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Working conditions and burnout syndrome in private bank branch employees in Ankara, Turkey

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Ethics Committee Approval
The study protocol was approved by Hacettepe University Non-Interventional Clinical Research Ethics Board on 27 September 2017 (application number: GO 17/790-35). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Burnout is a syndrome of physical exhaustion, prolonged fatigue, and helplessness reflected by negative attitudes on work, life, and other people around. The aim of this study is to investigate the relationship between burnout and working conditions in the banking sector, which has intense emotional demands.

Methods: The research group consisted of 1183 individuals working in 138 different branches. A data form questioning the working conditions and sociodemographic characteristics of the participants that may be related to the burnout level was filled with face-to-face interviews. Burnout level was determined using the Maslach Burnout Inventory. This was planned as a cross-sectional research.

Results: Higher levels of burnout was determined in those who thought that their family income was insufficient, who had to work more than 8.5 hours per day, who were exposed to physical or mental violence, those with chronic diseases and finally, workers who thought they dealt with too many customers in a day.

Conclusion: It appears that the burnout levels of the employees can be reduced by arrangements at corporate and individual levels in addition to the regulations that can be realized within the legislation.

Keywords: Bank branch employees, Burnout, Maslach Burnout Inventory, Working conditions

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Introduction

According to the World Health Organization, health is not merely the absence of disease and disability, but a state of complete spiritual and social well-being [1]. One of the most important determinants of health is working conditions. There are many alternatives for each product and service in competitive businesses, and the fact that these alternatives are not vastly different from each other coarsen the working conditions of the employees in the service sector. One of the consequences is burnout syndrome.

In daily language, burnout refers to losing one's power and being unable to strive for a specific purpose. In some sources, burnout is defined as the exhaustion of spiritual and physical energy, which results in a reaction to stress at work, whereas in some other sources, it is described as the depletion of energy, the loss of power and exhaustion that are brought about by excessive energy, power and resource consumption which turns into a case where an employee feels lack of meaningful contribution to his/her work [2,3]. According to Maslach, burnout is characterized by physical exhaustion, long-term fatigue, helplessness, and hopelessness, observed in people who encounter intense emotional demands in the work environment and in those who are constantly forced to work face-to-face with other people. This mood appears as a syndrome that occurs when the emotions are reflected with negative attitudes towards work, life, and other people around. In the Maslach model, burnout includes three components: Emotional exhaustion, depersonalization, and personal accomplishment. Emotional exhaustion refers to the stress dimension of burnout and the reduction of emotional and physical resources of an individual, depersonalization indicates the interpersonal dimension of burnout which is represented with negative, rigid, and unresponsive attitude to the people who are dealt with, and low level of personal accomplishment stands for the mood in which a person tends to evaluate himself in a negative way [4].

Set forth as the disease of this era, anyone can find themselves in burnout during everyday life, especially under challenging working circumstances. Most of the time, successful individuals who have started their business life with big dreams and ideals report burnout, such that they feel emotionally worn out for varied reasons after a while, lose interest in the business environments they have formerly been sensitive to and their feelings of personal accomplishment decrease [2]. This inevitably leads to a decrease in their performance, loss of respect and sensitivity to the work they do, besides the people they work with and the people they serve, which eventually results in losing their commitment to their work and related setting [5,6].

Employees with a sense of burnout cannot be expected to be fully healthy individuals physically, mentally, and spiritually. Burnout may temporarily lead to mental and physical disorders such as musculoskeletal diseases, cardiovascular system diseases, diabetes, metabolic disorders, skin diseases and allergies, and sometimes to chronic cases of such disorders [5,7,8]. It is well-known that burnout also has negative consequences for the social environment, families and working lives of individuals involved.

Burnout creates a significant loss of labor, which is detrimental to the institutions. Considering that the key factor leading to burnout is the highly demanding work conditions, it is apparent that measures must be taken institutionally.

Within the banking sector, an individual encounters intense emotional demands and is expected to be constantly working with other people face-to-face [9]. Banking is a sector in which burnout is often experienced, and consequently, a domain where loss of power, productivity (absenteeism of employees), and loss of labor (desires for early retirement or switches of sectors) are realized [10,11]. In this study, we aimed to determine the relationship between the working conditions in the banking sector and burnout rate, and present perspectives on related measures and solutions at institutional and individual levels.

Materials and methods

There are 25 private banking companies in Ankara, Turkey. Among them, the general directorates of 17 agreed to participate in our study, with 407 branches. The population of the study consists of 4,000 employees in total (distributed according to the units worked at: 857 at operations units, 916 at teller units, 2,227 at costumer services/marketing units). The sample size was calculated with the help of the known sampling method formula of the universe and determined as 1200 participants. The calculated sample size was distributed proportionally to the total number of employees in banks using stratified random sampling, and the number of employees to be included in the sample from each bank was determined. Relevant branches were selected using the method of random numbers, and 20% of the bank branches were considered reserve branches. Thus, the study group consists of 1,183 employees from 138 branches who agreed to participate in the study and filled out the data collection form in face-to-face interviews.

In the study, burnout level was assessed with Maslach Burnout Inventory (MBI). Developed by Maslach & Jackson in 1981, MBI is a measurement tool implemented specifically for occupational areas that require face-to-face relationships and the sectors that aim to serve people directly [12]. The inventory consists of three sub-dimensions listed as emotional exhaustion, reduced personal accomplishment, and depersonalization. Emotional exhaustion (EE) identifies stress dimension of burnout and implies the decrease of a person's emotional and physical sources with 9 questions (0 to 36 points). Depersonalization (DP) sub-dimension includes 5 questions (0-20 points), representing the interpersonal dimension of burnout which refers to negative, rigid attitudes and unresponsiveness to work. Consisting of eight questions (0 to 32 points), personal accomplishment (PA) sub-dimension refers to the tendency of a person to evaluate himself / herself negatively.

The validity and the reliability study of Turkish version of MBI was carried out by Ergin in 1992 [13]. Ergin determined that the 7-digit response options in the original form of the scale were not suitable for the conditions of the country, therefore the number of options was reduced to 5 items for adaptation [13]. No "cut-off point" was used for the sub-category scores of the MBI calculated during the assessments. This is due to the fact that

such cut-off points did not seem to be included in the studies conducted in Turkey [14].

The study protocol was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Board on 27 September 2017 (application number: GO 17/790-35). The participation was voluntary in the research process and informed consents of all participants were obtained. During a meeting, which was attended by banks and state authorities to regulate legislation, a preliminary presentation of the research results was delivered, and afterwards the opinions of the participants were taken into consideration in determining the recommendations for the prevention of burnout.

Statistical analysis

Data were analyzed with IBM SPSS Software Package Version 23 (SPSS Inc., Chicago, IL, USA). Numerical variables were presented as mean (SD), median, mode,1st and 3rd quartiles, minimum-maximum, and categorical variables were given in numbers (n) and percentages (%). Normal distribution of numerical variables was assessed with Shapiro-Wilk and Kolmogorov-Smirnov tests for the data with n<50 and n>50 scores. Non-parametric tests (Mann Whitney U test for two independent variables and Kruskal Wallis test for more than two independent variables) were used for non-parametric data. When significant results were obtained in Kruskal-Wallis test, the groups that created the difference were examined using Dunn multiple comparison test. The default *P*-value threshold for statistical significance was <0.05.

Results

Nearly two-fifth (42.1%) of study group was made up of males. More than half (56.7%) were in the 30-39 years age range with a mean age of 35.52 (6.19) years. Most were married (68.5%). More than half of the participants (54.7%) reported that they had children, most (60.6%) of which had one (Table 1). Frequency of having any after-work hobbies was 42.6%. Four out of every ten participants (41.0%) were smokers. Approximately half (52.8%) stated that they had never used alcohol. One-fifth of participants (20.7%) stated they worked out regularly. More than one-fifth of participants (23.7%) reported previously diagnosed chronic diseases, including musculoskeletal (19.3%), endocrine (18.4%), and cardiovascular diseases (13.0%).

Many of the participants (56.7%) were working at customer services (marketing) units and the others, at operations and teller units. Mean total working duration in the relevant occupation was 10.55 (6.51) years. Mean daily duration of work was 8.79 (0.92) hours. Nearly half (48.0%) reported working overtime. The majority (88.6%) chose the profession at their own will. Three quarters of the participant employees (75.1%) regarded the physical conditions of their workplace as appropriate. Nearly half (53.5%) found that the daily number of the customers they dealt with was rather high (Table 1). Nearly one-fifth (18.8%) stated that they had been exposed to physical or mental violence requiring treatment due to the circumstances of their occupation during their entire working lives. About half of participants (46.5%) evaluated their family income as inadequate.

By using MBI, scores of participating bank employees were calculated according to the sub-dimensions of the inventory. Mean scores for EE, DP, and PA were 17.70 (8.14), 6.04 (4.09), and 21.92 (4.17) respectively (Table 2).

Table 1: Distribution of some demographic characteristics of participants

		n	%
Age (years) (n=1172)	23-29	216	18.5
	30-39	665	56.7
	40-58	291	24.8
Marital status (n=1180)	Married	808	68.5
	Single	326	27.6
	Divorcee, Widow/widower	46	3.9
Number of children (n=584)	1	354	60.6
	2	215	36.8
	≥3	15	2.6
Family income (n=1166)	Quite adequate	14	1.2
	Adequate	522	44.8
	Inadequate	542	46.5
	Very inadequate	76	6.5
	No idea	12	1.0
Work unit (n=1180)	Customer services (marketing)	673	56.9
	Operations	270	22.9
	Teller Unit	237	20.2
Total duration of work (year) (n=1169)	≤5	327	28.0
	>5-10	308	26.3
	>10-15	291	24.9
	>15	243	20.8
Physical conditions of workplace (n=1167)	Very appropriate	150	12.9
	Appropriate	726	62.2
	Inappropriate	202	17.3
	Very inappropriate	63	5.4
	No idea	26	2.2
Daily number of customers (n=1173)	Very high	243	20.7
	High	385	32.8
	Appropriate	493	42.0
	Low	38	3.2
	Very low	14	1.2

Table 2: Distribution of Maslach Burnout Inventory Scores for bank employees

	Min-Max	Mean (SD)	Median	Mode	1st-3rd quartiles
MBI-EE (n=1166)	0-36	17.70 (8.14)	18	19	12-23
MBI-DP (n=1166)	0-20	6.04 (4.09)	6	4	3-9
MBI-PA (n=1154)	0-32	21.92 (4.17)	22	22	20-24

MBI-EE: Maslach Burnout Inventory emotional exhaustion sub-dimension, MBI-DP: Maslach Burnout Inventory depersonalization sub-dimension, MBI-PA: Maslach Burnout Inventory personal accomplishment sub-dimension, min: minimum, max: maximum, ss: standard deviation.

Scores of EE, DP, and PA sub-dimensions were not significantly different according to gender and marital status (P>0.05). The highest median score for EE sub-dimension was obtained from employees who were in their third decades (P=0.001). The lowest median score for DP sub-dimension was obtained from employees in the age group of 40-58 years. DP score significantly decreased with increasing age (P<0.001). The highest median score for PA sub-dimension was in the age group of 40-58 years, and significantly lower burnout level was also observed in this group compared to the age group of 30-39 years (P=0.006).

Employees without children had significantly higher median DP sub-dimension scores (P=0.009), but significantly lower median PA scores (P=0.034) than employees with children. When compared with employees who reported their family income as adequate, those reporting inadequate family income had higher median EE and DP sub-dimension scores (P<0.001), however, they had lower median PA scores (P<0.001).

Employees without any after-work hobbies were found to have higher median EE sub-dimension burnout scores (P<0.001) but lower median PA scores (P<0.001) (Table 3). Current smokers at the time of the research had higher median EE sub-dimension scores than non-smokers and ex-smokers (P=0.048). Employees reporting the absence of alcohol consumption had lower median DP scores than those reporting occasional or regular alcohol consumption (P<0.001).

Employees who work out regularly had lower median EE scores (P<0.001), but higher median PA scores (P=0.002) than the others. Employees with previously diagnosed chronic diseases had significantly higher EE and DP sub-dimension scores (P<0.001) (Table 3).

Table 3: Distribution of Maslach Burnout Inventory Scores according to some socio-demographic characteristics of bank employees

		Scores of Sub-dimensions of Maslach Burnout Inventory, median (1st-3rd quartiles)		
		Emotional exhaustion	Depersonalization	Personal accomplishment
Age groups	23-29	17 (11-22)	6 (3-9)	22 (19-25)
	30-39	19 (13-25)	6 (3-9)	22 (19-24)
	40-58	18 (11-22)	5 (2-7)	23 (20-25)
		P=0.001*	P<0.001**	P=0.006***
Having children	Yes	18 (12-23)	5 (2-8)	22 (20-25)
	No	18 (12-24)	6 (3-9)	22 (19-24)
		P=0.837	P=0.009	P=0.034
Family income	Adequate	15 (9-20)	4 (2-7)	23 (20-25)
	Inadequate	21 (15-26)	6 (4-9)	21 (19-24)
		P<0.001	P<0.001	P<0.001
Hobby	Yes	16(11-23)	5 (3-9)	23 (20-25)
	No	19(13-24)	6(3-9)	22 (19-24)
		P<0.001	P=0.169	P<0.001
Smoking status	Current smoker	19 (13-24)	6 (3-9)	22 (19-24)
	No	18 (11-23)	5 (3-8)	22 (20-25)
	Ex-smoker	18 (12-24)	6 (3-9)	22 (20-24)
		P=0.048	P=0.139	P=0.682
Alcohol consumption	Regular	21 (14-25)	7 (5-11.5)	21 (17-24)
	Occasional	18 (12-24)	6 (3-9)	22 (20-25)
	No	18 (12-23)	5 (2-8)	22 (20-24)
		P=0.125	P<0.001****	P=0.179
Doing sports regularly	Yes	16 (9-22)	5 (2-9)	23 (20-25)
	No	19 (13-24)	6 (3-9)	22 (19-24)
		P<0.001	P=0.149	P=0.002
Physician-diagnosed chronic disease	Yes	20 (14-26)	6 (4-10)	22 (19-25)
	None	17 (11-23)	5 (3-8)	22 (20-24)
		P<0.001	P<0.001	P=0.264

Bold values denote statistical significance at P<0.05 level. Multiple comparisons performed after evaluation of Kruskal-Wallis test results. Comparisons revealing significant differences are as follows: * 23-29 and 30-39 P=0.007; 30-39 and 40-58 P=0.007; ** 23-29 and 40-58 P=0.003; 30-39 and 40-58P<0.001 30-39 and 40-58 P=0.004; **** regular alcohol consumers and non-drinkers P=0.001; regular alcohol consumers and occasional drinkers P=0.037; occasional alcohol consumers and non-drinkers P=0.015.

Analysis of burnout status of employees according to units where they had worked did not reveal any significant differences in terms of EE, DP, and PA sub-dimension scores (P>0.05). Employees working more than 15 years had significantly lower median DP scores (P<0.001), yet they had higher PA scores (P=0.007) than the employees working for 15 years or less. Employees who worked more than 8.5 hours per day, who complained about working overtime, who chose the occupation without his or her own will, those who reported exposure to physical or mental violence due to the occupation conditions, and the ones who reported physical conditions of the workplace as inappropriate were revealed to have higher DP sub-dimension scores (P<0.001), but lower PA sub-dimension scores (P<0.05) (Table 4).

Employees who found daily number of the customers they deal with rather high had higher EE and DP scores than those who regarded the number as appropriate or low (P<0.001). Employees who found the daily number of the customers they dealt with appropriate had higher PA sub-dimension scores than those who perceived the number as high and low (P<0.001) (Table 4).

Table 4: Distribution of Maslach Burnout Inventory Scores according to some working life characteristics of bank employees

		Scores of Sub-dimensions of Maslach Burnout Inventory, median (1st-3rd quartiles)		
		Emotional exhaustion	Depersonalization	Personal accomplishment
Work unit	Teller	18 (13-24)	6 (4-9)	22 (19-25)
	Operations	18 (12-23)	5.5 (3-8)	22 (19-24)
		18 (12-24)	6 (2-9)	22 (20-24)
	Customer services	P=0.625	P=0.062	P=0.070
Total duration of work (year)	≤5	18 (12-23)	6 (3-9)	22 (19-24)
	>5-10	19 (12-24)	6 (3-9)	22 (19-24
	>10-15	19 (12.5-24)	6 (3-9)	22 (20-25)
	>15	17 (11.5-21.5)	4 (2-7)	23 (20-25)
		P=0.051	P<0.001*	P=0.007**
Daily duration of work (hour)	≤ 8.5	16 (9-21)	5 (2-7)	23 (20-25)
	>8.5	20 (14-25)	7 (4-10)	22 (19-24)
		P<0.001	P<0.001	P<0.001
Working overtime	Yes	15 (9-21)	5 (2-7)	23 (20-25)
	No	21 (15-25)	7 (4-10)	22 (19-24)
		P<0.001	P<0.001	P=0.001
Choice of the occupation by own will	Yes	17 (11-23)	5 (3-8)	22 (20-25)
	No	23 (19-28)	8 (5-11)	20 (17-22)
		P<0.001	P<0.001	P<0.001
Physical conditions of the workplace	Appropriate	16(10-21)	5 (2-7)	23 (20-25)
	Inappropriate	24 (20-28)	9 (6-11)	20 (18-23)
		P<0.001	P<0.001	P<0.001
Daily number of customers	High	21 (16-26)	7 (4-10)	22 (19-24)
	Appropriate	14 (8-20)	4 (2-7)	23 (20-25)
	Low	14.5 (10-19.5)	5 (3-7)	21 (19-23)
		P<0.001***	P<0.001***	P<0.001**
Exposure to physical or mental violence	Yes	25 (20-29)	8.5 (6-12)	20 (18-23.5)
	None	17 (10-22)	5 (2-8)	22 (20-25)
		P<0.001	P<0.001	P<0.001

Multiple comparisons performed after evaluation of Kruskal-Wallis test results. Comparisons revealing significant difference are as follows: * work >15 years and those with >5-10 years P<0.001; work >15 years and those with ≤5 years P<0.001; work >15 years and those with >10-15 years P=0.030; ** work >15 years and those with ≤5 years P=0.027; work >15 years and those with >5-10 years P=0.037; *** high and those found as appropriate P<0.001; high and those found as low P<0.001; **** high and those found as appropriate P<0.001; appropriate and those found them as low P=0.001.

Discussion

With its rapidly differing structure, working life forces business enterprises to compete more intensely, which may result in leading employees to a tug of war and causing psychosocial problems, such as burnout. The consequences of these problems can be observed on an individual or a family at economic and social levels. In this study, the burnout levels of branch employees of 17 private banks in Ankara were determined with Maslach Burnout Inventory Scores, like the other study conducted on the same subject, and found high [15]. It is important to calculate and quantify these scores, and each subscale should be assessed separately considering the risk factors, because the sub-headings related to the levels of burnout may have significantly different interpretations.

First, the relationship between socio-demographic characteristics and burnout was investigated in our study. No significant difference was found between male and female employees in terms of burnout levels in line with some other studies that showed no gender differences [16, 17]. In one study, emotional exhaustion and personal accomplishment scores of the female employees were higher than those of males [9]. However, there are some studies in the literature that have found burnout levels higher in males compared to females [18, 19]. In the study conducted by El Hadidive et al., it was stated that male bank employees may experience more burnout than female employees because they spend less time with family members than females, and it could be because males were more competitive than women in those working conditions [19]. No significant gender

differences were found in our study possibly because women and men participate equally in both work and family affairs, and banking does not rely on occupational gender segregation for men and women.

In the study, 30-39-year-old bank employees were more emotionally exhausted compared to the other age groups, while 40-58-year-old employees were less exhausted in terms of the sub-dimensions of depersonalization and feelings of personal accomplishment. Similar to our findings, the study of Belias et al. determined that young employees had higher levels of emotional exhaustion in Greece. The reason for the prominent level of burnout among young employees was stated as the lack of experience, as well as the longer time they were subjected to pressure in the workplace while trying to prove that they could fulfill the role assigned to them [20]. Unlike these two studies, there are some studies reporting on increased levels of burnout with increasing age [18, 19]. El-Hadidi et al. [19] stated that the increase in burnout prevalence among older employees may have been due to the lack of adaptation to technological changes. In this research, the higher burnout rates among 30-39 year old employees compared to 20-29 and 40-58 year age groups may be due to the fact that people in this age group did not meet their expectations after working for a while, they perceived discouraged due to switching jobs, and therefore felt obliged to continue in their current conditions.

In terms of depersonalization and a sense of personal accomplishment, it can be said that the fact that the 40-58 year age group is less exhausted than the 20-29 and 30-39 age groups may be because they are less susceptible to adverse work conditions as a result of prolonged intense professional life experience.

Those without children were more exhausted in terms of depersonalization and sense of personal accomplishment than the ones with children. Similar to the results of our study, Brauchli et al. [21] found a higher level of burnout in the group not living with children. The fact that employees with children tend to be more responsible, share their energies among the family, social or business life, and thus feel the obligation to make more plans for the future may cause them to feel less exhausted about their work.

There are some studies that investigate the relationship between burnout level and monthly income of employees in different sectors which found that low income level was associated with higher burnout levels [22, 23]. Whereas Li and colleagues [10] did not find a significant relationship between monthly income and burnout, in our study, it was revealed that the bank employees who did not consider their family's monthly income as sufficient seemed to be significantly more exhausted emotionally, and in terms of depersonalization and sense of personal accomplishment than those who regarded it as sufficient. Shortage of income in employees creates a state of anxiety independent of their professions. Furthermore, the fact that bank employees are engaged in the financial transactions of customers whose income levels are higher than themselves may cause them to feel less satisfied with their own income levels, and consequently make them feel more exhausted. In addition to meeting basic needs due to low-income level, not being able to allocate money and time to social and cultural activities can also negatively and considerably affect one's mood.

It can be argued that because of the increasingly difficult working conditions in today's world, employees are unable to allocate material resources and time to hobbies, which are thought to protect from burnout. In our study, it was found that 42.6% of the employees had an after-work occupation (hobby) as a regular activity other than their profession. Malini et al. stated in their study with bank employees that 70% of the employees were not engaged in occupations, and thus banks needed to have a steady closing time to allow their workers for pastime activities [24]. In our study, bank employees with no after-work pastime activities were more emotionally exhausted and had worse sense of personal accomplishment than those who do. Therefore, encouraging employees to engage in hobbies, organizing social activities that can be held together, and allocating time to such facilities may contribute to the decrease in their burnout levels.

Smoking, intense alcohol consumption and low physical activity are among the risky health behaviors which are associated with burnout in the literature. Bolat et al. reported that smoking urologists experienced higher levels of burnout than non-smoker urologists [25]. Campos et al. revealed that prison employees with alcohol consumption had higher burnout levels than sober ones [26]. The prevalence of smoking habit among the bank employees participating in the study was 41.0%. However, the frequency of tobacco use in Turkey is 27.1% [27]. The rate of smoking among employees of banks is above average in Turkey. Regarding the emotional exhaustion sub-dimension of burnout, the bank employees who smoke seem to be experiencing more burnout feelings than the ones who do not use it or quit. In-house interventions to reduce burnout levels of the employees can help improve their performance and decrease risky health behaviors. Also, national, and international non-smoking establishments' interventions to reduce smoking consumption of employees should be taken into consideration and similar studies should be conducted in our country too. Another health behavior investigated in our study was alcohol consumption. Less burnout was revealed for the depersonalization sub-dimension of burnout in non-users compared to regular and occasional users.

It can be considered that there is a two-way relationship between burnout and physical activity. Individuals with higher levels of burnout may be less physically active, whereas lower levels of physical activity may lead to more burnout. In a study by Olson et al., it was stated that physicians who engaged in physical activities appeared to have experienced less burnout than those who did not, in accordance with a national guideline defining a specific physical activity at work [28]. In our study, bank employees who do not work out regularly had higher levels of emotional exhaustion and less feelings of emotional exhaustion. Similarly, El-Hadidi et al. [19] carried out a study with bank employees in Egypt and revealed that burnout cases were higher among those who did not engage in physical activities. In Taiwan, an intervention research was conducted to determine the relationship between physical activities of bank employees and their burnout levels. High-intensity, low-intensity, and non-exercise groups were compared, and the levels

of burnout were higher among those who did not engage in regular exercise [29]. Physical activity helped to reduce burnout levels in employees [6].

It can be observed that working conditions that cause burnout are also related to some chronic diseases. Honkomen et al. [8] reported that musculoskeletal and cardiovascular system diseases were common in burnt out individuals. In patients with chronic diseases, burnout was more frequent in terms of emotional exhaustion, and depersonalization sub-dimensions compared to healthy individuals. One quarter of the bank employees participating in our study had a chronic disease diagnosed by a physician. The most common diagnosis is related to musculoskeletal diseases. In their study with embassy employees, Aghilinejad et al. [30] determined higher levels of burnout among employees with musculoskeletal disorders. Melamed's study [31] showed that employees with higher levels of burnout developed musculoskeletal pain twice as frequent as those with low levels. Another study revealed that increased burnout levels were associated with an increased risk of developing musculoskeletal pain after 18 months of follow-up process [32]. Ergonomic regulation of the working area to prevent musculoskeletal complaints, providing adequate light foods, creating conditions for each working person in spaces that allow communication with other individuals may be appropriate.

In our study, there were no significant differences in emotional exhaustion, depersonalization, and the sense of personal accomplishment scores among the teller, operation, and customer service (marketing) units of the banks. Although bank employees work less face-to-face with each customer, those in the teller, whose only job are solely to realize transactions, are obliged to work under intensive workload and quota applications. Today, arising from the structure of the sector, a pressure to achieve target banking transactions seems to have been created for each unit.

When the groups were compared in terms of working time at the bank, the personal accomplishment scores of employees working for 15 years and over were significantly higher than those of the other groups (5 years and under, 5-10 years, 10-15 years), whereas the scores obtained from the depersonalization subscale were lower. In a study conducted in Spain, individuals with a working period of more than 30 years had lower levels of emotional exhaustion, which is another dimension of burnout [9]. The above-mentioned results regarding the total year of working seem to be in line with the burnout scores of the 40–58-year age group participants in our study. As stated earlier, as the age and working years increase, so does endurance for professional life experience and problems in working life.

The cut-off point data for daily working time were revealed as 8.5 hours due to the accumulation of the relevant data. Burnout levels were significantly higher among employees who worked overtime, which presented challenges for the sub-dimensions of emotional exhaustion, and depersonalization as well as the sense of personal accomplishment compared to those who worked 8.5 hours or less. There are some studies with comparable results in the international literature [10, 19].

When the employees were compared in terms of their willingness to choose the banking profession, it was found that those who did not opt for their own job willingly had higher levels of burnout in terms of emotional exhaustion, depersonalization, and the sense of personal accomplishment. There are similar findings revealed in another study in Turkey [15]. One can consider that those who make their choice of profession consciously and willingly tend to be more successful in fulfilling the requirements of the profession as well as confronting the difficulties they are not involved in during their working life, which seems to reduce burnout eventually.

According to Dias and Angelico, burnout is triggered by the factors of organizational context such as working organization, physical environment, and industrial relations [6]. In this respect, employees who think that their working environment is physically appropriate may experience less burnout as they might do their jobs more comfortably and become more motivated. In line with these results, we found that employees who considered the physical conditions of the bank they worked in suboptimal were more exhausted emotionally, and in terms of depersonalization, and sense of personal accomplishment than the employees who regarded the physical conditions as appropriate.

Emotional burnout dimension scores of the employees with more intense workloads are higher or there seems to be a positive correlation between burnout and high workload [33]. Similarly, in our study, we determined that bank employees, who perceived the number of customers they dealt with daily as too many, had more burnout in terms of emotional exhaustion and depersonalization than those who did not. When evaluated in terms of the sub-dimensions of the burnout scale, these results may be related to the negative feelings towards the people whom they serve due to the decrease in the emotional and physical resources, however, small amount of workload (as it has been found in this study), as well as the excessive workload, may lead to the tendency of the relevant person to consider themselves in negative light.

Approximately one-fifth of the bank employees participating in the study stated that they were subjected to physical or mental violence that would require treatment. Emotional exhaustion, depersonalization and personal accomplishment sub-dimension scores of these employees were significantly higher than the others. In parallel to our study findings, Tanrıverdi et al. [34] revealed that emotional burnout increased with the perceptions of bank employees of the psychological violence they were exposed to, and that the employees who thought that they were subjected to psychological violence had the intention of leaving their current job to achieve individual happiness and career goals.

Limitations and strengths of the study

The inclusion of private bank employees only and exclusion of public bank employees limits this study. The strength of the study is its large sample and the combined evaluation of burnout-related factors, such as working conditions and sociodemographic and psychological factors.

Conclusion

Under some working conditions, the level of burnout was higher among the bank employees. By increasing the number of employees in banks, it can be ensured that there is no more need for overtime. The work areas can be ergonomically

rearranged to prevent musculoskeletal complaints. The wages of bank employees can be regulated considering the economic conditions (transportation expenses, kindergarten allowances, meal fees, etc.). Besides, it must be ensured that an employee can develop in areas outside of the working life, which encourages them to participate in hobbies. In addition, institutions can consider organizing social activities (picnics, football tournaments, etc.), as well as allocating time to be spent for themselves. Before starting to work, new employees can be provided information about the profession, and participate in an orientation program. Consulting with occupational health and safety professionals and organizing training and awareness programs related to burnout syndrome may also be beneficial.

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The role of saline irrigation of subcutaneous tissue in preventing surgical site complications during cesarean section: A prospective randomized controlled trial

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Abstract

Background/Aim: Following cesarean section, wound complications develop in 3 to 30% of the patients. The purpose of this study is to evaluate the effect of subcutaneous saline irrigation during caesarean section on postoperative surgical site complications.

Methods: This prospective randomized controlled study was conducted between November 17, 2020 and December 16, 2020 at Medipol University, Private Nisa Hospital. A total of 230 women undergoing elective cesarean delivery were divided into 2 groups. The subcutaneous tissue was irrigated with saline solution in group 1 (n=115), and not irrigated in the control group (n=115). On the 7th postoperative day, the surgical site was evaluated for hematoma, seroma, wound dehiscence, and superficial surgical site infection.

Results: The incidences of seroma (7% vs. 15.7%, *P*=0.013), hematoma (6.1% vs. 15.7%, *P*=0.024) and superficial surgical site infection (4.3% vs. 11.3%, *P*=0.035) were significantly lower in the saline irrigation group, while the groups were similar in terms of wound dehiscence (*P*=0.176).

Conclusion: Saline irrigation of the subcutaneous tissue during cesarean section decreased the rates of seroma, hematoma, and superficial surgical site infections significantly.

Keywords: Cesarean section, Subcutaneous tissue irrigation, Surgical site infection, Wound dehiscence, Seroma, Hematoma

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Ethics Committee Approval
The study was approved by Istanbul Medipol University Clinical Research Ethics Committee. Written approval was obtained from Private Nisa Hospital before the data collection phase (Reference number: 10840098-772.02-E.61616, Date: 17/11/2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Introduction

The incidence of cesarean section, one of the most common surgical procedures [1], has increased significantly in the last two decades, especially in developed countries [2]. After surgical procedures, wound complications develop in 3 to 30% of the patients [3]. There are 2 types of surgical site complications: Infectious and non-infectious (seroma, hematoma, wound dehiscence) [4, 5]. The incidence of surgical site infections (SSIs) ranges between 3% and 15% [6]. Today, thanks to modern antibiotic prophylaxis, infection rates after cesarean section have decreased but have not been eliminated completely [7]. Therefore, besides prophylactic antibiotics, other options have been considered in reducing infections after cesarean section.

In two separate meta-analyses in the literature, it was found that the irrigation of subcutaneous tissue with povidone iodine solution, topical antibiotic and saline solution just before the closure of the skin lowers the risk of surgical site infections [8, 9]. There are also studies emphasizing that irrigation of the subcutaneous tissue with saline solution decreases non-infectious wound complications such as seroma and hematoma [10].

This study aimed to investigate the effect of irrigation of the subcutaneous tissue with saline solution during caesarean section on post-cesarean infectious and non-infectious surgical site complications.

Materials and methods

This prospective randomized controlled study was conducted between November 17, 2020 and December 16, 2020 at Medipol University, Private Nisa Hospital. Ethics committee approval, institutional review approval and informed consents of the patients were obtained before the collection of data (Reference number: 10840098-772.02-E.61616, date: 17/11/2020). During conduction of this study, 1964 Helsinki Declaration, and ethical guidelines regarding studies on human participants were conformed with.

Five hundred pregnant women presented to the obstetrics outpatient clinics of Medipol University, Private Nisa Hospital between November 17, 2020-December 16, 2020. Two hundred and eighty underwent cesarean delivery, of which 128 were primiparae and 152, multiparae. G*Power (version 3.1) was used to calculate the sample size of the study. A literature review demonstrated that irrigation of subcutaneous tissue had an effect on postpartum surgical site complications [10]. Considering the literature review and relevant scientific literature, the minimum sample size was calculated as 220 (n = 110 for each group) with a type 1 error of 0.05 and a power of 0.95 ($\alpha = 0.05$, $1-\beta = 0.95$). However, bearing in mind the possible losses during the study, we decided to include 115 participants in each group.

The patients with even protocol numbers were included in the saline irrigation group, while those with odd protocol numbers constituted the control group. Randomization was generated using a computer-based random number generator with a 1:1 allocation (https://stattrek.com/statistics/random-number-generator.aspx). The experiment and control groups were enrolled into a list by the researchers. To avoid bias and to standardize the surgical procedure, all patients were operated by the same surgical team.

The subcutaneous tissue was irrigated with 200 ml of saline solution (0.9% NaCl) in patients in the experimental group (Group 1, n=115), and not irrigated in those in the control group (n=115) before the skin was closed.

Patients between 20-40 years of age with a gestational age of 37-42 weeks who were to undergo cesarean section for the first or second time were included in the study. Those with an active infection, premature rupture of membranes, surgical drains, previous abdominal surgery, subcutaneous tissue thickness of >3 cm, allergic reaction, anemia, thrombocytopenia, preoperative leukocytosis, and patients using steroids/antibiotics or undergoing emergency caesarean section (acute hemorrhage, fetal distress), along with those with a body temperature above 38°C were excluded from the study.

Data collection procedure

All patients underwent the same standard pre-surgical preparations. Routine abdominal scrubs were used to clean the patients in all the groups. The following surgical method was followed in all patients: A Pfannenstiel skin incision was performed. Two grams of cefazolin sodium was administered to the patients intravenously for prophylaxis as soon as the umbilical cord was clamped. After uterine and peritoneal closure, the fascia was closed continuously with a 1/0 vicryl suture. Before closure, the subcutaneous tissue was irrigated with 200 ml of saline solution (0.9% NaCl) in the study group and not irrigated in the control group. Subcutaneous bleeding was stopped with electro-cauterization, and the skin was closed with a 3/0 Vicryl Rapid suture. All participants underwent routine postoperative care. Surgical dressing was changed 24 hours after the surgery and then at the 48th hour the patients were discharged from the hospital.

Patients' demographic characteristics, preoperative hemoglobin and hematocrit levels, duration of the operation, C reactive protein and procalcitonin values at the 24th postoperative ^{hour} and evaluations of the surgical site in terms of hematoma, seroma, wound dehiscence and superficial surgical site infection were performed through inspections and abdominal ultrasonography on the 7th postoperative day.

Seroma was diagnosed in the presence of serous fluid drainage without any signs of infection. Hemorrhagic drainage without any signs of infection indicated hematoma. Wound dehiscence was defined as the separation of the skin without infection. Purulent discharge or erythema, fever, induration, and tenderness in the surgical site, which required separation of the incision, indicated an infection.

Serum PCT levels were measured with the LUMI test (Berlin, Germany) and recorded as ng/ml. Serum CRP concentrations were assayed using a Cobas 6000 analyzer (Switzerland) and recorded as mg/dL.

The primary outcome of the study was the detection of surgical site complication rates.

Statistical analysis

Kolmogorov Smirnov test was used to find out whether the variables were distributed normally. Continuous variables were compared using independent samples t-test or Mann-Whitney U test. The categorical data were compared using Chi-

squared or Fisher's exact tests. *P*-values of less than 0.05 were considered statistically significant. The data were analyzed with IBM SPSS V23.

Results

This study included 230 pregnant women who underwent elective cesarean section. The comparison of the groups in terms of demographic characteristics demonstrated no differences in terms of age, BMI, and gestational age ($P>0.05$ for all).

The groups were similar with regards to preoperative hemoglobin and hematocrit levels, postoperative hemoglobin and hematocrit levels and duration of the operation ($P>0.05$). However, postoperative 24th hour CRP ($P<0.001$) and Procalcitonin ($P<0.001$) values were different. The mean CRP and procalcitonin values of the saline and control groups were 25 mg/dL vs 35 mg/dL and 0 ng/ml vs 0.1 ng/ml, respectively (Table 1).

Table 1: Comparison of the groups in terms of their demographic characteristics and laboratory values

	Saline solution group (n=115) Mean (SD)	Control group (n=115) Mean (SD)	*P*-value*
Age (Year)	30 (5.59)	29 (5.15)	0.334
BMI(kg/m2)	30.72(8.77)	30.66(8.69)	0.657
Gestational age (weeks)	38.1 (1.23)	38.3 (1.75)	0.304
Preoperative Hb (g/dL)	12.61 (1.18)	12.52 (1.24)	0.637
Preoperative HCT%	35.21 (2.11)	36.33 (1.71)	0.377
Postoperative Hb (g/dL)	11.61 (1.18)	11.81 (1.27)	0.053
Postoperative HCT%	33.26 (1.91)	33.57 (2.11)	0.486
Operation duration (min)	30.93 (11.11)	30.35 (14.07)	0.054
Postoperative 24th hour CRP mg/dl	25.01 (5.2)	35.23 (5.7)	0.001
Postoperative 24th hour PCT (ng/ml)	0.01 (0.11)	0,10 (0.05)	0.001
Postoperative fever 1st week ^{o}C	36.20 (2.30)	36.89 (2.7)	0.001

* Mann-Whitney U Hb: hemoglobin, HTC: hematocrit, CRP: C Reactive Protein, PCT: procalcitonin, VAS: Visual analog score

The incidences of seroma (7% vs. 15.7%, $P=0.013$), hematoma (6.1% vs. 15.7%, $P=0.024$) and superficial surgical site infection (4.3% vs. 11.3%, $P=0.035$) were significantly lower in the saline irrigation group, while the groups were similar in terms of wound dehiscence ($P=0.176$) (Table 2).

According to logistic regression analysis, the incidences of seroma, hematoma, and SSI were lower in the saline group compared to the control group (seroma: OR=0.51, 95%:0.22-1.16, RR:0.55, $P=0.037$; hematoma: OR=0.34, 95%:0.14-0.87, RR:0.38, $P=0.020$; SSI: OR=0.43, 95%:0.15-1.17, RR:0.46, $P=0.048$) (Table 3).

Table 2: Comparison of the groups in terms of the surgical site complications

	Saline solution (n=115) n %	Control (n=115) n %	*P*-value*
Seroma	8 (7)	18 (15.7)	0.013
Hematoma	7 (6.1)	18 (15.7)	0.024
Wound Separation	9 (7.8)	6 (5.2)	0.176
Superficial surgical site infection	5 (4.3)	13 (11.3)	0.035

χ^2: chi-square test statistics * Frequency (percentage)

Table 3: Comparison of the saline with the control group

	OR	Seroma 95%CI	RR OR	Hematoma 95%CI	RR OR	Surgical site infection 95% CI RR
Saline solution	0.40	0.16-0.96	0.44 0.34	0.14-0.87	0.38 0.35	0.12-1.03 0.38

OR: Odds ratio; CI: confidence interval; RR: relative risk

Discussion

In this study, there were significant differences between the study and control groups in terms of seroma, hematoma, and superficial surgical site infection development, while the groups were similar in terms of wound separation.

Consecutive stages of wound healing are hemostasis, inflammation, epithelialization, fibroplasia and maturation, and the entire process takes about 2 to 4 weeks. Hematoma is the collection of blood in the tissue, which occurs when blood leaks out of blood vessels into the surrounding tissue after an injury. Seroma is the accumulation of inflammatory exudate in the tissue due to surgical trauma [11]. The incidence of non-infectious surgical site complications such as seroma and hematoma after cesarean section ranges between 3% and 30%, which may result in wound dehiscence and surgical site infection [3, 12].

One of the most effective methods of preventing wound complications after surgery is the irrigation of the subcutaneous tissue. Irrigation removes debris and blood clots in the surgical site and reduces the possibility of seroma and hematoma development. In the literature, there are different opinions related to this issue. In their meta-analysis, Müller et al. [8] reported that irrigation of surgical sites with a topical antibiotic, povidone-iodine solution or saline solution reduced the risk of SSIs. However, in another meta-analysis, while the irrigation of surgical site with povidone iodine solution had a low impact on SSI, antibiotic irrigation had no effect [13]. In this study, there was a statistically significant difference between the group that underwent subcutaneous irrigation during cesarean section and the control group in terms of superficial surgical site infection development. We think that this difference stems from the fact that the samples included heterogeneous patient populations with different surgical site infections.

Different solutions are used for the irrigation of the subcutaneous tissue. However, the most preferred one is the saline solution since it is an isotonic solution. Saline solution does not adversely affect healing of the wound site, and it is used to remove blood clots and necrotic tissues from the wound. The net effect of irrigation with saline in reducing wound infection is unknown. The review of the literature demonstrated that while in some studies, irrigation of the subcutaneous tissue with saline solution decreased surgical site infections [14], in some others, there was no significant difference [9, 15, 16]. In their study, Aslan Çetin et al. [10] irrigated surgical sites of the women who underwent cesarean section with saline solution, reducing the risk of hematoma and seroma by 51% and 69% respectively. However, they did not find a significant difference in terms of surgical site infection and wound separation. Similarly, in our study, the incidence of seroma, hematoma and surgical site infection was lower in the saline group compared to the control group (seroma: OR=0.51, 95%:0.22-1.16, RR:0.55, hematoma: OR=0.34, 95%:0.14-0.87, RR:0.38, SSI: OR=0.43, 95%:0.15-1.17, RR:0.46).

Strengths and limitations of the study

A review of the literature demonstrated that there are a limited number of studies investigating both non-infectious and infectious surgical site complications in patients whose subcutaneous tissues were irrigated with Saline solution during

caesarean section. We believe that our study can contribute to the literature on this subject.

The limitation of our study is the nongeneralizability of our results, since we included pregnant women who were not in active labor and who were to undergo cesarean section for the first or second time. We recommend that future studies include larger samples of diverse groups to overcome this limitation.

Conclusion

In the present study, saline irrigation of the subcutaneous tissue of pregnant women during cesarean section decreased the rates of seroma, hematoma, and superficial surgical site infections significantly. However, there were no differences between the groups in terms of wound dehiscence. Prospective studies with larger patient groups are required to investigate this easily applicable and cost-effective method without any major side effects.

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Characteristics of pediatric injuries due to road traffic accidents and their effects on mortality

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Abstract

Background/Aim: Road traffic accident (RTA)-related injuries may cause morbidity and mortality in childhood. We aimed to investigate these injuries in terms of affected body regions, time of the accident, gender, and age, determine the factors affecting mortality, and evaluate the casualties' demographic features and discharge status.

Methods: This retrospective cohort study included patients aged under 18 years who were victims of RTAs and presented to the emergency department of our tertiary university hospital between 01/01/2015 and 31/12/2019. Patients' age, gender, time, and mechanism of the accident, affected body region, type of injury, and clinical outcomes were recorded and analyzed.

Results: A total of 137 pediatric patients met the inclusion criteria, among which 95 (67.2%) were males, and 42 (32.8%) were females. Five of the six patients who died were males. RTAs most occurred in summer (45.3%), in August (17.5%) and on Saturdays (25.5%). Among the affected systems, extremity injuries ranked first (36.5%), and head traumas ranked second (30.7%).

Conclusion: In our study, presentations with out of vehicle traffic accidents (OVTAs) (motorcycle, bicycle, agricultural vehicle, or pedestrian) were more common (75.1%). Pediatric RTAs caused many injuries, especially extremity traumas, which were more serious in children under 15 years of age. In these patients, intracranial hemorrhage, rib fractures, and liver lacerations were evaluated as more severe injuries. Because of the limited number of the cases, we could not investigate the effects of traffic accidents on child mortality.

Keywords: Emergency service, Pediatric trauma, Road traffic accidents

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Ethics Committee Approval
The Duzce University Ethics Committee approved this study with the 19/10/2020 dated and 2020/222 numbered decision. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Introduction

Road traffic accidents (RTAs) remain a significant global public health problem, with increased deaths, disabilities, and financial consequences [1]. In 2018, the World Health Organization (WHO) estimated that 1.35 million individuals died, and 20 to 50 million were seriously injured or disabled due to RTAs annually worldwide. RTAs are the leading cause of childhood deaths. A total of 55611 children were injured, and 665 children died due to RTAs in 2018. RTAs rank fourth among the global causes of death in children aged between 5-14 years. Among these deaths, 38% of the children were pedestrians [2-4].

Children are a particular risk group in RTAs, and serious RTA injuries are multifactorial [5]. Half of all deaths on the roads worldwide involve pedestrians, motorcycle, and bicycle riders. This is due to the lack of energy-absorbing safety devices during an impact [8]. Motor vehicle accidents in rural areas tend to be more severe. All these factors contribute to the increased death rate [6]. Children make up an essential part of the pedestrians. Studies have shown that young children have lower danger detection ability and are more prone to impulsive traffic actions. They have trouble assessing the car's approach speed, and therefore, interpret the car's distance as more than it is [7]. Pedestrian children are less visible to a driver due to their smaller body mass, and owing to their lesser body surface area, they are more exposed to multiorgan injury [8]. Another risk is that young children are not secured in child safety seats while traveling in motor vehicles [9].

RTAs rank first among trauma-related pediatric emergency service presentations [10]. Numerous scoring systems have been developed to use a common language in trauma patients. Scoring systems provide information about the relationship between treatment and outcomes [11]. Injury Severity Score (ISS) is the "gold standard" among anatomical injury severity indicators in the trauma population [12,13]. Glasgow Coma Score (GCS), one of the physiological scoring systems used in patient follow-up from the time of admission, is a simple, objective scoring system that can indicate consciousness level and is commonly used in the reliable evaluation of the degree of coma [14].

Trauma cases first present to emergency departments. Data on pediatric RTAs are limited in the literature. In this study, we aimed to investigate pediatric RTA cases in terms of affected body regions, time of the accident, gender, and age, determine the factors affecting mortality and evaluate demographic features and discharge status of the injured pediatric patients who presented to our emergency department within five years.

Materials and methods

Study design and setting

In this retrospective cohort study, we included patients under 18 years of age who were victims of RTAs and presented to the emergency department of our tertiary university hospital between 01/01/2015-31/12/2019. Patients' age, gender, time, and mechanism of accident, body region, type of injury, and clinical outcomes were recorded and analyzed. Patients older than 18 years were excluded.

Our study protocol was approved by Duzce University Ethics Committee on 19/10/2020 with the decision numbered 2020/222.

Study population

Patients aged under 18 years who presented to the emergency department between 01/01/2015 and 31/01/2019 due to road traffic injuries (RTIs) were evaluated according to the demographic data such as age and gender, GCS, ISS, time of presentation, mechanism of the incident, site of injury, length of stay in the emergency department, department of referral, and duration of hospitalization. Statistical correlations were investigated between these parameters and mortality.

Statistical analysis

The normality of continuous data was examined with the Shapiro-Wilk test. The differences between the two groups were analyzed using the Mann-Whitney U test. The correlation between the two categorical variables was assessed with Fisher's Exact test. Continuous variables were expressed as median (IQR) and minimum-maximum values, while categorical data were presented as percentages. All statistical analyses were performed with IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp, USA) software. $P<0.05$ was considered statistically significant.

Results

A total of 137 pediatric patients aged between 0-18 years who presented to the emergency department (ED) due to RTAs between 2015 and 2019 were included. These patients' median age was 14 (8.5-16) years, and 67.2% were males. Of all patients, 71.5% had an accident with motor vehicles other than motorcycles, bicycles, and agricultural vehicles (referred to as “other vehicles”). The least common presentation to the ED was due to bicycle accidents (n=6, 4.4%). Motorcycle, bicycle, and agricultural vehicle accidents were evaluated as out of vehicle road traffic accidents. Of the 98 patients who had RTA with the other vehicle types, 25 (18.2%) had out of vehicle traffic accidents, and 39 (28.5%) had in-vehicle traffic accidents. The remaining cases were unrecorded road traffic accidents since there was no information in the archive about their type. Of all accident victims, 55.5% presented between 4:00 – 11:59 PM.

RTAs most occurred in summer (n=62, 45.3%), in August (n=24, 17.5%), and on Saturdays (n = 35, 25.5%).

Extremity injuries were the most common (n=50, 36.5%), and chest injuries were the least common (n=10, 7.3%) following RTAs. The patients were most frequently diagnosed with extremity fractures (58.4%). Skull fracture and ICH were found in 15.3% and 14.6% of the patients, respectively. On the other hand, pneumothorax (PTX) or hemothorax was found in 7.3% and liver laceration, in 6.6%.

The maximum and minimum ISS and GCS values were 3-41 (median:11), and 3-15, respectively. GCS score was 15 in 120 patients.

The most consulted department was the neurosurgery clinic (n=105, 76.6%), followed by pediatrics (n=96, 70.1%) and orthopedics and traumatology (n=96, 70.1%). Patients were most hospitalized in the orthopedics and traumatology clinic (n=55, 40.1%). The minimum and maximum duration of hospitalization were one hour (n=2, patients who died within 1 hour of

admission) and 911 hours with a median value of 51 (24.5-110) hours.

Of the patients who presented to the ED due to RTAs, six (4.4%) died. The median age was 5.5 (4-11.75) years in patients who died and 14 (9-16) years in those who survived. Of the patients who died, 17% were females, and 83% were males. No statistically significant differences were found between ages and genders in terms of mortality (P=0.057, P=0.663, respectively) (Table 1).

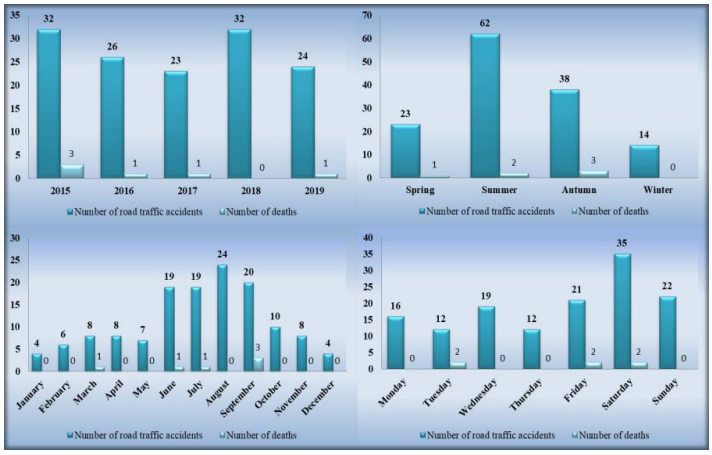
Table 1: Demographic features of the patients and general facts about RTAs

	Total (n=137)	Survived (n=131)	Died (n=6)	*P*-value
Age				0.057
Med (IQR)	14 (8.5-16)	14 (9-16)	5.5 (4-11.75)	
Min-Max	0-18	0-18	1-17	
Gender - n(%)				
Female	45 (32.8)	44 (97.8)	1 (2.2)	0.663
Male	92 (67.2)	87 (94.6)	5 (5.4)	
Vehicle type - n(%)				
Bicycle	6 (4.4)	6 (100)	0 (0)	0.253
Motorcycle	20 (14.6)	20 (100)	0 (0)	
Agricultural vehicle	13 (9.5)	11 (84.6)	2 (15.4)	
Other motor vehicles[a]	98 (71.5)	94 (95.9)	4 (4.1)	
Type of RTA with other motor vehiclees[b]- n(%)				
Pedestrian struck	64 (46.7)	64 (100)	0 (0)	0.516
In-vehicle RTA	39 (28.5)	37 (94.9)	2 (5.1)	
Not recorded	34 (24.8)	32 (94.1)	2 (5.9)	
Incident time - n(%)				
08:00-15:59	46 (33.6)	43 (93.5)	3 (6.5)	0.706
16:00-23:59	76 (55.5)	73 (96.1)	3 (3.9)	
00:00-07:59	15 (10.9)	15 (100)	0 (0)	

(IQR): Interquartile range, [a] other motor vehicles other than bicycle, motorcycle and agricultural vehicles, [b] Type of RTAs that occurred with other vehicles.

The number of traffic accidents and deaths at various times is shown in Figure 1.

Figure 1: Numbers of road traffic accidents and death according to different times



Mortality was significantly lower in patients diagnosed with long bone fractures, while it was significantly higher in patients diagnosed with ICH, rib fractures, and liver laceration (P=0.004, P=0.040, P=0.009, P=0.050, respectively). No mortality occurred among the patients diagnosed with extremity fractures, while near-mortality was higher by 12.4%, 47%, and 19.1% in the patients diagnosed with ICH, rib fractures, and liver laceration, respectively, than those who had no such diagnosis.

ISS was significantly higher, and GCS was significantly lower in the patients who died (P<0.001). The median ISS and GKS scores were 11 (6-16) and 15 (15-15) in the patients who survived, and 28 (20.25-29.75) and 3 (3-4.25) in those who died. Table 2 shows the analysis of all injury sites and diagnoses of the patients.

Table 2: Site of injury and diagnosis of the patients

		Total (n=137)	Survived (n=131)	Died (n=6)	*P*-value
Site of injury- n(%)					
GBT	No	104 (75.9)	100 (96.2)	4 (3.8)	0.631
	Yes	33 (24.1)	31 (93.9)	2 (6.1)	
Head	No	95 (69.3)	91 (95.8)	4 (4.2)	1.000
	Yes	42 (30.7)	40 (95.2)	2 (4.8)	
Chest	No	127 (92.7)	123 (96.9)	4 (3.1)	0.062
	Yes	10 (7.3)	8 (80)	2 (20)	
Abdomen	No	115 (83.9)	112 (97.4)	3 (2.6)	0.052
	Yes	22 (16.1)	19 (86.4)	3 (13.6)	
Extremity	No	87 (63.5)	81 (93.1)	6 (6.9)	0.086
	Yes	50 (36.5)	50 (100)	0 (0)	
Diagnosis- n(%)					
STT	No	126 (92)	120 (95.2)	6 (4.8)	1.000
	Yes	11 (8)	11 (100)	0 (0)	
Incision*	No	134 (97.8)	128 (95.5)	6 (4.5)	-
	Yes	3 (2.2)	3 (100)	0 (0)	
Amputation*	No	136 (99.3)	130 (95.6)	6 (4.4)	-
	Evet	1 (0.7)	1 (100)	0 (0)	
Long Bone Fracture	No	57 (41.6)	51 (89.5)	6 (10.5)	0.004
	Yes	80 (58.4)	80 (100)	0 (0)	
Head region diagnoses- n(%)					
Fracture	No	116 (84.7)	112 (96.6)	4 (3.4)	0.229
	Yes	21 (15.3)	19 (90.5)	2 (9.5)	
Trauma	No	129 (94.2)	123 (95.3)	6 (4.7)	1.000
	Yes	8 (5.8)	8 (100)	0 (0)	
ICH	No	117 (85.4)	114 (97.4)	3 (2.6)	0.040
	Yes	20 (14.6)	17 (85)	3 (15)	
Pneumocephalus *	No	134 (97.8)	129 (96.3)	5 (3.7)	-
	Yes	3 (2.2)	2 (66.7)	1 (33.3)	
Chest region diagnoses- n(%)					
Rib fracture	No	133 (97.1)	129 (97)	4 (3)	0.009
	Yes	4 (2.9)	2 (50)	2 (50)	
Pneumothorax - Hemothorax	No	127 (92.7)	123 (96.9)	4 (3.1)	0.062
	Yes	10 (7.3)	8 (80)	2 (20)	
Lung Contusion*	No	136 (99.3)	131 (96.3)	5 (3.7)	
	Yes	1 (0.7)	0 (0)	1 (100)	-
Abdominal diagnoses- n(%)					
Abdominal trauma	No	132 (96.4)	126 (95.5)	6 (4.5)	1.000
	Yes	5 (3.6)	5 (100)	0 (0)	
Liver laceration	No	128 (93.4)	124 (96.9)	4 (3.1)	0.050
	Yes	9 (6.6)	7 (77.8)	2 (22.2)	
Spleen laceration	No	132 (96.4)	127 (96.2)	5 (3.8)	0.203
	Yes	5 (3.6)	4 (80)	1 (20)	
Kidney laceration *	No	136 (99.3)	130 (95.6)	6 (4.4)	-
	Yes	1 (0.7)	1 (100)	0 (0)	
ISS					
Med (IQR)		11 (6-18)	11 (6-16)	28 (20.25-29.75)	<0.001
Min-Max		3-41	3-41	18-32	
GCS					
Med (IQR)		15 (15-15)	15 (15-15)	3 (3-4.25)	<0.001
Min-Max		3-15	3-15	3-8	

* It could not be analyzed due to the insufficient number of samples, (IQR): Interquartile range

No statistically significant differences were found between consulted departments, including neurosurgery, ophthalmology, pediatric surgery, plastic surgery, thoracic surgery, and ENT clinics in terms of mortality (P=0.178, P=0.308, P=1.000, P=1.000, P=1.000; respectively). Five of the 25 pediatric patients were admitted to the pediatric intensive care unit, and one of the two patients hospitalized in the Anesthesiology and Reanimation clinic died. There was a significant difference between hospitalization durations in terms of mortality (P<0.001). Table 3 shows the analysis of the consulted and hospitalized departments, and duration of hospitalization.

Table 3: Departments of consultation, hospitalization status, findings of the department and time of hospitalization

		Total n=137	Survived n=131	Died n=6	*P*-value
Consulted departments- n(%)					
Neurosurgery	No	32 (23.4)	30 (93.8)	2 (6.3)	0.624
	Yes	105 (76.6)	101 (96.2)	4 (3.8)	
Ophthalmology	No	130 (94.9)	124 (95.4)	6 (4.6)	1.000
	Yes	7 (5.1)	7 (100)	0 (0)	
Pediatric Surgery	No	41 (29.9)	41 (100)	0 (0)	0.178
	Yes	96 (70.1)	90 (93.8)	6 (6.3)	
Plastic surgery	No	129 (94.2)	124 (96.1)	5 (3.9)	0.308
	Yes	8 (5.8)	7 (87.5)	1 (12.5)	
Thoracic surgery	No	133 (97.1)	127 (95.5)	6 (4.5)	1.000
	Yes	4 (2.9)	4 (100)	0 (0)	
Orthopedics	No	41 (29.9)	39 (95.1)	2 (4.9)	1.000
	Yes	96 (70.1)	92 (95.8)	4 (4.2)	
ENT	No	128 (93.4)	122 (95.3)	6 (4.7)	1.000
	Yes	9 (6.6)	9 (100)	0 (0)	
CVS*	No	135 (98.5)	129 (95.6)	6 (4.4)	-
	Yes	2 (1.5)	2 (100)	0 (0)	
O&G*	No	136 (99.3)	130 (95.6)	6 (4.4)	-
	Yes	1 (0.7)	1 (100)	0 (0)	
Urology*	No	136 (99.3)	130 (95.6)	6 (4.4)	-
	Yes	1 (0.7)	1 (100)	0 (0)	
GS*	No	134 (97.8)	128 (95.5)	6 (4.5)	-
	Yes	3 (2.2)	3 (100)	0 (0)	
PICU*	No	136 (99.3)	130 (95.6)	6 (4.4)	-
	Yes	1 (0.7)	1 (100)	0 (0)	
Clinics of Hospitalization- n(%)*					
Pediatric Intensive Care		25 (18.2)	20 (80)	5 (20)	
Anesthesiology and Reanimation		2 (1.5)	1 (50)	1 (50)	
Neurosurgery		30 (21.9)	30 (100)	0 (0)	
Neurosurgical Intensive Care		1 (0.7)	1 (100)	0 (0)	-
Pediatric Surgery		19 (13.9)	19 (100)	0 (0)	
Thoracic Surgery		2 (1.5)	2 (100)	0 (0)	
Obstetrics and Gynecology		1 (0.7)	1 (100)	0 (0)	
Ear-Nose-Throat Diseases		2 (1.5)	2 (100)	0 (0)	
Orthopedics and Traumatology		55 (40.1)	55 (100)	0 (0)	
Duration of hospitalization (hours)					
Med (IQR)		51 (24.5-110)	53 (26-111)	1.5 (1-11.25)	<0.001
Min-Max		1-911	3-911	1-36	

* It could not be analyzed due to the insufficient number of samples, (IQR): Interquartile range

Discussion

In this retrospective study, presentations of vehicle traffic accidents (motorcycle, bicycle, agricultural vehicle, and pedestrian) were higher (75.1%). A low mortality rate was observed in the patients because most vehicles cannot over speed due to geographical conditions. Pediatric RTAs caused many injuries, especially extremity traumas, and were more serious under 15 years of age. In these patients, intracranial hemorrhage, rib fractures, and liver lacerations were evaluated as more serious injuries.

Classification according to the affected body region can help estimate the death rate in RTA patients. The literature has proposed that patients with severe cerebral and abdominal injuries have a high mortality rate. Clinically significant traumatic brain injury and abdominal injury have been observed with musculoskeletal system injuries [15]. It was reported in another study that solid organs such as the spleen, liver, and kidneys are the most damaged organs [16,17]. In the present study, supporting the literature, head trauma was found in 50%, and abdominal and thoracic trauma, in 33% of the patients who died. When the body was regionally examined, extremity trauma ranked first, head trauma second, and abdominal trauma, third. Of the patients with head trauma, six also had extremity injuries and five had abdominal injuries. Isolated region traumas were more common among our patients. Of the patients with an abdominal injury, 9 had liver lacerations, five had spleen lacerations, and one, kidney laceration.

According to the Turkish Statistical Institute (TSI) data, accidents are more common on the roads without traffic lights, traffic signs, or traffic officers. No specific pediatric data could be found [18]. This study was conducted in a rural area with underdeveloped socioeconomic conditions. Mortality is less common in patients following RTAs in a rural area due to vehicles which cannot overspeed because of geographical conditions. Pedestrians, bicycle, and motorcycle drivers are very vulnerable to severe injuries. Risky time zones when RTAs have occurred more commonly included school entrance and exit periods in both morning and afternoon and work rush hours [19].

In a study from our country by Kucuker et al. [20], 41.8% of the injuries were due to in-vehicle accidents and 41.2% due to out of vehicle accidents, whereas in our study, 43% of morbidity and 60% of mortality occurred due to out of vehicle traffic accidents. In another study from our country, RTAs occurred most frequently on weekends and summer days at 12:01 PM and 6:00 PM when traffic was heavy. The accidents occurred out of a vehicle in 57.5% and in-vehicle in 42.5% [21,22].

Supporting the literature, in our study, 103 (75.1%) patients presented to the emergency service due to out of vehicle RTAs (motorcycle, bicycle, agricultural vehicle, or pedestrian). Forty-six patients presented to the emergency department between 08:00 AM and 4:00 PM, and 76 between 4:00 PM and 11:59 PM. The higher rate of RTAs in the evening can be explained by rush hours due to both work and school exit. Besides, in our study, the accidents occurred most on the weekends in summer. Differently, 33.3% of the deaths occurred due to an agricultural vehicle and 66% due to other motor vehicles. This was attributed to the seasonally prolonged summer days, increased time of harvest in agriculture, and children spending more time outdoors. For these reasons, we think that extra measures should be taken regarding traffic in the summer.

Several trauma scoring systems were developed to reduce the rate of morbidity and mortality in children with trauma, including ISS and GCS [12]. After admission to the hospital, the main mortality risk factors include being male, under 15 years of age, and coma. Death risk related to a low GCS has gradually increased, and 54% of those in a severe or deep coma died in the hospital. Most of the patients had a normal GCS, but 1.9% of all RTA victims were in severe or deep coma in our study, consistent with the literature [23].

In another study, the rate of RTAs increased with age, and those aged between 15-19 years were at the highest risk. This was attributed to the change in the used roads as children grow due to increased risk-taking behaviors and distractibility, and the fact that young people are more active in social life. The rate of mortality was higher in males compared to females [24]. In a study from our country, there was male gender dominance in RTAs, and this result was per Turkey Statistics [25,26]. In RTAs, young males more predominantly died [27,28]. Our results were similar to those of the studies conducted in Ethiopia and Gambia that found low rates of admission and mortality [29,30].

The entire bodies of the children are affected by traumas since they have a small body mass and body surface area. Lacerations, penetrating injuries, crush injuries, visceral damage, fractures, and amputations may be seen in pediatric RTAs, which may affect all body regions. In a study conducted from July 2005 through July 2017, the most frequently injured body regions in

RTA patients included lower extremities, chest, upper extremities, head, and spine [16]. In a study by Kourouma et al. [23], 86% of the patients were treated in the emergency department without being admitted to the hospital services. The predominant injury included soft tissue and fractures in about 10% of the patients, mainly in the extremities. Head and lower extremities were the most common anatomic regions of injuries. We evaluated hospitalized patients only. Limb and head trauma were the most common. STT rates were low in patients. According to our study, lower extremity fractures were more common and upper extremity fractures were less common. These results are in accordance with the previous studies in the literature.

In another study from our country, patients were hospitalized in the orthopedics and traumatology (n:124, 36.3%) and neurosurgery (n:87, 25.5%) departments, supporting our data, and the regions most exposed to trauma in patients were the head-neck and extremities [31].

Limitations

Its retrospective nature and limited number of patients were the two main limitations of this study.

Conclusion

Pediatric RTAs are more common under the age of 15 years and outside the vehicle. Although limb injuries are most common, more serious injuries such as intracranial hemorrhage, rib fractures, and liver lacerations are also possible. We could not detect the effect of RTAs on child mortality because of the limited number of cases.

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Effect of type 2 diabetes mellitus on survival in metastatic pancreatic cancer

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The ethics committee approval was obtained from the Ethics Committee Board of University of Health Sciences Okmeydani Training and Research Hospital (ID:48670771-514.10). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Many epidemiological studies describe a relationship between pancreatic cancer (PC) and Diabetes mellitus (DM). However, there are not enough studies investigating the effect of DM on survival of patients with metastatic PC. The purpose of this retrospective study was to investigate the effect of DM and its treatment on survival of patients with metastatic PC who received chemotherapy (CT) as first line treatment.

Methods: Patients with metastatic PC who were followed up at the department of medical oncology between 2006 and 2018 were enrolled in this retrospective cohort study. Patients aged 18 years and over, who had metastatic disease at diagnosis and were treated with CT were analyzed. Patients with DM were stratified into two groups based on the history of medical treatments used for DM as follows: Oral antidiabetic (OAD) and OAD + insulin combination.

Results: Following results were obtained after analyzing the medical records of 372 patients with metastatic PC, among which 125 (33.6%) had type II DM at the time diagnosis: The median age of the patients was 61 (range: 28-83) years. There were 136 (36.6%) female patients, and the median overall survival (OS) was 9.0 months in patients without DM, and 7.0 months (P=0.023) in those with DM. OS was 8.0 months in diabetic patients using OAD+insulin combination compared to 7.0 months in those receiving OAD (P=0.614) only. Multivariate analysis revealed that the presence of DM [Hazard ratio (HR), 1.43)], Eastern Cooperative Oncology Group Performance Status 3 (HR, 1.62), treatment with gemcitabine+Nab-paclitaxel (HR, 0.29) or folfirinox (HR, 0.46), and CA 19-9 level (HR, 1.01) were factors related to OS.

Conclusion: In our study, we observed that the presence of DM adversely affected survival in metastatic PC patients who received CT as first line treatment; however, whether these patients used OAD or OAD+insulin combination did not affect survival.

Keywords: Pancreas cancer, Diabetes mellitus, Fasting plasma glucose, Survival, Prognosis

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Introduction

Exocrine pancreatic cancer (PC) is an extremely lethal malignancy. It is the fourth leading cause of cancer-related deaths in the United States. Worldwide, it is the eighth leading cause of deaths in both females and males, with incidence and mortality rates varying by gender and race [1-3]. The most common type of PC is pancreatic ductal adenocarcinoma (PDAC). Only 15-20% of patients can be diagnosed at an early stage, with a poor prognosis even after achieving an R0 resection [1, 4].

Type II diabetes mellitus (DM) is a chronic disease characterized by hyperglycemia, insulin resistance, and impairment of insulin secretion. The prevalence of DM has increased dramatically over the past decade due in large part to obesity and sedentary lifestyle [5, 6]. There have been many studies showing that the risk of PC increases in diabetic patients. In a meta-analysis, the risk of PC was approximately 2-fold higher in patients with DM compared to those without DM [7]. In a prospective cohort study, those with a plasma fasting glucose (FPG) level above 200 mg/dl were at least 2 times more likely to die from PC than those with FPG level ≤119 mg/dl [8]. Similarly, another prospective study showed that elevated FPG level, insulin concentration, and insulin resistance were significantly correlated with the risk of PC [9].

Many epidemiological studies describe the relationship between DM and PC [7, 10-13]. However, there are not enough studies investigating the effect DM on survival of patients with metastatic PC. Nakai et al. found that the presence of DM had no prognostic effect on PC in a study including 250 metastatic PC patients [14]. Choi et al. analyzed metastatic PC patients receiving chemotherapy (CT) and reported that patients with PC accompanied by DM tended to survive longer than those without DM [15]. However, in a recent study with 350 metastatic PC patients, presence of long-term DM (≥4 years) negatively affected survival [16].

The present study was designed to assess the effects of DM and its treatment on survival of patients with metastatic PC who received CT as first-line therapy.

Materials and methods

Patient enrollment

Patients with PC, who were treated and followed up from 2006 through 2018 at the department of medical oncology, Prof. Dr. Cemil Taşcıoğlu Training and Research hospital, were analyzed retrospectively. The inclusion criteria were defined as follows: Age equal to or greater than 18 years, PC patients with complete medical data, metastatic stage, and those treated with CT. Besides the patients not meeting the eligibility criteria mentioned above, histology other than PDAC and patients with type I DM were excluded from the study. Laboratory data such as FBG, CA19-9, and CEA were obtained before the initiation of CT. A total of 372 patients with PC who met the inclusion criteria were enrolled in the analysis.

Ethics approval

All the stages and related procedures of the present study were performed in accordance with the Declaration of Helsinki. The approval of study was obtained from the Ethics Committee of the Prof. Dr. Cemil Taşcıoğlu Training and Research Hospital (ID: 48670771-514.10).

Data collection

The clinical and demographic features of all patients, such as age, gender, ECOG PS, history of smoking, alcohol use, comorbidities, body mass index (BMI), treatment of DM, the interval between the diagnosis of DM and PC, grade, the site of metastasis, the development or presence of deep venous thrombosis (DVT), FPG at the time of diagnosis, the levels of CEA and CA 19-9 before CT treatment, the first-line CT regimen, and final status were obtained carefully from the hospital medical records.

Stratification

Patients with PC were divided into two groups according to presence of type II DM at the time of diagnosis. Next, pancreatic cancer patients with DM were stratified into two groups based on the history of medical treatments used for DM as follows: Oral antidiabetic (OAD) and OAD + insulin combination.

Statistical analysis

Statistical Package for the Social Sciences 22.0 for Windows (IBM Corp. 2013) was used for analysis. Numerical variables were analyzed using student t-test if normally distributed, and Mann Whitney U test was used otherwise. The comparison of the rates between the groups was carried out with the chi-square test. Survival analyses were conducted using Kaplan-Meier method. Determinant factors were examined with cox regression analysis. Forward stepwise model was performed for the factors with *P*-value <0.200. An overall 5% Type-I error level was used to infer statistical significance. Median overall survival (OS) was defined as the time from the date of diagnosis to the date of death or last follow-up.

Results

A total of 372 PC patients metastatic at diagnosis, 125 (33.6%) of which had type II DM, were included. The median age was 61 (range, 28-83) years. Of the 372 patients, 136 (36.6%) were female. ECOG PS was 3 in 38 (10.2%) patients. Smoking history was present in 208 (55.9%) patients. Among those with DM, 65 (52%) patients received insulin + OAD, while 60 (48%) patients used OAD. The median time from the date of DM diagnosis to the date of PC development was 12 months (Table 1).

At the time of diagnosis, the sites of metastasis in decreasing order were the liver (n: 297, 79.8%), peritoneum (n: 53, 14.2%), lung (n: 50, 13.4%), distant lymph nodes (n: 20, 5.4%), bone (n: 18, 4.8%), and others [spleen, kidney, adrenal (n: 6, 1.6%)] (Table 1).

The treatment regimens used for PC, in decreasing order, were single-agent gemcitabine (37.1%), cisplatin + gemcitabine (32.0%), FOLFIRINOX (19.6%), gemcitabine + Nab-paclitaxel (4.3%), gemcitabine + capecitabine (3.8%), and FOLFOX (3.2%) (Table 1).

The median age of PC patients with DM was 64 years (range, 45-81), which was longer than that of those without DM. In addition, some parameters were more frequent in diabetic group, including female gender, HT, Grade 3 tumor, and increased FPG (Table 1).

Table 1: Patient data

Characteristic		Patients (n= 372) n	%	DM (-) (n= 247) n	%	DM (+) (n=125) n	%	*P*-value
Age (year)	Median (min-max)	61 (28-83)		59 (28-83)		64 (45-81)		<0.001
	≥65	134	36.0	73	29.6	61	48.8	0.001
	<65	238	64.0	174	70.4	64	51.2	
Gender	Men	236	63.4	166	67.2	70	56.0	0.034
	Women	136	36.6	81	32.8	55	44.0	
ECOG PS	0-1	231	62.1	157	63.6	74	59.2	0.731
	2	103	27.7	66	26.7	37	29.6	
	3	38	10.2	24	9.7	14	11.2	
Smoking	Yes	164	44.1	101	40.9	63	50.4	0.081
	No	208	55.9	146	59.1	62	49.6	
	Active	146	69.5	100	68.5	46	71.9	0.072
	Ex-smoker	62	29.5	46	31.5	16	25.0	
Alcohol use	yes	18	4.8	13	5.3	5	4.0	0.616
Comorbidity	HT	79	21.2	30	12.1	49	39.2	<0.001
	CIHD	27	7.3	15	6.1	12	9.6	0.216
	COPD	22	5.9	14	5.7	8	6.4	0.777
	CHF	12	3.2	9	3.6	3	2.4	0.521
BMI (Kg/m^2)	Mean (SD)	24.9 (4.9)		24.6 (4.2)		26.0 (4.2)		0.211
DM treatment	Insulin + OAD	65	52.0			65	52.0	
	OAD	60	48.0			60	48.0	
Time interval between DM diagnosis and PC development (year) Median (min-max)		12 (6-46)				12 (6-46)		
grade	I	15	4.0	8	3.2	7	5.6	0.002
	2	269	72.3	193	78.1	76	60.8	
	3	88	23.7	46	18.6	42	33.6	
The site of metastasis at diagnosis	liver	297	79.8	200	81.0	97	77.6	0.444
	Peritoneum	53	14.2	33	13.4	20	16.0	0.491
	Lung	50	13.4	29	11.7	21	16.8	0.177
	Distant LN	20	5.4	12	4.9	8	6.4	0.533
	Bone	18	4.8	13	5.3	5	4.0	0.592
	Other (spleen, kidney, and surrenal)	6	1.6	4	1.6	2	1.6	0.989
DVT	No	333	89.8	224	90.7	109	87.9	0.404
	Yes	38	10.2	23	9.3	15	12.1	
FPG (mg/dL)	Mean (SD)	136.2 (71.8)		108.9 (21.7)		155.4 (71.8)		0.001
CEA (ng/mL)	Mean (SD)	219.1 (2319.6)		256.6 (2852.3)		229.5 (1739.9)		0.484
CA 19-9 (U/mL)	mean (SD)	4352.1 (31295.1)		5514.8 (37985.8)		3671.9 (8195.1)		0.360
First-line regimen	FOLFIRINOX	73	19.6	48	19.4	25	20.0	0.782
	Gemcitabine	138	37.1	91	36.8	47	37.6	
	gemcitabine + Nab-paclitaxel	16	4.3	9	3.6	7	5.6	
	FOLFOX	12	3.2	10	4.0	2	1.6	
	Gemcitabine+ capecitabine	14	3.8	10	4.0	4	3.2	
	Cisplatin ± gemcitabine	119	32.0	79	32.0	40	32.0	
Final status	Dead	347	93.3	228	92.3	119	95.2	0.293
	Alive	25	6.7	19	7.7	6	4.8	

CIHD: Chronic ischemic heart disease, COPD: Chronic obstructive pulmonary disease, CHF: Congestive heart failure, FPG: Fasting plasma glucose, CA19-9: carbohydrate antigen 19-9, CEA: carcinoembryonic antigen, CIHD: Chronic ischemic heart disease, DM: Diabetes mellitus, DVT: deep vein thrombosis, ECOG PS: Eastern Cooperative Oncology Group Performance Status, FOLFIRINOX: Fluorouracil: leucovorin, irinotecan, and oxaliplatin, g/dL, Grams Per Deciliter, HT: hypertension, LN: lymph node, ng/mL, Nano-gram/milliliter, OAD: Oral antidiabetic combination, OS: overall survival, U/mL, Units per milliliter.

During a median 10-month follow up, 347 (93.3%) patients died. Median OS was 9.0 months (95 % CI, 7.7-10.2) in patients without DM vs. 7.0 months (95 % CI, 5.4-8.5) in those with DM (Log rank *P*=0.023) (Figure 1). OS was 8.0 months (95 % CI, 5.7-10.2) in diabetic patients using OAD + insulin combination compared to 7.0 months (95 % CI, 5.1-8.8) in those receiving OAD (Log rank *P*=0.614) (Figure 2).

In univariate analysis, presence of DM (HR, 1.277, 95% CI, 1.020-1.598), ECOG PS 3 (HR, 1.629, 95% CI, 1.133-2.341), and treatments with gemcitabine + Nab-paclitaxel (HR, 0.412, 95% CI, 0.227-0.746) or FOLFIRINOX (HR, 0.450, 95% CI, 0.331-0.610) were determined as factors affecting survival. Multivariate analysis indicated that presence of DM (HR, 1.433, 95% CI, 1.109-1.852), ECOG PS 3 (HR, 1.628, 95% CI, 1.081-2.241), treatments with gemcitabine + Nab-paclitaxel (HR, 0.293, 95% CI, 0.146-0.586) or FOLFIRINOX (HR, 0.465, 95% CI, 0.327-0.661), and elevated CA 19-9 (HR, 1.001, 95% CI, 1.000-1.002) were the independent predictors of OS (Table 2).

Table 2: Univariate and multivariate analysis for OS

Characteristic		Univariate analysis for OS HR	95 % CI for HR	*P*-value	Multivariate analysis for OS HR	95 % CI for HR	*P*-value
Age (Year)	>65 vs. ≤65	1.014	0.814-1.262	0.903			
Gender	Female vs. Male	0.891	0.713-1.112	0.306			
Smoking	Yes vs. No	0.890	0.718-1.102	0.286			
DM	Yes vs. No	1.277	1.020-1.598	0.032	1.433	1.109-1.852	0.006
HT	Yes vs. No	0.831	0.640-1.079	0.165			
CIHD	Yes vs. No	0.851	0.566-1.280	0.439			
COPD	Yes vs. No	1.008	0.654-1.544	0.970			
CHF	Yes vs. No	0.893	0.501-1.590	0.701			
BMI	kg/m^2	1.000	0.958-1.045	0.993			
ECOG PS	0-1	Ref.		0.001	Ref.		0.036
	2	1.509	1.185-1.922	0.001	1.269	0.956-1.683	0.099
	3	1.629	1.133-2.341	0.008	1.628	1.081-2.241	0.020
Grade	3 vs. 1-2	1.078	0.843-1.376	0.547			
Liver metastasis	Yes vs. No	0.845	0.636-1.121	0.242			
Peritoneum metastasis	Yes vs. No	0.900	0.669-1.209	0.483			
Lung metastasis	Yes vs. No	1.211	0.891-1.643	0.220			
Distant LN metastasis	Yes vs. No	0.856	0.531-1.379	0.523			
Bone metastasis	Yes vs. No	0.763	0.467-1.245	0.280			
Other	Yes vs. No	1.209	0.538--2.713	0.646			
DVT	Yes vs. No	1.180	0.833-1.669	0.350			
First-line regimen	Gemcitabine	Ref.		<0.001	Ref.		<0.001
	Gemcitabine + Nab-paclitaxel	0.412	0.227-0.746	0.003	0.293	0.146-0.586	0.001
	FOLFOX	0.893	0.493-1.616	0.707	1.270	0.653-2.456	0.481
	Gemcitabine + capecitabine	0.632	0.356-1.120	0.116	0.576	0.250-1.321	0.193
	Gemcitabine + cisplatin	0.836	0.650-1.074	0.161	0.865	0.651-1.150	0.320
	FOLFIRINOX	0.450	0.331--0.610	<0.001	0.465	0.327-0.661	<0.001
Glucose	mg/dL	0.999	0.996-1.002	0.540			
CEA	ng/mL	0.999	0.999-0.1001	0.388	0.999	0.999-1.001	0.053
CA 19-9	U/mL	0.999	0.999-1002	0.105	1.001	1.000-1.002	0.044

Figure 1: Overall survival in all patients according to the presence of diabetes mellitus

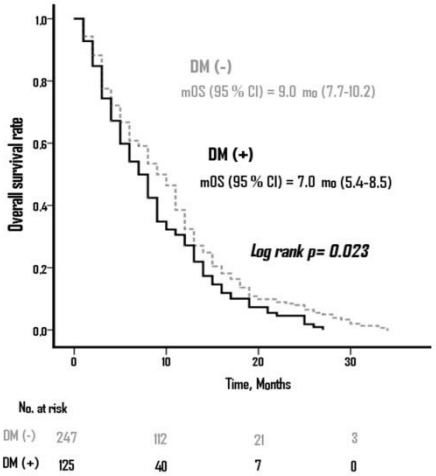
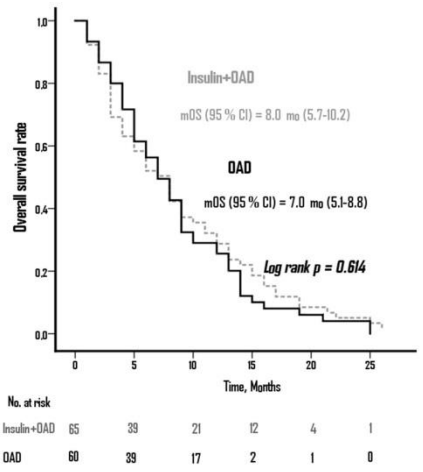


Figure 2: Overall survival in patients with diabetes mellitus according to the anti-diabetic treatment



Discussion

The present study investigated the impact of DM and its treatment on the survival of metastatic pancreatic cancer patients treated with CT, concluding that DM adversely affected survival in pancreatic cancer patients, but treatment for DM was not associated with it.

Undoubtedly, DM is a major and growing health problem which is related to significant comorbidities. Epidemiological data revealed an increased risk of PC with DM. There are also several studies showing that anti-diabetic drugs may significantly reduce the risk of PC and therefore increase the survival of affected patients [17-19]. Most studies examining the effect of DM on PC prognosis have been performed with patients who underwent surgery for PC and the results are therefore conflicting. In a study of 74 surgically resected PC patients, uncontrolled severe hyperglycemia rather than the presence of DM negatively affected survival after pancreatic cancer resection [20]. However, in a study by Lee et al. [21] including patients who underwent resection for PC, the presence of DM at diagnosis significantly reduced both disease-free survival and OS; with a median OS of 28 months in diabetic patients compared to 33 months in those without DM. The median time from DM diagnosis to PC development was shorter than 2 years. More recently, another study reported that patients with DM have more aggressive tumors and higher surgical morbidity, concluding that they have significantly shorter survival than those without DM and this effect is more pronounced in patients undergoing neoadjuvant CT [22]. Similarly, in a meta-analysis involving 6 studies, survival was significantly shorter in PC patients with DM who received adjuvant CT, compared those without DM [23].

Choi et al. [15] performed a study enrolling 183 advanced-stage PC patients, of which 160 had DM, reporting the median OS as 8.4 months in patients with DM vs. 7.5 months in those without DM. Authors also showed that median OS was 11.0 months in patients using metformin compared to 7.9 months in those not receiving metformin, suggesting that patients with DM tended to have longer OS than those without DM. In addition, metformin treatment was associated with longer OS. Likewise, in another study, OS was 13.3 months in advanced-stage PC patients with DM, while it was 10.0 months in those without DM. However, neither DM nor anti-diabetic therapy had a prognostic effect on disease survival [14].

In a meta-analysis by Ma et al. [23] analyzing both early- and advanced-stage PC patients, the risk of mortality was high in patients treated with CT. Another meta-analysis performed by Mao et al. [24] found that the effect of DM on OS was associated with the tumor stages and the duration of DM. Recently, Lizumi et al. [16] conducted a study with metastatic PC patients who had DM and received a single-agent gemcitabine. When patients were divided into 2 groups based on the duration of PC development after DM diagnosis as short-term DM (n: 87, <4 years) and long-term DM (n: 45, ≥4 years), long-term DM was associated with shorter PFS and OS. Similarly, in our study, median OS was significantly shorter in PC patients with DM. Only in 9 (7.2%) patients, the time between DM and PC diagnosis was ≤ 4 years. However, no significant relationship between treatments used for DM and survival was found in our study.

Previous studies have shown that DM is associated with some poor prognostic factors, including a higher tumor stage, a more aggressive clinical behavior, greater rates of lymph node metastasis, and increased perineural invasion [21, 25-27]. In our study, shorter survival in patients with DM is likely due to the more aggressive nature of tumor.

Our study included relatively greater sample size compared to the previous studies, providing a real-life data. In addition, we could analyze the effect of using OAD or insulin treatment on survival.

Limitations

Due to its retrospective nature, the results of our study might be inherently flawed by selection bias. Moreover, HbA1C levels of the patients were missing. The data regarding the OAD or insulin medication could not be given in detail.

Conclusion

Summing up, we observed that the presence of DM adversely affected disease survival in metastatic PC patients who received CT as first line treatment, however, whether these patients used OAD or insulin + OAD did not affect survival. Our findings need to be confirmed by larger studies.

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Retrospective analysis of the use of 22-gauge and 25-gauge needles for EUS-guided fine needle aspiration of solid lesions

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Ethics Committee Approval
The study protocol was approved by the ethics committee of Gaziosmanpasa Hospital (Approval number: 2020/190). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Data on the comparison of diagnostic yields of 22-gauge (22G) and 25-gauge (25G) needles used in endoscopic ultrasound guided fine needle aspiration (EUS-FNA) biopsy usually include solid pancreatic masses. In our study, we compared the diagnostic yield, safety, and performance characteristics of 22G and 25G needles in the EUS-FNA of various solid lesions in or adjacent to the upper gastrointestinal wall and suspicious lymph nodes.
Methods: In this retrospective cohort study, we enrolled patients who underwent EUS-FNA using 22G and 25G needles between August 2018 and January 2020. We compared EUS-FNA results with histological findings in operated patients and long-term clinical follow-up results in non-operated patients.
Results: Seventy-nine patients (40 patients with 22G needles) were enrolled. There were pancreatic solid masses in 50 (63.3%) patients, subepithelial lesions in 13 (16.5%), suspicious lymph nodes in 12 (15.2%), and various lesions adjacent to the lumen in 4 (5.1%) patients. The diagnostic yield of 22G and 25G needles were 92.5% and 94.9%, respectively, which were similar (P=0.664). EUS-FNA of 2 pancreatic masses required a crossover from a 22G needle to a 25G needle due to lesion stiffness. The technical success rate for the lesion type was 100% and 95% for 25G and 22G needles, respectively (P=0.160). No major complications were observed with either needle.
Conclusions: The 25G needle was not superior to the 22G needle in terms of diagnostic yield and safety profile in EUS-FNA of solid lesions. The use of 25G needles in hard masses can provide ease of puncture.

Keywords: EUS-FNA, cytopathology, 22-gauge needle, 25-gauge needle

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Introduction

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is a widely used method to accurately obtain tissue from suspicious lesions of the gastrointestinal lumen and adjacent structures [1, 2].

The diagnostic accuracy of EUS-FNA in pancreatic masses is over 85% and has high sensitivity (75% to 92%) and specificity (82% to 100%) [3]. In addition, low complication rates of 1-2% have been reported [4]. The most common complications are bleeding, pancreatitis, or perforation [5].

The needles used in EUS-FNA are 19-gauge (19G), 22-gauge (22G), and 25-gauge (25G), and the most used needle in the world is 22G [6]. Needle size is thought to affect diagnostic accuracy and complication rate. With a thicker needle, more samples can be obtained, but it may result in contamination of the sample with blood and decrease diagnostic efficiency. The 22G needle is more difficult to penetrate hard pancreatic masses, and its less flexibility limits its use in situations where the endoscope must be bent. However, the 25G needle is easier to use in calcified hard masses and transduodenal procedures due to its thin and flexible nature. In addition, samples are less contaminated with blood because they are less traumatic [2, 4]. For these reasons, the decision of which needle to use should be evaluated according to risks and benefits. In studies, the diagnostic yield and safety profile of 22G and 25G needles in EUS-FNA is generally limited to pancreatic masses [7]. There are fewer studies evaluating non-pancreatic masses.

In this study, we compared the diagnostic yield, safety, and performance characteristics of 22G and 25G needles in EUS-FNA of solid pancreatic masses, subepithelial lesions, and suspicious lymph nodes.

Materials and methods

This study was carried out in the Health Sciences University Gaziosmanpaşa Hospital. Patients with suspected solid mass lesions in or around the upper gastrointestinal tract wall who underwent the EUS-FNA procedure with 22G and 25G needles (Boston Scientific; Natick, MA, USA) between August 2018 and January 2020 were included in the study. Cystic lesions were included in the study if they had solid nodules or if malignancy was suspected, others were excluded.

Demographic characteristics, clinical findings, lesion characteristics, pathological findings, and follow-up results of the patients were analyzed retrospectively. Computed tomography (CT) or magnetic resonance imaging (MRI) of the lesions were available in all patients.

The study protocol was approved by the ethics committee of Gaziosmanpasa Hospital (Approval number: 2020/190) and conformed with the Declaration of Helsinki. All included patients provided informed consent.

Intervention

A linear array echoendoscope (Fujifilm EG-580UT, Tokyo, Japan) was used for EUS guided sampling. Patients were sedated with meperidine hydrochloride and midazolam or propofol. All procedures were performed by the same endosonographer. The size of the needle to be used was decided by the endosonographer according to the location and character of the lesion, and needle availability. There was no pathologist on-site at the time of EUS-guided sampling. During the sampling process, 3 passes were applied in most patients and the needle was moved back and forth within the lesion at least 6 times in each pass. In the first pass, negative pressure was applied with the slow pull technique of the stylet. In others, the stylet was removed, and negative pressure was applied with a 10 ml syringe. If there was excessive contamination with blood in the previous pass, suction was not applied with a syringe. The materials obtained were placed on glass slides and in formalin solution.

Cytological malignancy diagnosis confirmed by histopathology in patients who underwent surgery was considered true positive. Diagnoses of patients who did not undergo surgery were confirmed by CT, MRI, fluoro d-glucose positron emission tomography, or ^{68}Ga DOTATOC positron emission tomography, together with clinical follow-up. Benign cytological diagnosis or suspected diagnosis obtained in EUS-guided sampling was confirmed by at least 12 months of clinical follow-up and repeated CT or MRI. Non-cellular specimens or specimens containing indeterminate material due to contamination with blood were considered non-diagnostic material.

Statistical analysis

The normality of distribution of numerical variables was tested by Shapiro Wilk test. Student's t-test and Mann Whitney U test were used to compare normally and non-normally distributed variables, respectively, in two independent groups. Relationships between categorical variables were evaluated with the Chi-square test. SPSS 22.0 Windows version package program was used for analysis. $P<0.05$ was considered significant.

Results

A total of 79 patients who underwent EUS-FNA with 22G and 25G needles in solid lesions in the upper gastrointestinal wall or adjacent to it were enrolled in the study. There were 40 patients (25 males, 15 females) in the 22G needle group and 39 patients (27 males, 12 females) in the 25G needle group. The mean ages were 57.62 (13.17) years and 62.41 (12.54) years in the 22G and 25G needle groups, respectively ($P=0.104$). There was no significant difference between the two groups in terms of location ($P=0.498$) and size ($P=0.645$) of lesions (Table 1).

Table 1: Baseline characteristics

	22G (n = 40)	25G (n = 39)	*P*-value
Sex, males, n (%)	25 (62.5)	27 (69.3)	0.631
Age, mean (SD), years	57.62 (13.17)	62.41 (12.54)	0.104
Location of lesion, n (%)			
Pancreatic masses	24 (60)	26 (66.7)	
Subepithelial lesions	9 (22.5)	4 (10.2)	0.498
Lymph nodes	5 (12.5)	7 (17.9)	
Others	2 (5)	2 (5.1)	
Correct diagnosis, n (%)	37 (92.5)	37 (94.9)	0.664

SD: standard deviation, 22G: 22-gauge, 25G: 25-gauge

EUS-FNA was performed for 50 (63.3%) solid pancreatic masses, 13 (16.5%) subepithelial lesions, 12 (15.2%) suspicious lymph nodes, and 4 (5.1%) solid lesions adjacent to the gastrointestinal lumen. The mean diameter of the mass lesions in the long axis was 31.04 (15.71) mm among all patients. The mean sizes of the lesions are shown in Table 2.

Of the pancreatic lesions, 29 (58%) were located in the head of the pancreas, 3 (6%), in the uncinate process, and 18 (36%), in the body-tail region. EUS-FNA was performed with a 25G needle in 16 (55.2%) of the lesions on the head of the pancreas and a 22G needle in 13 (44.8%). A 25G needle was used in 7 (38.9%) of the pancreatic body-tail lesions and a 22G needle was used in 11 (61.1%). 25G needle was used in 3 (100%) of pancreatic uncinate process lesions because of its manipulability. Thirty-eight pancreatic lesions were malignant (30 adenocarcinomas, 1 metastasis from small cell lung cancer, 1 metastasis from squamous lung cancer, 1 metastasis from renal cell carcinoma, 3 neuroendocrine tumors, and 2 cystic tumors) and 9 were benign. One neuroendocrine tumor was less than 20 mm in size and no growth in tumor size was observed during follow-up. The cytological diagnosis could not be made in 1 case in which a 22G needle was used because the sample was contaminated with blood and in 1 case where the sample was insufficient. One case had a false negative result with a 25G needle, and the patient underwent surgical resection according to MRI and clinical findings. There was evidence of malignancy on surgical histopathology. None of the patients had false-positive results (Table 3).

Table 2: Types and diameters of lesions

	Lesion characteristics				
	22G needle		25G needle		*P*-value
	n	Mean diameter, mm (SD)	n	Mean diameter, mm (SD)	
Pancreatic masses	24	32.1 (12.7)	26	29.2 (11.7)	0.409
Subepithelial lesions	9	35.5 (21.8)	4	44.7 (38.4)	0.587
Lymph nodes	5	18.4 (7.0)	7	24.6 (13.1)	0.364
Other lesions	2	42.5 (10.6)	2	37.0 (9.9)	-
All lesions	40	31.7 (15.2)	39	30.4 (16.3)	0.645

SD: standard deviation, 22G: 22-gauge, 25G: 25-gauge

Table 3: Final diagnosis for the 22-gauge and 25-gauge needle groups

	22G needle n = 40	25G needle n = 39
Pancreatic masses, n		
Adenocarcinoma	14	16
Metastasis	1	2
Neuroendocrine tumor	2	2
Mucinous neoplasm	1	0
Pseudopapillary tumor	0	1
Chronic pancreatitis	2	3
Lymphangioma	1	0
Normal pancreas	1	1
Nondiagnostic/Incorrect diagnosis	2	1
Subepithelial lesions, n		
GIST	5	2
Gastric leiomyoma	2	2
Gastric aberrant pancreas	1	0
Neuroendocrine tumor	1	0
Lymph nodes, n		
Malignant	2	3
Benign	2	4
Nondiagnostic	1	0
Others, n		
Mesothelioma	1	0
Metastasis of adenocarcinoma	1	0
Duodenal GIST	0	1
Nondiagnostic	0	1

22G: 22-gauge, 25G: 25-gauge, GIST: Gastrointestinal stromal tumor

Of the gastric subepithelial lesions, 6 of 7 cases of gastrointestinal stromal tumor (GIST) had malignant features and their mean diameter was 59.5 (22.4) mm. One patient had two malignant neuroendocrine tumors, one of the lesions was 30 mm in size in the stomach wall, and the other was 57 mm in size and adhered externally to the large curvature area of the stomach. Of the lymph nodes, 5 had metastases, 1 had granulomatous lymphadenopathy, and 5 were normal lymph nodes. The sample obtained from 1 lymph node with a 22G needle was insufficient for diagnosis.

One of the 4 lesions in the other group was a large mediastinal mass that could not be characterized by samples on the EUS-FNA. No progress was observed in the lesion in the 2-year follow-up of the patient who refused surgery.

Surgical histopathology was present in pancreatic masses in 10 (38.5%) cases for the 25G needle and in 7 (29.2%) cases for the 22G needle. In others, the diagnosis was supported by clinical follow-up and imaging. Surgical resection was performed in 11 (36.7%) patients with pancreatic adenocarcinoma, 16 (53.3%) patients received chemoradiotherapy, 3 (10%) patients were treated conservatively. In addition, 3 neuroendocrine tumors, 2 cystic tumor cases, and 1 case with false-negative cytology results were operated for pancreatic lesions. Surgical resection was performed in 6 cases of GIST and 1 neuroendocrine tumor in gastric subepithelial lesions.

There was no significant difference between the 22G and 25G needles in terms of accuracy of cytological diagnosis (P=0.664). The rates of diagnosis with 22G and 25G needles were 92.5% and 94.9%, respectively. The diagnosis could not be made in 3 (7.5%) cases with 22G needle and 1 (2.5%) case with 25G needle. In addition, a false negative diagnosis was made in 1 (2.5%) case with a 25G needle.

The mean follow-up time for lesions evaluated as benign and suspicious was 532 (128) days. There was no progression in these lesions during follow-up.

The technical success rates of both needles were 100% according to the localization of the lesions. In addition, EUS-FNA of 2 hard pancreatic masses required a crossover from a 22G needle to a 25G needle and was successful with a 25G needle. The technical success rate for the lesion type was 100% and 95% for 25G and 22G needles, respectively (P=0.160).

No major complications were observed in patients after EUS-FNA. One patient had mild abdominal pain and mild amylase and lipase elevation after obtaining a sample from the solid nodule within the pancreatic cystic lesion with a 22G needle, but symptoms regressed within 24 hours.

Discussion

The results of our study showed that 25G needle is not superior to 22G needle in EUS-FNA of solid pancreatic masses, subepithelial lesions, and suspicious lymph nodes. Diagnostic yields and safety profiles of both needles were similar. The technical success rates for the lesion type were 100% and 95% for 25G and 22G needles, respectively. In addition, EUS-FNA performance in our series was comparable to other studies.

The selection of needle size in EUS-guided sampling is complex and may vary according to the type and localization of the lesion [8]. Endosonographers prefer 25G needles in transduodenal approach and pancreatic uncinate lesions because of its flexibility and easier manipulation [9, 10]. Sakamoto et al. [11] reported the technical success of 25G and 22G needles in pancreatic uncinate lesions as 100% and 33.3%, respectively. In addition, 22G needle penetration into calcified and fibrotic hard masses is more difficult than 25G needle [2, 12]. In our study, a 25G needle was preferred for pancreatic uncinate process lesions. None of the patients required a change from a 22G needle to a 25G needle due to the transduodenal approach in

pancreatic head masses. However, due to the lesion stiffness, 2 pancreatic masses required cross-over in EUS-FNA from a 22G needle to a 25G needle and was successful with a 25G needle. The difference between them was not significant. Although the technical success rate in hard masses is better with the 25G needle, the reason for the insignificance of difference may be the sparse number of cases. From the point of view of the endosonographer, the 25G needle is easier to advance, especially when the tip of the echoendoscope is angled, and it is easier to pass through hard, calcified masses. However, due to the 25G needle's thin gauge, it tends to bend more when at maximum height.

Although it is thought that larger needles may increase diagnostic yield by obtaining more samples in EUS-FNA, many studies have shown that needle size is not effective in diagnostic yield [4,6,7]. However, Sakamoto et al. [11] showed that the 25G needle (91.7%) was superior to the 22G (75.0%) and the tru-cut needles (45.8%) in achieving a cytological diagnosis. Camellini et al [2] investigated whether a 25G needle reduced the number of passes compared to a 22G needle during EUS-guided sampling but found no differences. In our study, the diagnostic efficiency of the two needles were similar. In EUS-FNA of all lesions, the diagnostic yield of the 22G needle was 92.5%, and that of 25G needle was 94.9%. The number of non-diagnostic materials was 3 (7.5%) for a 22G needle. For the 25G needle, there was 1 (2.5%) non-diagnostic material and 1 (2.5%) false-negative result. False-negative case was diagnosed as a malignancy on surgical histology.

Our study had a longer follow-up period than other studies with an average follow-up period of 532 (128) days in lesions considered benign or suspicious. No progress was observed in the lesions, clinical or imaging studies of the cases followed.

It has been suggested that the usefulness of EUS-FNA is limited in subepithelial lesions [13]. It was observed that insufficiency was more pronounced in small lesions and non-mesenchymal tumors [14]. However, in mesenchymal tumors, problems with immune staining in EUS-guided samples and the inability to determine mitotic index are among the factors limiting its usefulness [13, 15]. In our series, there were few subepithelial lesions (n=13), and since most of these lesions were mesenchymal tumors, the usefulness rate of EUS-FNA was high. However, histology was still required for the exact determination of the mitotic index.

In EUS-FNA of lymph nodes, Vilmann et al. [4] showed that with a large series of patients, the 25G needle had slightly better performance than the 22G needle (94% vs 89%). However, a study with a smaller patient series reported excellent performance for both needles in lymph node EUS-FNA [2]. In our study, we had a small lymph node group and while the diagnosis was made in all cases in the 25G needle group, it could not be diagnosed in 1 case due to insufficient material in the 22G needle group.

EUS-FNA complication rates in pancreatic masses are between 1-2% and it is generally a safe procedure [10, 16, 17]. Pancreatitis, infection, bleeding, and perforation are among these complications. In our study, there was no clinically significant complication in either needle. Only 1 patient had mild abdominal pain, mild amylase and lipase elevation after 22G needle EUS-FNA of the solid nodule within the pancreatic cystic lesion, and the patient's complaints improved after 24 hours of observation.

Limitations

The limitation of our study includes its retrospective design, where it is not possible to determine the number of the needle passes and the amount of material obtained according to the number of passes. We also had few patients in subgroups, and it was a single-center study. We did not have a histological diagnosis of non-surgical cases. However, our study had a long follow-up period for benign and suspicious cases. Additionally, the fact that all EUS-FNAs were performed by the same endosonographer may have eliminated operator-dependent variations.

Conclusions

Both 22G and 25G needles provide comparable diagnostic yields and have similar safety profiles in EUS-FNA of solid lesions. However, a 25G needle may be preferred in calcified and fibrotic hard masses due to ease of puncture.

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Effect of rutin on experimentally induced small intestinal ischemia reperfusion injury in rats: A biochemical and histopathological evaluation

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Abstract

Background/Aim: The large amount of oxygen presented to the ischemic tissue in reperfusion causes the formation of excess free oxygen radicals and results in oxidative damage. Rutin is a flavonoid with potent antioxidant and anti-inflammatory effects. The aim of this study is to examine the effect of rutin on I/R-induced small intestinal (ileum) oxidative damage in rats.
Methods: The animals were divided into three groups as follows: Intestinal ischemia-reperfusion (IIR), 50 mg/kg rutin+intestinal ischemia reperfusion (RIIR) and sham operation (Sham). Rutin was administered at a dose of 50 mg/kg by oral catheterization one hour prior to thiopental sodium anesthesia. Distilled water was administered with the same method to IIR and Sham groups as a solvent. To induce intestinal ischemia in RIIR and IIR groups, the superior mesenteric artery was suspended from the point where it left the aorta, and ischemia was induced for 45 minutes with the help of an atraumatic microvascular clamp followed by 60 minutes of reperfusion. Biochemical and histopathological examinations were performed on the dissected ileal tissues.
Results: The amount of MDA and MPO activity increased, while tGSH levels and CAT activity decreased significantly in the intestinal tissue of the IIR group compared to sham group ($P<0.001$**)**. Rutin treatment decreased the increase in MDA and MPO activity and increased the decrease of tGSH levels and CAT activity significantly compared to the IIR group ($P<0.001$**)**. Histopathological changes such as PNL infiltration, edema, hemorrhage, and destruction were observed in the ileal tissue of the rats in the IIR group. However, there were no pathological findings in the RIIR group treated with rutin except for mildly dilated congested blood vessels.
Conclusion: Rutin may be useful against intestinal I/R oxidative damage in clinical practice.

Keywords: Rutin, Small intestine, Ischemia, Reperfusion, Rat

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Introduction

Small intestinal ischemia is a serious and frequent clinical condition caused by the occlusion of the superior mesenteric artery for several reasons (arterial thrombosis, embolism, Henoch-Schonlein purpura, invagination, drowned inguinal hernia, tumor, fibrotic tape) [1]. In clinical practice, reperfusion of the ischemic tissue is provided to protect the tissue from necrosis caused by ischemia, prevent high mortality and morbidity, and regain organ functions. However, it has been found that reperfusion exposes ischemic organs to the risk of late cellular necrosis and therefore limits the recovery of function and increases tissue damage [2]. The reason is that oxygen, which is abundantly presented to ischemic tissue during reperfusion, converts hypoxanthine to xanthine along with xanthine oxidase accumulated during ischemia, and causes the formation of excess radical oxygen species (ROS) [3]. ROSs, namely superoxide anion ($O2\cdot^{-}$), hydroxyl radicals (•OH), hydrogen peroxide (H2O2), hypochloric acid, and nitric oxide, can easily react with the cell components, alter their chemical structure, and cause damage [4]. ROSs damage membrane lipids, nucleic acids, enzymes and receptors. As is known, membrane lipids are the most sensitive structures to ROSs. The most important effect on lipids is the stimulation of lipid peroxidation (LPO) [3]. In intestinal ischemia reperfusion (I/R) injury, a decrease in antioxidant defense systems is also observed in parallel with the increase in malondialdehyde (MDA) [5]. Increased cytokine release is also involved in the pathogenesis of intestinal I/R injury [6].

Rutin (3,3,4,5,7 - pentahydroxyflavone - 3 - rhamnoglucoside) is a vitamin P1 flavonoid [7]. It is known that rutin has antioxidant, anti-inflammatory properties and inhibits polymorphonuclear granulocyte infiltration [8]. Recent studies have reported that rutin also inhibits the increase in proinflammatory cytokines and LPO end-product MDA, and the decrease in endogenous glutathione [9]. There are no studies in the literature investigating the protective effect of rutin on small intestinal I/R injury. The aim of this study was to analyze the effect of rutin on I/R-induced small intestine (ileum) oxidative injury in an experimental rat model using biochemical and histopathological methods.

Materials and methods

Animals

Eighteen albino Wistar male rats weighing 290-300 grams were used in the experiment. All rats were obtained from Ataturk University Medical Experimental Application and Research Center. The animals were housed and fed in groups at 22°C under appropriate conditions before the experiment. Animal experiments were performed in accordance with the National Guidelines for the Use and Care of Laboratory Animals and approved by Atatürk University Local Animal Ethics Committee for Animal Experiments, dated: 31/01/2019, meeting number:1, judgment no:3.

Chemicals

Thiopental sodium used in the experiment was obtained from I.E ULAGAY (Turkey), and rutin was obtained from Solgar (United States).

Experimental Groups

Animals were divided into three groups: Intestinal ischemia-reperfusion (IIR), 50 mg/kg rutin + intestinal ischemia-reperfusion (RIIR) and sham operation (Sham).

Experimental Procedure

Anesthesia administration

Surgical procedures were performed under sterile conditions. Rats were anesthetized with 25 mg/kg intraperitoneal (i.p.) thiopental sodium injections and xylazine inhalation at appropriate intervals. After injection of thiopental sodium, the rats were allowed to stand for the appropriate period of surgery. The period in which animals remained stationary in the supine position was considered the appropriate period of anesthesia for surgery [10].

Surgical and pharmacological procedures

50 mg/kg of rutin was administered orally with a catheter to the RIIR group (n-6) one hour before thiopental sodium anesthesia. Distilled water was administered with the same method to the RIIR and Sham groups as a solvent. During anesthesia, all rats were placed in the supine position, a 3.5-4 cm long incision was made on the anterior part of the abdomen, and laparotomy was performed. Sham group did not undergo any surgical procedures and the incision was closed with surgical suture. To induce small intestinal ischemia in the RIIR and IIR groups, the superior mesenteric artery (SMA) was suspended at the point where it left the aorta and ligated for 45 minutes with the help of an atraumatic microvascular clamp. Then, the midline laparotomy incision was sutured (3/0 silk). Following the ischemia period, the silk suture was removed and the laparotomy incision was re-opened. The bulldog clamp placed in the SMA of the rats was opened and removed. Reperfusion was induced for one hour in this group, and the laparotomy incision was closed with continuous suture using 3/0 silk. At the end of this period, the animals were sacrificed with high dose thiopental anesthesia (50 mg/kg) and the ileal tissues were removed. Biochemical and histopathological examinations were performed in the dissected ileal tissues. The results were comparatively evaluated between the groups.

Biochemical procedures

Sample preparation

Potassium phosphate buffer with pH=6 containing 0.5% HDTMAB (0.5% hexadecyl trimethyl ammonium bromide) was completed to 2 mL in 1.15% potassium chloride solution for MDA determination, and in phosphate buffer with pH=7.5 for other measurements and homogenized in icy environment. The homogenate was then centrifuged at +4 °C for 15 minutes at 10000 rpm. The supernatant portion was used as the analysis sample.

MDA analysis

The method of Ohkawa H et al. was used for MDA measurement [11]. This method is based on the spectrophotometric measurement (at a wavelength of 532 nm) of the absorbance of the pink colored complex formed by thiobarbituric acid (TBA) and MDA at a high temperature (95°C). The homogenates were centrifuged at 5000g for 20 minutes and these supernatants were used to determine the amount of MDA. 250 µl of homogenate, 100 µl of 8% sodium dodecyl sulfate (SDS), 750 µl of 20% acetic acid, 750 µl of

0.08% TBA and 150 µl of distilled water were pipetted into the test tubes and vortexed. The mixture was incubated at 100 °C for 60 minutes, then 2.5 ml of n-butanol was added to the mixture and spectrophotometrically measured. The amount of red color formed was read at 532 nm using 3 ml cuvettes and the amount of MDA of the samples was determined while considering the dilution coefficients by using the standard graph prepared from the previously readied MDA stock solution.

Determination of myeloperoxidase (MPO) activity

MPO activity was measured according to the modified method of Bradley et al. [12]. The homogenized samples were frozen and centrifuged at 1500 g for 10 min at 4°C. MPO activity in the supernatants was determined by adding 100 mL of the supernatant to 1.9 mL of 10 mmol/L phosphate buffer (pH 6.0) and 1 mL of 1.5 mmol/L o-dianisidine hydrochloride containing 0.0005% (wt/vol) hydrogen peroxide. The changes in absorbance at 450 nm of each sample were recorded on a UV-vis spectrophotometer [12].

Total glutathione (tGSH) analysis

The amount of GSH in the total homogenate was measured according to the method of Sedlak and Lindsay with some modifications [13]. The sample was weighed and homogenized in 2 mL of 50 mmol/L Tris–HCl buffer containing 20 mmol/L EDTA and 0.2 mmol/L sucrose at pH 7.5. The homogenate was immediately precipitated with 0.1 mL of 25% trichloroacetic acid, and the precipitate was removed after centrifugation at 4200 rpm for 40 min at 4 °C. The supernatant was used to determine GSH level. A total of 1500 µL of buffer (200 mmol/L Tris–HCl buffer containing 0.2 mmol/L EDTA at pH 7.5), 500 µL supernatant, 100 µL 5,5-Dithiobis (2-nitrobenzoic acid) (DTNB) (10 mmol/L) and 7900 µL methanol were added into a tube and vortexed and incubated for 30 min in 37°C. DTNB was used as a chromogen and it formed a yellow-colored complex with sulfhydryl groups. The absorbance was measured at 412 nm using a spectrophotometer (Beckman DU 500, USA). The standard curve was obtained by using reduced glutathione.

Catalase (CAT) analysis

Activity is based on the measurement of decrease in absorbance when H_2O_2 is converted to H_2O through CAT, at 240 nm. For CAT measurement, 0.5 g of tissue was removed, 4.5 mL of 50 mM K-phosphate buffer (pH 7.8) was added on it and the mixture was homogenized. The homogenate was centrifuged at 18000 g for 60 min at 4°C and the supernatants were used as a resource of enzyme for measurement of the catalase activity. H_2O_2 solution of 1.5mL was put into quartz spectrophotometer cuvette and after adding 1.5 mL of sample solution, the stopwatch was run immediately as the final solution was 20 mM. After turning the cuvette upside-down, absorbance was read on the spectrophotometer at 240 nm with 15 seconds intervals for 3 minutes and recorded [14].

Histopathological examination

Intestinal tissues removed from the rats were fixed in 10% formalin solution for 24 hours. Sections of 4-micron thickness were obtained from the paraffin blocks following routine tissue monitoring and stained with hematoxylin & eosin. All sections were evaluated under light microscopy (Olympus BX 52, Tokyo, Japan) by a pathologist who was not aware of the treatment protocols.

Statistical analysis

All data were subjected to the Kruskal-Wallis test using SPSS version 18.0 software (IBM Corporation, Armonk, NY, USA). Differences between groups were obtained using Wilcoxon Rank sum tests with Bonferroni corrections. $P<0.05$ was considered significant. The results were expressed as mean and the standard error of the mean (SEM).

Results

Biochemical Findings

As shown in Figure 1, the amount of MDA in the intestinal tissue exposed to I/R significantly increased compared to the sham group ($P<0.001$). In the rutin group, the amount of MDA decreased compared to the I/R group ($P<0.001$).

I/R procedure applied to intestinal tissue significantly increased MPO activity in the tissue compared to the sham group ($P<0.001$) (Figure 1). However, in the rutin group, MPO activity decreased compared to the I/R applied group and the difference between these two groups was statistically significant ($P<0.001$).

Also, I/R procedure led to a decrease in tGSH in intestinal tissue. The amount of tGSH in the I/R-treated intestinal tissue decreased significantly compared to the sham and rutin groups ($P<0.001$) (Figure 2).

Similarly, I/R procedure resulted in a decrease in CAT activity in the intestinal tissue compared to sham group. However, rutin significantly prevented the decrease in CAT activity in the intestinal tissue of the animals undergoing I/R procedure ($P<0.001$) (Figure 2). The difference in CAT activity between the group treated with rutin and the sham group was insignificant ($P=0.117$).

Figure 1: MDA levels and MPO activity in the ileum tissue of study groups (* p<0.001 according to IIR group)

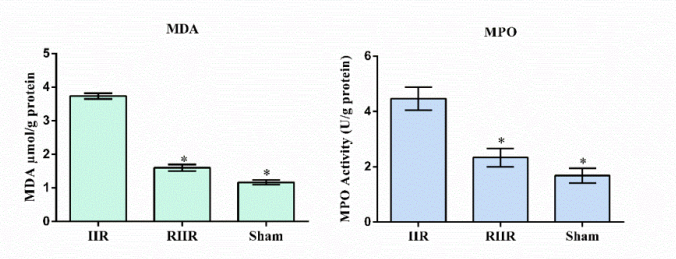
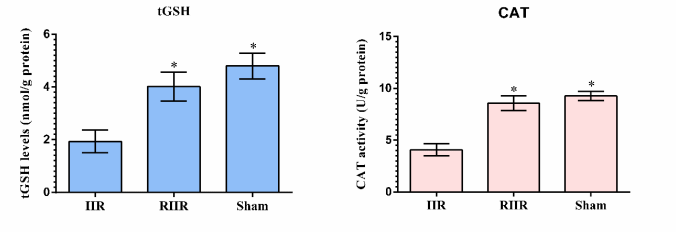


Figure 2: tGSH levels and CAT activity in the ileum tissue of study groups (* p<0.001 according to IIR group)



Histopathological findings

As seen in Figure 3, no histopathological findings were observed in the ileal tissue of the animals in the sham group. However, evident PNL infiltration, edema, hemorrhage, and destruction were observed in the ileal tissue of the rats undergoing I/R procedure (Figure 4). There was no pathological finding in the ileal tissue of the RIIR group, except for mildly dilated congested blood vessels (Figure 5).

Figure 3: Ileal tissue section of Sham group animals (HEX100)

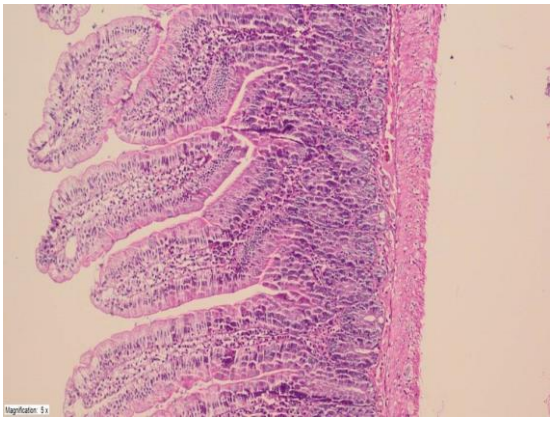


Figure 4: A section showing the polymorphonuclear (plain arrow) leukocyte infiltration, edema, hemorrhage and destruction (double-sided arrow) of the ileum tissue of the IIR group (HEX-400)

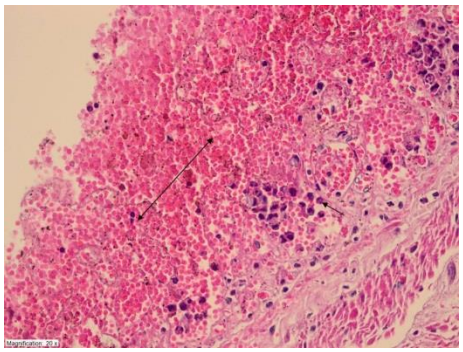
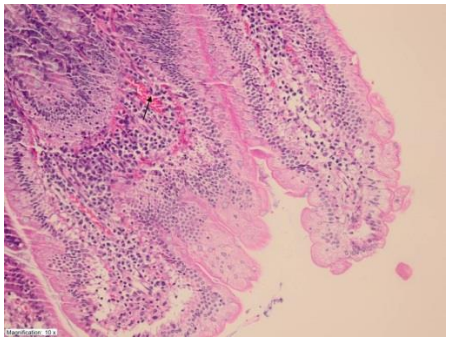


Figure 5: A section showing the dilated congested blood vessels in the intestinal tissue mucosa of RIIR group (HEX-200)



Discussion

In this study, the effect of rutin on I/R induced experimental small intestinal oxidative damage in rats was investigated biochemically and histopathologically. Reperfusion is an important procedure for recovering organ and tissue functions lost during ischemia. However, molecular oxygen presented to the ischemic tissue by sudden and excessive amounts of blood during reperfusion may lead to increased ROS production and oxidative stress [2,3]. ROSs initiate oxidative damage by inducing LPO in cell membranes [15]. During reperfusion, the ROSs that initiate the LPO reaction also cause a decrease in cellular antioxidant defense systems [16]. MDA caused by ROS-associated LPO reaction is responsible for tissue damage [17]. Therefore, ischemia duration is reduced and the damage occurring during reperfusion period is minimized with early diagnosis and appropriate treatment methods [18]. Living organisms develop a large number of protection mechanisms (antioxidants) in their cells against the harmful effects of ROSs. These mechanisms exert their effects both by inhibiting the production of radicals and preventing the detrimental effects of the radicals formed [19]. However, if the naturally occurring antioxidants are insufficient in neutralizing ROSs, the oxidant/antioxidant balance is disrupted in favor of the oxidants and oxidative damage is observed. Therefore, antioxidants are highly important in the prevention and treatment of various tissue damages related to oxidative stress [20].

In our study, we investigated the effect of rutin against I/R oxidative damage and found that rutin significantly prevented the increase in MDA and MPO levels in rat intestinal tissue and the decrease in tGSH and CAT levels. This shows that rutin inhibits the disruption of oxidant/antioxidant balance in favor of the oxidants in the intestinal tissue, which occurs during the I/R procedure. Nayki et al. reported that rutin significantly inhibited I/R-related MDA increase in ovarian tissue [21].

Rutin was also reported to protect the stomach from I/R oxidative damage by preventing the increase in MPO activity in gastric tissue [22]. MPO enzyme is specific for polymorphonuclear leukocytes (PNL) in the tissue. PNLs accelerate the production of ROSs in the ischemic tissues via the myeloperoxidase (MPO) enzyme systems they contain, and cause $O2\cdot^{-}$ formation. The resulting superoxide reacts with MPO to produce more reactive oxygen radicals such as H2O2, OH, hypochloric acid, and N-chloramine, all of which cause an increase in tissue damage [16].

Our results show that the oxidant/antioxidant balance in the I/R treated small intestinal tissue is disrupted in favor of the oxidants. This indicates that endogenous antioxidants are inadequate in reducing I/R-related oxidative stress in the intestinal tissue. However, the fact that tGSH level in the rutin group was very close to that of the healthy group indicates that rutin prevents the oxidant/antioxidant balance in intestinal tissue from changing in favor of the oxidants. GSH is a tripeptide consisting of L-glutamate, L-cysteine, and glycine and it is found in many cells. Catalyzed by the enzyme glutathione peroxidase (GPx) which contains selenium in its active zone, GSH reacts with H2O2 and organic peroxides and shows antioxidant activity by removing H2O2 from the cells. GSH chemically detoxifies H2O2 and organic oxides and protects cells from ROS damage [19]. Although there are no studies investigating the effect of rutin on the amount of tGSH in I/R administered intestinal tissue, it has been shown to prevent the decrease of tGSH due to I/R in ovarian tissue [21]. Another parameter used to evaluate antioxidant activity is the CAT enzyme. This enzyme catalyzes hydrogen peroxide to molecular oxygen and water [23], and is mostly localized in peroxisomes. It is found in high amounts in blood, bone marrow, mucosa structures, liver, and kidneys[24]. Arslan A et al. also used CAT as an antioxidant parameter to evaluate oxidative damage in the small intestine [25].

In this study, our biochemical results were consistent with histopathological findings. I/R procedure was shown to cause a significant increase in PNL infiltration in the intestinal tissue. As is known, the accumulation of PNL in tissues is an indication of inflammatory reaction in the tissue. Tuboly E et al. reported that PNL infiltration is an important component in the development of intestinal tissue damage. In addition, they stated that the inhibition of PNL infiltration was important in the treatment of intestinal I/R injury [26]. As can be seen from our experimental results, PNL infiltration was more severe in intestinal tissue with high MPO activity. This is because MPO

has been shown to be an activated PNL product. The results of Zheng X et al. also support our histopathological findings [27]. Furthermore, significant edema was detected in the intestinal tissue treated with I/R. In their study, Teke Z et al. reported that edema associated with I/R oxidative injury decreased with antioxidant therapy [28]. In the present study, it was shown that I/R procedure caused histopathological findings in the intestinal tissue such as hemorrhage and destruction. In the experimental study of Soydan G et al, it was emphasized that structural disorders developed in the intestinal tissue after I/R [29]. In the literature, histopathological findings such as destruction, hemorrhage, PNL infiltration, and edema have been associated with oxidative stress [30]. It is known that rutin has antioxidant and anti-inflammatory effects. However, there are no biochemical and histopathological studies investigating the protective effect of rutin on intestinal I/R injury. On the other hand, there are histopathological studies showing that rutin prevents I/R damage in different organs and tissues through its antioxidant and anti-inflammatory effects [21,22].

Evaluating the effects of rutin on ischemia and reperfusion periods separately reveals more information about the treatment strategies and examining the biochemical and histopathological effects of rutin at different doses informs about the dose-dependent improvement. The dose dependent effect of rutin needs to be shown for clinical usage. All the above-mentioned limitations of this study exist due to the lack of resources, but future studies are planned accordingly.

Conclusion

I/R procedure caused an increase in enzymatic and non-enzymatic oxidant parameters and a decrease in antioxidant parameters in intestinal tissue. This shows that I/R creates oxidative stress in the intestinal tissue. Biochemical and histopathological investigations revealed that rutin inhibits I/R related oxidative damage in intestinal tissue. This property of rutin suggests that it may be useful in clinical settings against I/R oxidative damage in intestinal tissues.

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Thrombocytopenia and its effect on mortality and morbidity in the intensive care unit

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Ethics Committee Approval
The study was approved by Bezmialem University non-interventional research ethics committee with the number 2011-KAEK-42 2016703-01. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Thrombocytopenia is a common hematological abnormality among patients in the intensive care unit (ICU). The development of thrombocytopenia in the ICU usually indicates severe organ system dysfunction rather than a primary hematological disorder. We aimed to determine the incidence, causes, and clinical results of thrombocytopenia in patients followed up in ICU.
Methods: In this retrospective cohort study, 165 patients who were followed up in the ICU with thrombocyte counts below 150,000 /uL were included and causes of thrombocytopenia, along with its effects on mortality and intensive care stay were investigated.
Results: Thrombocytopenia was determined in 30.1% of the patients in the ICU. The cause of thrombocytopenia was sepsis in 33 (20.0%) of the patients and disseminated intravascular coagulation (DIC) in 20 (12.1%) patients. During the study period, 115 (69.7%) of 165 thrombocytopenic patients and 173 (45.1%) of 383 patients without thrombocytopenia died. Mortality was significantly higher in patients with thrombocytopenia. Mortality significantly increased when platelet count decreased, even with similar APACHE II scores.
Conclusion: The most common causes of thrombocytopenia in the ICU were sepsis and DIC. Thrombocytopenia is common in the ICU and increases mortality rates.

Keywords: APACHE II, Intensive care, Mortality, Sepsis, Thrombocytopenia

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Introduction

Thrombocytopenia is defined as blood platelet count remaining below the accepted normal limits [1]. Values below 150,000/uL are considered thrombocytopenia [1-3]. It is a common hematological abnormality among patients admitted to the intensive care unit (ICU). From a clinical perspective, the development of thrombocytopenia in the ICU usually indicates severe organ system dysfunction and physiological decompensation rather than a primary hematological disorder. Thrombocytopenia is associated with adverse clinical outcomes, including bleeding, transfusion, and death. Few deaths can be directly attributed to bleeding [3,4], the risk of which is inversely proportional to the platelet count [5,6]. Its management is directed primarily at the underlying disorder [5]. Bleeding is not expected in platelet values above 100,000/uL, including major surgical interventions [6]. Major bleeding risk increases with values below 20.000/uL, and there is a risk of life-threatening bleeding at values below 10,000/uL.

Thrombocytopenia is a quite common laboratory disorder in intensive care patients. The incidence of thrombocytopenia varies between 35-44% in studies previously conducted on ICU patients [7, 8]. Identifying the underlying cause of thrombocytopenia is vital in determining patient management and treatment regimens. In the light of all these results, we aimed to determine the incidence of thrombocytopenia in ICU patients, the underlying causes, and clinical consequences, and investigate its contribution to mortality and morbidity, considering that the presence and severity of thrombocytopenia may be a prognostic marker in patients in the intensive care unit.

Materials and methods

Study design

Patients admitted to the ICU of Izmir Metropolitan Municipality Esrefpasa Hospital and University of Health Sciences, Okmeydanı Training and Research Hospital between April 2016 and December 2019 were included in the study. The study was approved by Bezmialem University non-interventional research ethics committee with the number 2011-KAEK-42 2016703-01 and signed informed consent forms were obtained from the relatives of all patients participating in the study.

Patients

Adult patients over 18 years of age who were followed up for at least one day in the ICU were included in the study. A platelet count of <150,000 /μL indicated thrombocytopenia. Patients with thrombocytopenia at admission to the intensive care unit or those who developed thrombocytopenia during ICU hospitalization were included in the study. Peripheral blood smears were examined, and Wright-Giemsa staining was used as the peripheral smear dye. Thrombocyte, white blood cell count, hemoglobin, INR, aPTT values, the lowest platelet count, D-Dimer, and Fibrinogen values of the patients with suspicion of consumption coagulability and the APACHE II score calculated during the hospitalization of each patient were recorded. The age and gender of the patients, reasons for intensive care admission, underlying chronic diseases, if any, whether they were thrombocytopenic during admission to intensive care, the cause of thrombocytopenia, and the length of stay in the ICU of those who were discharged or transferred to the wards were noted. Complete blood count, peripheral blood smear, coagulation parameters, fibrinogen, D-dimer, urea and creatinine, blood electrolytes, liver enzymes, and bilirubin levels, hepatitis markers, autoimmune markers from suspected patients, and bone marrow aspiration and/or biopsy results, if present, were examined. Bone marrow biopsies of 95 patients and aspirates of 119 patients were assessed. Neither of these procedures were performed in patients currently unfit for the procedure, who died before they could be performed, those with drug or heparin-related thrombocytopenia whose condition improved after the suspicious agent was discontinued, and those with suspected pseudo-thrombocytopenia. According to the recommendations of the Turkish Hematology Association regarding the patients' platelet count, the patients were divided into five groups as follows: Those with platelet counts between 100,000-149,000 uL/mm^3, 50,000-99,000 uL/mm^3, 20,000-49,000 uL/mm3, 10-19,000 uL/mm^3 and <10,000 uL/mm3. A platelet count below 50.00 uL/mm^3 was defined as severe thrombocytopenia.

Scale

APACHE scoring is one of the systems used in determining the mortality rate in the ICU and evaluating treatment efficiency. APACHE II, a version of the APACHE system, has been used in ICUs since 1985. For APACHE II, the worst values of the following variables within the first 24 hours of intensive care admission are used: Age, fever, respiratory rate, heart rate, mean arterial blood pressure, Glasgow coma scale, serum creatinine value, hematocrit, white blood cell count, arterial blood pH, sodium, potassium, and alveolo-arterial pressure gradient. While calculating, a score is determined according to the presence of chronic organ failure, immunosuppression status, emergency or elective surgical operation status, and the presence of acute renal failure, and the expected mortality of the patient is estimated. In our study, the APACHE II score of the patients was calculated by the intensive care physician team. The patients were divided into four groups according to their APACHE II scores as below 10, between 10-24, between 25-34, and those above 35.

Statistical analysis

SPSS 17.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum - maximum where necessary). Chi-square test or Fisher's test were used for comparison of categorical variables. In the comparison of continuous measurements between the groups, the normality of distributions was checked. Student-t test or One-way Analysis of Variance were used for normally distributed parameters, and Mann Whitney U test or Kruskal Wallis test were used for non-normally distributed ones. Spearman correlation test was used to check for correlation between variables. Risk factors for mortality were determined by Logistic Regression analysis. $P<0.05$ was considered statistically significant in all tests.

Results

During the study period, 548 patients (325 males, 223 females) with a mean age of 57.2 (16.4) (min: 18, max: 91) years

were followed in the ICU. Thrombocytopenia was observed in 165 (61 female, 104 male) patients (30.1%). While 134 (81.2%) of these patients had thrombocytopenia during admission to ICU, 31 (18.8%) developed thrombocytopenia during hospitalization. Clinical features of patients who had thrombocytopenia in the ICU are summarized in Table 1.

Table 1: Clinical features of patients with thrombocytopenia

Variable	n=165	%
Gender		
Male	104	63.0
Female	61	37.0
Pre-admission thrombocytopenia		
Yes	134	81.2
No	31	18.8
Malignancy		
Yes	66	40.0
No	99	60.0
APACHE II score		
10-24	20	12.1
15-19	49	29.7
20-24	58	35.2
25-34	26	15.8
<34	12	7.3
The lowest number of thrombocytes		
Below 10,000 / uL	14	8.5
Between 10-19,000 / uL	30	18.2
Between 20 and 49,000 / uL	62	37.6
Between 50 and 99,000 / uL	46	27
Between 100 and 149,000 / uL	13	7.9

The median APACHE II score calculated on the first day of admission to ICU was 22 (min: 10, max: 42). The distribution of APACHE II scores and the lowest number of thrombocyte counts of the patients are summarized in Table 1.

In 27 patients (16.3%), thrombocytopenia was due to known hematological malignancies, in 33 patients (20.0%) due to sepsis, in 13 patients (7.8%) due to cytotoxic chemotherapy, 20 (12.1%) patients had drug-related thrombocytopenia and 20 (12.1%) had thrombocytopenia due to DIC. Seventeen patients (10.3%) had thrombocytopenia due to hypersplenism and 7 patients (4.2%) had immune-thrombocytopenia (primary or secondary). Eight patients (4.9%) had thrombocytopenia because of solid tumor metastasis to the bone marrow. Six patients (3.6%) were evaluated as TTP. Five patients (3.0%) had heparin-associated thrombocytopenia. The cause of thrombocytopenia could not be determined in nine patients (5.4%).

The laboratory data analyzed at the admission and during discharge from the ICU are summarized in Table 2.

Table 2: The laboratory data analyzed at the admission and during the discharge from the ICU

Variable	Mean (SD)	Median (min-max)	*P*-value
Platelet (first)	99.6 (120.8)	67 (5-846)	0.001
Platelet (discharge)	61.1 (68.7)	46 (4-560)	
Platelet (lowest)	45.4 (33.3)	37 (4-163)	0.001
WBC (first)	15.1 (41.4)	8 (0-510)	0.030
WBC (discharge)	10.0 (9.30	7 (0-41)	
Hemoglobin (first)	9.4 (2.1)	9 (5-17)	0.360
Hemoglobin (discharge)	9.3 (1.8)	9 (5-14)	
INR (first)	1.6 (0.7)	1.4 (0.9-7)	0.332
INR (discharge)	1.8 (1.6)	1.4 0.9-17)	
APTT (first)	38.1 (19.4)	33 (14-141)	0.001
APTT (discharge)	47.4 (29.2)	37 12-148)	

The mean platelet count of the patients included in the study at the time of hospitalization was 67,000 /μL and the mean lowest platelet count during hospitalization in ICU was 37,000 /μL. A statistically significant decrease in the platelet count was observed in patients during hospitalization (*P*=0.001). The mean white blood cell count and aPTT values were also altered significantly (*P*=0.03); however, hemoglobin, or INR levels did not significantly change during hospitalization in the ICU (Table 2).

In this study, 115 (69.7%) of 165 thrombocytopenic patients and 173 (45.1%) of 383 patients without thrombocytopenia died. Accordingly, mortality was significantly higher in patients with thrombocytopenia (*P*=0.020). While the mean length of stay of all patients transferred to the ward or discharged during the study was 5.9 (1.3 days), the mean length of stay for those with thrombocytopenia was 6.1 (3.7) days. There was no statistically significant difference between thrombocytopenic and non-thrombocytopenic ICU patients regarding the length of stay in ICU (*P*=0.064).

Table 3: Comparison of patients with and without malignancy

	Malignancy				
	Present (n:66)		Absent (n:99)		
	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)	*P*-value
Age	58.5 (17.2)	60 (20-91)	55.2 (15.0)	57.5 (18-84)	0.136
PLT first	109.8 (132.6)	76 (6-846)	84.2 (99.6)	52.5 (5-601)	0.114
PLT last	73.1 (83.2)	55 (4-560)	43.1 (29.9)	34.5 (5-129)	0.002
PLT lowest	51.1 (34.9)	41 (4-163)	36.8 (29.0)	26 (5-123)	0.005
WBC first	10.9 (7.8)	9 (0-37)	21.3 (64.5)	8 (0-510)	0.469
WBC last	9.9 (8.2)	8 (0-41)	10.2 (10.7)	6 (0-37)	0.286
Hgb first	9.5 (2.1)	10 (5-17)	9.3 (2.1)	9 (5-14)	0.409
Hgb last	9.4 (1.6)	9 (5-14)	9.1 (1.9)	9 (5-14)	0.155
INR first	1.6 (0.7)	1.4 (0.9-7)	1.5 (0.5)	1.4 (0.9-3.4)	0.967
INR last	1.7 (1.0)	1.3 (0.9-8.2)	1.9 (2.1)	1.4 (0.9-17)	0.518
aPTT first	37.3 (17.1)	34 (17-104)	39.3 (22.7)	32 (14-141)	0.993
aPTT last	49.9 (32.1)	38 (17-148)	43.7 (23.8)	36 (12-135)	0.446
APACHE II	21.3 (6.4)	20 (12-40)	22.9 (5.5)	22.5 (10-42)	0.026

When patients with and without an underlying malignant disease were compared, no significant difference was found between the platelet values, coagulation parameters, hemoglobin, and white blood cell values during admission (Table 3). The mean lowest platelet values and mean last measured platelet counts of patients with and without malignancy were significantly different.

The mean APACHE II score of patients with malignancy was significantly higher (*P*=0.026). The results of patients with or without malignancy are summarized in Table 3.

Some laboratory data of survivors and non-survivors are compared in Table 4.

Table 4: Comparison of laboratory data of alive or death patients

	Non-survivors	Survivors	*P*-value
The lowest platelet values detected	30.000 / uL (5000-563000)	57.500 (4.000-138.000)	0.001
The last platelet count	37.000 / uL (4000-533000)	70.000 / uL (4000-563.000)	0.001
The last INR	1.4 (0.9 - 8.8)	1.3 (0.9 - 17)	0.040
The last aPTT	42 sec (12- 148)	32 sec (19- 81)	0.030
APACHE II	24 (13- 42)	18 (10- 30)	0.001

Twenty-seven (87.09%) of 31 patients who had no thrombocytopenia at admission, but developed thrombocytopenia during ICU stay, died. In the same period, while the ICU overall mortality was 52.5%, the mortality of non-thrombocytopenic patients was 45.1% (173/383 patients), and the mortality of thrombocytopenic patients included in our study was 69.7%. Accordingly, the mortality of patients who did not have thrombocytopenia at admission but developed thrombocytopenia while in the ICU was significantly higher than the others (*P*=0.001).

Seventy-eight (61.4%) of 127 patients with APACHE II scores between 10-24, 25 (96.2%) of 26 patients with APACHE II scores between 25-34, and all 12 patients (100%) with APACHE II score of 35 and above died. Accordingly, the mortality of the patients examined in our study significantly increased with APACHE II scores (*P*=0.001).

In our study, no significant relationship was found between the APACHE II score, genders, and the lowest platelet

value. However, mortality significantly increased as the lowest platelet count decreased (P=0.003), and as the platelet count decreased in patient groups with the same APACHE II score (P=0.002).

Discussion

Thrombocytopenia is quite common in ICU patients, and important in terms of determining the underlying causes, predicting clinical results, and determining treatment regimens. In numerous studies, thrombocytopenia rates in the ICU varies between 35-45% and approximately half of these patients developed thrombocytopenia during intensive care hospitalization [9,10]. In the studies of Provan et al. and Strauss et al., this rate was between 35% and 44%, and in the study conducted by Singh et al., thrombocytopenia rate was between 20-40% [11-13]. In our study, the rate of thrombocytopenia in the ICU was 30%, which was similar to the previous studies [14-17]. In the study of Singh et al., the rates of patients with thrombocyte count below 100,000 / uL varied between 20-40% [13]. In the studies conducted by Knöbl et al. [17] and Hanes et al. [18] the rates of those with a thrombocyte level below 100.000 /uL and 50.000 /uL were between 20-25% and 12-15%, respectively. In our study, thrombocytopenia rates were similar to those in the literature, but the rate of patients with severe thrombocytopenia was 65%, which was higher than previously reported.

In a study by Provan et al. [11], while the overall mortality of patients in the ICU was 19.5%, and the mortality of patients with and without thrombocytopenia were 33% and 9.3%, respectively. The mortality of patients with thrombocytopenia at admission to the ICU was 34%, and the mortality of those who developed thrombocytopenia during ICU hospitalization was 31.9%. In the study conducted by Hoogendoorn et al. [20], the intensive care mortality of thrombocytopenic patients was 1.6%, that of non-thrombocytopenic patients was 4.4%. In the same study, the hospital mortality of thrombocytopenic patients was 22.1%, and that of non-thrombocytopenic patients was 7.8%. According to the results of our study, the overall mortality in the ICU, and the mortality of thrombocytopenic and non-thrombocytopenic patients were higher than those previously reported in the literature. In our study, as in other studies, the mortality of patients with thrombocytopenia was significantly higher than overall mortality and that of non-thrombocytopenic patients.

Acute Physiology and Chronic Health Evaluation (APACHE) scoring is one of the systems used in determining the mortality rate and evaluating treatment efficiency in intensive care units [21, 22]. Warren et al. [16] found the APACHE II score as 26.9 (6.9) in patients who died and 23.5(5.4) in patients who survived, and reported that the higher the score, the higher the mortality. In another study, it was observed that 50% and 72.2% of patients with APACHE II scores of ≥15 and ≥20, respectively, did not survive [23]. It is noteworthy that mortality increases significantly in patients with APACHE II scores between 21-25 [24, 25]. In our study, as the APACHE II score increased, so did mortality significantly, and the APACHE II score was significantly higher among non-survivors.

In our study, the mortality of patients who did not have thrombocytopenia at the beginning but developed thrombocytopenia during ICU hospitalization was significantly higher than that of the other patients. There was a positive correlation between the lowest level of platelets and mortality, and the lowest platelet values reached in patients with malignancy were significantly lower. In our study, no significant relationship was found between the APACHE II score and the lowest platelet value obtained. As platelet count decreases, mortality increases significantly in patients with similar APACHE II scores, which suggested that thrombocytopenia may be an independent marker for mortality. Moreover, even if the severity of the underlying disease and the general condition of the patients were similar, the patients with thrombocytopenia were more mortal and as thrombocytopenia deepened, mortality increased. Thrombocytopenia may be an independent predictive marker for mortality in intensive care patients. We think that our study contributes to the literature in this respect.

Limitations

The first limitation of this study is its retrospective nature, and secondly, we analyzed the results of all thrombocytopenic patients without analyzing the underlying causes, which may also affect mortality.

Conclusions

Thrombocytopenia was highly prevalent in the ICU in our study, with sepsis as etiology in the first place, and DIC in the second place. The mortality of patients with thrombocytopenia was significantly higher than the overall mortality and mortality of non-thrombocytopenic patients, and as thrombocytopenia deepened, mortality increased. This was independent of the APACHE II score. Patients who did not have thrombocytopenia at the beginning but developed thrombocytopenia during intensive care follow-ups had higher mortality than those with thrombocytopenia during intensive care admission. However, studies and meta-analyses in a larger series will contribute to the subject.

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Serum pregnancy-associated placental protein-a (PAPP-A) levels are increased in polycystic ovary syndrome (PCOS) in women with oligo-anovulation

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Ethics Committee Approval
The approval (PAU-GOKAEK, 29.12.20/76838) was obtained from Pamukkale University Ethical Committee. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Pregnancy associated placental protein-A (PAPP-A) is a zinc-binding metalloproteinase with a key role in insulin like growth factor (IGF) pathway, and potential atherogenic effects. There is little information in the literature regarding PAPP-A levels in Polycystic ovary syndrome (PCOS). We aimed to investigate the serum PAPP-A levels among non-obese women with PCOS as a cardiovascular risk marker.

Methods: Non-obese women of reproductive age (18-35 years of age) diagnosed with PCOS according to Rotterdam Consensus Conference criteria were included in this case-control study. Serum PAPP-A levels were compared with independent samples t-test between two main groups (PCOS and control) and investigated in PCOS subgroups as PCOS patients were further classified according to main phenotypes (hyperandrogenism and oligo-anovulation).

Results: A total of 41 women with PCOS and 40 age- and body mass index- matched controls were included in the analysis. The serum PAPP-A levels of the control and PCOS groups, and of PCOS patients with hyperandrogenism were similar (P=0.128, P=0.261, respectively). However, the serum PAPP-A levels of those with oligo-anovulation was higher than those without (P=0.006), and that of women without oligo-anovulation was comparable to that of the control group (P=0.613).

Conclusion: Lean and young PCOS women with oligo-anovulation had increased serum levels of PAPP-A when compared to women without. Prospective studies are needed to uncover the long-term cardiovascular risk of elevated PAPP-A levels in PCOS women with oligo-anovulation.

Keywords: Polycystic ovary syndrome, Cardiovascular disease, Pregnancy associated placental protein-A, PAPP-A

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Introduction

The most prevalent reproductive-age endocrine disease is polycystic ovary syndrome (PCOS) [1]. It is a multisystemic and heterogeneous disease with an estimated prevalence of 5-15% that depends on the applied criteria [2]. PCOS is diagnosed when oligo-anovulation, polycystic ovarian morphology (PCOM), biochemical and/or biochemical hyperandrogenism (HA) and their combinations are present, which forms the phenotypes [3]. Besides its reproductive complications such as oligo-anovulation and infertility, PCOS also carries a considerable risk of future medical comorbidities and long-term risks including insulin resistance, diabetes mellitus, hypercholesterolemia, cardiovascular disorders, and microvascular dysfunction [4-6]. To date, the exact pathophysiology of the development of PCOS and PCOS phenotypes is poorly understood. Therefore, the interplay between the PCOS phenotypes and long-term comorbidities remain to be elucidated.

Cardiovascular diseases (CVD) continue to be the major causes of female mortality [7]. Although they usually occur mostly in late reproductive and postmenopausal periods, risk factors begin to affect patients from a young age Evaluation of conventional cardiovascular risk factors, such as lipid profiles, blood pressure, glucose levels, insulin resistance and anthropometric measures such as body mass index (BMI) in these cases is critical in the follow-up and in later years [8]. However, there is scarce evidence for the association of novel markers indicating future CVD risk with PCOS phenotypes.

Pregnancy associated placental protein-A (PAPP-A) is a zinc-binding metalloproteinase that belongs to the Metazincin family, which interacts with the pathway of insulin like growth factor (IGF). PAPP-A was first isolated from plasma during human pregnancy in 1974 [9]. Further studies showed that it is widely expressed in multiple tissues along with syncytiotrophoblasts and extravillous trophoblasts and is associated with the inflammation process and atherosclerosis [10,11]. PAPP-A has a prominent role in IGF system, reconfiguring some subgroups of insulin-like growth factor binding proteins (IGFBPs). It is strongly anabolic by IGF-dependent cellular effects [10]. Noteworthy, mouse models have shown that lifespan was increased in the absence of PAPP-A [12,13]. These findings indicate the detrimental effects of PAPP-A in IGF dependent inflammatory process. However, its potential atherogenic effects are not related with IGF-inflammation pathway. PAPP-A also promotes procoagulant activity by Akt-NF-kB pathway in human endothelial cells [14]. In atherosclerotic plaques, PAPP-A was highly expressed and is related to increased risk of atherosclerotic plaques rupture [11].

IGF pathway plays crucial roles in follicular development including recruitment, apoptosis, growth, steroid hormone synthesis [15]. Eventually, altered physiology in PCOS is associated with long-term CVD risk. However, the literature is limited regarding PAPP-A levels in PCOS. Therefore, in this study, we aimed to investigate the serum PAPP-A levels among lean PCOS women as a cardiovascular risk marker.

Materials and methods

Subjects

This was a case-control study conducted at a university hospital setting. Ethical committee approval (PAU-GOKAEK, 29.12.20/76838) was obtained, and all participants gave informed consent before inclusion to the study. Young, non-obese women of reproductive age (18-35 years of age) who visited the hospital were invited to participate in the study. The Rotterdam criteria was used for the diagnosis of PCOS. Controls were recruited from healthy women and matched for age and body mass index (BMI). The control group consisted of women with regular menses who had normal ovarian morphology documented in the early follicular phase. Exclusion criteria were as follows: BMI ≥ 27 kg/m^2, age ≥ 35 years, diagnosed with a systemic disease such as cardiac disease, diabetes, liver disease, kidney disease etc., current, or up to 6 months of previous hormonal contraceptive use, a history of ovarian surgery.

Clinical data collection

Baseline characteristics, history, and BMI were recorded for each patient. The body mass index (BMI) was calculated as body weight (kg) / height (meters) squared. All subjects were evaluated by sonography using Voluson E 730 Pro (GE Healthcare, Istanbul, Turkey). Diagnosis of PCOS was achieved by the presence of at least two of the following criteria: (1) Clinical and/or biochemical hyperandrogenism, (2) Oligo-anovulation and (3) Ultrasonographic features of polycystic ovaries (PCO). Biochemical hyperandrogenism is defined by total and/or free testosterone levels above the upper limit or calculated free androgen index (FAI) > 5. Oligo-anovulation was defined as menstrual cycles of ≥35 or ≤23 days or skipping at least three consecutive menstruation cycles.

Blood sampling and biochemical analysis

Serum samples were obtained after an overnight fast and analyzed immediately or centrifuged and stored until analysis at −20°C. PAPP-A was assayed using enzyme-linked immunosorbent assay (ELISA). Serum concentrations of SHBG, total testosterone, DHEAS, prolactin, and TSH were measured by electrochemiluminescent immunoassay with a inter and intra-assay coefficient of variation (CV) of < 5%. Radioactive immunoassay method was used for the detection of serum levels of androstenedione and free testosterone. The plasma glucose levels were calculated by the hexokinase method. (HOMA-IR) was determined using the formula of homeostatic model assessment (HOMA) (fasting serum insulin [uIU/mL] x fasting plasma glucose [mmol/L]/22.5). Serum levels of Total cholesterol, high-density lipoprotein (HDL), and triglycerides were found using an enzymatic colorimetric assay. Analyses were performed on the Cobas e602 (Roche Diagnostics GmbH, Manheim, Germany).

Statistical analysis

Data analysis was conducted using the R Statistical Computing software version 3.5.3 (Vienna, Austria), with R commander 2.6 package and SPSS 13 (SPSS, Inc., Chicago, IL) and SPSS 20 package (SPSS, Inc., Chicago, IL). Continuous variables were first examined by both visual inspection and the Shapiro-Wilk test. Normally distributed variables were evaluated using a Student t-test, while non-normally distributed continuous

variables were compared by Mann-Whitney U Test. Quantitative variables were expressed as mean (SD).

The sample size in each group was calculated as 40 (G*Power 3.1). This sample size yielded 90% power with an alpha error of 0.05 for detecting an effect size of 0.75 for the difference in PAPP-A measurement in women with a BMI below 27 kg/m^2, according to the previous report of Ozturk et al. [16].

Correlation was performed by Bivariate Pearson's test between parameters. A multiple linear regression model was built to perform multivariable analysis for exploring independent factors related with PAPP-A levels. All parameters were presented as mean (SD) or frequency (%). Statistical significance level was set at $P<0.05$.

Results

A total of 41 PCOS women and 40 age- and BMI-matched controls were analyzed. According to inclusion criteria all women had BMIs below 27 kg/m^2. Basic characteristics of the participants are summarized in Table 1. Women with PCOS had significantly higher levels of AMH (10.0 (5.1) ug/l vs. 4.5 (2.5) ug/l, $P<0.001$), free testosterone (2.7 (1.2) ng/l vs. 1.9 (0.7) ng/l, $P=0.001$), SHBG (43.7 (19.6) nmol/l vs. 53.1 (19.3) nmol/l, $P=0.035$), total testosterone (0.5 (0.2) ug/l vs. 0.3 (0.1) ug/l, $P=0.001$), free androgen index (FAI) (5.1 (3.5) vs. 3.0 (2.9), $P=0.009$), and LH/FSH ratio (2.2 (1.3) vs. 1.2 (0.9), $P=0.001$) when compared to controls (Table 2).

Table 1: Basic characteristics metabolic parameters of the study population

	Control (n=40)	PCOS (n=41)	*P*-value
Age (years)	24.3 (4.2)	23.1 (3.2)	0.134
BMI (kg/m^2)	22.3 (2.8)	22.2 (2.7)	0.953
Fasting glucose (mg/dl)	90.3 (7.3)	89.5 (6.4)	0.616
HOMA-IR	2.1 (1.3)	2.6 (2.1)	0.304
TC (mg/dl)	176.5 (28.6)	172.5 (27.0)	0.527
LDL (mg/dl)	98.4 (25.5)	95.8 (26.2)	0.665
HDL (mg/dl)	62.9 (16.3)	58.7 (15.6)	0.252
TG (mg/dl)	76.0 (33.5)	92.1 (40.3)	0.062

PCOS: polycystic ovarian syndrome, BMI: body mass index, AMH: anti Mullerian hormone, HOMA-IR: homeostatic model assessment of insulin resistance, TC: total cholesterol, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TG: Triglycerides

Table 2: Hormonal parameters of the study population

	Control (n=40)	PCOS (n=41)	*P*-value
AMH (ug/l)	4.5 (2.5)	10.0 (5.1)	<0.001
Free testosterone (ng/l)	1.9 (0.7)	2.7 (1.2)	0.001
SHBG (nmol/l)	53.1 (19.3)	43.7 (19.6)	0.035
Total testosterone (ug/l)	0.3 (0.1)	0.5 (0.2)	0.001
Free Androgen Index	3.0 (2.9)	5.1 (3.5)	0.009
DHEA-S (ug/dl)	280.0 (94.9)	297.4 (117.6)	0.492
Androstenedione (ng/ml)	2.1 (0.9)	2.6 (1.5)	0.122
LH/FSH ratio	1.2 (0.9)	2.2 (1.3)	0.001

PCOS: polycystic ovarian syndrome, AMH: anti Mullerian hormone, SHBG: sex hormone binding globulin, DHEAS: dehydroepiandrosterone sulfate, LH/FSH: luteinizing hormone/ follicle-stimulating hormone

The control and PCOS groups were comparable in terms of serum PAPP-A levels (1.82 (0.66) ng/m vs. 2.03 (0.63) ng/m, $P=0.128$). We further compared PAPP-A levels after defining PCOS subgroups according to the presence of HA and oligo-anovulation. PCOS women with and without HA had similar serum PAPP-A levels (2.0 (0.7) ng/m vs. 2.2 (0.6) ng/m, $P=261$). Serum PAPP-A was higher in the PCOS women with oligo-anovulation compared to the control group (2.3 (0.5) ng/m vs. 1.8 (0.7) ng/m, $P=0.006$). However, PCOS women without oligo-anovulation had comparable PAPP-A levels with the control group (1.7 (0.6) ng/m vs. 1.8 (0.7) ng/m, $P=0.613$) (Figure 1).

Serum PAPP-A levels were not significantly correlated with age (r=-0.117, $P=0.300$) or BMI (r=-0.002, $P=0.989$) among the study population. PCOS women were also separately analyzed for the correlation of PAPP-A with metabolic and hormonal parameters; however, none of these comparisons yielded significant results. We further performed a multiple linear regression analysis for age, BMI, oligo-anovulation, FAI and AMH as independent parameters to predict PAPP-A levels. This analysis revealed oligo-anovulation to be a predictor of serum PAPP-A levels even after controlling for age, BMI, FAI and AMH, which may have confounding effects. Table 3 summarizes the results of the multiple linear regression model for predicting PAPP-A levels.

Figure 1: Comparison of serum PAPP-A levels (OA: oligoanovulation, *P=0.003, **P=0.006)

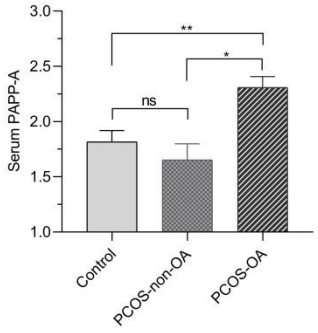

Table 3: Multiple regression model for predicting PAPP-A levels

	Unstandardized coefficient	95% CI		t statistics	*P*-value
		Minimum	Maximum		
Oligo-anovulation	0.509	0.132	0.887	2.697	0.009
Age	-0.036	-0.094	0.022	-1.245	0.218
BMI	0.005	-0.054	0.064	0.161	0.872
AMH	-0.012	-0.050	0.027	-0.617	0.540
FAI	0.037	-0.015	0.088	1.417	0.162

CI: confidence interval, BMI: body mass index, AMH: anti Mullerian hormone, FAI: free androgen index

Discussion

The aim of the present study was to compare serum levels between PCOS and controls and analyze whether any other variables were associated with PAPP-A levels. For this purpose, a case control study was conducted among 81 age- and BMI- matched non-obese young women. Overall, no difference in PAPP-A levels were observed between the PCOS and control groups. However, when PCOS women were further analyzed in subgroups of phenotypes, serum PAPP-A levels were higher in women with PCOS who had oligo-anovulation than the control group and PCOS patients without oligo-anovulation. A multiple regression analysis also revealed oligo-anovulation to be a predictor of serum PAPP-A levels even after controlling for the confounding effects of age, BMI, FAI and AMH. In other words, presence of oligo-anovulation per se was associated with increased PAPP-A levels when all other factors were controlled.

Öztürk et al. [16] evaluated the serum levels of PAPP-A in patients with PCOS, age-and BMI -matched controls. They found no significant difference of median serum levels of PAPP-A (1.7 ng/ml versus 1.8 ng/ml, respectively, $P=0.328$) between PCOS patients and controls. However, a subgroup analyses related to BMI revealed that among women with BMI <27 kg/m^2, patients with PCOS exhibited higher PAPP-A levels than controls (2.1 ng/ml versus 1.8 ng/ml, respectively, $P=0.018$). When women with PCOS were investigated among themselves in terms of BMI, lean PCOS cases had higher levels of PAPP-A (2.1 ng/ml versus 1.5 ng/ml, $P=0.002$). PAPP-A levels were also

negatively correlated with age, BMI, and triglyceride levels. The authors concluded that PAPP-A might be a clinical indicator for the cardiovascular risk evaluation in a subgroup of young patients with BMI <27 kg/m^2 using PAPP-A. Apart from cardiovascular risk, these results also suggested that increased PAPP-A levels may be associated with abnormal folliculogenesis in lean PCOS groups due to higher IGF activity independent of excess fat tissue. Since IGF system has a significant role in FSH resistance at the granulosa level and androgen-dominant milieu in PCOS, this topic needs further evaluation.

In our study, the patients with PCOS and control group were comparable regarding their HOMA levels, which prevented the possible bias related with the increase in cardiovascular risk associated with metabolic syndrome and insulin resistance. Our findings were interesting for demonstrating high serum PAPP-A levels in PCOS patients with oligo-anovulation. Since this was a case control study, our results were not conclusive in defining the direction of causality for the correlation between increased levels of PAPP-A and oligo-anovulation. Further investigations are needed including tissue levels of PAPP-A in this subgroup of women.

Due to the unfavorable cardio-metabolic profile, women with PCOS are considered at increased risk for cardiovascular disease (CVD). In fact, previous studies exploring subclinical atherosclerosis showed increased carotid- intima media thickness and arterial stiffness, and impaired flow mediated dilatation [4,17,18]. Moreover, several large cohort studies confirmed that these women are at increased risk for CVD [19,20]. However, some authors consider that cardiovascular risk in these patients are related to traditional risk factors of obesity, hypertension, or dyslipidemia [21]. On the other hand, PCOS is a heterogeneous disorder with substantial variations between the phenotypes [22,23]. Distinct mechanisms can mediate the cardiovascular risk in different phenotypes. Hormonal disturbances or chronic oligo-anovulation that eventually result in disturbed hormonal milieu can be one of these possible alterations. In this study, we found that ovulatory abnormalities were associated with increased serum PAPPA levels, independent of other classical CVD risk factors.

During the follow-up and management of PCOS patients, the heterogeneous nature of the disease can sometimes be ignored. Insufficient consultation on the comorbidities and long-term risks of the disease is not uncommon. There is remarkable clinical variation in the presentation of the syndrome throughout life. Patients with PCOS may experience considerable additional cardiovascular comorbidities along with advanced age. The American College of Obstetricians and Gynecologists [24] emphasizes that BMI, fasting lipid profile, and metabolic syndrome components should be evaluated in all PCOS cases. However, there is a need for defining novel markers to determine the risk of cardiovascular disease in distinct PCOS phenotypes. Our results indicated that oligo-anovulation may be independently associated with an increase in long-term cardiovascular risk. One interesting point of this finding is that the PAPP-A levels of PCOS patients without oligo-anovulation was similar to those of controls. Further prospective studies are needed to define additional cardiovascular disease risk markers in this subgroup of women.

Consuegra-Sanchez et al. [11] reviewed currently available data about PAPP-A to assess its predictivity for CVD. The authors also discussed some of the criticisms regarding the value of this marker in clinical practice. They concluded that PAPP-A may have a role atherosclerotic lesion development and may relate to the instability of the atheromatous plaque. However, the exact mechanism of PAPP-A in cardiovascular disease pathogenesis is yet to be explained. Papanastasiou et al. [25] conducted a systematic review of the current literature to determine the prognostic value of PAPP-A for cardiovascular events among patients presenting with chest pain. The authors investigated 8 studies according to the inclusion criteria. One important limitation of this review was the use of different assays for circulating PAPP-A measurements resulting in heterogeneity in cut- off values and patient stratification. However, it did not restrain the meta-analytic approach to quantitatively synthesize research findings for each of the articles. This meta-analysis supported that PAPP-A levels were predictive for especially early complications of cardiovascular events. The authors proposed that it may be related to fluctuation of the inflammation over time. However, there is still lack of prospective studies to draw conclusions for the prognostic value of PAPP-A in women with PCOS.

Strength and limitations

There are two major strengths in this study. First, we analyzed a homogeneous group of PCOS women who were strictly evaluated according to Rotterdam criteria. Second, we excluded obese women, which allowed us to avoid the confounding effects of obesity. Our results indicate that PAPP-A levels holds promise for cardiovascular risk stratification in distinct PCOS phenotypes. To our knowledge, this is the first study demonstrating a positive association between chronic oligo-anovulation and PAPP-A, which is also a marker for cardiovascular risk. The main limitation of this study was its case control design that precludes us from determining the direction of the association between oligo-anovulation and elevated PAPP-A levels. Second, the relationship between PAPP-A levels and cardiac function was not explored. However, the homogeneous group of women recruited stands as a strength for eliminating the confounding effects of insulin resistance and obesity. There can be several sources of bias in this study: First, selecting a lean group (BMI < 27 kg/m^2) may limit the generalization of these results to entire population, and second, diagnosis of PCOS may raise discrepancies when different diagnostic criteria are used. These should be considered when comparing these results with others. Prospective studies are needed to uncover the long-term cardiovascular risk of elevated PAAP-A levels in PCOS patients with oligo-anovulation.

Conclusions

Serum PAPP-A levels are similar in the control and PCOS groups. However, lean, and young PCOS patients with oligo-anovulation have increased serum levels of PAPP-A when compared to women without. This association is independent of the confounding effects of age, BMI, FAI and AMH.

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Comparison of biopsy results of HPV 16/18 and non-16/18 HPV positive patients with a normal PAP test: A tertiary center experience

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Ethics Committee Approval
This study was approved by the Medical Specialty Training Board of Dr. Lutfi Kirdar Training and Research Hospital (Approval ID: 2019/514/148/26). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Optimal management for HPV positive and cytology negative patients remains a controversial issue. Immediate colposcopy is suggested for HPV 16/18 positive patients, whereas patients with non 16/18 HPV oncogenic virus positive are recommended to co-test after a year. In this study, we aim to compare the immediate colposcopic biopsy results between HPV 16/18 and non-16/18 HPV positive patients with cytology negative patients.

Methods: In this prospective cross-sectional study, we included 1028 HPV positive and cytology negative patients who were screened for cervical cancer between January 2017 and 2019. Liquid based preparations were used for cytology samples (ThinPrep Pap Test). Cervical specimens were analyzed with Hybrid Capture for HPV types. Patients underwent colposcopic examination, biopsy procedure and endocervical curettage.

Results: A total of 424 (41.2%) patients were HPV 16/18 positive, while 604 (58.8%) were non-16/18 oncologic HPV positive. Colposcopic biopsy results of the patients revealed that of the HPV 16/18 positive patients, 246 (23.9) had no dysplasia, 101 (9.8) had LGSIL and 77 (7.5%) had HGSIL. Among the non 16/18 positive patients, 422 (41.1%) had no dysplasia, 144 (14%) had LGSIL and 38 (3.7) had HGSIL. All patients were referred for endocervical curettage, which resulted as follows: Among HPV 16/18 patients, 384 (37.4%) had no dysplasia, 21 (2%) had LGSIL and 19 (1.8%) had HGSIL. Five hundred seventy-one non 16/18 positive patients had no dysplasia, 26 (2.5%) had LGSIL and 7 (0.7) had HGSIL. The comparison of colposcopic biopsy results of HPV 16/18 and non-16/18 HPV positive patients were different in terms of no dysplasia and HGSIL (P=0.001 and P=0.001, respectively), while LGSIL results were similar. The endocervical curettage biopsy results of the patients revealed a significant difference in HGSIL results (P=0.03). The two groups were similar with respect to reports of no dysplasia and LGSIL.

Conclusion: Direct referral of the patients, who are expected to be lost to follow-up, could be convenient for non-16/18 HPV positive patients with negative cytology to reduce progression of cervical cancer and the psychological burden of HPV positivity.

Keywords: HPV 16, HPV 18, Colposcopy, PAP test

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Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection [1] which is proven to cause cancers in anogenital tract (cervical, vaginal, vulvar, anal), along with the head and neck regions [2, 3]. Cervical cancer screening is adopted worldwide. Pap cytology or HPV genotyping are the most common methods. In our national screening program in Turkey, only HPV genotyping is conducted. If the result is positive, cytology is used for triage. HPV test alone is found to be more sensitive than cytology alone [4]. New triage methods are also under investigation, such as pi16/Ki-67 dual-stained cytology or molecular triage markers [5, 6].

The debate for best option of cervical cancer screening continues. The most prevalent co-test result is "Cytology negative, non-16/18 high-risk HPV positive" [7]. According to The American Society for Colposcopy and Cervical Pathology (ASCCP), colposcopy should be suggested to the patients with abnormal cytology results regardless of the type of a positive HPV result [8]. Patients with positive tests for HPV 16/18 should also be referred for colposcopy even they are negative for intraepithelial lesions and malignant cytology (NILM). Patients positive for HPV types other than 16/18 are recommended to have co-tests repeated after one year because of the possibility of spontaneous regression [8, 9]. However, there are studies suggesting that non 16/18 HPV positive patients should undergo immediate colposcopy to avoid the risk of overlooking cervical intraepithelial neoplasia [9]. Direct referral for colposcopy is not suggested in ASCCP guidelines, however, larger studies should be conducted regarding follow-up results and patients lost to follow up in this approach.

In this study, we aimed to evaluate the colposcopic biopsy and endocervical curettage results of NILM and HPV-positive patients who presented to our clinic to determine the optimal management.

Materials and methods

In this retrospective cross-sectional study, we included patients with NILM cytology results and HPV positive patients aged between 30-65 years, who were admitted to a tertiary center between January 2017-2019. Exclusion criteria included patients with a history of cervical intraepithelial neoplasia, abnormal Pap test results and pregnancy. Patients' ages, education level, monthly income, marital status, obstetric history, and employment status were noted. Ethics approval was obtained from the local ethics committee, and all patients signed informed consent forms (2019/514/148/26).

Liquid based preparations were used for cytology samples (ThinPrep Pap Test). Cervical specimens were analyzed with Hybrid Capture for HPV types 16, 18 and twelve other high-risk HPV types including type 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68. Colposcopic biopsy and endocervical canal curettage were performed according to pathological findings in colposcopy and history of the patients. Colposcopy was performed with colloquial device (colposcope 1D-21100, Leisegang GmbH, 2014-03, Germany), which can augment up between 4.5- 30 using a green filter. First, the cervix was cleaned with saline, acetic acid was applied, and acetowhite areas and vascular pathologies were determined. Then, the cervix was stained with Lugol's solution, and iodine-free areas were spotted. Random biopsies were taken from four quadrants if there were no specific lesions. Endocervical curettage was performed if there were suspicious lesions or inadequate transformation zone observation. Pap test results were reported in accordance with the Bethesda system. Cervical biopsy results were interpreted according to The Lower Anogenital Squamous Terminology system, as LGSIL and HGSIL. Biopsy results were rendered pursuant to World Health Organization. Follow-ups after the procedures were planned in accordance with the 2012 ASCCP [4].

Statistical analysis

The data was analyzed using Statistical Package for the Social Sciences software version 24. The normality of data distribution was evaluated by Kolmogorov-Smirnov and Shapiro-Wilk tests. Levene's test was used for homogeneity of variances. Nominal variables were given as number of cases and percentages, descriptive variables were shown as mean (standard deviation). Chi-square test was used to compare the categorical data and ratio comparisons. Post-hoc analysis was performed for binary comparisons of groups. Adjusted p values were calculated after Bonferroni correction. Statistical significance was $P<0.05$.

Results

In this study, we included 1320 patients with NILM cytology and positive HPV results who were admitted to our hospital. Among them, 292 patients were excluded due to history of cervical intraepithelial neoplasia and abnormal cytology. Two patients positive for HPV 16/18 had cervical cancer in their cervical biopsy results; they were also excluded from the study to preserve the normality of distribution. The study was completed with 1028 patients and the biopsy results were evaluated.

The mean age of the patients was 44.28 (8.82) (26-66) years. In the study population, we found that 424 patients (41.2%) were HPV 16/18 positive, and 604 (58.8%) were non-16/18 oncologic HPV positive (Figure 1). All patients underwent cervical biopsy and endocervical curettage. Pathology results of the patients are summarized in Table 1.

The patients were divided into two groups and cervical biopsy results were compared. Group 1 consisted of HPV 16/18 positive patients, and Group 2 included patients positive for non-16/18 oncogenic types. Results of the patients were classified as normal, LGSIL and HGSIL. We found that no dysplasia results were significantly higher in non-16/18 HPV oncogenic type group (n=422 (69.8%)), compared to the HPV 16/18 positive group (n=246, (58.0%)) ($P=0.001$), while HGSIL results were significantly lower (n=38, 6.2% vs. n=77, 18.1%, p=0.001). LGSIL results were similar (Table 2).

Figure 1: Flow-chart of the study

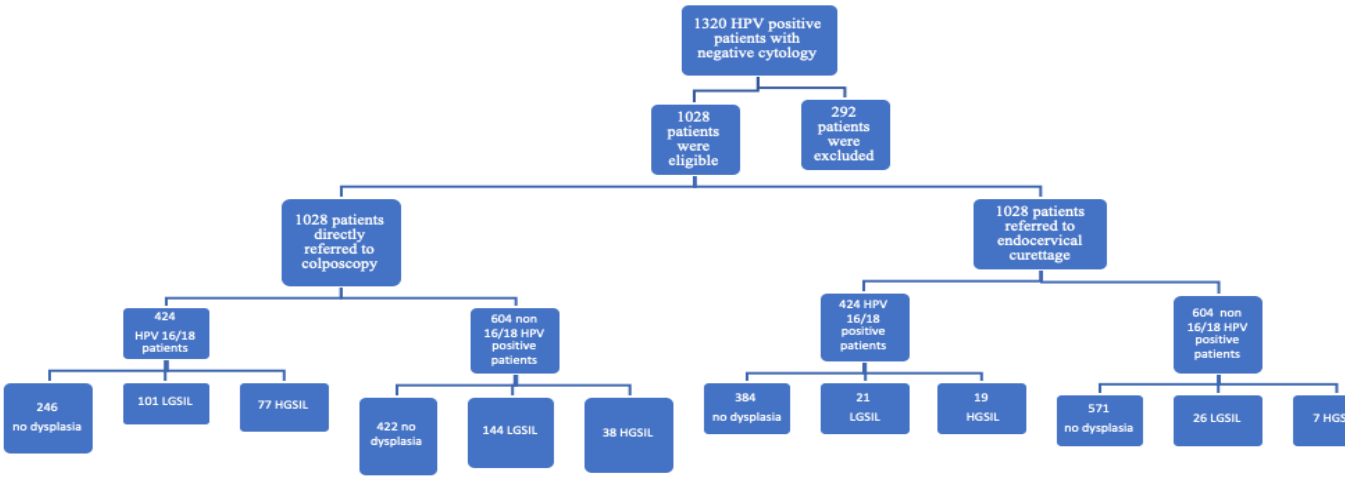

Table 1: HPV, cervical cancer and ECC biopsy results of the patients

HPV screening result	Eligible female patients n=1028	
	n	%
HPV 16/18 +	424	41.2
Non 16/18 +	604	58.8
Cervical biopsy results		
Normal	668	65
LGSIL	245	23.8
HGSIL	115	11.2
Endocervical curettage		
Normal	955	92.9
LGSIL	47	4.6
HGSIL	26	2.5

Table 2: Comparison of colposcopic biopsy results of HPV 16/18 and non 16/18 patients

Colposcopic biopsy results	HPV 16/18 positive n (%)	non 16/18 HPV positive n (%)	*P*-value	*P*-value[1]
No dysplasia	246 (58.0)	422 (69.8)	<0.001	0.001
LGSIL	101 (23.8)	144 (23.8)		0.600
HGSIL	77 (18.1)	38 (6.2)		0.001

[1] *P*-value of post-hoc analysis after Chi-square test

The endocervical curettage (ECC) results of the patients were also compared. Results of the patients were classified as normal, LGSIL, HGSIL. According to the post-hoc analysis, patients with no dysplasia were insignificantly higher in the non-16/18 HPV positive group (P=0.34), and no significant differences were found in terms of LGSIL results (P=5.29). However, HGSIL results differed, with 7 (1.1 %) detected among non 16/18 HPV-positive patients and 19 (4.4 %) detected among those with non-16/18 HPV positivity (P=0.03). When the three categories of cytology results (no dysplasia, LGSIL and HGSIL) were compared between the two groups, ECC results significantly differed (P<0.001) (Table 3).

Table 3: Comparison of endocervical curettage biopsy results of HPV 16/18 and non 16/18 patients

ECC biopsy results	HPV 16/18 positive n (%)	non 16/18 HPV positive n (%)	*P*-value	*P*-value[1]
No dysplasia	384 (90.5)	571 (94.5)	<0.001	0.340
LGSIL	21 (4.9)	26 (4.3)		0.529
HGSIL	19 (4.4)	7 (1.1)		0.030

[1] *P*-value of post-hoc analysis after Chi-square test

Discussion

Cervical cancer is a public health problem worldwide, with an estimated 528,000 new cases and 266,000 deaths per year [10, 11]. In Turkey, cervical cancer is the 10th most observed cancer [12]. Mortality and morbidity due to cervical cancer mostly affects low and middle-income countries [10]. This may be due to low socio-cultural status or inappropriate screening programs. Optimal management strategies for cervical cancer screening are still controversial. The aim is to detect cervical cancer in the early phase with a low-cost and less invasive method.

Addressing the Need for Advanced HPV Diagnostics (ATHENA), a large population-based study, confirms that HPV screening is more sensitive than cytology alone for detecting ≥CIN 3 lesions. Besides, a negative HPV test is more reliable for long-time protection than cytology [13]. Therefore, it was expected to exclude cytology and move on with HPV in the first place for cervical cancer screening [14]. However, cytology and HPV test are still being interpreted together in guidelines. The algorithms of positive HPV and abnormal cytology is well-established in ASCCP guidelines [15]. Approach to HPV-positive patients who are negative for intraepithelial lesion and malignancy cytology (NILM) remain a controversy. The results of the Population Based Screening Study Amsterdam (POBASCAM) study revealed that only HPV screening is safe, also stating that the lack of further evaluation of the normal cytology results could constitute bias between groups [16]. In our study, we evaluated the colposcopic and endocervical curettage results of the patients.

The most common result obtained in screening programs is non-16/18 oncologic positivity with normal cytology [17]. National screening programs aim to lower the risk below 2% for ≥CIN 3 lesions [18, 19]. In our study, we found a HGSIL incidence of 3.7%, which is higher than expected. This could be related to consequences of the discrete health-care policies of the countries [20]. In the Netherlands, according to Vrije Universiteit Medical Centre-Saltro laboratory population-based cervical screening (VUSA- screen) study, patients are followed with cytology in 0th, 6th and 18th months for a corresponding negative predictive value [21]. However, this procedure is patient-dependent and up to 28-33% of the patients were lost to follow-up in the studies [19]. We also have a lot of patients who did not attend their follow-up regularly in our clinic, which decreases the

benefits of screening, as these patients could not be treated in the early stages. If optimal follow-up is not expected, more invasive methods would be justified to prevent any delays in treatment.

Castle et al. [13] performed a sub-analysis of the patients of ATHENA study and concluded that adding HPV typing to cytology enabled a more sensitive and efficient screening method for cervical cancer. Combined liquid-based cytology and HPV testing are shown to increase the sensitivity by 4% compared to HPV alone for ≥CIN 3 lesions. However, the number of positive patients screened also increased by 35.2%. Adding HPV genotyping to the triage was found to increase colposcopy sensitivity, and addition of positive predictive value (PPV) proved more successful than ASC-US, but less successful when alone. When HPV 16,18 genotyping is adopted for NILM cytology, the sensitivity and PPV for ≥CIN 3 are 53.8 % and 10.2%, respectively. HPV genotyping reduces interobserver reproducibility and workforce. There are other cytology and molecular triage strategies. For example, p16/Ki 67 dual- stained cytology has a similar sensitivity for ≥CIN 3, but higher specificity [22-24]. Wright Jr. published a sub-study nested into ATHENA trial and concluded that p16/Ki-67 dual stained cytology was more sensitive and efficient for colposcopy than routine cytology or HPV 16/18 genotyping [13]. Furthermore, the increase of adenocarcinoma necessitates better triage methods for HPV-positive/ NILM cytology patients [7]. It is found that 50% of HPV-positive/NILM women could develop cervical adenocarcinoma, which cytology is less effective in identifying [25].

The potential harms of direct referral to colposcopy are increase in patients' anxiety and the risk of the procedure [26]. We found that HPV results of the patients decreased their quality of life, irrespective of their cytology result, in a study conducted in our center. As direct referral to colposcopy is the most sensitive method for detecting high grade lesions with a sensitivity of 89.9% for ≥CIN 3 lesions, we used this method on our patients [27] and found that we would have missed 3.7% percent of the patients for follow-up with HGSIL had we not utilized cytology for triage. It is also shown that screening with HPV alone had the highest relative sensitivity and lowest relative specificity for ≥CIN 2 lesions (1.68 and 0.71, respectively) [28].

HPV with cytology and HPV genotyping triage had the highest relative specificity (1.04) and lowest relative sensitivity (0.92 and 0.85, respectively) [29]. Cytology and colposcopy should be used as complementing methods to reduce more invasive procedures such as conization or LEEP [30].

Non 16/18 HPV types have a prominent place in HPV screening programs because they are the most reported result of co-testing [7]. In the assessment of colposcopic biopsy results of 300 patients who tested positive for oncogenic non 16/18 HPV types, no significant associations were found between the age groups and in the number of HPV types detected [31]. On the other hand, we found a statistically significant difference of colposcopy results between patients positive for HPV 16/18 and non-16/18 oncogenic type. We also determined that HPV 16/18 and oncogenic types significantly differed in terms of endocervical curettage biopsy results. Clinicians should consider that the possibility of cervical intraepithelial neoplasia is 23.8% for LGSIL and 6.2% for HGSIL in colposcopic biopsy and 4.3 % for LGSIL and 1.1% for HGSIL in endocervical curettage [31,32]. To reduce mortality and morbidity related to cervical cancer, more precise algorithms should be constituted [33].

The strengths of our study include the high number of patients and the fact that it was carried out in a tertiary center. However, there are also some limitations: We did not assess the risk factors thoroughly, such as smoking and multiple sexual partners, and long-term follow-up results were not evaluated.

Conclusion

Direct referral of the patients could increase the number of the colposcopies performed. However, it is known that the half of the patients left to follow up would also require colposcopy eventually. Patients who are presumed to be lost to follow-up could be also directly referred for colposcopic biopsy. This approach would increase the benefit of the cervical cancer screening by reducing the number of patients lost to follow-up, HPV-related psychological burden, and advanced cervical cancer treatment costs.

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The effect of change in educational model on surgical antimicrobial prophylaxis

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Ethics Committee Approval
Permission was granted by Ordu University Faculty of Medicine local ethics committee (Date: 19.12.2019, No: 2019-181). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Surgical antibiotic prophylaxis is one of the important steps in preventing surgical site infections. Compliance with the guidelines is particularly important and there are problems in this regard. Innovative approaches are needed in education. In our study, the effects of the novel face-to-face training and feedback model, with which we obtained positive results, were shown.

Methods: In this retrospective cross-sectional study, surgical site infections and the use of antibiotics in surgical prophylaxis in all patients undergoing certain operations were examined in pre-determined departments. The quarterly or annual changes in compliance rates were compared with the new education model.

Results: A total of 3697 clean surgeries were assessed in three departments. The cardiovascular surgery department had annual compliance rates of 2.5% and 8.6% in 2010 and 2011, respectively, which increased between 2012-2017 from 64.5%, 90.7%, 85.4%, 98.8%, 90.6% to 97.4%, respectively (P<0.001), with the new training model. In the Orthopedics and Traumatology department, within eight 3-month periods between 2014 and 2016, compliance rates increased from zero to 92.4% (P<0.001). The general surgery department had a 3.3% compliance rate at the beginning of 2015, which increased up to 98.3%, 95.3%, 96.8% and 93.5% in three-month intervals in 2017 (P<0.001). No significant changes were identified in surgical site infection rates.

Conclusion: Continuous training, monitoring and feedback is required for guideline compliance in surgical antibiotic prophylaxis. We think narrow-scoped and target-oriented face-to-face training is effective and applicable.

Keywords: Antibiotics, Surgical site infection, Prophylaxis, Education, Intervention

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Introduction

Surgical site infections (SSI), the most observed nosocomial infections [1], increase duration of stay in the hospital and the intensive care unit, along with mortality rates [2]. The use of preoperative antibiotics for prophylactic purposes is a major step in preventing surgical site infections [3]. Guidelines regarding the antibiotics, doses and durations recommended according to surgery type are published by national and international organizations [4]. In line with scientific publications and guidelines, every organization implements these by creating their own directives. The use of prophylactic antibiotics with broader spectrum than necessary and for longer durations results in side effects, increased cost, and antibiotic resistance. As a result, hospital infection control committees perform surveillance, feedback, and training studies in line with their duties and responsibilities. However, it is highly challenging to create permanent behavior changes in Turkey, as in the entire world. In this study, we aimed to report the outcome of a new training model which provided dramatically positive results when applied in some departments with lower antibiotic compliance rates than targeted despite classical feedback and training studies.

Materials and methods

In line with infection control committee decisions, surgical site infections in clean surgical operations in pre-determined departments and the suitability of antibiotic prophylaxis used in these operations were observed.

Within this scope, cardiac surgery surveillance results in 2010-2017, hip and knee prosthesis operation surveillance outcomes in the Orthopedics and Traumatology Department in 2014 and 2016 and thyroid operation surveillance results in the General Surgery Department in 2015 and 2017 were retrospectively investigated to reveal the effects of the new training model.

In line with the surgical prophylaxis guidelines which were created by the infection control committee, and provided to surgeons, prophylaxis was not used for thyroid surgery, and cephazolin was used in knee and hip prosthesis operations and cardiac surgeries for a maximum of 24 and 72 hours, respectively.

Classic training involved the invitation of all branches and clinicians to the hospital conference room for a seminar given by infectious diseases specialists. The new training model only targeted clinicians in the relevant branch and was held as an interactive chat around the same table either in their clinical ward or in a small meeting room. Clinicians were informed about inappropriate antibiotic use rates on both clinical and individual clinician basis and the desired procedure was clearly communicated.

Surveillance was performed by infection control nurses and data were reported in 3-month intervals.

In our study, the CVS department rates are provided annually, while General Surgery and Orthopedics and Traumatology clinical data are presented in three-month intervals for non-consecutive two-year periods.

Statistical analysis

The Statistical Package for Social Sciences (IBM SPSS for MacOS, Ver.21) program was used for statistical analysis. Independent groups of categorical variables were compared with the chi-square test. Significance level was defined as $P<0.05$. Intragroup comparisons were carried out by the two-proportion z-test with Bonferroni correction for significant chi-square test results.

Results

The total number of surgeries in the CVS clinic was 2591, with the distribution shown in Table 1. In this clinic, the compliant prophylaxis rate was only 2.5% in 2010. Written feedback was given to clinicians and classic seminar training studies were held for the whole hospital. With similar poor results (8.6% incompliant) in 2011, the infection control team held a meeting to determine a new training strategy with more targeted focus. At the end of 2011 and in the first 3 months of 2012, CVS clinicians were invited twice, and the new meeting model was implemented. Dramatic positive responses were obtained in the following two years. The compliant prophylaxis rates for all years in the CVS clinic are shown in Table 2 and variation by year is presented in Figure 1.

Table 1: Surgery numbers and yearly distribution in cardiovascular surgery clinic

	2010	2011	2012	2013	2014	2015	2016	2017	Total
AAA	11	32	31	14	21	27	11	9	156
CARD	47	91	57	71	80	42	58	54	500
CABPS	215	248	262	183	234	259	250	284	1935
Total	273	371	350	268	335	328	319	347	2591

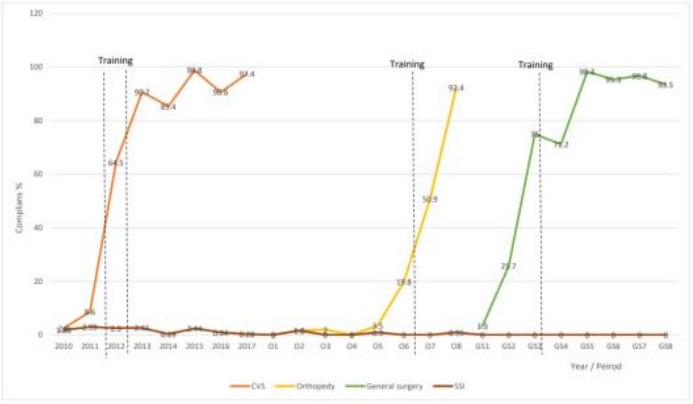
AAA: Aorta aneurysm, CARD: valve surgery, CABPS: Coronary artery by-pass surgery

Table 2: Variation in antibiotic prophylaxis compliance rates and surgical site infection rates according to year in the cardiovascular surgery clinics

Years	Compliance rate	Compliance* %	Form of incompliance**	SSI rates† % (rate)
2010	7/273	2.5[a]	100/0	1.83[a] (5/273)
2011	32/371	8.6[b]	100/0	2.99[a] (11/371)
2012	226/350	64.5[c]	99/1	2.5[a] (9/350)
2013	243/268	90.7[d]	60/40	2.61[a] (7/268)
2014	286/335	85.4[d]	94/6	0.29[b] (1/335)
2015	324/328	98.8[e]	50/50	2.44[a] (8/328)
2016	289/319	90.6[d]	84/16	0.94[a] (3/319)
2017	338/347	97.4[e]	88/12	0.28[b] (1/347)

* Difference between groups without common letters is significant, $P<0.001$, ** Duration incompliance/antibiotic choice incompliance (%), † Difference between groups without common letters is significant, $P<0.001$, SSI: Surgical site infection

Figure 1: Prophylaxis compliance rates and surgical site infection rates in clinics



CVS: Cardiovascular surgery, GS: General surgery, SSI: Surgical site infections, O: Orthopedics and Traumatology

The knee and hip prosthesis operations in the Orthopedics and Traumatology department were monitored in 2014 and 2016. The number of surgeries was 255 in 2014 (152 knee prostheses and 103 hip prostheses) and 366 in 2016 (232 knee prostheses and 134 hip prostheses), with a sum of 621 operations. Data from all 3-month periods in 2014 and the first 3-month period in 2016 were close to zero. The new training model

was implemented, and 19% compliance rate was observed in the second period of 2016. The compliance rates increased in the following periods to reach over 90%. Rates are presented in Table 3 and Figure 1.

In the general surgery clinic, a total of 485 thyroid surgeries were observed with 305 in 2015 and 180 in 2017. In the 3rd period in 2015, the new training model meeting was held with general surgery clinicians. While the highest compliance rate was 75% in 2015, rates were above 90% in all periods in 2017. The periodic variation in compliance rates through the years is shown in Table 4 and Figure 1.

Table 3: Variation in antibiotic prophylaxis compliance rates and surgical site infection rates according to year in the Orthopedics and Traumatology clinic

Years	Period	Compliance * Rate	Compliance %**	SSI Rate %
2014	1. Period	0/113	0[a]	0
	2. Period	1/63	1.6[a]	1.6 (1/63)
	3. Period	1/50	2[a]	0
	4. Period	0/29	0[a]	0
2016	1. Period	4/113	3.5[a]	0.9 (1/113)
	2. Period	18/91	19.8[b]	0
	3. Period	29/57	50.9[c]	0
	4. Period	97/105	92.4[d]	0.95 (1/105)

* In 2014 all antibiotic use durations were incompliant, while in 2016 97% were duration incompliant and 3% were antibiotic choice incompliant, ** Difference between groups without common letters is significant, *P*<0.001, SSI: Surgical site infection

Table 4: Variation in antibiotic prophylaxis compliance rates and surgical site infection rates according to year in the general surgery clinic

Years	Period	Compliance Rate*	Compliance %**	SSI Rates (%)
2015	1. Period	4/125	3.3[a]	0
	2. Period	19/74	25.7[b]	0
	3. Period	30/40	75[c]	0
	4. Period	47/66	71.2[c]	0
2017	1. Period	59/60	98.3[d]	0
	2. Period	41/43	95.3[d]	0
	3. Period	30/31	96.8[d]	0
	4. Period	43/46	93.5[d]	0

* Compliant prophylaxis number/total number of surgeries, **34% non-cephazolin antibiotic selection present. Difference between groups without common letters is significant, *P*<0.001, SSI: Surgical site infection

Discussion

The data in this study show that narrow scope and target-oriented face-to-face training positively affected compliance rates at satisfactory levels. However, this improvement and positive advance required time. Additionally, it is necessary for interaction between units and feedback to continue after the intervention for the increased compliance rates become permanent. In our study, despite the shorter use of narrow-spectrum antibiotics for surgical prophylaxis, an increase in SSI rates was not observed.

When the preoperative antibiotic prophylaxis use in Turkey is investigated, prevalence studies found that 40.9% of cases used incompliant antibiotics and 29.1% prescribed them for incompliant durations. Antibiotics with incompliant use for surgical prophylaxis were mostly ceftriaxone, glycopeptides, and aminoglycosides. Again, a study found that nearly half of surgical interventions did not comply with guidelines in terms of duration of prophylactic antibiotic use [5]. In a study in Turkey assessing a total of 2398 patients with preoperative antibiotic prophylaxis, after training and surveillance were performed for 8 months, correct timing of the first antibiotic dose rose from 91.7% to 99.0%, while excessive antibiotic use fell from 77.0% to 44.7%. Full compliance rates to guidelines rose from 15.5% to 40.2% [6]. A study by Prado et al. created a prophylaxis guide prepared by a team of surgical department representatives, which was signed by all parties. According to this guide, preparation forms were completed and signed by surgeons to request antibiotics. Just as in the control system of the hospital pharmacy, the compliant surgical prophylaxis rate rose from 56.4% to 100% [7].

Training does not always have the desired effect, or the same training may be successful in some clinics and hospitals, and not in others [8-11]. Effective training comprise work involving multidisciplinary approaches encompassing more administrative and technical strategies [12, 13]. One of the greatest fears of surgeons is that a patient will develop a surgical site infection, which results in unnecessary broad spectrum and long-term antibiotic use, especially for operations with foreign objects, prosthesis use and those involving vital systems, like the cardiovascular system. However, prophylactic antibiotic use is only one of the SSI prevention stages, and unnecessarily long and broad-spectrum agent use does not resolve deficiencies and errors in other stages.

In the face-to-face training and feedback model, we discussed the clinical compliance rates and hesitations about the topic in more detail, so we observed increased chance of ensuring consensus about prophylaxis administration. Additionally, we think that informing surgeons about the lack of increase in SSI rates despite the use of short-term and narrow-spectrum antibiotics during feedback increased future compliance with the prophylaxis guides and made it more permanent.

Countries and even hospitals should prepare their own surgical antibiotic prophylaxis guidelines in line with local resistance data and international guidelines. We can say the inclusion of surgeons while creating these guides and protocols will be beneficial to increase compliance. When infection was suspected based on clinical and/or laboratory findings, rapid and effective infectious disease consultations were performed, and we saw that inter-clinical confidence, and consequently, guideline compliance, increased.

In Turkey, since 2003, the use of broad-spectrum antibiotics requires the approval of an infectious disease specialist from the first dose. Some antibiotics, like third generation cephalosporins and quinolones, require approval after 3 days of use. This requirement is supported by hospital automation systems and inappropriate antibiotic use for treatment and prophylaxis by other branch clinicians has been significantly overcome. It caused a significant improvement in antibiotic use in our country [14, 15]. Antibiotics like ampicillin sulbactam and cephazolin do not require infectious disease specialist approval, which explains increased incompliance in terms of antibiotic choice in our hospital compared to duration.

Limitations

Data in our study were retrospectively obtained from the national hospital infection surveillance network and the surveillance forms of our hospital's infection control committee. Therefore, only selected antibiotics and the duration of use could be investigated. The compliance in terms of antibiotic timing, additional dose administration and dose information could not be determined. Additionally, these surveillance and report forms did not include demographic information about the patients. It is necessary to try new training strategies which will create a convincing and lasting effect in this regard.

Conclusions

Organizations are required to determine policies to monitor surgical prophylaxis and antibiotic use and provide appropriate training as well as give feedback. It is important that these processes requiring continuity are effective and permanent. Creative implementations unique to each unit may be required. We think that rather than training the organization in general, narrow-scope comprehensive face-to-face training models targeting specific units may be more effective and should be recommended.

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Research article

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Myocardial infarction with non-obstructive coronary artery disease, a retrospective cohort study: Are plaque disruption and other pathophysiological mechanisms the same disease?

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Ethics Committee Approval
University of Health Sciences Gülhane Training and Research Hospital Ethics Committee decision number and date: 19/194, 14/05/2019. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Myocardial infarction with non-obstructive coronary arteries (MINOCA) is an increasingly recognized entity. Recent studies have shown that MINOCA is not a benign syndrome, with younger MINOCA patients having outcomes comparable to their myocardial infarction with obstructive coronary artery disease (MI-CAD) counterparts. In this study, we will describe the demographic, clinical and angiographic characteristics of MINOCA patients in our hospital.
Methods: In this retrospective cohort study, all patients who underwent coronary angiography with the diagnosis of acute coronary syndrome during September 2016-April 2019 were screened and those with MINOCA were detected. We described the demographic, clinical, and angiographic characteristics of MINOCA patients and compared the etiologic and pathophysiological mechanisms.
Results: A total of 3855 patients with acute coronary syndrome were screened and 155 were diagnosed with MINOCA, with a total prevalence of 4.02%. Among them, 48.4% were female and the overall mean age was 55.04 (13.57) years. Plaque disruption was the most common cause of MINOCA (48.4%), which was followed by microvascular dysfunction and slow flow (9.7%). We compared plaque disruption and other causes to find that age (58.31 (13.76) vs 51.89 (12.68) P=0.003), hypertension (37 (48.7%) vs 25 (31.6%) P=0.034), prior coronary artery disease history (16 (21.1%) vs 2 (2.5%) P=0.001) and creatinine clearance (67.35 (IQR: 25.8) vs 74.0 (IQR: 28.58) P=0.009) were higher in patients with plaque disruption than those without.
Conclusions: MINOCA is a diagnosis of exclusion with numerous potential causes. The etiological and pathophysiological mechanisms of plaque disruption are different from other causes of MINOCA and the correct treatment approach determines the prognosis.

Keywords: Microvascular dysfunction, MINOCA, Plaque disruption, SCAD, Vasospasm

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Introduction

Depending on the population examined, around 5%–15% of patients with acute myocardial infarction (MI) present without any significant stenosis (<%50) in their coronary arteries [1-3]. Although this patient group has been known for many years and is mentioned with different names in the literature, it has not received the necessary attention [4, 5]. In 2012, Beltrame suggested that the myocardial infarction with non-obstructed coronary arteries (MINOCA) would be appropriate for identifying this patient group [6]. MINOCA patients have an increased risk of future adverse events comparable to those of MI with obstructive coronary arteries (MI-CAD) patients [7]. A recent meta-analysis reports that the 1-year mortality as high as 4.7% [2, 7]. SWEDEHEART registry data revealed that mortality was 13.4% during a mean follow-up of 4.1 years [8]. All these results show that MINOCA is a quite common disease with high mortality and morbidity in the long term.

In contrast to MI-CAD, the underlying pathophysiology of MINOCA is most likely heterogeneous. Several mechanisms, such as coronary spasm, plaque disruption, a rapidly dissolved thrombus, dissection, microvascular dysfunction, inflammation, and imbalance in myocardial oxygen supply/demand, have been proposed [1-3]. MINOCA patients have a lower prevalence of traditional coronary arteries disease risks factors, such as hypertension (HT), hyperlipidemia (HL), diabetes mellitus (DM), tobacco abuse, and a family history of MI. It is more common in female patients [1-3]. All these factors make diagnosis and treatment of MINOCA challenging in daily clinical practice. The present study aimed to describe the demographic, clinical and angiographic characteristics of MINOCA patients and compare the etiologic mechanism.

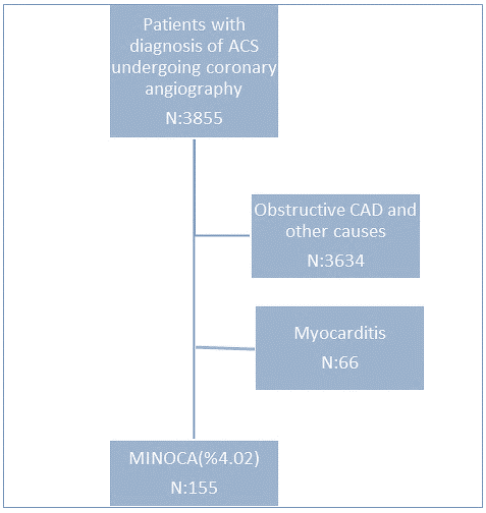
Materials and methods

In this retrospective cohort study, patients who were admitted to the emergency department with chest pain and high cardiac troponin levels between September 2016 and April 2019 and underwent coronary angiography due to acute coronary syndrome were identified from hospital and file records. After excluding patients with obstructive coronary artery disease and other probable causes, MINOCA patients were identified and included in the study. A recent scientific statement from The American Heart Association (AHA) working group has suggested the following diagnostic criteria for MINOCA: (I) Acute myocardial infarction criteria as defined by the “Fourth Universal Definition of Myocardial Infarction [9]” (II) Non-obstructive coronary arteries on angiography, (III) No specific alternate diagnosis for the clinical presentation [3]. Non-coronary diseases, such as pulmonary embolism, myocarditis, Takotsuba cardiomyopathy, which cause cardiac enzyme elevation and chest pain, were excluded from the definition of MINOCA and the study [3]. Patients over 18 years of age with elevated cardiac biomarkers and non-obstructive coronary arteries (<50%) in coronary angiography were included in the study, while patients with other causes of cardiac enzyme elevation like pulmonary embolism, cardiomyopathy, severe renal impairment, aortic dissection, myocarditis and Takotsuba cardiomyopathy, those with sepsis, stroke, multi-organ failure, malignancy or any clinical condition associated with poor prognosis were excluded. All procedures were performed in accordance with the Declaration of Helsinki and the study was approved by the local ethics committee (University of Health Sciences Gülhane Training and Research Hospital Ethics Committee decision number and date: 19 / 194, 14 / 05 / 2019).

All participants’ medical histories, routine laboratory tests and cardiac biomarkers, echocardiography, and electrocardiography (ECG) results were obtained from the hospital database. In our hospital, cardiac magnetic resonance imaging (MRI) is not performed in all patients to exclude patients with myocarditis in the diagnostic algorithm of MINOCA. However, myocarditis is clarified by cardiac MRI in patients who are at elevated risk clinically, electrocardiographically and echocardiographically for the diagnosis of myocarditis.

A total of 3855 acute coronary syndrome patients were investigated. Coronary angiography images were evaluated by at least two specialist cardiologists at our center and patients without occlusive coronary artery disease were identified. The degree of coronary artery stenosis was determined by averaging at least 2 invasive cardiologists' visual evaluation decisions and the quantitative angiography (QCA) measurements. The study flow chart is shown in Figure 1. The pathophysiological mechanisms of MINOCA were investigated from the coronary angiography images of patients. Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are not routinely used in our center. In the literature, vulnerable plaque morphology was defined angiographically in the studies performed before IVUS and OCT. Based on those studies, we determined that irregular borders or intraluminal lucency, haziness, slowing of the flow rate in the lesion area are characteristic of vulnerable plaque [10, 11]. Routine provocation test is not performed for the detection of epicardial coronary vasospasm, which is diagnosed according to the clinical and angiographic images of the patient.

Figure 1: Study flow chart (ACS: Acute coronary syndrome, CAD: Coronary artery disease, MINOCA: Myocardial infarction with non-obstructive coronary artery disease)



Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) statistical software (version 20.0; IBM SPSS Inc., Chicago, IL, USA). Continuous variables were evaluated for normal distribution using the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as mean (standard deviation, SD), whereas non-

normally distributed continuous variables were expressed in median (IQR: Inter Quartile Range). Continuous variables were analyzed with sample t-test or Mann-Whitney U test. Categorical variables were expressed as percentages when appropriate and they were compared with chi-square and Fisher exact tests. A *P*-value <0.05 was considered statistically significant.

Results

A total of 3855 acute coronary syndrome patients were evaluated retrospectively and 155 (4.02%) were diagnosed with MINOCA. Myocarditis was also considered in MINOCA in consensus reports published during the period when MINOCA was first described [1, 2, 4]. In our study, when we included myocarditis in our analysis, the total number of patients diagnosed with MINOCA increased to 221 and the frequency increased to 5.73%. However, a recent study suggests that it is not appropriate to include myocarditis in MINOCA, which is why our entire analysis comprises 155 patients [3].

The mean age of our study population was 55.04 (13.57) years, and 48.4% were female. The incidence of HT and DM were 40% and 21.3%, respectively. The median ejection fraction and troponin values of the MINOCA patients were 60 (IQR: 10) and 403 (IQR: 1252), respectively. ST elevation was observed in 5 (3.2%) patients on admission ECG. Eighteen (9.9%) patients had a history of coronary revascularization, all of which had plaque disruption as MINOCA etiology.

There was a total of 5 (3.2%) patients with mechanical prosthesis valves, among which 2 had mitral metallic valves, and 3 had aortic metallic valves. Their coronary angiography results were normal or coherent with slow flow phenomena. They were considered high-risk patients for coronary embolism even though the plaques could not be demonstrated with IVUS and OCT. Three (1.94%) patients were diagnosed with SCAD. The diagnosis and classification of these patients were made according to angiographic images. While two complied with type 2B SCAD class according to the Saw classification, one patient complied with the Type 3 SCAD class and all the patients were medically treated [12, 13].

In-hospital mortality was seen in 1 patient, who had coronary vasospasm and did not respond to medical and invasive treatment, dying at the 6th hour of hospitalization. Details of the demographics and clinical characteristics of the study population are presented in Table 1.

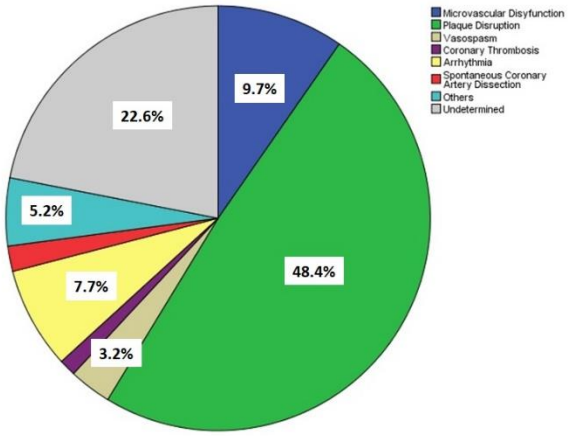
Table 1: Baseline characteristics of the study the population

	All patients (n = 155)
Age, mean (SD)	55.04 (13.57)
Sex (Female) (%)	48.4%
Diabetes Mellitus (%)	21.3%
Hypertension (%)	40%
Cerebrovascular Accident (%)	2.6%
Tobacco Use (%)	9%
Peripheral Vascular Disease (%)	0%
Ejection Fraction (%) Median (IQR)	60 (10)
Creatinine clearance	
MDRD (mL / min / 1.73m2) Median (IQR)	72.6 (28.5)
Wight Blood Cell (x10^3 cells UL) Median (IQR)	9.0 (4.7)
C-Reactive protein (mg / L) Median (IQR)	6.3 (12.15)
Hs Troponin I (pg / ml) Median (IQR)	403 (1252)
Duration of Hospitalization (days) Median (IQR)	1 (1)

MDRD: Modification of Diet in Renal Disease

In our study, based on angiography images, clinical features and laboratory results, plaque disruption was the most common cause of MINOCA (48.4%). The second most common cause was microvascular dysfunction and slow flow (9.7%), followed by arrhythmia (7.7%) The pathophysiology causing cardiac biomarker elevation in 22.4% of patients was not fully understood and classified as undetermined (Figure 2). We decided to compare patients with plaque disruption and other causes. Age (58.31 (13.76) vs 51.89 (12.68) *P*=0.003), HT (37 (48.7%) vs 25 (31.6%) *P*=0.034), prior coronary artery disease history (16 (21.1%) vs 2 (2.5%) *P*=0.001) and creatinine clearance 69.35 (IQR: 25.8) vs 74.0 (IQR: 28.58) *P*=0.009) were higher in patients with plaque disruption than those without. All these parameters were analyzed by multiple logistic regression, and a correlation was found between prior coronary artery disease history and plaque disruption (*P*<0.008, Beta: -2.09, Wald: 6.99).

Figure 2: The causes of MINOCA



DM was insignificantly more prevalent in the group with plaque disruption. Inflammatory markers and ejection fraction were similar between the two groups but Hs troponin I and duration of hospitalization were insignificantly higher in patients with plaque disruption than those without (Table 2).

Table 2: Comparison of plaque disruption and other causes

	Plaque Disruption (n:76)	Others (n:79)	*P*-value
Age, mean (SD)	58.31 (13.76)	51.89 (12.68)	0.003
Female gender, n (%)	34 (44.7%)	41 (51.9%)	0.37
Diabetes Mellitus, n (%)	21 (27.6%)	12 (15.2%)	0.08
Hypertension, n (%)	37 (48.7%)	25 (31.6%)	0.034
Cerebrovascular Accident, n (%)	2 (2.6%)	2 (2.5%)	0.96
Prior Coronary artery disease (%)	16 (21.1%)	2 (2.5%)	0.001
Ejection Fraction (%)			
Median (IQR)	60 (10)	60 (10)	0.37
Creatinine clearance			
MDRD (mL / min / 1.73m2)			
Median (IQR)	69.35 (25.80)	74.0 (28.58)	0.009
Wight Blood Cell (x10^3 cells UL)			
Median (IQR)	9.26 (5.24)	8.90 (3.10)	0.53
C-Reactive protein (mg / L)			
Median (IQR)	9.34 (30.03)	6 (9.51)	0.32
Hs Troponin I (pg / ml)			
Median (IQR)	366 (1281)	208 (686)	0.10
Duration of Hospitalization (days)			
Median (IQR)	2 (1.75)	1 (1)	0.16

Among patients with plaque disruption, 59.6% had only plaques and wall irregularities in their coronary arteries, 6.7% had 30% stenosis and 33.7% had 30-50% stenosis (Figure 3). There were no differences between demographic and clinical features in this sub-group (Table 3).

The coronary angiograms of the patients revealed that 56.1% had plaques and less than 50% stenosis in their coronary arteries. Coronary angiography was normal in 29% of the patients. The diagnosis of normal coronary arteries is used for completely normal coronary arteries without plaque, wall irregularities, slow flow, vasospasm, dissection, and thrombus.

Slow flow was observed in 7.7% of patients, while vasospasm was present in 3.2% (Figure 4). Eighteen patients (11.6%) had a coronary stent or coronary artery bypass grafts, but no occlusive lesions.

Table 3: Comparison of plaque disruption subtypes

	Minimal plaque	30% plaque	30-50% plaque	*P*-value
Age				
Median (IQR)	25 (26)	33	55.5 (19.25)	0.53
Ejection Fraction (%)				
Median (IQR)	60 (5)	40	60 (10)	0.34
Creatinine clearance				
MDRD (mL /min / 1.73m2)				
Median (IQR)	74 (27.95)	89	63.8 (27.3)	0.84
Wight Blood Cell (x10^3 cells UL)				0.22
Median (IQR)	9.0 (4.48)	9.24 (3.87)	9.26 (6.23)	
C-Reactive protein (mg / L)				
Median (IQR)	5.51 (18.64)	33.5	9.4 (35)	0.02
Hs Troponin I (pg / ml)				
Median (IQR)	479 (1302)	1884	667 (1093)	0.37
Duration of Hospitalization (days)				
Median (IQR)	2 (1)	1.5	1 (2)	0.98

Figure 3: Distribution of subtypes of plaque disruption

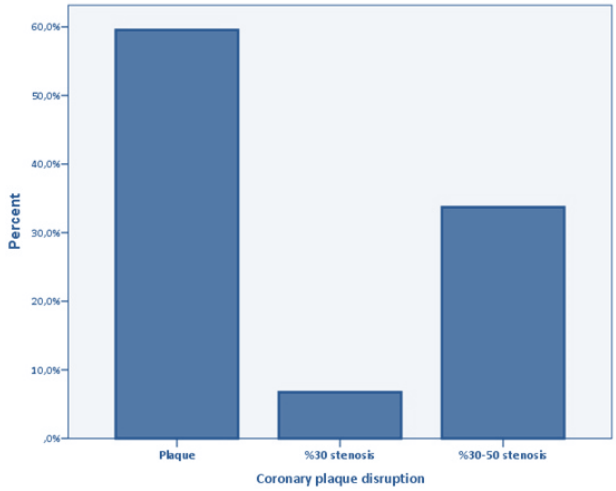
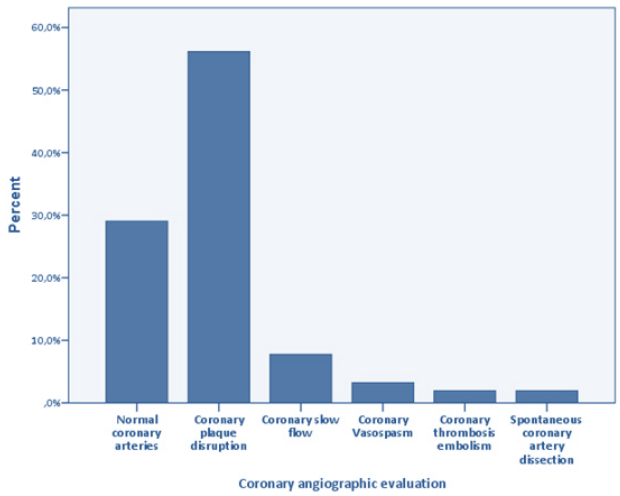


Figure 4: Coronary angiography evaluation results



Discussion

To the best of our knowledge, the present study is the first one to identify basal demographic characteristics of the Turkish MINOCA cohort. We showed that MINOCA patients represent a sizable proportion of MI patients referred for invasive assessment in Turkey and it is prevalence is about 4.02%. The frequency of MINOCA was 5-15% in recent reports, which include both coronary and non-coronary pathologies [2,3,8]. The main reason for the decrease in the frequency of MINOCA is that the disease was clearly defined, and myocarditis and other non-coronary causes were removed from the diagnostic algorithm in the 2019 AHA report [3].

In line with previous reports, we found MINOCA patients to be younger than obstructive coronary artery disease patients. In the current MI-CAD trials, the mean age was 61-62 years [14, 15]. Although female predominance of MINOCA is reported in the literature, the rates were almost equal among males and females in our study [16]. In the study by Jędrychowska et al. [16], no difference was found between the sexes in terms of clinical course and prognosis.

Our study also showed that MINOCA patients had a lower risk profile than other MI-CAD trials [14,15]. However, as we classify our patients into those with plaque disruption and other causes of MINOCA, the risk factors for cardiovascular disease in the plaque disruption group were similar to those of other MI-CAD studies [14,15]. These results showed us that MINOCA due to plaque disruption has similar pathophysiology and risk factors as MI-CAD, and similar medical treatment protocols should be implemented to improve long-term outcomes [3]. In a meta-analysis of MINOCA studies, Pasupathy et al. showed that there was no significant difference in hypertension, diabetes mellitus, tobacco use between MINOCA and MI-CAD patients [2,14,15].

Similar to the literature, the most common cause of MINOCA was plaque disruption in our trial. However, plaque disruption was decided by two invasive cardiologists with the evaluation of ECG, echocardiography, and angiographic images. To clarify the diagnosis and pathophysiology of MINOCA, intracoronary imaging should be performed, but routine uses of IVUS and OCT are not available in our country [17]. If IVUS or OCT could be performed in patients with normal coronary angiography, which were classified as "undetermined", plaque disruption could be detected in many. Opolski et al. [17] showed plaque disruption (24%), coronary thrombus (18%) and eroded plaque (11%) in 53% of MINOCA patients in their study utilizing OCT. Reynolds et al. [18] showed that plaque disruption was present in 38% of their patients in their study using IVUS. OCT provides higher spatial resolution than IVUS, allowing more detailed and complete visualization of plaque pathology [19].

Other rare causes of MINOCA are microvascular dysfunction, slow flow phenomenon, coronary vasospasm, coronary embolism, thrombosis, and arrhythmia attacks. Although spontaneous episodes may be fortuitously documented for diagnosis of coronary vasospasm, provocative spasm testing is often required to establish the diagnosis. In studies using the provocation test for the diagnosis of vasospasm, the frequency increases to 46% [20]. Another rare but significant cause of MINOCA is coronary embolism and thrombosis. A systematic review which examines inherited hypercoagulability state in MINOCA patients showed up to 10% genetic mutation [2]. Therefore, all patients with thrombophilia suspected for clinical and coronary angiographic features should undergo hematological and genetic research.

Considering its clinical findings, cardiac MRI was performed in every patient suspected of myocarditis, and those diagnosed with it were excluded from the study. We cannot

perform cardiac MRI for every MINOCA patient due to logistic limitations in our hospital and country. In a small-scale study of 21 patients, Gościniak et al. [21] performed cardiac MRI in all patients diagnosed with MINOCA to reveal that 38% had myocarditis. In our study, patients strongly suspected of myocarditis were excluded from the study based on cardiac MRI, a procedure all patients did not undergo. In line with these results, performing cardiac MRI could be a major factor affecting the results.

Limitations

Our study has many limitations. First, this was a small, single-center, and retrospective study. The most important limitation is the visual assessment of coronary angiographic images and the lack of IVUS and OCT use. We did not compare our MINOCA data with MI-CAD patients and did not routinely use provocative tests for the diagnosis of vasospasm. Also, hereditary thrombophilia was not evaluated among all patients, but a suspected group. Because of these limitations, there is a margin of error of the data obtained in our study, but we think it is important that it reflects actual Turkish data.

Conclusion

MINOCA constitutes an important proportion of myocardial infarction patients. The pathophysiology of the disease has been better understood with intracoronary imaging (IVUS and OCT) studies. Considering this information in the literature, the diagnosis and treatment continue to be updated. The etiological and pathophysiological mechanism of plaque deterioration are different from other causes of MINOCA and the correct treatment approach determines the prognosis. However, there are many shortcomings in our country. In our study, we wanted to shed light on these points and our hospital cohort of MINOCA.

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Drug addiction profile and monitoring liver functions tests of addicts at a specialized psychiatric treatment center

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Ethics Committee Approval
The Scientific and Ethical Committee of the Department of Pharmacy, Faculty of Medicine. Reference number: 05/DPH/FC/SEC/2020. Date: 21/March/2020. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Drug addiction a public health problem, which Algeria cannot escape from. According to the Algerian National Office for the Fight Against Drug Abuse and Addiction (ONLCDT), 9,680 drug addicts were treated in the first half of 2019. The lack of information and prevalence data continues to impede determining the extent of drug use in Africa. This study aims to determine the profile of drug abuse consumption in a specialized psychiatric treatment center and identify the impact of drug use on the disruption of liver function in patients admitted to the center in 2019.
Methods: In this retrospective cohort study, we used the data of 80 drug addicts in statistical analyses.
Results: Males were more prevalent than females (92% vs 8%), and most patients were living in urban areas (67%). The majority were married (84%) and unemployed (58%). The ages of most addicts (52%) ranged between 21 - 40 years. The mean duration of drug use was 5.15 years (SD=2.3). Cannabis was the most prevalent (n=34, 20%) drug used, followed by ecstasy (MDMA) (n=28, 17%), and others (cocaine 15%, alcohol 15%, amphetamine 10%, benzodiazepine 11%, LSD 10%, nicotine 6%). The mean number of drugs abused per patient was 2.35. The most marked observation from data comparison was the significant correlation between drug abuse duration and liver function tests (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, bilirubin) ($P<0.05$). Hepatic serology results show that 16% and 7.5% were hepatitis C and hepatitis B positive, respectively.
Conclusion: Given the differences in sociodemographic and drug addiction, further studies involving a large population are needed to identify the factors associated with drug addiction. Algeria has few rehabilitation centers, all of which are limited in clinical capacities and need to be improved.

Keywords: Drug addiction, Liver functions tests, Epidemiology, Drug treatment center

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Introduction

Drug addiction has become a serious public health issue. According to the most recent global drug survey in 2019, 35 million people worldwide suffer from drug-related disorders, while only 1 in 7 people worldwide receive treatment. Eleven million people injected drugs in 2017, 1.4 million of which were HIV and 5.6 million of which were hepatitis C positive, as reported by the United Nations Office on Drugs and Crime (UNODC) [1]. According to the Algerian National Office for the Fight Against Drug abuse and Addiction (ONLCDT), 9,680 drug users were treated in the first half of 2019. Algerian drug policy is aimed at minimizing drug supply and sale, although promising standards are set for regulation, prevention, and treatment [2]. The lack of information and prevalence data also impedes the assessment of drug use in Africa.

Drug consumption usually causes liver injury, and in some cases, there are almost no signs, which may result in further damage and lack of early diagnosis. All addictive drugs such as alcohol may have adverse effects [3]. Liver injury caused by drugs is diagnosed with elevated levels of hepatic enzymes and bilirubin [4]. Our research aimed to evaluate the drug abuse profile in a specialized psychiatric treatment center and identify the impact of drug use on the disruption of liver function in patients admitted to the center in 2019. Estimating the prevalence of regional drug use is critical in measuring the amount and severity of this health problem. Decisions regarding the provision of medical services by governments, decision-makers, and funding should be made based on these data [5].

Materials and methods

The population of this retrospective cohort study is composed of 80 drug abuse patients who presented to the treatment and detoxification center of Oran, located in North West Algeria, from January 2019 to January 2020.

Addiction assessment criteria were based on DSM-5 (Diagnostic and Statistical Manual of Mental Disorders). The patients self-reported the drugs consumed, and the following liver function tests were obtained to establish the relationship between drug use and liver function disorders: Bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT) and hepatic serology. Any patient admitted to the psychiatric treatment center regardless of sociodemographic characteristics and drug use were included in the study, and those with any other liver diseases were excluded. Upon admission, a toxicology and medical report was drawn up for each patient, containing the socio-demographic information, type of drug addiction, liver function tests, and withdrawal treatment.

Statistical analysis

Statistical analysis was performed by Excel 2013 and SPSS V25, and significance was analyzed with linear correlation coefficient r and P-value. The bibliographic references were managed by the Mendeley software.

Results

Sociodemographic characteristics

We used the data of 80 patients in statistical analyses. Males were more prevalent than females (92% vs 8%), and most patients were living in urban areas (67%). The majority were married (84%) and unemployed (58%). The mean duration of drug use was 5.15 years (SD=2.3), with 45% of patients with a history of drug abuse for more than 5 years (Table 1).

Table 1: Repartition of Socio-demographic characteristics of drug addicts

Socio-demographic characteristics		n= 80	% (prevalence)
Gender	Male	74	92
	Female	06	08
Marital situation	Single	67	84
	Married	13	16
Education level	Primary	09	11
	Middle	36	45
	Secondary and more	35	44
Profession	Unemployed	46	58
	Employed	34	42
Duration of drug use	< 2 year	17	21
	2 - 5 year	27	34
	> 5 year	36	45
Age range	< 20 year	17	21
	20 - 40 year	41	51
	41 - 60 year	18	23
	> 60 year	04	05
Habitat	Urban	54	67
	Rural	26	33

Prevalence of drugs-use

Cannabis was the most prevalent (n=34, 20%) drug used, followed by ecstasy (MDMA) (n=28, 17%), alcohol and cocaine (15% for both), benzodiazepine (11%), and amphetamine (n=16, 10%). LSD and nicotine use were less prevalent (10% and 6%, respectively) (Figure 1).

Polydrug addiction

The mean number of drugs used among patients was 2.35, the rate of any polydrug (2 or 3 drugs) use was 92% (n=74) (Figure 2).

All patients were dependent both physically and psychologically (n=80, 100%).

Drug treatment

The main therapy protocol used in our study consists of fluoxetine (n=54, 34%), amitriptyline (n=52, 32%) and carbamazepine (n=42, 26%), and levomepromazine secondarily (n=13, 9%) (Figure 3).

Figure 1: Distribution of frequency of drug used

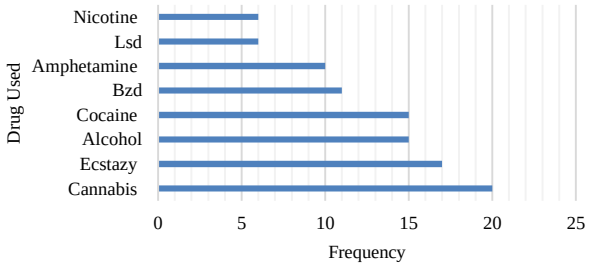


Figure 2: Distribution of prevalence of polydrug addiction

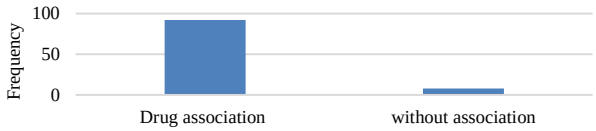
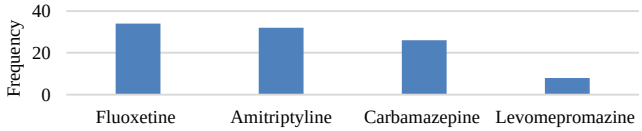


Figure 3: Distribution of the prevalence of drug treatment



Liver function tests

Results of liver function tests are represented as boxplot. The mean values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) were 73.75 UI/L (Med=65, Min=31, Max=166), 68 UI (Med=61.5, Min=27, Max=159), 43 UI (Med=40.5, Min=19, Max=93), 210 UI (Med=202, Min=139, Max=328), and 72 UI (Med=69.5, Min=45, Max=105), respectively (Figures 4-8).

Figure 4: Measures of position AST

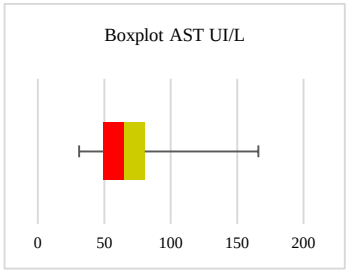


Figure 5: Measures of position ALT

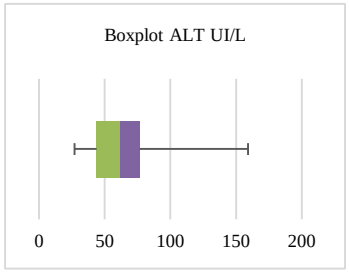


Figure 6: Measures of position Bilirubin

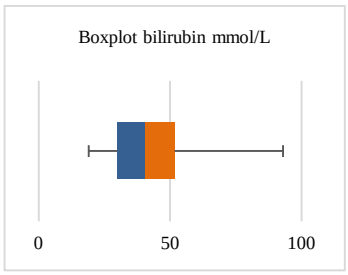


Figure 7: Measures of position ALP

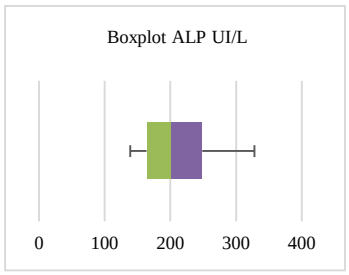
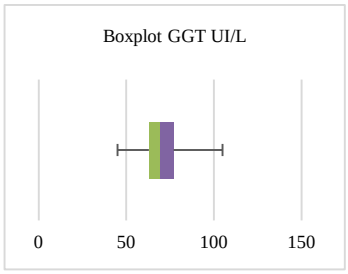


Figure 8: Measures of position GGT



The relationship between the duration of drug use and various biological parameters (AST, ALT, ALP, GGT, and Bilirubin) of the liver were determined with a linear correlation curve, calculating the p-value (p) and the linear correlation coefficient (r) for each variable (Figure 9). There were significant correlations between changes in AST (r = 0.76, $P<0.05$), ALT (r = 0.78, $P<0.05$), Bilirubin (r = 0.85, $P<0.05$), GGT (r =0. 86, $P<0.05$), ALP (r=0.53, $P<0.05$) and drug abuse.

Hepatitis serology

Among all, 16% were hepatitis C and 7.5% were hepatitis B positive, while all patients were hepatitis A negative (Figure 10).

Figure 9: Correlation between liver function tests and duration of drug use

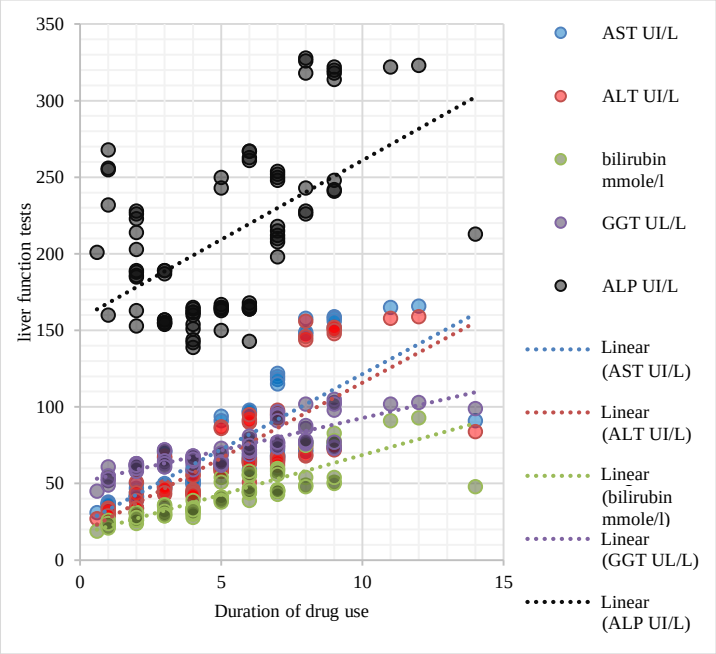
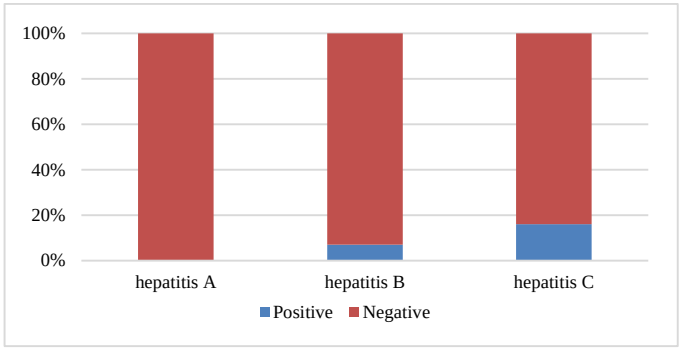


Figure 10: Repartition of frequency of hepatitis serology



Discussion

Socio-demographic characteristics of drug addicts

The mean age of patients admitted to the psychiatric center was 32.5 years, 92% were male and most patients' age ranged between 21 – 40 years (51%). Gender disparities were significant ($P<0.05$). Multiple studies have consistently shown that substance abuse is a youth problem [6,7]. Similar to ours, a Turkish study revealed a higher proportion of males (82.4%, n=1623) than females (17.6%, n=346) [8].

According to a survey, the mean age of drug addicts admitted to a private clinic in the Accra Metropolis (GHANA) was 29.24 years, 80% were males, and 33.3% had left school at the secondary level [9].

We can confirm that drug addiction is a male problem, and gender differences have always been present. The inequality in gender distribution may be due to, some degree, the innate differences between sexes in their readiness to learn certain behaviors. Males are associated with aggression, violence, independency, and adventurism, which are potent factors in the initiation of drug addiction [10].

Forty-five percent of patients have a drug consumption history exceeding 5 years. Puberty is commonly considered a critically risky period for the initiation of drug-use, with multiple studies showing associations between age at first drug-use and the occurrence of abuse or dependence. Drug addiction is increased among individuals who began the use of such

substances in puberty or early adolescence than most of those beginning use during adulthood [11, 12].

Single patient frequency is highest (84 %) compared to married patients. Several studies have shown that marriage accelerates a decrease in drug use when compared to those who remain single. N. Sinha concluded that marriage was cited as a protective factor against drug use, but this has been affected by several factors, such as quality spare time, a more mature relationship, a sense of responsibility, and intimacy [13].

The education levels of 66% of patients in our study is quite low. The causes often include ignorance, which may account for this elevated level of dropouts at secondary school due to drug abuse. Galea et al. [14] concluded that there is a connection between the level of addiction and level of education.

In our study, most drug abusers are unemployed. Work decreases drug abuse, and entry into the workplace seems to be an opportunity to abandon drug use for most people [15].

Majority of our patients live in urban areas (67%), which could be a factor promoting drug use. According to Galea et al. [16], urban residents are more numerous than those in rural areas. Immigration to cities, linked to industrialization and modernization, has been described as a contributing factor to drug addiction, creating favorable conditions for both widows and drug users.

Several studies have shown the relationship between increased drug use and different socio-demographic characteristics (gender, age, habitat, marital status, poverty, low education level, onset of use) [17-19]. Our results are almost similar to the results of a Moroccan study focused on the epidemiological specificities of psychiatric patients [20].

Drug use profile

Cannabis is the most common drug used in our study (20%). Algeria is a transit country for cannabis, and in 2018, 31,936,386 kg of cannabis resin was seized according to the Algerian National Office for the Fight Against Drug abuse and Addiction [21].

During 2018, according to the INCB report, at least 16 countries from all regions of Africa reported seizures of cannabis herb, resins, and plants. Cannabis continues to be the main drug of abuse [22].

In the European Union, cannabis is the most widely tried substance (55.4 million males and 36.1 million females), lifetime cannabis use levels vary considerably from one country to another, ranging from about 4% of adults in Malta to 45% in France [23]. In 2007, the European school survey on alcohol and other drugs (ESPAD) indicated that 31% of 16-year-olds recognized that they had already smoked cannabis in their lifetime, this influence of early entry into drug use can be linked to social problems, school failure, or delinquency [24]. A similar research in Turkey clarified that cannabis was the most prevalent drug used (60.1%) followed by solvents/inhalants (38.3%) and ecstasy (33.4%) [8]. Cannabis is still the most used drug in Côte d'Ivoire, and it affects more than 93.75% of the population using illicit drugs [25].

The second most consumed drug in our study is Ecstasy/MDMA (3, 4-methylenedioxy-N-methylamphetamine) (17%). The use of "ecstasy" over the past year is estimated at 21.3 million people globally, corresponding to 0.4 percent of the global population aged 15–64. Past year use of "ecstasy" is relatively high in Oceania (2.2 percent for Australia and New Zealand), West and Central Europe (0.9 percent), and North America (0.9 percent) [26]. According to a study by Li-Tzy W concerning the potential heterogeneity of ecstasy or MDMA users, approximately 1.6% (n=562) of adult participants (N=43,093) reported lifetime ecstasy use [27].

Cocaine consumption in our study took third place, along with alcohol, at 15%. Globally, an estimated 18.1 million people were past-year users of cocaine in 2017, corresponding to 0.4 percent of the global population aged 15–64. Past-year use of cocaine is high in Oceania (2.2 percent for Australia and New Zealand), North America (2.1 percent), Western and Central Europe (1.3 percent), and South America (1.0 percent). In parts of Asia and West Africa, increasing amounts of cocaine have reportedly been seized, which indicates that cocaine use could potentially increase, especially among the affluent, urban segments of the population, in sub-regions where such use had previously been low [26]. The annual global average alcohol consumption in 2016 is 6.4 liters per person older than 15, in Algeria, it represents a low level of 0.9 liters per person [28].

We see wide geographical differences. Alcohol consumption is particularly low in many countries across North Africa and the Middle East, close to zero. At the upper end of the scale, alcohol consumption across Europe is highest at around 15 liters per person per year [29].

Globally, alcohol dependence was the most prevalent drug of dependence, with 63.5 million (57.5- 69.9) estimated cases in 2015, and an age-standardized average of 843.2 (763.7-927.3) per 100 000 people [30].

The prevalence of alcohol use in the United States is estimated to be approximately 48% for those aged 12 years and older, with almost 8% of those aged 12 to 20 engaging in binge drinking (National Institute on Alcohol Abuse and Alcoholism) [NIAAA] in 2017.

Although benzodiazepines are invaluable in the treatment of anxiety disorders, they have some potential for abuse and may cause dependence or addiction, as indicated by our study estimation at 11%. Intentional abusers of benzodiazepines usually have other drug abuse problems. Benzodiazepines are typically a secondary drug addiction used mainly to increase the high concentration from another drug or to offset the adverse effects of other drugs. The legitimate use of benzodiazepines leads to few cases of addiction [31].

As per Lagnaoui, R. the prevalence of current use of BZD was 7.5%. It was higher among women (9.7%) than men (5.2%), and among the unemployed, and increased with age. The duration of BZD use was more than 6 months in 75.9% of users [32].

Problems related to intravenous amphetamine use have historically been more acute in the countries of Northern Europe. By contrast, methamphetamine problems are more evident in the Czech Republic and Slovakia. According to a 2015 estimate for Germany, 0.19% of adults use amphetamines. Amphetamine users are likely to make up the majority of the 2,234 consumers with stimulant issues (0.18%) reported in Latvia in 2017. In the Czech Republic, the problematic use of methamphetamine in adults (aged 15 to 64) was estimated at 0.50% in 2017 (34,700

users). Estimate for Cyprus was 0.03%, or 176 consumers. Amphetamines are the drugs for which the gender gap is lowest [23].

While regular use of hallucinogenic and dissociative drugs, in general, has remained relatively low in recent years, one study reported that the United States ranks first among 36 nations in the proportion of high school students ever using LSD or other hallucinogens in their lifetime (6 percent versus 2 percent in Europe) (Hibell, 2012) [33].

Tobacco smoke has been included in our study for nicotine addiction, which represents 6% of other drugs. A retrospective, descriptive, and comparative study of all patients treated in the smoking unit of the University Hospital Complex of Albacete during the years 2008-2012 included 1484 patients, of which 48.6% were female. The mean age was 46.8 years, and the mean age of starting smoking was 17.6 years. The mean number of previous attempts to quit was 1.48, and the mean number of cigarettes smoked was 25.39 [34]. The proportion of tobacco consumption in the Ivory Coast lie between 27.5% and 36% in the general population and between 14% and 24% among high school students [25].

Polydrug addiction

The 2018 National Survey on Drug Use and Health, produced by the Nigerian government with support from the European Union and UNODC and released in January 2019, is the first-ever comprehensive survey of drug use conducted in the country. It analyses data collected from 38,850 households and 9,344 high-risk drug users. The report found that in drug addiction, polydrug use was very common, as nearly 95 percent of high-risk users and almost half of other users reported having consumed more than one drug in the previous year [22], like our study, in which 92% of patients are polydrug users. The proportion of any polysubstance use was 60.2% (n=1185) in another study conducted in the child and adolescent dependence center in Istanbul, Turkey [8]. Contrary to these findings, studies from developed countries reported a lower rate of polysubstance use in treatment-seeking children and adolescents. The rate of polysubstance use was 45% in a study conducted in a dependence center in Australia [35].

Treatment

Determining the prevalence of drug addiction and dependence is the means to initiate appropriate treatment and intervention coverage [36]. Addiction is a chronic disease that tends to recur when treatment is interrupted, thus, long-term treatment is recommended. The same principles apply in the detoxification from nicotine dependence using nicotine replacement and from sedative (ethanol) dependence using another sedative such as a benzodiazepine. Withdrawal of the stimulant (cocaine and amphetamine) typically requires no treatment, but rapid return to drug use is frequent [37].

The treatment of addicted patients must always be individualized. This requires a complete evaluation so that coexisting medical, psychiatric, and social problems can be addressed as needed. The types of medications that have demonstrated efficacy in combination with behavioral therapy in the prevention of relapse can be classified as agonists (including partial agonists), antagonists, and anti-craving medications that work through a variety of mechanisms. Vaccines are an experimental approach that is currently being evaluated in clinical trials [38, 39].

The therapy used in our study is levomepromazine (8%) for the treatment of psychotic disorders, fluoxetine (34%) and amitriptyline (32%) for depressive disorders and carbamazepine (26%) for bipolar disorders.

Liver function tests

Patients with substance use disorders are at increased risk of a range of medical and psychiatric disorders. Levels of consumption can still contribute to end-organ (i.e., liver) damage [40].

Liver function tests (LFTs) refer to measurements of serum bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT) [41]. Increased serum liver enzymes, alanine transaminase (ALT), aspartate transaminase (AST) and gamma-glutamyl transferase (GGT) are markers of inflammation and oxidative stress, for detecting alcohol and drug use [42]. Among the drugs that can also cause liver disorders are cocaine and MDMA [43].

Ninety-eight percent of patients in our study have increased AST, 96% have increased ALT, 100% have increased GGT, 99% have positive ALP and 99% have increased bilirubin levels. The correlation between these results and the duration of drug abuse use is significant for all liver function tests, demonstrating the increase of these enzymes with the increase of the duration of consumption ($P<0.05$).

A recent global systematic review including 55671 records in 179 countries reports that globally, an estimated 15.6 million people injected drugs in 2015, 8.2 million of which were HCV antibody, and 1.4 million people of which were HBsAg positive. This is equivalent to 52.3% and 8.9% of people who inject drugs globally, respectively. In East and North Africa, 48.1% of individuals who inject drugs are HCV and 8.1% are HBV positive [44]. Our study also showed that HCV prevalence (16.2%) is higher than that of HBV (7.5%).

The UNODC World Drug Report stated that among drug-injectors, 51.7%, equating to 6.1 million people, were HCV-positive, and 13.1%, equating to 1.6 million, were HBV-positive [45].

Conclusions and recommendations

The increase in drug addiction in Algeria seems to be concomitant with its progress on a global level and is linked to the economic, social, and cultural crises the country faces. This is not a reason to stay away from the study's issues. We can help to solve these anomalies; several recommendations are proposed:

- Organize awareness sessions in the school and university environment. Knowing that most of the consumption begins in adolescence, prevention targeting this population is a priority.
- Generate appropriate support and publication on the impact of drug use on the liver and ensure dissemination to the broadest spectrum inside the society.

The present study overcomes a major limitation of the national surveys. Given the differences in sociodemographic and drug addiction, further investigation is necessary to identify the factors associated with drug addiction. There are few drug use

treatment centers in Algeria, which are constrained in clinical and therapeutic capacities. The service will have to be extended.

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The relationship between vitamin 25(OH)D level and hematological parameters in newly diagnosed women with fibromyalgia syndrome

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The study was approved by Bursa Yuksek Ihtisas Training and Research Hospital Clinical Trials Ethics Committee (11.04.2018/ 2011-KAEK-25 2018 / 04-10).
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Abstract

Background/Aim: Chronic inflammation may play a role in the pathogenesis of fibromyalgia syndrome (FMS). Several hematological markers are prothrombotic, and markers of systemic inflammation. Vitamin D (VitD) level can affect FMS and has an anti-inflammatory effect. The aim of this study is to investigate the relationship between hematological parameters and VitD in FMS and its effect on disease severity.

Methods: The prospective case-control study included 90 newly diagnosed female patients with FMS (group 1) and 90 healthy volunteers (group 2). Pain and fatigue were evaluated by visual analogue scale (VAS). Disease severity was evaluated by FMS Impact Questionnaire (FIQ) in FMS. Neutrophils, lymphocytes, platelets, platelet distribution width (PDW) and mean platelet volume (MPV) were obtained from complete blood count results in both groups. Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were calculated. 25(OH)D concentration was measured. Patients were divided into 3 groups according to vitamin D levels (VitD < 10 ng/ml, 10-30 ng/ml and >30 ng/ml.)

Results: The mean MPV and vitamin D levels were significantly higher in group 2 (P=0.001, P<0.001 for both), whereas median PDW was significantly higher in group 1 (P<0.001). Among FMS patients grouped according to VitD levels, only PLR level was significantly different (P=0.049). In subgroup analysis, PLR was significantly higher in the group with VitD < 10 ng/ml compared to the group with vitD levels between 10-30 ng/dl (P=0.024). There was no significant relationship between VitD levels and clinical and laboratory parameters (P>0.05). There was a significant inverse relationship between FIQ and PLR (P=0.022).

Conclusion: VitD deficiency may be a risk factor for FMS (cut-off is<14.6 ng/ml). In FMS, high PDW and high PLR in patients with VitD<10 ng/ml are indicative of a prothrombotic condition which can be aggravated by inflammation. We think that complete blood count and VitD levels can support the diagnosis and predict cardiovascular risk in FMS.

Keywords: Fibromyalgia, Inflammation, Platelet activation, Platelet distribution width, Vitamin D

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Introduction

Fibromyalgia Syndrome (FMS) is a chronic painful syndrome characterized by widespread pain and tender points, accompanied by a group of symptoms including sleep disturbance, morning stiffness, fatigue, irritable bowel [1]. FMS can be observed alone or as a comorbidity accompanying other rheumatic diseases [2]. It affects 2-4% of the population worldwide and is predominant among women [3]. The etiology and pathogenesis of FMS has not yet been clearly explained, however, central, and autonomic nervous system dysfunction, cytokines, neurotransmitters, hormones, immune system, and environmental stress factors were held responsible. It is thought that chronic inflammatory process may play a role in the pathogenesis of fibromyalgia [4], but there are no reliable laboratory markers that indicate disease activity or severity in fibromyalgia. Recently, studies in FMS have focused on markers of inflammation derived from complete blood counts because they are cheap and easily accessible [5,6]. Simple hematological markers such as neutrophil/lymphocyte ratio (NLR), platelet distribution width (PDW), mean platelet volume (MPV) and platelet/lymphocyte ratio (PLR) have been identified as markers of systemic inflammatory response and have been reported to support the diagnosis in FMS [7]. Platelet count, PDW and MPV are also predictors of platelet activation and have been associated with an increased risk of cardiovascular disease due to arterial thrombosis. Inflammation may increase arterial and venous thrombus formation [5,8]. Few studies in this area have reported conflicting results regarding these parameters in patients with FMS when compared to healthy individuals [5, 9, 10].

Vitamin D mainly affects calcium homeostasis and bone structure [11]. However, recent research has shown that it also influences tissues other than bone tissue. It has been assumed that vitamin D has anti-inflammatory properties which contribute to pain relief. In the studies, a relationship was shown between vitamin D deficiency and chronic pain. FMS symptoms such as fatigue, diffuse muscle pain and weakness have also been observed in individuals with vitamin D deficiency [12].

Furthermore, a link between hypovitaminosis D and cardiovascular risk has been established. Vitamin D exerts its effect on the cardiovascular system by regulating inflammatory, oxidant and immune processes leading to the progression of atherosclerosis [13]. Vitamin D may also have a regulatory effect on platelets, for Vitamin D receptors have been identified in platelets. Vitamin D deficiency has been associated with endothelial dysfunction [14].

In the light of this information, we thought that there may be a relationship between hematological parameters known as markers of subclinical inflammation, prothrombotic state and serum vitamin D levels in fibromyalgia, which may affect the severity of the disease. However, we could not reach sufficient data in the literature review.

In this study, we aimed to investigate the relationship between hematological parameters and serum vitamin D level in newly diagnosed female patients with Fibromyalgia syndrome and its effect on disease severity.

Materials and methods

The study was conducted between November 2018 - April 2019 in Physical Medicine and Rehabilitation outpatient department of Bursa Yuksek Ihtisas Training and Research Hospital. It was approved by local ethics committee (Bursa Yuksek Ihtisas Training and Research Hospital Clinical Trials Ethics Committee /11.04.2018/ 2011-KAEK-25 2018 / 04-10). All participants were informed about the study and signed a written consent form.

Female patients aged 18-65 years newly diagnosed with FMS according to the ACR 2013 revised form [15] were included in the study. Chronic systemic disease, inflammatory rheumatic disease (AS, RA, SLE), having clinically or laboratory proven acute or subacute infection, hypertension, and dyslipidemia, those with psychiatric, neurological, endocrinological and hematological diseases, patients with disorders of the calcium metabolism, pregnant or breastfeeding patients, and Vitamin D, nonsteroidal anti-inflammatory and anticoagulant drug users were excluded from the study.

The study group consisted of 90 female patients (Group 1) diagnosed with primary FMS, while the control group consisted of 90 age and gender matched healthy volunteers (Group 2). Age, body mass index (BMI) (kg/m^2) and demographic data of all participants were recorded. Tenderness in FMS patients was assessed by applying 4 kg/cm^2 pressure on 29 specific body points. Pain and fatigue levels were evaluated by visual analogue scale (VAS) and disease severity was evaluated by FMS Impact Questionnaire (FIQ).

FIQ is a valid and reliable method for assessing the impact of the disease on daily life in patients with FMS [16]. The Turkish version of the FIQ was validated by Sarmer et al. [17]. This scale measures 10 distinctive parameters: Physical function, well-being, inability to work, difficulty at work, pain, fatigue, morning fatigue, stiffness, anxiety, and depression. The maximum score for FIQ is 100 and higher scores indicate increased disease severity. In the intensity analysis, total FIQ scores between 0-38 represent low impact, those between 39-58 represent moderate impact, and those between 59-100 indicate severe impact.

Five milliliters of venous blood samples were collected from all participants from the antecubital region at 08.00 AM after one night of fasting into tubes with tripotassium ethylenediamine tetra acetic acid (EDTA) and studied within two hours of collection. Hematological indices were analyzed by a Mindray BC 6800 Haematology Analyser (M68LHLYSE, Nanshan Shenzhen, China). Neutrophils, lymphocytes, platelets, PDW and MPV values obtained from complete blood count were recorded. The neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were calculated. 25-hydroxyvitamin D [25(HO)D] concentration was measured by the ELISA method. Patients with FMS were divided into 3 groups based on 25(HO)D concentration, as follows: <10 ng/ml: Severe insufficiency, 10-30 ng/ml: moderate insufficiency, > 30 ng/ml: Normal [18].

Statistical analysis

The suitability of continuous variables to normal distribution was examined by Shapiro Wilk test. Normally and non-normally distributed continuous variables were expressed as

mean (standard deviation), and median (minimum-maximum), respectively. Categorical variables were reported as n (%). Mann Whitney U test and independent samples t-test were used for comparisons of continuous and discrete variables between the FMS and control groups, and chi-square test was used for comparisons of categorical variables. Kruskal Wallis or ANOVA tests were used in comparisons between vitamin D groups. After the Kruskal Wallis test, the groups were compared in pairs using Dunn test. The correlation between hematological parameters and vitamin D level, pain VAS, fatigue VAS and FIQ total score were examined using correlation analysis and Spearman correlation coefficient was calculated. Internal consistency of the FIQ scale was examined by reliability analysis and Cronbach alpha coefficient. Receiver operator characteristic (ROC) curve analysis was performed to estimate the sensitivity and specificity of vitamin D level for predicting the presence of FMS. The Cronbach α value for the overall scale was α = 0.79. SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.) was used for statistical analysis and $P<0.05$ was considered statistically significant.

Results

A total of 90 female patients with FMS aged between 22-56 years (median 37.50) and 90 healthy female volunteers aged between 21-55 years (median 41) were included in this study. The groups were similar in terms of age, BMI, smoking and marital status (Table 1).

There was no significant difference between the two groups in terms of leukocyte, neutrophil, lymphocyte, platelet values and NLR. The mean MPV level was significantly higher and mean PDW level was significantly lower in the control group ($P=0.001$, $P<0.001$, respectively), while Vitamin D levels were significantly lower in the patient group ($P<0.001$) (Table 1).

Only PLR significantly differed between FMS patient subgroups categorized according to vitamin D levels ($P=0.049$). In subgroup analysis, PLR level was significantly higher in the group with vitamin D level < 10 ng/ml compared to the group with vitamin D levels between 10-30 ng/ml ($P=0.024$). There was no significant difference between the groups with vitamin D levels>30 ng/ml and <10 ng/ml according to PLR level ($P=0.152$ and $P=0.557$, respectively) (Table 2).

A significant correlation was found between vitamin D level and age. Vitamin D levels increased with increasing age ($P=0.029$). There was no significant relationship between vitamin D levels and clinical and laboratory parameters ($P>0.05$). There was an inverse significant relationship between FIQ score and PLR level (r=-0.024, $P=0.022$) (Table 3).

Receiver operator characteristic curve analysis was performed to estimate the sensitivity and specificity of vitamin D for predicting the presence of FMS, and the cut-off point for vitamin D was determined as ≤14.66 ng/ml. The area under the curve for vitamin D was 0.72 (sensitivity 75.56%, specificity 61.36%, $P<0.001$), showing that a vitamin D ≤14.66 ng/ml was significantly related to an increased risk of FMS (Figure1).

Table 1: Demographic, clinical, and laboratory characteristics of the FMS and control groups

	FMS n=90	CONTROL n=90	*P*-value
Age (year)	37.50(22-56)	41(21-55)	0.114[a]
BMI (kg/cm^2)	25.47(18.31-41.53)	25.95(19.72:38.63)	0.940[a]
Smoking	16(27.10%)	24(27.90%)	0.917[b]
Marital status			
Single	9(10.10%)	17(19.10%)	
Married	75(84.30%)	67(75.30%)	0.233[b]
Widow	5(5.60%)	5(5.60%)	
FIQ	59(20-94)	-	-
Pain VAS	7(0-0)	-	-
Fatigue VAS	8(0-10)	-	-
WBC (K / uL)	7.43(4.10-12.07)	7.13(3.32-12.71)	0.408[a]
NEU (× 10 ^{3} / uL)	4.35(1.40-8.32)	4.10(1.69-9.31)	0.320[a]
LYM (× 10 ^{3} / uL)	2.21(1.20-4.50)	2.25(0.42-4.26)	0.463[a]
PLT (× 10 ^{3} / uL)	275(163-444)	262(149-469)	0.402[a]
PCT (%)	0.25(0.15-2.89)	0.26(0.15-0.39)	0.253[a]
PDW (%)	16.20(15.30-17.40)	16(15.10-16.80)	<0.001[a]
MPV (fL)	9.37(1.58)	9.94(1.02)	0.001[c]
NLR	1.81(0.48-3.86)	1.73(0.78-10.69)	0.851[a]
PLR	114.53(52.67-263.85)	115.96(55.40-428.33)	0.782[a]
Vitamin D (ng/dl)	8.50(4.20-52.85)	17.11(4.20-58.89)	<0.001[a]

Data are presented as mean (standard deviation), median (minimum- maximum) and n%. a: Mann Whitney U Test, b: Chi-Square Test, c: Independent samples t-test, MPV: Mean platelet volume, PDW: Platelet distribution width, NLR: Neutrophil-lymphocyte ratio, PCT: Plateletcrit, PLR: Platelet-lymphocyte ratio, NEU: Neutrophil count, LYM: Lymphocyte count, PLT: Platelet count, WBC: White blood cell

Table 2: Clinical and laboratory parameters according to 25(OH)D levels in patients with FMS

	Vit D< 10 n=51	Vit D 10-30 n=34	Vit D >30 n=5	*P*-value [d]
FIQ	56(20-90)	59(21-94)	57(24-83)	0.966[d]
Pain VAS	7(3-10)	7(0-10)	8(1-10)	0.948[d]
Fatigue VAS	8(2-10)	8(0-10)	8(1-10)	0.962[d]
WBC (K / uL)	7.47(4.66-10.20)	7.26(4.32-12.07)	6.90(4.10-11.10)	0.971[d]
NEU (× 10 ^{3} / uL)	4.64(2.49-7.37)	4.08(1.40-8.32)	4.70(2.40-7.60)	0.613[d]
LYM (× 10 ^{3} / uL)	2.20(1.20-4.50)	2.42(1.30-4.38)	1.77(1.40-3)	0.063[d]
PLT (× 10 ^{3} / uL)	281(163-444)	264(174-371)	254(191-283)	0.225[d]
MPV (fL)	9.30(7-12.30)	9.70(6.90-11.60)	9.30(7.90-11.20)	0.396[d]
PCT (%)	0.25(0.15-0.40)	0.25(0.16-2.89)	0.22(0.18-0.28)	0.337[d]
PDW (%)	16.30(15.50-17.40)	16.20(15.40-17.20)	16.20(15.30-17.30)	0.299[d]
NLR	1.90(1-3.86)	1.66(0.48-3.48)	2.53(1.64-3.53)	0.068[d]
PLR	122.31(52.67-263.85)	105.57(60.29-215.38)	143.50(79-171.88)	0.049[d]

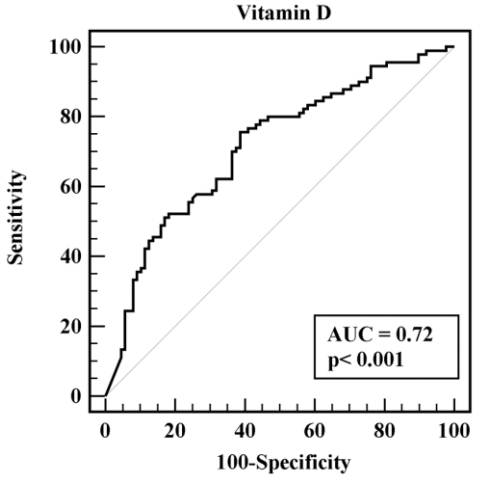
Data are given as mean (standard deviation), median (minimum- maximum) and n%. d: Kruskal Wallis Test

Table 3: The relationship between 25(OH)D levels and clinical and laboratory parameters in patients with FMS

	Vit D		Pain VAS		Fatigue VAS		FIQ	
n=90	r_s	*P*-value	r_s	*P*-value	r_s	*P*-value	r_s	*P*-value
AGE	0.23	0.029	-0.11	0.293	-0.10	0.332	-0.09	0.379
WBC	-0.08	0.427	0.02	0.873	-0.05	0.615	0.02	0.845
NEU#	-0.15	0.160	0.02	0.877	-0.11	0.288	-0.02	0.839
LYM#	0.08	0.446	0.06	0.572	0.12	0.273	0.16	0.144
PLT	-0.08	0.446	-0.17	0.116	-0.11	0.315	-0.14	0.197
MPV	0.05	0.665	0.17	0.101	0.14	0.178	0.12	0.278
PCT	-0.04	0.724	-0.02	0.872	0.06	0.552	-0.01	0.922
PDW	-0.08	0.435	-0.09	0.427	-0.05	0.611	-0.13	0.240
NLR	-0.13	0.236	-0.05	0.625	-0.18	0.096	-0.17	0.112
PLR	-0.12	0.276	-0.17	0.118	-0.16	0.129	-.024	0.022
VIT D	-	-	-0.04	0.747	0.01	0.995	0.03	0.793

r_s: Spearman correlation coefficient

Figure 1: Receiver-operator characteristic (ROC) curves for determining the presence of FMS status. The area under the curve (AUC) for vitamin D is 0.72 with $P<0.001$.



Discussion

Our results showed that serum vitamin D levels were lower in patients with FMS compared to healthy subjects and did not affect the clinical activation findings, but PLR level, one of the markers of subclinical inflammation / thrombotic activation, increased in patients with Vitamin D levels below 10 ng/ml. Although the results of this study showed that serum PDW level was higher in patients with FMS compared to healthy controls, it did not correlate with

disease activity.

Even though fibromyalgia is not known as an inflammatory disease, secondary systemic symptoms are difficult to explain. There are no reliable laboratory markers indicating fibromyalgia disease activity or severity. However, recent studies have shown that inflammatory mechanisms play a key role in pathogenesis. Cytokines and neurotransmitters, such as IL-6, IL-8 and TNF-α, which are biochemical mediators of inflammation, are abnormal in FMS patients [4, 19]. In clinical practice, these markers cannot be used for diagnostic purposes. Therefore, studies in FMS have focused on markers of inflammation derived from complete blood counts because they are cheap and easily accessible [5,9].

It has been shown that simple hematological markers such as MPV, PDW, NLR, platelet (PCT) and PLR reflect inflammatory burden and disease activity in various diseases [7,20-22].

In FMS, increased platelet count, MPV and PDW have been identified as risk factors for cardiovascular disease, but studies have shown conflicting results. When compared with the control group, Aktürk et al. [5] found that MPV value was significantly higher and PDW value was lower in patients with FMS. On the contrary, Molina et al. [10] found PDW values higher and MPV values lower in patients with FMS. Al-Nimer et al. [23] found a significant increase in both MPV and PDW values in newly diagnosed women with FMS. It is thought that these contradictory results may be caused by differences in the characteristics of the working groups. Our results showed that there was no significant difference in platelet counts in women with FMS compared with healthy controls; however, PDW values were significantly higher and MPV values were significantly lower. This result was consistent with the results of Molina et al. [24] PDW is a measure of variability in platelet size and increases during platelet activation. PDW is used to identify fractions of large platelets that are more enzymatically and metabolically active. MPV is associated with platelet size, platelet activity and function. Larger platelets are more active than smaller ones [25]. It is thought that PDW is more specific than MPV as an indicator of platelet reactivity because it is not affected by single platelet distension caused by platelet swelling [10]. Our results may suggest platelet hyperactivation, which may contribute to the prothrombotic status of FMS patients by showing a high PDW value. Oxidative stress promotes platelet hyperactivation and consequently increases the risk of arterial thrombosis [26]. Studies have shown that oxidative stress increases in patients with FMS, and patients with FM may be prone to a prothrombotic state in which oxidative stress may contribute [27].

NLR and PLR have been described as a prognostic marker of systemic inflammatory response [10]. Elevated blood NLR has been shown to be associated with increased disease activity in many systemic, rheumatologic diseases [20, 22]. Aktürk et al. [5] found that NLR levels were higher in patients with FMS compared to healthy controls and argued that the diagnosis was supportive. Molina et al. [10] found that PLR levels were high in patients with FMS compared with healthy controls and emphasized that increased inflammation triggers prothrombotic status. However, neither of those studies evaluated the relationship between markers of inflammation and clinical activation findings such as pain, fatigue, daily living activity in FMS. There are few studies evaluating this relationship in the literature. El-Nimer et al. [6] showed that NLR and PLR were significantly higher in patients with FMS and significantly correlated with the total revised FIQ score. On the contrary, Yıldırım et al. [28] evaluated only MPV in patients with FMS and found no association between MPV and pain, fatigue, and FIQ. Our results showed no significant difference between the groups in terms of NLR and PLR values. In our study, we examined all hematological markers such as MPV, PDW, NLR, PCT, PLR, and found only an inverse relationship between FIQ score and PLR.

Many studies have shown that low serum 25 (OH) vitamin D levels increase the risk of cardiovascular disease [29] by altering platelet and endothelial functions, increasing oxidative stress, and activating inflammatory pathways [30]. A study showed that vitamin D levels <20 ng/ml were associated with increased cardiac risk and that MPV levels were significantly higher in the vitamin D ≤10 ng/ml group compared with healthy controls [31].

In the literature, there are many studies about FMS and vitamin D deficiency in chronic pain with contradictory results. While there are studies showing that vitamin D levels are significantly lower in FMS patients compared to healthy controls [32, 33], there are also studies that cannot find a relationship between vitamin D deficiency and FMS [34,35]. The large heterogeneity between the studied groups and the low power of most studies have been shown as the reasons for this inconsistency [36]. Our results showed statistically significantly lower vitamin D values in patients with FMS compared with the healthy control group. According to Roc analysis, we found an increased risk for FMS incidence in patients with vitamin D < 14.6 ng/ml. We categorized vitamin D levels as <10 ng/ml, 10-30 ng/ml and <30 ng/ml and observed that the clinical activation we evaluated with pain VAS, fatigue VAS and FIQ was not affected by vitamin D levels. We also observed that only the PLR level, one of the inflammatory/prothrombotic markers, was statistically significantly higher in the vitamin D <10 ng/ml group compared to the group with vitamin D levels between 10-30 ng/ml. When VitD <10 ng/ml group and VitD >30 ng/ml were compared, we did not observe a significant difference. This may be due to the small number of patients in the VitD >30 ng/ml group. However, in our study, we found no correlation between vitamin D level and clinical and laboratory activation. Yıldırım et al. [29] showed that vitamin D deficiency may increase MPV values, which is a risk factor in cardiovascular

diseases. The difference of our study is that we studied inflammatory/prothrombotic markers other than MPV.

Limitations

We performed this study on newly diagnosed female patients, but we did not distinguish between premenopausal and postmenopausal females. In our study, a significant correlation was found between age and vitamin D. This may be because postmenopausal women have been careful to use the natural source of vitamin D because of their high awareness of osteoporosis.

Conclusion

Our results showed increased PDW levels in FMS and confirmed that PDW was a predicting marker in FMS. At the same time, the results of our study showed that the incidence of FMS increases in patients with VitD <14.6 ng/ml, and there is an inflammatory condition associated with an increase in PLR levels in patients with VitD <10 ng/ml. Based on this, we thought that low VitD levels in patients with FMS may trigger inflammation and contribute to the risk of cardiovascular disease with a prothrombotic effect. In patients with FMS, complete blood count and vitamin D levels, which are easily accessible and inexpensive, can support the diagnosis and predict cardiovascular risk. The effect of VitD supplementation on hematological parameters in FMS needs to be investigated. We believe that larger-scale studies involving homogeneous groups are needed.

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Relationship between the severity of carpal tunnel syndrome and lipid profile in patients with tip 2 diabetes mellitus

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Ethics Committee Approval
Ethics committee approval was received for this study from the ethics committee of Bulent Ecevit University School of Medicine (Decision No: 2020/09).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Diabetes mellitus (DM) accelerates the development of neuropathy, and carpal tunnel syndrome (CTS) is the most common form of entrapment neuropathy. The pathogenesis of diabetic neuropathy is multifactorial with its vascular and metabolic factors. In this study, we aimed to evaluate the relationship among the electrophysiological severity of CTS, lipid profile and serum atherogenic index in patients with Type 2 DM.
Methods: In this hospital-based retrospective cross-sectional study, we retrospectively evaluated 202 type 2 DM patients, who presented to the electrophysiology laboratory of Zonguldak Bulent Ecevit University Faculty of Medicine between 2016-2019 and investigated the relationship among the electrophysiological severity of CTS, lipid profile and serum atherogenic index of 131 patients diagnosed with CTS.
Results: The patients with CTS had significantly higher values of fasting blood glucose and HbA1c compared to those without CTS (P=0.010). In terms of the severity of CTS, the patients were divided into three groups as mild, moderate, severe. In terms of the lipid panel, the mean values of cholesterol, triglyceride, and HDL-C were similar among the groups (P=0.098, P=0.321, P=0.706), while LDL-C levels were higher in the severe CTS group. (P=0.024). There was a significant positive correlation between age (R=0.126 P=0.004), HbA1c (R=0.245, P=0.002) and CTS severity.
Conclusion: We identified a relationship between CTS severity and LDL-C. CTS should be considered in patients with DM and hyperlipidemia. Further larger-scale studies with control groups are recommended.

Keywords: Carpal tunnel syndrome, Low-density lipoprotein, Cholesterol, Serum atherogenic index

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Introduction

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy, which occurs when the median nerve is compressed as it passes under the carpal ligament at the wrist [1]. It is more common in females [2]. Most CTS cases are idiopathic; however, there are many associated risk factors such as recurrent trauma, metabolic and hormonal changes, smoking, female gender, and obesity [1,3-6]. Diabetes mellitus (DM) accelerates CTS, and multiple etiopathogenetic factors, both vascular and metabolic, are responsible for the development of neuropathy [7]. Endothelial dysfunction and atherosclerosis have a significant impact on microvascular and macrovascular complications in patients with diabetes. Diabetic and entrapment neuropathies are the most common among the microvascular complications in diabetic patients [8]. Microangiopathic changes in vasonervorum due to atherosclerosis lead to the development of neuropathy by negatively affecting the nutrition of peripheral nerves. It also affects the neuronal membrane lipid content and causes the development of both entrapment neuropathy and polyneuropathy. Hypercholesterolemia, especially high low-density lipoprotein cholesterol (LDL-C) has also been associated with fibrinogenesis in many organs and peripheral nerves [8,9].

In this study, we aimed to evaluate the relationship between the electrophysiological severity of carpal tunnel syndrome, lipid profile and serum atherogenic index in patients with diabetes mellitus.

Materials and methods

In our study, we retrospectively evaluated 202 type 2 DM patients who visited the electrophysiology laboratory of Zonguldak Bulent Ecevit University Faculty of Medicine between 2016-2019 and underwent Electromyography (EMG). We aimed to evaluate the relationship between the electrophysiological severity of CTS, lipid profile and serum atherogenic index of 131 patients diagnosed with CTS. EMG results, recent (including 3 months before and after the EMG date) blood test results (glycated hemoglobin a1c (HbA1c), fasting blood glucose, white blood cell, TSH, Free T4, LDL-C, high-density lipoprotein cholesterol (HDL-C), cholesterol, triglyceride), demographic data (age, gender), Body Mass Index (BMI) and duration of diabetes of each patient included in the study were obtained from the patient files.

The exclusion criteria for the study included patients with chronic infection, malignancy, hypertension, peripheral artery disease, cerebrovascular diseases, entrapment neuropathies, and other diseases that cause neuropathy (B12 deficiency, rheumatological diseases, chronic kidney disease, vasculitis, drug-related), and patients on antilipidemic drugs, with a BMI greater than 25 kg/m^2 and with an EMG result indicating polyneuropathy.

Patients underwent standard electrophysiological study. All physiological studies were performed with 2 channeled Medelec EMG device. In all recordings, superficial electrodes were used. In motor conduction studies, the median, ulnar, peroneal and tibial nerves were stimulated, and compound muscle action potentials (CMAPs), distal latency (DL) and nerve conduction velocities (NCVs) were recorded. Sensory responses were obtained with orthodromic methods. In sensory conduction studies, the median, ulnar and sural nerves were stimulated, and sensory conduction velocities (SCVs), sensory response peak latencies and sensory action potentials (SAPs) were recorded.

Nerve conduction velocities below 50 m/s in the upper limb and 40 m/s in the lower limb, median nerve SAP amplitude below 12 μV, CMAP amplitude below 5 mV and motor DL values above 4.0 ms, ulnar nerve SAP amplitude values below 8 μV, CMAP amplitude below 5 mV and motor distal latency above 4.0 ms, posterior tibial nerve CMAP amplitude values below 4 mV, peroneal nerve CMAP amplitude below 2 mV, and sural nerve SAP amplitude below 10 μV were considered abnormal values.

Electrophysiological classification of all subjects in terms of CTS severity is as follows [10].

Mild Carpal Tunnel Syndrome: Prolonged median sensory latency ± reduced amplitude of median sensory nerve action potential below the normal values

Moderate Carpal Tunnel Syndrome: Prolonged median sensory latency and prolonged median motor distal latency

Severe Carpal Tunnel Syndrome: Prolonged median motor and sensory distal latency with low or absent median compound muscle action potential

Statistical analysis

The data obtained in the research were analyzed using SPSS (Statistical Package for Social Sciences) for Windows 22.0 software package. Number, percentage, mean, and standard deviation were used as descriptive statistical methods in the evaluation of the data. Mann Whitney U test was used to compare two non-normally distributed groups of variables and Chi-square tests were used for categorical variables. One-way ANOVA and Kruskal Wallis tests were used in groups showing normal and non-normal distributions, respectively, to determine the significant differences among the means of three or more independent groups. Ordinal Logistic Regression Analysis was used to examine the adjusted relationships. For all statistical analyses, P-value<0.05 indicated significance.

Results

CTS was observed in 131 of 202 patients. The patients with CTS had significantly higher values of fasting blood glucose and HbA1c compared to those without (P=0.010) (Table 1).

Forty-five patients had mild, 50 patients had moderate, and 36 patients had severe CTS. There were sixty females, and 71 males. Patients with mild, moderate, and severe CTS had mean ages of 61.44 (10.77) years, 62.4 (11.20) years, and 65.58 (10.03) years, respectively (P=0.229). CTS was more severe among females (P=0.045) (Table 2). The mean duration of diabetes, HbA1c, and fasting blood glucose levels of the groups were similar (P=0.481, P=0.379, P=0.364), just as mean 25(OH) Vitamin D levels. There was no statistical difference among the groups in terms of kidney function tests and electrolytes (Table 3). The mean values of cholesterol, triglyceride, and HDL-C did not significantly differ between the groups (P=0.098, P=0.321, P=0.706), while the LDL-C levels did (P=0.024). The mean values of Triglyceride/HDL-C,

Cholesterol/HDL-C, and LDL-C/HDL-C, which are approved as the atherogenic index, were similar among all groups (P=0.237, P=0.202, P=0.660) (Table 3).

The ordinal logistic regression analysis, which was carried out to determine the cause-effect relationship between LDL-C, HDL-C, TG, age, and HbA1c and the severity of CTS, was significant. There was a significant positive correlation between age (R=0.126 P=0.004), HbA1c (R=0.245, P=0.002) and CTS severity (Table 4).

Table 1: Laboratory characteristics of patients with and without CTS

	Without CTS Median (Min-Max)	With CTS Median (Min-Max)	*P*-value
Glycated HbA1c (%)	6.9 (4.6-13.1)	7.9 (5.3-14.2)	0.010
Fasting blood glucose level (mg/dl)	125 (85-374)	163 (85-532)	0.010
Cholesterol(mg/dl)	193 (36-372)	187 (71-356)	0.726
LDL-C(mg/dl)	111 (43-281)	113 (51-213)	0.750
Triglyceride(mg/dl)	153 (90-538)	157 (55-1287)	0.613
HDL-C(mg/dl)	47 (28-140)	44 (42.5-85)	0.083
Triglyceride /HDL-C (AIP)	3.3 (0.06- 14.38)	3.35 (0.14-45.96)	0.312
Cholesterol /HDL-C	4.28 (0.26-7.55)	4.37 (0.2- 12.71)	0.378
LDL-C/HDL-C	2.37 (0.75-5.98)	2.5 (0.12- 5.71)	0.487
25(OH) Vitamin D	21.65 (5-73.7)	18.4 (1.1- 53.2)	0.181
Urea	33 (15-222)	39,5 (15-189)	0.009
Creatinine	0.8 (0.1-7.3)	0.9 (0.5-5.9)	0.021
GFR	87 (10-125)	78.5 (10-149)	0.120
Calcium	9.6 (7.1-10.8)	9.6 (7.7-11.4)	0.369
Magnesium	1.9 (1.4-2.8)	1.96 (1.4-2.8)	0.101
Sodium	140 (134-145)	139 (134-141)	0.445

CTS: Carpal Tunnel Syndrome, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, AIP: atherogenic index of plasma, GFR: Glomerular Filtration Rate

Table 2: Gender among CTS groups of increasing electrophysiological severity

	n=131	Female (n=60)	Male (n=71)	*P*-value
Mild CTS	45	15	30	0.045
Moderate CTS	50	23	27	
Severe CTS	36	22	14	

CTS: Carpal Tunnel Syndrome

Table 3: Laboratory characteristics of CTS groups of electrophysiological severity

	Mild CTS* Median (min-max)	Moderate CTS Median (min-max)	Severe CTS Median (min-max)	*P*-value
Age	62 (29-79)	64 (31-88)	65 (43-84)	0.229
Duration of diabetes	10 (3-30)	15 (1-41)	12 (3-28)	0.481
Glycated HbA1c (%)	7.8 (5.3-14.2)	8.4 (5.6-13.1)	7.75 (5.5-13.7)	0.379
Fasting blood glucose level (mg/dl)	152.5 (85-418)	165.5 (85- 532)	188 (93-442)	0.364
Cholesterol(mg/dl)	193 (110-306)	174 (71-290)	1915 (90-356)	0.098
LDL-C(mg/dl)	116 (58-202)	92 (51-213)	125 (44-209)	0.024
Triglyceride(mg/dl)	128 (55-465)	168 (62-570)	164 (74-1287)	0.321
HDL-C(mg/dl)	47 (28-85)	42,5 (19-76)	44 (23-74)	0.706
Triglyceride /HDL-C (AIP)	2.88 (0.75-10.81)	3.96 (0.22-14.16)	3.45 (0.14-45.96)	0.237
Cholesterol /HDL-C	4.21 (2.05-6.86)	4.26 (0.02-7.08)	4.57 (2.96-12.71)	0.202
LDL-C/HDL-C	2.42 (0.91-4.45)	2.37 (0.12-5.11)	2.74 (1.45-5.71)	0.660
25(OH) Vitamin D	14.4 (5.7-53.2)	18.4 (3-45.3)	17.25 (1.1-45.5)	0.523
Urea	38.5 (22-155)	38 (15-173)	42.5 (31-189)	0.611
Creatinine	0.8 (0.5-5.40)	0.9 (0.5-6.1)	0.9 (0.5- 5.9)	0.339
GFR	80 (15-117)	81 (10-149)	67 (15-118)	0.395
Calcium	9.6(8-10.5)	9.6 (7.3-11.10)	9.5 (8.20-11.40)	0.890
Magnesium	2.0 (1.6-2.6)	1.9 (1.5-2.8)	1.9 (1.4-2.6)	0.369
Potassium	4.4 (3.3-5.6)	4.7 (2-5.8)	4.7 (3.5-5.7)	0.119
Sodium	140.5 (134-147)	139 (129-146)	139 (135-143)	0.107

CTS: Carpal Tunnel Syndrome, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, AIP: atherogenic index of plasma, GFR: Glomerular Filtration Rate

Table 4: Correlation between Glycated HbA1c, age and CTS severity

Variable	r	*P*-value
Glycated HbA1c	0.245	0.002
Age	0.126	0.004

Discussion

DM is a chronic systemic disorder with a variety of complications, including the musculoskeletal system [11]. It is one of the important risk factors for CTS, and it is thought that the lifetime risk of symptomatic CTS in Type I diabetes mellitus is high [12]. In many studies, higher rates of CTS were observed in patients with type 2 DM [11-15]. In our study, CTS was observed in 65.5% of patients with type 2 DM, which is consistent with other studies.

Carpal tunnel syndrome is more common in female patients and frequently affects those aged between 40-60 years [6]. Similar to these findings, in the present study, the patients with CTS were aged 62.83±10.85 years. In contrast to many studies, 54.5% of the patients in the present study were male [13,16]. Fasting blood glucose and HbA1c values were significantly higher in patients with CTS. Perkins et al., and Islam et al. found that patients with CTS had higher HbA1c in comparison to patients without CTS in their study, similar to our findings [17,18]. Pasnoor et al. showed that in diabetic patients, vascular disorders, such as hypoxia or ischemia due to chronic hyperglycemia, cause focal and multifocal neuropathies, while symmetrical polyneuropathies mostly result from metabolic causes [15,19].

In this study, most cases were mild and moderate in terms of CTS severity. Similar results were also found in many previous studies regarding severity [20-22]. We also observed that CTS was more severe among females.

In this study, age and HbA1c were independent risk factors for CTS severity. The results of the studies investigating the relationship between age and CTS severity were similar [20,23].

A low axonal density may lead to median nerve neuropathy. Advanced glycation end-products have been found to increase the production of circulating inflammatory cytokines and vascular endothelial growth factor may cause impaired microvascular circulation, resulting in demyelination and axonal degeneration in the median nerve [24]. HbA1c values were significantly higher in patients with CTS but a few studies have determined the relationship between electrophysiological severity of CTS and HbA1c [25].

Hypercholesterolemia and especially the increase in high LDL-C levels were associated with CTS [26]. A study by Nakamichi and Tachibana [9] showed that high LDL-C levels increased its prevalence. In another study, a correlation was found between the LDL-C level and the severity of CTS [26]. Hypercholesterolemia and particularly high LDL-C have been associated with fibrogenesis. In idiopathic CTS, the proliferation of the intraneural connective tissue causes enlargement of the median nerve within the carpal tunnel. Physiologically, the amount of connective tissue in the median nerve in the carpal tunnel is increased compared to the areas without entrapment, and in CTS, connective tissue reproduces, and the nerve expands. Oxidative LDL-C, which increases collagen production through transforming growth factor-beta, a highly fibrogenic cytokine, thus increasing fibrogenesis, causes CTS [6,9]. In this study, we found that high LDL-C levels were significantly correlated to the electrophysiological severity of CTS, especially in patients with severe CTS. There are few studies on the relationship between fat levels and the electrophysiological severity of carpal tunnel syndrome [23]. Atherogenic index of plasma (AIP) is calculated as the ratio between the triglyceride value and high density lipoprotein value (mg/dL). (TG/ HDL-C) AIP is a major risk factor for metabolic syndrome and cardiovascular diseases [27]. The high TG / HDL ratio causes endothelial dysfunction, impaired endoneuronal blood flow, nerve hypoxia and ischemia,

and consequently, neuropathy. Miric et al. [28] showed that AIP was higher in patients with type 2 DM who developed neuropathy. In our study, patients with moderate and severe CTS had insignificantly higher AIP values than those with mild CTS. Future case-control studies with larger samples are recommended.

Limitations

This was a hospital-based retrospective cross-sectional study. Our sample size was limited to only 131 individuals. Further large-scale prospective studies are recommended.

Conclusion

Our study identified a relationship between CTS severity and LDL-C. HbA1c and age were independent risk factors for CTS severity. Diabetes is a well-known risk factor for CTS, a disease which should be considered in patients with DM and hyperlipidemia.

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Comparison of the procedure results of ectopic papillae encountered during ERCP procedure with the procedure results of papillae with normal localization

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Ethics Committee Approval
The Ethics Committee of Afyonkarahisar Health Sciences University Medical Faculty approved the study (date: 05.07.2019, no: 244).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: In Endoscopic retrograde cholangiopancreatography (ERCP), Ampulla of Vater is found on the posteromedial wall of the second part of the duodenum. However, ectopic expansion of the common bile duct to the 3rd or 4th part of the duodenum or the proximal stomach, pylorus, or bulb was reported in the literature. This study primarily aims to investigate the risk of complications in patients with ectopic papillae and evaluate the applicability of endoscopic sphincterotomy in these patients.
Methods: In this a case-control study, the data of 3,048 patients who underwent ERCP procedure in the ERCP unit of our clinic between January 2013 and December 2018 were retrospectively analyzed, and 30 patients with ectopic bulbar papillae and 30 randomly selected patients with normally localized papillae were compared in terms of age, gender, duration of the procedure, post-procedural biochemical tests, cannulation success, precision rate, postprocedural pancreatitis complications and the need for analgesics. Power analysis was performed with the G*power 3.1.9.7 package program (1-B = 0.95, alpha = 0.05). With a power of 0.954, the sample size to be reached was thirty-three for each group.
Results: The rate of pancreatitis complications was higher in patients with ectopic bulbar papillae (50%) compared to those without (16.7%) (P=0.006). Even though the rate of pre-cut was higher in patients with ectopic bulbar papillae (33.3%) compared to patients with normally localized papillae (13.3%), this difference was not statistically significant (P=0.063). Cannulation success in patients with ectopic bulbar papillae (83.3%) was insignificantly lower than in patients with normally localized papillae (90.0%) (P=0.353). The need for both narcotic and non-steroidal anti-inflammatory analgesics was higher in patients with ectopic bulbar papillae (P<0.001, P=0.005, respectively).
Conclusions: It should be kept in mind that ectopic biliary drainage may be found in an alternative location when no papillae are observed in the expected anatomical region. The complication risks, including pancreatitis, are increased in the intervention of ectopic papillae. Novel studies showing that endoscopic sphincterotomy and pre-cut are successfully used in patients with ectopic papillae are needed.

Keywords: Endoscopy, Endoscopic Retrograde Cholangiopancreatography (ERCP), Ectopic papilla, Pancreatitis

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Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a method of imaging the canals that drain the gallbladder, liver, and pancreas with the help of a duodenoscope, contrast agent, and X-rays. Ampulla of Vater is endoscopically visualized; bile ducts and pancreatic ducts are cannulated. Thus, liver, gallbladder, pancreas, bile, and pancreatic duct pathologies can be diagnosed, and problems within the ducts can be intervened with therapeutic approaches [1,2].

Ampulla of Vater is found on the posteromedial wall of the second part of the duodenum. The common bile duct, on the other hand, extends down the medial wall of the descending part and opens into this part. However, ectopic expansion of the common bile duct to the 3rd or 4th part of the duodenum or the proximal stomach, pylorus, or bulb was reported in the literature [3-5].

Cannulation of the ectopic papillae is difficult during ERCP as it is quite far away from the duodenoscope. In this case, operating in a long position would be the most appropriate solution. ERCP is difficult in these patients and requires high endoscopic skills, experience, and familiarity with these cases. There are studies showing that sphincterotomy is risky in these cases because it causes complications such as perforation and bleeding. Therefore, it can be intervened using a choledochal balloon after dilatation [6].

The ERCP procedure results of thirty patients with ectopic bulbar papillae who were diagnosed with choledocholithiasis in our clinic were compared with those performed in patients with normally located papillae. Endoscopic sphincterotomy was performed to patients with ectopic bulbar papillae using pre-cut when necessary, not balloon dilatation, and the results of the procedure were compared.

This study primarily aims to investigate the risk of complications, which are reportedly increased in patients with ectopic papillae and evaluate the applicability of endoscopic sphincterotomy in patients with ectopic papillae.

Materials and methods

The results of 3,048 patients who underwent ERCP in the ERCP Unit of the General Surgery Department of the Medical Faculty Hospital between January 2013 and December 2018 were retrospectively analyzed. Thirty patients with ectopic bulbar and thirty with normally localized papillae were randomly selected among them.

Only patients with choledocholithiasis were included in the study and those younger than 18 years of age, who could not tolerate general anesthesia, patients with acute pancreatitis, cholecystitis, empyema, portal hypertension, malignancy, bleeding disorders, and those who underwent upper gastrointestinal surgery (such as subtotal gastrectomy) were excluded from the study.

Examination of patient files revealed that similar anesthesia protocols were used during the procedures. All procedures were performed by the same general surgeon.

Thirty patients with ectopic bulbar papillae and thirty randomly selected patients with normally localized papillae were compared in terms of age, gender, duration of the procedure, post-procedural biochemical tests (Alanine transaminase-ALT, Aspartate aminotransferase-AST, Amylase, Gamma-glutamyl transferase-GGT), cannulation success, postprocedural pancreatitis complications, and the need for analgesics. Amylase value being three times higher than normal and typical abdominal pain were considered sufficient criteria for pancreatitis.

Ethics committee approval

The Ethics Committee of Afyonkarahisar Health Sciences University Medical Faculty approved this study with the decision of the General Surgery Department Board dated 05.07.2019 and numbered 244, and a signed informed consent form was obtained from all patients.

Statistical analysis

The power analysis of the study was performed with the G*power 3.1.9.7 package program. (1-B = 0.95, alpha = 0.05). With a power of 0.954, and the sample size to be reached was thirty-three for each group.

The data were registered into an Excel document, transferred to the IBM SPSS 23 program, and evaluated with proper statistical methods. Data checks were performed to prevent data entry errors before continuing to analysis. The normality assumption of continuous variables was examined, and analyses were performed according to whether the normality assumption was met.

Categorical variables were given as frequency and percentage while continuous variables were presented as mean, standard deviation, and minimum-maximum. Independent samples and Mann-Whitney U tests were used to compare normally and non-normally distributed continuous two-level variables, respectively. The relationships between categorical variables were examined by the Chi-square analysis/Fisher's exact test. The significance level was accepted as $P<0.05$ in all analyses.

Results

A total of sixty patients, thirty with ectopic bulbar papillae and thirty with normally localized papillae were included in the study. Of all patients, thirty-one were female (51.7%) and twenty-nine (48.3%) were male. Among those with ectopic and normally localized papillae, fourteen (46.6%) and seventeen (56.6%), respectively, were females.

The mean and standard deviation values of the treatment duration, age, and biochemical parameters of the patients included in the study were presented in Table 1. The age range of all patients varied between 32 and 93 years, the mean age was 66.08 (15.96) years. The duration of the procedure varied between 21 and 76 minutes, with a mean of 47.62 (12.85) minutes.

The mean GGT, ALT, AST and amylase levels of all patients were 153.47 (85.89) U/L, 70.68 (59.70) U/L, 79.18 (66.21) U/L, and 315.33 (444.34) U/L, respectively.

Frequencies and percentages of patients in terms of cannulation success, pre-cut rate, postprocedural pancreatitis complications, and the need for analgesics were presented in Table 2. Twenty (33.3%) patients had pancreatitis complications, 14 (23.3%) patients underwent pre-cut, cannulation was successful in 52 (86.7%), 26 (46.3%) patients needed narcotic

analgesics, and 47 (78.3%) patients needed non-steroidal analgesics.

Table 1: The mean and standard deviation values of the treatment duration, age, and biochemical parameters of the patients included in the study

	n	Min	Max	Mean	SD
Age (years)	60	32	93	66.08	15.96
Processing time (minutes)	60	21	76	47.62	12.85
Gamma-glutamyl transferase (GGT) (U/L)	60	57	451	153.47	85.89
Alanine aminotransferase (ALT) (U/L)	60	25	273	70.68	59.70
Aspartate aminotransferase (AST) (U/L)	60	28	292	79.18	66.21
Amylase (U/L)	60	15	2102	315.33	444.34

n: Number of patients, SD: Standard deviation

Table 2: Frequencies and percentages of patients in terms of cannulation success, precut rate, postprocedural pancreatitis complications, and the need for analgesics

Clinical Conditions	Frequency (%)
Pancreatitis complication	20 (33.3)
Pre-cut rate	14 (23.3)
Cannulation success	52 (86.7)
The need for narcotic analgesics	26 (46.7)
Need for nonsteroidal analgesics	47 (78.3)

The independent samples t-test was used in independent samples to compare the duration of treatment and mean age of patients in the two groups. The duration of the procedure in patients with ectopic bulbar papillae (52.57, (15.35)) was significantly higher than that of patients with normally localized papillae (42.67, (7.06)) (P=0.003). The mean age of patients with ectopic bulbar papillae was insignificantly lower (P=0.068).

Mann-Whitney U test was used to compare biochemical parameters of patients (Table 3). The GGT, ALT, and AST values of patients with ectopic bulbar papillae were significantly, and amylase levels were insignificantly higher compared to those of patients with normally localized papillae (P<0.001, P=0.031, P=0.013, and P=0.108, respectively). Pancreatitis was more frequent among those with ectopic papillae (P=0.006), while the rate of pre-cut were similar between the two groups (P=0.063). Cannulation was almost equally successful among the two groups (P=0.353). The need for narcotic and non-steroidal anti-inflammatory analgesics were significantly higher in patients with ectopic bulbar papillae (P<0.001, and P=0.005, respectively) (Table 4).

Table 3: Comparison of biochemical parameters of patients with ectopic bulbar papillae and patients with papillae with normal localization

	Patients with ectopic bulbar papillae				Patients with normally located papillae						
	Min	Max	Mean	SD	Min	Max	Mean	SD	*U*	*z*	*P*-value
GGT (U/L)	73	451	195.10	87.05	57	321	111.83	62.01	154.00	-4.38	0.008
ALT (U/L)	25	273	93.30	74.61	26	129	48.07	25.01	304.00	-2.16	0.031
AST (U/L)	28	292	105.20	82.62	32	137	53.17	26.32	281.50	-2.49	0.013
Amylase (U/L)	15	2102	428.80	510.40	56	1328	201.87	338.43	341.50	-1.61	0.108

SD: Standard deviation, Mann - Whitney U test, P<0.05

Table 4: Comparison of patients with ectopic bulbar papillae and patients with papillae with normal localization in terms of cannulation success, precut rate, postprocedural pancreatitis complications, and the need for analgesics

Clinical Conditions		Patients with normally located papillae (%)	Patients with ectopic bulbar papillae (%)	χ2	*P*-value
Pancreatitis complication	No	25 (83.3)	15 (50)		
	Yes	5 (16.7)	15 (50)	7.50	0.006
Precut rate	No	26 (86.7)	20 (66.7)		
	Yes	4 (13.3)	10 (33.3)	3.35	0.063
Cannulation success	No	3 (10.0)	5 (16.7)		
	Yes	27 (90.0)	25 (83.3)	.57	0.353
The need for narcotic analgesics	No	25 (83.3)	9 (30)		
	Yes	5 (16.7)	21 (70)	17.38	0.005
Need for nonsteroidal analgesics	No	11 (36.7)	2 (6.7)		
	Yes	19 (63.3)	28 (93.3)	7.95	0.005

χ2: Chi-square analysis, P<0.05.

Discussion

The papilla of Vater typically enters through a 1 cm to 2 cm-long intramural tunnel inclined posteromedial to the second part of the duodenum. It sometimes may open abnormally, including the stomach [7-9], the pyloric canal, the duodenal bulb [10-13], and the third or fourth part of the duodenum [14]. We conducted a retrospective cohort study comparing patients with ectopic papillae opening to the duodenal bulb, which is the most common ectopic site in our clinic, with patients with normally localized papillae.

The rate of abnormal opening of the common bile duct is reported as 5.6%-23% due to a limited number of cases in rare studies on the extrahepatic biliary tree [4,5,11].

Lurje reported that the papilla opened to the third part of the duodenum in 16 (8.26%) of 194 autopsy cases [15]. Lindner et al. found that in 17.9% of 1,000 patients who underwent intraoperative cholangiography, the papilla of Vater opened to the distal second part of the duodenum, the third part of the duodenum, or the fourth part of the duodenum [14]. Dowdy et al. found that the distance between the papilla of Vater and pyloric sphincter was less than 5 cm in 4 of 100 autopsy cases [16].

The etiology of this abnormal opening is unknown, but there are opinions that developmental errors during embryogenesis may be a causal factor. The liver originates from the hepatic diverticulum, and it forms the cranial part (pars hepatica), the intrahepatic and common hepatic ducts as well as the caudal part (pars cystica), gallbladder, and cystic ducts [17]. The most accepted hypothesis about the ectopic opening of the common bile duct was explained by Boyden. According to this hypothesis, if the lower cleft occurs too early in the first weeks of embryogenesis, pars hepatica develops into a duct draining into the pyloric region by leaving the stomach above the growth region which separates it from the duodenum [18].

In the literature, more than 80% of the cases with ectopic biliary drainage were male. In the study conducted by Sarıtas et al. [19], 90% of the patients were male. Similar findings were reported in the studies of Guerra et al. [20], Sung et al. [21], and Ersöz et al. [22], which suggests an etiological relationship with embryonic abnormality caused by the Y chromosome. However, this can also be observed in female patients, like the female patient with ectopic papilla opening to the pyloric part of the stomach in the study by Nasseri-Moghadam et al. [23]. Also, in the study of Sezgin et al. [24], 5 of 11 patients with ectopic papillae were females. Of the patients with ectopic bulbar papillae in our study, fourteen were female (46.6%). Contrary to earlier studies, there was no difference in terms of gender between patients with ectopic and normally localized papillae.

In the studies of Sezgin et al. [24], Disibeyaz et al. [6], and Saritas et al. [19], the age ranges of the patients were 42-87 years, 36-78 years, and 38-74 years, respectively, with median ages of 59.2 years, 55 years, and 54 years, respectively. In our study, patients with ectopic bulbar papillae were between 33 and 90 years of age, and their mean age was 62.33 years.

Earlier studies focused on the indications for the procedure of patients with ectopic papillae, the largest series of ectopic opening were reported by Lee et al. [10], and most patients in this series had choledocholithiasis or cholangitis. The

most common indication for ERCP in patients with ectopic papilla was choledocholithiasis in the study conducted by Sezgin et al. [24]. Other indications included acute pancreatitis, common bile duct dilatation, extrahepatic cholestasis, cholangitis, and complications of bile fistula and laparoscopic cholecystectomy. Cholangitis was detected in 59% of the patients in the study conducted by Disibeyaz et al. [6]. The patients included in our study had choledocholithiasis, the most common indication in the literature.

One of the parameters we evaluated, unlike the other studies, is the duration of the procedure, which was significantly longer in patients with ectopic papillae. This may be due to technical reasons such as the examination of the area of the duodenum up to the bulbar region, a long-axis approach to the ectopic papilla, and difficult cannulation during deciding the localization of the papilla.

Another important parameter in the study is the biochemical tests in the follow-up of patients after the ERCP procedure. AST, ALT, GGT values were significantly, and amylase values were insignificantly higher compared to those of patients with normally localized papillae. These biochemical parameters are directly proportional to pancreatitis. Elevated levels of ALT and GGT were present in fifty-two patients (97%) before the procedure [6]. However, there are no studies in the literature comparing biochemical parameters after the procedure, and our study can be presented as a pioneering study in this field.

Patients with ectopic papillae are difficult to cannulate [25-28]. Disibeyaz et al. [6] successfully removed stones in 59% of the patients with stones in the common bile duct when compared with another study involving ectopic bulbar papilla series. In our study, no statistically significant difference was found in terms of choledochal cannulation. Our study also shows that choledochal cannulation can be performed successfully in patients with ectopic papillae.

Pancreatitis developed in five patients with normally localized papillae, and in fifteen patients with ectopic bulbar papillae. This parameter is directly proportional to the high amylase test result after the procedure in patients with ectopic bulbar papillae. The higher incidence of the need for NSAIDs and narcotic analgesics in patients with ectopic bulbar papillae after the ERCP procedure is also related. Cannulation was tried in four patients with normally localized papillae via pre-cut while the common bile duct was cannulated with the help of a pre-cut procedure in ten patients with ectopic bulbar papillae. Our study shows the usability of the pre-cut procedure in ectopic papillae cases. Besides, duodenal biliary reflux and stasis are significantly seen in patients with ectopic papillae due to the loss of the inclined course of the pancreatic duct and common bile duct in the duodenal wall. Not only gastric juice, but also pancreatic juice and bile juice can contribute to recurrent peptic ulcers [21]. There is a need for studies on peptic complaints in these patients.

It has been suggested that there is a slit-like opening that does not have a sphincteric structure at the entrance of the choledochal duodenum in patients with ectopic papillae, and sphincterotomy carries a significant risk of difficulty and retro duodenal perforation in these cases [29,30]. However, perforation was not encountered in patients undergoing choledochal cannulation and pre-cut in our study. Retroperitoneal perforation occurred in the intrapancreatic segment of the common bile duct after dilatation of the common bile duct with a 12 mm balloon in the study by Ersöz et al. [22], and perforation and bleeding occurred during sphincterotomy in one patient in the study by Disibeyaz et al. [6]. Dacha et al. [31] suggest that a regular, a forward viewing gastroscope should be used to visualize the stomach better, and no major sphincterotomy should be performed due to the substantial risk of perforation.

Strengths and limitations

Since ectopic papillae is a rare entity, the study could not be conducted with more patients, despite power analysis calculations showing that thirty-three patients were needed in each group.

Strengths of the study were the referral of multiple ERCP procedures from various hospitals to our tertiary hospital, so we had the opportunity to examine ectopic papillae, and evaluate the procedures and complications that should be considered in the intervention of these patients. On the other hand, we think that further, larger scale studies are needed on ectopic papillae.

Conclusion

ERCP has a particularly prominent place in the diagnosis and treatment of biliary, liver, and pancreatic diseases. Frequent use of ERCP increases the number of cases diagnosed with ectopic papilla although ectopic papilla is a rare finding. It should be kept in mind that ectopic biliary drainage may be found in an alternative location when no papillae are observed in the expected anatomical region, and bile-stained slit like biliary orifice should be investigated in the first, third, or fourth parts of the duodenum, stomach, and pylorus.

It is necessary to support with our results with other studies. The treatment does not only consist of the operation. Other endoscopic treatments, such as endoscopic sphincterotomy and pre-cut procedure, can be successfully performed. More caution should be exercised for pancreatitis complications that may occur after the procedure in patients with ectopic papillae.

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Proximal femur fracture, analysis of epidemiology, complications, and mortality: A cohort with 380 patients

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Ethics Committee Approval
The study was approved by the Keçiören Health Practice and Research Hospital Ethics Committee (date: 15.05.2020, number: 43278876-929). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Among all orthopedic injuries, hip fractures continue to have high morbidity and mortality. While the epidemiological features of proximal femoral fractures (PFF) have often been defined, there are studies which examine the relationship between the complications of the types of PFF and mortality. The aim of this study was to determine the frequency of PFF types and investigate the relationship between complications of subtypes and mortality.

Methods: This study included 380 patients aged >40 years who underwent surgery for a PFF. The fractures were classified according to localization as intertrochanteric femur fracture (ITFF), femoral neck fracture (FNF) and subtrochanteric fracture (STF). Patient demographic data (age, gender, comorbidities) were recorded, and modified Charlson comorbidity scores were calculated. Major surgical complications (infection, dislocation, implant failure) were defined as those requiring additional surgery, and minor surgical complications (cellulitis, wound site problems, pressure sores, deep vein thrombosis) as those not requiring surgery. Mortality rates were examined at 1, 3 and 12 months postoperatively. The fracture subtypes were compared with respect to surgical complications (major and minor), non-surgical complications and mortality rates. Mortality risk factors were determined according to final mortality status.

Results: The patients included 235 females and 136 males (F/M=2/1) with a mean age of 78.5 (12.1) years. Three hundred and thirty (86.5%) patients were aged >65 years and 50 (13.5%) were aged <65 years. The fractures were classified as 225 (60%) ITFF, 120 (32%) FNF, and 26 (7%) STF. Surgical complications and complications not related to surgery were seen in 35 (9.2%) and 25 (6%) patients, respectively. Mortality occurred within one month in 17 (4.6%) patients, in three months in 32 (8.6%) and within the first year in 97 (26%). No significant difference was found between fracture types with respect to mortality in 1, 3, and 12 months (P=0.51, P=0.641, P=0.2 respectively). The mortality rates of ITFF and FNF were highly similar (1, 3, 12-month mortality: P=0.943, P=0.939, P=0.946 respectively). In the comparison between the surviving and non-surviving groups, age, Charlson comorbidity index, prolonged stay in intensive care, and non-surgical complications were significantly increased in the non-surviving group (P<0.001, P<0.001, P=0.03, P=0.005 respectively).

Conclusion: ITFF is common among PFF. While there was no relationship between fracture types in PFF, complication and mortality, a correlation was found between mortality and age, Charlson comorbidity score, prolonged stay in intensive care, and non-surgical complications.

Keywords: Hip fracture, Proximal femur fracture, Epidemiology, Mortality, Complication

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Introduction

Hip fractures are common in orthopedic surgery and constitute 20% of the orthopedic workload [1]. Approximately 90% of hip fractures occur in patients aged >65 years and are often the result of a low-energy fall from the same level [2]. In 1999, there were 1.66 million hip fractures worldwide and in parallel with increasing life expectancy, this is expected to surpass 6.26 million by 2050 [3].

Hip fractures are classified as intracapsular (femur neck fracture) and extracapsular (intertrochanteric and subtrochanteric femur fracture). This classification directs surgical treatment so that while osteoporotic femoral neck fractures (>65 years of age) are treated with arthroplasty, in young femoral neck fractures where union is expected and in intertrochanteric and subtrochanteric femoral fractures, the aim of treatment is to obtain osteosynthesis [4]. Despite all the advances in treatment approaches there has been no change in mortality rates over the years, and 1-year mortality rates have been reported as 20%-40%, and in-hospital mortality as 5% [5,6].

In addition to mortality, another problem for these patients is not regaining the pre-fracture quality of life [7]. To be able to reduce the high mortality rates of hip fractures, this subject has often been investigated in literature to be able to determine the risk factors and develop healthcare services. Numerous studies report that non-surgical and unchangeable risk factors are predominant in mortality, such as age, more than one comorbidity, dementia, and the preoperative independence score [8-10].

Most hip fractures are intertrochanteric fractures, while subtrochanteric fractures account for the lowest percentage [11]. Trochanteric fractures increase with age because of the decrease in bone density in the trochanteric region with ageing, and reduced resistance to shear forces. In epidemiological studies that have examined proximal femoral fractures (PFF), subtrochanteric fractures have been reported in a young patient group [12]. Despite the determination of epidemiological features of PFF, there have been limited comparisons of the complications of PFF types and mortality. The aim of this study was to determine the frequency of PFF types and investigate the relationship between complications and mortality for the prediction of prognosis.

Materials and methods

Patients

The design and protocol of this retrospective cohort study were approved by the Keçiören Health Practice and Research Hospital Ethics Committee (date: 15.05.2020, number: 43278876-929). The study procedures followed the principles of the Helsinki Declaration.

The records of 392 patients who were treated for proximal femoral fracture (PFF) in the department of Orthopedics and Traumatology at Keçiören Health Practice and Research Hospital between 2015-2018 were examined. Patient data were retrieved from the hospital electronic data system and patient records. A total of 12 patients were excluded from the study, 2 because of poor general condition, 3 did not wish to be included, 2 had femoral head fractures, and 5 were aged <40 years. Thus, the study included 380 patients aged > 40 years, who were operated for PFF. Three hundred and eighty patients with PFF constituted 22% of the 1710 patients treated surgically because of trauma in our clinic in the designated study period.

The fractures were classified according to localization as intertrochanteric femur fracture (ITFF), femoral neck fracture (FNF) and subtrochanteric fracture (SFF). Patient demographic data (age, gender, comorbidities) were recorded, and modified Charlson comorbidity scores were calculated. Differences were examined according to the frequency of fracture type and demographic data. Changes and the relationship with fracture subtype were examined according to the years.

Variables

Examinations were made of the postoperative length of stay in hospital, postoperative stay in the Intensive Care Unit (ICU) and surgical (major and minor) and non-surgical complications. Non-surgical complications were limited to complications determined during hospitalization. Major surgical complications (infection, dislocation, implant failure) were defined as those requiring additional surgery, and minor surgical complications (cellulitis, wound site problems, pressure sores, DVT) as those not requiring surgery. The mortality data of patients were retrieved from the hospital system and the official national registration system. Mortality rates were examined at 1, 3 and 12 months postoperatively. The fracture subtypes were compared in terms of length of hospital stay, requirement for postoperative ICU, surgical complications (major and minor), non-surgical complications and mortality rates. The relationship between fracture types and mortality was evaluated with the 1, 3, and 12-month mortality rates.

In the examination of the risk factors for mortality, the patients were grouped as survivors and non-survivors. Age, gender, Charlson comorbidity score, stay in ICU, surgical complications (major and minor) and non-surgical complications were evaluated with respect to mortality.

Clinical treatment and surgery

Immediately after admittance of the patients, mechanical and medical DVT prophylaxis was started. Internal treatments were applied to patients before the operation. After the necessary workup for anesthesia, surgery was performed as soon as the general medical status of the patient allowed. Infection prophylaxis was administered to all patients preoperatively. Proximal femoral nail (PFN) was performed to patients with ITFF and STF. For patients with FNF, internal fixation with cannulated screw was used in those <60 years of age and bipolar endoprosthesis to those aged >60 years.

Postoperative follow-up

All patients were mobilized on postoperative day 1 or 2 with a walker. Weight-bearing was allowed as tolerated postoperatively. The patients were called for follow-up examinations at 2-week intervals and the joint range of movement (ROM) was checked. In the follow-up examinations, patients with fixation were assessed with respect to union and implant failure (cut-out, cut-true and lateral sliding), and patients with endoprosthesis were assessed in terms of dislocation and infection.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS v.22 software, and at a confidence interval of 95%. Qualitative data were presented as frequency distribution and quantitative data, as mean, minimum and maximum values. Inter-observer and intra-observer reliability were assessed using the interclass coefficient. Demographic values and complications of the type of PFF were evaluated with the Kruskal Wallis and Chi-square tests. The follow up and complication data of patients with ITFF and FNF were evaluated with Mann Whitney U-test and Chi-square test. The complications of the three groups were compared using the Chi-square test. Kruskal Wallis test was applied in the evaluation of the Harris Hip Score according to additional surgical procedures. Correlations between mortality status and risk factors were assessed with frequency distribution and the Spearman correlation test.

Results

The mean follow-up time was 23.2 (8.4) months (range, 12-36 months). The patients included 235 females and 136 males (F/M=2/1) with a mean age of 78.5 (12.16) years; 330 (86.5%) patients were aged >65 years and 50 (13.5%) were aged <65 years. The demographic data of the patients are presented in Table 1.

In 15 (5%) patients, the hip fracture was bilateral. The fractures were classified as 225 (60%) ITFF, 120 (32%) FNF, and 26 (7%) SFF. Intra-articular and extra-articular fractures were found in 250 (67.5%) and 120 (32.5%) patients, respectively. Complications related and not related to surgery were seen in 35 (9.2%) and 25 (7%) patients, respectively. Twenty-six (6.2%) patients with a major surgical complication required additional surgery. The mortality rates were 4.6% within 1 month, 8.6% within 3 months and 26% in the first year postoperatively (Table 1).

Table 1: Demographic data of the patients

	n=380	%, mean
Age	78.5 (12.1)	
<65	50	13.5
>65	330	86.5
Gender		
Female	235	63
Male	136	36
Follow-up (month)	12-36	23.2 (8.4)
Bilateral	15	5
Charlson comorbity index	0-9	5.6 (1.6)
Subtype		
Intertrochanteric fracture	225	60.6
Femur neck fracture	120	32.3
Subtrochanteric fracture	26	7
Surgical complication	35	9.2
Major surgical complication	26	6.2
Minor surgical complication	9	3
Infection	9	1.5
Non-surgical complication	25	6
Reoperation	26	6.2
<3 months	14	3.2
>3 months	12	3
Mortality	123	33
<1 month	17	4.6
<3 months	32	8.6
<12 months	97	26

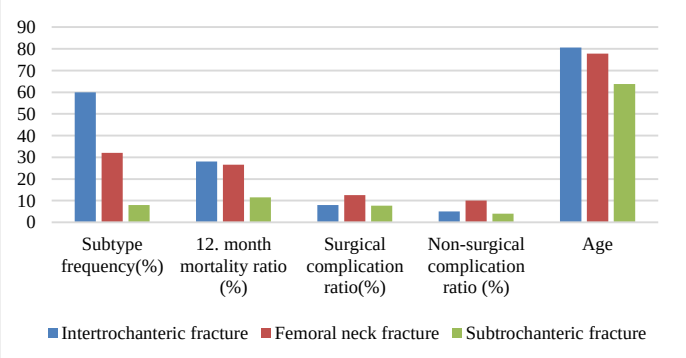
The fractures were compared according to types as intertrochanteric, femoral neck and subtrochanteric. A significant difference was observed in age and Charlson index scores of the patients (P<0.001, P<0.001). Fracture types were similar in terms of mortality in 1, 3, and 12 months (P=0.51, P=0.641, P=0.2). The mortality rate of patients with STF at 12 months (11%) was insignificantly lower than that of patients with FNF (27%) and ITFF (28%) (P=0.2).

The fracture types were similar with respect to major and minor surgical complications, non-surgical complications, and mortality rates (Table 2 and Figure 1). Non-surgical complications included pulmonary embolism (2%), cerebrovascular event (1.8%), myocardial infarct (1%), and kidney failure (2%). ITFF implant failure was seen in 3%, and dislocation in FNF was observed in 2.5%. Infection was seen in 9 (2.5%) patients, 3 ITFF, 6 FNF (P=0.04).

Table 2: Differences in proximal femoral fracture subtype

	Intertrochanteric fracture	Femur Neck Fracture	Subtrochanteric Fracture	*P*-value
Hips	225 (%60)	120 (%32)	26 (%7)	371
Age	80.6 (9.8)	70.8 (11.6)	73.8 (20.1)	<0.001*
<65	19 (%38)	19 (%38)	12 (%24)	<0.001*
>65	205 (%64)	101 (%31)	14 (%4,3)	
Gender				
Female	141 (%62)	79 (%65,8)	15 (%57.7)	0.632
Male	84 (%37)	41 (%34.2)	11 (%42.3)	
Charlson comorbidity score	4,9 (1.7)	4,7 (1.7)	2.9 (2.4)	<0.001*
Postoperative Intensive Care Unit	150 (%66)	70 (%58)	12 (%46)	0.163
Postoperative hospitalization day	2.7	4.1	2.7	<0.001*
Surgical Complication	18	15	2 (%7.7)	0.392
Major Surgical Complication	13 (%6.5)	11 (%9)	2 (%7.7)	0.410
Infection	3 (%1)	6 (%5)		0.04*
Dislocation		3 (%2.5)		-
Implant failure	8 (%3)			-
Refracture		1(%1)		0.350
Nonunion	2 (%1)		2 (%7.7)	0.108
Minor surgical complication	5	4		0.542
Non-surgical complication	12 (%5)	12 (%10)	1 (%4)	0.167
Pulmonary embolism	4	4	1	0.576
Myocardial infarct	2	1		0.891
Cerebrovascular disease	4	3		0.684
Acute renal failure	3	4	1	0.328
Mortality	9.5 (7)	7,5 (4.9)	8.6 (5.7)	0.498
<1 month	11 (%4.9)	6 (%5)		0.510
<3 month	21 (%9.3)	10 (8.3)	1 (%3.8)	0.641
<12 month.	63 (%28)	32 (%26,7)	3 (%11.5)	0.2

Figure 1: Demographics and follow-up data of the patients



The vast majority (93%) of the fractures comprised ITFF and FNF, so these two groups were compared. They were similar in terms of age, gender, or comorbidity rates (P=0.09, P=0.482, P=0.07), however, significantly differed with respect to postoperative length of stay in hospital and infection rates (P=0.03, P=0.04). No differences were detected in surgical (major and minor) and non-surgical complication rates (P=0.234, P=0.782, P=0.09), or in 1, 3, and 12-month mortality rates (P=0.943, P=0.939, P=0.946) (Table 3).

The mean follow-up period was 23.2 (8.4) months, and 123 patients did not survive. When the surviving and non-surviving patients were compared, age, Charlson morbidity score, postoperative stay in ICU > 2 days and non-surgical

complications were significantly higher in the non-surviving group (P<0.001, P<0.001, P=0.03, P=0.005 respectively). Mortality was not correlated with gender, postoperative requirement for ICU, or surgical complications (P=0.163, P=0.34, P=0.91 respectively) (Table 4).

Table 3: Comparison between Intertrochanteric and femoral neck femoral fracture

	Intertrochanteric Fracture	Femoral Neck Fracture	*P*-value
Hips	225 (%60)	120 (%32)	
Age	80,6 (9.8)	77,8 (11.6)	0.09
<65	19 (%9)	19 (%15)	0.08
>65	205 (%91)	101 (%85)	
Gender			
Female	141 (%62)	79 (%65,8)	0.482
Male	84 (%37)	41 (%34.2)	
Charlson comorbidity score	4,9 (1.7)	4,7 !1.7)	0.07
Postoperative Intensive Care Unit	150 (%66)	70(%58)	0.763
Postoperative hospitalization duration (day)	2.7	4,1	0.03*
Surgical Complication	18 (%8)	15 (%12.5)	0.234
Major Surgical Complication	11(%5.5)	10 (%9)	0.284
Infection	3 (%1)	6 (%5)	0.04*
Dislocation		3 (%2.5)	-
Implant failure	8		-
Refracture		1	0,550
Nonunion	2		0.955
Minor surgical complication	5	4	0.782
Non-surgical complication	12 (5)	12 (%10)	0.090
Pulmonary embolism	4	4	0.273
Myocardial infarct	2	1	0.831
Cerebrovascular disease	4	3	0.384
Acute renal failure	3	4	0.122
Mortality	9.5 (7)	7,5 (4.9)	0,246
<1 month	11 (%4.9)	6 (%5)	0.943
<3 month	21 (%9.3)	10 (8.3)	0.939
<12 month	63 (%28)	32 (%26,7)	0.946

Table 4: Comparison between mortal and alive groups

	Alive group (n=248)	Mortal group (n=123)	*P*-value
Age	75.7 (13.3)	86 (6.7)	<0.001*
Gender (F/M)	151/97	84/39	0.163
Charlson comorbidity score	4.1 (1.7)	5.6 (1.1)	<0.001*
Postoperative Intensive Care Unit	132	100	0.340
Intensive Care Unit >2 day	20	40	0.03*
Non- Surgical complication	11	16	0.005*
Surgical complication	23	11	0.910

Discussion

High mortality rates are seen in hip fractures in the first year (20%-40%). In a study that examined American and European data, it was reported that in a 10-year follow-up period, although mortality rates fell after the first year, they were noticeably higher than those of the normal population [13]. The foremost risk factors are age, comorbidity, and the preoperative independence score, while modifiable risk factors include high BMI, cigarette smoking, living in an old people's home, and late surgery (>2 days) [14-16]. In the demographic differences in PFF cases, STF is seen at a younger age and the frequency of ITFF increases with advancing age [11,12]. In a study by Kannus et al. [11] that examined the epidemiological feature of hip fractures, ITFF was seen at an older age and entailed greater hospital costs. The hypothesis of the current study was that ITFF would be seen at an older age and would have a higher mortality rate.

While the results of this study showed no correlation between fracture types and mortality, the mortality rates of ITFF and FNF were similarly high. The factors affecting mortality were age, Charlson comorbidity score, prolonged stay in ICU, and non-surgical complications.

Majority of osteoporotic fractures are hip, vertebrae, and distal radius fractures, and those causing most concern are hip fractures [17]. PFFs constitute 22% of all the trauma surgery operations in our clinic and were observed to form a large part of trauma surgery. A substantial proportion of PFF are osteoporotic fractures caused by low-energy trauma [18]. The mean age at which PFF is seen has increased over the years with ageing populations and is over 70 years of age in all studies [19].

In the current study, the mean age of the patients was 78.5 (12.16) years and 86.5% were aged over 65 years. PFF is an injury of the elderly. While FNF and ITFF are seen at similar rates at younger ages, the frequency of ITFF increases with advancing age [19]. The prevalence of fractures in this region is attributed to the decrease in bone density in this region with ageing [20]. In the current study, ITFF and FNF were seen at the same rate in patients aged <65 years, while ITFF comprised 64% of the fractures seen in patients aged >65 years. STF constitutes the main difference for PFF.

In a study by Yoon et al, STF was found in 3%, with a rate varying between 2% and 10% in different populations, and the frequency of these fractures increased in patients aged <60 years [21]. In the current study, the mean ages of all PFF patients and STF patients were 78.5 (12.1) years and 63.83 (20.1) years, respectively. Subtrochanteric fractures were seen at a younger age and the Charlson comorbidity scores were lower in these patients.

High first-year mortality rates (17%-38%) for PFF have been reported in literature. In the current study, 1-year mortality rate was 26%, and first-month mortality rate was 4.6%. Frost et al. examined early mortality and reported in-hospital mortality rate as 5%, which was explained by congestive heart disease and liver failure in addition to age [22]. Indexes have been developed to calculate survival determined by the physiological activity level [23,24]. In the current study, early non-surgical complications of the patients were examined, and included pulmonary embolism (2%), cerebrovascular event (1.8%), myocardial infarct (81%) and kidney failure (2%), all of which had a mortal course.

The mean follow-up period of this study was approximately 2 years and the final mortality rate was 33%. Within the second year, mortality was 7%, and despite continuing, the mortal course decreased. When the variables of the survivors and non-survivors were examined, age, Charlson comorbidity score, late mobilization and non-surgical complications appeared prominent. In every study in literature, age is an unchangeable risk factor, and this is followed by comorbidities [8-10,14,15]. In some studies, the number of comorbidities has been stated, and in others the Charlson and modified Charlson comorbidity scores have been used [9,15]. The preoperative level of physical activity is a determinant of mortality [25].

Of the surgical factors that can be changed, early surgery is strongly recommended, and although there is debate about this period, it is recommended that surgery is performed together with the application of internal treatments within 48 hours [26,27]. In the current study, fracture types were an unchangeable factor which did not affect mortality. Similar mortality rates were observed for ITFF and FNF. In the surgical treatment of ITFF, there is currently support for minimally invasive fixation options for arthroplasty [28]. That there was no variation in the ITFF mortality rates could be explained by the performance of minimally invasive surgeries.

Different complications are seen according to the fracture types and surgery selected. In FNF, dislocation is more prominent, in ITFF, implant failure, and in STF, non-union. In the current study, ITFF implant failure occurred in 3% and FNF dislocation, in 2.5%. ITFF implant failure, which is a major surgical complication, has been reported at a rate of 5% in the literature [29]. Infection was more frequent in the FNF group than the other two groups. As arthroplasty is used in FNF, infection is frequent in this region and FNF has been reported to be a risk for infection [30].

No significant difference was observed between PFF types in terms of major and minor surgical complications. Although it was thought that major surgical complications could influence mortality, that was not the case. Even if surgical complications do not affect mortality, they are a factor in continuing morbidity and increasing hospital costs [12]. Non-surgical complications can be seen in all types and affected mortality.

There were some limitations to this study, primarily that it was a single-center study. Multi-center studies with more patients would be of more guidance for national data. Different surgical treatments can be used in PFF at the surgeon's discretion, therefore the differences in surgeries performed according to treatment centers could be considered a limitation. However, a strong aspect of the study was that standard treatments were used according to the fracture types, consistent with current literature. Therefore, as the treatments were standard and current, the data of the last 3 years were used.

Conclusion

ITFF is common in PFF fractures. While no relationship was found between fracture types with complication and mortality, there was a correlation between mortality and age, Charlson comorbidity score, prolonged stay in intensive care, and non-surgical complications.

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The risk factors and maternal adverse outcomes of stillbirth

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Ethics Committee Approval
This study was approved by the Bursa Yuksek Ihtisas Training and Research Hospital, University of Health Sciences ethics committe local ethics committee with a decision number 2011-KAEK-25 2020/03-14 in 4th of March 2020 All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Stillbirth is a devastating complication of the pregnancy. Contemporary studies have exposed several reasons; however, most of the cases are still unexplained. Stillbirth delivery could cause various maternal complications. We aimed to evaluate the maternal complications and reveal the risk factors for stillbirth.

Methods: A case-control study was performed at a high-volume university-affiliated research and training hospital between June 2016 and June 2020. The study population was divided into two groups as women who delivered stillbirth (study group) and live birth (control group). Patients' characteristics, birth weight and gender of the newborn, hospital stay, delivery type, concomitant diseases in pregnancy such as preeclampsia, gestational diabetes mellitus, fetal anomaly, preterm premature rupture of the membranes and complications such as uterine atony, abruptio placenta, postpartum hemorrhage, disseminated intravascular coagulation, and uterine rupture were evaluated from the medical records and compared between groups.

Results: A total of 46019 births occurred during the study period. The number of women who delivered stillbirth was 520 with a rate of 11.2 per 1000 births. The control group included 6521 patients. Comparison of the groups revealed that women delivering stillbirth were older (P<0.001), had longer hospital stay (P<0.001), lower newborn birth weight (P<0.001), and more babies with congenital anomalies (P<0.001) than the control group. The women in stillbirth group experienced more preterm premature rupture of the membranes (P<0.001), preeclampsia (P<0.001), gestational diabetes mellitus (P<0.001), abruptio placenta (P<0.001), postpartum hemorrhage (P<0.001), and disseminated intravascular coagulation (P<0.001). The rates of severe obstetric and postpartum complications were 14.2% and 12.1%, respectively. Multivariate logistic regression analysis revealed that fetal anomaly (OR 3.170; 95% CI 1.592-6.315, P<0.001), gestational diabetes mellitus (OR 15.203; 95% CI 8.368-27.621, P<0.001) and abruptio placenta (OR 18.221; 95% CI 9.121-36.402, P<0.001) increased the risk of stillbirth.

Conclusion: Stillbirth delivery could lead to severe maternal complications that can threaten maternal vitality. Close delivery follow-up is essential, especially during the early postpartum period. Care should be taken for postpartum complications such as disseminated intravascular coagulation and postpartum hemorrhage. Furthermore, patients should be examined carefully for abruptio placenta. Stillbirth deliveries should be carried out in fully equipped hospitals.

Keywords: Abruptio placenta, Gestational diabetes mellitus, Maternal complication, Stillbirth

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Introduction

Stillbirth can be assumed as the most dramatic end of the fairytale. Patients, physicians, and all health care providers are affected by the consequences of stillbirth. Even a live birth could cause trauma and depression, bereavement of the baby may lead to serious psychological, economical, biological outcomes. Therefore, stillbirth rates are as important as maternal mortality rates, which is considered one of the most important general indicators of the health system. An underestimated topic, it is the problem of the low and middle-income countries, especially African countries. It has been stated that about 98% of stillbirths occur in these countries. However, this percentage could be the seen part of an iceberg, because stillbirth definition involves a baby born with no signs of life at or after 28th week of gestation with a birth weight of ≥1000 g [1,2]. The definition varies especially in developed countries in terms of the gestation week (≥20 weeks or 22 weeks) and birth weight (≥ 350 gr or 500gr) [3,4]. The incidence of stillbirth in America was 5.96 in 1000 live births. Almost half were born before the 28th week of gestation and the rates tend to decrease compared to previous years [5]. The evolution of medicine and increased opportunities had an essential role in decreasing stillbirth rates. Women with diabetes used to experience stillbirth by approximately 65% in the 1920s however, patients with advanced glycemic control carry almost the same risk as those without diabetes [6,7]. Similarly, adequate treatment of preeclampsia (PE), hypertensive disorders, Rhesus alloimmunization, intrauterine growth restriction, preterm premature rupture of membranes (PPROM), and infections had also essential roles in decreasing stillbirth rates.

Despite these interventions, stillbirth is still a devastating obstetric complication. Management of stillbirth delivery is also a compelling issue. Two of the three components of the labor- the 3Ps, passageway, passenger, and power, are defective. Many women's labor would start and end within 1 or 2 weeks of fetal demise spontaneously, however, if the expectant interval prolongs more than 3 weeks, disseminated intravascular coagulation (DIC), placental abruption or uterine rupture may occur [8]. Our hospital is one of the referral centers for complicated deliveries. First, we aimed to determine the maternal outcomes and complications in women with stillbirth. Then, the risk factors for stillbirth were evaluated via prepartum circumstances, delivery complications, operative obstacles, and postpartum processes in this study.

Materials and methods

This retrospective study was conducted at a high-volume university-affiliated research and training hospital between June 2016 and June 2020. It was approved by the Bursa Yuksek Ihtisas Training and Research Hospital, University of Health Sciences Ethics Committe with the decision number 2011-KAEK-25 2020/03-14 in 4th of March 2020. The Declaration of Helsinki guidelines were followed.

The deliveries during the study period were evaluated and data were collected from the hospital registry and the patients' hospital files. The study population was divided into two groups as those giving stillbirth and live birth (control). Patients with multiple pregnancies and comorbid diseases were excluded from the study. Patients' characteristics, birth weight, hospital stay, and delivery type were examined. Concomitant diseases in pregnancy such as PE, gestational diabetes mellitus (GDM), fetal anomaly and PPROM, and the complications such as uterine atony, abruptio placenta, postpartum hemorrhage (PPH), DIC and uterine rupture were assessed from the patients' files, hospital registry and operation notes. Women who experienced uterine atony, abruptio placenta, DIC, interventions for PPH such as B-Lynch suture, Bacri Balloon Tamponade, hypogastric artery ligation, re-operation, hysterectomy, uterine rupture, bladder injury, intraabdominal hemorrhage, and need for blood product transfusion were included in a group titled "Severe Obstetric Complication." Patients who experienced febrile morbidity, endometritis, retained placenta, the need for blood product transfusion in the post-partum period, wound infection or dehiscence, thromboembolic events, need for reoperation, and maternal death were enrolled in a group titled "Postpartum Complication". The sociodemographic characteristics and delivery outcomes of patients were compared between the two groups.

Statistical analysis

Statistical analysis was conducted using SPSS software, version 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Armonk, NY, USA). Shapiro Wilk test was performed to evaluate whether the variables were distributed normally. Non-normally distributed continuous variables were expressed as median (minimum-maximum), while categorical variables were presented as frequency and percentages. Mann Whitney U test was used to compare non-normally distributed continuous variables between two groups while Chi-square or Fisher's exact test was performed for categorical variables. Multivariate logistic regression analysis was used to predict risk factors for stillbirth. A *P*-value <0.05 was considered statistically significant.

Results

A total of 46019 births occurred during the study period. The number of stillbirths was 520, with a rate of 11.2:1000 births. Obstetric outcomes and maternal complications were increased, maternal age was significantly higher (P<0.001), hospital stay was longer (P<0.001) and birth weight were lower (P<0.001) in the stillbirth group. Moreover, the women in stillbirth group experienced more adverse perinatal complications such as fetal anomaly (P<0.001), PPROM (P<0.001), PE (P<0.001), GDM (P<0.001), abruptio placenta (P<0.001), uterine rupture (P<0.001), uterine atony (P<0.001), PPH (P<0.001) and DIC (P<0.001). The rates of severe obstetric and postpartum complications were 14.2% and 12.1%, respectively in the stillbirth group, both significantly higher than the livebirth group (P<0.001).

Individual investigation of severe obstetric complications revealed that hysterectomy was performed in six patients. Two of them were re-operated due to massive hemorrhage, and two patients underwent hysterectomy due to placenta accreta spectrum. Two patients were admitted to the adult intensive care unit due to massive bleeding and massive blood product transfusion.

No significant difference was found between stillbirth and control groups in terms of delivery type, baby gender, and the presence of placenta previa. The sociodemographic characteristics and perinatal features of the study population were presented in Table 1.

Estimated risks of stillbirth associated with risk factors were calculated by logistic regression analysis and demonstrated in Table 2. Compared with the control group, patients with fetal anomaly, GDM and abruptio placenta had a 3.1-fold (OR 3.170; 95% CI 1.592-6.315, $P<0.001$), 15.2-fold (OR 15.203; 95% CI 8.368-27.621, $P<0.001$) and 18.221-fold (OR 18.221; 95% CI 9.121-36.402, $P<0.001$) increased risk of stillbirth, respectively.

Table 1: The sociodemographic characteristics and perinatal features of the study population

	Stillbirth (n=520)	Live Birth (n= 6521)	*P*-value
Age (years)	28 (14-45)	24 (13-44)	<0.001[a]
Race (n, %)			<0.001[b]
• Turkish	358 (68.8%)	3933 (60.3%)	
• Foreign	162 (31.2%)	2588 (39.7%)	
Delivery Type (n, %)			0.313[b]
• Vaginal	330 (63.5%)	4281 (65.6%)	
• Cesarean	190 (36.5%)	2240 (34.4%)	
Hospital Stay (day)	3 (1-25)	2 (1-20)	<0.001[a]
Baby gender (n, %)			0.06[b]
• Male	286 (55%)	3303 (50.7%)	
• Female	234 (45%)	3218 (49.3%)	
Birth weight (gram)	1402 (500-5300)	3200 (500-5350)	<0.001[a]
Birth weight (n, %)			<0.001[b]
• >4000g	10 (1.9%)	287 (4.4%)	
• 2500-4000g	108 (20.8%)	5733 (88%)	
• 2500-1500g	125 (24%)	412 (6.3%)	
• 1500-1000g	103 (19.8%)	41 (0.6%)	
• 1000-500g	174 (33.5%)	48 (0.7%)	
Fetal Anomaly (n, %)	48 (9.2%)	27 (0.4%)	<0.001[b]
PPROM (n, %)	16 (3.1%)	46 (0.7%)	<0.001[b]
Preeclampsia (n, %)	41 (7.9%)	93 (1.4%)	<0.001[b]
GDM (n, %)	36 (6.9%)	73 (1.1%)	<0.001[b]
Abruptio placentae (n, %)	64 (12.3%)	24 (0.4%)	<0.001[b]
Placenta previa (n, %)	5 (1%)	26 (0.4%)	0.06[b]
Uterine Rupture (n, %)	4 (0.8%)	6 (0.1%)	0.001[b]
Uterine Atony (n, %)	11 (2.1%)	13 (0.2%)	<0.001[c]
PPH (n, %)	24 (4.6%)	58 (0.9%)	<0.001[b]
DIC (n, %)	40 (7.7%)	24 (0.4%)	<0.001[b]
Severe Obstetric Complications (n,%)	76 (14.6%)	188 (2.9%)	<0.001[b]
Postpartum Complications (n, %)	63 (12.1%)	143 (2.2%)	<0.001[b]

a: Mann-Whitney U test, b: Chi-square test, c: Fisher's exact test, DIC: Disseminated intravascular coagulopathy, GDM: Gestational diabetes mellitus, PPH: Postpartum hemorrhage, PPROM: preterm premature rupture of membranes

Table 2: Multivariate logistic regression analysis to predict risk factors for stillbirth

	P-value	Odds ratio	95% CI for Exp(B)	
			Lower	Upper
Age	<0.001	1.001	0.883	0.922
Race	0.931	0.988	0.752	1.298
Birth weight	<0.001	1.002	1.002	1.002
Fetal anomaly	0.001	3.170	1.592	6.315
PPROM	0.082	0.370	0.150	0.917
Preeclampsia	0.078	0.478	0.260	0.881
GDM	<0.001	15.203	8.368	27.621
Abruptio placenta	<0.001	18.221	9.121	36.402
Uterine Rupture	0.588	1.740	0.234	12.921

GDM: Gestational diabetes, PPROM: preterm premature rupture of membranes

Discussion

Stillbirth is the disastrous end of pregnancy. Despite the economic costs for the countries and the governments, the psychological consequences are tremendous for the families [9]. Almost 98% of the cases occur in low and middle-income countries, and one of the reasons for these high rates is difficulty of access to health care. The Millennium Development Goal has declared to decrease the stillbirth rates below 12 per 1000 births in all countries by 2030 [10]. Most of the developed countries have already reached that target nonetheless, approximately 23600 stillbirths occurred annually in America and the rates hardly decreased during the last decade [5]. The stillbirth rate of our hospital was 11.2 per 1000 births, which can be considered a success due to the millennium target. Our rates might be higher than those in the peripheral centers because of being a referral center in that region. Contemporary studies have reviewed the possible reasons for stillbirth. Evaluation of the stillbirth was suggested in terms of detailed medical and obstetric history, an autopsy of the baby, placental pathology, genetic evaluation, Lupus, feto-maternal hemorrhage diseases, infections, inherited thrombophilia, endocrinologic diseases [11,12]. Despite these all investigations, most stillbirths remained unexplained.

The purpose of the study was to determine the characteristics of the patients and the maternal outcomes of women who experienced stillbirth. These women were older than the controls however, the median age of the patients was 28 years. The rate of women ≥ 35 years old was 22%. Recent studies also reported that advanced age was related to stillbirth; however, it was not easy to determine the proper threshold age for stillbirth [13,14]. The quality of the oocytes diminishes with age, which might be the reason for the increment of stillbirth, along with the adverse maternal and neonatal outcomes. Birth weight was lower in the stillbirth group. The rates of the babies <1000gr and <1500 gr were 33% and 53% respectively. These rates were also crucial because the stillbirth rates tend to decline in the third trimester in America however, the rate remained stable in women who experienced stillbirth within the second trimester [15]. In almost 10% of the women in the stillbirth group, the babies had fetal anomalies. It was obvious that congenital anomalies were one of the main reasons of stillbirth [16], yet the reason for the high rate was that the women in our country did not accept termination of the pregnancy even if the anomaly was incompatible with life, due to cultural beliefs. Approximately 40% of the patients who gave birth in our hospital were Syrian immigrants. Ethnicity was thought as a cause in increasing stillbirth, such as the non-Hispanic black race [12]. Comparison of the groups in terms of race was significantly different; however, we did not find any significant differences between the Turkish and Arabic women in multivariate logistic regression analysis.

Delivery type of women who gave stillbirth and live birth did not differ significantly. Obstetric conditions such as abruptio placenta, placenta previa totalis, fetal presentation, cephalopelvic examination, and history of uterine scar were the main determinants of the management. Some authors depicted that the labor would start spontaneously within 1-2 weeks after the death of the fetus, yet we did not consider expectant management in any of our patients [11, 17]. Women were at risk of coagulopathy abnormalities unless the delivery occurred within 3-4 weeks after fetal demise [8,18]. Forty patients experienced DIC with a rate of 7.7% in this study. One of the reasons for the high rate of DIC could be related to the high number of patients with abruptio placenta and preeclampsia. Although the benefit of serial laboratory tests for DIC has not been exposed properly, between admitting the patient and the delivery, we obtain serial laboratory tests like fibrinogen, complete blood parameters, and prothrombin time daily.

We use misoprostol, dinoprostone, or oxytocin to initiate or augment uterine contractions. For women without history of uterine scar, 200-400 micrograms of misoprostol was administered every 4-8 hours interval via the vaginal or

sublingual route in the second trimester. An intra-amniotic balloon was used on the second day of the labor induction. Approximately 50 to 80 cc of saline solution was infiltrated into the balloon. Half dose of misoprostol was used in women with earlier uterine scars. Use of dinoprostone, misoprostol (with a dose of 25-50 microgram via vaginal or oral route every 4 hours) are recommended in patients without cesarean history. Oxytocin could be administered in women with or without earlier uterine scars in the 3rd trimester of gestation. We do not recommend prostaglandins for women with uterine scar history. Repeat cesarean operation is also preferable in these patients. Maternal wish for the delivery type is essential.

Considering that all adverse maternal outcomes, such as uterine atony, PPH, DIC, postpartum complications, and obstetric complications, were more frequent in the stillbirth group, expectant management was not appropriate for our clinic. All these complications differed significantly in stillbirth patients. Studies in the literature revealed that women with stillbirth had an increased risk of serious adverse maternal outcomes [19-22]. These complications occurred during the postpartum period, thus, early intervention such as utilizing uterotonics agent after the delivery, and reserving blood products before delivery might decrease their rate.

The factors increasing the risk of stillbirth were age, birth weight, fetal anomaly, GDM, and abruptio placenta. Preeclampsia was assumed as one of the biggest risk factors for stillbirth [2,22,23]. Women with stillbirth experienced preeclampsia more than the control group; however, the multivariate logistic regression analysis revealed that preeclampsia did not increase the risk of stillbirth. That could be related to the close follow up in prenatal care. Almost all women diagnosed with preeclampsia were hospitalized and utilized adequate treatment at our hospital. During hospital stay, these patients were informed about fetal well-being and obstetric emergencies. PPROM might be a risk factor for stillbirth, yet it was not always possible to distinguish whether the rupture of membranes was the reason or the result of stillbirth. Gestational diabetes mellitus and abruptio placenta increased stillbirth rate with the odds ratios 15 and 18, respectively. It was well known that pre-existing diabetes was associated with stillbirth and adverse maternal outcomes [7, 24]. Contemporary studies determined that GDM was related to stillbirth, similar to our study [6, 25]. Even the pathophysiology of the relationship between GDM and stillbirth could not be enlightened properly, the undoubted fact is that the glycemic control of the patients with GDM or preexisting diabetes would protect fetuses from mortality. Our study revealed that abruptio placenta was the most crucial cause of stillbirth, like those in the literature. Abruptio placenta not only causes stillbirth but also maternal adverse outcomes such as uterine atony, peripartum hysterectomy, and DIC, especially in delayed cases [8,17,26,27]. Approximately half of the placenta abruptio cases could not be detected by ultrasound, especially acute abruption [28]. We perform immediate delivery in the suspicion of placenta abruptio by clinical findings or ultrasonographic evaluation. Women with stillbirth had longer hospitalization periods. It is well known that pregnancy is a disease that predisposes to thrombosis. Prolonged hospital stay and immobility are the major risk factors for thrombosis. Patients should be encouraged to mobilize and utilization of low molecular weight heparin is essential to prevent embolism [29].

One of the aims of this study was to evaluate severe complications. Seventy-six patients (14.6%) experienced severe complications including hysterectomy, re-operation, blood product transfusion, and need for intensive care unit admission, which revealed that stillbirths should be delivered in fully equipped hospitals when possible.

Limitations

Despite its single-center nature, the number of patients included in each study group was high. Its retrospective design was a limitation, and we could not obtain the anthropometric parameters of the patients.

Conclusion

Stillbirth is a disaster for families. Delayed intervention could also cause serious maternal adverse outcomes. Abruptio placenta and GDM were the main risk factors for stillbirth. GDM screening and adequate glycemic control might protect the fetuses. Emergent delivery in abruptio placenta is crucial. The type of delivery should be tailored individually based on obstetric history, gestational week, and fetal conditions. To avoid embolism, mobilization and low molecular weight heparin should be administered.

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Single incision-two port laparoscopic tubal ligation versus conventional three port laparoscopic tubal ligation: A prospective comparative study

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Ethics Committee Approval
This study was approved by İstanbul Medipol University Faculty of Medicine Ethic Committee (01/2019/51-605).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Most women who have completed childbearing request tubal ligation, as it is an effective and irreversible form of contraception. Single incision laparoscopic surgery (SILS) which is currently standard in most surgical specialties, eliminates multiple port incisions and provides faster recovery with better cosmesis. However, there is less data about single incision laparoscopic bilateral tubal ligation. We aimed to compare the results of single-incision-two port laparoscopic tubal ligation and conventional three port laparoscopic tubal ligation.

Methods: Patients who desired tubal ligation procedure as a contraceptive method were randomly allocated to two groups as single-incision-two port laparoscopic tubal ligation (Group 1) and conventional three port laparoscopic tubal ligation (Group 2) between April 2015 to January 2020 in the Obstetrics and Gynecology clinics of two university hospitals. A prospective comparative study was conducted, and sixty patients were included in each group, which were compared in terms of operation time, blood loss, length of hospital stay, complications, port site hernia, postoperative pain score, conversion rate, cosmesis and failure of sterilization.

Results: There was no need to convert to open surgery in either group. Average blood loss was similar between the groups (107.6 ml vs 98.4 ml, P=0.14). Operating time was significantly longer in group 2 compared to group 1 (38 minutes vs. 26 minutes, P=0.02). Higher pain scores were observed in group 2 compared to group 1 at the 24th postoperative hour (2.21 vs 3.82, P=0.012). Patients in group 1 were more satisfied with the single incision in the umbilicus based on cosmetic outcome scores (4.88 vs 3.16, P=0.018). There were no reported intraoperative complications in either group. No port site hernias and failure of sterilization were observed in any of the patients. All patients were followed up for a mean of 19 months (range: 12–60 months).

Conclusion: Single incision two port laparoscopic tubal ligation does not increase the risk of complications and appears safe. It provides better cosmetic outcomes and lower pain scores compared to conventional laparoscopy.

Keywords: Single incision laparoscopy, Tubal ligation, Conventional laparoscopy

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Introduction

Minimally invasive approaches are currently standard in most surgical specialties. Single incision laparoscopic surgery (SILS) is the most recently developed method. It eliminates multiple port incisions and provides faster recovery with better cosmesis [1,2]. The first single incision laparoscopy was performed in gynecology for tubal ligation as a contraception method in the 1970s [2]. Then, ovarian cystectomies, myomectomies, even hysterectomy procedures were successfully performed with SILS all over the world [3-6]. Although less postoperative pain, better cosmesis and faster recovery are its main advantages over conventional laparoscopy and millions of women undergo tubal ligation for contraception worldwide each year, there is limited data on single incision-two port laparoscopic tubal ligation procedure in the literature. In Turkey, Taşdemir et al. [3] reported their experience of single incision two port laparoscopic tubal ligations on three patients. Our aim in this study was to compare the results of single-incision-two port laparoscopic tubal ligation and conventional three port laparoscopic tubal ligation.

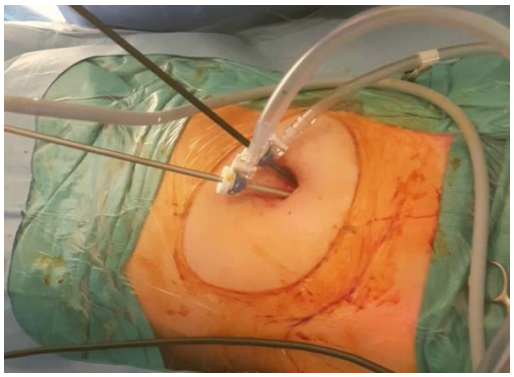
Materials and methods

In this prospective study, 120 patients who wanted tubal ligation procedure as a contraceptive method were randomly allocated to single-incision-two port laparoscopic tubal ligation (Group 1) or three port conventional laparoscopic tubal ligation (Group 2) at two tertiary centers from April 2015 to January 2020. This study was approved by İstanbul Medipol University Faculty of Medicine Ethic Committee (01/2019/51-605). Written and signed informed consent was obtained from each patient. Demographic features of patients, operation time, blood loss, length of hospital stay, complications, postoperative pain score, conversion rate, satisfaction of cosmetic outcome, port site hernia and failure of sterilization were recorded and compared. All procedures were performed by two surgeons experienced in minimally invasive endoscopic surgery, who perform two hundred laparoscopic cases annually.

One hundred and twenty patients aged 31 to 49 years (mean: 41.5 (4.16) years) were randomly assigned to undergo single-incision-two port laparoscopic tubal ligation (group 1, n=60) or three port conventional laparoscopic tubal ligation (group 2, n=60) according to a computer-generated table of random numbers. First, power analysis was conducted with definitive measurements to determine the size of the ideal sampling. The effect size was calculated according to VAS score, as d=0.80. The sample size was calculated as thirty-nine for both groups with an error level of 5% and a power of 95%. The number of patient populations reached a minimum of sixty for each subgroup. Patients for whom anesthesia would pose a high risk (score > III, according to an American Society of Anesthesiologists [ASA] score), those with histories of abdominal surgery, diagnosed with endometriosis and who underwent laparoscopic tubal ligation procedures concomitant with other gynecologic procedures like ovarian cystectomies, myomectomies, or ectopic pregnancies were excluded from the study.

All patients were prepared similarly in a lithotomy position under general anesthesia. No prophylactic antibiotic was administered. Patients in Group 1 were operated as first published by Taşdemir et al. [3]. A one cm vertical skin incision was made in the umbilicus with a scalpel. Then, a five-millimeter trocar was inserted through the abdominal cavity with a five-millimeter 30-degree camera. The 30-degree Trendelenburg position was maintained; pneumoperitoneum up to 15 mm Hg pressure with carbon dioxide insufflation was assured. Afterwards, a second five-millimeter accessory port was introduced through the same skin incision on a different fascial plane, one centimeter away from the first trocar (Figure 1). A five-millimeter endoscopic monopolar scissor was introduced into this accessory trocar; the proximal and mid-portion of the tubes were coagulated and cut with monopolar diathermy bilaterally. After trocars were removed, fascia was sutured with an interrupted 1-0 Vicryl (Ethicon, Istanbul, Turkey) suture. Umbilical skin was restored subcutaneously with 3-0 Rapid Vicryl (Ethicon, Istanbul, Turkey) suture. Patients in Group 2 were operated with conventional three port laparoscopy. Similarly, a 30-degree camera port was inserted into the umbilicus and two five-millimeter accessory ports were inserted above the inguinal crest. The mid portion of the tubes were retracted with a forceps through accessory port and the proximal and mid-portion of the tubes were coagulated and cut bilaterally with monopolar diathermy through the other accessory port.

Figure 1: The view of two 5-mm trocars inserted into single umbilical incision



Patients' demographic features, body mass index (BMI), operation time (calculating from the first umbilical skin incision to the end of suturing the umbilical skin), amount of blood aspirated from the operation field to the suction machine with excluded intraperitoneal washing liquid, number of accessory ports needed, intraoperative complications, length of hospital stay, pain score and cosmetic outcomes were analyzed and compared. Postoperative pain was assessed according to a visual analogue scale (VAS) from 0 (no pain) to 10 (worst pain imaginable) on the postoperative sixth and twenty-fourth hours [8]. A standard analgesic protocol was implemented with the use of an intravenous nonsteroidal anti-inflammatory drug (tenoxicam, 20 mg) twice a day. An opioid analgesic (tramadol, 50 mg) was added when patients experienced no relief from pain. Satisfaction with cosmetic outcomes was evaluated through face-to-face interviews with all patients, assessed on a scale from 1 (lowest satisfaction) to 5 (highest satisfaction) three months after the operation.

Statistical analysis

We used SPSS® software, version 20.0 (IBM Corp;2011; Armonk, NY) to analyze the collected data, which

were summarized as mean (range) or median (range). Patient demographic data, operating times, and hospital stays were compared using the parametric t-test. A nonparametric Mann-Whitney U test was used to compare pain scores and cosmetic outcomes, and a Fisher exact test was used for comparing complications. A *P*-value of 0.05 was considered statistically significant.

Results

A total of 120 patients were enrolled in this study from April 2015 to January 2020. The patients' characteristics are presented in Table 1. The two groups were similar in terms of age, caesarean section histories, ASA scores, and BMI. Sixty single-incision-two port laparoscopic tubal ligation (group 1, n=60) and sixty conventional three port laparoscopic tubal ligation (group 2, n=60) procedures were successfully completed; there was no need to convert to open surgery in either groups. Two cases in group 1 and one case in group 2 required one extra port due to severe intraabdominal adhesions. However, it was not statistically significant (P=0.24).

Table 1: Patients' characteristics

Characteristic	Group 1	Group 2	*P*-value*
Age(years)	41.5(2.16)	40.5(3.12)	0.23
BMI (kg/m2)	27.6(5.16)	28.4(4.58)	0.22
C/S (n)	2.1(2.26)	2.4(2.66)	0.31
ASA score	1.88(0.56)	1.76(0.48)	0.24

Values are presented as mean (standard deviation). * Paired t test was used, ASA: American Society of Anesthesiology, BMI: Body Mass Index

There were no complications during surgery such as bleeding, vessel, or bowel injury in either of the groups. Average blood loss was similar between the groups. Operating data are shown in Table 2. Operating time was significantly longer in group 2 compared with group 1 (38.5 minutes vs. 26.5 minutes; P=0.02). Higher pain scores were observed in group 2 versus group 1 at the 24th postoperative hours (P<0.05). Two umbilical port site infections in group 2 were treated with antibiotherapy. Port site hernia and failure of sterilization was not observed in any of the groups during a mean follow-up of 19 months (range, 12–60 months). Cosmetic outcome scores showed statistically significant differences between the groups (P<0.05). Patients in group 1 were more satisfied with the single incision into the umbilicus (Table 3).

Table 2: Operation data

Variable	Group 1	Group 2	*P*-value*
Operating time(min)	26.5 (2.16)	38.5(3.12)	0.02
Blood loss(ml)	107.6(5.16)	98.4(8.58)	0.14
Conversion	0	0	1.00
Need to extra port(n)	2	1	0.24

Values are presented as mean (standard deviation). *Paired t test was used.

VAS pain scores of patients in group 2 was significantly higher compared to group 1 at the sixth and twenty-fourth postoperative hours.

Correlation between operative time and VAS score was assessed. Pearson correlation test showed that the pain score correlated with operative time (P<0.001). Postoperative data are shown in Table 3.

Table 3: Postoperative data

Variable	Group 1	Group 2	*P*-value*
VAS**	3.25(1.16)	4.52(1.12)	0.031
VAS***	2.21(1.08)	3.82(2.14)	0.012
Narcotic analgesic use(n)	0	4	0.001
Hospitalization(day)	1.1(0.26)	1.4(0.66)	0.320
Cosmetic result	4.88(1.56)	3.16(0.98)	0.018

Values are presented as mean (standard deviation), * Mann Whitney U test was used, ** Sixth postoperative hour visual analogue scale, *** First postoperative day (24th hour) visual analogue scale

Discussion

Tubal ligation procedure accounts for about 10-40% of all contraceptive methods worldwide [7]. We performed at least one hundred laparoscopic tubal ligation procedures with three ports annually up to mid-2015 in our hospital. In this study, we tried to compare safety and efficacy of single incision two port laparoscopic tubal ligation with conventional three port laparoscopic tubal ligation. SILS provides better cosmesis, less trauma, less blood loss and less pain [4,6]. A single incision laparoscopic tubal ligation is an easier and less technically challenging procedure when compared with ovarian cystectomy, myomectomy, and hysterectomy procedures performed with single incision laparoscopy. The rapid development in medical technology has enabled surgeons to adopt laparoscopy rapidly. Even tubal ligation procedures are performed under local anesthesia with microlaporoscopy or office laparoscopy in some centers [7]. Laparoscopic tubal ligation is an effective birth control method. However, physicians should inform all couples about the rates of failure. We try to pay attention to coagulate and cut especially two portions of the tubes (the proximal and mid portion) bilaterally in both techniques. During a mean of 19 months follow up, we did not encounter failure of sterilization with either of the two methods. In a series of 1000 laparoscopic sterilizations performed with only one incision and electrocoagulation without cutting, the total failure rate was 1.6% [8]. The probable reason of failure after laparoscopic tubal ligation is incomplete transection, which causes recanalization after a while [8]. Studies showed that electrocoagulation offers slightly less failures when a substantial part of the tube or two segments are destroyed by experienced hands [9]. The mean age of the study population was 45 years with the range of 35 to 52 years in our study. Age is important for deciding on the contraceptive method as some young patients may regret this decision later. The methods for laparoscopic sterilization include silicone rubber rings, silastic band, spring clip and Filshie clip application, all of which offer a better chance of reversal comparative to laparoscopic electrocoagulation [9,10]. No patients regretted their decision in our study population. A significant concern about SILS is the risk of trocar site hernia [11]. It was reported as 2.2% in a randomized controlled trial including 1705 patients, while this rate was 0.7% in the conventional laparoscopic surgery group (odds ratio 2.26, 95 % confidence interval 1.00–5.08, P=0.05) [11]. The main advantage of single incision two port laparoscopic technique as performed in group 1 is that there is no need of using an access device like SILS port™ (Covidien, Mansfield, Massachusetts) , R- Port™ (Advanced Surgical Concepts, Wicklow, United Kingdom), Octoport™ (Dalim, Seoul, Korea) and GelPort™(Applied Medical, USA). Although the marketing of these new access devices allowed surgeons to use more than two instruments and an endoscope through the umbilical port only, the total cost of surgery and risk of umbilical site hernia increased significantly. In addition, single port laparoscopic surgery is more challenging due to limitations of triangulation and frequent collisions between instruments [12]. However, insertion of a second trocar 1 cm away from the optic trocar through a different fascial plane facilitates the triangulation of instrument in this technique. It also improves cosmetic outcomes,

as documented in Table 3**.** Deviation of the uterus contralaterally by an assistant with manual manipulation into the vagina will facilitate the visualization of the tubes. Hence, there is no need of inserting the third trocar for retraction of the tuba. If significant difficulty is encountered at any time during the surgery, an additional port should always be considered. Although less data is currently available about the single incision two port laparoscopic tubal ligation in the literature, the overall complication rate is low and the technique seems safe. Like gynecologists, general surgeons have used this technique since 1997 for cholecystectomy and appendectomy procedures [14-16]. Their studies also support the feasibility and safety of the procedure with no major complications reported.

Limitations

Our limitations include reflecting the experience of two centers only, and small number of cases. Also, feasibility and safety of the procedure depends on physician experience and skill in laparoscopy. SILS surgery may need more experience compared to conventional laparoscopic three port surgery.

Conclusion

Single incision two port laparoscopic tubal ligation does not increase the risk of complications and appears safe. It provides better cosmetic outcomes, which may be important for female patients. When it is performed by experienced surgeons, it is as successful and safe as conventional laparoscopic tubal ligation. However, further, multicenter, comparative studies with larger series are necessary to evaluate the safety and feasibility of this technique.

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Nerve sparing feminizing genitoplasty with corporal septum excision in non-classic congenital adrenal hyperplasia

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Ethics Committee Approval
Ethical committee approval was obtained from Istanbul Medipol University, Faculty of Medicine Ethical Committee (Aproval number: 36423-11.08.2018).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

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

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Abstract

Background/Aim: Non-classic congenital adrenal hyperplasia (CAH) is a milder form of CAH. The CYP21A2 gene is involved in the etiopathogenesis of both severe (classic) and mild (non-classic) form CAH, however, genetic mutations in non-classic CAH result in less impairment of 21-hydroxylase activity. Therefore, as in classic CAH, patients with non-classical CAH have no signs and symptoms of cortisol deficiency. Instead, there may be signs of hyperandrogenism that can appear later in childhood or in early adulthood. Due to excess androgenic effect on clitoris, labia minora, majora and the vagina, feminizing genitoplasty should be performed to make gender identities consistent and reshape the proper genital anatomy for sexual intercourse. However, there are few studies and controversy on feminizing genitoplasty procedures in adulthood. In this study, we aimed to design a new procedure to spare the nerves of the clitoris as well as the clitoral body, along with the cavernous tissue.
Methods: This is a case series of nine patients with a mean age of 24.8 years diagnosed with non-classic CAH who underwent feminizing genitoplasty, in which nerve-sparing clitoroplasty was performed with corporal septum excision by ventral approach. Initially, diagnostic cystoscopy was performed to detect the level of vaginal confluence into the urogenital sinus. The enlarged clitoris was degloved from 10 mm proximal to the glans up to the symphysis pubis. Corporal septum was excised from the ventral part of the clitoris up to the bifurcation of crura. Neurovascular bundle was preserved completely dorsally, and the clitoris was folded over itself and fixed at the level of crural bifurcation at 3 and 9 o'clock positions. Degloved clitoral preputium was used as Byars' flaps for labiaplasty. A perineal inverted U incision was made and the vaginal introitus was enlarged with this flap. Female Genital Image Scale (FGIS) was used in the assessment of patients' postoperative genital self-image.
Results: Feminizing genitoplasty (nerve-sparing clitoroplasty with corporal septum excision, labiaplasty and perineal flap vaginoplasty) was performed in nine patients diagnosed with non-classic CAH. The mean operation time was 112 minutes with a range of 90-140 minutes. Urogenital sinus mobilization was not performed as the vaginal confluence into urogenital sinus was low in cystoscopy. Patients were re-assessed at 1 month, 3 months and 6 months postoperatively. FGIS scores showed that four patients were "very satisfied," one patient was "satisfied," 2 patients were "moderately satisfied", and one patient was "dissatisfied." The maximum follow-up was 2 years with no recorded short or long-term complications.
Conclusion: Nerve sparing clitoroplasty with corporal septum excision is a good option with satisfactory long-term results for non-classic CAH patients. However, we need many more comparative studies to decide the gold standard method for optimal physiologic and cosmetic outcomes in CAH patients.

Keywords: Feminizing genitoplasty, Congenital adrenal hyperplasia, Clitoroplasty

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Introduction

Congenital adrenal hyperplasia (CAH) is the most common sexual development disorder of individuals with 46XX genotype [1]. The incidence of CAH is one in 15,000 newborns [2]. A number of enzymatic defects in the production of cortisol cause a shunting of cortisol precursors to an alternate metabolic pathway, which results in an excess production of adrenal androgens (i.e., DHEA, androstenedione, and testosterone). 21-hydroxylase deficiency is the most common enzymatic defect, and a wide array of clinical features can be observed according to the level of impairment in cortisol and aldosterone biosynthesis [3]. There are three clinical phenotypes as follows: Classic salt-wasting (most severe), classic non-salt-wasting (simple-virilizing), or non-classic (mild or late-onset). Non-classic CAH is a milder form of the disease**.**

There is a close relationship between genotypic CYP21A2 mutations and phenotype [4]. However, genetic mutations associated with non-classical CAH result in less impairment of 21-hydroxylase activity. In the most severe form, concomitant aldosterone deficiency leads to salt wasting, while patients with non-classic CAH do not have cortisol deficiency. They have signs and symptoms of hyperandrogenism that are seen later in childhood or early adulthood. Although it is a milder form of the disease, they cannot have sexual intercourse without a feminizing genitoplasty procedure. Hirsutism, clitoromegaly, voice thickening, masculine muscle structure are other important problems of non-classic CAH female patients. The main aim of treatment in female patients with mild or non-classic CAH is controlling excess androgen and transforming its virilizing effect to feminizing. However, the surgical method for feminizing genitoplasty is controversial. We aimed to share our experience on nerve sparing feminizing genitoplasty with corporal septum excision in non-classic CAH patients.

Materials and methods

We retrospectively reviewed the files of nine female patients diagnosed with mild CAH who underwent feminizing genitoplasty at two university hospitals between 2012-2020. All patients were married with a mean age of 24.8 years (range: 21 - 32 years) and presented with enlarged clitoris with inability to have sexual intercourse. Physical exam revealed clitoromegaly, vaginal stenosis and increased perianal distance (Figure 1). The uterus and ovaries were normal in pelvic ultrasound. Chromosome analysis was performed in all patients and resulted as 46XX. Their medical therapy was planned by an endocrinologist. They did not start cortisol replacement, and instead, Spironolactone, an aldosterone antagonist, was administered for its anti-androgenic effect. Ethinylestradiol and cyproterone acetate combination was added to medical therapy to speed up the regression of the virilizing signs and symptoms. Ethical committee approval was obtained from Istanbul Medipol University, Faculty of Medicine Ethical Committee (Approval number: 36423-11.08.2018). All patients read and signed the informed consent forms.

Surgical technique

All patients were operated under general anesthesia and the procedure began with diagnostic cystoscopy to exclude high confluence of urogenital sinus. Then, a 14F urinary catheter was inserted into the bladder, and the perianal trigone was marked with a sterile pencil (Figure 2a). A stay suture was placed for traction at the 12 o'clock position on the glans (Figure 2b). A circumcisional incision was made 10 mm proximal to the glans dorsally and 2 mm ventrally all around the shaft. The clitoris was degloved from 10 mm proximal to the corona up to the symphysis pubis (Figure 2c). Corporal septum was excised ventrally up to the bifurcation of crura (Figure 2d). Neurovascular bundle was preserved completely dorsally. The clitoris was folded over itself and fixed at the level of crural bifurcation at 3 and 9 o'clock positions (Figure 2e). Degloved clitoral preputium was used as Byars' flaps for labia minora reconstruction (Figure 2f). Then, a perineal inverted U incision was made, with which the vaginal introitus was enlarged (Figure 2g). A vaginal tamponade with estrogen cream was inserted into the vagina (Figure 2h).

Figure 1: Preoperative appearance of the external genitalia of a non-classic CAH patient

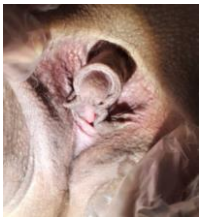
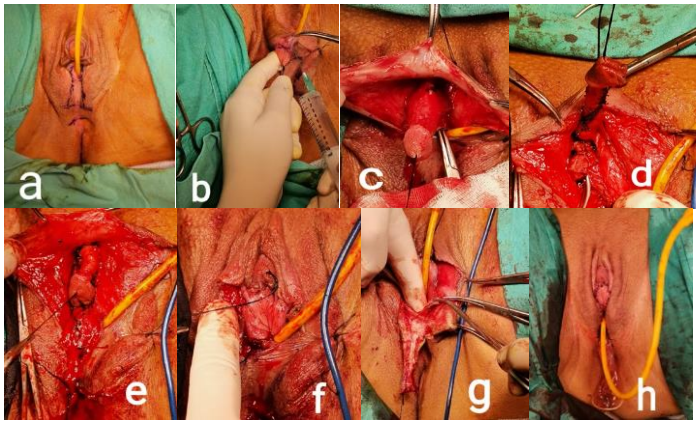


Figure 2: Step by step nerve sparing feminizing genitoplasty with corporal septum excision procedure



Patients were hospitalized for two nights. Control examinations were performed at one week, six weeks and three months postoperatively. Vaginal mold tamponade and urethral catheter were removed at the control examination at the first postoperative week. Female Genital Image Scale (FGIS), including 12 items, was used for the patients to rate their genital satisfaction along a five-point Likert-type scale from 1 = "Very satisfied" to 5 = "Very dissatisfied" at the control examination at three months postoperatively [5].

Results

Feminizing genitoplasty (nerve sparing clitoroplasty with corporal septum excision, labiaplasty and perineal flap vaginoplasty) was performed in nine patients diagnosed with non-classic CAH. The mean operation time was 112 minutes with a range of 90-140 minutes. Urogenital sinus mobilization was not performed as the vaginal confluence into urogenital sinus was low at cystoscopy. Preoperative mean clitoral size was 7.2 cm (6.8 cm-8.8 cm), which decreased to a mean of 2.3 cm (1.2 cm-2.6 cm) postoperatively. All patients started sexual

activity 8 weeks later. FGIS scale scores obtained three months later showed that four patients were “very satisfied,” one patient was “satisfied,” two patients were “moderately satisfied,” and one patient was “dissatisfied” (Table 1). The mean follow-up period was 13 months with a range of 8 to 26 months. There were no significant short- or long-term complications.

Table 1: Patients’ FGIS scale scores

FGIS scale	n (%)
1-Very Satisfied	4(44.4)
2- Satisfied	1(11.1)
3-Moderate	2(22.2)
4-Dissatisfied	1(11.2)
5-Very Dissatisfied	1(11.1)

Discussion

Females with classic CAH are usually diagnosed at birth with noticeable penis-like appearance of the clitoris. In-utero exposure of excess fetal adrenal androgens lead to clitoral enlargement. On the other hand, females with non-classic CAH are not diagnosed so early. They are usually diagnosed later in childhood or early adulthood. Most cases are referred to the physicians due to inability to have sexual intercourse when they get married. Their internal genitalia are anatomically female, and they have regular or irregular menstrual cycles. Their phenotype is influenced by the severity of the CYP21A2 mutations and 21-hydroxylase enzyme defect, leading to virilization of the external genitalia at varying levels. Physicians should be informed about the other conditions that can cause enlargement of the clitoris, such as exogenous in-utero androgen exposure due to the pregnant mother suffering from masculinizing tumors such as arrhenoblastoma [Ovarian Sertoli-Leydig cell tumors (SLCTs)] of the ovary or exogenous topical androgen use [6-8]. Some reports state that clitoral enlargement can be secondary to neurofibromatosis [9]. Another important condition causing idiopathic clitoromegaly in females is prematurity [10].

The main purpose of feminizing genitoplasty procedure is providing a proper width vaginal introitus and decreasing clitoral size to obtain a feminine genital appearance. It is documented in some studies that the clitoral length may vary according to ethnicity, like penile length [11]. However, the normal range for each ethnic race is not determined precisely. Considering our country, the mean clitoral length of Turkish newborns was reported as 4.93 (1.61) mm in a research [12]. Our study populations’ preoperative mean clitoral length was 7.2 cm. The clitoris is attached by the suspensory ligament to the front of the symphysis pubis]. However, the size of free part varies considerably as it has cavernous tissue [13]. For example, the clitoral body is 1–3 cm long in the flaccid state [14]. A physician first suspects clitoromegaly on physical examination. It is currently defined as a clitoris longer than 1 cm in newborns [15]. Parity can also affect clitoral size but age, body mass index and oral contraceptive use do not [16]. The most important step while reducing clitoral size is to preserve the neurovascular bundle of the clitoris. Poppas et al. described the nerve sparing ventral clitoroplasty procedure [17]. They examined the nerves in situ using optical coherence technology**.** Many women who underwent infant genitoplasty in 1980s were mutilated because the importance of clitoral sensation was not known at the time [18]. Old surgical techniques are no longer used, while nerve-sparing clitoroplasty has become widely adopted since the 2000s. The infants operated with old techniques report decreased sensation of the clitoris, and some of them are anorgasmic [19]. One study found the rate of anorgasmia to be as high as 40% [20].

Extensive clitoral resection should not be performed. A clear understanding of clitoral anatomy is important for surgical reconstruction. As in the human penis, nerves in the clitoris form an extensive network around the tunica of the dorsal corporeal body. The nerve-free zone is found in the midline, at 12 o'clock position [21]. For this reason, operation starts with a traction suture placed on clitoral glans at 12 o’clock. Nowadays, more effort is made to preserve nerves, which we also hoped to achieve with dorsal nerve-sparing clitoroplasty. In addition, we did not completely remove the corpus cavernosum ventrally. The human clitoris has two corporeal bodies that are smaller but analogous with the penis. A fibrous midline septum exists on the ventral aspect and extends approximately halfway into the glans [21]. We tried to excise this septum to be able to fold the clitoris over itself, hence decreasing clitoral size while preserving the corporal body.

To the best of our knowledge, this is the first study reporting dorsal nerve-sparing clitoroplasty performed on non-classic CAH adult females, because most studies are conducted on classic CAH during the newborn or childhood period. We could assess patients’ postoperative cosmetic and functional outcomes with FGIS more clearly as they were all sexually active adults. There were two major limitations to this study. One was the small sample size and the other, lack of a control group.

Conclusion

Nerve sparing clitoroplasty with corporal septum excision may be a good option with satisfactory long-term results for non-classic CAH patients. However, we need more comparative, multicenter studies to determine a gold standard method for achieving the optimal physiologic and cosmetic outcome in CAH patients. In the future, we hope to improve surgical techniques to preserve the corporal body in addition to nerve bundle.

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Serum adropin and nitric oxide levels in missed abortus cases

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All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Missed abortus is an emergency obstetric pathology, defined as intrauterine fetal viability loss before the 20th week of pregnancy. It is known that there is a correlation between endothelium dysfunction, neovascularization, hemodynamic regulation and adropin and nitric oxide levels. In this study, it is intended to research the possible roles of adropin and nitric levels in etiopathogenesis.

Methods: In this case-control study, a total of fifty-nine volunteers, including healthy pregnant women and missed abortion cases, were included in the study. They were divided into 2 groups, as healthy individuals (Group 1, n=29), and those diagnosed with missed abortus (Group 2, n=30). Group 2 patients were followed weekly until β-HCG values fell below 5 ng/ml after termination. Serum adropin and nitric oxide levels were measured in all participants and those diagnosed with missed abortion when negative β-HCG value was obtained after termination.

Results: Serum adropin and nitric oxide levels were significantly low in the missed abortus group (P=0.03) compared to healthy pregnant women, and in the missed abortus group compared to those whose β-HCG fell below 5 ng/ml after termination (P=0.02), while nitric oxide levels were similar in the latter comparison (P=0.38). Regarding age, body mass index, obstetric parameters, and other biochemical parameters, the two groups were similar (P>0.05 for each).

Conclusion: This is the first research which evaluates adropin levels in missed abortus cases. Lower adropin and nitric oxide levels in missed abortus cases, and their increase after post-termination show that they may be playing a role in abortus etiopathogenesis.

Keywords: Missed abortus, Adropin, Nitric oxide

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Introduction

Missed abortus is an emergency with intrauterine fetal viability loss and diagnosed with no fetal cardiac activity in ultrasonography. Clinically, 12-15% of the noticed pregnancies are concluded with abortus between the 4th and 20th weeks. According to the World Health Organization, the disposal of all embryo, fetus, and their counterparts out of the uterine cavity before the 20th week of pregnancy and/or the newborn weighing less than five hundred grams is called abortus [1]. Besides vaginal bleeding, missed abortus cases have an important place in terms of obstetric practice due to maternal obstetric complications. The treatment of missed abortus is emptying the uterus surgically or medically. In pathological examination, hemorrhage into decidua basalis and necrotic changes with degenerations on placental villi can be seen. Fetal, maternal, and paternal causes are in the etiopathology. Malformations, and chromosomal anomalies in the fetus, and immunological causes, endocrine defects, uterine anomalies, drug use, environmental factors and trauma in the mother are among the causes [2]. Besides these known factors, vascular endothelial damage may cause ischemic damage progression by preventing the implantation of fetus to the endometrium or preventing the development of the fetus by inhibiting placental functions, therefore any situation that causes vasoconstriction may result with missed abortus.

Adropin is a peptide hormone composed of seventy-six amino acids. First defined by Kumar et al. [3] in 2008, it plays a role in protecting endothelial functions, vascular hemostasis, and neovascularization. It has a half-life of 3 to 30 minutes. Its effect on the endothelium is first studied by Lovren et al. [4] in 2010 and results attesting these hypotheses were obtained. In the study of Dong Lin et al. on hypertensive diseases complicating pregnancy, serum adropin levels were low in this group and its determination in the early days of the pregnancy allowed the detection of risky patients [5].

Nitric Oxide (NO) has a noticeably short half-life (2-30 seconds) due to its free radical structure, remarkably high affinity, a low molecular weight, and is reactively secreted. Beginning with smooth muscle relaxation, it plays major roles in physiologic and pathophysiologic pathways. With its vasodilator effect, it increases local blood flow, regulating blood pressure and protecting endothelium. Independent of receptors, it can diffuse easily through the membranes. With all its properties, NO is an ideal messenger [6,7].

In the light of this information, we think that in addition to their protective nature on endothelial structure and function, due to their angiogenetic, smooth muscle relaxant and vasodilator effects, both adropin and nitric oxide may play a role in the implantation and growing of fetus, perfusion of placenta and continuation of it functions. Thus, they may be involved in the etiopathogenesis of missed abortus.

Materials and methods

This case-control study was conducted in July 2016 - October 2016 in Kafkas University Medical Faculty Training and Research Hospital, Gynecology & Obstetrics Clinic. It was started after the approval of Kafkas University Medical Faculty Ethics Committee was obtained, dated 25.05.2016 (Decision No: 6). The patients were informed about the study, and they all signed informed consent forms before the start.

Twenty-nine healthy pregnant women under 20 weeks of gestation (Group 1) with no complaints or ailments and 30 patients (Group 2) diagnosed with Missed Abortus for the first time were included in the study (n_{total}=59). Missed abortion cases in Group 2 were terminated and followed weekly until the β-HCG value fell below <5 ng/ml. Serum adropin and nitric oxide levels were researched for healthy pregnant women, missed abortus cases whose β-HCG did and did not decrease below 5 ng/ml.

People with abortus history, cigarette-alcohol consumption, teratogen drug use, endocrinologic-hematologic diseases, uterine anomalies, a space-occupying lesion in the uterus, trauma history, cases with infection findings, systemic diseases like DM and HT and the ones in the missed abortus group with poor general condition and DIC were excluded from the study. Demographic data (age, gravida, parity, abortus and curettage), BMI, pregnancy weeks of the cases were noted. All cases' complete blood count parameters (hemoglobin, hematocrit, white blood cells, platelet), fasting blood sugar, TSH, Free T3, Free T4, ALT, AST, Urea, Creatinine, Prothrombin Time (seconds) and INR, and Active Partial Thromboplastin Time levels were evaluated.

Collection of blood samples

Five milliliters of fasting venous blood samples were obtained from the cases in the morning between 08:00-10:00. Hormonal and biochemical measurements obtained from the venous blood samples were studied on the same day. Also, to prevent the disintegration of peptides, the serums were centrifuged, stored in -80°C in tubes washed with aprotinin until analyzed.

Adropin and NO level measurement procedure

On the study day, after being melted in the room temperature, samples were analyzed in Fırat University Hospital Medical Biochemistry Laboratory using the ELISA procedure with ready-made commercial kits (Human Adropin AD ELISA Kit, EASTBIOPHARM CO LTD, Inc. Code:ck-e90267 and Human Nitric Oxide NO ELISA Kit, EASTBIOPHARM CO.LTD, Inc. Code: CK-E11333) per the instructions of the manufacturer. The reference ranges for adropin and nitric oxide were 5-1000ng/L and 2-600 μmol/L, respectively.

Statistical analysis

SPSS 20.0 package program was used for statistical analyses. Continuous variables were expressed as median (25-75 percentage) and standard deviation according to their distribution. Independent variables were compared with T-Test and Mann Whitney U Test, while Wilcoxon Test was used to compare dependent variables. The relationship between studied parameters was assessed with Pearson and Spearman correlation analysis. In power analysis, a sample size of 59 individuals, including 29 controls and 30 patients, had α=0.05, 1- β=0.85 and d=0.8. A *P*-value of <0.05 was considered statistically significant.

Results

Twenty-nine healthy pregnant women before the 20th gestational week with no complaints (Group 1) and thirty cases who were diagnosed with missed abortus for the first time (Group 2) were included in the study, with a total of fifty-nine volunteers. The missed abortus cases underwent dilation and curettage, and were followed up until their β-HCG levels fell below 5 ng/ml. In these patients, when β-HCG levels became negative, their physiology and metabolism is likely similar to those of non-pregnant women.

Demographic and obstetric attributes of groups

No significant differences were found between the groups in terms of age (*P*=0.92), gravida (*P*=0.14), parity (*P*=0.48), number of living children (*P*=0.20) and body mass index (*P*=0.06) (Table 1).

Laboratory parameters

The hemoglobin (*P*=0.72), hematocrit (*P*=0.26), thrombocyte (*P*=0.10), leucocyte (*P*=0.31), fasting blood sugar (*P*=0.20), ALT (*P*=0.11), AST (*P*=0.10), Urea (*P*=0.85), Creatinine (*P*=0.24), TSH (*P*=0.73), Free T4 (*P*=0.06), Free T3 (*P*=0.08), Prothrombin Time second (PTZsec) (*P*=0.32), Prothrombin Time INR (PTZinr) (*P*=0.66), Active Partial Thromboplastin Time (aPTT) (*P*=0.12) levels were similar between groups 1 and 2 (Table 2).

Table 1: Demographic and obstetric features of the groups

Variable	Healthy Pregnant (Group 1) (n=29)	Missed Abortus (Group 2) (n=30)	*P*-value
Age	27.9 (6.1)	27.8 (6.1)	0.92
Gravida	2.3 (1.6)	2.9 (1.8)	0.14
Parity	0.9 (1.2)	1.6 (1.3)	0.48
Number of living children	0.8 (0.9)	1.5 (1.1)	0.20
Body Mass Index	24 (3.5)	25.2 (4.5)	0.06

Median (standard deviation), Statistical significance P<0.05

Table 2: Biochemical features of healthy pregnant women and missed abortion cases

Variable	Healthy Pregnant (Group 1) (n=29)	Missed Abortus (Group 2) (n=30)	*P*-value
Leukocyte (10^3)	7.5 (2.1)	8.9 (2.5)	0.31
Hemoglobin (g/dL)	12.8 (1.3)	12.9 (1.1)	0.72
Hematocrit (%)	38.1 (3.5)	39.1 (3.4)	0.26
Thrombocyte (10^3)	253 (60.3)	285 (85.4)	0.10
ALT (U/L)	18.3 (8.9)	14 (8.8)	0.11
AST (U/L)	17.9 (3.4)	16.5 (3.3)	0.10
Glucose (mg/dL)	90.6 (16.2)	96.7 (19.6)	0.20
Urea (mg/dL)	18.4 (5.8)	18.7 (5.7)	0.85
Creatinine (mg/dL)	0.6 (0.1)	0.6 (0.1)	0.24
TSH (IU/mL)	2.1 (1.4)	1.6 (0.1)	0.73
Free T3 (ng/dL)	3.1 (0.9)	3.7 (1.4)	0.08
Free T4 (ng/dL)	0.1 (0.2)	0.9 (0.1)	0.06
PTZsec (sec)	12.1 (1.1)	12.4 (1.4)	0.32
PTZinr (sec)	0.1 (0.1)	0.1 (0.1)	0.66
aPTT (sec)	99.9 (5.9)	103.5 (10.8)	0.12

Median (standard deviation), Statistical significance P<0.05

Comparison of adropin and nitric oxide levels

Adropin (*P*=0.03) and NO (*P*=0.04) levels were significantly lower in missed abortus cases compared to healthy pregnant women (Table 3).

Comparison of adropin and NO levels among missed abortion cases, between patients whose β-HCG values did and did not fall below 5 ng/ml after termination

The adropin and NO levels of missed abortus patients were lower than those whose β-HCG levels fell below 5 ng/ml after termination. The difference between adropin levels was significant (p=0.02), while that between nitric oxide levels was not (p=0.38) (Table 4).

Table 3: Adropin and NO levels in healthy pregnant women and missed abortus cases

Variable	Healthy Pregnant (Group 1) (n=29)			Missed Abortus (Group 2) (n=30)			*P*- value
	Median	IQR 25%	IQR 75%	Median	IQR 25%	IQR 75%	
Adropin (ng/L)	71.1	53.2	160.4	61.8	35.1	79.3	0.03
NO (μmol/L)	84.1	59.5	225.7	60.6	41.8	86.7	0.04

IQR: Inter quartile range

Table 4: Adropin and NO levels in cases of missed abortion and missed abortion cases where β-HCG blood value fell below 5 ng/ml after termination.

Variable	Group 2 Missed abortion (n=30)			Group 2 Missed abortion cases β-HCG blood value falls below <5 ng/ml after termination (n=30)			*P*-value
	Median	IQR 25%	IQR 75%	Median	IQR 25%	IQR 75%	
Adropin (ng/L)	61.8	35.1	79.3	124.8	40.3	175.5	0.02
NO (μmol/L)	60.6	41.8	86.7	76.9	40.4	172.1	0.38

Discussion

Even though there is intrauterine fetal viability loss in missed abortus cases, just like the other abortus types, because of the lack of cervical dilatation, expired fetal material may not be completely expelled. This may lead to serious metabolic complications of the mother, including coagulation defects and bleeding. The most lethal complication is disseminated intravascular coagulation. The risk of DIC is directly associated with gestational age and the time passed after the death of the fetus. Today, numerous factors have been defined about the etiopathogenesis of missed abortus, but it is still researched as an up-to-date topic.

Adropin, a newly discovered peptide, is spotted in liver, brain, kidney, heart, pancreas, muscle, vascular endothelial cells, and human umbilical vein endothelial cells [4, 8, 9-11]. It plays a role in preserving endothelial function, vascular hemostasis, and neovascularization. Primarily starting with relaxing the smooth muscles, NO affects by increasing local blood flow, regulating systemic blood pressure, and preserving endothelium with its powerful vasodilator effect [6].

It is known that endothelial nitric oxide synthase (eNOS) enzyme plays a role in the maintenance of vascular physiology and placental vascularization [12]. Adropin upregulates the expression of eNOS (VEGFR2) with the -phosphatidylinositol3-kinase-AKt pathway, increasing endothelial NO production, thus supporting the endothelial function, and protecting perfusion and angiogenesis [4].

In a study on the effect of adropin on the endothelium with Balb/c mice by Lovren et al. [4], high proliferation in endothelial cells and conversion to capillary tube form were seen with exogenous administration of adropin. The results show that adropin has a protective and integrity-providing role in the endothelium. Again, in patients with Type 2 diabetes mellitus with known endothelial dysfunction, low levels of adropin were found, which showed a relationship between adropin and endothelial dysfunction [13]. In the study of Dong Lin et al., serum adropin levels were low in patients with hypertensive diseases that complicate pregnancy [5]. As is known, hypertension is related to endothelial dysfunction and placental vascular dysfunction is one of the causes of preterm labor [14]. Studies show that eNOS plays a pivotal role in placental vascular function [15]. Low levels of Adropin in the circulation and thus low NO production can cause placental dysfunction and preterm labor [11].

By the result of our study, it can be said that pregnancies end with missed abortus due to significantly low levels of adropin and NO, endothelial dysfunction, vascularization defects and perfusion defects secondary to vasoconstriction. The fact that adropin and NO levels are increased as β-HCG becomes negative after termination in missed abortus cases supports our idea. Low levels of adropin and NO in missed abortion cases may play a role in etiopathogenesis, but the significance in the difference of adropin levels show that adropin may be even more crucial in this mechanism compared to NO.

In a study by Paradisi et al. [16], compared to healthy pregnant women, serum NO concentrations were higher in the non-pregnant control and lower in the missed abortus group. The low NO levels detected in missed abortus have been reported cause vasoconstriction in the uterine vascular bed and abortus due to decidual platelet aggregation activation. Also, in our study, the NO levels were significantly lower in the missed abortus group compared to healthy pregnant women. These results are parallel with the studies in the literature.

Missed abortus is important in obstetrics practice due to its frequent occurrence. Although many factors have been defined in the etiopathogenesis, comprehensive studies are needed to figure out the yet unknown causes to prevent maternal and fetal losses. Contrary to the findings of our study, a significant increase in maternal adropin levels was detected in a study conducted in cases with severe intrauterine growth retardation. The authors explained this by the probability that fetal development may have occurred despite existing endothelial dysfunction, and the compensatory regulatory feedback mechanism to meet the energy need [17].

Limitations

The sparse sample size, self-reporting of maternal-paternal chromosomal disease history, and lack of exclusion of genetic and histopathologic investigation in abortus material after the termination are the factors that limit our study.

Conclusion

It was not fully revealed in our recent findings whether low levels of adropin and NO in the missed abortus group is associated with endothelial dysfunction, or a result of an unknown reason pathology endothelial dysfunction, vasospasm, insufficient perfusion. Further research is needed for elucidation.

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Changing epidemiology and risk factors for candidemia in critically ill patients

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Ethics Committee Approval
Ethics Committee of Bakirkoy Dr. Sadi Konuk Education and Research Hospital, date:14.05.2018 and number:2018/182.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Candidemia is a common cause of bloodstream infections in critically ill patients, resulting in high mortality and morbidity. This retrospective case-control study was designed to identify epidemiological characteristics and risk factors for candidemia in an intensive care unit.

Methods: A total of 166 patients hospitalized in the intensive care unit between January 2013 and December 2017 were included in this case-control study. Candidemia was defined as at least one positive blood culture for *Candida* spp. with fever or other clinical findings consistent with infection. Patients who acquired candidemia more than 48 hours after admission represented the case group (n=83). Control group (n=83) consisted of case-matching patients who were hospitalized during the same period and did not develop candidemia.

Results: In the candidemia group *Candida albicans* (57.8%) was the most common species, followed by *Candida glabrata* (13.3%) and *Candida parapsilosis* (12%). The rate of *C. albicans* decreased from 69.2% to 50% during the five-year study period. Out of 83 candidemia infections, 36 (43.4%) were associated with central venous catheters. *C. parapsilosis* had an increasing rate in parallel with central venous catheter-associated candidemia rates. When comparing cases and controls, in univariate analysis, Sequential Organ Failure Assessment (SOFA) score, blood transfusion, central venous catheter placement, intubation, gastrointestinal surgery and total parenteral nutrition were significantly more common in the candidemia group ($P<0.05$ for each). The rate of the patients whose C*andida* scores were higher or equal to 3, was significantly higher in candidemia group ($P=0.03$). According to the multivariate analysis, SOFA scores ($P<0.001$, OR:1.25, 95% CI:1.15-1.37), gastrointestinal surgery ($P=0.03$, OR:2.60, 95% CI:1.10-6.12), central venous catheter ($P=0.04$, OR:2.62, 95% CI:1.05-6.57) and total parenteral nutrition ($P=0.02$, OR:2.61, 95% CI:1.12-6.06) were independent risk factors for candidemia, while enteral feeding ($P=0.02$, OR:0.27, 95% CI:0.09-0.80) was protective against.

Conclusion: The result of our study is an evidence of the changing epidemiology of candidemia, which showed a shift towards non-*albicans Candida* spp. over the years. The increasing rate of *C. parapsilosis* and central venous catheter-associated candidemia has highlighted the need for more attention to the central line care and hand hygiene. Our study also revealed that critically ill patients with high SOFA score, gastrointestinal surgery, central venous catheter, and total parenteral nutrition have an elevated risk for developing candidemia. Unless necessary, limitation of total parenteral nutrition, and ensuring the earlier implementation of enteral feeding may be protective from candidemia.

Keywords: Candidemia, Epidemiology, Intensive care unit, Risk factors

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Introduction

Candida species are normally colonized in the oral cavity, skin and intestinal tract of humans and becomes pathogenic due to various risk factors, such as consumption of broad-spectrum antibiotics, exposure to invasive procedures, malignancy, human immunodeficiency virus (HIV) infection, organ transplantation and prolonged hospital stay [1]. Candidemia is one of the most common causes of bloodstream infections (BSIs) in the world. In the United States of America (USA), between 2013–2017, the incidence of candidemia was 9:100.000 individuals with a variety by geographic location and patient population. Centers for Diseases and Prevention (CDC) estimates that approximately 25,000 cases of candidemia occur nationwide each year [2,3]. According to the data of the European Center for Disease Prevention and Control (ECDC), *Candida* spp. was the eighth cause of intensive care unit (ICU)-acquired BSIs in Europe in 2016 and 2017 [4, 5].

While *Candida albicans* is still considered the leading cause of candidemia, increasing rates of non-*albicans Candida* species have been reported to account for almost 50% of all candidemia [6]. Because candidemia is a common cause of BSIs in critically ill patients resulting in high mortality and morbidity, each hospital needs to identify its own candidemia data. This study aims to evaluate the epidemiologic characteristics of candidemia cases, distribution, and comparison of *Candida* isolates, and identify the risk factors for candidemia in our ICU.

Materials and methods

This retrospective case-control study was conducted in our 612-bed tertiary care, university-affiliated hospital, a referral center for several hospitals in the vicinity. Our hospital has a 31-bed Anesthesiology and Reanimation ICU, nine-bed neurology ICU, 16-bed coronary ICU, seven-bed cardiovascular ICU, 26-bed neonatal ICU, and a 16-bed pediatric ICU. This study was performed in Anesthesiology and Reanimation ICU which accepts patients from both internal medicine and surgical wards. The study approval was obtained from the Ethics Committee of Bakirkoy Dr. Sadi Konuk Education and Research Hospital (No: 2018/182 -14/05/2018).

Adult patients (at least 18 years old) hospitalized in the ICU between January 2013 and December 2017 who acquired candidemia more than 48 hours after admission were included in the study and represented the study group. Candidemia was defined as at least one positive blood culture for *Candida* spp. with fever or other clinical findings consistent with infection. In cases with recurrent candidemia, only the first episode was included in the study. Control group consisted of patients who were hospitalized in ICU during the same period and did not develop candidemia. Control patients were selected from the electronic hospital records and matched 1:1 with the cases in terms of age and Acute Physiology and Chronic Health Evaluation (APACHE) II scores. For randomization, among case-matched patients who were hospitalized during the same period, with similar ages and APACHE II scores, those who were admitted earlier in ICU was selected as controls.

The patients under 18 years of age who had candidemia in the first 48 hours of ICU admission or in other wards before ICU admission were excluded from the study.

Demographic characteristics, invasive procedures before candidemia (for cases) or within 2 weeks after admission (for controls), such as a central venous catheter (CVC), urinary catheterization, endotracheal intubation, total parenteral nutrition (TPN), history of surgery up to one month before candidemia (for cases) or before hospitalization (for controls) were recorded. Quantitative variables such as Sequential Organ Failure Assessment (SOFA) scores, APACHE II scores, age, length of stay and duration of antifungal treatment were also recorded. *Candida* scores were calculated by adding 2 points for severe sepsis, 1 point for TPN, 1 point for surgery, and 1 point for multifocal *Candida* colonization. Patients were followed up until discharge from ICU or death. All data were collected from the patients' files and the records of the infection control committee of our hospital.

Conventional mycological methods such as colony morphology, germ tube test, and Phoenix Yeast ID panel (Becton Dickinson Diagnostics, Sparks, ABD) were used for identification of *Candida* species. Antifungal susceptibility tests were performed with broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) M27-A3 document [7, 8]. The unidentified non-*albicans Candida* isolates were named as "other non-*albicans Candida* spp."

Statistical analysis

Statistical Package for Social Sciences version 25.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Descriptive data were presented as mean (standard deviation), frequency, median, and percentage values. Chi-Square test and Fisher's Exact test were used for comparing categorical variables. The normality of continuous variables was tested with the Kolmogorov Smirnov test. Normally and non-normally distributed continuous variables were compared with Student's t-test and Mann-Whitney U test, respectively. Significant variables in the univariate analysis were evaluated with the multivariate logistic regression analysis to determine independent risk factors. *P*-values less than or equal to 0.05 were considered statistically significant.

Results

A total of 166 cases, including 83 candidemia and 83 non-candidemia patients, were included in the study between January 2013 and December 2017. In the candidemia group, *C. albicans* was the most common species (n=48, 57.8%), followed by *Candida glabrata* (n=11, 13.3%), *Candida parapsilosis* (n=10, 12%), *Candida krusei* (n=7, 8.4%), and *Candida tropicalis* (n=3, 3.6%). In four of 83 patients (4.8%), non-*albicans Candida* isolates could not be identified. During the five year study period, the rate of *C. albicans* was 57.8% (n=48) and the rate of non-*albicans Candida* species was 42.2% (n=35). The distribution of *albicans* and non-*albicans Candida* species among the years was presented in Figures 1 and 2. Candidemia occurred in a median of 14 days (Interquartile range [IQR]: 15-26 days) after admission. Fever was higher than 38 degrees in only 50.6% of candidemia patients at the time of blood culture positivity. Out of 83 candidemia infections, 36 (43.4%) were

CVC associated. Incidence of CVC-associated candidemia patients among the years and the distribution of species was shown in Figures 3 and 4.

Figure 1: Frequency of *Candida albicans* and non-*albicans Candida* spp. from 2013 to 2017

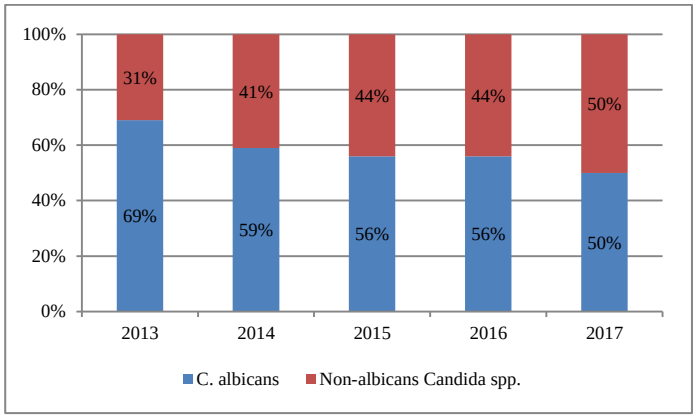


Figure 2: Overall distribution of *Candida* species isolates during the study period

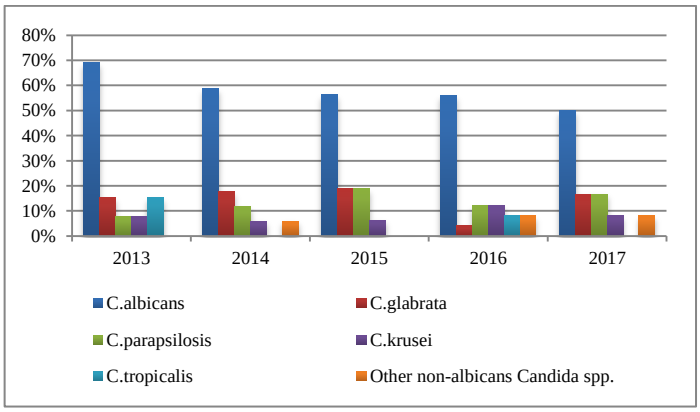


Figure 3: Frequency of CVC associated and non-CVC associated candidemia between 2013 and 2017

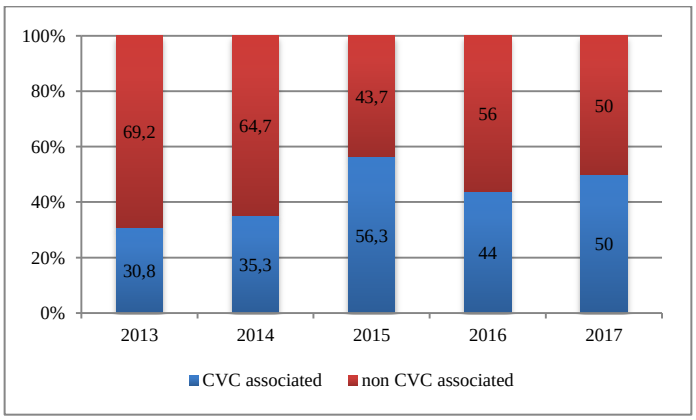
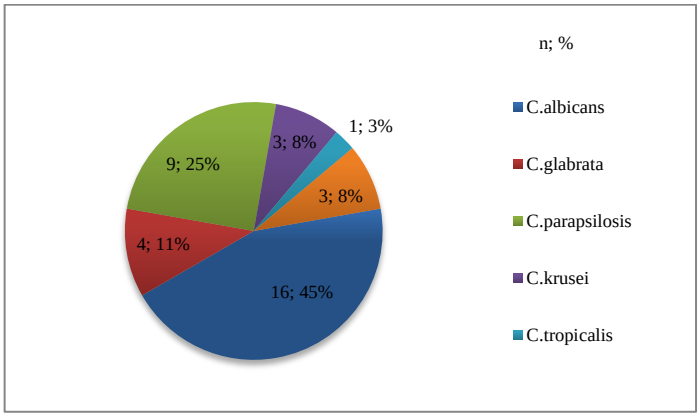


Figure 4: Distribution of *Candida* species in CVC associated candidemia patients



When comparing the cases with *C. albicans* and non-*albicans Candida* in terms of demographic characteristics, underlying diseases, invasive procedures, and mortality, the rate of diabetes mellitus (DM) and percutaneous endoscopic gastrostomy (PEG) were higher in *C. albicans* group (P=0.01, OR: 10.10, 95% CI: 1.23-82.49, P=0.03, OR: 3.96, 95% CI: 1.03-15.18) (Table 1). There was no significant difference between the two groups in terms of APACHE II and SOFA scores, mortality rates, length of stay in ICU, median day of candidemia onset and, duration of antifungal therapy. The rate of antibiotic usage before candidemia was also similar in both groups.

Table 1: Characteristics of *Candida albicans* and non-*albicans* candidemia

	Patients with *Candida albicans* (n=48)	Patients with non-*albicans Candida* spp. (n=35)	*P*-value
Male gender, n (%)	27 (56.3)	20 (57.1)	0.93
Age, year, mean (SD)	57 (16.80)	53.37 (21.18)	0.38
APACHE II, median (IQR)	22 (17-27)	20 (14-23)	0.07
SOFA, median (IQR)	12 (9-18)	13 (11-19)	0.36
Day of candidemia, day, median (IQR)	15 (5-22)	12 (3-27)	0.63
Fever ≥38°C at the time of candidemia, n (%)	22 (55)	20 (64.5)	0.41
Candida spp. isolation at least one site of the body other than blood, n (%)	26 (60.5)	16 (55.2)	0.65
Length of stay, day, median (IQR)	31 (19-47)	27 (20-38)	0.32
Duration of antifungal treatment, mean (SD)	16.52 (7.44)	13.74 (9.60)	0.23
Hypertension, n (%)	9 (18.8)	5 (14,3)	0.59
Congestive heart disease, n (%)	1 (2.1)	0 (0)	1
Diabetes mellitus, n (%)	11 (22.9)	1 (2.9)	0.01*
Chronic renal failure, n (%)	6 (12.5)	3 (8.6)	0.72
Cerebrovascular disease, n (%)	5 (10.4)	0 (0)	0.07
Malignancy, n (%)	10 (20.8)	5 (14.3)	0.44
Chronic obstructive pulmonary disease, n (%)	2 (4.2)	1(2.9)	1
PEG, n (%)	13 (27.1)	3 (8.6)	0.03*
Tracheostomy, n (%)	31 (64.6)	17 (48.6)	0.14
Central venous catheter, n (%)	40 (83.3)	28 (80)	0.69
GIS surgery, n (%)	21 (43.8)	18 (51.4)	0.48
Intubation, n (%)	46 (95.8)	31 (88.6)	0.23
Enteral feeding, n (%)	43 (89.6)	30 (85.7)	0.73
Nasogastric tube, n (%)	46 (95.8)	31 (88.6)	0.23
Total parenteral nutrition, n (%)	33 (68.8)	24 (68.6)	0.98
Hemodialysis/CRRT, n (%)	21 (43.8)	15 (42.9)	0.93
Mortality, n (%)	34 (70.8)	25 (71.4)	0.95

SD: Standard deviation, APACHE: acute physiology and chronic health evaluation, SOFA: sequential organ failure assessment, IQR: interquartile range, PEG: percutaneous endoscopic gastrostomy, GIS: gastrointestinal system, CRRT: continuous renal replacement therapy, * p≤0.05, the difference between two groups is statistically significant.

To identify the risk factors for candidemia, we compared the patients with and without candidemia. The characteristics of these groups and the results of the univariate analysis were shown in Table 2. The ratio of *Candida* spp. isolation in at least one part of the body other than blood, such as urine or endotracheal aspirate, and median SOFA scores were significantly higher in the candidemia group (P=0.02, P=0.001, respectively). Blood transfusion, CVC placement, intubation, gastrointestinal system (GIS) surgery and TPN were significantly more common in the patients with candidemia (P=0.01, P=0.05, P=0.04, P=0.004, P=0.04). The rate of the patients whose *Candida* scores were higher or equal to 3 was significantly higher in candidemia group (P=0.03). Significant variables in univariate analysis were included in multivariate analysis and, logistic regression was used to establish a significant model. According to the results of logistic regression analysis, SOFA score (P<0.001, OR: 1.25, 95% CI: 1.15-1.37), GIS surgery (P=0.03, OR: 2.60, 95% CI: 1.10-6.12), CVC placement (P=0.04, OR: 2.62, 95% CI: 1.05-6.57) and TPN (P=0.02, OR: 2.61, 95% CI: 1.12-6.06) were independent risk factors for candidemia, while enteral feeding (P=0.02, OR: 0.27, 95% CI: 0.09-0.80) was protective (Table 3). Mortality rates were also significantly higher in candidemia patients (P=0.001).

Table 2: Univariate analysis of risk factors for candidemia in ICU

	Patients with candidemia (n=83)	Patients without candidemia (n=83)	*P*-value	OR	95% CI
Male gender, n (%)	47 (56.6)	48 (57.8)	0.87	1.05	0.56-1.94
Age, year, mean (SD)	55.47 (18.74)	55.41 (20.01)	0.98		
APACHE II, median (IQR)	21 (16-25)	19 (16-24)	0.26		
SOFA, median (IQR)	12 (10-18)	8 (6-11)	<0.001×		
Hospitalization before ICU, n (%)	30 (36.1)	29 (34.9)	0.87	1.05	0.55-1.99
Length of stay, day, median (IQR)	31 (18-46)	27 (20-38)	0.32		
Candida score≥3, n (%)	33 (39.8)	20 (24.1)	0.03×	2.07	1.06-4.05
Underlying diseases, n (%)					
Hypertansion	14 (16.9)	19 (22.9)	0.33	0.68	0.31-1.47
Congestive heart disease	1 (1.2)	5 (6)	0.21	0.19	0.02-1.66
Diabetes mellitus	12 (14.5)	16 (19.3)	0.40	0.70	0.31-1.60
Chronic renal failure	9 (10.8)	7 (8.4)	0.59	1.32	0.46-3.73
Cerebrovascular disease	5 (6)	7 (8.4)	0.54	0.69	0.21-2.28
Malignancy	15 (18.1)	18 (21.7)	0.56	0.79	0.37-1.71
Chronic obstructive pulmonary disease	3 (3.6)	5 (6)	0.21	0.58	0.13-2.53
Invasive procedures, n (%)					
PEG	16 (19.3)	12 (14.6)	0.42	1.41	0.62-3.20
Trakeostomy	48 (57.8)	53 (63.9)	0.42	0.77	0.41-1.45
Blood transfusion	57 (68.7)	41 (49.4)	0.01×	2.24	1.19-4.22
Central venous catheter	68 (81.9)	57 (68.7)	0.05×	2.06	1-4.27
Urinary catheter	82 (98.8)	78 (94)	0.21	5.25	0.60-46
Surgery	54 (65.1)	49 (59)	0.42	1.29	0.68-2.42
GIS surgery	39 (47)	21 (25.3)	0.004×	2.61	1.35-5.04
Intubation	77 (92.8)	68 (81.9)	0.04×	2.83	1.04-7.70
Enteral feeding	73 (88)	64 (77.1)	0.07	2.16	0.93-5
Nasogastric tube	77 (92.8)	79 (95.2)	0.51	0.65	0.17-2.39
Total parenteral nutrition	57 (68.7)	44 (53)	0.04×	1.94	1.03-3.66
Hemodialysis/CRRT	36 (43.4)	31 (37.3)	0.42	1.28	0.69-2.39
Drain	47 (56.6)	43 (51.8)	0.53	1.21	0.65-2.23
Mortality, n (%)	59 (71.1)	38 (45.8)	0.001×	2.01	1.53-5.53

ICU: intensive care unit, SD: Standard deviation, PEG: percutaneous endoscopic gastrostomy, GIS: gastrointestinal system, CRRT: continuous renal replacement therapy, IQR: interquartile range, APACHE: acute physiology and chronic health evaluation, SOFA: sequential organ failure assessment, × p≤0.05, the difference between two groups is statistically significant.

Table 3: Multivariate analysis of risk factors for candidemia in ICU

	Patients with candidemia (n=83)	Patients without candidemia (n=83)	*P*-value	OR	95% CI
Candida score≥3, n (%)	33 (39.8)	20 (24.1)	0.26	1.69	0.66-4.29
Blood transfusion, n (%)	57 (68.7)	41 (49.4)	0.44	1.36	0.61-3.03
Central venous catheter, n(%)	68 (81.9)	57 (68.7)	0.04×	2.62	1.05-6.57
GIS surgery, n (%)	39 (47)	21 (25.3)	0.03×	2.60	1.10-6.12
Intubation, n (%)	77 (92.8)	68 (81.9)	0.97	0.97	0.28-3.39
Total parenteral nutrition, n (%)	57 (68.7)	44 (53)	0.02×	2.61	1.12-6.06
Enteral feeding, n (%)	73 (88)	64 (77.1)	0.02×	0.27	0.09-0.80
SOFA, median (IQR)	12 (10-18)	8 (6-11)	<0.001×	1.25	1.15-1.37

OR: odd's ratio, CI: confidence interval, SOFA: sequential organ failure assessment, IQR: interquartile range, × *P*≤0.05, the difference between two groups is statistically significant.

Antifungal susceptibility tests could be performed in only 44.5% (n=37) of the candidemia patients. According to the results, in *C. albicans*, fluconazole resistance was 8%, and no resistance to amphotericin B and echinocandins was observed. In non-*albicans Candida* species, fluconazole resistance was 80% in *C. glabrata*, only one strain among *C. parapsilosis* was resistant to fluconazole. Among candidemia patients, 84.3% (70/83) had antibiotic consumption before the onset of candidemia, carbapenems being the most used.

Discussion

We report the epidemiological data and risk factors for candidemia in the ICU of a tertiary care regional referral center. The candidemia incidence in our ICU was 2.88 per 1000 patient-days with an all-cause mortality rate of 71.1%. In various studies, candidemia incidence in ICU is reported as 0.24-34.3 patients per 1000 admissions [9, 10]. The two large multinational studies, "The Extended Prevalence of Infection in Intensive Care (EPIC II) study" and "European ICU project (EUCANDICU)" reported a prevalence of 6.87 and 5.52 per 1000 admissions, respectively, for candidemia among ICU patients [11, 12]. In comparison to the results of nationwide studies, the incidence of candidemia in our ICU was lower than that in other countries. This result was associated with few numbers of neutropenic patients with hematologic or oncologic malignancy in our study.

Although *C. albicans* is traditionally known as the leading cause of candidemia worldwide, in recent years, a shift towards non-*albicans Candida* spp. has been reported [13-15]. In a multicenter study with 2496 patients from the United States and Canada, in 62.5% of participating sites, non-*albicans Candida* spp. accounted for>50% of all cases of invasive candidiasis [13]. In a recent study conducted in the ICU and surgical wards in China, *C. albicans* was isolated in only 33.8% of candidemia cases [14]. Similarly, the proportion of non-*albicans Candida* spp. exceeded *C. albicans* in another study from the Asia-Pacific region [15]. From different regions of our country, rates of *C. albicans* in candidemia were reported as 75% by Tukenmez Tigen et al, 72% by Yılmaz Karadag et al, 52.4% by Mermutluoglu et al. and 57% by Arslan et al [16-19]. In compliance with these studies, *C. albicans* was the overall leading cause of candidemia in our study, but with a decreasing rate from 69.2% to 50% during the study period. We observed that the species distribution is changing from *C. albicans* towards non-*albicans* spp. in our institution, compatible with the literature. *C. glabrata* and *C. parapsilosis* were the most common non-*albicans Candida* species in our study and, especially the increasing frequency of *C. parapsilosis* over the years was striking. *C. parapsilosis* is known to show a propensity to colonize the catheters by adhering to the surface through a fibrin sheath [20]. As we observed that the distribution of CVC associated candidemia was in parallel with the distribution of *C. parapsilosis*, the upward trend of *C. parapsilosis* was attributed to this finding. Thus, nine (90%) of ten candidemia caused by *C. parapsilosis* were related to the central catheter. Our study also showed that the proportion of CVC associated candidemia was considerable in our institute and it is essential to reduce these rates. Efforts should be made to increase hand hygiene compliance and improve central line care.

Recent studies indicated that the risk factors associated with the increased rates of non-*albicans Candida* spp. were major operations, GIS surgery, TPN, hemodialysis, blood transfusions, malignancy, chemotherapy, and previous use of fluconazole [21-23]. In our study TPN, hemodialysis and CVC rates were similar in both *C. albicans* and non-*albicans Candida* spp. groups. History of GIS surgery was insignificantly more common in the non-*albicans Candida* spp. group. In *the C. albicans* group, rates of DM and PEG were significantly higher than that in the non-*albicans Candida* spp. It is known that patients with DM have an increased susceptibility to infections. In a recent study, Gursoy et al. [24] suggested that there is a higher presence of intestinal *C. albicans* colonization in diabetic patients. Similar to our study, Al Dorzi et al. [25] found that insulin-treated DM rates were higher in *C. albicans* than non-*albicans Candida* spp. in their study conducted at the ICUs of two tertiary care centers.

There are many studies in the literature concerning the risk factors for the development of candidemia. Presence of CVC, TPN, broad-spectrum antibiotic usage, history of surgery, blood transfusion, length of hospitalization, urethral catheterization, and chronic renal failure were the risk factors for candidemia [23, 26, 27]. In our study, the presence of CVC, blood transfusion, intubation, TPN, and GIS surgery were more common in the candidemia group compatible with the literature.

Although the rates of surgical interventions were similar in both groups, GIS surgery was significantly higher in the candidemia group (Table 2). Similar to our study, Das et al. determined that the risk of developing candidemia is higher in the patients with a history of GIS surgery than other types of surgical interventions [27]. The gastrointestinal system is known as the habitat of *Candida* species and from the impaired mucosa barrier of GIS, *Candida* spp. can translocate into the bloodstream, causing candidemia [28].

Colonization with *Candida* species is known as a prerequisite for candidemia. In recent studies, *Candida* colonization rate in the ICU was reported as 50-100% and invasive candidiasis developed in 3-25% of the patients who had *Candida* colonization [29, 30]. In our study, the isolation of *Candida* spp. in the samples other than blood was significantly higher in the candidemia group.

Identifying the patients at high risk of candidiasis is crucial for both early initiation of antifungal treatment and avoiding unnecessary use of antifungal therapy. A score named "*Candida* score" was identified in 2006 by Leon et al. in a multicenter study conducted in ICUs, and in 2009, a significant association between the rate of invasive candidiasis and the increasing values of the "*Candida* score" was demonstrated [31,32], which is calculated as follows: *Candida* score = 0.908 × (total parenteral nutrition) + 0.997 × (surgery) + 1.112 × (multifocal *Candida* species colonization) + 2.038 × (severe sepsis) and a score >2.5 is significant for invasive candidiasis. In 2009, they used a rounded *Candida* score, calculated as follows: 1 × (total parenteral nutrition) + 1 × (surgery) + 1 × (multifocal Candida colonization) + 2 × (severe sepsis) and if score is smaller than 3, invasive candidiasis is highly improbable. Our results were in accordance with Leon's data. In the candidemia group, 40% of the patients had a score ≥3, significantly higher than the non-candidemia group.

In multivariate analysis, CVC, TPN, GIS surgery, and SOFA scores were independent risk factors for candidemia, compatible with the literature. As we know that SOFA scores assess the severity of organ dysfunction in critically ill patients, the result of our study supported the fact that more severely ill patients are at higher risk for *Candida* infections. As a striking result of multivariate analysis, enteral feeding was determined as a protective factor for candidemia (OR: 0.27, 95% CI: 0.09-0.80). This can be explained by the fact that enteral feeding is more physiological than parenteral nutrition and can protect the patient from the catheter-related infections caused by TPN.

Limitations

The retrospective a single-center design of the study are its major limitations. Another limitation is that antifungal susceptibility tests were performed in nearly half of the patients. Because of the small sample size of the strains that had antifungal susceptibility tests, the resistance ratios may not be generalizable. Nevertheless, our study provides important epidemiological findings that can be useful in the management of candidemia.

Conclusion

The result of our study is evidence of the changing epidemiology of candidemia and showed a shift towards non-*albicans Candida* spp. over the years. The most common non-*albicans Candida* species in our ICU were *C. glabrata* and *C. parapsilosis*. Fluconazole resistance in *C. glabrata* should be considered before using azoles in empirical treatment. The increasing rate of *C. parapsilosis* and CVC-associated candidemia has highlighted the need for more attention to central line care and hand hygiene. Also, as another finding of our study, half of the patients had no fever during candidemia, which may lead to delay in diagnosis and treatment. History of GIS surgery, TPN, CVC, and high SOFA scores in ICU patients are independent risk factors for candidemia. Besides, enteral nutrition was a protective factor. Unless necessary, limitation of TPN use and ensuring the earlier implementation of enteral feeding will be effective in preventing candidemia.

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Judet's quadricepsplasty after total hip arthroplasty and Thompson's quadricepsplasty: A case report

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The authors stated that the written consent was obtained from the patient presented with images in the study.

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Abstract

Judet quadricepsplasty provides a gradual release of knee extension contracture occurring due to intrinsic and extrinsic reasons. We herein present a 68-year-old male patient with a fragmented right femur AO (arbeitsgemeinschaft für osteosynthesefragen) Type A3 fracture, which occurred because of an in-vehicle traffic accident 30 years ago. The fracture was fixed with an anterior plate-screw with open reduction, and knee extension contracture had developed after the operation. The distinctive features of this case include a previous, unsuccessful, ipsilateral V-Y quadricepsplasty, an ipsilateral total hip arthroplasty with anterior approach six months ago and a persistent extension contracture for over 30 years. Gradual releasing techniques, as described by Judet, were performed under general anesthesia and sterile conditions with the patient in supine position. Intraoperatively, two displaced screws were detected on the anterior femur, which had adhered to the vastus medialis muscle, and fibrosed. Adhesions were dissected and screws were removed. Before the release of the proximal adhesion of the rectus muscle, a forced external rotation of hip joint was performed to assure that adequate fibrotic tissue had formed on the anterior facet of the joint capsule to prevent anterior instability. Five recurrent knee joint effusions developed after surgery, which were aspirated by needle. Joint fluids were clear and there were no reproductions of any microorganisms. By the end of an uneventful, two-year follow-up period, final knee range of motion was 0-90 degrees. Loss of extension and extensor muscle power had entirely improved by 6 months. In a patient with hip prosthesis, provided that adequate fibrosis has formed on the anterior facet of the joint capsule, rectus release may not cause instability. In cases resistant to rehabilitation, if there is implant, fibrosis or hypertrophic callus which may cause irritation at any level of the knee extensor mechanism, we suggest their resection for a more even anterior cortex contour.

Keywords: Contracture, Hip joint, Hip prosthesis, Knee joint

Introduction

Judet quadricepsplasty provides a gradual release of knee extension contracture occurring due to intrinsic and extrinsic reasons. It carries decreased risks of iatrogenic quadriceps rupture and extension lag compared to V-Y or Thompson methods [1-3]. The distinctive features of this case include a previous, unsuccessful, ipsilateral V-Y quadricepsplasty, an ipsilateral total hip arthroplasty with anterior approach six months ago and a persistent extension contracture for over 30 years. To the best of our knowledge, there are no reports of Judet quadricepsplasty after unsuccessful V-Y quadricepsplasty, or of contractures of more than 20 years in the English literature. Anterior approach to the ipsilateral hip for arthroplasty may cause an instability due to rectus femoris muscle release.

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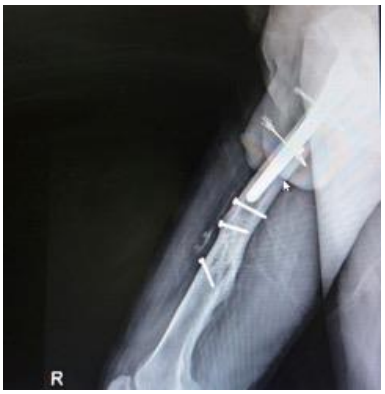
Case presentation

This research was approved by the IRB of the author's affiliated institution and the patient's informed consent was obtained for publication. The study was performed following the ethical standards of the Declaration of Helsinki. A 68-year-old male was admitted with preoperative fixed extension contracture of the right knee lasting for over 30 years. The patient's medical history revealed that he had been admitted to hospital for a traffic accident and right femur AO (arbeitsgemeinschaft für osteosynthesefragen) Type A3 fracture. The fracture was fixed with open reduction and internal fixation with plate and screws. He revealed that postoperative knee ROM (range of motion) exercises were painful. Despite serious rehabilitation and removal of the plate and some screws, right knee ROM was decreased to 0-10 degrees in 6 months. Four years ago, another center tried to release the contracture with Thompson quadricepsplasty. However, all gains were lost within the first year of the operation. Six months ago, he was admitted to a local hospital because of ipsilateral severe hip pain. THA (total hip arthroplasty) with anterior capsulotomy was performed for severe hip joint arthrosis. On his first visit, he presented with severe right knee extension contracture with 0-10 degrees active ROM. He was able to walk, hip and ankle movements and lower extremity muscle functions were regular. Quadriceps femoris muscle contraction was satisfactory. Two screw heads were protruding on the anterior femoral cortex on plain radiography (Figure 1).

Figure 1: Lateral thigh x-ray shows anteriorly protruding screw heads



Knee cartilage quality was satisfactory in knee MRI (magnetic resonance imaging). Under general anesthesia and with the patient in supine position, a release was performed gradually following classic Judet's technique. The first incision was made mid anteriorly, in accordance with the previous incision scar. With this single incision, MCL (medial collateral ligament), medial capsule, and adhesions in the joint and lateral side were released (Figure 2).

Two displaced screws were detected on the anterior femur cortex during the release. There were excessive fibrosis and adhesions around the screw heads. Fibrotic tissues were resected, adhesions were released, and screws were removed. The second stage was rectus femoris muscle release from a 3 cm-long oblique bikini incision (Figure 3,4). The anterior capsule of the hip prosthesis was palpated with fingers, and simultaneously, the hip was extended, and externally rotated. The capsule was thick enough.

Figure 2: Collet shows intraarticular hypertrophic fat and fibrosis

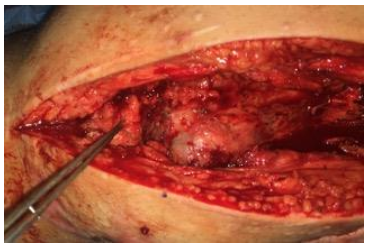
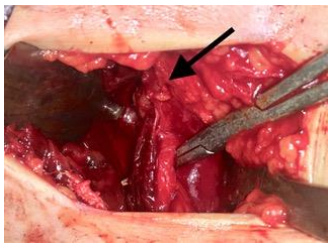


Figure 3: Clamp elevates the rectus femoris muscle.



Without rectus femoris muscle support in the anterior, the joint did not destabilize (Figure 5). The rectus femoris muscle origin was then released from the Spina Iliaca Anterior Inferior.

Figure 4: Rectus muscle cut from the anterior inferior iliac spine. The broad origin was more extensive than previously thought.

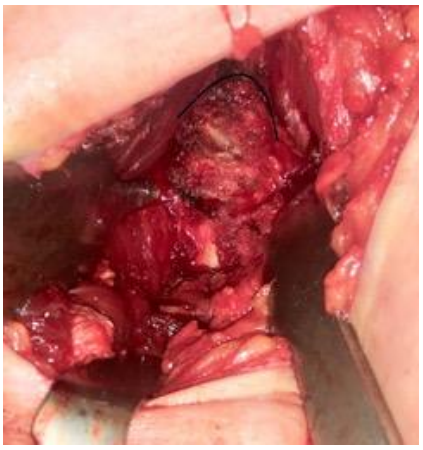
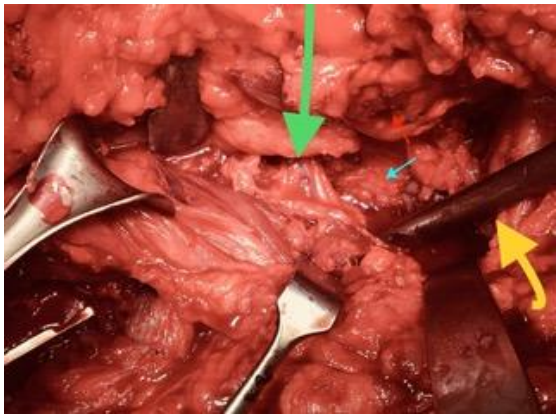


Figure 5: Vastus lateralis muscle is shown (Green arrow: The still intact transverse branch of lateral femoral circumflex artery, Blue arrow: Fibrosis over anterior capsule, Yellow arrow: Benneth elevator is on the superior side of collum femoris, Red arrow: Rectus muscle was cut)

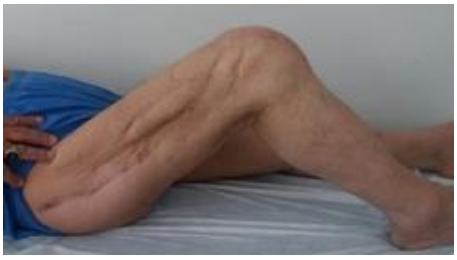


Forty-five degrees flexion was obtained at this stage. The third stage was the proximal release of the vastus complex from the anterior femur neck, and the last stage was the release of tensor fascia lata. A longitudinal lateral incision was made across the thigh, and tensor fascia lata was lengthened with multiple transverse incisions. Distally, this lateral incision was slightly curved medially and combined with an anterior midline incision. Epidural analgesia was given for postoperative pain control. Knee active-assisted exercises were started immediately. No brace or CPM (continuous passive motion) machine was used. On the second postoperative day, the wound was redressed, and the drains were removed. Lower extremity strengthening and ROM exercises, walking, and weight-bearing exercises were included in the rehabilitation program. A total of five recurrent knee joint effusions developed after surgery, which were aspirated by needle. Joint fluids were clear and there was no

growth of any microorganisms. Apart from this, no complications developed.

The final ROM was 0-130 degrees perioperatively. Wound healing was eventless, and the extension lag was improved totally at the end of 6 months. By the second year of follow-up, final knee ROM was 0-90 degrees, there were no extension lag, and no other complications (Figure 6). The result was ‘’Good’’ according to Judet’s criteria [1].

Figure 6: Postoperative 2 years knee flexion



Discussion

Patellar adhesions, arthrofibrosis, fracture callus on the anterior femoral cortex, skin adhesions to extensor muscles, external fixator pins and scar tissue are some of the reasons of knee extension contracture [2, 4]. Judet’s quadricepsplasty is an effective procedure that increases flexion range with lower extension lag risk. Extension lag, from which our patient suffered for six months, is more prominent with the Thompson technique [5]. This may be due to proximal release. To prevent extensor lag, V-Y plasty should be avoided, and postoperative active quadriceps exercises should be started immediately [6]. Post-operative patient compliance to rehabilitation is essential for quadricepsplasty [7].

To the best of our knowledge, no study investigates proximal rectus femoris muscle release based on ipsilateral total hip arthroplasty. If the surgeon expects to have enough fibrosis around the hip or use a posterior approach for total hip arthroplasty procedure, loss of rectus femoris muscle support may be accepted. In this case, the examination of the hip joint before the surgery revealed preoperative periarticular fibrosis, and limited external rotation, which did not cause any pain or instability. Thus, we planned the release six months after the hip prosthesis surgery.

Whether to perform total knee arthroplasty along with Judet procedure should be decided before surgery with x-rays and MRI (magnetic resonance imaging). In this case, there was no chondrolysis, knee cartilage quality was good and knee arthroplasty was not considered. If extension contracture has occurred due to an extra-articular fracture, the cartilage will be similar to one buried in the sand because of the lack of movement. Thus, preoperative evaluation of knee joint with MRI may avoid performing unnecessary knee prosthesis. In our opinion, the reason for contracture despite the previous V-Y Quadricepsplasty was two screw heads protruding on the anterior femoral cortex, which were irritating the extensor apparatus.

Conclusion

Ipsilateral hip prosthesis may not be a restraint for Judet Quadricepsplasty if the periarticular fibrosis is thick enough. Also, all implants and callus formations which contact the extensor apparatus should be resected; otherwise, contracture will recur because of postoperative pain during rehabilitation.

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A case report of adult-onset Still's disease of a patient presenting with the symptoms of intraparotid lymphadenopathy

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Abstract

Adult-onset Still's disease (ASOD) is rare in adults. We herein report a 21-year-old female patient with swelling on right cheek, fever, sore throat, and myalgia for two months. The radiologic, pathologic, laboratory and serologic investigations led to no specific diagnosis. Our case fulfilled 3 major (fever, arthralgia, and leukocytosis) and 4 minor (pharyngitis, lymphadenopathy in the neck and parotid gland, abnormal liver function test and negative for Rheumatoid arthritis) criteria for the diagnosis of ASOD according to Yamaguchi et al. This was a rare case presenting with intraparotid lymph nodes and diagnosed with ASOD. After corticosteroid treatment, all symptoms, liver function tests and inflammatory parameters regressed to normal ranges.

Keywords: Still's disease, Intraparotidal lymphadenopathy, Pharyngitis, Fever

Introduction

Adult-onset Still's disease (AOSD) is a rare inflammatory disorder. The initial symptoms of the disease include arthritis, daily high fever, and skin rash [1]. The etiology of AOSD, which was first described by George F., is still unknown [2]; however, it is thought to be related to bacterial infections such as yersinia enterocolitica, mycoplasma pneumoniae [3] and viral infection, such as rubella [4]. The diagnosis is made by exclusion of infection, malignancy, and rheumatologic disorders. Elevated ferritin levels are considered particularly valuable for the diagnosis of the disease.

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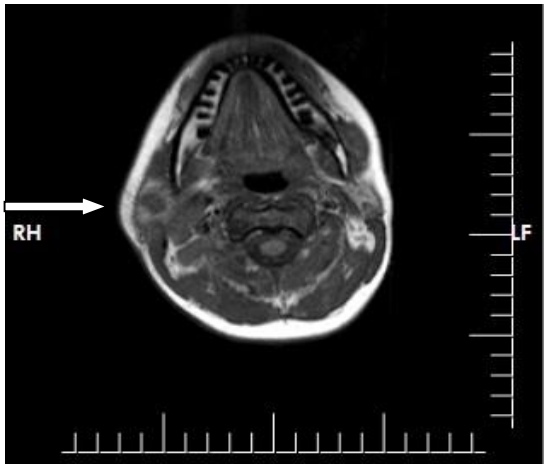
Case presentation

A 21-year-old female patient presented to the ear, nose, and throat (ENT) department with complaints of swelling on her right cheek, sore throat, myalgia, arthralgia, and fever for 2 months. She had no other symptoms. The patient's medical history included tonsillitis episodes (2-3 times per year) and no autoimmune and chronic diseases in her family medical history.

Physical examination revealed pharyngo-tonsillitis and swelling on her right cheek. Her blood pressure was 130/75 mmHg, her heart rate was 90 beats per minute (bpm), there were multiple lymph nodes in her neck and her body temperature was 39.0^{0}C (102.2 °F). Two grams of ampicillin/sulbactam was administered per day for five days, but no change was observed in the symptoms.

The neck ultrasound and MRI scan showed intraparotid lymph nodes (27x14 mm) and numerous lymph nodes at levels 2, 3 and 5 (Figure 1).

Figure 1: MRI showing intraparotid lymph node



A lymph node biopsy was performed on the neck for exclusion of lymphoma and tuberculosis, which revealed no signs of malignancy, tuberculosis, and other diseases, except nonspecific reactive paracortical hyperplasia (RPH).

Laboratory test results were as follows: White blood cell count: 24.120/mm^3 (normal range: 4-10x10^3/mm3), neutrophil ratio: 84.9%, C-Reactive Protein level: 20 mg/dl (normal range is 0-0.5 mg/dl), ferritin: 3720.39 ng/ml (normal range is 4.63-204), AST: 254 U/L (normal range is 5-34 U/L), ALT: 236 U/L (normal range is 0-33 U/L), and urine and stool culture were normal (Table 1).

Table 1: Laboratory test results

Test	Result	Unit	Normal Range
White Blood Cell	24.120	*/uL	4000-10000
Neutrophils	84.9%	%	43-65
C-Reactive Protein	20	mg/dl	0-0.5
Ferritin	3720.39	ng/ml	4.63-204
AST	254	U/L	5-34
ALT	236	U/L	0-33
Urine Examination	Normal		Normal
Culture	Normal		Normal

Among immunologic tests, CCP (anti-cyclic citrullinated peptide) was negative for Rheumatoid arthritis, just as lupus anticoagulant test (LAC), anticardiolipin IgG-IgM, and complement C_3-C_4 and anti dsDNA (ELISA) sensitivity were normal.

The serologic test results showed that Anti-HIV, mono test, Brucella agglutination test, Gruber-Widal test for Salmonella were negative, Parvovirus B19 Ig G-M were normal, and Weil-Felix test for rickettsia, CMV IgM and Toxoplasma IgG-IgM were negative.

Discussion

ENT doctors must be careful while diagnosing AOSD as there are no pathognomonic signs of this disease. Yamaguchi et al. [5] reported the diagnostic criteria of AOSD as follows:

- Major criteria:
  1. Fever >39 ^{0}C, lasting one week or more
  2. Arthralgia two weeks or more
  3. Skin rash
  4. Leukocytosis with at least 80% granulocytes
- Minor criteria:
  1. Sore throat
  2. Lymphadenopathy
  3. Hepatomegaly or splenomegaly
  4. Abnormal liver function tests
  5. Negative results for antinuclear antibody and Rheumatoid factor

In our case, we eliminated lymph node malignancy, infections, and other rheumatic disorders. The case presented with 3 major criteria, namely, fever, arthralgia, and leukocytosis with 84.9% neutrophils and 4 minor criteria, including pharyngitis, lymphadenopathy in the neck and parotid gland, abnormal liver function tests (AST 254 U/L, ALT 236 U/L), and negative Anti CCP results. Ferritin level was also remarkably high (3720.39 ng/ml). This was a rare case presenting with intraparotid lymph nodes and diagnosed with AOSD. We administered 80 mg methylprednisolone per day for one week, followed by 10 mg methylprednisolone per day for one month. All symptoms (swelling on the cheek, sore throat, myalgia, arthralgia, and fever), as well as liver function tests and inflammatory parameters returned to normal. No complaints or relapse of AOSD symptoms has been observed since corticosteroid treatment.

Conclusion

Adult-onset Still's Disease (AOSD) is rare and should be considered in patients presenting with fever, lymphadenopathy in the neck, sore throat, arthralgia, and myalgia.

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Covid-19 associated acute encephalopathy features on computed tomography: A case report

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Abstract

More than 83,000,000 individuals have encountered Covid-19 disease, caused by novel severe acute respiratory syndrome - Coronavirus-2 (SARS-CoV-2). Besides systemic and respiratory symptoms, neurologic involvement has begun to be discussed recently. As severe involvement, only a few meningoencephalitis and encephalopathy cases were reported in the literature. We herein present a 65-year-old male Covid-19 patient with signs of hemorrhagic encephalopathy, along with literature review.

Keywords: Covid, Brain, Imaging, CT

Introduction

According to updated data, more than 83,000,000 individuals were infected with the novel coronavirus called severe acute respiratory syndrome - Coronavirus-2 (SARS-CoV-2), and nearly 360,000 deaths were reported. Patients mostly present with fever and respiratory symptoms like cough, shortness of breath and respiratory distress, and less often, with diarrhea. These symptoms are now well-known by clinicians and the public, due to dire consequences of this disease [1].

In addition to systemic and respiratory symptoms, neurologic involvement of SARS-CoV-2, like other coronaviruses (CoVs), is recently discussed with increasing frequency in the literature [2-5]. The neuroinvasive potential of SARS-CoV-2 and neurologic symptoms such as headache, nausea, and vomiting were reported by Li et al [6]. Today there are five reported meningoencephalitis and encephalopathy cases in the literature, which show severe and exceedingly rare central nervous system involvement of SARS-CoV-2 [7-11].

We herein report acute encephalopathy in a patient who developed somnolence and blackout, incompatible with his respiratory distress and expected progress of Covid-19 disease.

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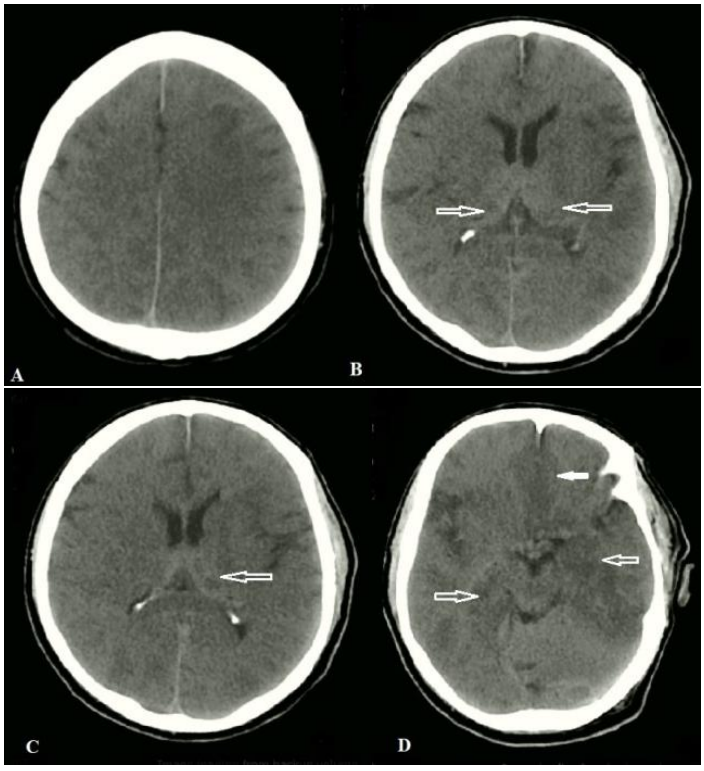
Case presentation

A 65-year-old male patient presented to our hospital with throat ache, dyspnea, fever, and weakness, with a history of praying at a mosque two weeks ago and umrah visit the previous month. He was pre-diagnosed with Covid-19 and hospitalized. The general condition of the patient begun to deteriorate as he was transferred to the intensive care unit on the second day, requiring mechanical ventilation. After the definitive diagnosis of Covid-19 infection with detection of SARS-CoV-2 viral nucleic acid in PCR test from nasopharyngeal swab specimen, treatment protocol was followed, and lung findings regressed. However, although the patient did not receive sedatives for three days, his neurological manifestations progressed, and he became comatose. Blood tests were not significant for the progression of disease. Cerebrospinal fluid analysis was negative for SARS-CoV-2.

On the third day of coma, a computed tomography (CT) was performed, which showed generalized brain edema with patchy hypodense areas in bilateral temporal lobes and anterior cingulate gyrus region, which led us to the diagnosis of encephalopathy. Focal hypodense changes in the thalamus were most probably compatible with necrotizing and hemorrhagic areas (Figure 1).

Figure 1: Head CT demonstrated effacement of cerebral sulci without midline shift (A). Focal hypodense changes in bilateral thalamus suggesting hemorrhagic areas (arrows) (B, C). Focal hypodense areas in bilateral temporal lobe (open arrows) and anterior cingulate gyrus areas (arrow) suggesting parenchymal involvement of encephalopathy (D).



We do not have a Magnetic Resonance Imaging (MRI) device in our hospital to detect hemorrhagic areas and verify the diagnosis of the disease. Due to the probability of the requirement for further neurologic treatment, the patient was referred from our chest diseases hospital to a university hospital. He had a cardiac arrest a day later, did not respond to treatment and died. The patient consent form for this case report was obtained from his family.

Discussion

A growing evidence shows neurotropism is one of common features of CoVs. The novel SARS-CoV-2, with high homology to SARS-CoV, may invade the central nervous system (CNS) to induce neuronal injury. Although the exact route of CoVs is still not reported, there are two proposed routes to CNS migration. One of them is hematogenous dissemination of the virus with infected leukocytes through compromised endothelial cells of the blood-brain barrier. The other strongly suggested mechanism is the peripheral invasion of the virus by anosmia and ageusia in Covid-19 patients. The peripheral invasion can start from nasal mucosa to olfactory bulb and thereafter spread to critical brain areas, such as the thalamus and brainstem. This trans-synaptic transfer may also occur via the Vagus nerve to brainstem. Brainstem involvement with critical neuroanatomic interconnections may clarify the dysfunction of the cardiorespiratory center and the death of infected patients.

Meningoencephalitis and acute encephalopathy of the brain are the most critical types of neuronal involvement of viral infections that can result in death or serious sequelae. Besides clinical and laboratory examination, imaging is a powerful tool for the diagnosis and follow-up of the disease. Viral encephalitis and meningoencephalitis may present with diffuse brain edema, focal hypoattenuating areas, leptomeningeal and gyral enhancement or exactly normal findings on brain CT. The three reported Covid-19 associated meningoencephalitis and encephalitis cases presented with normal brain CT findings [8, 10, 11]. MRI findings of encephalitis and meningoencephalitis are more diagnostic with focal or diffuse parenchymal / leptomeningeal involvement and contrast enhancement as in the case of Moriguchi et al. [8]. Probably published in Chinese, we could not reach the clinical and imaging information of the case reported by Xiang et al. [7].

Acute necrotizing encephalopathy (ANE) is characterized by acute encephalopathy with poor prognosis and high mortality rate. CT findings include hypodense thalamic, putaminal, cerebral, cerebellar and brainstem abnormalities, like in the case reported by Poyiadji et al. [9]. Including hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions, the MRI findings of their case was also compatible with ANE. In our case, diffuse brain edema, patchy hypodense areas in temporal lobes and anterior cingulate area and bilateral thalamic hemorrhage as seen by hypodense lesions were suggestive of hemorrhagic encephalopathy in comatose state. Due to the lack of MRI in our hospital, the diagnosis could not be verified.

Conclusion

The increasing number of Covid-19 infected individuals worldwide is pushing clinicians and radiologists to become aware of rare and new findings. They must consider the possibility of neuronal invasion and its clinical sequelae in patients with COVID-19. This is one of very few reported cases of Covid-19-associated acute encephalopathy and will not be the last one as Covid-19 pandemic is foreseen to proceed in the future.

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