaths is higher in Asian countries than in Western countries; it is also higher in Iran as one of the middle-income countries in the Middle East (4,5). In Iran, stroke is one of the major causes of mortality and disability (6). Identifying the risk factors of stroke and its incidence increase life expectancy (7). Risk factors for stroke include male gender, smoking, and high levels of alcohol consumption (1,8). The mortality rate of stroke in every country depends on various factors, such as the social class and geographical area of the affected people. The incidence of stroke in developed countries is 5 cases per 1,000 persons. However, the incidence rate in developing countries is about 5-10 cases per 1,000 individuals (9). In the study conducted by Mazdeh and Seif Rabiei (10), the

overall mortality rate of stroke patients was determined to be 59.19%. Stroke patients are susceptible to many neurological and non-neurological complications. Neurological complications are less common than non-neurological ones but occur sooner (11). Post-stroke complications are the leading causes of death in the acute and subacute stroke phases (12). These complications, though not life-threatening, lead to prolonged hospitalization, adverse functional outcomes, and delayed rehabilitation. Most of these complications occur within the first weeks of stroke (13). According to studies conducted in the first trimester of stroke, mortality rates within the first week of stroke are very high but gradually decrease (14). The major risk factors of post-stroke complications include being of an older age, experiencing highly severe stroke, having a previous disability, as well as related diseases, such as diabetes mellitus (DM), hypertension (HTN), and ischemic heart diseases (IHD) (15). The prognosis and mortality of stroke patients depend on stroke complications and the interaction among age, sex, stroke severity, and its type (16). Since mortality is an important health indicator, and stroke is preventable, it is vital to know more about its risk factors so as to analyze the stroke rate and its related burden (9,17).Therefore, this study was conducted to determine the in-hospital mortality rate of stroke and its related factors at Ali-Ibn-Abi Talib Hospital of Rafsanjan.

Methods

In this retrospective cross-sectional study, the records of patients who died at Ali-Ibn-Abi Talib Hospital of Rafsanjan from March 2012 to March 2017 due to stroke were investigated. In all patients, stroke (as defined by the World Health Organization) indicates the onset of localized neurologic symptoms that last longer than 24 hours, result in death, or are confirmed by a neurologist based on the evidence of stroke in computed tomography (CT) scans or magnetic resonance imaging (MRI) scans (18). The study was approved by the Ethics Committee under the code: (IR.RUMS.REC.1395.145), in accordance with the Helsinki Criteria. The inclusion criteria were the definitive diagnosis of stroke by a neurologist, experiencing an acute stroke occurrence (not longer than 72 hours from the onset of symptoms to the patient referral), and being older than 18 years at the time of stroke. In contrast, the exclusion criteria included having cerebral lesions, such as tumors, infections, and traumatic brain injuries that were potentially fatal, having incomplete information for the records, experiencing death at the time of admission to the cardiopulmonary resuscitation room, and having an indefinite cause of death. This study was conducted based on the data present in the files of stroke patients using a checklist. The checklist included general patient information, such as age, sex, smoking habits, as well as the presence or absence of underlying diseases, including DM, HTN, high blood cholesterol, atrial fibrillation (AF), IHD, the past or present history of stroke, and surgical interventions. The time interval between referring to the hospital and death was determined by the researcher based on the exact time of referral and the death recorded in patient records. The information required was provided by the researcher using the checklist developed to determine the frequency of in-hospital stroke deaths by the type of stroke [ischemic, intracranial hemorrhage (ICH), or subarachnoid hemorrhage (SAH)], the location of the lesion in the brain, the size of the lesion by brain imaging (CT scans or MRI scans), as well as the help of a neurologist. The location of the lesion in the brain in ischemic stroke was classified into anterior and posterior circulations. In ICH, it was classified into thalamus, basal ganglia, the cerebellum, the pons, and lobar hemorrhage. The size of the lesion in ischemia was classified into lacunar, minor, as well as major, and in hemorrhage, it was classified into extensive and non-extensive (19). Access to the patients' CT scans or MRI scans was possible using the Hospital Information System based on the patients' file numbers. The causes of death or deadly complications following a stroke were determined by an investigator and a physician based on the evidence in the patients' files, a CT scan, or a brain MRI. Death in stroke patients could have been caused by one or more cases of stroke complications, including neurological complications, cardiac complications, infections, renal failure, venous thromboembolism, or other complications. In this study, neurological complications being the causes of death were divided into the three groups of cerebral edema, intracranial HTN, as well as herniation and hemorrhagic transformation, which were grouped together. In addition, SAH and brainstem stroke, both of which are fatal, were grouped separately. In addition, the fatal complications of cardiovascular diseases were classified into the four categories of myocardial infarction, congestive heart failure, fatal cardiac arrhythmias, and sudden cardiac death. Post-stroke fatal infections included pneumonia, sepsis, meningitis following surgical intervention, thromboembolisms, including pulmonary embolism, as well as other complications, such as multiple organ dysfunction and disseminated intravascular coagulation. In cases where patient death was not justified by either evidence in the file or brain imaging and where none of the subsequent stroke complications could be considered as the cause of patient death, the cause of patient's death would be considered to be sudden cardiac arrest. Incomplete files were excluded from the study. In addition, some samples including non-diagnostic stroke (2 samples), non-acute stroke (2 samples) because of the passing of more than 72 hours from the onset of the symptoms, being younger than 18 years (1 sample), and incomplete file information (1 sample) were excluded from the study.

Statistical Analysis

After recording the information on risk factors by checking the patients' files in the checklist, the data were entered into

SPSS 20 Software and analyzed. Frequency tables, graphs, as well as mean and standard deviation indices were used to describe the data. A p value less than 0.5 was considered significant.

Results

Out of the total 2,199 stroke patients admitted to Ali-Ibn-Abi Talib Hospital of Rafsanjan from March 2012 to March 2017, 85.58% (1,882 cases) had ischemia and 14.42% (317 cases) had bleeding. In-hospital mortality rates in ischemic stroke and in cerebral hemorrhage were 7.54% (142 cases) and 17.98% (57 cases), respectively. In addition, a total of 9.04% (199 cases) died during hospitalization. The mean age of dead patients was 75.28±14.83 years. In addition, 78.4% of the patients (156 patients) were older than 65 years. Out of 199 cases of death following stroke, 57.8% (115 deaths) and 42.2% (84 deaths) were female and male, respectively. In addition, smoking history accounted for 15.1% (30 cases), and the major underlying disease in stroke patients who died was HTN at 68.3% (n=136) followed by stroke history and DM at 36.2% (n=72) and 35.7% (n=71), respectively. The highest frequency of mortality based on the stroke size was 56.34% (n=78) in major ischemia, 70.2% (n=33) in extensive intracerebral hemorrhage, and 100% in severe SAH (n=10). The minimum and maximum time intervals between referral and death in the study population was 1 day and 97 days, respectively, with the mean and standard deviation of 53.13±24.12. In addition, 50.3% and 90.5% of the deaths occurred during the first week and the first month after stroke, respectively. In other words, the frequency of the deaths was higher in the first week but gradually decreased. In addition, 12.1% of the patients who died due to stroke (n=24) had undergone brain surgery interventions. There was no significant difference in the type of stroke between the males and females and between the positive and negative cases in the variables of smoking, DM, HTN, and hypercholesterolemia. The most common complications leading to death in patients were neurological complications (48.7%, n=97) followed by infections (23.1%, n=46), cardiac complications (18.1%, n=36), and thromboembolism (5.5%). There was a statistically significant difference between the ischemic and hemorrhagic AF groups (p=0.001), with AF having been present in 31.7% of ischemic cases, while only 7% of hemorrhage cases had a history of AF. There was a history of IHD in 35.9% and 21.1% of ischemic cases and hemorrhage cases, respectively. In addition, there was a statistically significant difference between ischemic stroke and hemorrhage in terms of IHD (p=0.04). A history of stroke was also present in 40.8% and 24.6% of ischemic cases and hemorrhagic cases, respectively. In the ischemic group, the number of patients over the age of 65 years was significantly higher than the hemorrhagic group (86.6% vs 57.9%, p=0.0001). The results are presented in Table 1. All patients with neurological complications (100%) died within less

Table 1. Comparison frequency of age group, sex, smoking and underlying diseases according to the type of stroke in the study population

Variable		Ischemic- stroke		Hemorrhagic stroke		Total		p value
		n	%	n	%	n	%	
Age group	<65 yrs	19	13.4	24	42.1	43	21.6	<0.001
	>65 yrs	123	86.6	33	57.9	156	78.4	
Sex	Male	60	42.3	24	42.1	84	42.2	0.98
	Female	82	57.7	33	57.9	115	57.9	
Smoking history	Positive	20	14.1	10	17.5	30	15.1	0.53
	Negative	122	85.9	47	82.5	169	84.9	
Diabetes	Positive	52	36.6	19	33.3	71	35.7	0.66
	Negative	90	63.4	38	66.7	128	64.3	
HTN	Positive	98	69	38	66.7	136	68.3	0.74
	Negative	44	31	19	33.3	63	31.7	
High cholesterol	Positive	30	21.1	7	12.3	37	18.6	0.14
	Negative	112	78.9	50	87.7	162	81.4	
AF	Positive	45	31.7	4	7	49	24.6	<0.001
	Negative	97	68.3	53	93	150	75.4	
IHD	Positive	51	35.9	12	21.1	63	31.7	0.04
	Negative	91	64.1	45	78.9	136	68.3	
History of CVA	Positive	58	40.8	14	24.6	72	36.2	0.03
	Negative	84	59.2	43	75.4	127	63.8	

Yrs: Years, HTN: Hypertension, AF: Atrial fibrillation, IHD: Ischemic heart diseases

than 30 days, while 81.4% of the patients with non- neurological complications died within less than 30 days. Thus, there was a statistically significant difference (p=0.001) between the two groups of neurological and non-neurological complications in this respect. The frequency of death in less than 30 days in ischemic stroke cases and in hemorrhage cases was 89.4% and 93%, respectively, which indicated no significant difference between the two groups. In addition, there were no significant differences between the major and extensive groups with the minor and lacunar groups, as well as between the two age groups (Table 2). In addition, 69.8% of the patients over the age of 65 years and 42.9% of patients below the age of 65 years had neurological complications, and there was a significant difference between the two age groups (p=0.01). Neurological complications occurred in 77.2% of hemorrhagic stroke patients, yet these complications occurred in only 37.3% of the patients with ischemic stroke; thus, there was a significant difference between the ischemic and hemorrhagic groups (p=0/000). There was also a significant difference between the two stroke size groups (p=0.001), with 62.8% of the major and extensive strokes having had neurological complications and 27.6% of the patients with minor, lacunar, and non-major strokes having had neurological complications.

Discussion

In the present study, among 2,199 stroke patients admitted to Ali-Ibn-Abi Talib Hospital of Rafsanjan from March 2012 to March 2017, 199 patients died during hospitalization, and the frequency of in-hospital mortality among stroke patients during the mentioned period was 9.04%, which was consistent with past studies (20-26). The percentage is higher in developing countries than in developed ones, indicating that middle- and low-income countries, including Iran, need to improve the treatment and care of stroke patients. In addition, this percentage is lower than that of other studies conducted in Iran or in underdeveloped countries, which is possibly due to the early diagnosis of stroke in patients or because of recent advances in stroke treatment and care at Ali-Ibn-Abi Talib Hospital of Rafsanjan (27). In this study, 85.58% of the patients had ischemic stroke, and 14.42% of them had hemorrhage. This finding is in line with the results of the study conducted by Firoozabadi et al. (21), who reported ischemia at 85.4% as well as with the statistics in major neurological sources that accounted for 90% of ischemic and 10% of hemorrhagic stroke (1). In the present study, the in-hospital mortality rate of stroke in ischemia and in hemorrhage was 7.54% and 17.98%, respectively. In many studies, including those of Khatri et al. (28), Oveisgharan et al. (29), Collins et al. (30), and Farhoudi et al. (22), the rate was significantly higher in hemorrhage. Therefore, the fatality rate of bleeding is higher in hemorrhage than in ischemia. According to the findings of the present study, the highest frequency of in-hospital mortality was 78.4% for patients over the age of 65 years and 57.8% for females. In addition, the mean age of the dead patients was 75.28 years. Although the mortality rate in this study was relatively high, the mean age of dead patients was higher than in most of other studies. For instance, the mean age of dead patients was 64.3 years in Borhani-Haghighi's (20) study, 67 years in Shah et al.'s (23) study, 69.9 years in Farhoudi et al.'s (22) study, 74.12 years in Ong et al.'s (31) study, and 79.9 years in Roquer et al.'s (32) study. The frequency of mortality in the age group over 65 years in these studies was 10-19% lower than that of the present study, as it was 60% in Borhani-Haghighi's (20) study, 69.9% in Farhoudi et al.'s (22), 70.69% in Shah et al.'s (23) study, and 67.5% in Ong et al.'s (31) study. The frequency of mortality was higher in men than in women in the studies of Borhani-Haghighi (20), Farhoudi et al. (22), Roquer et al. (32), and Shah et al. (23); in contrast, in Ong et al.'s (31) study, similar to the present study, the mortality rate was higher in women than in men due to the more common AF and more severe stroke in women. According

Table 2. Comparison the frequency of time leading to death in stroke patients according to type of complication, stroke type, size of stroke and age group

Variable		≤30 days		>30 days		Total		p value
		n	%	n	%	n	%	
Complication (leading to death)	Neurologic	97	100	0	0	97	100	<0.001
	Non-neurologic	83	81.4	19	18.6	102	100	
Type of stroke	Ischemic	127	89.4	15	10.6	142	100	0.44
	Hemorrhagic	53	93	4	7	57	100	
Size of stroke	Non-major Non-extensive	67	88.2	9	11.8	76	100	0.40
	Major Extensive	111	91.7	10	8.3	121	100	
Age group	<65 yrs	40	93	3	7	43	100	0.51
	>65 yrs	140	89.7	16	10.3	156	100	

Yrs: Years

to past studies on stroke patients at Ali-Ibn-Abi Talib Hospital of Rafsanjan, stroke was more prevalent in women than in men, and this could have been the cause of the higher mortality rate in women who participated in the present study (33). Among the underlying diseases, the highest frequency of the in-hospital mortality of stroke for HTN was 68.3%. The order of frequencies of other underlying diseases in this study included the history of stroke (36.2%), DM (35.7%), IHD (31.7%), AF (24.6%), and hypercholesterolemia (18.6%), respectively. Only 15.1% of dead patients were smokers. In the studies of Shah et al. (23), Doğan et al. (34), and Ong et al. (31), HTN had the highest mortality rates of 60%, 85.4%, and 82.5% among the underlying diseases, respectively. However, the mortality rate was higher among smokers at about 35.8%, 34.4%, and 66.2%, respectively, which was higher than that of the present study, which could have been due to the different form of registration of positive cases of smoking in the files of the present study (23). Cardiovascular risk factors, including DM, HTN, IHD, AF, hypercholesterolemia, the history of stroke, and smoking are among the risk factors for post-stroke complications, and some of them increase the risk of mortality (13). Hence, identifying these factors in patients with acute stroke as well as adopting accurate treatment and care procedures in these patients could be effective in reducing the complications or risks of death. According to the results of the present study, the most frequent mortality according to the size of the stroke in all three types of stroke was for large lesions (major and extensive), which accounted for 56.34% of the cases in the ischemic type, 70.2% in ICH, and 100% in SAH. In addition, the highest incidence rate of death in ischemic stroke was within the anterior circulation range (78.17%) and in ICH, followed by the basal ganglia and lobar hemorrhage (42.6% each) as well as thalamic hemorrhage (17%). Hofmeijer et al. (35) have found out that the brain infarct size is a major determinant of fatal brain edema, and the larger the brain infarct size is, the greater the risk of fatal brain edema will be. In Ong et al.'s (31) study, the mortality rate was higher in the anterior circulation than in the posterior circulation, and large anterior circulation infarcts were associated with high mortality rates. In the present study, the most common complications leading to the death of patients were neurological complications (48.7%) followed by infections (23.1%), cardiac complications (18.1%), and pulmonary embolism (5.5%). In the same vein, Prosser et al.'s (14) study showed that the most common complications leading to death were neurological complications followed by cardiac complications, infections, and other complications. In Mogensen et al.'s (36) study, neurological complications were the most common cause of death within the first month after stroke. Zhang et al. (37) and Balami et al. (38) have concluded that a reduction in the incidence of post-stroke fatalities, which mainly include pneumonia, cardiovascular complications, and arterial embolism according to clinical evidence, reduces post-stroke mortality rates. In addition, improving the diagnosis and treatment of neurological complications in the acute post-stroke phase could improve patient survival and reduce the burden of stroke. Therefore, identifying the risk factors of these complications is necessary because many of such complications are preventable, and early diagnosis and treatment could be effective in reducing them. In the present study, the average time interval between the patients' referral and death was 12.24 days, which is approximately similar to that of Heuschmann et al.'s (25) study (10.6 days), but it is different from the studies of Farhoudi et al. (22) (25.8 days) and Doğan et al. (34) (8 days). In Farhoudi et al.'s (22) study, the longer time interval between referring to the hospital and death could have been due to better stroke care and the younger age of the patients died. In the present study, 50.3% of the deaths occurred in the first week, and 90.5% of them occurred in the first month after stroke. Mortality rates in the first week after stroke were reported to be 57.4% and 66% in Farhoudi et al.'s (22) study and in Heuschmann et al.'s (25) study, respectively (25). The study of Prossor et al. (14) showed that mortality rates were very high in the first week after stroke and gradually decreased afterwards. Mortality rates of less than 30 days and more than 30 days of admission in the two groups showed a significant difference ($p<0.001$) between neurological complications and non-neurological complications; accordingly, all patients with neurological complications died in less than 30 days. Numerous studies have shown that neurological complications occur earlier than other stroke complications and are associated with premature death following direct brain injuries (11,12,15,39). According to the findings of the present study, there was no significant difference between ischemic and hemorrhagic groups in terms of gender, smoking, DM, HTN, and hypercholesterolemia; however, the positive history of stroke, AF, IHD, as well as being older than 65 years were more significantly prevalent in ischemia than in hemorrhage. The main difference between other studies and the present one in analyzing different types of stroke in terms of risk factors is that none of them has investigated the types of stroke in the group of dead patients. Roquer et al. (32) have found out that DM, HTN, AF, and IHD increase the severity of stroke and the risk of in-hospital mortality in acute ischemic stroke. According to the findings of the present study, the prevalence of neurological complications is significantly higher than that of non-neurological complications in ischemia compared to hemorrhage, in major and extensive stroke compared to minor, lacunar, and non-extensive strokes, as well as in patients younger than 65 years compared to those older than 65 years. However, there has been no significant difference in the frequency of death-related complications between males and females as well as between positive and negative cases in terms of smoking and underlying disease variables. The results of the studies of Chen et al. (40) and Jaramillo et al. (41) showed that younger patients were more prone to fatal brain edema than older ones, which was attributed to brain atrophy and the presence of more space

around the brain of the elderly in Hacke et al.'s (42) study. In addition, Hofmeijer et al. (35) have found out that the brain infarct size is a major determinant of fatal brain edema.

One of our major limitation was the retrospective type of study, in which we could not follow the patients precisely during their admission. Another limitation was the incompleteness of some cases' documents that made them excluded from our study. The third limitation was the unknown cause of death in some cases' hospital files. The absence of a control group may be a problem for us. On the other hand, a sufficient number of cases in our study was one of our strength points. The second strength of the study was long-term duration and the existence of a treatment center for stroke patients. As a result, it is possible to generalize the results to the total population of stroke patients.

Conclusion

According to our study, neurologic complication, infections, cardiac complications, and thromboembolism are the most frequent causes of death in stroke patients. The future of stroke care and the rate of mortality depend on our early management of complications and controlling of risk factors. It is recommended that subsequent prospective studies be conducted to have full access to patient information. In addition, designing a control group makes the comparison of different risk factors in dead stroke patients and living ones.

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Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee under the code: (IR.RUMS.REC.1395.145), in accordance with the Helsinki Criteria (protocol number: 31/20/4, date: 31.01.2017).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.V., S.A., Design: A.V., S.A., Data Collection or Processing: Z.K., S.A., A.M.A., N.J., Analysis or Interpretation: Z.K., Literature Search: A.V., S.A., A.M.A., Writing: A.V., Z.K.

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Analysis of demographic and clinical characteristics of primary myelofibrosis and post-polycythemia vera/essential thrombocythemia myelofibrosis patients

Pınar Akyol, Abdulkerim Yıldız, Murat Albayrak, Hacer Berna Afacan Öztürk, Senem Maral, Merih Reis Aras, Fatma Yılmaz, Buğra Sağlam, Mesut Tığlıoğlu, Ümit Yavuz Malkan

University of Health Sciences Turkey, Diskapi Yildirim Beyazit Training and Research Hospital, Clinic of Hematology, Ankara, Turkey

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Corresponding Author:
Pınar Akyol, M.D., University of Health Sciences Turkey, Diskapi Yildirim Beyazit Training and Research Hospital, Clinic of Hematology, Ankara, Turkey

ORCID:
orcid.org/0000-0003-3829-289X

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ABSTRACT

Aims: Primary myelofibrosis (PMF) and post-polycythemia vera (PV) or essential thrombocythemia (ET) myelofibrosis (MF) have many common features in terms of clinical course and laboratory findings. However, there are insufficient studies showing the etiological or morphological differences between these patients. The aim of this study was to compare the hemogram parameters, routine biochemical markers, presence of Janus kinase-2 (JAK-2) V617F gene mutation and allele burden, and spleen sizes and also to analyze the clinical courses of these two patient groups regarding to thromboembolic complications, leukemic transformation, overall survival (OS), and treatment modalities.

Methods: This retrospective study included patients who were diagnosed with PMF and post-PV/ET MF in the Diskapi Yildirim Beyazit Training and Research Hospital between 2008 and 2019. PMF and post-PV/ET MF patients were compared in terms of demographic data, laboratory parameters and clinical features.

Results: Evaluation was made on a total of 31 patients (16 PMF, 15 post-PV/ET MF). The mean follow-up period was 31.1 months. JAK-2 mutation was detected in 62.5% of PMF patients and in 80% of post-PV/ET MF patients. Thromboembolic complications developed in 12.5% of PMF patients and in 13.3% of post-PV/ET MF patients. The mean OS of patients was 28.7 months in the PMF group and 18.5 months in the post-PV/ET MF group. No significant difference was observed between the two groups in terms of OS.

Conclusions: We found that clinical characteristics of PMF and post-PV/ET MF patients such as hemogram and biochemical values, absence of JAK-2 mutation and allele burden, and spleen sizes were similar. We also found that patients showed a similar clinical course in terms of thromboembolic complications, acute leukemia transformation and survival.

Introduction

Myelofibrosis (MF), characterized by fibrosis in the bone marrow, could be *de novo* [primary MF (PMF)], as well as developing in the clinical course of polycythemia vera (PV) or essential thrombocythemia (ET) (1). PMF is included in the category of "myeloproliferative neoplasms" (MPN) in the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia (2). The other group, which is categorized as post-PV MF and post-ET MF, is diagnosed according to the criteria determined by the International Working Group for MPN Research and Treatment (IWG-MRT) (3).

Patients present with clinically characteristic laboratory features such as anemia, splenomegaly due to extramedullary hematopoiesis, increased serum lactate dehydrogenase (LDH) level and stromal changes in the bone marrow (eg collagen fibrosis, osteosclerosis) (4). The most common laboratory abnormality in PMF is anemia and in 50% of patients, hemoglobin (Hb) is <10 g/dL at the time of diagnosis. The most common

symptoms are early satiety, fatigue, abdominal distention and left upper quadrant pain associated with splenomegaly. Unlike PMF, these symptoms are observed in PV and ET patients after the development of MF (5).

In PMF, scoring systems such as Dynamic International Prognostic Scoring System (DIPSS) or DIPSS-plus are generally used to determine the prognosis. DIPSS is based on five clinical and laboratory parameters: age >65, white blood cell (WBC) count >25x10^9/L, peripheral blast cells >1%, Hb <10 g/dL and the presence of B symptoms. In addition to DIPSS, cytogenetic data, platelet count and blood transfusion requirement are included in the DIPSS-plus (6,7). However, these systems are insufficient to determine the prognosis in post-PV/ET MF (8). An alternative prognostic model for these patients is required to determine the prognosis and treatment decision.

PMF is a disease of the elders and the median survival is 4-7 years (9). Transformation to MF usually occurs 7-20 years after diagnosis in ET and PV patients and this leads to decreased survival (10). Causes of death include leukemic transformation, thrombosis, infections, bleeding and complications of portal hypertension (11).

PMF and post-PV/ET MF have many common features with clinical course and laboratory findings such as extramedullary hematopoiesis resulting in bone marrow fibrosis and splenomegaly, varying degrees of cytopenia(s) and a leuko-erythroblastic blood picture (10). However, there are insufficient studies showing the etiological or morphological differences between these patients. In this context, the aim of this study was to contribute to the literature by comparing PMF and PV/ET patients who developed MF regarding to hemogram parameters, routine biochemical markers, presence of Janus kinase-2 (JAK-2) V617F gene mutation and allele burden, and spleen sizes. At the same time, to compare the clinical course of these two patient groups, thromboembolic complications, leukemic transformation, overall survival (OS), and treatment modalities were examined.

Methods

This retrospective study included 31 patients who were diagnosed with PMF and post-PV/ET MF in the Hematology Department of Diskapi Yildirim Beyazit Training and Research Hospital between 2008 and 2019. All patients over the age of 18 years were included in the study.

No exclusion criteria were determined in the study. All data of the living patients were examined until the last outpatient control and all data of the dead patients were examined until the date of death. OS was determined as the time from the date of diagnosis until the date of death.

The diagnosis of PMF was made according to the WHO criteria (2), and the IWG-MRT group criteria were used for the diagnosis of PPV-MF and PET-MF (3). The two groups were compared in terms of demographic and clinical features. The diagnosis date, demographic and clinical features, physical examination findings, mutation analyses, treatment management and follow-up times of all the patients were recorded. Hematological parameters including Hb, hematocrit (Hct), leukocyte (WBC), neutrophil, lymphocyte, monocyte, platelet, platelet distribution width (PDW), mean platelet volume (MPV), LDH, ferritin and vitamin B12 levels were examined. DIPSS (7) was used to determine the prognosis of the patients. Survival analyses were performed.

Statistical Analysis

Data obtained in the study were statistically analyzed using SPSS Statistics version 20 Software (IBM, Armonk, NY, USA). Descriptive data were given as percentages. The independent sample t-test (t-table value) was used to compare two independent groups with normal distribution of the measurement values, and the Mann-Whitney U test (Z-table value) was applied to data not showing normal distribution. χ2-cross tables were used to examine the relationships between qualitative variables. The Cox regression model was also applied to the parameters (age, gender, presence of splenomegaly, size of spleen, JAK-2 mutation status and allele burden, bone marrow fibrosis grade, Hb, Hct, leukocyte (WBC), neutrophil, lymphocyte, monocyte, platelet, PDW, MPV, LDH, ferritin and vitamin B12 levels, platelet to lymphocyte ratio, neutrophil to lymphocyte ratio, monocyte to lymphocyte ratio, DIPSS and presence of thromboembolic complication) evaluated by univariate analysis. Two-sided p-values <0.05 were considered statistically significant. The Kaplan-Meier test was applied for survival analysis. The log-rank (Mantel-Cox) test was used for OS comparisons between the patient groups.

All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. Approval for this study was granted by the Diskapi Yildirim Beyazit Training and Research Hospital Local Ethics Committee (protocol number: 90/06, date: 22.06.2020).

Results

Evaluation was made on a total of 31 patients, including 16 PMF and 15 post-PV/ ET MF. The demographic and clinical characteristics of the patient groups are given in Table 1 (the data of the post-PV/ET MF group are the data after MF development).

The PMF group comprised of seven (43.7%) females and nine (56.2%) males with a mean age of 66.50±11.72 years. The post-PV/ET MF group comprised of seven (46.6%) females and eight (53.4%) males with a mean age of 57.07±15.96 years.

Splenomegaly was detected at the time of diagnosis in all PMF and post-PV/ET MF patients. When the size of the spleen was examined, there was no statistically significant difference between the two groups.

JAK-2 V617F gene mutation was detected in 10 (62.5%) of PMF patients and 12 (80%) of post-PV/ET MF patients. In terms of JAK-2 V617F mutation positivity, there was no statistically significant difference between the two groups. JAK-2 V617F mutation allele burden of ≥60% was detected in 70% of PMF patients and in 90% of post-PV/ET MF patients. The allele burden was not determined to affect OS in patients with MF.

When the patients were examined in terms of the treatment they received, hydroxyurea (HU) in 13 (81.3%) and ruxolitinib in three (18.7%) of PMF patients were preferred as the first-line

Table 1. The distribution of demographic and disease characteristics of the patient subgroups (n=31)

Variable	PMF (n=16)	Post-PV/ET MF (n=15)	p
Age year (mean ± SD)	66.50±11.72	57.07±15.96	0.184
Gender n (%)			
Female	7 (43.7)	7 (46.6)	0.5
Male	9 (56.2)	8 (53.4)	
Splenomegaly n (%)			
Yes	16 (100)	15 (100)	0.2
No	0	0	
Median spleen size mm (min-max)	211.07 (151-295)	205.9 (142-280)	0.738
JAK-2 V617F mutation n (%)			
Positive	10 (62.5)	12 (80)	0.29
Negative	6 (37.5)	3 (20)	
JAK-2 mutant allele burden n (%)			
0-29%	1 (10)	1 (10)	0.9
30-59%	2 (20)	1 (10)	
60-100%	7 (70)	9 (90)	
Bone marrow fibrosis grade median (min-max)	3.0 [2.0-4.0]	3.0 [2.0-4.0]	0.727
Hb g/dL (mean ± SD)	11.78±2.77	11.05±2.47	0.447
Hct (mean ± SD)	36.46±8.98	34.27±8.74	0.497
WBC count, $x10^9$/L median (min-max)	21.9 [4.8-43.3]	7.5 [3.8-43.2]	0.055
Neutrophil count, $x10^9$/L median (min-max)	17.7 [2.5-37.5]	5.2 [1.5-34.9]	0.085
Lymphocyte count, $x10^9$/L median (min-max)	2.2 [0.6-8.0]	1.6 [0.7-3.9]	0.226
PLT count $x10^9$/L median (min-max)	261.5 [119.0-1074.0]	293.0 [126.0-1166.0]	0.502
PLR median (min-max)	127.9 [18.9-716.0]	244.3 [50.0-790.8]	0.323
NLR median (min-max)	7.5 [1.8-23.7]	3.7 [0.9-15.8]	0.429
MLR median (min-max)	0.3 [0.1-1.1]	0.3 [0.1-0.5]	0.553
LDH U/L median (min-max)	663.0 [212.0-1157.0]	433.0 [271.0-1467.0]	0.141
Ferritin ng/mL median (min-max)	96.6 [7.6-602.0]	133.2 [8.5-967.0]	0.232
Vitamin B12 pg/mL median (min-max)	518.46±208.36	451.57±269.63	0.480
DIPSS score n (%)			
Low	3 (18.8)	2 (13.3)	0.2
Intermediate-1	5 (31.3)	10 (66.7)	
Intermediate-2	4 (25)	3 (20)	
High	4 (25)	0 (0)	
Thromboembolic complication n (%)			
Yes	2 (12.5)	2 (13.3)	0.945
No	14 (87.5)	13 (86.7)	
Mean follow-up period (month)	29.3	33.0	0.81
Final situation n (%)			
Alive	11 (68.8)	12 (80)	0.24
Exitus	5 (31.2)	3 (20)	

PMF: Primer myelofibrosis, Hb: Hemoglobin, Hct: Hematocrit, PLT: Platelet, WBC: White blood cell, LDH: Lactate dehydrogenase, PLR: Platelet to lymphocyte ratio, NLR: Neutrophil to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio, DIPSS: Dynamic International Prognostic Scoring System, JAK-2: Janus kinase-2, SD: Standard deviation, PV/ET: Polycythemia vera/essential thrombocythemia, MF: Myelofibrosis, mm: Milimeter, min-max: Minimum-maximum

treatment. The median follow-up period of these patients with the first-line treatment was 13.5 months (range, 1-92 months). During this follow-up period, 31.5% of the patients responded to the first-line treatment and the treatments are still continuing. In 62.5% of patients, second-line treatment was initiated due to adverse effects or unresponsiveness. In the second-line treatment, ruxolitinib was preferred in four (80%) patients and anagrelide was started in one (20%) patient. In the treatment of patients in the post-PV/ET MF group, HU treatment was continued in seven (46.7%) patients after MF development and ruxolitinib treatment was initiated in 8 (53.3%) patients. In this group, the median duration of first-line treatment was 16.5 months (range, 2-82 months). During this period, the response rate to the treatment was 66.6% and the treatments are still ongoing. In 13.3% of patients, the second-line treatment was initiated due to adverse effects or unresponsiveness. As a second-line treatment, one (33.3%) patient underwent allogeneic stem cell transplantation (ASCT), interferon-alpha was initiated in one (33.3%) patient and ruxolitinib was preferred in one (33.3%) patient. The detailed statistics of the patient treatments are given in Table 2.

Throughout the follow-up period, thromboembolic complications developed in 12.5% of PMF patients and in 13.3% of post-PV/ET MF patients. There was no statistically significant difference between the two groups in terms of thromboembolic complications. Acute myeloid leukemia transformation was observed in one (6.25%) patient from the PMF group during the follow-up period.

Table 2. Treatment data of patients (n=31)

Variable	PMF (n=16)	Post-PV/ET MF (n=15)
First-line treatment n (%)		
Hydroxyurea	13 (81.3)	7 (46.7)
Ruxolitinib	3 (18.7)	8 (53.3)
First-line treatment duration day, median (min-max)	13.5 [1.0-92.0]	16.5 [2.0-82.0]
Hydroxyurea (as 1st line treatment) n (%)		
Continues	3 (23)	5 (71.4)
Unresponsiveness/inadequate response	3 (23)	1 (14.2)
Side effect	3 (23)	
Exitus	4 (31)	1 (14.2)
Ruxolitinib (as 1st line treatment) n (%)		
Continues	2 (66.6)	5 (62.5)
Unresponsiveness/inadequate response	-	1 (12.5)
Side effect	-	-
Exitus	1 (33.3)	2 (25)
Second-line treatment n (%)		
ASCT	-	1 (33.3)
Anagrelide	1 (20)	-
INF-alfa	-	1 (33.3)
Ruxolitinib	4 (80)	1 (33.3)

ASCT: Allogenic stem cell transplantation, INF: Interferon, PV/ET: Polycythemia vera/essential thrombocythemia, MF: Myelofibrosis, PMF: Primary myelofibrosis, min-max: Minimum-maximum

The mean follow-up was 31.1 months (range, 1-107.5 months). The mean OS of patients was 28.7 months (range, 1-93.4 months) in the PMF group, and 18.5 months (range, 1.2-107.5 months) in the post-PV/ET MF group. As a result of the log-rank (Mantel-Cox) test, no significant difference was observed between the two groups in terms of OS ($p>0.05$). During the follow-up period, mortality developed in 31.2% of the PMF patients and in 20% of the post-PV/ET MF patients.

Discussion

MF is characterized by fibrosis in the bone marrow stroma and extramedullary hematopoiesis. Philadelphia chromosome negative MPNs all tend to progress to the myelofibrotic stage. Post-PV MF occurs in about 20% of PV patients at least 10 years after the diagnosis. In contrast, post-ET MF is less common, occurring in <1% of cases in 10 years and <10% in 15 years of follow-up (1). In contrast to the data in literature, the frequency of MF transformation was observed to be higher in the ET patients. This difference may be due to the fact that some patients were mistakenly diagnosed with ET while they were pre-fibrotic MF in the past. In the diagnostic criteria revised in 2016, WHO recommended performing bone marrow biopsy for the diagnosis of ET to prevent this situation and bone marrow findings were accepted as the major criteria.

Approximately 65% of PMF patients have JAK-2 V617F gene mutation. In a previous study, JAK-2 V617F mutation positivity was determined in all post-PV MF patients and in 60% of PMF patients (1). In another study, the frequency of JAK-2 V617F mutation, similar to the previous study, was detected in both PMF and post-PV MF patients (12). In the current study, JAK-2 V617F mutation was detected in 62.5% of the PMF patients and in 80% of the post-PV/ET MF patients, which was consistent with the literature.

Almost all of the current study patients with both PMF and post-PV/ET MF had an allele burden of ≥60%. However, no effect of allele burden on OS was detected in this study. Similarly, in a study conducted in the Mayo Clinic, no correlation with the mutant allele burden and increased risk of leukemic transformation or splenectomy was observed in PMF patients (13).

Mutations in calreticulin (CALR) (20-25% of patients) and MPL (myeloproliferative leukemia virus oncogene) (5-10% of patients) genes have also been observed in PMF. Apart from these, spot mutations have been detected in myeloid genes such as ASXL1, TET2, EZH2, IDH1/IDH2 in 80% of patients

(14). These genetic variations seen in PMF are considered to be the reason for the heterogeneity of the disease in terms of clinical course and OS. For example, CALR-mutant PMF patients have a more indolent clinical course (15). In contrast, high risk of leukemic transformation has been detected in PMF patients without JAK-2, CALR or MPL mutation (16). As CALR and MPL mutation analysis was not available in our hospital until 2018, these cytogenetic tests could not be applied to all the current study patients, so they were not included in the statistical studies.

OS in PMF is worse than in other classic MPNs, ranging from 3.5 to five years (17).

When MF develops during the course of PV or ET, the patient's quality of life deteriorates due to increased constitutional symptoms and their survival is shortened due to extramedullary hematopoiesis and cytopenia-related reasons (9). Although most share clinical features, post-PV/ET MF patients may have significantly different disease characteristics in terms of presentation or prognosis than patients with PMF. For example, post-PV/ET MF is a slow-progressing clonal transformation from a proliferative neoplasm to bone marrow failure, while PMF has a faster and more aggressive clinical course (1). The expected life expectancy of PV and ET, which generally shows a benign clinical course, is almost the same as that of the general population, but the development of MF shortens survival. In the current study, no statistically significant difference was observed. Similarly, in a study by Boiocchi et al. (1) on PMF and post-PV MF patients, there was no difference between the two groups in terms of survival.

Acute leukemia transformation is most frequently observed in PMF among the MPNs. The incidence of acute leukemia transformation in the first 10 years after diagnosis varies between 10% and 20% (18,19). The leukemia transformation risk of post-PV/ET MF patients is also similar to that of PMF patients (17). In one of the largest PMF studies, acute leukemia transformation was observed at a rate of 3.9% in a total of 2,333 PMF patients (17). Leukemia transformation was observed in only one (6.25%) of the 16 patients with PMF in the current study, and in the post-PV/ET MF patients, no leukemia transformation was observed during follow-up.

Although ASCT is the only curative treatment for PMF or post-PV/ET MF, palliative treatment options such as HU are more frequently preferred (20). Treatment of MF patients is focused on reducing constitutional symptoms associated with splenomegaly. In this context, the JAK1/2 inhibitor, ruxolitinib, is successfully used (21). While the most preferred agent in the first-line treatment in the current study PMF patients was HU, ruxolitinib was started in approximately half of the PV and ET patients who developed MF.

The retrospective design of the study was the most important limitation of this study. Other disadvantages were the relatively short follow-up period and the low number of patients. The number of cases was too low for the comprehensive comparisons that were aimed. Cytogenetic studies have also gained importance in the prognosis of these diseases. The impact of CALR and MPL mutations on fibrosis is controversial and more studies are needed to clarify this relationship.

Conclusion

We found that clinical characteristics of PMF and post-PV/ET MF patients such as hemogram and biochemical values, absence of JAK-2 V617F mutation and its allele burden, and spleen sizes were similar. We also found that patients showed a similar clinical course in terms of thromboembolic complications, acute leukemia transformation and survival.

Moreover, it should be kept in mind that if MF develops in PV and ET patients who have good clinical course, prognosis worsens and survival decreases. Therefore, these patients should be followed in terms of MF.

Ethics

Ethics Committee Approval: Approval for this study was granted by the Diskapi Yildirim Beyazit Training and Research Hospital Local Ethics Committee (protocol number: 90/06, date: 22.06.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A., Concept: P.A., M.A., Design: A.Y., Data Collection or Processing: S.M., M.R.A., Analysis or Interpretation: H.B.A.Ö., F.Y., Ü.Y.M., Literature Search: B.S., M.T., Writing: P.A.

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Approach to chest wall masses: Analysis of a single-center outcomes

Hakan Işık[1], Merve Şengül İnan[1], Okan Karataş[2], Ersin Sapmaz[1], Hasan Çaylak[1], Sedat Gürkök[1], Onur Genç[1], Alper Gözübüyük[1]

[1]University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Thoracic Surgery, Ankara, Turkey

[2]Ataturk State Hospital, Clinic of Thoracic Surgery, Sinop, Turkey

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Corresponding Author:
Hakan Işık, M.D., University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Thoracic Surgery, Ankara, Turkey

ORCID:
orcid.org/0000-0002-7602-4434

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ABSTRACT

Aims: The chest wall has a heterogeneous structure consisting of bone, cartilage, and soft tissue. Due to its complexity, many pathologies may present as chest wall masses. The present study aimed to analyze the data of patients with a chest wall mass, who were admitted to a tertiary center.

Methods: We retrospectively evaluated the medical records of patients with a chest wall mass, who were admitted between January 2003 and December 2019. The data related to age, gender, chief complaints on admission, tumor localization, requirement of surgical treatment, length of hospital stay, histopathological diagnosis, recurrence, morbidities and mortality were recorded.

Results: The total sample included 185 patients [mean age (range): 37.6 years (12 to 88), male gender: 144 (77.8%)]. The mean length of hospitalization was 6.62 days (1-35). The most common complaints on admission were a palpable mass (n=60, 32.4%), pain (n=59, 31.9%), and pain and a palpable mass (n=36, 19.4%). Surgery was required in 166 (89.8%) patients. More than one surgery was performed in 8 (4.8%) patients. There were 118 (71%) benign and 48 (29%) malignant histopathologic results. The most common primary chest wall malignancies were chondrosarcoma and Ewing sarcoma.

Conclusions: The majority of patients with a chest wall mass underwent surgery in this 16-year dataset. Chondrosarcoma and Ewing sarcoma were the most common primary malignancies. While most were benign tumors, a secondary intervention was required in a small percentage of patients.

Introduction

The chest wall has a heterogeneity that includes bone, cartilage, and soft tissues. Therefore, a patient with a chest wall mass can have different etiological causes. While benign lesions are the most common in their etiology, most of the malignant lesions are formed by metastatic lesions. Primary chest wall malignancies are rare and constitute 5% of thoracic malignancies (1).

The distinction of benign and malign chest wall masses is important for determining the surgical approach (2). Wide resections are performed to fulfill oncological principles and to obtain a clean surgical border in the resection of malignant masses. Proper reconstruction of the defect in the chest wall after these wide resections is important. Although chest wall resections are relatively easy surgeries to perform, reconstruction surgeries are much more difficult and complex procedures where the personal factors of the patient come to the fore. Traditional techniques, such as the use of prolene mesh (PM) and metal bars, are the most frequently used methods in reconstruction. The use of complex implants that are individualized and produced with a 3D printer stands out as a good alternative to classical methods (3,4). In the present study, we aimed to evaluate of the 16-year surgical experience of a tertiary hospital thoracic surgery clinic in chest wall masses.

Methods

Electronic medical records and patient files of inpatients and outpatients admitted between January 2003 and December 2019 were reviewed. A total of 200 patients with chest wall masses were identified, and 185 (92.5%) of them were included in the study. Age, gender, complaints on admission, tumor localization, the requirement for surgery, length of hospital stay, histopathologic diagnosis, recurrence, morbidities and mortality data were recorded. This study was approved by the Institutional Ethics Committee of Gülhane Training and Research Hospital (approval date: June 5, 2018, approval number: 18/164). Written informed consent was provided from all patients.

Preoperative radiologic examination findings were evaluated to record the localization, size, invasion of neurovascular structures, and distant metastases. The most common imaging technique was computed tomography of the chest. Moreover, magnetic resonance imaging, ultrasonography, and scintigraphy examinations were performed for indications, such as the evaluation of the size and depth of soft tissue tumors, determination of soft tissue invasion in bone-derived tumors, investigation of brain metastasis, and for cancer staging purposes before the positron emission tomography (PET) scan. Data of PET scans to screen distant organ metastasis were available since 2006.

Statistical Analysis

The Statistical Package for the Social Sciences, version 25 (Inc., Chicago, IL, USA) was used for the statistical analysis. Descriptive and categorical variables of 185 patients in the study were expressed as mean, number and percentage as measure of central tendency.

Results

A total of 7,604 registries were examined and 200 patients with chest wall mass diagnosis were identified. Patients with a chest wall invasion and metastases of lung cancer were excluded (n=15). Six of these patients had a chest wall mass due to lung cancer metastases and nine had a T3 tumor that invaded the chest wall. Primary chest wall tumor (n=39) and chest wall metastases of cancers other than lung cancer were included in the study (n=9). Thus, the final analysis included the records of 185patients.

The gender distribution of 185 patients was shown [mean age (range): 37.6±1.19 years (12 to 88), male gender: 144 (77.8%)]. The mean length of hospital stay was 6.62±6.49 days (1-35). Among the most common complaints on admission, a palpable mass in 60 (32.4%) patients, pain in 59 (31.9%) patients, and pain and palpable mass in 36 (19.4%) were the most common ones. Twenty patients (10.8%) were asymptomatic and they were referred to the clinic upon the incidental detection of lesions in the chest wall during examinations performed for other reasons. In seven (3.7%) patients, chest wall lesions were identified during their routine check-up after diagnosis and treatment of other organ malignancies. Table 1 shows the distribution of patients by complaints.

Surgery was performed on 166 (89.7%) patients and 19 (10.3%) patients did not undergo surgery. Eleven of those patients who did not undergo a surgical procedure were followed-up due to clinical and radiological findings. The preliminary diagnoses of these patients were lipoma and callus formation of old fractures. The remaining eight patients were indicated for operation after radiological and clinical evaluation; however, surgery was not performed because the patients did not accept the procedure. The most common preliminary diagnosis in this group was elastofibroma dorsi.

Concerning the preoperative diagnostic procedures in 166 patients, 48 (28.9%) patients had fine-needle aspiration biopsy and tru-cut biopsy. While this procedure was performed for diagnosis in 43 (25.9%) patients, it was detected that the final diagnosis was made by excisional biopsy in four (2.4%) patients and by incisional biopsy in one (0.6%) patient.

Eight patients (4.8%) underwent multiple surgical interventions. Three of these were due to desmoid tumors and one was due to local recurrence of fibrous dysplasia. One intervention was a wide resection required for a safe surgical margin due to the millimetric proximity of the tumor to the surgical border in routine pathological examination with a diagnosis of pleomorphic sarcoma. Two interventions were due to lung metastases identified in routine controls performed after primary chest wall sarcoma resection. One intervention was performed for revision in the early period due to flail chest resulting from insufficient chest wall reconstruction.

The majority of patients who underwent surgical treatment consisted of patients with benign chest wall tumors (n=118 benign, n=48 malignant). Of the malignant lesions, 39 (81.2%) were primary chest wall tumors and nine (18.8%) were metastatic tumors. The distribution of these lesions is summarized in Table 2.

The patients who underwent wide resection were discussed at the multidisciplinary council, which included a plastic surgeon, and a final decision was made for surgery and the reconstruction

Table 1. The complaints of patients on admission (n=185)

Complaint at the time of admission	Number of patients (n)	Percentage (%)
Palpable mass	60	32.4
Pain	59	31.9
Palpable mass and pain	36	19.4
Asymptomatic	20	10.8
Tumor follow-up patient	7	3.8
Dyspnea	2	1.1
Cough	1	0.6

Table 2. Histopathological diagnoses (n=166)

Malign	n=48	Benign	n=118
Metastasis	9	Lipoma	24
Chondrosarcoma	8	Fibrous dysplasia	19
Ewing sarcoma	8	Enchondroma/ osteochondroma	18
Multiple myeloma	4	Elastofibroma dorsi	12
Malignant fibrous histiocytoma	3	Old fracture healing (regenerative tissue)	11
Solitary plasmacytoma	3	Desmoid Tumor	9
Fibrosarcoma	3	Hemangioma	7
Osteosarcoma	2	Schwannoma	2
Pleomorphic sarcoma	2	Lymphangioma	2
Malignant nerve sheath tumor	2	Nodular fasci	2
Malign mesenchymal tumor	2	Langerhans cell histiocytosis	2
Synovial sarcoma	1	Tuberculosis	2
PEComa	1	Foreign body reaction	2
		Inflammatory myofibroblastic tumor	1
		Hydatid cyst	1
		Simple bone cyst	1
		Eosinophilic granuloma	1
		Thyroglossal duct cyst	1
		Paranganglioma	1

strategy was determined. In 20 operations performed on 17 (10.2%) patients, prosthetic material was used for chest wall reconstruction after wide resection. Materials used were 10 PM, 5 PM + methyl methacrylate (MMA), 2 PM + titanium bar, 1 PTFE mesh + titanium bar, 2 custom-made titanium implants in three-dimensional printer. Pectoralis major muscle flap in one patient, latissimus dorsi muscle flap in one patient, and rectus abdominis muscle flap in one patient were used by the plastic surgeon for soft tissue repair.

In one patient, reconstruction was performed with titanium bar and PM after the resection of a 27x22x18 cm chondrosarcoma originating from the anterior chest wall (Figure 1). The patient could not be extubated due to a flail chest which developed due to insufficient reconstruction. Later, the patient was re-evaluated, and an effective reconstruction was achieved with the custom-made titanium implant produced with a three-dimensional printer (Figure 2), and the patient was extubated.

No preoperative death occurred; however, seven (4.2%) patients developed major complications. One patient was treated with debridement and long-term anti-biotherapy due to postoperative wound infection. Intraoperative massive hemorrhage developed in two patients who underwent hemangioma surgery and wide chest wall resection. The hemorrhage control performed with the appropriate method and blood replacement were completed without morbidity and mortality in both surgeries. Flail chest developed after wide chest wall resection and reconstruction in two patients. One of these patients was treated with the support of a mechanical ventilator without the need for additional surgery, while the other patient was re-operated on and stabilization was achieved (Figures 1, 2). Pulmonary embolism was seen in two patients in the postoperative period and both were successfully treated with medical treatment.

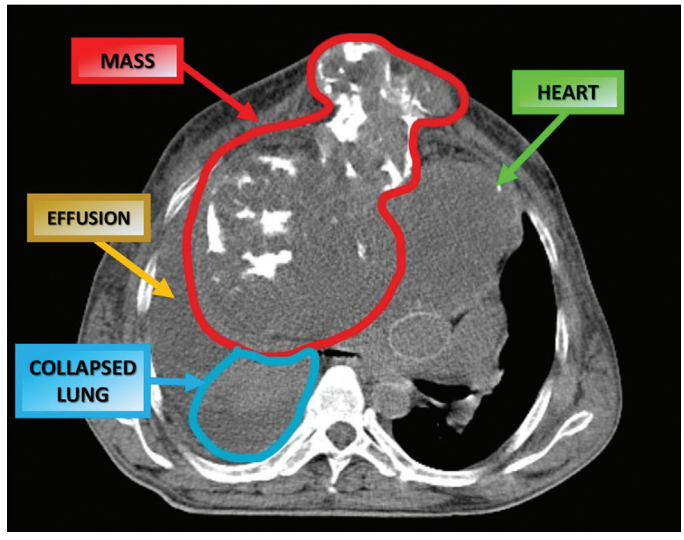

Figure 1. Red: Giant mass originated from the anterior chest wall (chondrosarcoma). Green: Heart deviated to the left hemithorax. Yellow: pleural effusion. Blue: Right lung with total collapse due to compression of the mass

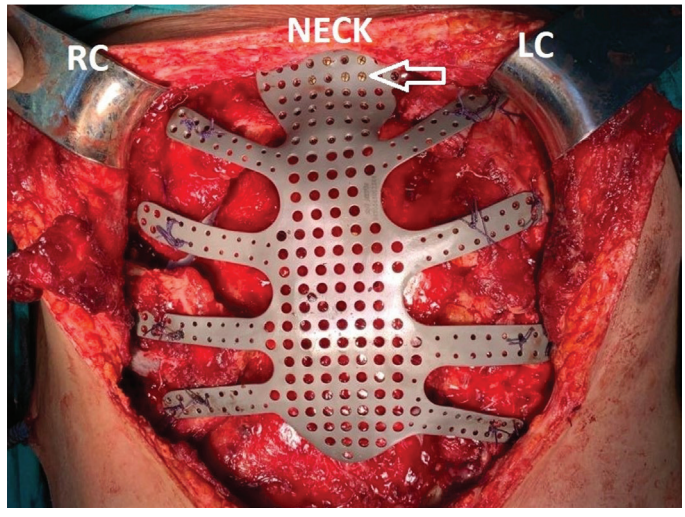

Figure 2. Chest wall reconstruction applied with custom-made titanium implant produced on a 3D printer (RC: Right clavicula, LC: Left clavicula, Arrow: Titanium screw)

Discussion

The existing literature suggests that approximately half of the primary chest wall masses are malignant (5). In the present study, we revealed 48 malignancies against 118 benign lesions. Thus, in contrast to the literature, benign cases were significantly more common in our study. The chest wall contains many different tissues; a significant number of the complaints at the time of admission was for pain and the presence of a palpable mass. The presence of pain has been associated with poor prognosis (6). At least one of these two complaints was present in 155 of the patients (83.7%).

Benign-malignant differentiation of the lesion may not be possible with anamnesis, physical examination, and radiological imaging. However, the most decisive stage in the clinicians' determination of treatment strategies in approaching chest wall lesions is to make this histopathological distinction. Knowing the nature of a lesion, benign or malignant, facilitates the management of the process. Fine-needle aspiration biopsy may be used in most lesions. Due to its size, anatomical relation, and nature, the need for incisional or excisional biopsy may arise. Incorrect histopathological diagnosis may lead to incomplete resection and relapse.

Despite advanced chemotherapy and radiotherapy regimens, surgery is still essential for the treatment of many chest wall lesions. Total excision should always be targeted particularly to prevent relapse. However, sometimes complete excision of the lesion requires a wide chest wall resection. A compatible, effective, and cosmetically acceptable reconstruction method should be determined for such patients. Choosing the wrong method may result in the development of respiratory failure by disrupting the pulmonary functions in the patient. Besides, the reconstruction material to be used should have high tissue compatibility and should not cause a local infection. For this purpose, in addition to classical methods such as PM, MM, and titanium bar, we use custom-made titanium implants produced in 3D printer, which is a new technology. The method for the management of reconstruction of wide defects depends mainly on the experience of the clinic. For choosing the right material, each patient should be evaluated individually, and a decision should be made accordingly (7).

Malignant tumors of the chest wall are mostly of bone origin and the 5-year survival time is below 60%. The most common primary malignant tumor is chondrosarcoma (8). According to data of our series, the most common malignancies in the chest wall were metastases and the primary malignant tumors were chondrosarcoma and Ewing sarcoma. In the treatment of chondrosarcoma, the only definite cure reported is complete surgery. Wide resection should not be avoided to prevent relapse (9,10). In 3 of the 8 chondrosarcoma patients in the series, a wide resection above 10 cm requiring reconstruction was performed. Upon the development of postoperative flail chest in one patient, a special titanium implant was produced with the 3D laser printer technology and placed in the second surgery. Therefore, both respiratory functions could be preserved, and an unacceptable aesthetic appearance could be prevented.

The authors noted that Ewing sarcoma and condrosarcoma are the most common primary chest wall malignancies. Unlike the literature, we noticed that the number of Ewing sarcomas was equal to that of chondrosarcoma. Ewing sarcoma is a very rare primary chest wall malignancy, but it is noteworthy that it was equal in number with chondrosarcoma in our series. Multiple myeloma (MM) is in the second place after chondrosarcoma and Ewing sarcoma. The mean age of four patients with rib-induced MM in the series was 66.2 years and the first symptom was pain. Despite radiotherapy and chemotherapy after total resection, 5-year survival in MM has been reported to be below 10%. The mean follow-up period of the patients was 26.2 months, and 2 patients passed away (11,12).

In two of the patients, a high-grade bone tumor, osteosarcoma, was present. In one of these patients, osteosarcoma developed in the fifth rib after radiotherapy for breast cancer. After a wide chest wall resection, the defect was reconstructed using a titanium bridge and PM (Figure 3). The development of osteosarcoma in rib, whose primary malignancy is very rare, was noteworthy. The authors consider that with the increase of RT practice, more radiation-induced osteosarcoma originating from the chest wall may be encountered in the future (13). The most effective treatment method for malignant tumors is surgery. The entire involved costa with the upper and lower costa should be partially resected with the surrounding soft tissue with a safe area of at least 4-6 cm (14).

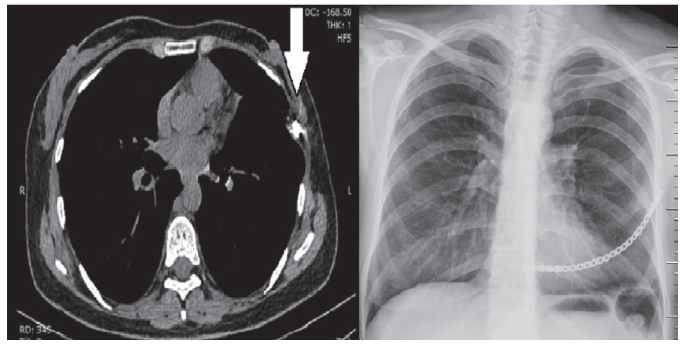

Figure 3. Preoperative view of the mass in the left fifth rib and postoperative chest X-ray showing titanium bridge

The benign chest wall lesions that were most frequently detected in the patients were lipoma, fibrous dysplasia, and osteochondroma. Ribs are a very rare localization for osteochondromas, the most common benign tumor of bone. In the study, 11 patients who underwent surgery had osteochondroma and seven patients had chondroma. Partial sternum resection was performed in one patient since the

chondroma originated from the sternum. It is very important to clinically differentiate these bone and cartilage tumors from chondrosarcoma. Although the chondrosarcoma transformation of osteochondromas is reported as less than 1%, it still must be kept in mind (15,16).

Fibrous dysplasia accounts for 1% of primary bone tumors. Although the optimal treatment strategy is still uncertain, there is a surgical indication of pain and conservative treatment in unresponsive patients (17). In the study, fibrous dysplasia was detected in 19 patients. Only one of these patients was asymptomatic, and the rest were admitted to the hospital with pain. The tumor was localized in the costa of patients, and none had concomitant endocrinopathy. For this reason, surgical treatment was preferred. In one patient, partial vertebral resection was performed in addition to the rib resection. While recurrence was seen only in one patient in this group, no mortality was encountered during an average follow-up of 47 months. These results show that surgery is an effective method in fibrous dysplasia.

Desmoid tumor is a pathology that does not metastasize but has a locally aggressive structure. Although desmoid tumor has a benign histologic profile, some authors categorize it as malign, due to its local aggressive growth pattern. Surgical treatment was applied again in three of nine patients who underwent resection with the diagnosis of local recurrence. This high recurrence rate demonstrates the need for a wide safe range in desmoid tumor surgery such as malignant lesions. The most accurate approach in preventing local recurrence is to provide a negative surgical margin (18,19).

Lipoma and Elastofibroma dorsi are common soft tissue lesions of the chest wall. Elastofibroma dorsi occurs more frequently in females and mostly over the age of 55 years (20). There were a total of 12 (7.2%) patients, including three males and nine females, who underwent operation due to the diagnosis. In the study, the mean age was calculated as 46.9 years, younger than studies in the literature.

The study has limitations as it is a single-center retrospective study; thus, a selection bias could not be neglected. Also, the small sample size of the study population limits the generalizability of the findings.

Conclusion

The majority of patients with a chest wall mass underwent surgery in this 16-year dataset. The majority of tumors were in benign types. The most common malignant type chest wall was mass metastasis, whereas chondrosarcoma and Ewing sarcoma were the most common primary malignancies. Unlike the literature, Ewing sarcomas were more common in our series. A secondary intervention was required in a small percentage of patients with a chest wall mass.

Ethics

Ethics Committee Approval: This study was approved by the Institutional Ethics Committee of Gülhane Training and Research Hospital (approval date: June 5, 2018, approval number: 18/164).

Informed Consent: Written informed consent was provided from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Ç., S.G., O.G., A.G., Concept: E.S., S.G., Design: H.I., M.Ş.İ., E.S., Data Collection or Processing: H.I., M.Ş.İ., Analysis or Interpretation: H.Ç., S.G., Literature Search: H.I., M.Ş.İ., O.K., Writing: H.I., M.Ş.İ., O.G.

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

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Optimal time for remote ischemic preconditioning for liver protection in experimental major liver resection

Ümit Alakuş[1], Mehmet F. Can[2], Fevzi Nuri Aydın[3], Muharrem Öztaş[1], İsmail H. Özerhan[2], Talha Sarıgöz[4], Abdurrahman Şimşek[1], Yusuf Peker[1]

[1]University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of General Surgery, Division of Gastrointestinal Surgery, Ankara, Turkey

[2]Lokman Hekim University Hospital, Clinic of General Surgery, Ankara, Turkey

[3]Diskapi Yildirim Beyazit Training and Research Hospital, Clinic of Biochemistry, Ankara, Turkey

[4]Kayseri City Hospital, Clinic of General Surgery, Kayseri, Turkey

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Corresponding Author:
Ümit Alakuş, M.D., University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of General Surgery, Division of Gastrointestinal Surgery, Ankara, Turkey

ORCID:
orcid.org/0000-0002-6756-3583

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ABSTRACT

Aims: Due to the liver's rich blood supply, the control of inflow is mandatory if major resection is being planned. In this regard, temporary portal triad clamping is widely used. However, ischemia-reperfusion injury (IRI) in the liver is inevitable following interruption. Remote ischemic preconditioning (IPC) was shown to ameliorate injury in the target organ in various animal models. This experimental animal study was conducted to determine optimal preconditioning frequency to use in liver surgery that promotes potential mediators associated with protection.

Methods: Male Wistar-Albino rats (n=72) were divided into 8 groups. In group 1 (sham), only the left lobe of the liver was resected without any preconditioning. In group 2, the left lobe of the liver was resected using 30 min of portal triad clamping. In other groups, prior to resection using the same procedure with group 2, 6 different remote IPC protocols (5 to 10 min ischemia plus 10 to 20 min reperfusion) were applied by clamping the femoral artery. Serum tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) level analysis, liver function tests, and histological examination were performed using the TUNEL staining to study apoptosis.

Results: Compared to group 2, serum serum TNF-α and IL-6 level analysis and liver function tests did not show any difference. There was also no difference between the intervention groups and controls in histopathologic examination and apoptotic cell counts.

Conclusions: Remote IPC protocols we studied in this experiment did not blunt hepatic IRI in rodents.

Introduction

Due to the liver's rich blood supply, the control of inflow is mandatory if major resection is being planned. Temporary portal triad clamping is used widely to reduce bleeding during transection of the liver, but ischemia and subsequent reperfusion causes injury and direct cell damage through complicated inflammatory events (1,2).

The proposal of ischemic preconditioning (IPC) was first made by Murry et al. (3,4) following their experience with dog myocardium. They postulated that brief episodes of ischemia could prepare the target tissue for sustained ischemic attack. Later, this concept was adapted to the liver surgery. However, direct IPC by the occlusion of portal inflow was shown to disrupt regeneration capacity of the liver (5,6).

The idea was worked up further by Przyklenk et al. (7) in canines and they reported that remote IPC at a distant vascular bed could result in decreased target organ injury after sustained occlusion. Various studies have investigated the role of remote

IPC in several organs including the liver (8,9). However, there is no consensus on the mechanism responsible and the optimal timing of the method in the setting of liver surgery (10).

In this study, based on reported benefits of remote IPC in the target organ, it was postulated that by using remote IPC, we could prepare liver tissue for further ischemia-reperfusion injury which is an inevitable result of portal triad clamping. The aim of this experimental animal study was to determine and optimize the ideal time for remote IPC that would protect liver function and histomorphology the best after liver IRI in rats. In this regard, six different remote IPC procedures were modeled and we sought the potential benefit of remote IPC during liver resection in an animal model. Remote IPC was applied after the isolation of the right femoral artery rather than limb tourniquet which provided precise ischemia.

Methods

Animal Experiments

The study was conducted at Gülhane Military of Academy of Medicine with the approval of Gülhane Military of Academy of Medicine Animal Studies Ethics Committee numbered 2011-41-11/48 and in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council Institute for Laboratory Animal Research, US, Washington, National Academies Press, 1996).

Before the experiment, sample size was determined to be 72 to have 80% power and to demonstrate statistical difference between the planned protocols. The effect size of this experimental animal study was 0.5 and the significance level was accepted at 0.05.

Seventy-two one-month-old Wistar Albino rats weighed 315±35 gram were used. The rats were held in metal cages, fed with standard laboratory chow diet and watered with ambient temperature at 22±2 °C. They were randomized into 8 groups (Table 1).

Anesthesia Induction

They were fasted for 12 hours before surgery. General anesthesia was maintained with Ketamine (Ketalar®, Parke Davis and Co. Inc., 40 mg/kg) and Xylazin (Rompun®, Bayer Ag, Leverkusen, Germany; 5 mg/kg).

Surgical Procedure

The rats were placed in supine position. The procedures were performed by a surgeon for standardization in accordance with the principles of asepsis and antisepsis. Abdominal area was incised in a bilateral subcostal fashion and if remote IPC was being planned, right inguinal region was cut vertically over the femoral artery trace. The method of remote IPC was carried out by dissecting the femoral artery, vein and nerve. The femoral artery was isolated and occluded with a microvascular clamp (Vasculostatt-Scanlan, St Luis, USA). The time of occlusion and reperfusion periods varied according to the study groups. After the completion of IPC, the inguinal incisions were sutured with 3/0 polypropylene (Figure 1).

Liver exploration was performed through a bilateral subcostal incision. First, lobar anatomy of the rats was explored. Falciform ligament was cut. Hepatoduodenal ligament was dissected if Pringle's maneuver was planned. For the maneuver, microvascular clamp was used and hepatoduodenal ligament was occluded for 30 minutes. The pedicle of left lateral section was found, tied with 5/0 silk, and cut. Later, connections of the left medial lobe were tied and cut. With the resection of the left lateral lobe and left medial lobe, nearly 40% of the liver was resected. Following 30 minutes of total occlusion, clamp was removed and reperfusion was initiated. The bilateral subcostal incision was closed using 3/0 polypropylene (Table 1, Figure 2).

In group 1, after the completion of resection and in the other groups, following 180th minute after the removal of the portal clamp, the rats were explored again. For the biochemical analysis, intracardiac blood samples were obtained and for the histopathological evaluation, remnant liver tissue was resected. The rats were sacrificed.

The blood samples were centrifuged for 10 minutes at 3.000 Xg and the serum was stored at – 80-degree Celsius. The remnant liver tissue was fixed in 10% formaldehyde. The changes in liver histomorphology was evaluated under light microscope with hematoxylin-eosin (H&E) staining and terminal

Table 1. The study protocol

Study protocol			
Groups	**Remote ischemic preconditioning**		**Liver resection**
1	Resection only		
2	No ischemia	No reperfusion	30 min liver ischemia + resection
3	5 min ischemia	10 min reperfusion	30 min liver ischemia + resection
4	5 min ischemia	20 min reperfusion	30 min liver ischemia + resection
5	10 min ischemia	10 min reperfusion	30 min liver ischemia + resection
6	10 min ischemia	20 min reperfusion	30 min liver ischemia + resection
7	5 min ischemia + 5 min reperfusion (2 times)		30 min liver ischemia + resection
8	10 min ischemia + 10 min reperfusion (2 times)		30 min liver ischemia + resection

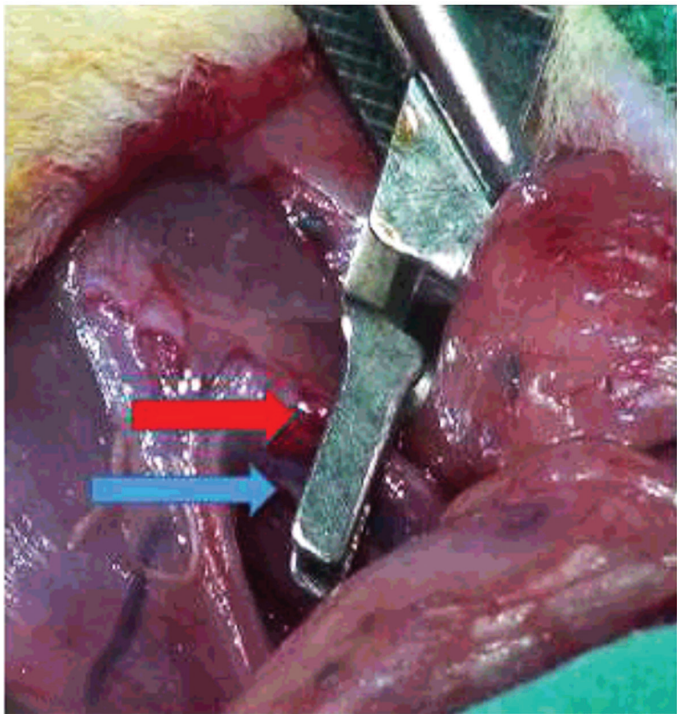

Figure 1. Clamping of femoral artery for remote ischemic preconditioning protocol
Red arrow: femoral artery; blue arrow: femoral vein

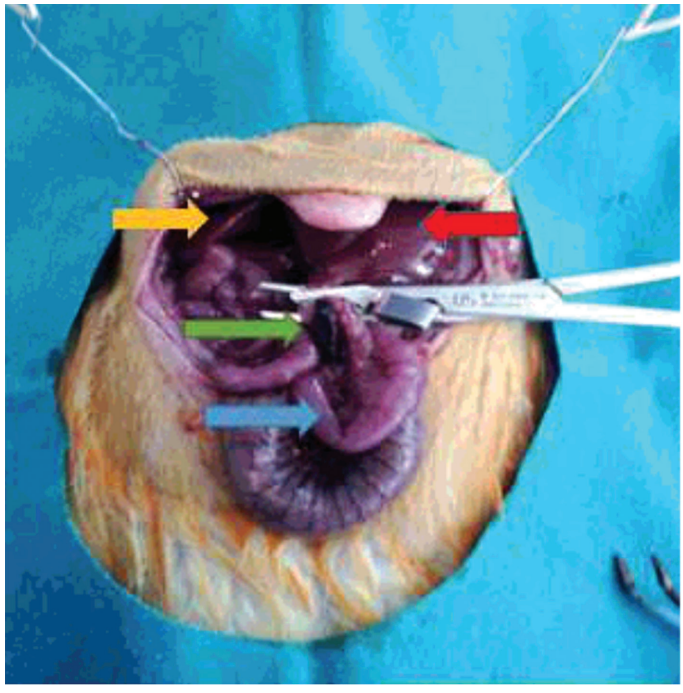

Figure 2. Pringle maneuver (hepatoduodenal ligament occlusion)
Yellow arrow: liver (right lobe); red arrow: liver (left lobe); green arrow: hepatoduodenal ligament; blue arrow: intestines

deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay. The degree of liver injury and apoptosis levels were recorded for statistical analysis by a pathologist blinded to the study.

Biochemical Analysis

Serum TNF-α and IL-6 Levels

From the serum samples, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), total bilirubin (TB), alkaline phosphatase (ALP), and gamma glutamyl transferase (GGT) levels were calculated. Calculation of serum TNF-α and IL-6 levels were made using enzyme-linked immunosorbent assay kits and according to the producer's recommendation (eBioscience, Vien, Austria, catalog number BMS622, BMS625) in Sinergy Plate Reader (Bio-Tek Instruments Inc, Winooski, VT, USA) at 450 um.

Liver Enzymes

Serum transferases, LDH, TB, ALP and GGT were measured with a standard spectrophotometric method with an automated clinical analyzer (JCA-BM9030; JEOL, Ltd., Tokyo, Japan).

Histopathological Evaluation

Following reperfusion, at the 3rd hour, remnant liver tissue was resected and fixed. After the dehydration process, tissue was embedded in paraffin blocks. The sections were cut at 4 μm thickness and the liver structure was examined by H&E stain and TUNEL assay.

Hematoxylin-eosin Staining

The sections were evaluated under light microscope for determining the degree of liver injury using H&E stain. A modified example of the scale which was designed by Camargo et al. (11) was used (Grade 0: Minimal or no evidence of injury, Grade 1: Cytoplasmic vacuolation or mild injury with focal nuclear pyknosis; Grade 2: Moderate injury characterized by cytoplasmic vacuolation, hepatocyte ballooning degeneration, sinusoidal dilatation and congestion, loss of intercellular borders; Grade 3: Moderate injury characterized by areas of coagulation necrosis, cytoplasmic hypereosinophilia, wide sinusoidal dilatation and congestion; Grade 4: Severe coagulation necrosis with disintegration of hepatic cords, hemorrhage).

TUNEL Assay

Each section was evaluated by an expert pathologist blinded to the study. Apoptotic index was calculated as Lai et al. (12) used in their study using the proportion of positive stained cells to total cells in 5 different areas and the degree of apoptosis was scored as 1 for 1-33%, 2 for 34-66%, and 3 for 67-100%.

Statistical Analysis

For the statistical analysis, Statistical Package for Social Sciences software (SPSS version 15.0, SPSS Inc., Chicago, IL, USA) was used. The data were presented using number, percentage, mean, standard deviation, median, minimum and maximum values. The chi-squared test and the Fisher's Exact

test were used to compare the batch process data. For the analysis of continuous variables without normal distribution, the Mann-Whitney U test was used.

Results

Serum TNF-α Levels

Regarding the serum TNF-α, significantly lower values were observed in group 1 compared to group 2. When group 2 and the IPC groups were evaluated, group 3, 4 and 8 were found to have significantly lower levels ($p<0.05$). On the other hand, group 6 and 7 had also lower levels of serum TNF-α, but this difference was not significant ($p>0.05$).

Serum IL-6 Levels

Although observed levels of IL-6 were lower in group 1, there was not significant difference between group 1 and group 2 ($p>0.05$). When group 2 was compared to the other groups, significant decrease was not observed in the IPC groups.

Total Bilirubin

There was not significant difference between group 1 and group 2 considering TB levels ($p>0.05$). When group 2 was compared to the other groups, significant difference was not observed ($p>0.05$).

Liver Enzymes

In comparison to group 2, lower levels of AST and ALT were observed in group 1 but this difference was not significant ($p>0.05$). In addition, there was not significant difference between the IPC groups and group 2 with regard to AST and ALT. Concerning ALP, GGT and LDH, statistically significant difference was not observed among the groups.

Hematoxylin-eosin Staining

The sections were evaluated under light microscope by a pathologist blinded to the study in terms of the degree of liver injury. Neither grade 3 nor grade 4 injury was observed. Between group 1 and group 2, there was not statistically significant difference regarding H&E staining ($p>0.05$) (Table 2). In both groups, similar rate of liver injury was observed. When group 2 was compared to the groups with IPC protocol, the degree of general histopathological liver injury did not differ among the groups. Between-group comparisons showed no statistically significant decrease in liver injury scores in the groups with IPC protocol (group 2 vs. group 3, $p=0.153$; group 2 vs. group 4, $p=0.150$; group 2 vs. group 5, $p=1.000$; group 2 vs. group 6, $p=1.000$; group 2 vs. group 7, $p=0.354$; group 2 vs. group 8, $p=0.288$).

Table 2. The comparison of group 1 and group 2 with regard to hematoxylin-eosin staining

	n (%)		p*
H&E	**Group 1**	**Group 2**	
Grade 0	4 (44.4)	3 (33.3)	1.000
Grade 1	5 (55.5)	6 (66.6)	

*Fisher's Exact test.
H&E: Hematoxylin-eosin

TUNEL Assay

The apoptotic index result in group 1 was found to be significantly lower than group 2 ($p<0.05$). When group 1 was compared to the other groups with preconditioning method, the apoptosis index was detected to be lower in group 1 ($p<0.05$). There was not statistically significant difference between group 2 and the other groups that IPC was applied (group 2 vs. group 3, $p=0.569$; group 2 vs. group 4, $p=0.516$; group 2 vs. group 5, $p=0.219$; group 2 vs. group 6, $p=0.514$; group 2 vs. group 7, $p=0.630$; group 2 vs. group 8, $p=0.282$). Remote IPC was not found to decrease apoptotic IRI in the liver (Table 3).

Table 3. The comparison of group 1 and 2 in terms of apoptosis in evaluation with TUNEL assay

	n (%)		p*
TUNEL staining	**Group 1**	**Group 2**	
0%	9 (100)	2 (22.2)	0.002
1-33%	0 (0)	6 (66.6)	
34-66%	0 (0)	1 (11.1)	

*Fisher's exact test.
TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labeling

Discussion

Recent progress in the liver surgery has led to the wide range of methods available for resection. The concept of remote IPC was first described by Przyklenk et al. (7) in canine heart model. Due to doubtful ischemic periods and direct trauma to vascular structures, clinic application is limited (9). Considering the reported protective effects of remote IPC, potential benefits and various cycles were investigated with the animal model of liver resection in this study. Six remote IPC methods, which were all differentiated in terms of time interval, were employed in the light of the literature. Nonetheless, we were not able to demonstrate significant improvement in postoperative liver injury following partial liver resection, which is largely in agreement with the previous studies from different authors. None of the proposed remote IPC methods provided potential benefit in liver resection.

Although introduced in 1908, the Pringle's (13) maneuver is yet the most common applied technique to reduce bleeding and associated complications during parenchymal liver resections. It is based on total occlusion of hepatic pedicle. As a result of that application, IRI in the remnant liver tissue is still a problem awaiting for solution. The remote IPC method was shown to be beneficial for reducing IRI in the heart, kidney and lung (14,15). In 1986, Murry et al. (3,4) studied the effects of repeated brief

episodes of IPC, either single or multiple, on canine myocardium and reported salutary results with respect to sustained ischemia. In the following years, Przyklenk et al. (7) carried this idea a bit further and defined remote IPC. They indicated that brief episodes of remote IPC protected remote virgin myocardial tissue from sustained ischemic insult. These studies have revealed that IPC of an organ reduces the degree of injury in the target tissue during continuous ischemia by unknown mechanisms (9). In their review, Robertson et al. (16) have indicated that the effects of remote IPC on IRI partially relies on the release of adenosine and L-arginine. In another rodent study, Oberkofler et al. (17) identified a platelet-dependent axis that could mitigate hepatic IRI.

Impact of remote IPC on the liver was evaluated by Kanoria et al. (9) in an experimental rabbit study. In this study, the right hind legs of rabbits were subjected to 3 cycles of 10-min ischemia and reperfusion. They observed significant difference after remote IPC in aminotransferase levels, peripheric oxygen saturation and hepatic blood flow. In the work of Guimarães Filho et al. (18), 6 cycles of 4-min ischemia and 4-min reperfusion on the right hind limb were employed. While plasmatic ALT levels were significantly lower, IL-6 levels were significantly higher in the remote IPC group. Also, there was a clear reduction in necrosis in the remote IPC group histopathological evaluation. In this study, we did not observe significant changes in LDH, ALP, TB, GGT and IL-6 levels among the groups. Although aminotransferases were lower in group 1, statistically significant results were not observed. Although again reperfusion times were similar to Kanoria et al. (9) and Guimarães Filho et al.'s (18) study, we contributed unexpected insignificant results to the remote IPC method we used and partial liver resection procedure because there was no other difference between their model and this study. Liver resection might have caused additional trauma. In another study, Jia et al. (15) investigated the impact of remote IPC on the liver grafts and concluded that 3 cycles of 5-min remote IPC seemed to be more efficacious during liver transplant. However, they applied remote IPC on both of the hindlimbs and they did not use portal triad clamping as in our study. As an alternative method, Kageyama et al. (19) applied intestinal remote IPC consisting of 2 four-minute superior mesenteric artery clamping separated by 11-minute declamping. In their model, it was shown that the intestines could also be a target for remote IPC. Furthermore, release of serum transaminases, LDH, IL-6 and TNF-α were decreased in the intestinal remote IPC group compared to the sham group.

On the other hand, in this work up, we observed significantly lower levels of TNF-α in group 3, 4 and 8. In these groups, 5-min ischemia and 10-min reperfusion; 5-min ischemia and 20-min reperfusion; 2 cycles of 10-min ischemia and 10-min reperfusion were applied, respectively. However, we could not find clear explanation for lower levels of TNF-α in those. There was not significant difference in histopathological examination. Furthermore, in the aforementioned studies, remote IPC was induced using limb tourniquet or bundle occlusion but in this rodent trial, only femoral artery was clamped subsequent to detailed dissection because it was postulated that selective blockage of the femoral artery could overcome possible inadequate blood occlusion and nerve paralysis due to the use of tourniquet. Nevertheless, we associated the unsatisfactory results with this choice of technique. In the study of Zhang et al. (20), they also attributed dissatisfying results to the dissection of the femoral artery and vein rather than limb ischemia. Limb ischemia could cause stress on skeletal muscles and might induce an unknown interaction between target organ and muscle (21,22). Further studies should be planned to clarify this mechanism. Apart from the method of remote IPC, this study also differentiated from the similar ones as left lobectomy was performed. Most of the others collected samples after the completion of IPC. Actually, we aimed to simulate clinical practice but we concluded that this procedure might have negative effect on remnant liver and it could be the reason behind unsatisfactory results. In a different study, Gustafsson et al. (23) clamped the femoral artery of Wistar rats to induce remote IPC and also could not demonstrate its beneficial effect. Their explanation was that short period of IPC, which was 10 minutes, caused inadequate effect. Considering all the above-discussed factors, investigated remote IPC protocols were not enough to blunt hepatic IRI in this rodent trial.

The experience in animal models has been translated to clinical practice, as well. The first clinical trial was conducted by Clavien et al. (24), who studied the effect of remote IPC with a cycle of 10-min ischemia and 10-min reperfusion on the remnant liver. Promising results, which were indicated by lower serum transferase levels, were achieved. In the recent pilot study of Kanoria et al. (25), they studied the outcome of remote IPC, which was induced through three 10-min cycles, in patients undergoing major liver resection due to colorectal cancer metastasis. They were able to show protective effects of remote IPC and safety of tourniquet application. Robertson et al. (26) studied with transplant recipients. They induced remote IPC using limb tourniquet through three 5-min cycles and reported that there was no evidence of decrease regarding IRI in the short-term but long-term studies are needed. Also, these studies have shown that limb tourniquet is a safe procedure to employ remote IPC. In the systematic review of Farooqui et al. (27), 12 studies were included and it was concluded that the translation of remote IPC to clinical practice should be considered with caution due to heterogeneity of populations and preconditioning set-ups. Therefore, the remote IPC protocols should be discussed widely for future patients who will greatly benefit from this preconditioning.

Our study has some limitations. It can be evaluated that the liver ischemia of 30 minutes we applied may be an insufficient time to demonstrate the effectiveness of remote IPC. In the literature, protective effect of remote IPC by inducing liver ischemia for a longer time has been shown in studies.

However, several other researchers used partial clamping techniques. In our study, unlike other studies, the results of liver resection can be thought to have negative effect. However, as is known, the Pringle maneuver is a bleeding reducer that is often required during liver resection. Our efforts to include liver resection in the study aimed to simulate the clinical practice and scenario encountered correctly. Another limitation in our study is that we did not evaluate the late effects of the remote IPC. However, in our opinion, the demonstration of biochemical and histopathological damage and TUNEL method demonstration of apoptosis is sufficient to examine the subject procedure (28).

Conclusion

In conclusion, since the description of remote IPC, it has been a focus of extensive research. However, there is still no clear explanation of a mechanism. While there are various factors affecting outcomes such as heterogenous participants, different methods of IPC and application site, none of the trials has been successful in showing any benefit of remote IPC to reduce IRI or clinically relevant consequences. Yet, it is still worth considering as a potential method for reducing hepatic IRI during liver surgery.

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Ethics

Ethics Committee Approval: The study was conducted at Gülhane Military of Academy of Medicine with approval of Gülhane Military of Academy of Medicine Animal Studies Ethics Committee (no: 2011-41-11/48) and in accordance with Guide for the Care and Use of Laboratory Animals (National Research Council Institute for Laboratory Animal Research, US, Washington, National Academies Press, 1996).

Informed Consent: This was an animal study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ü.A., M.F.C., F.N.A., M.Ö., İ.H.Ö., A.Ş., Y.P., Concept: Ü.A., M.F.C., F.N.A., M.Ö., İ.H.Ö., T.S., A.Ş., Y.P., Design: Ü.A., M.F.C., M.Ö., İ.H.Ö., T.S., A.Ş., Y.P., Data Collection or Processing: Ü.A., M.F.C., F.N.A., M.Ö., İ.H.Ö., T.S., Analysis or Interpretation: Ü.A., M.F.C., F.N.A., M.Ö., İ.H.Ö., T.S., Literature Search: Ü.A., M.F.C., M.Ö., İ.H.Ö., T.S., A.Ş., Y.P., Writing: Ü.A., M.F.C., M.Ö., İ.H.Ö., T.S., A.Ş., Y.P.

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Temporary withdrawal of immunosuppressive treatments in patients with hidradenitis suppurativa during COVID-19 pandemic: A retrospective cross-sectional study

Pelin Esme, Burcu Beksaç, Ercan Çalışkan

University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Dermatology and Venereology, Ankara, Turkey

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Corresponding Author:
Pelin Esme, M.D., University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Dermatology and Venereology, Ankara, Turkey

ORCID:
orcid.org/0000-0001-6339-2185

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ABSTRACT

Aims: There is currently no evidence-based guideline to show how to manage immunosuppressive treatment in patients with hidradenitis suppurativa (HS) during the Coronavirus disease-2019 (COVID-19) pandemic. Therefore, we updated our routine clinical protocol to 1) inform patients with ongoing treatment about the potential risks of their medications in the case of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection, 2) discuss opt out of treatment temporarily, and 3) perform a closer follow-up on a monthly basis. The aim of this study was to evaluate the clinical outcomes in patients with HS, who suspended and continued immunosuppressive therapy following COVID-19 outbreak.

Methods: This retrospective study included patients with HS, who had been receiving biologic/immunosuppressive treatment when the COVID-19 pandemic was announced. Those who withdrew treatment for any reason or continued were analyzed. The primary endpoint was physician-diagnosed disease exacerbation. The secondary outcomes were changes in visual analogue scale (VAS) and COVID-19 diagnosis.

Results: A total of 37 patients were included in the analysis. The majority of the patients were on adalimumab treatment (n=33). Fifteen (40.5%) patients withdrew the treatment for COVID-19 related concerns. During 83.2±0.6 days of follow-up following the withdrawal, all patients in this group had at least one exacerbation. Also, the mean VAS score increased from 5.7±0.56 to 8.6±0.57 (p=0.001). On the other hand, three patients (13.6%) who continued the treatment reported worsening in disease course, 12 patients (54.5%) remained stable and seven of them (31.9%) had clinical relief. We did not observe any confirmed SARS-CoV-2 infection in any of our 37 HS patients.

Conclusions: The present study suggests that even a temporary withdrawal of biologic/immunosuppressive treatments may have significant adverse consequences on disease course and quality of life in patients with HS. These individuals may safely continue the treatment provided that maximum measures are taken to avoid COVID-19 infection.

Introduction

Coronavirus disease-2019 (COVID-19), which is caused by the novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) virus, has quickly spread worldwide and become a global public health emergency with a wide spectrum of disease severity (1). After it was declared a pandemic by the World Health Organization on March 11th, 2020 (2), understandable concerns about patients with a chronic disease and/or under immunosuppressive therapy have arisen among clinicians and controversies about the follow-up and management of these patients to minimize the mortality and morbidity have been in question.

Hidradenitis suppurativa (HS) is a painful and destructive chronic skin disorder of which clinical control is difficult even under normal circumstances. Biological agents, especially tumor necrosis factor-alpha (TNF-α) inhibitors, are cornerstone of the treatment of moderate to severe HS (3).

Although HS itself is not considered as a major risk factor for COVID-19 (4), it should be noted that some of its frequent medical comorbidities including obesity, hypertension, diabetes mellitus, cardiovascular disease and smoking may increase susceptibility to COVID-19 or worsen its prognosis (5,6). More importantly, although a minimally increased risk in infections and nasopharyngitis was reported, there was not an increased rate of other upper respiratory infections in HS patients on adalimumab treatment in PIONEER 1 and 2 trials (7). Clinical outcomes of HS patients under immunosuppressive therapy are still a topic of debate and as of today, there is no clear guideline for the management of HS patients vis-à-vis RNA virus infections (8).

The first case of COVID-19 was announced on March 11th, 2020 in Turkey and several measures such as closure of schools, lockdowns at weekends and national holidays, and complete lockdown for young and elderly population were taken by the government to restrict case numbers. Also, the government provided patients to take chronically taken medications (e.g. biologics) from the pharmacy without any prescription with the aim of keeping patients with a higher risk of COVID-19 related death away from the hospital. As daily case numbers declined, almost all preventive measures were lifted by June the 1st, 2020. There were 163,942 confirmed cases in the country by this date. During this period, our outpatient and inpatient clinics were also restricted since a majority of our staff started working for the COVID-19 clinics. Therefore, all HS patients were contacted and followed up through telephone calls during the described "heavy" pandemic period between 15th March and 30th May 2020.

In this study, we aimed to investigate the effects of the COVID-19 pandemic on the continuation/cessation rates of immunosuppressive treatments in HS patients, clinical outcomes of these treatments as well as the extent to which patients were affected by the pandemic (whether they underwent COVID-19 and if they did, what the outcome was). Of the 198 HS patients currently being followed-up in our clinic, we mainly aimed to focus on clinical outcomes of HS patients under immunosuppressive medications whose medical management became more challenging during the pandemic. Since we would not consider interfering with the medications of a patient who benefited from biologic treatment, this pandemic gave us a unique opportunity to observe the clinical outcomes of discontinuation of immunosuppressive treatment in HS patients, which would not be possible under normal circumstances.

Methods

This retrospective cross-sectional study was carried out in accordance with the permission of Turkish Ministry of Health (issue number: 2020-08-18T17_00_38) and approved by Gülhane Local Ethics Committee (2021-21, 28.01.2021). Thirty-seven HS patients who were on immunosuppressive therapies before the announcement of the first COVID-19 case in Turkey were included in the study. Clinical [Hurley stage, 10-point visual analogue scale (VAS) score, current and past treatments] as well as demographic data were obtained from the HS patients' database of our clinic. Between March 15th and May 30th, 2020, all patients were contacted through telephone and were informed about the potential impact of HS treatment on their risk of getting COVID-19 and having severe disease, as well as preventive measures and symptoms of COVID-19. They were also explained that our clinic would not be able to perform dermatology outpatient clinic services for a then uncertain duration, since our staff had been appointed to the COVID-19 clinics. The decision to continue or to stop the treatment was taken by the joint consideration of the patient and physician, taking risk factors for each individual into account. Monthly follow-ups were performed through phone calls. In June 2020, after COVID-19 restrictions were ended, all 37 patients were invited for a clinical visit. Post-lockdown VAS score was calculated and compared to pre-lockdown VAS score for each patient. A short questionnaire involving COVID-19 history, change in smoking habits and weight during the lockdown period was applied for each patient.

Statistical Analysis

Statistical analyses were performed by using IBM SPSS (statistical package for social sciences) for Windows, version 22.0 package program. Numerical variables were shown as mean±standard deviation or median (minimum-maximum). Categorical variables were shown by number and percentage. Since pre- and post-lockdown VAS scores did not exhibit normal distribution, the Mann-Whitney U test was used to compare these variables. The chi-square test, where appropriate, was employed to compare these proportions in different groups. A p-value of less than 0.05 was considered to show a statistically significant result.

Results

A total of 37 patients (26 male/11 female) were included in the study. The mean age was 39.81±12.79 years. The median disease duration was eight years (minimum-maximum: 1-29). Most patients were at Hurley stage 3 (Table 1). Out of 37 patients, 33 (89.2%) were under treatment with adalimumab. Other treatments were secukinumab, ixekizumab, certolizumab pegol and methotrexate (Table 1). At least one comorbidity accompanied HS in 21 (56.7%) patients (Table 1).

Fifteen patients (14 adalimumab; 1 secukinumab) discontinued the treatment during the lockdown, for a mean period of 83.18±0.61 days. All patients in this interrupted treatment group reported aggravation in HS during this period. In the continued treatment group, seven patients had improved while three had worsened disease. Remaining patients

reported stable disease (Table 2). The interrupted treatment group exhibited significantly worsening disease compared to the continued treatment group (p=0.001). Post-lockdown VAS scores were significantly higher in the interrupted treatment group (p=0.001) (Table 2). After a detailed clinical examination throughout June, adalimumab treatment was reintroduced in 12 out of 15 patients in the interrupted treatment group while treatments of two patients under adalimumab and one patient under secukinumab were switched to certolizumab pegol due to decreased treatment response under adalimumab since pre-pandemic period. The mean VAS score of these 12 patients after the reintroduction of adalimumab was regressed from 8.6±0.57 to 7±4.6 at the end of two months and did not return to pre-lockdown VAS levels (p=0.072). None of the patients had had symptoms of COVID-19 or a confirmed SARS-CoV-2 infection. No hospitalization or deaths due to COVID-19 occurred in this cohort.

For smokers (27/37-72.9%), the number of cigarettes consumed daily increased by 10-50% during these two-and-a-half months. The mean body mass index was 28.82±4.64; nine (24.3%) and three (8.1%) of 37 patients reported a weight gain of 2-5 kilograms and more than 5 kilograms, respectively, throughout the lockdown. Two patients started using antidepressant medications due to uncontrolled anxiety of getting SARS-CoV-2 infection.

Table 1. Clinical characteristics of patients involved in the study

Clinical characteristics		n	%
Hurley stage	Stage 1	0	0
	Stage 2	5	13.5
	Stage 3	32	86.5
Treatment modality	Adalimumab	33	89.1
	Ixekizumab	1	2.7
	Secukinumab	1	2.7
	Certolizumab pegol	1	2.7
	Methotrexate	1	2.7
Comorbidities (n=21)	Diabetes mellitus	8	21.6
	Hyperlipidemia	8	21.6
	Hypertension	7	18.9
	Cardiovascular disease	6	16.2
	Psychiatric disease	5	13.5
	Spondyloarthropathy	2	5.4
	Inflammatory bowel disease	1	2.7
	Familial Mediterranean Fever	1	2.7

Discussion

There is currently no evidence-based management guideline for HS during the pandemic. However, it is generally not recommended to interrupt immunosuppressive medications, unless there are signs of active COVID-19 (5), due to the risk of HS exacerbation and possible loss of efficacy after the reintroduction of the same treatment (1,6,8). Although there are not many studies presenting the clinical outcomes of HS patients during the COVID-19 pandemic, recent publications have been summarized in Table 3. In a study by Galán Sánchez et al. (9), only 2 of 12 patients under adalimumab treatment, who were over 50 years old with several comorbidities, exhibited symptoms suggestive of SARS-CoV-2 infection, but the disease was not confirmed. In another study, 2 of 75 HS patients who were treated with adalimumab had a history of contact with confirmed COVID-19 positive individuals, but nasal and pharyngeal swab examinations were negative in both (10). In our study, none of our 37 HS patients presented any symptoms of SARS-CoV-2 infection. This may be because the patients were all contacted and informed about the ways to prevent the infection. Moreover, since the government took necessary measures to reduce spread of COVID-19 by giving the under-risk population (those over 65 years, and those having a chronic disorder or taking immunosuppressive medications) permission to stay home and not to work throughout the pandemic, our patients were probably very careful to stay home during the heavy pandemic period. Additionally, none of our patients admitted having a SARS-CoV-2 positive person in their close contact.

HS is characterized by increased levels of some proinflammatory cytokines and interleukins (IL) such as IL-6, IL-10, IL-12, IL-17, IL-23, IL-1β and TNF-α (12). TNF-α is also found to be higher in COVID-19 infection and increased levels of TNF-α showed a strong correlation with disease severity. Blockade of TNF-α has not only critical role in the management of HS, but it might also reduce the severity of COVID-19 and control the "cytokine storm" which is considered a poor prognostic factor

Table 2. Treatment status of 37 hidradenitis suppurativa (HS) patients on immunosuppressive agents during Coronavirus disease-2019 pandemic and HS outcome at the end of May 2020

		Disease status perceived by patient			VAS score	
Treatment status	**n**	**Worsened**	**Improved**	**Stable**	**Pre-lockdown**	**Post-lockdown**
Continued	22	3	7	12	5.32±0.58	5.18±0.53
Interrupted	15	15	0	0	5.7±0.56	8.6±0.57
		P value: **0.001***			P value: **0.001***	

N: number of patients, VAS: Visual analogue scale
*Analysis performed with the Mann-Whitney-test

Table 3. Summary of studies presenting clinical outcomes of hidradenitis suppurativa patients under immunosuppressive treatment

	n* of COVID-19 patients	Total number of patients under immunosuppressive treatment		Symptoms	Diagnostic confirmation
Galán Sánchez et al. (9)	2	12	Adalimumab	Respiratory infection, ageusia, anosmia and radiographic changes	Neither patients were tested.
Marasca et al. (10)	2	75	Adalimumab	Only recent contact risk without any symptom	Both patients were negative
Rozzo et al. (11)	0	46	Adalimumab	None	-
		11	Secukinumab		
		2	Apremilast		
Current study	0	33	Adalimumab	None	-
		1	Secukinumab		
		1	Certolizumab		
		1	Ixekizumab		
		1	Methotrexate		

COVID-19: Coronavirus disease-2019
*Number of patients who presented highly suggestive symptoms for COVID-19 infection under immunosuppressive therapy

in COVID-19 disease (1,6). Today, it is not possible to make a clear conclusion about whether TNF-α blockers are in effect as a protective or a facilitating factor for COVID-19 disease in HS, and large scaled observational studies are necessary to clarify this confusion.

In this study, all of 31 HS patients who were smokers were found to have increased the number of cigarettes consumed daily about by 10-50%, 12 of 37 patients admitted gaining weight, and 2 of them needed antidepressant medications during 2.5-month lockdown period. Therefore, we would like to underline that comorbidity screening including smoking, obesity, metabolic syndrome and depression may become even more important in situations of increased stress level such as lockdowns and social distancing in which daily physical activities are restricted. Clinicians should be aware of that exacerbated comorbidities will make treatment process of HS even more challenging.

It is already known that treatment success in HS decreases in 12 weeks after discontinuation or dose reduction of adalimumab (13). Sotiriou et al. (14) reported that the mean time to relapse was 11 weeks after the discontinuation of adalimumab. In the current study, we recorded exacerbations in all patients within 83 days -just about 11.85 weeks- and our results were very similar to those in previous studies. Although physical and psychological stress is one of the potential effects of pandemic and may accelerate flare-ups in HS, our results underlines that discontinuation of treatment is the most important factor that determines the duration of exacerbation.

In the current study, 15 of the 37 patients discontinued their immunosuppressive therapies and after a detailed clinical examination throughout June, all patients were put back on biologic therapies. Twelve out of 15 patients were reintroduced on adalimumab while three patients' treatments were switched to certolizumab pegol. Although follow-up period comprising June and July 2020 is not enough to make a proper inference after the reintroduction of the immunosuppressive therapies, we would like to underline that four patients reported lower treatment response with the reintroduction of adalimumab when compared to first treatment experience. In brief, our real life data results support the clinicians' concerns about lower efficacy due to anti-drug antibody formation after the cessation of treatment. Considering PIONEER trials (13,15), to minimize the risk of anti-drug antibody formation, it seems more rational to switch adalimumab every week treatment to every other week instead of cutting off completely, if the patient has a higher risk for COVID-19 and a treatment modification is absolutely required.

While this study comprises a small number of patients and lacks serological and molecular studies to confirm the presence or absence of SARS-CoV-2 infection as a limitation, we believe that it will provide important insights to achieve evidence-based management guidelines for the relevant issue. We are aware of that the evaluation of clinical response and disease severity solely by VAS without any objective scoring system (i.e. HISCAR, HS-PGA or Sartorius) is insufficient to make a realistic comparison. However, since face-to-face clinical visits could not be performed due to the pandemic period, VAS was a decent tool to understand the disease perception of patients.

Conclusion

Consequently, considering decreased efficacy after the reintroduction of immunosuppressive therapies as observed

in our study and the absence of any severe COVID-19 case reported under biologic treatments, HS patients should be recommended to continue their current treatment throughout the COVID-19 pandemic, unless they show signs and symptoms of infection. Another important point is that we currently do not know when the pandemic will be under control, and HS is a debilitating disease which thoroughly affects quality of life. Therefore, in our opinion, stopping the treatments of these patients would do more harm than benefit. However, patients under biologic or immunosuppressive therapies should be enlightened about the risks and benefits of withdrawing or continuing their treatments, and decisions should be made on a case-by-case basis considering HS disease severity, life conditions of the patients (whether they work or stay at home, and if they will be able to conform to the necessities of their treatment by maintaining social distancing etc.), medical comorbidities of the patients and also the COVID-19 burden of the country. It is also logical to follow-up patients closer until risks and outcomes about the COVID-19 become clearer.

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Ethics

Ethics Committee Approval: This retrospective cross-sectional study was carried out in accordance with the permission of Turkish Ministry of Health (issue number: 2020-08-18T17_00_38) and approved by Gülhane Local Ethics Committee (2021-21, 28.01.2021).

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: P.E., E.Ç., Concept: P.E., B.B., E.Ç., Design: P.E., B.B., E.Ç., Data Collection or Processing: P.E., E.Ç., Analysis or Interpretation: P.E., B.B., E.Ç., Literature Search: P.E., B.B., E.Ç., Writing: P.E., B.B., E.Ç.

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Sleep disorders in multiple sclerosis

Yusuf Alper Akın[1], Büşra Sümeyye Arıca Polat[2]

[1]*Bilecik State Hospital, Clinic of Neurology, Bilecik, Turkey*

[2]*University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Neurology, Ankara, Turkey*

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Corresponding Author:
Büşra Sümeyye Arıca Polat, M.D., University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Neurology, Ankara, Turkey

ORCID:
orcid.org/0000-0001-9337-4041

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ABSTRACT

Aims: Previous studies have reported that sleep disorders are frequently seen in patients with multiple sclerosis (MS). In this study, we aimed to investigate the frequency and related factors of sleep disorders in these patients.

Methods: In this cross-sectional study, sleep disorder was assessed using the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS). Fatigue, generalized pain, anxiety, depression symptoms, restless legs syndrome (RLS) and urinary dysfunction were evaluated using the Fatigue Severity Scale (FSS), visual analogue scale (VAS), Hospital Anxiety and Depression Scale (HAD), and RLS Rating Scale and Scales for Outcomes in Parkinson's disease-Autonomic. Logistic regression analysis was used to assess the potential associations between a sleep disorder diagnosis and the investigated conditions.

Results: Fifty-six patients [age (mean±standard deviation): 36.2±2.8 years; female: 30.4%] were included. Fifty percent of the patients scored 5 or more according to PSQI. ESS, HADS, FSS and VAS scores of patients with sleep disorder were significantly higher than those of patients with no sleep disorder ($p=0.002$, $p=0.001$, $p<0.001$, and $p<0.001$, respectively). Logistic regression analysis showed significant associations between sleep disorder and fatigue [Odds ratio (OR): 6.54 (95% confidence interval (CI): 1.08-39.57, $p=0.041$)], depression [OR: 9.82 (95% CI: 1.47-65.6), $p=0.018$], and generalized pain disorders [OR: 1.79 (95% CI: 1.23-2.3), $p=0.002$].

Conclusions: Our results show that half of the patients with MS suffer from sleep disorders. Sleep disorders in this group are associated with fatigue, depression, daytime sleepiness, common body pain, and immunomodulatory treatment.

Introduction

Multiple sclerosis (MS) is an autoimmune disease characterized by demyelination and axonal loss in the central nervous system (CNS). The prevalence is 120/100.000 (1). Sleep disorders are frequently seen in patients with MS. It is known that half of the patients have sleep disorders (2,3). The frequent sleep disorders in MS are insomnia, sleep apnea, restless leg syndrome (RLS), narcolepsy, circadian rhythm disorders, and rapid eye movement sleep behavior disorder. These disorders can result in daytime sleepiness, fatigue, depression, and pain (4,5). Factors related to sleep disorders in MS patients have been investigated in previous studies. Demographic characteristics such as age, gender, and socioeconomic status and other factors including MS subtype, disease duration, severity of disability, treatment, especially immunomodulatory drugs, and disease-related factors such as urinary incontinence, body pain, depression, anxiety disorder, and night cramps have been reported to cause sleep disorders (6-8).

Unfortunately, sleep disorders in MS are not sufficiently focused in clinical practice, although they are commonly seen. It is very important to determine the sleep disorders in patients with MS and to arrange their treatments in terms of improving the quality of life of the patients.

Our aim in this study was to investigate the frequency of sleep disorders in patients with MS, and to explore the potential association between a sleep disorder diagnosis and common clinical conditions in these patients.

Methods

Patients

This study was conducted in Ankara University, Department of Neurology between September 2008 and January 2010. Fifty-eight patients who fulfilled the criteria for MS according to the revised McDonald diagnostic criteria were included in this cross-sectional observational study (9). Demographic and disease specific data including disease duration (based on symptom onset), attack frequency, MS subtype (relapsing remitting, primary progressive, secondary progressive) and medications used for MS prophylaxis [interferon-beta (IFN-β) 1a-1b, glatiramer acetate, mitoxantrone] were collected. All patients included in the study were in remission period. None of the patients received steroid treatment in the last three months. Patients with diseases that could be confused with MS, including systemic lupus erythematosus and CNS vasculitis, and patients with systemic diseases that might cause sleep disturbance (psychiatric disorders such as depression and anxiety disorders, prostate diseases such as benign prostatic hyperplasia) were excluded.

The patients were examined by the same neurologist and severity of disability was assessed by the Kurtzke (10) Expanded Disability Status Scale (EDSS). This scale is applied to eight functional area of the CNS, is graded by 0 to 10. 0 represents normal situation, 10 represents death by MS. The lower score predicts the less disability of the patient.

Clinical Assessments

The patients were interviewed face to face and the information was taken from them. Sleep disorders were evaluated using the Turkish version of the Pittsburgh Sleep Quality Index (PSQI) (11). PSQI includes 24 questions to assess the frequency and severity of information about sleep duration, sleep latency and special problems related to sleep, 19 questions are self-assessment questions, 5 is replied by the spouse of roommate of the patient, used only for clinical information and does not count towards scoring. Based on the previously recommended cut-off value (11), the patients included in the study were categorized into two groups (PSQI score ≥5 “sleep disorder”, and PSQI score <5 “no sleep disorder”).

Daytime sleepiness and sleep status were assessed by using the Epworth Sleepiness Scale (12). In this scale, people are asked about the likelihood of falling asleep during the daily activities and they are required to rate it between 0 and 3 points. The scale has 8 items. The evaluation is done as follows: 0-5: Normal, 6-10: Normal but excessive daytime sleepiness, 10-12: Excessive but mild daytime sleepiness, 12-15: Excessive but moderate daytime sleepiness, 16-24: Excessive daytime sleepiness.

To assess the level of fatigue of the patients, the Turkish version of Fatigue Severity Scale (FSS) was used (13). This scale assesses level of fatigue with 9 questions. All questions are replied and scored as 1 (I don’t agree at all) - 7 (I totally agree). FSS score is the average value of these nine questions. Higher scores indicate increased severity of fatigue.

The items related to urinary dysfunction (8-13) of the Scales for Outcomes in Parkinson’s disease-Autonomic (SCOPA-AUT) scale, which was mainly developed for Parkinson’s patients, were used to question urinary functionality (14). Relevant questions in this scale are scored as “0-Never, 1-Sometimes, 2-Regularly, 3-Recently, 4-catheter is used”. High score indicates severe urinary dysfunction.

The anxiety and depressive status of the patients were evaluated with the Hospital Anxiety and Depression Scale (HADS), which questions the life events of the last few days. HADS is a scale prepared to screen anxiety and depression in people with physical disorders. The scale is a feedback scale and consists of 14 items, 7 of which investigate the symptoms of depression and 7 of anxiety. The patient is required to give an answer that expresses how he has been feeling, considering the last few days. Answers are scored in a four-point Likert scale and between 0 and 3. Depression and anxiety questions are scored separately; 8-10 points borderline, 11 points and above are considered abnormal (15).

The patients were examined in terms of RLS. The International RLS Study Group (IRLSSG) developed “Restless Legs Syndrome Rating Scale”, which has five-questions minimal diagnostic criteria based on the patient’s history and additional criteria supporting the diagnosis were determined (16). Supporting features are not necessary for diagnosis but are helpful in uncertain cases. Those meeting all RLS diagnostic criteria were evaluated as RLS (+).

The visual analog scale (VAS) was used to assess common body pain. The patients were asked to score according to the severity of pain, with 0 points if there was no pain and 10 points for the most severe pain.

All procedures were performed in accordance with the Declaration of Helsinki, an approval was received from the Research Ethics Committee of Medical Faculty Ankara University (protocol number: 135-3915, date: 29.07.2008), and an informed written consent was obtained from all participants or legal representatives.

Statistical Analysis

Descriptive and quantitative data are given as mean and standard deviation. Demographic data and the PSQI scores of the two groups were compared using the Student’s t-test (for continuous variables) or a chi-square test (for categorical variables). A logistic regression analysis was further performed to assess the association between sleep disorders and related

factors. The significance threshold was set to p<0.05. SPSS Statistics 15.0 Software Package (SPSS Ltd., Chicago, IL, US) was used for the analysis.

Results

Of the 58 patients recruited in the study, two patients were excluded due to missing PSQI scores. The remaining 56 patients [39 women (69.6%)] were divided into two groups: patients with PSQI score ≥5, "with sleep disorder", (n=28) and PSQI score <5, "no sleep disorder", (n=28). Age, gender, marital status, education level and occupational status, presence of additional diseases (diabetes mellitus, systemic Behçet's disease, lumbar disk hernia, urticaria, varicosis, allergy, etc.), MS duration and average attack number, EDSS scores, presence of RLS and urinary dysfunction of two groups were similar. (Table 1). The subtype of MS was relapsing remitting in 96.4% (n=54), primary progressive in 1.8% (n=1) and secondary progressive in 1.8% (n=1) of the patients. Due to the small number of groups except for the relapsing remitting MS subgroup, statistical evaluation was not done between these subgroups.

Twenty-four of the patients (42.9%) did not use any medication for MS prophylaxis. Thirty-two patients (57.1%) were receiving disease modifying therapy (DMT). The most commonly used DMT was IFN-β (n=25). Being under DMT was statistically higher in patients with sleep disorders (p=0.03).

ESS, HADS, FSS and VAS scores of patients with sleep disorder were significantly higher than those of patients with no sleep disorder diagnosis (p=0.002, p=0.001, p<0.001, and p<0.001, respectively).

Risk factors for sleep disorders in patients with MS were investigated by the logistic regression analysis. Gender, number of MS attacks, medication, FSS, anxiety and depression according to HADS, urinary dysfunction according to SCOPA-AUT test, and common body pains according to VAS were evaluated. Independent association was found between fatigue, depression, generalized body pain and sleep disorders (Table 2).

Discussion

In this study, half of the MS patients had sleep disorders. In patients with sleep disorders, the frequency of being under DMT, daytime sleepiness, anxiety, depression, fatigue, and common body pain were higher than in the patients without sleep disorders. In addition, fatigue, depression and common body pain were found to be independent variables for sleep disorders in MS.

Sleep disorders are higher in MS patients than in the healthy population. In several studies, it has been reported that 42-65% of patients with MS describe sleep disorders (17). In the review published by Čarnická et al. (18), it was stated that the

Table 2. The association between fatigue, depression, generalized body pain and sleep disorders

	OR (95% CI)	p value
Common body pain	1.79 (1.23-2.6)	0.002*
Fatigue	6.54 (1.08-39.57)	0.041*
Depression	9.82 (1.47-65.6)	0.018*

OR: Odds ratio, CI: Confidence interval
*p value <0.05.

Table 1. Demographic and disease-related characteristics of groups with and without sleep disorders

	No sleep disorder (n=28)	With sleep disorders (n=28)	p value
Age (year), mean (±SD)	37.3 (±2.97)	35.28 (±3.72)	0.53
Gender male n, (%)	11 (19.7)	6 (10.7)	0.14
Marital status (married) n, (%)	15 (26.8)	17 (30.3)	0.58
Education (15 year and above) n, (%)	11 (19.6)	8 (14.3)	0.44
Current working status n, (%)	17 (30.3)	16 (28.6)	0.78
Additional disease n, (%)	10 (55.5%)	8 (44.4%)	0.57
MS duration (year), mean (±SD)	8.2 (±6.6)	6.8 (±5.1)	0.5
MS attack number mean (±SD)	3.4 (±3.6)	4.9 (±5)	0.17
EDSS score mean (±SD)	2.1 (±1.7)	1.4 (±1.2)	0.34
DMT n, (%)	12 (37.5)	20 (62.5)	**0.03***
Prevalence of RLS n,(%)	0 (0)	2 (3.6)	0.5
ESS score mean (±SD)	2.3 (±2.7)	5.6 (±4.4)	**0.002***
HADS-A score mean (±SD)	5.5 (±3.7)	9.6 (±4.5)	**0.001***
HADS-D score mean (±SD)	4.3 (±3.5)	8.5 (±3.8)	**0.000***
FSS score mean (±SD)	3.3 (±1.8)	5.2 (±1.2)	**0.000***
SCOPA-AUT score mean (±SD)	5 (±5.9)	5.4 (±3.3)	0.12
VAS score mean (±SD)	2.7 (±2.6)	5.7 (±2.5)	**0.000***

SD: Standard deviation, MS: Multiple sclerosis, EDSS: Expanded Disability Status Scale, DMT: Disease modifying therapy RLS, Restless legs syndrome, ESS: Epworth Sleepiness Scale, HADS-A: Hospital Anxiety and Depression Scale Anxiety score, HADS-A: Hospital Anxiety and Depression Scale Depression score, FSS: Fatigue Severity Scale, SCOPA-AUT: Scales for Outcomes in Parkinson's disease-Autonomic, VAS: Visual analogue scale.
*p value <0.05.

prevalence of sleep disorders was between 25% and 54%. In a broad-based cross-sectional study conducted with 1,063 patients, 13.3% of MS patients had mild sleep problems, 21.5% had moderate sleep problems, and 30% had severe sleep problems (3). Similarly, in another study, 47.5% of 120 patients with definite MS were classified as patients with sleep problems, scoring 5 or more points from the PSQI (19). The most common sleep problems in MS patients can be listed as difficulty falling asleep, frequent and/or early awakenings, breathing-related sleep disorders such as insomnia, snoring and sleep apnea, and RLS (2,20). In our study, in accordance with the literature, sleep disorders were found in 50% of MS patients according to PSQI.

It is known that sleep disorders in MS patients are associated with disease severity, depression, and fatigue. Sleep problems are the most frequent variable affecting MS-related fatigue (21). There are other studies showing the relationship between fatigue and sleep disorders (22-24). While the prevalence of insomnia is much lower in MS without depression, those with insomnia are at a high risk for depression (25). Depression worsens sleep disorders and there is a strong relationship between the two (20,26). Similarly, patients with MS with high anxiety levels are more likely to have sleep disorders than those without anxiety (27,28). In addition, it has been shown that patients who describe sleep disorders have more daytime sleepiness and that the treatment of sleep disorders will improve fatigue and daytime sleepiness (29,30). The results of our study also showed that depression, anxiety, daytime sleepiness, and fatigue were more common in the group with sleep problems, in line with the previous studies.

It is thought that sleep disorders in MS can be affected by sociodemographic and disease characteristics such as disease severity, duration, gender, age, and occupation, and urinary dysfunction (3,19). Urinary dysfunction, especially nocturia, can cause sleep disturbance and indirectly MS-related fatigue (22). In our study, unlike previous studies, no significant relationship was found between age, gender, occupation, disease severity, disease duration, urinary dysfunction and sleep disorders.

The prevalence of RLS in MS patients is reported between 4.2% and 19% (31). In a study from Turkey, RLS in patients with MS was found to be 2.55 times more than in the healthy population, and there was a relationship with depression and fatigue (32). RLS in MS patients causes sleep disorders and increases fatigue (17,20). In our study, the frequency of RLS was 3.6%, and this rate is lower than in other studies. Again, unlike the literature, we could not find a significant relationship between sleep disturbance and RLS. The reason for this may be the low number of patients.

Sixty-six % of MS patients describe common body pain, and 25% of them indicate that their pain is severe. It has been found that body pain is associated with disease severity, depression, and sleep disturbance (33). Chronic pain increases insomnia and leads to the impairment of sleep quality (34,35). The results of our study also confirm this finding.

IFN-β therapy modulates proinflammatory cytokines, changes the sleep patterns and impairs sleep structure. Sleep quality disturbance may be observed, especially on days of IFN injection (36,37). In our study, the medications used by the patients were determined as IFN-β1a (40.6%), IFN-β1b (37.6%), glatiramer acetate (18.7%) and mitoxantrone (3.1%), and a significant relationship was found between the medications and sleep disorders.

This study has some limitations. Although the presence of sleep disorders in MS patients and related patients and disease characteristics were examined in detail, it was not compared with healthy individuals in terms of sleep disorders. The small number of our sample is another limitation.

Conclusion

In conclusion, sleep disorders are frequent in MS patients and are associated with fatigue, depression, daytime sleepiness, common body pain and immunomodulatory treatment. It may be possible to increase sleep quality and reduce other symptoms with appropriate treatment of sleep disorders. Therefore, sleep disorders should be questioned in clinical evaluations of MS patients. Prospective randomized controlled studies with larger samples are needed to determine the related factors affecting sleep disorders.

Ethics

Ethics Committee Approval: All procedures were performed in accordance with the Declaration of Helsinki, an approval was received from the Research Ethics Committee of Medical Faculty Ankara University (protocol number: 135-3915, date: 29.07.2008).

Informed Consent: Informed written consent was obtained from all participants or legal representatives.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Y.A.A., Design: Y.A.A., B.S.A.P., Data Collection or Processing: Y.A.A., Analysis or Interpretation: Y.A.A., B.S.A.P., Literature Search: B.S.A.P., Writing: YAA, B.S.A.P.

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The role of nutritional indexes in predicting coronary artery disease severity in acute coronary syndrome

Hatice Tolunay, Suat Görmel, Serkan Asil, Salim Yaşar, Erkan Yıldırım, Ayşe Saatçi Yaşar, Murat Çelik, Uygar Çağdaş Yüksel, Cem Barçın

University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Cardiology, Ankara, Turkey

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Corresponding Author:
Hatice Tolunay, M.D., University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Cardiology, Ankara, Turkey

ORCID:
orcid.org/0000-0002-9407-3395

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ABSTRACT

Aims: The purpose of this study is to evaluate the association between nutritional status and coronary artery disease (CAD) severity in patients with acute coronary syndrome (ACS).

Methods: Patients with ACS who underwent coronary angiography were evaluated retrospectively. SYNTAX scores were calculated for each patient to determine the severity of CAD. The patients were divided into three groups based on their SYNTAX scores as low SYNTAX score (≤22), intermediate SYNTAX score (23-32) and high SYNTAX score (≥33). The Prognostic Nutritional Index (PNI) score was calculated with the formula using serum albumin and total lymphocyte count. The "The Control Nutritional Status (CONUT)" score was calculated by using three parameters which are serum albumin, total cholesterol and total lymphocyte count. Data on cardiovascular mortality and rehospitalization within six months of diagnosis were obtained from records.

Results: The study included 177 patients with ACS. The mean age of patients was 63.34±10.94 years and 64.4% were male. Patients with high SYNTAX score had statistically significantly lower PNI score and higher CONUT score than patients with low and intermediate SYNTAX scores. There was a positive correlation between SYNTAX score and CONUT score (r=0.256, p=0.002), and a negative correlation between SYNTAX score and PNI score (r=-0.328, p<0.001). Within six months of ACS diagnosis, patients with cardiovascular mortality and rehospitalization had lower PNI scores and higher CONUT scores. According to multivariate logistic regression analysis, CONUT score was an independent predictor for high SYNTAX score (odds ratio=1.584; 95% confidence interval=1.014-2.473; p=0.043).

Conclusions: In our study, nutritional status assessed by PNI and CONUT scores was associated with the extent of coronary atherosclerosis in patients with ACS.

Introduction

Cardiovascular risk factors are becoming more common and the incidence of acute coronary syndrome (ACS) is increasing (1). Despite the advancement of percutaneous and surgical procedures, the mortality rate associated with ACS is still high (2,3). Determining high-risk patients and especially modifiable risk factors is important in terms of primary prevention.

Malnutrition affects many people around the world and it is increasingly recognized as a potentially modifiable risk factor for cardiovascular diseases. Malnutrition is associated with poor prognosis in a wide variety of diseases including cancer (4,5), renal disease requiring dialysis (6), end-stage liver disease (7) and heart failure (8-10). Malnutrition also influences adversely the prognosis of patients with ACS (11).

Prognostic Nutritional Index (PNI) is a score that reflects a person's nutritional status based on serum albumin and total lymphocyte count (4). It is an easy and effective method to calculate. A low score is associated with malnutrition. PNI has been associated with inflammatory processes in several studies. Recently, the prognostic value of PNI in various malignancies

has been demonstrated (4). PNI is independently associated with long-term survival in patients hospitalized for heart failure with reduced or preserved ejection fraction (8,10).

The Control Nutritional Status (CONUT) score is a score calculated by serum albumin level, total cholesterol level and total lymphocyte count (12). Albumin represents protein levels, total cholesterol represents lipid metabolism, and lymphocyte count represents immune function. A high score means that the nutritional status is poor (7). The studies on the CONUT score have described the relationship between mortality and prognosis after surgery in cancer patients (13).

The SYNTAX score is a useful angiographic scoring system for determining the severity of coronary artery disease (CAD). It represents the degree of atherosclerotic burden and complexity of coronary lesions (14). The relationship between cardiovascular risk factors such as diabetes mellitus and hypertension and the severity of atherosclerosis is known, but it remains unclear whether there is a relationship between nutritional status and CAD severity in ACS. Accordingly, in this study, we aimed to investigate the association between SYNTAX score and nutritional status assessed by PNI and CONUT scores, and to evaluate whether nutritional status influenced cardiovascular mortality and re-hospitalization within six months of diagnosis in patients with ACS.

Methods

Patients who underwent coronary angiography with the diagnosis of ACS at Gülhane Training and Research Hospital were evaluated retrospectively. Patients who had previously undergone percutaneous or surgical revascularization, patients with acute or chronic inflammatory disease, severe valvular heart disease, renal or hepatic insufficiency, malignancy, and patients with other major diseases that might affect serum albumin and total lymphocyte counts were excluded from the study. We also excluded patients taking statins or triglyceride (TG) lowering medication before the onset of ACS.

Laboratory Measurements

The recorded data of the patients were evaluated retrospectively and blood glucose, creatinine, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, TG, hemoglobin, white blood cell counts, and total lymphocyte counts were retrieved from the electronic database. All nutritional factors were measured on the day of hospitalization with the diagnosis of ACS.

Evaluation of Nutritional Indexes

The PNI scores showing the nutritional status of all patients were calculated and recorded with the formula: 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (mm^3) (4).

CONUT score was calculated as shown in Table 1 based on previous studies (7,12). The cut-off values were 3.5 g/dL for serum albumin, 180 mg/dL for total cholesterol and 1600/mm^3 for total peripheral lymphocyte count.

Coronary Angiography

Two interventional cardiologists without the knowledge of the data of the participants analyzed coronary angiograms and the SYNTAX scores of all patients were calculated with a series of questions through a computer program. The SYNTAX scoring system contains 12 basic questions. The first three questions cover the dominance, the total number of lesions, and the vessel segment where the lesions are located. The last nine questions are to identify adverse lesion characteristics. Scores for each lesion are calculated separately and the total SYNTAX score is obtained by summing all these scores. We divided patients into three groups based on their SYNTAX scores as low SYNTAX score (≤22), intermediate SYNTAX score (23-32) and high SYNTAX score (≥33) (14). Data on cardiovascular mortality and rehospitalization within six months of their diagnosis were obtained from hospital records and the database of the Ministry of Health.

Statistical Analysis

Data analysis was performed with Statistical Package for the Social Sciences (SPSS) for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). The distribution of continuous variables was determined using the Kolmogorov-Smirnov test. Continuous data were defined as mean±standard deviation for normal distributions and median (minimum-maximum value) for skewed distributions. Categorical data were defined as the number of cases (%). Variables showing normal distribution between two independent groups were compared using the Student's t-test. Variables showing normal distribution between more than two independent groups were analyzed with the one-way ANOVA, and data not normally distributed were analyzed with the Kruskal-Wallis test. When the obtained p value was statistically significant, LSD or Conover's non-parametric multiple comparison test was used to know which group was

Table 1. Assessment of the nutritional status using the CONUT score

Parameters	Normal	Light	Moderate	Severe
Serum albumin (g/dL)	≥3.5	3.0-3.49	2.5-2.99	<2.5
Score	0	2	4	6
Total cholesterol (mg/dL)	≥180	140-179	100-139	<100
Score	0	1	2	3
Lymphocytes (/mL^3)	≥1600	1200-1599	800-1199	<800
Score	0	1	2	3

CONUT: Controlling Nutritional Status

different from others. Correlation degrees between variables were evaluated using the Pearson's correlation or Spearman correlation analysis.

Univariate ordinal logistic regression was used for risk factors thought to be associated with the SYNTAX score category. Risk factors with a one-variable logistic regression p value of <0.25 were included in the multivariate logistic regression model. The significance of each independent variable on the model was analyzed using the Wald statistics. With Nagelkerke R^2, how much independent variable explained dependent variable was evaluated. A p value of <0.05 was considered significant in all statistical analyses.

Results

Of the 550 patients who underwent coronary angiography with the diagnosis of ACS, 177 patients who met the inclusion criteria were included in the study. The mean age of the patients was 63.34±10.94 years and 64.4% were male. The demographic characteristics, body mass index, laboratory findings, ejection fraction, PNI scores, CONUT scores and SYNTAX scores of the patients are shown in Table 2.

Table 2. Demographic, clinical and laboratory characteristics of the patients (n=177)

Variable		Overall
Age, years		63.34±10.94
Gender, male		114 (64.4)
BMI, kg/m^2		27.17±2.54
Smoking		114 (64.4)
Hypertension		122 (68.9)
Diabetes mellitus		95 (53.7)
Hemoglobin, g/dL		13.47±1.96
WBC count, x10^9/L		9.41±8.24
Platelet count, x10^9/L		228.33±61.43
Lymphocyte, x10^9/L		1.94±0.65
Serum creatinine, mg/dL		1.10±0.66
Albumin, g/dL		3.85±0.43
Cholesterol, mg/dL		198.51±49.58
HDL cholesterol, mg/dL		44.37±9.87
LDL cholesterol, mg/dL		121.06±38.78
Triglyceride, mg/dY		166.31±86.59
LVEF (%)		49.17±11.88
PNI score		49.13±5.66
CONUT score		1 (0-7)
SYNTAX score		19.71±10.32
SYNTAX score	Low (≤22)	61 (34.5)
	Intermediate (23-32)	62 (35.0)
	High (≥33)	54 (30.5)

BMI: Body mass index, WBC: White blood cell, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, LVEF: Left ventricular ejection fraction, PNI: Prognostic nutritional index, CONUT: Controlling Nutritional Status. Continuous variables are expressed as either mean±standard deviation or median (minimum-maximum). Categorical data are expressed as percentage.

The mean PNI scores of low, intermediate and high SYNTAX score groups were 51.05±4.99, 49.89±5.17, and 46.10±5.75, respectively. A statistically significant difference was found between low and high SYNTAX score groups, and intermediate and high SYNTAX score groups in terms of PNI score (p<0.001, for both) (Table 3). The median CONUT scores of low, intermediate and high SYNTAX score groups were 1 (0-6), 1 (0-7), and 2 (0-7), respectively. In terms of CONUT score, a statistically significant difference was found between low and high SYNTAX score groups, and intermediate and high SYNTAX score groups (p=0.001 for both) (Table 3).

There was a low level of positive and statistically significant (r=0.256, p=0.002) correlation between SYNTAX score and CONUT score, while there was a low level of negative and statistically significant (r=-0.328, p<0.001) correlation between SYNTAX score and PNI score.

The mean serum albumin levels of low, intermediate and high SYNTAX score groups were 4.06±0.35, 4.02±0.41, and 3.71±0.43, respectively. The difference was statistically significant between low and intermediate SYNTAX score groups, and intermediate and high SYNTAX score groups (p<0.001, for both). However, there was no significant difference in terms of total lymphocyte count in patients with low, intermediate and high SYNTAX score groups (2.07±0.70, 1.92±0.57, 1.83±0.64, p=0.146).

Within six months of ACS diagnosis, patients with cardiovascular mortality and re-hospitalization had lower PNI scores and higher CONUT scores. A statistically significant difference was found in PNI score and CONUT score in all paired group comparisons (p<0.001, for all) (Table 4).

Patients with low SYNTAX score were included as the reference category in the logistic regression analysis. Diabetes mellitus was independent predictor for intermediate [odds ratio (OR)=2.288; 95% confidence interval (CI)=1.110-4.713; p=0.025] and high SYNTAX scores (OR=4.329; 95% CI=1.734-10.803; p=0.002). LDL cholesterol (OR=1.015; 95% CI=1.002-1.028; p=0.021) and CONUT score (OR=1.584; 95% CI=1.014-2.473; p=0.043) were independent predictors for high SYNTAX score (Table 5).

Table 3. PNI and CONUT scores in low, intermediate and high SYNTAX groups

	SYNTAX score			p
	Low ≤22	Intermediate 23-32	High ≥33	
PNI score*	51.05±4.99	49.89±5.17	46.10±5.75	<0.001[a, b]
CONUT score[β]	1 (0-6)	1 (0-7)	2 (0-7)	0.001[a, b]

Continuous variables are expressed as either *mean±standard deviation or βmedian (minimum-maximum). Continuous variables were compared with *One-Way ANOVA test or [β]Kruskal-Wallis test and the p value was set at 0.05. Significant differences were found between; [a]: Low vs. High, [b]: Intermediate vs. High.
CONUT: Controlling Nutritional Status, PNI: Prognostic Nutritional Index

Discussion

In our study, PNI and CONUT scores were significantly associated with SYNTAX score and CONUT score was an independent predictor for high SYNTAX score in patients with ACS. Besides, PNI and CONUT scores were associated with cardiovascular mortality and rehospitalization within six months of ACS diagnosis.

There are different nutritional scores to define malnutrition. The PNI and CONUT scores both involve the measurement of serum albumin level and total lymphocyte count. Unlike the PNI score, the CONUT score also takes into account serum cholesterol. The main protein in the blood is albumin and it is the determinant of oncotic pressure (15). Albumin is an acute phase reactant that can be reduced by decreased synthesis or increased loss in inflammation, liver diseases, renal failure and some gastrointestinal tract diseases. Low serum albumin level has been reported to be associated with poor prognosis in patients with heart failure (16). In our study, serum albumin levels were lower in patients with high SYNTAX scores than low and intermediate SYNTAX scores. Kurtul et al. (17) examined the association between serum albumin level and severity of CAD as measured by SYNTAX score in patients with ACS. They found that serum albumin level was inversely associated with high SYNTAX score and in-hospital mortality in ACS. High serum albumin level can be considered as a protective shield in acute events.

Table 4. PNI and CONUT scores in patients with re-hospitalization and cardiac death within six months

	Stable	Re-hospitalization	Death	p
PNI score*	50.57±4.63	44.84±4.05	38.90±5.27	<0.001[a, b, c]
CONUT score[β]	1 (0-6)	2 (0-6)	5 (2-7)	<0.001[a, b, c]

Continuous variables are expressed as either *mean±standard deviation or [β]median (minimum-maximum). Continuous variables were compared with *One-Way ANOVA test or [β]Kruskal-Wallis test and the p value was set at 0.05. Significant differences were found between; [a]: Stable vs. Re-hospitalization, [b]: Stable vs. Death, [c]: Re-hospitalization vs. Death.
CONUT: Controlling Nutritional Status, Prognostic Nutritional Index

Table 5. Predictors of intermediate and high SYNTAX scores with logistic regression analysis

	Univariate analysis				Multivariate analysis			
	Wald	OR	95% CI	p	Wald	OR	95% CI	p
Intermediate SYNTAX score								
BMI	0.672	1.056	0.927-1.202	0.412				
HT	0.004	1.024	0.482-2.178	0.950				
DM	5.034	2.288	1.110-4.713	**0.025**	5.034	2.288	1.110-4.713	**0.025**
Smoking	1.019	1.468	0.697-3.093	0.313				
Cholesterol	0.001	1.000	0.992-1.008	0.971				
LDL-C	0.221	1.002	0.993-1.012	0.639				
HDL-C	0.609	0.985	0.949-1.023	0.435				
TG	0.127	1.001	0.997-1.005	0.722				
PNI score	1.578	0.955	0.890-1.026	0.209				
CONUT score	0.593	0.892	0.852-1.443	0.441				
High SYNTAX score								
BMI	0.334	1.044	0.9021.210	0.563				
HT	0.339	1.268	0.570-2.823	0.560				
DM	10.523	3.596	1.660-7.792	**0.001**	9.860	4.329	1.734-10.803	**0.002**
Smoking	0.065	1.103	0.519-2.344	0.799				
Cholesterol	0.796	1.003	0.996-1.011	0.372				
LDL-C	2.709	1.008	0.998-1.018	**0.100**	5.340	1.015	1.002-1.028	**0.021**
HDL-C	0.052	0.996	0.961-1.032	0.819				
TG	0.529	0.998	0.994-1.003	0.467				
PNI score	17.093	0.839	0.772-0.912	**<0.001**	3.116	0.902	0.804-1.011	0.078
CONUT score	12.598	1.685	1.263-2.248	**<0.001**	4.092	1.584	1.014-2.473	**0.043**

CI: Confidence interval, BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol, OR: Odds ratio, TG: Triglyceride, CONUT: Controlling Nutritional Status, PNI: Prognostic Nutritional Index. Reference category: Low; *OR is statistically significant (CI does not include 1); Variables with p value <0.25 in univariant analysis were evaluated by multivariant analysis; p value <0.05 as significant level

The lymphocyte count decreases as a stress response in patients with ACS (18) and lymphopenia has been reported to be an early marker of myocardial infarction (19). While the lymphocyte count decreases, the peripheral neutrophil count increases in acute myocardial infarction and neutrophil/lymphocyte ratio predicts long term mortality in these patients (20). Further, Arbel et al. (21) demonstrated the correlation between neutrophil/lymphocyte ratio and severity of CAD in a cohort undergoing coronary angiography. In our study, no difference was found in total lymphocyte count between SYNTAX groups. In the review of the literature, we did not find any study clarifying whether there was a direct relationship between total lymphocyte count and CAD severity.

It has been demonstrated that malnutrition contributes to poor prognosis after acute coronary events. Yoo et al. (22) showed an association between undernutrition and poor clinical outcomes during hospitalization in patients with acute myocardial infarction. Recently, Raposeiras Roubín et al. (11) investigated the prevalence and prognostic effects of malnutrition in patients with ACS by using three different indexes; PNI score, Nutritional Risk Index and CONUT score. They found that malnutrition was prevalent in patients with ACS and was associated with all-cause mortality and major cardiovascular events including cardiovascular death, reinfarction or ischemic stroke. Their explanation for the poor prognosis of malnutrition in patients with ACS is that nutritional condition may be a proxy indicator of inflammation and a trigger for progression of atherosclerosis and plaque rupture. As inflammation and malnutrition occur concomitantly and these two conditions are closely associated with atherosclerosis, they have been recently referred together as “malnutrition-inflammation-atherosclerosis syndrome” (23).

The predictive value of PNI score for long term cardiovascular outcomes has also been reported in stable CAD patients (24). Chen et al. (25) investigated the predictive value of CONUT score in CAD patients undergoing percutaneous coronary intervention including stable and ACS patients. They found that an increased CONUT score was associated with adverse events after percutaneous coronary intervention. In the present study, CONUT score was an independent predictor for high SYNTAX score in patients with ACS. The combination of three parameters in the CONUT score may more accurately reflect immune and nutritional conditions. However, there is no consensus on which nutritional index should be used for patients with ACS. Regardless of which index is used, early recognition and treatment of malnutrition may provide improvement in many cardiovascular diseases. These nutritional indexes can help physicians to predict the extent and complexity of CAD.

Our study has some limitations. The study has a cross-sectional and retrospective design, so we do not have data showing the long term prognostic value of PNI and CONUT score rather than six-month data. With prospective studies including larger patient populations, the relationship between CAD and PNI, CONUT score, and long term prognostic clinical significance can be clarified.

Conclusion

In the present study, PNI and CONUT scores associate with the severity of CAD assessed by SYNTAX score in ACS. Adequate assessment of the nutritional status is important for identifying patients at high risk for CAD and selecting patients who can benefit from nutritional support and risk modification strategies. Our data should be supported by large-scale multi-center studies, including patients with stable angina pectoris.

Ethics

Ethics Committee Approval: The study was approved by the Ankara City Hospital Ethics Committee (date: 12/16/2020, decision no: E2-20-90).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.T., S.G., A.S.Y., Design: H.T., M.Ç., C.B., Data Collection or Processing: H.T., S.G., S.A., S.Y., Analysis or Interpretation: H.T., M.Ç., C.B., Literature Search: H.T., S.G., S.A., S.Y., U.Ç.Y., Writing: H.T., E.Y., M.Ç., A.S.Y.

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Acute pancreatitis as the initial presentation in systemic lupus erythematosus

Samarth Virmani, Shubha Seshadri, Sharath Madhyastha P., Akhya Sharma, Charan Thej Reddy

Manipal Academy of Higher Education, Kasturba Medical College, Clinic of Medicine, Manipal, India

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Corresponding Author:
Sharath Madhyastha P. Assoc. Prof., M.D, Manipal Academy of Higher Education, Kasturba Medical College, Clinic of Medicine, Manipal, India

ORCID:
orcid.org/0000-0003-2821-3473

Keywords: Acute pancreatitis, systemic lupus erythematosus, steroids

ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disorder involving multiple organ systems with varying manifestations. Acute pancreatitis as an initial presenting feature of SLE is extremely rare. A 21-year-old female patient presented with fever and severe abdominal pain for the past 20 days. Her history was unremarkable except for an abortion two months ago. She was diagnosed with both acute pancreatitis and SLE following a thorough evaluation.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects almost every organ of the body. Gastrointestinal tract involvement is seen in almost 50% of the cases. Acute pancreatitis as a complication of SLE is rare and mostly a flare-up in patients already having a preceding diagnosis of SLE. The frequency of SLE-associated pancreatitis is estimated between 0.2 and 8.2%. Such patients are known to have a higher disease activity index score as well as increased mortality. Here, we present a young patient who presented with acute pancreatitis and was diagnosed with SLE during her evaluation.

Case Presentation

A 21-year-old woman free of any comorbidities was admitted to the emergency room with abdominal pain and fever in the past 20 days. The pain was severe, non-radiating, and not associated with any aggravating or relieving factors. The grade of fever was low, which also showed an intermittent pattern. She also complained of vomiting following food intake in the last two weeks, which was non-bilious and non-bloody but contained food particles. She did not report regular alcohol intake and reported an abortion two months before her current complaints.

On physical examination, the patient looked distressed. Arterial blood pressure was 90/60 mmHg, pulse was 110 beats/minute, and oxygen saturation was 99% in the room. She was afebrile. There was severe tenderness in the epigastric area, with no palpable organomegaly. Bowel sounds were normal.

Routine blood tests revealed pancytopenia (hemoglobin: 10.9 g/dL, leucocyte count: 2260/mm^3, and platelet count: 71,000/mm^3). Liver function tests showed hypoalbuminemia (serum albumin: 2.96 g/dL) with normal liver enzymes and bilirubin levels. Serum amylase and lipase levels were elevated (1270 U/L and 2732 U/L, respectively). Abdominal computed tomography (CT) revealed acute interstitial edematous pancreatitis with moderate ascites and bilateral mild pleural

effusion (Figure 1). Serum triglyceride and calcium levels were normal. Microlithiasis and pancreatic divisum were excluded by endoscopic ultrasonography. Due to the history of abortion, an autoimmune disease panel was studied, which showed anti-neutrophil antibody was strongly positive with anti-dsDNA titer >800 IU/mL.

Serum creatinine and glomerular filtration rate were normal (0.8 mg/dL and 90 mL/min, respectively). Dipstick urine examination revealed 3+ proteinuria with no casts or crystals on microscopy. 24-hour urine protein level was 390 mg/24 hours.

The patient underwent kidney biopsy, which revealed diffuse global proliferative glomerulonephritis ISN class 4 A with thrombotic microangiopathy (activity score of 10/24 and chronicity score of 0/12). Serum C3 and C4 (10 U/mL and 3 U/mL, respectively) were also decreased.

The patient was started treatment with acute pancreatitis (AP) protocol. Following the diagnosis of SLE-induced pancreatitis, intravenous (IV) steroid treatment was added (dexamethasone 4 mg Q8H). Once her condition improved, she was switched to oral prednisolone (1 mg/kg body weight) and mycophenolate mofetil (1 g twice daily) due to lupus nephritis. The patient's condition gradually improved after the initiation of steroid therapy in around five days, and serum amylase and lipase also started to decrease. The patient is currently on regular follow-up without symptoms.

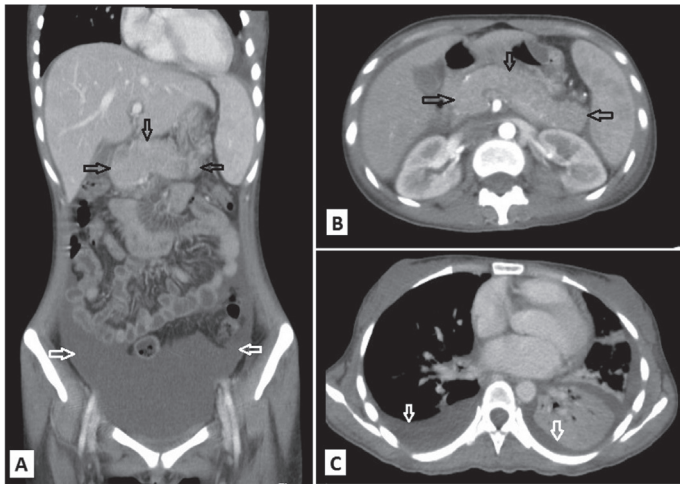

Figure 1. Computed tomography of abdomen (A: coronal, B, C: axial views): Pancreas appears bulky in size (A, B: black arrows) with minimal peripancreatic fluid collection. Mild to moderate ascites (A: white arrows) and bilateral mild pleural effusion (C: white arrows)

Discussion

SLE is a chronic autoimmune condition that can potentially affect various organ systems. The incidence of gastrointestinal (GI) manifestations is commonly underestimated due to the lack of significant abdominal symptoms in most patients (1). GI involvement and symptoms are seen in about 19.2-50% of patients with SLE (2,3).

Lupus-associated acute pancreatitis is one of the GI manifestations in SLE. SLE-associated acute pancreatitis has been associated with very high SLE Disease Activity Index Scores and extremely high mortality rates of approximately 10.3-68.4% (4,5).

The pathogenesis of SLE-associated pancreatitis is complex. Vascular damage (which includes vasculitis, intimal thickening, immune complex microunits, as well as occlusion of arteries and arterioles), excess production of autoantibodies, and abnormal cellular immune response are among the hypothesized factors (2). The major risk factors associated with SLE-associated pancreatitis are hypertriglyceridemia, psychosis, recent viral infection like cytomegalovirus, and drug toxicity (6,7). As mentioned above, our patient had no such significant risk factors for AP.

Patients with SLE-associated pancreatitis can have a wide range of presenting symptoms from asymptomatic (an elevation of pancreatic enzymes being the only abnormality) to acute (severe and/or fulminant) or chronic (self-limiting) features (8). Abdominal pain is the most common documented symptom, seen in about 90% of patients, along with nausea and vomiting in 75% and fever in 50% of the patients (1,4,7).

The diagnosis of acute pancreatitis is solely dependent on the presenting symptoms, physical examination, and basic diagnostic workup (e.g., pancreatic enzymes), supported by appropriate imaging. Elevation of serum amylase and lipase levels is the most common laboratory abnormality in lupus pancreatitis, although normal levels are not uncommon (1,7). In addition, other significant biochemical abnormalities noted were hypoalbuminemia (78%), liver function test abnormalities (65%), and elevated serum creatinine (44%) (1,4). Leukocytosis is relatively uncommon, occurring in only about 15% of the patients, whereas anemia, leukopenia, and thrombocytopenia have been seen in 81%, 59%, and 48% of cases in the literature, respectively (4). Our patient had elevated serum amylase and lipase levels with hypoalbuminemia, anemia, leucopenia, thrombocytopenia, and proteinuria.

Multiple factors are associated with increased mortality risk in patients with lupus-associated pancreatitis. Acute renal failure and thrombocytopenia may complicate a severe disease activity (4,7,9). The concern regarding steroid treatment is minimal for treatment of SLE in acute pancreatitis patients despite the chance of a toxic effect due to steroids. Previous studies have suggested steroid administration during an acute event of SLE pancreatitis (4,5,10). Our patient received IV steroids during hospitalization, followed by oral steroids at discharge, and was later started on mycophenolate mofetil to manage lupus nephritis.

Conclusion

Although rare, SLE-associated pancreatitis should be suspected in a patient with acute abdominal pain after excluding the common causative factors. Identification of SLE-associated symptoms may be helpful during evaluation. Lupus-induced acute pancreatitis can gain benefit from routine treatment of SLE.

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Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.S., Concept: S.S., S.M.P., Design: S.M.P., Data Collection or Processing: C.T.R., Analysis or Interpretation: S.M.P., C.T.R., Literature Search: S.V., A.S., Writing: S.V., A.S.

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Endoscopic follow-up of rectum thermal damage concurred with the blast effect of gunshot injury

Necattin Fırat[1], Ali Kağan Coşkun[2], Güvenç Cantilav[3], Ahmet Tarık Harmantepe[1]

[1]Sakarya University Faculty of Medicine, Department of General Surgery, Sakarya, Turkey
[2]University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of General Surgery, Ankara, Turkey
[3]Antalya Elmali State Hospital, Clinic of General Surgery, Antalya, Turkey

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Corresponding Author:
Necattin Fırat, M.D., Sakarya University Faculty of Medicine, Department of General Surgery, Sakarya, Turkey

ORCID:
orcid.org/0000-0003-0684-8187

Keywords: Rectum injury, gunshot injury, blast effect

ABSTRACT

Gunshot injuries can cause damage to the tissues due to mechanical or blast effects from bullets. In this type of injury in the pelvic area, a careful rectal examination is mandatory, and the patient may require a protective stoma in the presence of rectal injury. Rectal damage can be detected using laparoscopic and endoscopic techniques, resulting in lower morbidity and mortality. We here report a patient having rectum injury due to blast effect which resolved spontaneously without surgical intervention.

Introduction

Handguns or pistols are categorized as low-velocity firearms. Guns with muzzle velocities greater than 1000 m/sec are called high-velocity firearms (1). High-velocity missiles can cause a temporary cavity. There is a significant risk of vascular capillary and injury, as well as local tissue loss. The so-called contusion and concussion zones of such a projectile may be as large as 2 cm and 7 cm, respectively (2).

The greatest experience with the clinical process of traumatic rectum injuries has been derived from war-associated injuries. This type of injury usually progresses with high mortality, as it occurs with a gunshot and is accompanied by extensive tissue loss extending to complete rupture of the rectum (3). If the patient's condition is stable following abdominal injury, laparoscopy is an effective approach that can be used for both diagnostic purposes and treatment (4). However, when the injury is in the pelvic region, rectoscopy should also be added to laparoscopy in order to evaluate the retroperitoneal part of the rectum. If extraperitoneal rectal injury is observed, colonic diversion is the most appropriate approach for treatment (5). However, in the literature, there are some cases that have been successfully treated without extracolonic diversion in the extraperitoneal rectum injuries (6). The possibility of full-thickness rectum injury should not be ignored in the gunshot injuries of the pelvic region. Moreover, the possibility of perforation may also occur subsequently in the rectum due to the blast effect, which should be followed up at certain intervals with rectosigmoidoscopy.

Case Presentation

A 20-year-old male soldier (body weight: 65 kg, height: 170 cm) was admitted to the Viranşehir State Hospital due to gun injury. His medical history was unremarkable for any chronic illness. Vital signs were stable (arterial blood pressure: 110/70 mmHg, pulse: 65/min). His physical examination revealed extensive tenderness and distension in the abdomen. Bullet inlet hole was in the posterior femoral head on the right and the bullet exit hole was in the posterior femoral head on the left. Urinary catheter could not be placed. Rectal examination showed gross blood. Laboratory tests showed leukocytosis hemogram [hemoglobin (Hb): 14.8 g/dL, white blood cell (WBC): 23.3 K/UL, platelet (PLT): 187 K/UL] and normal blood chemistry. Abdominal tomography revealed fracture in the pelvic bone and leakage of contrast media into pelvis. There was no disruption in the integrity of the rectum (Figure 1, 2).

The patient underwent diagnostic laparoscopy to explore urethral, rectal, and intra-abdominal injury. It was observed that the bladder was filled with urine and a cystostomy catheter was inserted into the bladder to purge urine. Except for the retroperitoneal hematoma, no pathology was observed in the pelvic region in the abdomen. Rectal examination was performed using rectoscopy which revealed a hyperemic eroded area with 2 cm in diameter due to the blast effect of the bullet. The lesion surrounded the lumen in 90 degrees 12 cm proximal to the anal canal.

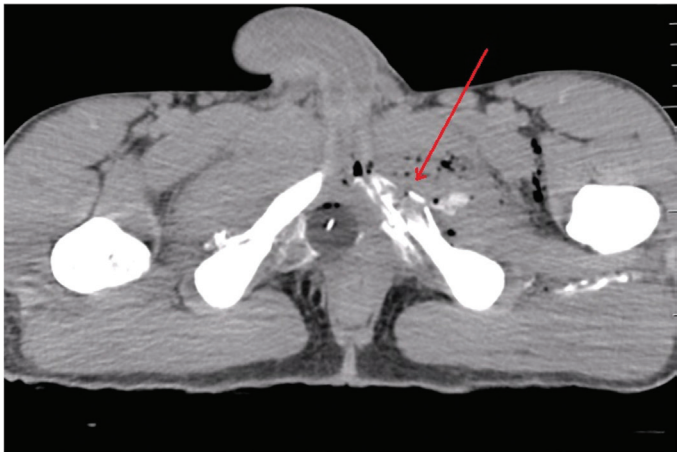

Figure 1. Fracture in the pelvic bone in abdominal computed tomography scanning

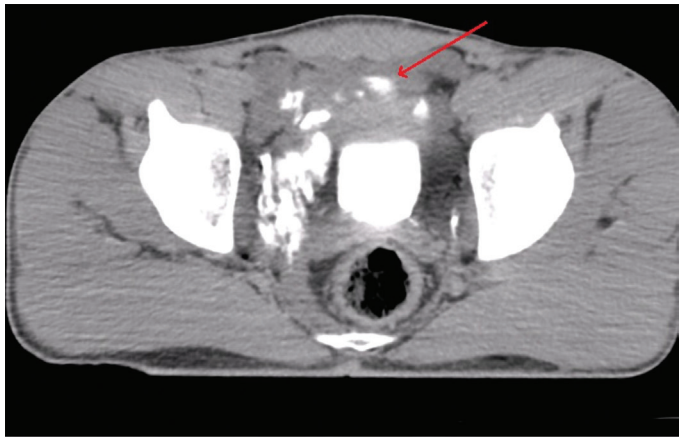

Figure 2. Leakage of contrast into pelvis in abdominal computed tomography scanning

The patient received antibiotic treatment with intravenous ceftriaxone and metronidazole. Vitals signs remained stable during follow-up, and blood tests at three-day follow-up was as follows: WBC: 11.1 K/UL, Hb: 12.2 g/dL, PLT: 148 K/UL, and C-reactive protein: 11.54 g/dL.

Control endoscopy was performed on postop 2. and 3. days (Figure 3, 4). The lesion gradually shrank, and the patient was discharged with a cystostomy catheter.

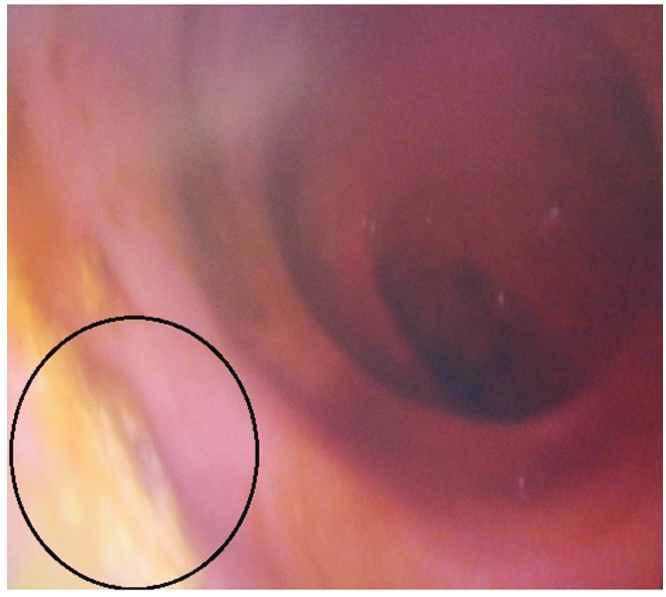

Figure 3. Rectum lesion, on postop 2nd day

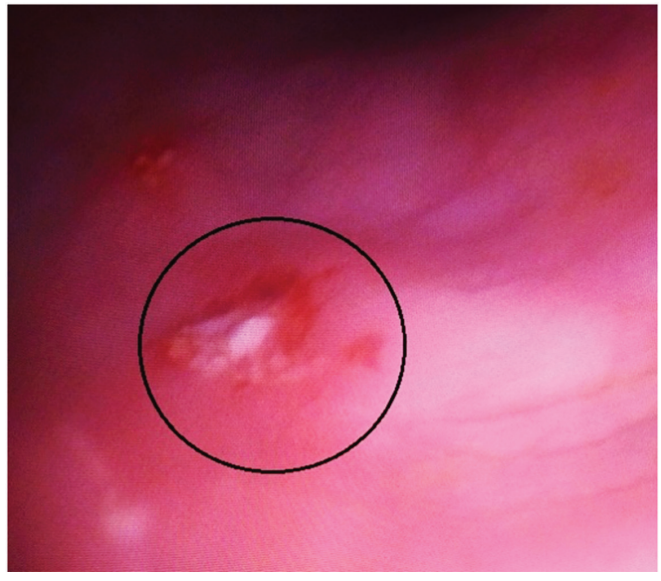

Figure 4. Rectum lesion, on postop 3rd day

Discussion

In gunshot injuries, morbidity and mortality vary according to the characteristics of the tissues. The bullet's mass and speed and the type of gun used are all involved in disrupting the tissue structures (7). With the blast effect in fire-arm injuries, the bullet causes damage to the region it enters and the surrounding tissues (8). If the patient has acute abdominal signs, the patient should be evaluated surgically. In studies conducted due to blunt abdominal trauma, laparoscopy reduces the number and complications of unnecessary laparotomies, provides faster recovery, and improves prognosis in surgical trauma patients (9). Gorgulu et al. (10) reported that the presence of colonic injury and the number of organs damaged (more than three) were the significant predictors of morbidity in penetrating abdominal gunshot wounds caused by high-velocity missiles and military rifle bullets. In our case, diagnostic laparoscopy was performed to determine whether the patient had an abdominal injury and whether the bullet caused damage to the intra-abdominal organs directly or blast effect. Anorectum and perineum injuries progress rapidly with high morbidity and mortality, especially in extraordinary conditions such as war and terrorism, due to possible additional injuries due to adjacent structures such as bladder, urinary tract, pelvis, and large vessel damage (11). Urethral injury should be suspected if a urinary catheter cannot be placed (11). The degree of soft tissue injury and contamination should be assessed in the first step in blunt or penetrating trauma events. Associated pelvic and perineal injuries should also be identified. Evaluation of sphincter integrity and mucosal/anodermal laceration is essential in the evaluation of these patients. Proctosigmoidoscopy should be performed to rule out associated rectal injury (12). Our patient underwent laparoscopy to assess whether the injury was associated with the abdomen, and glob vesicle was identified, and a cystostomy was performed. In addition, the erosional area detected 12 cm proximal to the rectum due to the blast effect was followed without diversion operation. Traumatic urethral injury is rare and can cause significant and long-term morbidity such as resistant urinary tract stenosis, incontinence, impotence, and infertility (13). If anastomotic urethroplasty cannot be performed due to the defect in the urethra under emergency conditions, a delayed repair can be performed in the urethra with a graft or flap at least three months after injury (14).

Conclusion

Even if the patient's condition is stable following a gun injury in the pelvis area, laparoscopy may be required to evaluate the potential injury to the intra-abdominal organs, and sigmoidoscopy may be required to evaluate the rectum. As in our case, rectum injury may occur due to blast effect but may recover without the need for a diversion surgery.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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Authorship Contributions

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A case of indirect carotid cavernous fistula presenting with proptosis and pulsatile exophthalmos

Gökhan Yüce[1], Adem Doğan[2]

[1]*University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Radiology, Ankara, Turkey*

[2]*University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Neurosurgery, Ankara, Turkey*

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Corresponding Author:
Gökhan Yüce, M.D., University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Radiology, Ankara, Turkey

ORCID:
orcid.org/0000-0003-3546-7965

Keywords: Flow diverter stent, carotid cavernous fistula, CCF superior ophthalmic vein

ABSTRACT

Carotid cavernous fistulas (CCF) are abnormal arteriovenous anastomoses between the internal carotid artery (ICA) and the cavernous sinus (CS). There are two broad categories of CCFs with different clinical presentations in direct and indirect form. Internal carotid artery and the CS in the "direct" or "high flow" CCF, and branches of the internal and external carotid artery in "indirect" or "low flow" CCF are found abnormally connected. In the present case, a CCF draining into the ophthalmic vein was detected between the ICA and the CSs. An endovascular flow diverter stent was inserted, and the fistula line was closed. The complaints of the patient immediately disappeared. In CCFs, the flowing stent can completely close the fistula line in a selected patient and appropriate localization.

Introduction

Carotid cavernous fistulas (CCF) are abnormal arteriovenous anastomoses between the internal carotid artery (ICA) and the cavernous sinus (CS). CCFs can be classified as spontaneous or traumatic according to the etiology and direct or indirect (dural) according to the anatomical features (1). In a direct CCF, arterial blood flows to the CS through the shunt in the intracavernous part of the ICA, causing high blood flow and high pressure. On the other hand, indirect (dural) CCFs result from the connection of the meningeal branches of the ICA with the CS, causing low blood flow and low pressure (1,2). Intracranial dural arteriovenous fistulas account for 10 to 15% of all intracranial arteriovenous malformations (3). Proptosis, ophthalmoplegia, headache, eyeball, sclera, and redness of conjunctiva may be observed. Depending on whether the indirect fistulas are drained anteriorly or posteriorly, different clinical manifestations may occur. In the treatment of cavernous carotid sinuses, endovascular flow converting stents may improve the clinical findings when used in a selected patient and appropriate anatomical location.

Case Presentation

A 58-year-old female patient presented to the ophthalmology clinic with a complaint of redness in her left eye for one month. Due to her prolonged complaints and neurological examinations, CCF was suspected. Digital substraction angiography revealed a low-flow indirect (type B) CCF associated with the CSs at the level of petrous and cavernous segments of the internal cerebral artery (segments C2-C3). No additional treatment was considered. The patient was re-admitted because of proptosis three months later. An urgent angiography showed increased

blood flow to the fistula, and an aggravated filling pattern in the left superior ophthalmic vein (SOV) showed (Figure 1). Neurological examination revealed pulsatile exophthalmos, proptosis, and conjunctival hyperemia. There was no systemic disease or trauma in the history of the patient. A flow diverter stent was placed to cover the localization of the branches feeding the fistula from the ICA. The stent was correctly opened. By the 3rd month, control angiography showed the fistula line was closed entirely (Figure 2), and exophthalmos and proptosis complaints resolved completely.

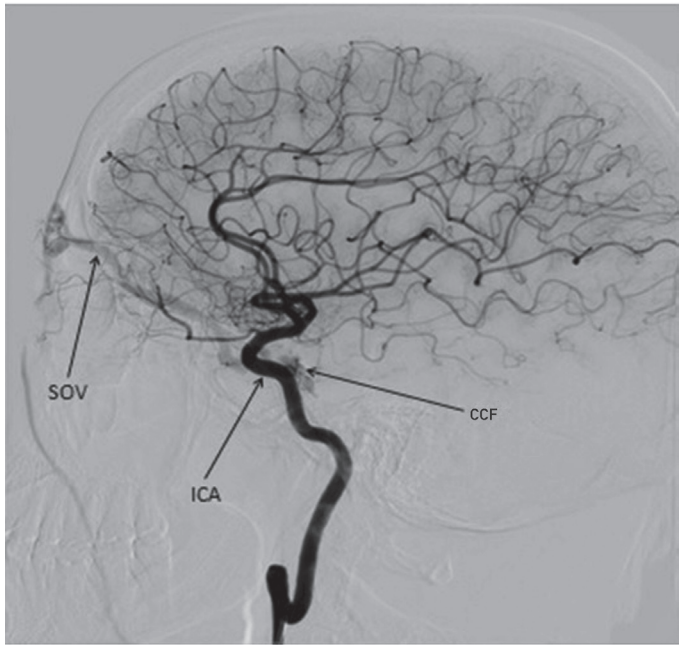

Figure 1. Preoperative angiographic image
SOV: Superior ophthalmic vein, ICA: Internal carotid artery, CCF: Carotid cavernous fistula

Discussion

CCF is the result of an abnormal connection between ICA and CS. CCFs can be classified according to etiology (spontaneous or traumatic), flow velocity (low or high flow velocity), or angiographic structure (direct or indirect) (1,2,4). Barrow et al. (1) are divided CCFs into four groups based on pathogenesis and arterial supply. In type A, also referred to as direct CCF, arterial blood passes through the shunt in the intracavernous part of the ICA to the CS, where high blood flow and high pressure are formed. Connections occur between the CS and dural branches of ICA in type B fistulas, CS and dural branches of the external carotid artery (ECA) in type C fistulas, CS and dural branches of both ICA and ECA in type D fistulas. Type B, C, D fistulas are indirect (dural) CCFs, and these fistulas are characterized by low flow and low pressure (1,2,4,5).

The classic presentation of direct, high-flow CCFs is the sudden onset of symptoms due to the direct passage of high-pressure arterial blood into the CS and ophthalmic vein and

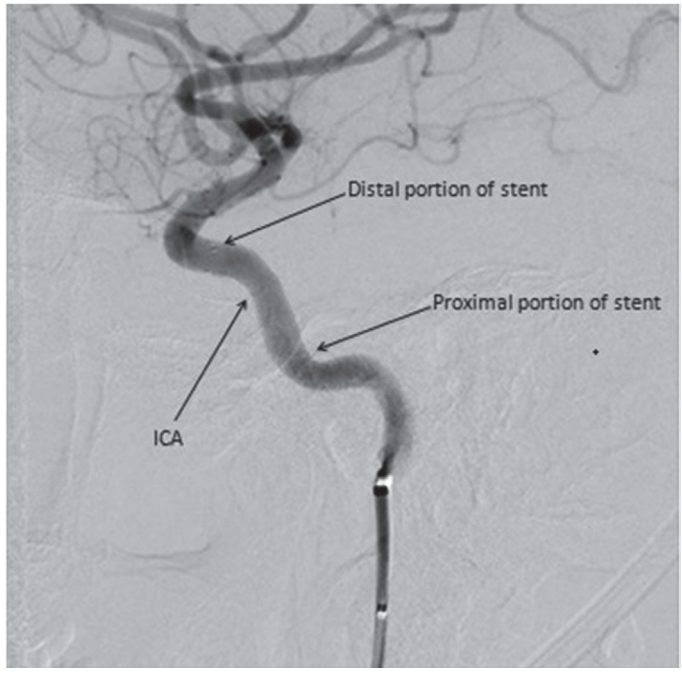

Figure 2. Postoperative third month (after flow diverter stent) angiographic image
ICA: Internal carotid artery

venous hypertension (2,4). Clinical findings in indirect CCFs are similar to the direct fistulas when drained from the anterior to superior and inferior ophthalmic veins, but the results are milder in indirect CCFs because of slow blood flow. Miller described the clinical manifestations of indirect CCFs based on whether the indirect fistulas drain into the anterior (superior and inferior ophthalmic veins) or posterior (superior and inferior petrosal sinuses) (6). Proptosis, congestion, and orbital murmur are not seen in the posteriorly drained fistulas. Therefore, they are defined as white-eyed shunts (7). The oculomotor nerve is most commonly affected (4,5,8-10). Most ocular congestion findings are absent, and unilateral orbital pain may occur. In our patient, we observed drainage into the SOV.

The clinical manifestations are milder in indirect CCFs (2,4,5). Conjunctival redness is the most prominent feature and can be misdiagnosed as conjunctivitis, episcleritis, or thyroid disease. Other findings include chemosis, proptosis, diplopia and ophthalmoparesis, retroorbital pain, increased intraocular pressure, and decreased visual acuity (2,5). Indirect CCFs often develop spontaneously, and spontaneous CCFs usually occur in the elderly and women. It may occur secondary to ruptured cavernous ICA aneurysms.

CCFs occur due to arterial wall defects after minor stress such as valsalva and cough in patients with a collagen vascular disease such as fibromuscular dysplasia and Ehler-Danlos syndrome. Arterial hypertension, atherosclerotic vascular disease, pregnancy, minor trauma, strains, and diabetes are among the predisposing causes (2,4).

CT angiography, magnetic resonance angiography, orbital ultrasonography, transorbital, and transcranial color Doppler imaging may be helpful in diagnosis. The gold standard diagnostic test is a selective angiography of bilateral ICAs and ECAs in all types of CCF. Treatment decision in CCF is dependent primarily on drainage pattern and symptoms (2,4,5). It is necessary to determine the exact location of the fistula in both types of CCFs and to identify the vessels and drainage pattern feeding the fistula before treatment. The most effective treatment is the obliteration of arterial-venous fistula connection through endovascular intervention and surgery. Another potential treatment option is stereotactic radiotherapy.

Conclusion

The patient was admitted with complaints of exophthalmos and proptosis, and angiography was performed to evaluate the risk of an aneurysm or other vascular pathology. An indirect CCF was identified, and a flow diverter stent was placed to close the fistula line.

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Ethics

Informed Consent: Written, informed consent was obtained from the patient for this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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Understanding the anxiety and the needs of families helps to prevent medicolegal issues

Kazım Emre Karaşahin

University of Health Sciences Turkey, Gülhane Faculty of Medicine, Department of Obstetrics and Gynecology, Ankara, Turkey

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Corresponding Author:
Kazım Emre Karaşahin, M.D., Prof., University of Health Sciences Turkey, Gülhane Faculty of Medicine, Department of Obstetrics and Gynecology, Ankara, Turkey

ORCID:
orcid.org/0000-0002-4624-4874

Keywords: Violence, health care worker, doctor-patient relationship, workplace violence

Dear Editor,

It has been my pleasure to read the original article “Determination of the anxiety and the needs of family members of critical care patients in emergency departments” by Demirtas et al. (1) in a recent issue of Gülhane Medical Journal. In this article, the authors have addressed some important points that should be considered in the communication between the patient, carers, and healthcare staff. This argument would be valid in emergency facilities and other clinical settings, particularly in large and crowded health care facilities. In this context, a few more comments could support the findings presented in the article.

Demirtas et al. (1) mentioned that active listening skills during communication with patients and families, verbal and nonverbal, should be practiced by the healthcare staff. They also mentioned that this would improve the efficiency of healthcare provision and prevent some potential conflicts and medicolegal issues in the hospital setting.

Some preventable “professional, patient-related, organizational, and societal factors” have long been known to trigger episodes of violence. Many of them may be related-but not limited- to overloading of admissions, patient complexity, poor communication skills, reciprocal rudeness, stress, anxiety, language and cultural barriers (2).

While emergency departments, as well as most other settings, are “loud and crowded that cause anxiety to the patient and carers” (1), the role of environmental factors in the reduction of anxiety and violence has not been sufficiently evidenced so far (3). Thus, good communication seems crucial to prevent distress that leads to conflicts and potential medicolegal issues.

The authors’ finding that communication was critically important, as mentioned by family members before physical comfort (1), is also supported by a previous article published by Kumari et al. (2), indicating improved communication combined with administrative support can help prevent most cases of violence. Law in Turkey and other countries discourages violence against medical staff. Moreover, any conflict between the two parts is just a waste of time and sources and has painful consequences that neither party desires. Therefore, preventing such conflicts should be the primary aim in all instances.

Finally, as an excellent clinical opinion, confirmed by more than 28 years of clinical experience, my suggestion is that, as concluded by Demirtas et al. (1), a healthy communication context must be met in patient–health care staff relations.

Ethics

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In reply Demirtaş et al.,

Ayla Demirtaş[1], Gülten Güvenç[1], Özlem Aslan[2], Emine Öksüz[1], Ayşe Kılıç Uçar[3]

[1]*University of Health Sciences Turkey, Gülhane School of Nursing, Ankara, Turkey*

[2]*Ufuk University, School of Nursing, Ankara, Turkey*

[3]*Istanbul Bilim University, Florence Nightingale School of Nursing, Istanbul, Turkey*

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Corresponding Author:
Ayla Demirtaş, PhD, RN, Assistant Professor, University of Health Sciences Turkey, Gülhane Faculty of Nursing, Ankara, Turkey

ORCID:
orcid.org/0000-0001-7952-770X

Dear Editor,

We are pleased to respond to the valuable comments (1) regarding our article titled "Determination of the Anxiety and the Needs of Family Members of Critical Care Patients in Emergency Departments" (2).

The study was planned when many new violence cases against healthcare staff in the emergency facilities appeared on media sources a couple of years ago, which drove our focus on patient relatives. Our results have shown that effective communication and cooperation between healthcare staff and relatives of the patients can prevent conflict and chaos in emergency services. Unfortunately, the risk of such unwanted events increases in the emergency services.

As emphasized by the authors of the correspondence, empathy with the patient and accompanying people, understanding their needs can yield good communication, which in turn increases the quality of care received by the patient and the carer. As such, the relatives or the carers may feel more confident with the healthcare service, and negative thoughts and behaviors can be prevented (3-5).

Notwithstanding, our results cannot be generalized to other settings like primary care services, home care or outpatient clinics of tertiary care facilities.

Ethics

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