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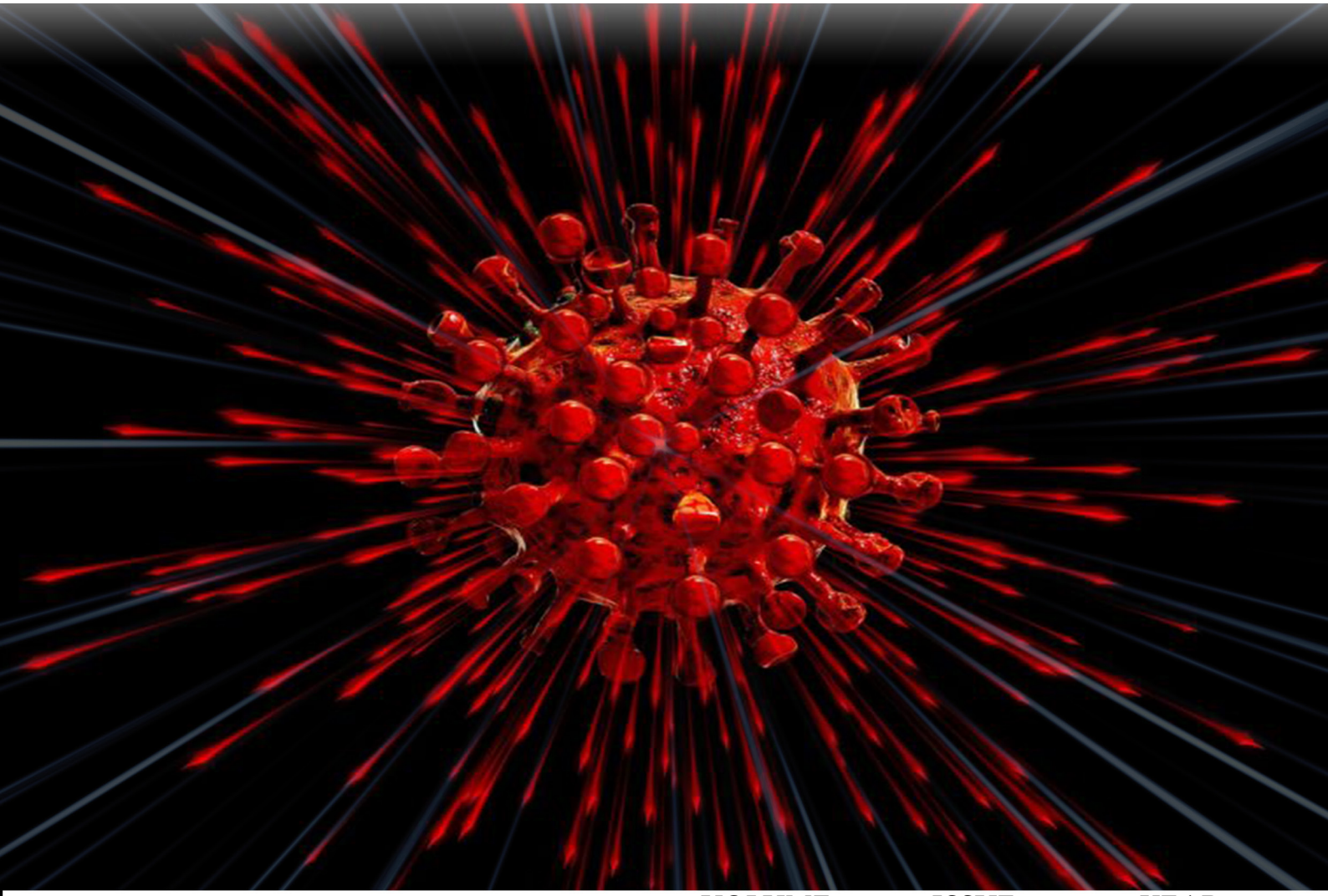

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The frequency and associated factors of pulmonary fibrosis by the twelfth month after community-acquired pneumonia

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ABSTRACT

Aims: Community-acquired pneumonia (CAP) is a term used to describe an acute lung infection that develops outside of a hospital setting. Radiological sequelae may remain in a certain part of these patients that may affect their lives. We aimed to investigate the frequency of sequelae parenchymal lesions and influencing factors in patients with community-acquired pneumonia.

Methods: This retrospective study included patients diagnosed with CAP. First, patients who were admitted to the chest diseases outpatient clinic for any reason and who were treated with the diagnosis of CAP in the emergency department 12 months ago at the earliest were selected. Among these patients, patients with thorax computed tomography (chest-CT) under the control of the chest diseases outpatient clinic were included in the study. Chest-CT results, demographic data and laboratory data were evaluated.

Results: A total of 80 patients, 32 (40%) female and 48 (60%) male, diagnosed with CAP were included. The mean age of our patients was 56.83±13.41 (min-max: 18-71). Twenty-three (28.75%) of the patients did not have pathology in the control chest-CT, while 57 (71.25%) patients had various levels of sequelae changes. Of the sequelae observed in 57 patients, 34 (42.5%) had single linear atelectasis or single band formation or ectasia in a single bronchus, while fibrotic structure was detected in 23 (28.75%). Five (6.25%) patients had pulmonary fibrosis. Age and smoking have a statistically significant effect on the presence of fibrosis in patients with CAP.

Conclusion: Mild to severe fibrotic changes were observed in one-third of our patients one year after CAP treatment. In our study, fibrotic changes were found to be highly correlated with age and smoking.

Keywords: Pneumonia, fibrosis, age, smoking

INTRODUCTION

Pneumonia can be defined clinically and radiologically as the presence of signs of lung consolidation with acute infection of the lung parenchyma distal to the terminal bronchioles.[1] Community-acquired pneumonia (CAP) describes a lung infection that develops during daily life.[1] CAP is responsible for a significant proportion of physician admissions, treatment expenses, work-school day losses and deaths all over the world.[2,3] Although infectious disease related deaths are gradually decreasing due to the widespread use of antibiotics and effective immunization policies, CAP still high morbidity and mortality.[1] Pneumonia is the fourth common cause of mortality and the first common cause of mortality due to all infections in Turkey and worldwide.[1,4] CAP is the leading cause of morbidity and mortality in America, occurring in 649-847 adults per 100,000 population, causing approximately 1.6 million hospitalizations per year.[4]

In Turkey, pneumonia ranks first in deaths due to infection, and the mortality rate of pneumonia varies between 1-60% depending on the severity of the disease, and this rate increases significantly among hospitalized patients (10.3-60%).[5] According to the Ministry of Health statistics 2004, pneumonia accounted for 1.9% of all hospitalizations.[1] CAP risk factors are primarily defined as conditions that reduce the efficacy of the normal mechanisms of lung immunity. The predominant risk factors are age, chronic diseases and smoking.[6] The development of CAP is significantly associated with smoking. Passive smokers over 65years of age have an increased risk

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for CAP. An important dose-response relationship is evident for current smokers.[7] The frequency of pneumonia increases with age worldwide. McLaughlin et al.[8] found that, the rate of hospitalization for pneumonia was ten times higher in the elderly (>65 years of age) than in the younger population (about 2000 versus about 200 per 100,000 per year).

The accepted reference diagnosis in pneumonia should be based on detecting of pathogenic agents in lung specimens with suggestive clinical findings.[9] Early diagnosis and treatment of CAP is life-saving. In meta-analyses, it is stated that pneumonia treatment should be started within four hours and eight hours at the latest.[10] However; this cannot be accomplished in routine clinical practice for obvious practical reasons. Therefore, pneumonia is usually suspected when the person has complaints and signs of lung infection and is confirmed by the finding of a new infiltration area on radiological examination.[11]

The sequelae seen in pneumonia depend on the etiologic agent and the complications that develop during and after treatment. Linear bands, ectatic bronchial segments and fibrotic lung areas are observed in a particular proportion of patients with pneumonia.[12] These fibrotic structures and bands are known to be more common in viral infections, especially COVID-19.[13,14] Although some evidence suggests the role of viruses in the pathogenesis of pulmonary fibrosis, the role of bacteria is much less known; The only observational evidence was provided by Richter et al.[15] Infectious agents, including viruses and bacteria, can cause alveolar-epithelial cell damage and apoptosis. There are relatively few studies that have examined the role of infection in the development of pulmonary fibrosis. Those who have it point out that viruses play a crucial role as cofactors in the initiation and progression of fibrosis.[16]

Infections can induce pulmonary fibrosis by directly damaging the lung or causing damage through the immune system. After the pathogenic agent reaches the lung, inflammatory infiltration activates the immune system. Macrophages, neutrophils, eosinophils and Th^2 cells gather at the injury site, releasing numerous pro-inflammatory and pro-fibrotic cytokines/factors. The direct action of the pathogen and the combination of these factors promote pulmonary fibrosis, causing permanent and significant lung damage.[13] Molecular microbiological techniques emerging daily facilitate the study of microbial communities in the lung. Combining such techniques with careful longitudinal phenotyping of patients with pulmonary fibrosis makes it seems that it will be possible to elucidate the role of bacteria and viruses in the pathogenesis of the disease.[16]

Postinfectious parenchymal sequelae that develop in individuals may show loss of function according to the level of sequelae that develop in these individuals. We aimed to investigate the frequency of pulmonary fibrosis and other sequelae parenchymal lesions and and the factors affecting pulmonary fibrosis in patients with CAP.

METHODS

Participants and Study Design

The study was carried out with the permission of Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (Date: 10.10.2023, Decision No: 2464). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study included patients diagnosed with CAP. In this study, individuals over 18 years of age, regardless of gender who applied to the Chest Diseases Outpatient Clinic of the University of Health Sciences Şişli Hamidiye Etfal Training and Research Hospital between 01.08.2022 and 01.08.2023, were selected.

Firstly, patients who applied to the chest diseases outpatient clinic due to any complaint and underwent chest CT because pathology was detected in chest X-rays were selected for the study. The records of these patients were retrospectively analyzed using the hospital management system records. Twelve months ago, patients who received CAP treatment in the emergency department of our hospital were selected. Patients with complete file information at the time of initial CAP diagnosis (complaints, history information, examination findings, chest X-ray, computed tomography and laboratory tests) were included in the study. Patients with chest CT in the outpatient clinic of chest diseases were included in the study. Patients whose lung-CT reports were interpreted by the radiologist and whose reports were recorded in the hospital information system were also included in the study. In 2011, ATS, ERS, JRS and ALAT published a joint report and defined reticular densities, honeycomb findings (± traction bronchiectasis), predominant involvement of the subpleural and basal areas and the absence of findings incompatible with the usual interstitial pneumonia as interstitial fibrosis patterns.[17] Those with these radiological features were considered pulmonary fibrosis.

Patients with missing files, immune system disorders and malignancies were excluded. Also, patients with known interstitial lung disease and radiologically interstitial pathological appearance at the time of initial diagnosis of CAP were excluded. Patients medical records and charts were analyzed. Laboratory data of patients diagnosed with pneumonia; procalcitonin, C-reactive protein (CRP) and hemogram (neutrophil-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and platelet-lymphocyte ratio (PLR) were calculated and white blood cell (WBC) count value was examined). Due to the COVID-19 pandemic period COVID-19-PCR and other viral infection markers (respiratory syncytial virus, influenza, parainfluenza, adenovirus) were accepted as respiratory panels.

The x-ray/chest CT results of the patients received in the study in the emergency department were collected in 5 groups with the joint decision of the consultant (at least post-fellowship experience of ten years) participating in the study;

1-Pneumonia in one lobe,

2-Unilateral multisegmental pneumonia or bronchopneumonia,

3-Unilateral multilobar pneumonia,

4-Bilateral multisegmental pneumonia or bronchopneumonia,

5-Bilateral lobar pneumonia.

The chest CT results of the patients received in the study were evaluated in terms of sequelae lesions and collected in 5 groups;

0-Normal,

1-Single linear atelectasis/band formation, ectasia in a single bronchus,

2-Parenchymal fibrotic changes in the pneumonia area. The change area is less than the right middle lobe medial segment area,

3-Parenchymal fibrotic changes are present in the pneumonia area. The change area is more than the medial segment of right middle lobe but less than the entire right middle lobe,

4-Parenchymal fibrotic changes in the pneumonia area. The change area is more than the right middle lobe area.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences software (version 17.0; IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to test the data distribution. Continuous variables are presented as mean±standard deviation (SD) for those with a normal distribution or median (minimum-maximum) for those without a normal distribution. Categorical variables are presented as numbers and percentages n (%).The chi-square test was applied to crosscheck categorical data. Independent risk factors affecting radiological changes were analyzed by logistic regression, and the ROC curve was used to evaluate the diagnostic sensitivity, specificity, and optimal cutoff value of each index. Kruskal Wallis test was used to compare numerical parameters according to fibrotic changes subgroups, since the data did not show normal distribution. All analyses were appreciated at a 95% confidence interval and significance was appreciated at $p<0.05$.

RESULTS

Demographic Characteristics

This study included 80 patients with clinically and radiologically diagnosed CAP, regardless of gender. The mean age was 56.8±13.4. Thirty-two (40%) were female and 48 (60%) were male. The mean body mass index of the patients was 28.8±5.9. Thirty-seven (46.2%) our patients had chronic diseases; 15 (18.7%) had hypertension, 15 (18.7%) had diabetes mellitus, 11 (13.7%) had coronary artery disease and 4 (5%) had chronic kidney failure. According to smoking habits, 29 (36.3%) patients were current smokers, 31 (38.8%) had quit smoking and 20 (25%) had never smoked (Table 1).

Clinical Characteristics and Laboratory Findings

The most common complaint was cough, 67 (83.75%) of patients. Chest pain was present in 47 (58.75%) patients and sputum in 56 (70.0%). In addition, 49 (61.25%) patients had a fever, 43 (53.75%) shortness of breath and 7 (8.75%) hemoptysis. Mean values of laboratory results: fasting glucose 140.46±61.1 g/dl, alanine aminotransferase 31.4±21.3 U/L, aspartate aminotransferase 39.34±28.5 U/L, urea 34.6±19.4 mg/dL, creatinine 0.98±0.6 mg/dl, lactic dehydrogenase 315.7±116.3 U/L, ferritin 373.79±298.2 ng/ml, procalcitonin 0.64±2.1 ng/ml, C-reactive protein 100.36±69.3 mg/L, white blood cell count 9.66±4.1 10^9/ml, Neutrophil-lymphocyte ratio 8.42±8.2, monocyte lymphocyte ratio 0.52±0.4, platelet lymphocyte ratio 246.58±185. SARS-COV2-PCR and viral infection markers accepted as respiratory panels in our hospital (respiratory syncytial virus, influenza, parainfluenza, adenovirus) were negative.

Table 1. Baseline demographic and laboratory findings of the study population

Characteristics	Patients (n=80)
Gender, n(%)	
Female	32 (40%)
Male	48 (60%)
Age, year, mean±SD (minimum-maximum)	56.8 ±13.4(18-71)
BMI, year, mean±SD	28.8±5.9
Smoking, n(%)	
Smoking	29 (36.3%)
Qut	31 (38.7%)
Never smoked	20 (25.0%)
Chronic diseases, n(%)	
Hypertension	15 (18.7%)
Diabetes mellitus	15 (18.7%)
Chronic kidney failure	4 (5.0%)
Coronary artery disease	11 (13.7%)
Chronic heart failure	5 (6.2%)
Laboratory parameters, mean±SD	
White blood cell (10^9/ml)	9,66 ± 4.1
Procalcitonin (ng/ml)	0,64 ± 2.1
C-reaktive protein (mg/L)	100,36 ± 69.3
NLR	8,42 ± 8.2
PLR	246.58 ± 185
MLR	0.52 ± 0.4

BMI: Body mass index, SD: Standard deviation, NLR: neutrophil-to-lymphocyte ratio,PLR: platelet-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio

Radiological Findings

According to the radiological findings at the time of diagnosis of CAP in the emergency department: 36 (45%) patients had single lobe pneumonia, 9 (11.3%) unilateral multisegmental pneumonia or bronchopneumonia, 13 (16.3%) unilateral multilobar pneumonia, 14 (17.5%) multisegmental pneumonia or bronchopneumonia, and 8 (10%) bilateral lobar pneumonia. Patients with sequelae in chest CT taken during chest diseases outpatient clinic examination were divided into four groups. Chest CT was normal in 23 (28.8%) patients and 34 (42.5%) patients had single linear atelectasis/band formation and ectasia in a single bronchus. Eighteen (22.5%) patients had parenchymal fibrotic changes in the area where pneumonia was passed, the change area was less than the medial segment area of the right middle lobe. Three (3.8%) patients had parenchymal fibrotic changes in the area of pneumonia; the area of change was more than the medial segment of the right middle lobe but less than the entire right middle lobe, and 2 (2.5%) patients had pneumonia (Table 2).

Table 2. Distribution of sequelae lesions after 12 months based on the initial diagnosis

		Sequeale					
	n:80	Normal n (%)	Single linear atelectasis/ band formation, ectasia in a single bronchus n (%)	Parenchymal fibrotic changes in the pneumonia area, the change area is less than the right middle lobe medial segment area n (%)	Fibrotic changes are present in the pneumonia area, the change area is more than the right middle lobe medial segment but less than the entire right middle lobe n (%)	Fibrotic changes in the pneumonia area, the change area is more than the right middle lobe area n (%)	Total n (%)
First radiology	Pneumonia in one lobe,	14 (17.5)	18 (22.5)	4 (5.0)	4 (5.0)	0 (0)	36 (45.0)
	Unilateral multisegmental pneumonia or bronchopneumonia,	4 (5.0)	3 (3.75)	2 (2.5)	2 (2.5)	0 (0)	9 (11.25)
	Unilateral multilobar pneumonia	2 (2.5)	6 (7.5)	5 (6.25)	5 (6.25)	0 (0)	13 (16.25)
	Bilateral multisegmental pneumonia or bronchopneumonia	3 (3.75)	5 (6.25)	4 (5.0)	4 (5.0)	0 (0)	14 (17.5)
	Bilateral lobar pneumonia.	0 (0)	2 (2.5)	3 (3.75)	3 (3.75)	2 (2.5)	8 (10.0)
	Total	23 (28.75)	34 (42.5)	18 (22.5)	3 (3.75)	18 (22.5)	80 (100)

In Table 2, 23 (28,7%) patients did not have pathology in the control chest CT, while 57 (71.3%) patients had various levels of sequelae changes. Of the sequelae observed in 57 patients, 34 (42.5%) had single linear atelectasis or single band formation or ectasia in a single bronchus, while 23 (28.7%) showed fibrotic structure. Five (6.25%) patients showed signs of pulmonary fibrosis.

Correlation Analyzes of Radiological Lesions

Risk factors were evaluated for developing sequelae lesions and fibrosis. Age and smoking had a statistically significant effect on the development of fibrosis in CAP patients. This was statistically significant ($p < 0.05$). No effect was found between gender, CRP, NLR, MLR or PLR and the development of fibrosis in patients with CAP ($p > 0.05$) (Table 3).

A relationship was found between the CAP patients' age and the fibrotic changes The cut off value was 55.5 with a sensitivity of 77.2% and a specificity of 82.6% for age, which was statistically significant (Logistic Regression Analysis; $p=0.0001<0.01$). Change in age explains 36.4% of the presence of fibrosis. A one-unit enhancement in age increases the existence of fibrosis by 1.112 times. The effect of age risk factor on fibrotic changes is demonstrated by ROC analysis.

Table 3. Analysis of logistic regressions examining the impact of risk factors on radiological sequelae

Fibrosis risk factors	x^2	p (Model)	-2 Log likelihood	R^2	B	Standard deviation	Wald	sd	p	Exp(B)
Age	23.481	0.0001**	72.503	0.364	0.106	0.027	15.053	1	0.0001	1.112
Gender	0.01	0.92	95.973	0	0.051	0.505	0.010	1	0.92	1.052
Smoking	9.667	0.002**	86.317	0.163	1.094	0.383	8.142	1	0.004	2.986
CRP	3.727	0.054	92.257	0.065	0.008	0.004	3.125	1	0.077	1.008
NLR	3.514	0.061	92.47	0.061	0.086	0.057	2.283	1	0.131	1.090
MLR	0.307	0.579	95.677	0.005	-0.332	0.591	0.315	1	0.575	0.718
PLR	0.377	0.539	95.607	0.007	0.001	0.001	0.354	1	0.552	1.001

The vertical axis: Fibrosis risk factors, the horizontal axis: Statistical analysis values. Abbreviations: CRP: C-reactive protein, NLR: neutrophil-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, PLR: platelet-lymphocyte ratio,** statistically significant.

DISCUSSION

In this study, it was shown that two-thirds of the patients treated for CAPP had radiological sequelae. One year after CAP treatment, mild to severe fibrotic changes were observed in two-third of our patients. Minimal changes were observed in about one-third of patients, while moderate to severe fibrotic changes were observed in one-fourth of the patients. Five patients showed signs of pulmonary fibrosis. In our study, fibrotic changes were found to be highly correlated and smoking. Procalcitonin, CRP, NLR, MLR and PLR values had no predictor effect of on the development of fibrosis in CAP patients.

Presently, literature studies in the world have focused on the etiology, risk factors and related treatment strategies of CAP. The pathogen often seen in CAP is Streptococcus pneumonia.[18] Most radiological changes mentioned in studies have been

with age shown in viral pneumonia cases.[13,14] Our study is important in demonstrating radiological changes in a disease in where the major pathogen is bacteria. The diagnosis of CAP and therefore the rate of hospitalization have been shown to be higher in the older adults than in the younger.[8] In addition, smoking is a strong and independent risk factor for progressive pneumococcal disease in all age groups.[19] It is important to show the effect of these two factors on the sequelae that develop due to CAP.

After a lung infection, it is essential to repair the tissue architecture to regain the normal organ function of the lung. Pulmonary fibrosis and the associated remodeling of the lung can severely impair lung function and often have fatal consequences. Wilson and Wynn described the mechanisms of the development of pulmonary fibrosis in their review. In this review, they collected inflammation and healing in 3 stages (1-Injury, 2-Inflammation, 3-Fibroblasts contract) and stated that slowing or deficiency in any of these stages causes deterioration of tissue architecture.[20] Molyneaux and Maher investigated the pathogenesis of IPF. They said that bacteria and viruses have the potential to cause bronchial and alveolar epithelial cell damage and apoptosis and have the capacity to regulate the host response to damage in both types of agents.[16] **A**n article showed that individuals with lung fibrosis had a high bacterial load in the BAL fluid.[21] In our study, about a quarter of patients did not detect any pathology on chest CT after one year. Thirty-four patients had parenchymal changes, defined as 'single linear atelectasis or single band formation or ectasia in a single bronchus, which we did not associate with fibrosis. In eighteen patients, there were fibrotic changes in the pneumonia area and the area of change was less than the medial segment area of the right middle lobe. Five patients showed signs of pulmonary fibrosis.

Biological lung aging is characterized by structural changes and advancing loss of physiological totality, which leads to dysfunction. Although the mechanisms contributing to the aging process are unclear, nine putative distinguishing characteristics associated with the aging phenotype have recently been proposed. It is not accepted how these features contribute to the aging lung.[22] Studies have shown that aging imparts a profibrotic phenotype to fibroblasts and increases the severity of the fibrogenic response in IPF and non-IPF fibrotic lung disorders.[23,24] Delgado et al.[25] reported that NLRP3 inflammatory activity and oxidative stress increased with age contributing to the improving of pulmonary fibrosis. A review, it was stated that aging is related to a wide range of biological changes and is therefore a critical risk factor for pulmonary fibrosis. In the article, it is said that the improvement of pulmonary fibrosis is the result of multiple processes working together, including environmental and metabolic factors such as epigenetic, transcriptional, posttranscriptional, and often infection, in individuals who are susceptible or genetically predisposed due to aging.[26] Age had a statistically prominent effect on fibrosis in patients with CAP. Change in age explains 36.4% of the presence of fibrosis. A one-unit increase in age increases the presence of fibrosis by 1,112 times. ROC analysis showing the link between age and sequelae-fibrosis is observed in Figure.

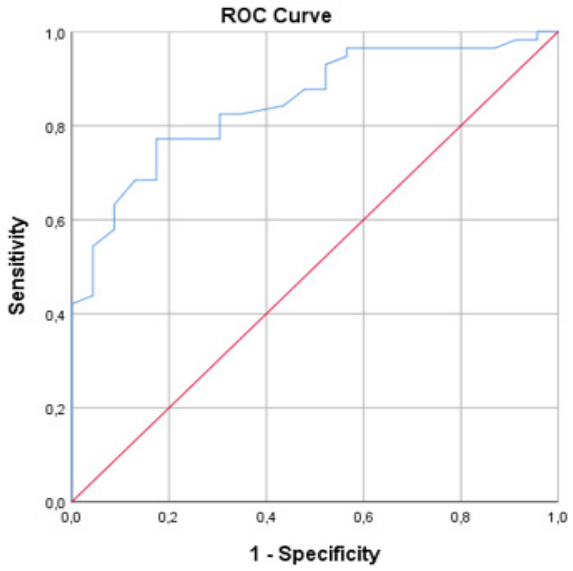

Figure. Demonstration of the effect of age risk factor on fibrotic changes by ROC analysis
* Sensitivity: 77.2%, Specificity: 82.6%, cut off: 55,5, Area Under Curve: 0,84(0,76;0,93)

Although numerous studies indicate that smoking subscribes to the development of lung fibrosis, it is not known how it subscribes to the pathogenesis of fibrosis. Among the risk factors for developing fibrosis, smoking appears to be the most potent risk factor with both sporadic and familial pulmonary fibrosis.[27] In the study, Bellou et al.[28] observed a dose-reply relationship between pack-years of smoking and lung fibrosis in smokers (HR per 1-pack-year increase, 1.013; 95% CI, 1.009–1.016). In a review, it was concluded that smoking increased the development of pulmonary fibrosis with a odds ratio of 1.39 (95% CI 1.01–1.91, I 2=29%).[29] Again, in a comprehensive review, it was stated that smoking is a well-known etiological factor linked to the development of lung cancer, obstructive pulmonary diseases and various types of interstitial lung disease.[30] In this review, it is emphasized that smoking contributes to the formation of fibrosis in the lungs and that both genetic and exogenous triggers such as allergens or infections play a role in this process. Smoking has a statistically considerable effect on the existence of fibrosis in our patients with CAP. Smoking explains 16.3% of the presence of fibrosis. Smoking increases the presence of fibrosis by 2.986 times.

Apart from age and smoking risk factors, we investigated the correlation of biomarkers performed in the emergency department at the time of diagnosis that may affect the development of fibrosis. There was no statistically prominent effect of procalcitonin, CRP, NLR, MLR and PLR values on the presence of fibrosis in our patients with CAP who participated in the study.

Limitations

Our study had several limitations. The most notable constraint was the absence of recorded medical histories. A considerable number of pneumonia patients were ineligible for inclusion in the study due to the absence of radiological

images. The second major limitation is that although a lot of CAP is diagnosed in the emergency department, diagnosis and treatment are performed without adequate confirmatory examination due to the patient density. This lack of examination may cause diagnosis and treatment errors. This caused the number of patients in the study to be less than expected.

CONCLUSION

As we know, community-acquired pneumonia is an infectious disease that affects all segments of society. Studies have mainly focused on its etiology and treatment. We investigated the frequency of fibrosis development, which is one of the outcomes of this disease. One year after undergoing CAP, bronchiectasis and atelectasis were observed in one-third of our patients. About one-third of them had mild to severe fibrotic changes. Fibrotic changes were highly correlated with age and smoking. More studies should be conducted on the sequelae fibrotic changes observed in patients. Our follow-ups continue to show long-term progression.

ETHICAL DECLARATIONS

Ethical Approval

This study was approved by the Ethics Committee of the University of Health Sciences Şişli Hamidiye Etfal Training and Research Hospital (10.10.2023/2464).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Evaluation of the effect of the quality and quantity of fluid drained due to pleural effusion on complications that may develop in intensive care unit

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ABSTRACT

Aims: Pleural drainage volume is very important for oxygenation and perfusion in patients with massive pleural effusion. However, there is still no clear data between the complications that may develop after pleural drainage and the optimal volume of fluid to be removed. The primary aim of this study was to evaluate the effect of the quality and quantity of pleural fluid drained due to pleural effusion in the intensive care unit (ICU) on the complications that may develop after drainage and to determine the optimal drainage volume to prevent complications. The secondary aim was to determine the risk factors affecting the development of complications after pleural effusion drainage.

Methods: A total of 176 patients who underwent pleural drainage for pleural effusion between April 1,2022 and December 31,2023 in an adult tertiary ICU were retrospectively analyzed. Demographic information, clinical follow-up information, quantity and quality of pleural effusion, laboratory values and complications were recorded and the relationship between these parameters and the amount of pleural fluid drained within 24 hours and complications were evaluated.

Results: ICU duration, ICU mortality, activated partial thromboplastin time (aPTT) and vasopressor requirement were found to be statistically significantly higher in patients with complications after pleural drainage procedure. In multivariate logistic regression analysis, female gender (odds ratio=0.455, p=0.049) and need for vasopressors (odds ratio=2.373, p=0.034) increased the risk of complications. There was no statistically significant difference between the amount of pleural fluid drained and complications. In addition, when the optimal amount of drained fluid required to prevent complications was analyzed, a cut off value could not be given.

Conclusion: In order to reduce the risk of complications that may develop after pleural drainage, we believe that paying more attention to the position during pleural drainage in patients receiving vasopressor support and performing pleural drainage with the help of ultrasound in patients whose position cannot be changed due to hemodynamic disorder will reduce the complication rate. We think that a decrease in the complication rate will be effective in terms of both cost and efficient use of ICU beds by reducing the length of ICU stay and ICU mortality. In our study, the quality and quantity of pleural fluid drained had no effect on the complications that may develop after drainage, and further studies with a larger patient population are needed to investigate this situation.

Keywords: Chest tube, complications, pleural effusion, pleural volume, pneumothorax

INTRODUCTION

Pleural effusion is a common finding in intensive care unit (ICU) patients. Drainage of pleural fluid is necessary in situations such as alleviating developing symptoms, making a diagnosis, and draining an infection site.[1] Pleural infection, such as empyema, is a high-mortality diagnosis that can be missed if pleural fluid analysis is not conducted. Thoracentesis can change the likely diagnosis of the effusion in up to 45% of patients. Although pleural drainage under ultrasound guidance is safer, serious complications such as internal organ injury, bleeding, and even death can occur during or after the drainage.[2]

Major complications of thoracentesis are rare.[3] The primary complications are pneumothorax, hemothorax, Inappropriate catheter positioning, infection, and re-expansion pulmonary edema (REPE), with pneumothorax being the most frequently observed complication, occurring with an incidence of 0-6%.[4,5]

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This is followed by hemothorax with an incidence of 1.6%.[6] It is thought that REPE, a rare complication, may be associated with the formation of excessive negative pleural pressure.[3]

The amount of fluid drained during pleural drainage is very important for oxygenation. Roch et al,[7] have found that an increase in the PaO_2/FiO_2 ratio occurs when the volume of pleural effusion drained is greater than 500 mL. Although consensus guidelines recommend limiting the volume of pleural fluid drained at any one time to 1.5 L as a method to reduce the risk of complications, some studies have shown reasonable safety even with larger drainage volumes reaching up to 6.5 L.[4,8] However, studies suggesting that REPE occurs as a result of draining large volumes emphasize the need to drain less than 1.5 L.[3, 4]

There are numerous studies indicating that the risk of pneumothorax increases with drainage volumes greater than 1.5 liters. On the other hand, a recent study has shown that the risk of complications is higher after small-volume drainages and that a drainage volume of 975 ml is the optimal threshold for complications.[3,5]

Many publications have stated that there is a need for further studies due to the lack of clear data on the optimal volume of fluid to be removed after pleural drainage and the complications that may develop. The primary aim of this study is to evaluate the quality and quantity of pleural fluid drained due to pleural effusion in the ICU, its impact on complications that may develop after drainage, and to determine the optimal drainage volume to prevent complications. The secondary aim is to identify risk factors that influence the development of complications after pleural effusion drainage.

METHODS

The study was carried out with the permission of Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee (Date: 27.03.2024, Decision No 2024-BÇEK/52.)

176 patients over the age of 18 who underwent pleural drainage due to pleural effusion were included in the study at the Adult Tertiary ICU of University of Health Sciences Ankara Atatürk Sanatorium Training and Research Hospital, between April 1, 2022, and December 31, 2023..

ICU patients over the age of 18, diagnosed with massive pleural effusion through clinical findings, physical examination, and radiological assessment, and who underwent pleural drainage were included in the study. Patients under the age of 18, those who had a pleural drainage catheter placed before ICU admission, those who had drainage of spaces other than the pleural cavity, and patients admitted to the ICU due to bleeding, pneumothorax, pleural infection, or pulmonary edema, as well as those lacking necessary data for the research, were excluded from the study.Considering the amount of pleural effusion on the PA chest roentgenogram, fluid covering more than 2/3 of the hemithorax was defined as a "massive" amount of fluid.[9]

Since a patient may undergo multiple drainage procedures and each procedure carries a risk of complications, each procedure was evaluated as a separate case. In our clinic, patients diagnosed with pleural effusion are assessed by the department of thoracic surgery, and pleural drainage is performed by an experienced doctor from the same department when deemed necessary. After pleural drainage, regular follow-up including plain chest radiographs, vital signs, physical examinations of the patients, laboratory values, and blood gas analyses are conducted to monitor for any complications. In the literature, all complications that developed after pleural drainage, including the most commonly reported complications such as pneumothorax, hemothorax, Inappropriate catheter position, pleural infection, and REPE, were recorded.

Patients' age, gender, additional diseases, Charlson comorbidity index score (CCIS), the volume of fluid drained within 24 hours via pleural drainage, the cause of the pleural effusion, presence of complications after drainage, need for vasopressors, mechanical ventilation support, length of ICU stay, ICU mortality, one-month mortality status, characteristics of the pleural effusion fluid (whether it is exudate or transudate), and laboratory values were recorded. Laboratory values included pleural fluid protein, pleural lactate dehydrogenase (LDH), and pleural culture results from the pleural fluid sample, as well as serum total protein, serum LDH, albumin, sodium, creatinine, glomerular filtration rate (GFR), leukocytes, hemoglobin, hematocrit, platelets, Prothrombin Time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and venous blood gas analyses sent on the day of the pleural effusion drainage. The parameters observed and the volume of fluid drained were compared with the presence of complications. Additionally, the optimal volume of fluid to be drained to prevent complications was investigated.

Statistical Analysis

Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables was normal or not was determined by the Kolmogorov Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean, standard deiviation, median (Min- max) for skewed distributions. Categorical data were described as a number of cases (%). Statistical analysis differences in not normally distributed variables between two independent groups were compared by Mann Whitney U test. Categorical variables were compared using Pearson's chi-square test or fisher's exact test.

Univariate and multivariate logistic regression analyses were performed to assess the association between complication the risk factors findings. Risk factors with a p-value < 0.25 in the univariate logistic regression model were included in the multivariate logistic regression analysis. Enter model used in multivariable logistic regression. Whether every independent variables were significant on model was analyzed with Wald statistic on multivariable logistic regression. It was accepted p-value <0.05 as significant level on all statistical analysis.

RESULTS

The data of 176 patients who underwent pleural drainage due to pleural effusion in a ten-bed adult tertiary general ICU were

retrospectively analyzed. Table 1 examined the relationship between the presence of complications developed after the pleural drainage procedure and the amount of fluid drained for each complication. However, no statistically significant difference was observed between the amount of fluid drained and the complications.

Table 1. Comparison of the amount of fluid drained and complications

Complications		Amount of fluid drained						
		n	Mean	Standard Deviation	Median	Min	Max	P
Pleural infection	No	168	1105.36	706.96	1000.0	300	4000	0.412
	Yes	8	825.00	249.28	800.0	600	1200	
Pneumothorax	No	150	1114.00	686.89	1000.0	300	4000	0.110
	Yes	26	969.23	741.23	700.0	300	3000	
Hemothorax	No	171	1088.89	695.15	1000.0	300	4000	0.633
	Yes	5	1220.00	752.99	900.0	300	2000	
Inappropriate catheter positioning	No	169	1108.28	703.26	1000.0	300	4000	0.144
	Yes	7	714.29	247.85	800.0	400	1000	
REPE	No	174	1087.93	697.50	900.0	300	4000	0.178
	Yes	2	1500.00	.00	1500.0	1500	1500	
Presence of complication	No	129	1141.09	713.12	1000.0	300	4000	0.081
	Yes	47	959.57	630.27	800.0	300	3000	

Continuous variables are expressed as median (Min-max),Mann Whitney u Test p=Level of Significance, p<0,05
REPE: Re-expansion Pulmonary Edema

According to the ROC curve analysis conducted to determine the optimal amount of fluid to be drained to prevent complications after pleural drainage, the area under the curve (AUC) was calculated as 0.586, and no statistically significant difference was found (p>0.05). This indicates that no specific cut off can be provided for the optimal amount of fluid drained to prevent complications (Table 2, Figure).

Table 2. ROC curve analysis for optimal amount of fluid drained

AUC	Std. Error	p	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.586	0.048	0.082	0.492	0.680

AUC:area under the curve

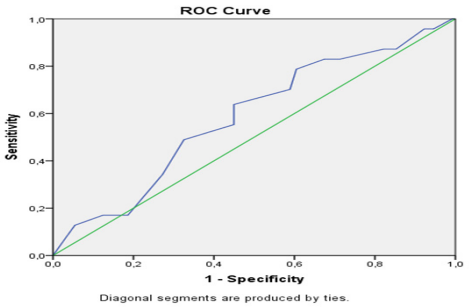

Figure. ROC curve analysis

When comparing the parameters examined in the study according to the presence of complications, the length of ICU stay and aPTT were found to be statistically significantly higher in those with complications (Table 3).When comparing other parameters examined in the study according to the presence of complications, the need for vasopressors and the ICU mortality rate were found to be statistically significantly higher in those with complications (Table 4).

Table 3. Comparison of variables with the presence of complications -1

	Complication		
	No	Yes	p
Age (year)	72.00 (29.00-99.00)	70.00 (33.00-90.00)	0.495
CCIS	8.00 (0-16.00)	7.00 (0-14.00)	0.114
Length of ICU stay (day)	10.00 (2.00-110.00)	17.00 (2.00-86.00)	0.015
Leukocyte (x103/µl)	10.80 (0.20-66.00)	11.10 (4.60-42.00)	0.879
Hemoglobin (g/dl)	11.00 (6.60-17.10)	11.00 (6.40-16.40)	0.692
Hematocrit (%)	34.40 (20.30-72.00)	35.30 (18.60-52.00)	0.799
Platelet (x103/µl)	262.00 (18.00-982.00)	236.00 (54.00-558.00)	0.179
PT (s)	14.00 (10.60-59.00)	14.40 (11.40-39.00)	0.969
aPTT (s)	26.70 (12.00-113.00)	29.50 (18.90-78.00)	0.032
INR	1.20 (0.90-5.60)	1.23 (0.90-3.70)	0.965
Sodium (mmol/L)	138.00 (122.00-185.00)	138.00 (118.00-158.00)	0.968
Creatinine (mg/dl)	0.96 (0.30-5.60)	0.90 (0.36-80.00)	0.991
GFR (mL/dk/1.73 m²)	83.00 (6.80-138.00)	72.00 (20.00-122.00)	0.894
Pleural protein (g/dl)	22.00 (11.10-49.00)	21.30 (8.70-99.00))	0.909
Total protein (g/dl)	48.00 (23.00-69.00)	50.00 (28.00-118.00)	0.941
LDH (U/L)	357.00 (146.00-987.00)	351.00 (71.00-725.00)	0.393
Pleural LDH (U/L)	165.00 (29.00-1934.00)	126.00 (35.00-15098.00)	0.159
Albumin (g/dl)	28.00 (12.50-42.00)	25.10 (17.00-40.00)	0.115
VBG pH	7.40 (6.90-7.67)	7.40 (7.03-7.65)	0.817
VBG pCO_2 (mmHg)	42.00 (20.10-146.00)	48.00 (19.20-144.00)	0.098
VBG pO_2 (mmHg)	41.80 (13.00-171.00)	40.00 (4.00-80.00)	0.927
VBG HCO_3 (mmol/L)	26.00 (13.00-50.80)	27.70 (11.40-53.30)	0.249

Continuous variables are expressed as median (min-max),Mann Whitney u Test p= Level of Significance, p<0,05
CCIS:Charlson Comorbidity Index Score, ICU:Intensive Care Unit, PT: Protrombin Time, aPTT: Activated Partial Thromboplastin Time, INR: International Normalized Ratio, GFR: Glomeruler Filtration Rate, LDH: Lactate Dehydrogenase: VBG: Venous blood gas, pCO2:Partial pressure of carbon dioxide, pO2: Partial pressure of oxygen, HCO3: Bicarbonate

A logistic regression analysis was conducted to identify factors that increase the risk of complications among the patients included in the study. Due to the very low number of patients in individual complications, it was applied for the total number of complications. A univariate logistic regression analysis was conducted for factors thought to be associated with the risk of complications. In the univariate logistic regression analysis, the need for vasopressors (odds ratio=2.342, p=0.018) was considered a factor that increases the risk of complications (Table 5).

Variables with a p-value <0.25 from the univariate analysis were included in the multivariate analysis. The multivariate logistic regression analysis found that being female (odds ratio=0.455, p=0.049) and the need for vasopressors (odds ratio=2.373, p=0.034) were factors that increased the risk of complications (Table 6). Since the number of patients with individual complications was very low in our study, a comparison was made for the total number of complications. However, when we looking at which complications these two risk factors increase separately, the number of patients with pneumothorax was 10, the number of patients with pleural infection was 3, the number of patients with inappropriate catheter was 2, the number of patients with hemothorax was

2, and the number of patients with REPE was 1 in the female gender. When those who needed vasopressors were analyzed, the number of patients with pneumothorax was 12, the number of patients with inappropriate catheters was 4, the number of patients with pleural infection was 1, the number of patients with hemothorax was 1 and the number of patients with REPE was 1.

Table 4. Comparison of variables with the presence of complications-2

		Complication				
		No		Yes		
		n	%	n	%	
Gender	Female	41	31.8%	21	44.7%	0.113
	Male	88	68.2%	26	55.3%	
1-Month Mortality	No	83	64.3%	24	51.1%	0.110
	Yes	46	35.7%	23	48.9%	
Vasopressor agent Support	No	98	76.0%	27	57.4%	0.017
	Yes	31	24.0%	20	42.6%	
Need for IMV	No	64	49.6%	20	42.6%	0.407
	Yes	65	50.4%	27	57.4%	
Need for NIMV	No	99	76.7%	30	63.8%	0.087
	Yes	30	23.3%	17	36.2%	
ICU mortality	No	93	72.1%	21	44.7%	0.001
	Yes	36	27.9%	26	55.3%	
Exuda/ Transuda	Exuda	80	62.0%	23	48.9%	0.119
	Transuda	49	38.0%	24	51.1%	

Categorical variables are expressed as either frequency (percentage). Chi square Test β p=Level of Significance, p<0,05
IMV:Invasive Mechanic Ventilation, NIMV: Non-Invasive Mechanic Ventilation, ICU: Intensive Care Unit

Table 6. Multivariate logistic regression analysis applied to determine factors affecting complications

	Multivariate Logistic Regression				
				95% C.I.for EXP(B)	
	Wald	p	OR	Lower	Upper
Gender (ref kat:female)	3.871	0.049	0.455	0.208	0.997
Amount of fluid drained	1.942	0.163	1.000	0.999	1.000
Exuda/ Transuda	0.779	0.378	1.431	0.645	3.173
Vasopressor agent support	4.488	0.034	2.373	1.067	5.279
NIMV	0.099	0.753	1.160	0.460	2.926
Length of ICU stay	0.757	0.384	1.009	0.988	1.031
CCIS	2.947	0.086	0.899	0.796	1.015
Platelet	1.680	0.195	0.998	0.995	1.001
aPTT	0.657	0.418	1.012	0.983	1.042
Serum LDH	1.399	0.237	0.998	0.996	1.001
Serum albumin	2.609	0.106	0.945	0.881	1.012
VBG pH	0.212	0.645	5.791	0.003	10191.444
VBG pCO_2	0.995	0.318	1.023	0.978	1.071
VBG HCO_3	0.033	0.856	0.991	0.900	1.091

Wald: test statistics, OR: odds radio, CI: Confidence interval. hosmer-lemeshow: p>0,05. p=Level of Significance, p<0,05. Statistically significant p-values are in bold.
NIMV: Non-Invasive Mechanic Ventilation, ICU: Intensive Care Unit, CCIS:Charlson Comorbidity Index Score, aPTT:activated Partial Thromboplastin Time, LDH: Lactate Dehydrogenase, VBG:venous blood gas, pCO2: partial pressure of carbon dioxide, HCO3: Bicarbonate

DISCUSSION

In this study of 176 patients who underwent pleural drainage for pleural effusion in ICU, it was found that being female and the need for vasopressors increased the risk of complications after pleural drainage. Additionally, the presence of complications was ssociated with higher aPTT, a longer ICU stay, and higher

Table 5. Univariate logistic regression analysis applied to determine factors affecting complications

	Univariate Logistic Regression				
				95% C.I.for EXP(B)	
	Wald	p	OR	Lower	Upper
Age	0.532	0.466	0.991	0.969	1.015
Gender	2.485	0.115	0.577	0.291	1.143
Amount of fluid drained	2.305	0.129	1.000	0.999	1.000
Exuda/ Transuda	2.404	0.121	1.704	0.869	3.341
Vasopressor agent support	5.591	0.018	2.342	1.157	4.741
Need for IMV	0.686	0.407	1.329	0.678	2.606
Need for NIMV	2.890	0.089	1.870	0.909	3.848
Length of ICU stay	2.612	0.106	1.014	0.997	1.032
CCIS	2.898	0.089	0.919	0.833	1.013
Leukocyte	0.106	0.745	1.006	0.971	1.042
Hemoglobin	0.189	0.664	0.968	0.838	1.119
Hematocrit	0.237	0.626	0.989	0.946	1.034
Platelet	2.561	0.110	0.998	0.995	1.000
PT	0.311	0.577	0.981	0.918	1.049
aPTT	1.751	0.186	1.016	0.992	1.041
INR	0.163	0.687	0.866	0.432	1.738
Sodium	0.004	0.948	0.999	0.956	1.043
Creatinine	0.909	0.340	1.046	0.953	1.148
GFR	0.006	0.941	1.000	0.989	1.010
Pleural protein	0.145	0.703	1.006	0.975	1.038
Serum Total protein	0.216	0.642	1.006	0.980	1.033
Serum LDH	1.648	0.199	0.999	0.996	1.001
Pleural LDH	1.001	0.317	1.000	1.000	1.001
Serum albumin	1.832	0.176	0.959	0.903	1.019
VBG pH	0.116	0.733	0.607	0.034	10.713
VBG pCO_2	3.439	0.064	1.017	0.999	1.034
VBG pO_2	0.079	0.779	0.997	0.978	1.017
VBG HCO_3	1.701	0.192	1.027	0.987	1.069

Wald: Test statistics, OR: Odds radio, CI: Confidence interval. hosmer-lemeshow: p>0,05. p=Level of significance, p<0,05. Statistically significant p-values are in bold.
IMV:Invasive mechanic ventilation, NIMV: Non-invasive mechanic ventilation, ICU: Intensive care unit, CCIS:Charlson comorbidity index score, PT: Protrombin time, aPTT: Activated Partial thromboplastin time, INR: International normalized ratio, GFR: Glomeruler filtration rate, LDH: Lactate dehydrogenase, VBG:venous blood gas, pCO2: Partial pressure of carbon dioxide, pO2: Partial pressure of oxygen, HCO3: Bicarbonate

ICU mortality rates. However, no statistically significant difference was observed between the amount of pleural fluid drained and the occurrence of complications, and no cut off value could be determined for the optimal amount of fluid to be drained to prevent complications.

Many studies have shown that spontaneous pneumothorax occurs more frequently in females.[10] A study involving patients who underwent pleural effusion drainage also found that the risk of complications was higher in female patients compared to males.[5] In our study as well, female gender was identified as a factor increasing the risk of complications after pleural drainage. This may be attributed to the lower body mass index (BMI) in females and the fact that a lower BMI is a risk factor for complications such as pneumothorax.[11]

Patients receiving vasopressor support with hemodynamic instability often have restricted mobility. Due to the potential hemodynamic side effects of further horizontal positioning, ultrasound-guided pleural drainage is recommended in these patients.[12] In a study conducted by Park et al.,[13] high mortality was found in patients with severe illness requiring

vasopressors during pleural drainage, and vasopressor use was associated with mortality. In this study as well, a higher complication rate was observed in patients receiving vasopressor support during the pleural drainage procedure. This situation is attributed to the inability to adequately position patients with hemodynamic disturbances receiving vasopressor support and the lack of ultrasound use during pleural drainage procedures in our hospital.

Generally, the use of anticoagulant or antiplatelet medications, high INR, high aPTT, and low platelet count are considered the best indicators of bleeding complications during thoracentesis.[3] The only absolute contraindication to thoracentesis is patient refusal, while a bleeding diathesis is a relative contraindication. Emergency thoracentesis should not be postponed even in the presence of a potential bleeding risk, depending on the risk-benefit ratio.[13] In our study, the aPTT value was found to be statistically significantly higher in those who experienced complications after pleural drainage.

Although thoracentesis is considered low risk, complications such as pneumothorax, bleeding, and REPE are known to increase morbidity, mortality, and healthcare costs.[15] In a study conducted by Bateman et al.,[14] the mortality rate of 1503 patients who underwent pleural fluid drainage was found to be 43.9%, and it was observed that in-patient, 1-month, 6-month, and 1-year mortality rates, as well as hospital and ICU stay durations, were higher in patients who underwent drainage compared to those who did not.[16] In another study involving 1092 patients, it was determined that complications developed after the placement of a chest tube led to an increase in hospital stay duration.[17] In our study, an increase in ICU duration and ICU mortality was also observed in those who developed complications after pleural drainage.

Pleural fluid drainage can improve the ventilation-perfusion ratio by allowing the collapsed lung parenchyma to re-expand.[18] Studies have suggested that the larger the volume of pleural effusion drained, the better the improvement in lung volume, respiratory mechanics, and oxygenation of the patient.[19,20] However, the likelihood of developing REPE increases as the volume of drained pleura fluid increases.[21] Therefore, there is no clear data on the safest volume of fluid to drain.[3,22] The literature continues to debate the preferred method of drainage and the optimal volume of fluid to be removed.[4] In our study, no statistically significant difference was observed between the amount of pleural fluid drained and complications. Furthermore, when investigating the optimal amount of fluid to be drained to prevent complications, no cut off value could be provided.

Limitations

Our study has some limitations. Due to its retrospective and single-center nature, the low number of patients resulted in comparing the total complication count instead of individually comparing parameters with evolving complications. Additionally, the lack of ultrasound usage during thoracentesis in our hospital prevented assessing whether there was a decrease in complications associated with ultrasound use.

CONCLUSION

Our study found that the incidence of complications following pleural effusion drainage was higher in female patients and those receiving vasopressor support. Furthermore, among those experiencing complications, higher aPTT values and higher ICU mortality rates, along with longer ICU stays, were observed compared to those without complications. To reduce the risk of complications, we believe that paying closer attention to patient positioning during pleural drainage in patients receiving vasopressor support, performing pleural drainage with ultrasound guidance in patients unable to change position due to hemodynamic instability, and prioritizing urgent pleural drainage in patients with elevated aPTT values will decrease the complication rate. We anticipate that these measures will not only reduce ICU length of stay and ICU mortality but also prove effective in terms of cost savings and efficient utilization of ICU beds. Our study did not find an association between the quality and quantity of pleural fluid drained in the ICU and the development of post-drainage complications. Therefore, further research with a larger patient population is needed to investigate this aspect.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee (Date: 27.03.2024 and Decision No 2024-BÇEK/52.)

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Shunt options for normal pressure hydrocephalus: a comparison of complications, overdrainage rates and neurological outcomes between integra low flow regulated and Codman Hakim programmable shunts

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ABSTRACT

Aims: Shunt surgery is the most commonly performed treatment for idiopathic normal pressure hydrocephalus, and shunt systems with different operating principles are employed. This study aimed to retrospectively compare programmable ventriculoperitoneal shunts and flow-regulated shunts in terms of complications, overdrainage rates, and neurological outcomes.

Methods: Between January 2020 and May 2022, 44 patients who underwent shunt operation with a diagnosis of idiopathic normal pressure hydrocephalus at our clinic were retrospectively analyzed. Patients were categorized into two groups: the programmable ventriculoperitoneal shunt and the flow-regulated shunt group. Demographic characteristics, complications, rates of insufficient drainage/overdrainage, and surgical outcomes were compared.

Results: There were 26 patients in the programmable ventriculoperitoneal shunt group and 18 patients in the flow-regulated shunt group. In the programmable ventriculoperitoneal shunt group, 14 patients (53.8%) required 27 shunt setting adjustments owing to excessive or inadequate drainage. Subdural effusion was observed in five patients (19.2%), and shunt revision was performed in one patient (3.8%). Subdural effusion was observed in two (11.1%) patients in the flow-regulated shunt group. One of these patients (5.5%) underwent shunt revision. There was no significant difference between the groups in terms of the development of subdural effusion and need for shunt revision ($p>0.05$). The rate of improvement in at least one of the symptoms was 53.8% in the programmable ventriculoperitoneal shunt group at the 1st-month postoperative outpatient follow-up. In the flow-regulated shunt group, this rate was 72.2% and there was no statistically significant difference. Both groups showed similar clinical improvement at the 1-year follow-up.

Conclusion: There was no difference between the groups in terms of neurological outcomes and the need for shunt revision. However, the use of flow-regulated shunts has demonstrated earlier rates of clinical improvement without the need for reprogramming.

Keywords: Idiopathic normal pressure hydrocephalus, overdrainage, flow-regulated valve, programmable valve

INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) is a chronic hydrocephalus syndrome characterized by balance and gait disturbances, cognitive dysfunction, and urinary incontinence.[1] iNPH is a form of dementia that can be effectively treated with shunt surgery.[1–4] However, surgical failure and complications are not uncommon.

One of the most critical factors influencing the surgical success in patients with iNPH is the accurate selection of the shunt valve used. In recent years, programmable ventriculoperitoneal shunts (PVS) utilizing differential pressure valves have become the most commonly used shunt types for iNPH.[5,6] The major advantage of PVS is the capability to adjust the opening pressure noninvasively using an external magnetic field.[5–7] However, the valve pressure is affected by magnetic fields (e.g., during a MRI).[8–11] In addition close patient follow-up is needed.

These disadvantages of PVS can be overcome by using flow-regulated shunt valves (FRS). The FRS possesses a mechanism that can self-regulate constant drainage rates independent of patient position and differential pressure.[12–15] The FRS do not require repeated pressure adjustments during patient follow-up.[12,13,15,16] FRS are not associated with the risk of changing opening pressures after exposure to magnetic fields.[15,17]

This study aimed to retrospectively compare PVS and FRS used in the surgical treatment of iNPH in terms of neurological outcomes, complications, and overdrainage rates.

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METHODS

The study was carried out with the permission of Ethical Committe of Medicana Bursa Hospital (Date:06.07.2023, Decision No: 03/2023). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. In our study, we retrospectively reviewed 44 adult patients who underwent shunt placement surgery with a diagnosis of iNPH between January 2020 and May 2022 at our department. Age, sex, symptoms, neurological examination findings, intraoperative and postoperative complications, and early and late postoperative outpatient follow-up data of the patients were assessed.

During the inclusion period, patients who presented with at least two symptoms of Hakim's triad (gradual gait disturbance, cognitive impairment, and urinary incontinence) were diagnosed with iNPH in accordance with clinical guidelines and radiological examinations.

Gait disturbance was assessed using the 10-meter walk test, and dementia was assessed using the Mini-Mental State Examination (MMSE). Urinary continence was assessed via interviews with patients and/or their caregivers.

For radiological examination, all patients underwent brain MRI, CSF flow MRI, and CT imaging. The Evans index was calculated in each patient by dividing the maximum width between the frontal horns of the lateral ventricles by the distance between the two inner tabulae. Patients with an Evans index of <0.30 were excluded from the study.

All patients displayed ventriculomegaly in their MRIs. Patients with a history of head trauma, intracranial hemorrhage, stroke, meningitis, or primary malignancy were excluded. Additionally, seven patients with insufficient examination data owing to technical reasons were not included in the study.

A ventriculoperitoneal shunt was placed in all patients. Surgical decisions were supported by an assessment of gait after a lumbar tap test, which involved draining 40 ml of CSF via lumbar puncture. Recovery after lumbar puncture was defined as subjective improvement reported by patients themselves and/or family members.

Ventriculoperitoneal Shunting Protocol

The surgical procedure involved the insertion of a ventricular catheter via a burr hole in the right frontal Kocher's point and the placement of a peritoneal catheter via a midline or paraumbilical mini laparotomy. Since programmable valves were regularly utilized in our clinic before 2021, Codman programmable valves (Johnson and Johnson, MA, USA) were employed for patients with iNPH prior to that year (PVS group). The Integra® NPH Low Flow Valve (Integra Life Sciences Services, Lyon, France) was used in the patient group diagnosed after 2021 (FRS group).

Brain CT and/or MRI scans were conducted routinely on the first postoperative day to verify the proper positioning of the ventricular catheter and during each postoperative follow-up visit to rule out radiological indications of excessive drainage. The patients attended follow-up visits on day 15; at 1, 3, 6, and 12 months; and subsequently on an annual basis. Complications and readmissions associated with the ventriculoperitoneal shunting procedure were documented.

Assessment of Shunt Response

The shunt response was assessed during outpatient follow-up visits at the neurosurgery clinic following the shunt surgery. A 20% improvement in the 10-meter walk test was considered significant. An increase of ≥2 in the MMSE score was considered significant. Owing to the retrospective design of the study, postoperative objective measures of gait and cognition were only available in approximately 80% of the patients. For the remaining patients, scores were acquired via interviews with the patients and/or their caregivers. Improvement in at least one symptom of the hakim's triad was considered significant for clinical improvement.

Statistical Analysis

Continuous variables were expressed in terms of mean ± standard deviation. Moreover, two-way anova was used for comparisons between the two groups according to normality test results. Categorical variables were presented as frequency and percentage values [n (%)] and compared using the pearson chi-square test. Statistical analysis was performed using GraphPad Prism 10 (GraphPad Software, San Diego, CA, USA). A p value of <0.05 indicated statistical significance.

RESULTS

The PVS group included 26 patients (14 men and 12 women). There were 18 patients (11 men and 7 women) in the FRS group. Men and women were equally distributed between the groups. The mean age was 60.3±15.4 years in the PVS group and 67.05±11.73 years in the FRS group. There was no significant difference between the groups in terms of age (p>0.05)

The presenting symptoms, general demographic characteristics and clinical status of patients with iNPH are presented in Table 1. The rate of improvement in at least one of the symptoms was 53.8% in the PVS group at the 1st-month postoperative outpatient follow-up.

In the FRS group, this rate was 77.7% and there was no statistically significant difference compared to the PVS group. However, in the PVS group, the clinical improvement rates of the patients exhibited a significant difference between the 1st-month and 3rd month control visits (p <0.05). After 3 months, there was no difference in clinical improvement despite pressure adjustment.

In patients undergoing FRS placement, there was no significant difference in the rate of clinical improvement between the 1st-month and 1-year control visits (p>0.05). During a mean follow-up period of 37.8±27.1 months (42.4 ± 30.2–29±20.4 months), 21 (80.8%) patients in the PVS group exhibited improvement in at least one of the iNPH symptoms. This rate was 77.7% in the FRS group. Both groups showed similar clinical improvement at the 1-year follow-up (p>0.05)

(Table 2) (Figure 1). In 14 patients (53.8%) in the PVS group, shunt settings required adjustment for a total of 27 times. Nine (34.6%) patients underwent shunt adjustment at least once owing to insufficient drainage and five (19.2%) patients owing to subdural effusion/hematoma formation (Table 3). In three (11.5%) patients, shunt pressure changes were insufficient and required subdural drainage. In two (7.7%) patients, subdural effusion resolved completely after pressure elevation (Figure 2). Two patients (7.7%) underwent shunt revision because of inadequate clinical improvement. Subdural effusion was observed in two (11.1%) patients in the FRS group.

Table 1. General demographic characteristics and clinical status of patients with idiopathic normal pressure hydrocephalus (iNPH) treated with programmable and flow-regulated shunt.

Variables	PVS (n=26) (%)	FRS (n=18) (%)
Sex		
Female	14 (53.8)	11 (61.1)
Male	12 (46.2)	7 (38.9)
Mean Age ± SD, Years	60.3 ± 15.4	67.1 ± 11.7
Symptoms at Presentation		
Dementia	23 (88.5)	17 (94.4)
Gait disturbance	24 (92.3)	18 (100)
Urinary incontinence	21 (80.8)	15(83.3)
Headache	9 (34.6)	7 (38.8)
Dizziness	3 (11.5)	4 (22.2)
Nausea/vomiting	1 (3.8)	2 (11.1)
Mean Duration of Symptoms ± SD, Months		
Dementia	28.8 ± 45.5	22.3 ± 33.1
Gait disturbance	17.2 ± 24.9	21.3 ± 35.5
Urinary incontinence	15.7 ± 21.6	13.7 ± 30.6
Comorbidities		
Diabetes	11 (42.3)	11 (42.3)
HT	15 (57.7)	15 (57.7)
Coronary artery disease	5 (19.2)	5 (19.2)
Thyroid goiter	2 (7.7)	2 (7.7)
Parkinson	3 (11.5)	3 (11.5)
Alzheimer's disease	2 (7.7)	2 (7.7)
Cerebrovascular disease	1 (3.8)	1 (3.8)

FRS: Flow-regulated shunt, PVS: Programmable ventriculoperitoneal shunt, Standard deviation

Table 2. Clinical improvement rates during follow-up in patients with idiopathic normal pressure hydrocephalus (iNPH) treated with programmable and flow-regulated shuns. There was no statistically significant difference between the clinical improvement rates in both groups.

Follow-up period	PVS (n=26) (%)	FRS (n=18) (%)	p value
Postoperative 15th day	12 (46.1)	11 (61.1)	0.7319
Postoperative 1st month	14 (53.8)	14 (77.7)	0.5211
Postoperative 3rd month	20 (76.9)	14 (77.7)	0.6554
Postoperative 6th month	20 (76.9)	14 (77.7)	0.6554
Postoperative 1st year	21 (80.7)	14 (77.7)	0.5788

FRS: Flow-regulated shunt, PVS: Programmable ventriculoperitoneal shunt

One of these patients (5.5%) required subdural drainage, and this patient underwent shunt revision. In the FRS group, one patient (5.5%) underwent shunt revision owing to insufficient drainage. There was no statistically significant difference between the groups in terms of the development of subdural effusion and need for shunt revision (p >0.05).

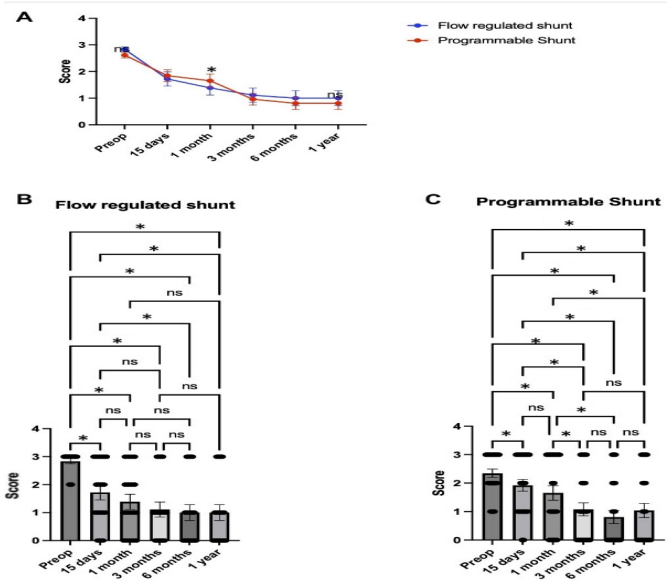

Figure 1. Comparison of clinical improvement rates of patients in PVS and FRS groups during 1-year follow-up.
FRS: Flow-regulated shunts, PVS: Programmable ventriculoperitoneal shunts , * Statistically significant (p<0.05) , ns: Not significant
Score: Each symptom of the Hakim's triad (gradual gait disturbance, cognitive impairment, and urinary incontinence) was scored 1 point and improvement in at least one symptom was considered significant for clinical improvement (maximum score: 3 (no improvement) and minimum score: 0 (complete improvement)).
A: Comparison of clinical improvement rates of patients in PVS and FRS groups during 1-year follow-up. Both groups showed similar clinical improvement at the 1-year follow-up.
B: Clinical improvement rates of FRS shunt patients during the follow-up period. FRS patients showed statistically significant improvement compared to the preoperative period in all follow-up periods. However, there was no significant difference between the clinical improvement rate at 1-month follow-up and the clinical improvement rate at the end of 1 year.
C: Clinical improvement rates of PVS shunt patients during the follow-up period. PVS patients showed statistically significant improvement compared to the preoperative period at all follow-up periods. However, there was no significant difference between the clinical improvement rate at the 3-month follow-up and the clinical improvement rate at the end of 1 year. During the follow-up period, recovery rates changed statistically significantly during the first 3 months, but no significant change was found after the 3rd month.

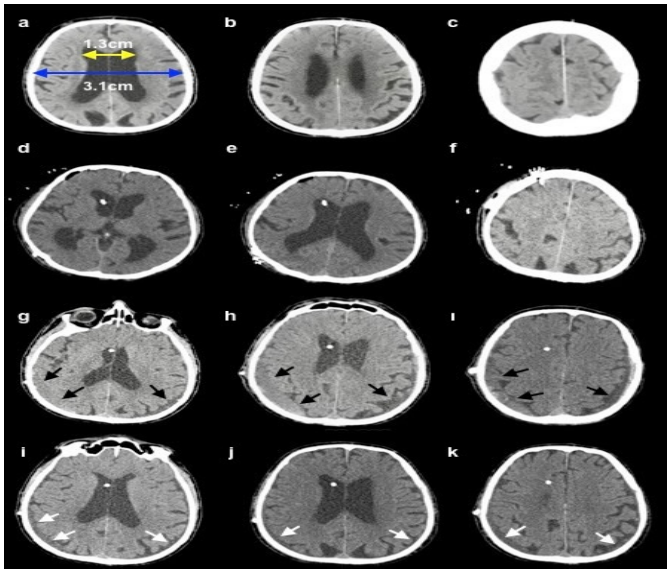

Figure 2. Serial axial computed tomography (CT) imaging scans of the brain of a patient with normal pressure hydrocephalus preoperatively and up to 3 months after programmable shunting (a-k). Preoperative axial images, Evans index >0.3. Evans index is defined as the ratio of the maximum width of the anterior horns (yellow arrow) to the maximum intracranial diameter (blue arrow) (a, b, c). Axial images in the first 24 hours postoperatively. The shunt catheter is in the anterior horn of the right lateral ventricle (d, e, f). Axial images at 1st month postoperatively show bilateral large subdural space. Subdural hematoma in the right parietooccipital region and subdural effusion in the left parietooccipital region (black arrow) are observed. After this imaging, the patient's shunt pressure setting was changed and increased (g, h, ı). Postoperative 3rd month axial images. Absorption of bilateral subdural hematoma and effusion (white arrow) and enlargement of bilateral hemispheres are seen (i, j, k)

Table 3. Number of shunt valve pressure settings changed due to over or inadequate drainage and clinical improvement in outpatient follow-up of idiopathic normal pressure hydrocephalus patients with ventriculoperitoneal programmable shunt.

PVS	Number of patients with adjusted valve pressure (n=26) (%)	Number of valve pressure adjustments (n=27)	Number of patients with clinical improvement (n=26) (%)
Inadequate drainage	9 (34.6)	16	7 (77.8)
Over drainage	5 (19.2)	11	2 (40)

PVS: Programmable ventriculoperitoneal shunt

In the PVS group, one patient (3.8%) experienced infection, which responded to medical treatment. During the early postoperative period, one patient (3.8%) in the PVS group developed an intraventricular hematoma. In addition, one patient (3.8%) in the PVS group who had coronary artery disease experienced a middle cerebral artery infarction on the first postoperative day. No catheter-related mechanical problems were observed in both groups (Table 4).

Table 4. Overall early (postoperative first 24 hours) and late postoperative (postoperative 6 months) complications following ventriculoperitoneal shunt surgery for idiopathic normal pressure hydrocephalus (iNPH) using programmable shunt and flow-regulated shunt. There was no statistically significant difference between early and late complications in both groups.

	PVS (n=26) (%)	FRS (n=18) (%)	p value
Early Complications			
Wound infection	1 (3.8)	0	0.49
Intraventricular hematoma	1 (3.8)	0	0.49
MCA infarct	1 (3.8)	0	0.49
Late Complications			
Subdural effusion/hematoma	5 (19.2)	2(11.1)	0.469
Subdural effusion/hematoma requiring drainage	3 (16.6)	1 (5.5)	0.497
Shunt revision	5(19.2)	2(11.1)	0.469

FRS: Flow-regulated shunt, MCA: Middle cerebral artery, PVS: Programmable ventriculoperitoneal shunt

DISCUSSION

In our study, there was no difference in clinical improvement rates between the FRS and PVS groups in the long-term. However, according to our findings, interestingly, in patients in the PVS group, the improvement rate at the 1st month follow-up (53.8%) was lower than that of at 1-year follow-up (80.8%) and the difference was statistically significant ($p<0.05$). In patients in the FRS group, the improvement rate was 72.2% at the 1st month control visit, which was not significantly different from that at 1-year control visit (77.7%) ($p>0.05$). This result can be viewed as a delayed clinical improvement in patients in the PVS group, possibly resulting from the insufficient drainage attributed to the initial high valve pressure.

Few publications in the literature have compared the efficacy of FRS and PVS so far.[13,14,17–20] Lund-Johansen et al.,[20] there was no statistically significant difference in the success rate of shunt surgery between patients undergoing FRS and PVS placement. Similarly, Weiner et al.[13] reported no statistically significant difference in shunt survival. In this regard, our study agrees with the existing literature. Therefore, complication rates owing to overdrainage and the incidence of mechanical problems related to the shunt should be prioritized when determining which shunt valve is to be employed.

In patients with PVS, over or under drainage can be prevented by changing the valve pressure.[21,22] Therefore, the use of PVS has been recommended in the guidelines for the treatment of iNPH published by the Japanese Normal Pressure Hydrocephalus Society in 2021.[23] Zemack et al.[6] reported that 42.4% of 583 patients with hydrocephalus treated using PVS placement required at least one valve pressure adjustment and that 64.6% of these patients displayed clinical improvement after the adjustment. Similarly, in a prospective European multicenter study by Klinge et al.[24], a total of 76 valve adjustments were performed in 36 patients during a 1-year follow-up of 115 patients who underwent PVS placement. While excessive or insufficient drainage was observed in 31% of the patients, only one patient required reoperation. Feletti et al.[21] reported that 37% of 102 patients with iNPH who underwent PVS placement required at least one valve pressure adjustment. In our study, 14 (53.8%) patients in the PVS group required a total of 27 adjustments to their shunt valve settings owing to either excessive drainage or inadequate clinical improvement.

The general approach in the use of PVS is to avoid overdrainage by initially adjusting to high pressures as overdrainage is more challenging to manage than insufficient drainage and may require repeat surgical procedures. In the literature, it has been shown that gradually decreasing the initial pressure from high to low values to achieve an optimal pressure setting can minimize the complication rate.[25,26] Farahmand et al.[26] suggested that the initial pressure be set at 120 mm H2O and adjusted based on clinical follow-up. However, starting from a high pressure setting requires multiple changes to reach the optimum pressure setting, and it is time consuming. Consequently, there may be a delay in the improvement of symptoms. In our study, the initial pressure was set at 110–120 mm H2O in patients undergoing PVS placement. During the follow-up of these patients, in five patients (19.2%), adjustment was made because of subdural effusion. Three patients (11.5%) required surgical intervention as their subdural effusion did not improve despite all adjustments. We believe that there could be several reasons for the development of subdural effusion in these patients despite the high initial pressure setting. First, although the initial opening pressure was adjusted to values specified in the literature, it is possible that the patient might have required a higher valve pressure. Of the patients in our study, there were two (7.6%) patients whose shunt pressure was increased in the first controls. The findings supported this theory. Second, excessive reduction of pressure in the valve settings might have been done to achieve clinical improvement. In our study, subdural effusion was detected in three (11.9%) patients 1 month after the first operation by decreasing the shunt valve pressure. Third, we observed that in some patients the pressure differences were very sensitive. Specifically, PVS allow adjustment in intervals of 10 mm H2O. However, owing to the absence of an anti-siphon mechanism, changes in the patient's position might have resulted in increased drainage, potentially leading to subdural effusion.

FRS are shunt systems with different characteristics that can be used in the treatment of iNPH. FRS self-regulate a constant amount of drainage independent of the patient's position and alterations in intracranial pressure. No external adjustment is required.[14,15,17] FRS aim to provide a consistent flow irrespective of changes in intracranial pressure.[19] The disadvantage of FRS is that it requires repeat surgical intervention in patients with excessive drainage.[5] However, this excessive drainage is not very common. Wetzel et al.[15] reported that flow-regulated valves are associated with low overdrainage rates and do not require reprogramming. Their study showed that approximately 80% of patients with iNPH treated with the Integra® NPH Low Flow Valve placement exhibited significant improvement on the iNPH rating scale and that the rate of improvement was stable at mid-term follow-up.[15]

In our study in the FRS group, subdural effusion was detected in two (11.1%) patients and surgical intervention was required in one patient (5.5%). Feletti et al.[21] demonstrated that in comparison with fixed-pressure shunts, the use of programmable pressure shunts led to a significantly lower rate of revision surgeries. Another aim of our study was to compare PVS and FRS in terms of overdrainage and repeat surgery rates. In our study, contrary to findings in the literature, no statistically significant difference was found between the two groups in terms of the development of subdural effusion and the rates of shunt revision surgery.

In addition, programmable valves are sensitive to magnetic fields and therefore require routine reprogramming when an MRI is performed. In their prospective study, Capitanio et al.[9] published a change of 40% in valve settings with 1.5-telsa MRI. Patients should visit a neurosurgery department after each MRI scan to either verify their valve settings via X-ray or have them readjusted. The type of FRS that does not require pressure adjustment may offer an alternative solution for patients who undergo frequent MRI examinations for other medical reasons or reside at a considerable distance from a hospital.[15]

In our study, patients with PVS placement underwent valve readjustment and/or X-ray control after each MRI, complicating follow-up for both the patient and the physician.

Early and late complications following shunt surgery in the treatment of iNPH have been documented in the literatüre.[22,27–29] Schenker et al.[28] observed in their series that 58% of patients with iNPH experienced some types of surgical complications; however, only approximately half of these complications required reoperation. In our study, there was no significant difference between the groups in terms of surgical complications (p>0.05) (Table 2).

CONCLUSION

Our findings support that the use of both FRS and PVS is effective and safe in the treatment of iNPH. The time to adequate clinical improvement is shorter in patients undergoing FRS placement than in those undergoing PVS placement owing to the lack of need for valve adjustment. Although iNPH guidelines advocate for the use of PVS, we believe that FRS may be a suitable option for eligible patients as well. Future prospective studies may further elucidate the difference in complications and neurological improvement rates between PVS and FRS.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethical Committe of Medicana Bursa Hospital (Date:06.07.2023, Decision No: 03/2023).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Relationship between patellar resurfacing and postoperative anterior knee pain in total knee arthroplasty

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ABSTRACT

Aims: To retrospectively demonstrate the effect of patellar resurfacing (PR) on the clinical and functional outcomes of total knee arthroplasty (TKA).

Methods: The files of 257 patients who presented to our clinic between 2013 and 2022 and underwent TKA due to the diagnosis of grade IV gonarthrosis were screened retrospectively. Thirty-two patients were excluded due to not attending regular follow-up, receiving steroid treatment, or being morbidly obese. The sample consisted of 225 patients, of whom 123 underwent PR (Group A) and 102 did not undergo PR (Group B). The Sperner classification was used to evaluate the level of patellar arthrosis. The effect of PR on postoperative clinical and functional outcomes in patients undergoing TKA was investigated using the WOMAC knee functional scoring and Visual Analog Scale (VAS) for clinical and functional evaluation at six, 12, and 24 months postoperatively.

Results: The presence of anterior knee pain wasstatistically significantly lower in Group A than in Group B (p=0.0001). There was no statistically significant difference between the comorbidity distributions of the groups. The preoperative-to-postoperative changes in the mean VAS and WOMAC scores were statistically significantly higher in Group A compared to Group B (p=0.0001 for both).

Conclusion: The implementation of PR in TKA may vary depending on countries, clinics, and even surgeons. In the current study, PR was found to contribute positively to the clinical and functional outcomes of patients by preventing complications such as anterior knee pain that may develop due to patellar arthrosis in the postoperative period.

Keywords: Arthroplasty, knee replacement, patella, osteoarthrosis, complications

INTRODUCTION

Total knee arthroplasty (TKA) is a commonly employed surgical intervention for advanced osteoarthritis, yielding favorable outcomes.[1,2] One of the most important complications that negatively affects the success of this surgical procedure is the complaint of anterior knee pain (AKP) that develops postoperatively. AKP is defined as pain that occurs in and around the patellar region of the knee worsens with movement and exercise and negatively affects an individual's social life. It is one of the most common causes of permanent problems that develop after TKA.[2-4] The patella is subject to dynamic contact within the trochlear groove of the femur. While there is no contact in full extension, contact begins at the lower end of the patella and increases with the flexion of the knee. The patella-femoral joint is typically exposed to stresses reaching up to 20 times the individual's body weight.[5]

AKP and patellofemoral disorders after TKA are important reasons leading to the need for revision surgery.[5,6] Many functional and mechanical factors play a role in the etiology of AKP. The articulation between cartilage and metal is not considered physiological, and long-term exposure to high stresses is considered to cause erosion of cartilage. Factors such as improper placement of knee prosthesis implants, deficiencies in implant design, and muscle imbalance result in an increase in patellar chondrolysis in the postoperative period, leading to the development of AKP.[6-8] Surgeons who favor patellar resurfacing (PR) suggest that the incidence of AKP decreases after TKA, resulting in higher patient satisfaction and lower complication rates. However, there is still no consensus among orthopedic surgeons concerning the application of PR in TKA. The decision of PR is contingent upon the orthopedist's

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preference, as well as the mission and experience of the clinic where the surgeon works.[7-9] While some surgeons advocate for routine PR, others argue that PR must not be performed, while there is a third group of surgeons suggesting that PR can be undertaken in the presence of specific indications.[10]

This study aimed to reveal the effect of PR on postoperative clinical and functional outcomes in patients who underwent TKA and explore the conditions under which the use of patellar components was necessary.

METHODS

The study was carried out with the permission of Ethical Committe of Sakarya University (Date:31.01.2023, Decision No: E-71522473-050.01.04-216228-22). The files of 257 patients with grade IV gonarthrosis who presented to our clinic between 2013 and 2022 and underwent TKA were screened retrospectively. Thirty-two patients were excluded from the study due to not attending regular follow-up, developing prosthesis infections in the postoperative period, receiving steroid treatment, Simultaneous bilateral TKA applied or being morbidly obese. The sample consisted of 225 patients, of whom 123 underwent PR (Group A) and 102 did not undergo PR (Group B) during TKA. Patellar arthrosis levels were determined by evaluating preoperative tangential knee radiographs according to the Sperner classification (Figure 1).

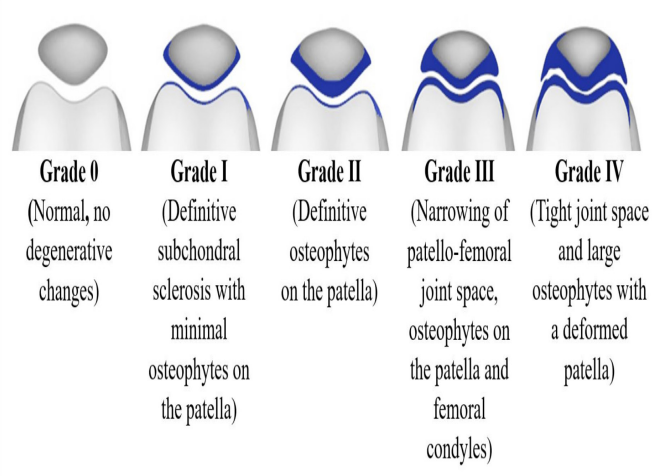

Figure 1. Sperner classification

All patients underwent surgery under epidural anesthesia and a tourniquet. The patients were prophylactically administered 3x1g of cephazolin, 1x6,000 IU of enoxaparin and analgesic treatment. The surgical procedure was performed using a midline long incision and median parapatellar deep exposure. The patella was rotated laterally by eversion. Extramedullary tibial alignment was performed with a plan to resect from the less affected lateral compartment. Intramedullary femoral alignment was undertaken using the balanced gap approach. For PR, an resection of approximately 5 mm was made, and patellar components made of three-peg and high-density polyethylene material were placed using cement. Cemented total knee prostheses of different brands (Wright, Stryker, Biomed, Concensus-Hayes Medical and Orthopedia) were used in all patients to protect the posterior cruciate ligament (Figure 2). After releasing the tourniquet, the layers were closed anatomically by inserting a suction drain to control bleeding. On the postoperative first day, the patients were mobilized, and passive exercises were started. The patients were allowed to bear full weight from day.[1] The effect of PR on the clinical and functional outcomes of TKA was investigated using the WOMAC knee functional score and the Visual Analog Scale (VAS) at six, 12, and 24 months postoperatively.

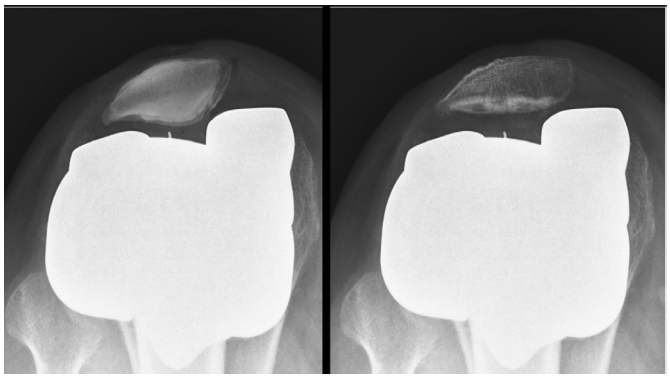

Figure 2. Patellar resurfacing preop –postop

Statistical Analysis

In this study, statistical analyses were performed using the Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA) package program. In the evaluation of the data, in addition to the use of descriptive statistics (mean and standard deviation), the distribution of the variables was examined with the Shapiro-Wilk normality test. The paired t-test was used in the preoperative and postoperative comparisons of normally distributed variables, the independent t-test was employed for the comparison of paired groups, and the chi-square test was conducted to compare qualitative data. The results were evaluated at the significance level of $p < 0.05$.

RESULTS

The mean age was 72.07±7.02 years in Group A and 72.49±7.27 years in Group B. All patients were female and had grade IV gonarthrosis. The average follow-up period was 34.53±5.14 months for all groups. During the postoperative follow-up, no wound healing problems were observed. Superficial skin infections occurred in three patients, who were treated with antibiotics. In the evaluations made according to the Sperner classification, the level of patellar arthrosis was classified as grade I-II in 143 patients and grade III-IV in 82. Among the patients with grade I-II arthrosis, PR was performed on 76 patients (53.15%), while it was not performed on the remaining 67 (46.85%). Of the patients with grade III-IV arthrosis, 47 (57.30%) underwent PYD, and 35 (42.70%) did not undergo PR. Postoperative AKP was observed in one (0.81%) of the 123 patients in Group A and 11 (10.78%) of the 102 patients in Group B. Since the clinical and functional complaints of the 11 patients in Group B with AKP increased, seven underwent revision surgery only with PR. In the postoperative follow-up

of these patients, AKP complaints started to resolve in the early period. No complications such as patellar fracture and aseptic loosening were observed after PR (Table 1).

Table 1. Statistical comparison of the operated groups

	Group A (n=123)		Group B (n=102)		p
Age (year)	72.07 ± 7.02		72.49 ± 7.27		0.657*
Grade I-II	76	61.79%	67	65.69%	
Sperner classification					
Grade III-IV	47	38.21%	35	34.31%	0.545+
Anterior knee pain	1	0.81%	11	10.78%	0.001+
Diabetes mellitus	20	16.26%	13	12.75%	0.458+
Hypertension	55	44.72%	52	50.98%	0.349+
Ischemic heart disease	7	5.69%	6	5.88%	0.951+
Vascular disease	3	2.44%	5	4.90%	0.321+
Renal disease	5	4.07%	4	3.92%	0.956+
Pulmonary disease	3	2.44%	2	1.96%	0.809+
Thyroid disease	4	3.25%	4	3.92%	0.787+
Operation time	49.19 ± 9.50		46.96 ± 8.36		0.066*
Preoperative VAS score	7.01 ± 0.9		7.05 ± 0.72		0.712*
Postoperative VAS score	2.47 ± 0.9		2.99 ± 1.1		0.0001*
p‡	0.0001		0.0001		
VAS score change %	64.74 ± 12.01		57.36 ± 15.8		0.0001*
Preoperative WOMAC score	58.66 ± 7.63		59.99 ± 6.32		0.161*
Postoperative WOMAC score	10.29 ± 4.61		12.46 ± 5.56		0.002*
p‡	0.0001		0.0001		
WOMAC score change %	82.97 ± 5.81		79.56 ± 8.01		0.0001*

*Independent-samples t-test, ‡Paired t-test+ chi-square test
Group A: patients who underwent patellar resurfacing, Group B: patients who did not undergo patellar resurfacing, VAS: Visual Analog Scale

The presence of AKP was found to be statistically significantly lower in Group A than in Group B (p=0.0001). No statistically significant difference was observed between the comorbidity distributions of Group A and Group B. There was also no statistically significant difference between the mean operation times of the groups (p=0.066). In both groups, the postoperative mean VAS scores were statistically significantly lower compared to their preoperative mean VAS scores (p=0.0001 for both) (Figure 3). Similarly, both groups had statistically significantly lower postoperative mean WOMAC scores compared to the preoperative period (p=0.0001 for both) (Figure 4).

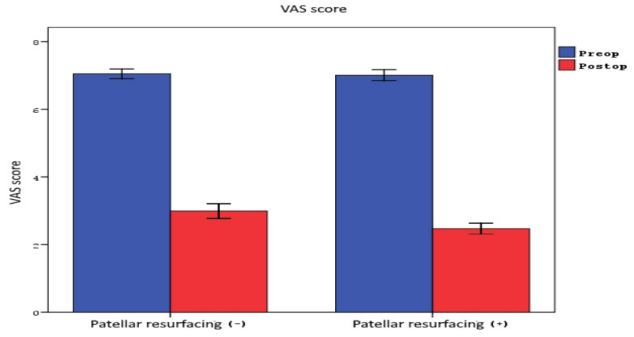

Figure 3: Mean VAS scores of the groups

According to the intergroup comparison, the mean postoperative WOMAC score of Group A was statistically significantly lower than that of Group B (p=0.002). Lastly, the mean preoperative-to-postoperative changes in the VAS and WOMAC scores were statistically significantly higher in Group A compared to Group B (p=0.0001 for both) (Figure 5).

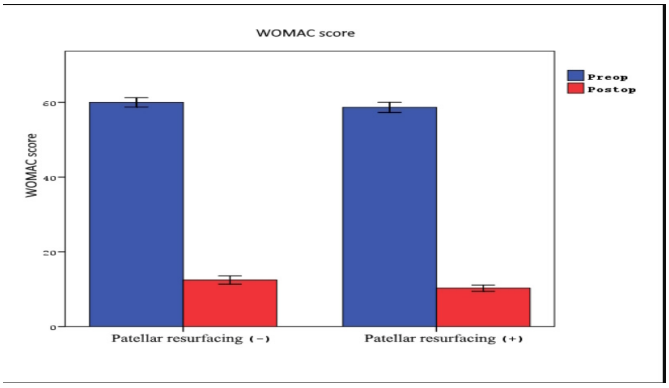

Figure 4. Mean WOMAC scores of the groups

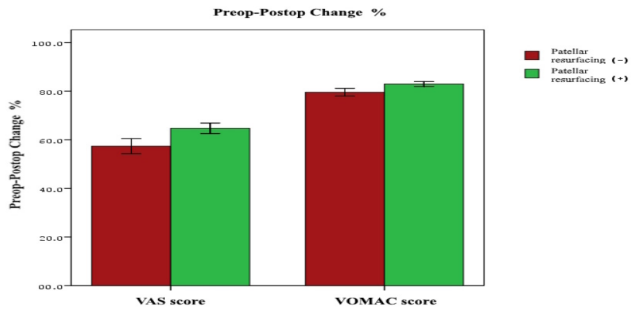

Figure 5. Preoperative-to-postoperative changes in VAS and WOMAC scores by group

DISCUSSION

TKA is a surgical procedure successfully applied in the current treatment of gonarthrosis and yields good clinical outcomes; however, certain complications, such as AKP, overshadow the success of the procedure and can be seen at rates reaching 8-10% in the postoperative period.[10] Although many factors that cause AKP have been documented after TKA, these complications are more common, especially in cases where PR is not applied.[11,12] Our study revealed a higher prevalence of AKP complaints following TKA in patients who did not undergo PR, starting in the postoperative sixth month. Due to the negative effect of AKP on the social and physical lives of patients, we consider that knee revision surgery for PR becomes inevitable. To prevent this situation, in which all other components may also be adversely affected by revision, we propose the routine application of PR during TKA, regardless of the level of patellar arthrosis, to achieve more positive clinical outcomes.

Although many studies suggest that there is no difference between TKA procedures with and without PR in terms of functional outcomes, in a study involving 124 patients (175 knees), Huang et al.[13] reported significantly higher rates of AKP in TKA procedures without PR at three-month and one-year follow-ups. They also noted a considerably lower incidence of patellar crepitus in cases where PR was performed. The

results obtained in our study align with the existing literature advocating for PR, demonstrating that PR minimizes postoperative AKP complaints. However, our study did not include data on the incidence of patellar crepitus. Matz et al.[14] suggested that in addition to PR, electro-cauterization of the terminal nerves around the patella could be beneficial in reducing AKP following TKA, based on the presence of numerous terminal nerves in this region. In our study, the area around the patella was denervated through cauterization prior to PR.

Peterson et al.[15] noted that the causes of AKP were multifactorial; therefore, the indication for PR should be determined very carefully, and the success rates varied between 50% and 60%. Sauer et al.[16] showed that PR not only provided better clinical outcomes but also reduced the possibility of revision surgery. Panni et al.[17] found that the risk of reoperation after PR was lower and that this may be effective in preventing AKP symptoms. Consistent with the literature, our study indicates that AKP complaints should not be attributed to a single cause, as multiple factors play a role in the etiology. We believe that PR reduces the risk of reoperation.

Fuchs et al.[18] determined that the patellar offset and the lateral patellar tilt decreased in patients who underwent PR, which may be related to AKP. However, the authors also noted that the effect of PYD on clinical and functional outcomes was very limited. Our study did not find evidence indicating a reduction in patellar offset and lateral patellar tilt in patients who underwent PR. Such complications are commonly observed in cases where proper patellar resection and accurate placement of the patellar component are not achieved. Fleaca et al.[19] emphasized the lack of a consensus on the use of PR during TKA and commented that AKP that developed in the post-TKA period was associated with more than one etiology; therefore, routine PR practice was not necessary. Evaluating patients who received zirconium ceramic implants without PR, Sato et al.[20] reported that the cartilage thickness in the patella decreased by half within five years compared to the preoperative period, and this negatively affected the clinical and functional outcomes of the patients. Parvizi et al.[21] observed no significant difference between the patients who underwent PR and those who did not undergo PR. Lastly, in a study aiming to reduce intra-patellar pressure with patelloplasty to minimize AKP, Ertürk et al.[22] concluded that this application did not have an advantage over other methods. We do not agree with the idea that reducing intra-patellar pressure through patelloplasty contributes to the alleviation of AKP complaints. Our study did not obtain any data supporting this claim.

In primary total knee arthroplasty, there are three strategies for patellar management. The first strategy is to always resurface the patella, the second is to never resurface it, and the third is to resurface the patella based on specific indications. However, different data supporting each of these strategies have been reported in the literature; therefore, it is evident that there is no consensus in the literature concerning the application of PR in TKA. Different ideas have been proposed depending on countries, clinics, and even surgeons.

Limitations

This study has certain limitations. First, the study was designed retrospectively, meaning that the patients were not randomized before surgery. Second, it is difficult to accurately evaluate the level of patellar arthrosis through observation using direct radiographs. Lastly, the absence of male patients in the patient groups had a negative impact on the evaluation of the data, hindering a gender-related comparison.

CONCLUSION

In this study, significant differences were found between the patients who underwent PR and those who did not undergo PR during TKA in terms of AKP complaints. TKA is a major surgical procedure, and we consider that PR will have a positive impact on the clinical and functional outcomes of TKA by preventing AKP complaints, potentially prophylactically, in the postoperative period. We consider that this study will shed light on future research and that there is a need for further studies involving more patients and evaluating more parameters.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethical Committe of Sakarya University (Date:31.01.2023, Decision No: E-71522473-050.01.04-216228-22).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

ANATOLIAN CURRENT MEDICAL

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Empowering paramedics to save teeth: a comprehensive assessment of their knowledge and skills in managing dental traumas

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ABSTRACT

Aims: Dental traumas are prevalent injury types worldwide, and the time of the first intervention is crucial for a favorable prognosis. Paramedics are often the first to arrive at the scene of dental trauma. The significance of paramedics' knowledge of dental trauma cannot be overstated, yet studies on this subject are limited. This study aims to assess the level of dental trauma knowledge among paramedics.

Methods: A Google Forms link measuring dental trauma knowledge level consisting of 17 questions was sent to 1576 participants via WhatsApp. The forms were fully and consistently completed by 300 participants (19.3%). The data collected through Google Forms were imported into Microsoft Excel for statistical analysis. *Statistical Analysis:* The Mann-Whitney U test was used to determine whether there was a difference between the categories. The Kruskal-Wallis H test was used to determine whether there was a difference between the categories of the qualitative variable and more than two categories in the quantitative variable since average distribution as sumptions were not met. The statistical significance level was taken as 0.05.

Results: There are 300 paramedics, with 159 males and 141 females. 87% of the participants did not receive any training regarding dental trauma. According to 85.3% of paramedics, dental traumas are considered an emergency situation. The most important type of dental trauma is avulsion. Only 21.7% of paramedics knew reimplantation was possible, while 78.4% believed that a dentist should do it. Research shows that 38.4% of paramedics prefer using a sterile sponge when storing avulsed teeth, while 10.7% prefer milk. 82.7% of the paramedics reported lacking the knowledge to handle dental traumas, and 84% expressed interest in receiving training.

Conclusion: The research revealed that paramedics have insufficient knowledge regarding dental trauma. Most participants stated their preference not to intervene in cases of dental trauma. They believed that a dentist or emergency physician should handle it.

Keywords: Paramedic, avulsion, dental trauma, dentoalveolar trauma, hank's balanced salt solution, ambulance

INTRODUCTION

Traumatic dental injuries are common in children and adolescents and can affect teeth and periodontium.[1] TDIs are responsible for facial injuries in around 5% of all trauma cases.[2] This highlights the importance of seeking prompt treatment in such patients. Convenient and accurate intervention is crucial for a favorable prognosis of a traumatized tooth.[1] Treating injuries and restoring traumatized teeth can pose a difficult challenge for patients, caregivers, and dental practitioners.[3] If treatment is delayed or incorrect, it can negatively impact the prognosis and result in tooth loss.[4] This can cause problems with appearance, functionality, finances, social interactions, and mental well-being.[5]

In cases of trauma, prompt intervention is crucial, and patients receive first aid at the accident scene, in ambulances, or in emergency service.[3] In emergency services, the focus is on treating conditions that pose a risk to the overall health of the patient, which may result in injuries to the teeth and surrounding tissues being overlooked.[6] As a result, numerous cases of dental trauma go untreated or receive incorrect

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treatment, resulting in further complications.[3,7] Improper treatment of injuries can result in short or long-term absence from physical activities, school, or work. According to a previous study, patients who experience dental trauma often seek treatment at hospital emergency services because dental clinics operating during regular business hours may not always be convenient or accessible.[3] Paramedics, nurses, and emergency physicians are typically the initial health professionals to attend to patients experiencing traumatic dento-alveolar injuries. It is crucial for health personnel, often the first responders in trauma cases, to possess a high level of knowledge and awareness about dental traumas to ensure proper care and treatment for patients.

This study aims to gather paramedics' opinions and first-hand encounters regarding dental injuries. It also seeks to evaluate their proficiency in dealing with such incidents and highlight the crucial role of their initial response in restoring affected teeth.

METHODS

The study was carried out with the permission of Afyonkarahisar Health Sciences University Faculty of Medicine Clinical Researches Ethics Committee (Date:7.7.2023, Decision No: 2023/304).A study was carried out in Turkey from August 2022 until March 2023. Paramedics working in public or private hospitals were invited to participate in the research and respond to data collection forms sent via WhatsApp® (WhatsApp, Menlo Park).

Sample Size Determination

The number of paramedics in Istanbul was calculated using data from the Ministry of Health in Turkey. Currently, there are 3,290 paramedics employed in hospitals, health centers, and emergency aid stations affiliated with the Ministry of Health. It was calculated that a minimum of 329 paramedics from Turkey are needed with 95% confidence and 5% tolerance.[8] During the study conducted in Istanbul city, 300 paramedics, which represents 9.2% of the total paramedics, were contacted.

The data collection form comprised two questions regarding demographic information and nineteen regarding knowledge and awareness of emergency dental injury treatment. These questions were previously used in similar studies found in literature and have undergone validity and reliability testing.

During the initial section of the questionnaire, participants were asked to provide their gender and age. Those who believed that Traumatic Dental Injuries were not an emergency were allowed to skip the questions in the third section and proceed to the other survey areas. Participants who responded affirmatively to the inquiry, "Can a dislodged tooth be reimplanted?" were guided to the 4th section, whereas those who replied negatively were redirected to the 6th section.The study in Turkiye involved sending out questions to 1576 individuals, but only 300 people completed all the questions and were included in the final results.

Statistical Analysis

The SPSS (Statistical Package for the Social Sciences package program version 21.0, IBM Corp., Armonk, N.Y., USA) program was used for data analysis. The Mann-Whitney U test was used to determine whether there was a difference between the qualitative variable and two categories in the quantitative variable since the assumptions of normal distribution were not met. The kruskal-wallis H test was used to determine whether there was a difference between the categories of the qualitative variable and more than two categories in the quantitative variable since average distribution assumptions were not met. The statistical significance level was taken as 0.05.

RESULTS

Out of the individuals who accessed the WhatsApp link and accurately completed the form, the response rate was 19.03%. Out of all the participants in the study, 159 (53.0%) were female, and 141 (47.0%) were male. 37.7% of participants were 18-25 years old, 31.7% were 25-30, 12.3% were 30-35, and 18.3% were over 35. When surveyed, 13.0% of individuals reported having received training on dental traumas. Of those individuals, 74.0% answered affirmatively, "Is a traumatic tooth injury considered an emergency?" If someone has a soft tissue injury in their mouth or face, like their lips, cheeks, or tongue, is it necessary to get treatment immediately? Of 300 respondents, 256 (85.3%) answered in the affirmative. On the other hand, only 70 people (23.3%) believed immediate treatment was necessary for a patient with a broken tooth who wasn't bleeding. During this survey, 25.3% of the participants favored searching for fragments of a broken tooth at the trauma scene. Additionally, 19.7% of the respondents believed that the broken parts of a tooth damaged due to trauma could be bonded. Table 1 responds to the remaining inquiries in the research. Out of the total number of paramedics surveyed, only 65 (21.7%) believed that teeth that have been avulsed of their sockets could be reimplanted. Only 18.4% of the 65 people knew the ideal replantation time of 30 minutes. The correct storage solution for an avulsed tooth, milk, was only known by seven people (10.7%) until reimplantation. Only 21 out of all the participants (7%) correctly identified avulsion as an example of dental trauma that requires emergency attention. Table 2 displays the correlation between the responses to the questions and the accuracy percentage of those responses. Did you receive any training or attend a course on Dental Trauma? Also, do you feel confident about your level of knowledge regarding oral and dental injuries? The percentage of correct answers provided for these questions differed significantly ($p=0.018$ and $p=0.028$, respectively). Experience in dental traumas correlates with higher accuracy in answering related questions. Those who answered yes had a 47.82±22.19% correct answer rate, compared to the average of 38.91±18.62%. Would you say your knowledge of oral and dental injuries is adequate?" Those who answered no to this question had a significantly higher percentage of correct answers than those who answered yes.

Table 1.

Variables		
Gender, n(%)	Woman	159 (53.0)
	Man	141 (47.0)
Age, n(%)	18-25	113 (37.7)
	25-30	95 (31.7)
	30-35	37 (12.3)
	>35	55 (18.3)
Have you encountered any cases of dental trauma in your professional career?	No	114 (38)
	Yes	186 (62)
Have you received any education or training regarding dental injuries? n (%)	No	261 (87.0)
	Yes	39 (13.0)
Is it necessary to seek emergency treatment for traumatic tooth injuries? n(%)	No	78 (26.0)
	Yes	222 (74.0)
Is it vital to seek medical attention immediately if someone experiences a soft tissue injury in their mouth or face, particularly in the lips, cheeks, or tongue? n(%)	No	44 (14.7)
	Yes	256 (85.3)
Is it necessary to seek urgent treatment if a patient has a broken tooth but no bleeding? n (%)	No	230 (76.7)
	Yes	70 (23.3)
Should fragments of a fractured tooth be searched upon arrival after trauma? n(%)	No	224 (74.7)
	Yes	76 (25.3)
Is it possible to reattachment the broken parts of a tooth damaged due to dental trauma? n(%)	No	241 (80.3)
	Yes	59 (19.7)
If a tooth is knocked out (avulsed), is it necessary to search for it at the accident scene? n(%)	No	230 (76.7)
	Yes	70 (23.3)
Is it possible to reimplant a tooth that has been displaced (avulsed)? n(%)	No	235 (78.3)
	Yes	65 (21.7)
What is the appropriate action for a knocked-out tooth (avulsed) that has come out of its socket? , n(%)	Emergency doctor, dentist	4 (6.2)
	Paramedic, emergency doctor, dentist	2 (3.1)
	Paramedic ambulance doctor, emergency doctor, dentist	6 (9.2)
	Dentist	51 (78.4)
	Victim or relative (if conscious)	2 (3.1)
Is it possible for a tooth reimplanted into its socket to heal once more? n(%)	No	7 (10.8)
	Yes	58 (89.2)
If your answer to the above question is yes, What is the ideal time to reimplant an avulsed tooth?	In the first 30 minutes	12 (18.4)
	Within 1 hour	12(18.4)
	Within 2 hours	7(10.7)
	Within 24 hours	19 (29.2)
	No Matter	15(23.7)
Where should the avulsed tooth be stored until it is reimplanted in its socket?	Sterile Sponge	25(38.4)
	Sterile Saline	20(30.7)
	Ice/Iced water	9(13.8)
	Milk	7(10.7)
	Saliva	4(6.15)
What kind of dental injury is considered an emergency?	Enamel fracture	5(1.6)
	Enamel-dentin fracture	5(1.6)
	Complicated enamel-dentin fracture	142 (47.3)
	Mobilized, bleeding tooth	43(14.3)
	Root fracture	13(4.3)
	Avulsed tooth	21 (9.17)
Do you feel confident in your understanding of oral-facial and dental injuries? n(%)	No	248 (82.7)
	Yes	52 (17.3)
Are you interested in receiving training regarding oro-facial and dental injuries? n(%)	No	48 (16.0)
	Yes	252 (84.0)
Correct Answer Percentage	Mean±SD	40,06±21.01
	Mean (min-max)	41,07 (0.00-100.00)

n: number

Table 2.

Variables		Correct Answer Percentage		
		Mean±SD	Mean(min-max)	p
Gender	Woman (n=159)	39.33±20.60	38.02 (0.00-100.00)	0.386a
	Man (n=141)	40.89±21.50	42.86 (0.00-90.00)	
Age	18-25 (n=113)	39.03±16.52	42.86 (0.00-70.00)	0.827b
	25-30 (n=95)	40.29±21.72	41.18 (0.00-100.00)	
	30-35 (n=37)	39.20±20.10	38.74 (0.00-80.00)	
	>35 (n=55)	42.33±19.86	42.83 (0.00-80.00)	
Have you encountered any cases of dental trauma in your professional career?	No (n=114)	36.68±19.56	26.46 (0.00-100.00)	0.042a
	Yes (n=186)	30.32±16.28	41.58 (0.00-90.00)	
Have you received any education or training regarding dental injuries?	No (n=261)	38.91±18.62	41.55 (0.00-90.00)	0.018a
	Yes (n=39)	47.82±22.19	50.00 (0.00-100.00)	
Do you feel confident in your understanding of oral-facial and dental injuries?	No (n=248)	40.96±18.87	42.86 (0.00-90.00)	0.028a
	Yes (n=52)	35.74±26.28	28.57 (0.00-100.00)	
Are you interested in receiving training regarding oro-facial	No (n=48)	35.64±21.69	28.57 (0.00-90.00)	0.088a
	Yes (n=252)	40.91±19.97	42.86 (0.00-100.00)	

a:Mann-Whitney U testi, b:Kruskal Wallis H testi, p<0,05

DISCUSSION

Dental avulsions are the most critical type of dental trauma. Still, they can be treated with early and correct intervention.[9] Health professionals other than dentists need to increase their knowledge about avulsion.[6] Although the dental trauma knowledge level of several groups, including doctors,[6] teachers,[10] and coaches,[11] has been assessed in scientific literature, only a few studies have evaluated the knowledge levels of paramedics and emergency medicine technicians.[12–15] In this research, 62% of participants experienced dental trauma at least once in their careers, consistent with previous studies.[3,6,16,17] However, insufficient information on dental trauma, avulsions, and maintenance was found, consistent with other studies.[12,13] One of the main reasons for this situation is the lack of education and training on handling dental emergencies and traumas. 87% of participants reported never receiving dental trauma training, consistent with previous studies.[13,14] Video and hands-on-course training on dental traumas should be provided with a way to measure effectiveness.[18]

Although dental injuries primarily affect children, adults are more likely to experience them due to severe maxillofacial trauma.[12] Paramedics, doctors, and nurses are mainly responsible for providing first aid in case of such injuries in emergency departments.[6,14] Early, correct, and adequate first intervention is crucial in dental injury cases, as the emergency department often lacks a dentist.[3,6] As the first healthcare professionals on the accident scene, paramedics require adequate knowledge of dental traumas and emergency interventions. According to previous studies, only 17.3% of paramedics feel confident enough to intervene in dental trauma patients despite it being a common injury.14,15 74% of the participants consider traumatic dental injuries emergencies, but 25.3% would not search for broken tooth fragments at the accident scene.

Similar to a study conducted in Turkey, our study found that although 74% of participants acknowledged that traumatic dental injury is an emergency, only 23.3% believed that emergency intervention was necessary if there was no bleeding in a broken tooth.[13] 85.3% of participants said bleeding in the orofacial area, particularly on the tongue, cheeks, and lips, warranted urgent intervention. It can be concluded that paramedics prioritize treating soft tissue bleeding over tooth fractures or avulsions.[14]

74.7% of participants said they wouldn't search for a broken tooth at an accident scene where dental trauma occurred. Similarly, 80.3% of respondents indicated that broken tooth fragments cannot be reattached. During the literature review, it was discovered that no prior research had been conducted on this topic. Hence, it is necessary to conduct more research on this topic to validate our findings.

The percentage of paramedics who would search for an avulsed tooth at the accident scene is 23.3%. The rate of paramedics who believe that reimplantation of avulsed teeth is possible is only 21.7%. The results of our study were consistent with previous studies conducted in Turkey[13] and other countries.[3,12,14] In contrast to our findings, a study conducted with paramedics and paramedic assistants in Germany revealed that 80% of the participants would search for avulsed teeth at the accident scene and consider the possibility of replantation.[7] The researchers who conducted the study concluded that this difference is most likely related to the training the paramedics participating in the study received. In this study, 78.4% of respondents believed only dentists should reimplant avulsed teeth into their sockets. Previous studies[3,14] and the International association of Dental Traumatology Guideline (IADT) have shown that this situation is invalid and incorrect.[2] Joybell et al.[19] found that 80% of the paramedics in their study, who had less than three years of experience, could perform tooth replantation themselves. Shaul et al.[14] found that only 6.8% of paramedics would attempt to replant avulsed teeth, similar to our study. According to the studies conducted by Diaz et al.,[3] almost half (43.9%) of the participants believed that reimplanted teeth could cause infections. Additionally, 21.9% of the participants were concerned about the possibility of the replanted tooth being avulsed again. In comparison, 21.9% believed that replanted teeth could cause damage to neighboring teeth and should not be replanted. It is commonly believed that individuals who are hesitant to perform reimplantation may benefit from additional information.[6,12,14,20]

The prognosis of dental avulsion injuries is positively affected by the time of reimplantation.1 The avulsed tooth should be re-implanted into its socket as soon as possible for optimal healing. According to IADT, this period is defined as the first half hour1 In this research, only 18.4% of the 65 participants who believed in the possibility of replacing avulsed teeth correctly identified the optimal time for replantation as within the first 30 minutes. It has come to light that there is a significant deficiency of information regarding this matter. There is a lack of research measuring the knowledge of the ideal time for replantation. In Wolfer et al.'s[7] research, 55.2% of participants believed avulsed teeth should be reimplanted immediately. Our research in Turkey resulted in worse outcomes than the study in Germany due to lower knowledge levels. According to a survey by Wolfer et al.,[7] only 56% of the participants received training on dental trauma.

Avulsed teeth should be replanted as soon as possible. If not, the cells of the periodontal ligament may start to lose their vitality.[2] One of the most critical factors determining the prognosis of replanted teeth after avulsion is the loss of viability of periodontal ligament cells[1] If the avulsed teeth cannot be immediately replanted, they should be stored in a solution that can preserve the viability of the periodontal ligament cells when they are outside the alveolar socket. Although the latest 2020 IADT guideline recommends Hank's Balanced Salt Solution as the best dental storage solution, accessibility in society is limited.[1] It is important to note that cold milk is the most readily available solution for storing an avulsed tooth in any society worldwide[1,2] Correct answers are rarely obtained in studies with various professional groups about whether avulsed teeth should be stored in milk.[6,10,11,21] In this research, only 2.3% of paramedics knew that milk could be used to store avulsed teeth. Only 10.7% of those who said their teeth could be replanted knew that avulsed teeth should be stored in milk. 38.4% of participants believed avulsed teeth could be stored in the sterile sponge, while 30.7% thought they could be stored in sterile saline. When these results were evaluated, it was sadly determined that all paramedics needed more knowledge. Aras et al.[13] reported that only 5.7% of participants in their study believed that avulsed teeth could be preserved in milk compared to other studies on the subject. 52.7% of participants reported that teeth can be transported in sterile saline, while 28.5% said movement in the sterile sponge. In a Lewandowski et al.[12] research, only 4% of 138 paramedics knew avulsed teeth could be stored in milk. 42% said it could be stored in sterile saline, and 34% said it was a sterile sponge.

In research conducted by Joybell et al.,[19] 10% of the 108 participating paramedics stated that avulsed teeth can be preserved in milk. The percentage of paramedics who believe it can be stored in sterile saline is only 14%. According to Lin et al.,[14] 15.9% of the 44 emergency medical technicians in their study believed milk is a suitable storage medium for avulsed teeth. The percentage of participants who preferred storage in sterile saline solution was 38.6%. According to Diaz et al.'s[3] study involving 82 participants and 43 paramedics, 42.7% of healthcare professionals recommended keeping avulsed teeth in sterile saline if they cannot be replanted within 30 minutes. Meanwhile, 8.5% of healthcare professionals suggested using a sterile sponge instead. Unfortunately, participants in this research were not provided with the option of milk. According to a study by Wolfer et al.[7] involving 500 paramedics, only 10.8% believed that avulsed teeth could be stored in milk. The percentage of participants preferred storing it in sterile saline was 31.6%, while only 4.4% preferred storing it in a sterile sponge. In research of medical doctors in 545 emergency rooms, Kuru & Duruk[6] found that 28% recommended milk, 72.3% recommended sterile saline, and 67.1% recommended sterile sponges for storing avulsed teeth.

The general conclusion from the above studies is that sufficient milk is not known as the ideal transport solution. Participants stated that avulsed teeth could be stored in sterile saline. It has been revealed that there is a significant lack of information on this subject. Paramedics and other healthcare professionals in the emergency department lack knowledge.[3,6] There is a need for studies to determine the changes in the level of knowledge by providing training to the participants on this subject.

Paramedics in the study were asked to identify dental emergencies. At the end of the survey, 47.3% of participants believed that complicated fractures involving enamel and dentin required immediate attention. Additionally, 14.3% thought that bleeding teeth needed urgent intervention, while only 9.17% believed that avulsed teeth required the same level of urgency. In a study with 44 emergency medical technicians, Lin et al.[14] found that 31.8% referred bleeding situations to a dentist, and only 6.8% would stop the bleeding first. Cruz-da-Silva et al.[20] found that 81% of participating paramedics were unfamiliar with dental avulsion. Joybell et al.[19] found that 28% of paramedics surveyed considered dental injuries urgent enough to require ambulance intervention. According to the survey, 68% of the respondents reported being knowledgeable about dental injuries. Aras and Doğan[13] found that only 74.5% of the 389 participating paramedics could stop bleeding in injuries they had previously treated. Although our results differ from these studies, it's evident that all participants lacked information.

In our study, only 17.3% of participants felt confident intervening with dental trauma patients. According to Wolfer et al.[7] research, 88.4% of the 677 participants completed dental trauma training. 44% of the participants reported insufficient knowledge about managing dental trauma. Nearly half of paramedics said that their activity on dental trauma was inadequate, with 45.9% expressing dissatisfaction with the level of instruction provided. 50.6% of paramedics reported insufficient practical knowledge of dental trauma. Joybell et al.[19] found that only 10% of 100 paramedic participants had received training on dental trauma. According to research, only 18% of paramedics have sufficient knowledge about dental concussions. Kuru&Duruk[6] found that 93.4% of emergency medicine doctors consider dental trauma training necessary, but only 88.6% have received it. It is evident from this study that emergency medicine doctors are better trained to provide accurate information regarding dental traumas, consistent with previous studies.

In our study, 84% of respondents felt that their knowledge and education on dental trauma were insufficient and expressed a desire to receive further training on the subject. According to research conducted by Wolfer et al.,[7] which involved 677 people, even though 88.4% of the participants had received training on dental trauma, 44% of them had inadequate knowledge regarding dental trauma. Furthermore, 68.8% of the participants desired to obtain more activity on the subject. 43.7% of the participants preferred hands-on course training, while 35.9% favored video training. In their research with 21 paramedics, Cruz-da-Silva et al.[20] found that 91.7% desired dental trauma training. Joybell et al.[19] found that only 18% of 100 paramedic participants felt their knowledge level was sufficient, while 66% expressed a desire for training on dental trauma.

It is important to note that this study has certain limitations. One of our significant limitations was our inability to access paramedic healthcare personnel. Delivering our questionnaire to constantly working paramedics and getting it filled out was challenging. It was found that a significant number of paramedics did not complete the questionnaire thoroughly or answered questions inconsistently. Because of these challenges, the study only included 300 paramedics. One limitation pertained to questions about avulsion. It was found that many participants provided multiple responses about the proper storage conditions for knocked-out teeth. The answers were examined individually and checked for consistency with the other questions. Participants who lacked knowledge or did not want to intervene in dental trauma were not asked about the post-avulsion treatment protocol. Some also declared their knowledge as insufficient. This research differs from the previously mentioned studies due to this particular situation. Participants in other studies were asked how to handle avulsed teeth before replantation, including washing and replantation. Our study had a limitation in that we only evaluated knowledge levels of dental trauma. It is possible to measure the increase in knowledge levels following the training. However, the challenges of delivering and consistently filling out the questionnaires caused a further decrease in the number of participants among paramedics.

CONCLUSIONS

The study conducted in Turkey revealed that nearly all paramedics have insufficient knowledge about dental traumas. Most participants stated that they preferred not to intervene in cases of dental trauma and believed that a dentist or emergency physician should handle it. However, as this situation is not common in practice and it is known to be the main factor leading to unsuccessful prognosis, paramedics should receive training on treating dental trauma. We believe that studies involving more participants will confirm our results on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Afyonkarahisar Health Sciences University Faculty of Medicine Clinical Researches Ethics Committee (Date:7.7.2023, Decision No: 2023/304).

Informed Consent

Because the study was designed survey study, no written informed consent form was obtained from participants.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Comparison of classical and anchorage methods in sacrospinous ligament fixation

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ABSTRACT

Aims: Pelvic organ prolapse (POP) is a common condition that affects the quality of life in women. As a natural consequence of the aging population, it is believed that POP will increase in the next 40 years. With the increase in life expectancy, there is an expected rise in reconstructive surgical procedures to correct pelvic floor disorders. POP can occur in three vaginal compartments: anterior, apical, and posterior. The apical compartment includes uterine prolapse, cervix, or vaginal cuff prolapse. Our primary objective was to compare the surgical outcomes of the method using the classic technique with pelvic floor anchorage (anchoring).

Methods: This retrospective cohort study consisted of women with POP-Q (Pelvic Organ Prolapse Quarejment) grade 2 and above in the apical compartment. In the sample size calculation, G power analysis was performed with α: 0.05 and 80% accuracy. Forty-eight women were included in the study, with 24 of them undergoing the classic method and the other 24 receiving sacrospinous ligament fixation (SSLF) using a pelvic floor anchoring device. The results of both surgical methods were compared in terms of anatomical recurrence.

Results: There was no statistically significant difference observed between the postoperative measurements of the C points. However, the difference in the C level between preoperative and postoperative measurements for patients who underwent the classic SSLF operation was statistically significantly higher compared to those who underwent the Anchorage SSLF procedure.

Conclusion: When comparing the classic and anchoring systems for the SSLF procedure, no difference was observed in terms of recurrence. However, the classic method was found to be more successful in restoring apical prolapse.

Keywords: Apical prolapse, SSLF, pelvic organ prolapse

INTRODUCTION

Pelvic organ prolapse (POP) is a common condition that affects the quality of life in women.[1] As a natural consequence of the aging population, it is believed that POP will increase in the next 40 years.[2] With the increase in life expectancy, there is an expected rise in reconstructive surgical procedures to correct pelvic floor disorders. POP can occur in three vaginal compartments: anterior, apical, and posterior. The apical compartment includes uterine prolapse, cervix, or vaginal cuff prolapse.[3] Apical and anterior prolapse often coexist, making apical restoration important during the correction of anterior prolapse.[4] Sacrospinous ligament fixation (SSLF) has been described as a vaginal approach for apical prolapse restoration. In the classic traditional posterior approach, along with the advantages of repairing defects like cystocele, rectocele, enterocele, it carries the risks of pudendal nerve injuries, vascular injuries, dyspareunia, chronic pelvic pain, and postoperative de novo recurrence in the anterior compartment.[5]

After the ban on the use of vaginal meshes by the FDA in 2019, there has been a renewed interest in natural tissue repair with SSLF.[6] In this study, our primary objective was to compare the surgical outcomes of the method using the classic technique with pelvic floor anchorage (anchoring).

METHODS

The study was carried out with the permission of of the Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committe (Date: 26.12.2022, Decision No: 368). All procedures

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were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective cohort study consisted of women with POP-Q (Pelvic Organ Prolapse Quarejment) grade 2 and above in the apical compartment, treated at a tertiary center between April 2020 and July 2022. Forty-eight women were included in the study, with 24 of them undergoing the classic method and the other 24 receiving sacrospinous ligament fixation (SSLF) using a pelvic floor anchoring device. Patients with emergency cases, malignancy, immunodeficiency, or connective tissue diseases were excluded from the study. Demographic data and characteristic features of the patients were recorded. The comparison of both methods included the start and end times of anesthesia (surgery duration) in the operating room, intraoperative blood loss, and perioperative complications, which were added to the patient data. Complications were classified according to the Clavien-Dindo classification. All operations were performed by the same surgical team.

Postoperative surgical failure was evaluated by independent surgeons, not part of the operating team, using the POP-Q system. Anatomical anterior compartment recurrence was defined as ≥ stage II (Aa or Ba ≥-1 cm), apical prolapse relapse as ≥stage II (C ≥-1 cm), and posterior vaginal wall prolapse as ≥stage II (Ap or Bp ≥-1 cm). Postoperative follow-up was scheduled routinely at the first year, postoperative 6th and 12th months, and then annually thereafter.

Surgical Operation Methods

Classic SSLF: Following the infiltration of the posterior vaginal wall, the pararectal space was dissected by deviating the rectum to the right after an incision in the mid-lower third of the vagina. The surgeries were performed unilaterally. After the sacrospinous ligament was dissected from the connective tissue, it was sutured to the apex of the vagina with a non-absorbable permanent suture. Depending on the surgeon's decision, anterior and/or posterior colporrhaphy was performed for patients with cystocele or rectocele.

Anchorage SSLF: Following the infiltration of the posterior vaginal wall, the pararectal space was dissected by deviating the rectum to the right after an incision in the mid-lower third of the vagina. The connective tissue over the sacrospinous ligament was dissected, and then the sacrospinous ligament was fixed using a pelvic floor anchoring device. The unique non-absorbable permanent suture from the device was used to suture the vaginal apex. The surgery was performed unilaterally. Depending on the surgeon's decision, anterior and/or posterior colporrhaphy was performed for patients with cystocele or rectocele.

Statistical Method

SPSS 15.0 for Windows software was used for statistical analysis. Descriptive statistics were presented as follows: for categorical variables, counts and percentages were used, and for numerical variables, mean, standard deviation, median, minimum, and maximum values were provided. Chi-square test was used to compare proportions between groups. For independent two-group comparisons of numerical variables, Student t-test was used when the normal distribution assumption was met, and Mann-Whitney U test was used when the assumption was not met. The significance level (alpha) was set at $p<0.05$.

RESULTS

In the Classic SSLF and Anchorage SSLF groups, the mean age was 59.8±6.3 and 60.0±6.5, respectively. There were no statistically significant differences in demographic and characteristic features between the two groups of patients who underwent the two types of surgeries (Table 1).

Table 1. Demographic and characteristic features of patients

		Classic	Anchorage	p
Age; Mean ± SD (min-max)		59h.8±6.3 (48-69)	60.0±6.5 (49-71)	0.929*
BMI; Mean ± SD (min-max)		27.6±1.4 (25-30)	28.0±1.0 (26-30)	0.238#
Smoker; n (%)		7 (29.2)	10 (41.7)	0.365£
Systemic disease; n (%)	None	11 (45.8)	7 (29.2)	0.642£
	DM	0 (0.0)	1 (4.2)	
	HT	8 (33.3)	9 (37.5)	
	CAD	3 (12.5)	2 (8.3)	
	COPD	0 (0.0)	1 (4.2)	
Menopause Duration (years); Mean ± SD (min-max)		13.0±6.5 (2-22)	16.0±5.8 (4-26)	0.094*

*Student t Test #Mann Whitney U test £ Chi-square test
(BMI: body mass index, DM: Diabetes mellitus, CAD: Coronary Artery disease, HT: Hypertension, COPD: Chronic Obstructive pulmonary disease)

Between the two surgical procedures, there was no difference observed in terms of hospitalization duration. The average surgery duration for patients who underwent the classic SSLF operation was 80 minutes, which was significantly longer than those who underwent the Anchorage SSLF procedure *($p<0.001$)*. Regarding complications, no Grade >3b complications were observed according to the Clavien-Dindo classification in our study. In the classic SSLF group, 3 patients experienced dyspareunia, 2 patients had gluteal area paresthesia, and 1 patient had ischiorectal area hematoma. In the Anchorage SSLF group, 2 patients developed gluteal area paresthesia. The median follow-up duration for the patients was 12 months. The recurrence rate in both groups was 16.7%, and there was no statistically significant difference. The findings are summarized in Table 2.

Both surgeries' Ba, C, and Bp points according to the POP-Q scale are summarized in Table 3. There was no statistically significant difference observed between the postoperative measurements of the C points. However, the difference in the C level between preoperative and postoperative measurements for patients who underwent the classic SSLF operation was statistically significantly higher compared to those who underwent the Anchorage SSLF procedure.

Table 2. Surgical Characteristics				
		Performed surgery		
		Classic SSLF	Anchorage SSLF	p
Additional Operations; n (%)	CA	21 (87.5%)	22 (91.7%)	-
	CA+CP	3 (12.5%)	2 (8.3%)	
Surgery duration in minutes; Mean±SD (min-max)		80 (45-105)	32.5 (30-65)	<0.001#
Estimated bleeding amount in ml; Mean±SD (min-max)		80 (50-95)	80 (60-200)	0.059#
Intraoperative/ postoperative complication(s); n (%)	None	18 (75%)	22(91.7%)	
	Hematoma	1 (4.2%)	0	
	Paresthesia	2 (8.3%)	2 (8.3%)	
	Dyspareunia	3 (12.5%)	0	
Follow-up period; median (min-max)		12 (7-16)	12 (4-16)	0.338
Relapse; n (%)		6 (25%)	6 (25%)	1.000

#Mann Whitney U test, CA: Anterior colpography, CP: Posterior colpography, , SSLF: Sacrospinous ligament fixation

Table 3. Preoperative and postoperative POP-Q measurements				
		Classic SSLF	Anchorage SSLF	
		Median (min-max)	Median (min-max)	p#
Ba: cm	Pre-op	2.5 (1-6)	3 (1-6)	0.538
	Post-op	-2 (-3-3)	-2 (-3-3)	0.341
C	Pre-op	4.25 (2.5-7)	3 (1-5.5)	<0.001
	Post-op	-4.5 (-6-4)	-4 (-6-3)	0.288
Bp	Pre-op	2 (1-2)	2 (1-2)	0.118
	Post-op	-1.5 (-3-2)	-2 (-3-1)	0.327

#Mann Whitney U test

DISCUSSION

The results of SSLF procedures may vary; however, they are frequently used for the restoration of apical prolapse. In a randomized study conducted in Denmark in 2019, the follow-up results of SSLF operations for apical prolapse showed recurrence in 32% of the patients after a 5-year follow-up.[7] A meta-analysis conducted by Coolen et al.[8] reported recurrence rates ranging from 35% to 81%. In a study by Wu CJ and colleagues in Taiwan, the one-year objective cure rate was found to be 82.5%.[9] In our study, the recurrence rates for both methods were similar at the one-year follow-up (25%). A similar Swedish study comparing the anchorage method with classic SSLF showed that relapse symptoms and the number of reoperated patients were slightly more common in the anchorage technique; the one-year asymptomatic period in the anchorage and classic methods were observed at 71.5% and 78.7%, respectively. However, patient satisfaction was similar in both groups.[10] In other studies, when the pelvic floor anchorage technique was used for SSLF, objective success rates ranged from 67% to 95% .[11,12]

Although studies related to SSLF show differences in methods, techniques, and surgical procedures, in a comparison between unilateral and bilateral SSLF, it was reported that two patients (3.84%) in the unilateral group experienced vaginal cuff prolapse recurrence, while no recurrence was observed in the bilateral SSLF group.[13] Another study on apical prolapse showed that in patients with a genital hiatus larger than 4 cm, cuff prolapse recurrence could be anticipated.[14] While rare, SSLF can have serious intraoperative and postoperative complications. The most common complication is bleeding due to pudendal vessel injuries. Other complications include pudendal and sciatic nerve injuries, bladder injuries, gluteal pain, and suture abscesses.[15,16] In our study, in the classic SSLF group, 3 patients experienced dyspareunia, 2 patients had gluteal area paresthesia, and 1 patient had an ischiorectal area hematoma. In the Anchorage SSLF group, 2 patients developed gluteal area paresthesia. These complications were not severe and resolved within the following weeks with analgesics. In a meta-analysis study involving 4,120 cases, it was observed that abdominal sacrocolpopexy (ASC) had a higher success rate and lower recurrence rate compared to SSLF. Patients who underwent SSLF had more postoperative dyspareunia. SSLF cases showed shorter surgery duration, minimal bleeding, fewer gastrointestinal complications, and fewer wound infections compared to ASC cases.[17] Apical prolapse patients or those undergoing SSLF, particularly in older ages with comorbidities and potential complications related to general anesthesia, were shown to benefit from SSLF performed under local anesthesia.[18] This approach offers a significant advantage for patients who cannot undergo general anesthesia and have cuff prolapse.

In a study conducted by Salman et al.,[13] using anchorage technique for SSLF, the average surgery duration was 76.6±10.7 minutes for unilateral cases and 80.5±11.8 minutes for bilateral cases. In another study involving 55 patients, a prospective cohort study with classic SSLF reported a surgery duration of 60 minutes (ranging from 20 to 165 minutes).[19] In another study using anchorage for SSLF, the average surgery duration was 40 minutes (ranging from 20 to 90 minutes).[20] In our study, the surgery duration for unilateral classic SSLF was 80 minutes (ranging from 45 to 105 minutes), while for unilateral SSLF with Anchorage, it was 32.5 minutes (ranging from 30 to 65 minutes). The presence of additional conditions such as simultaneous cystocele, rectocele, or incontinence problems in the patients may have contributed to the longer surgery duration. However, regardless of these additional procedures, the use of anchorage in SSLF significantly reduces the surgery duration.

When looking at the studies, it can be observed that there are similar recurrence and complication rates, as well as studies showing higher recurrence and complication rat es. The reason for this could be the lack of a standardized protocol for SSLF. This indicates that there is a surgical learning curve for SSLF, and the surgeon's experience is crucial. The limitations of the study were a relatively small patient cohort and a short follow-up duration. In the future, prospective studies with larger patient cohorts and longer follow-up periods for apical prolapse in SSLF would be more beneficial.

CONCLUSION

When comparing the classic and anchoring systems for the SSLF procedure, no difference was observed in terms of recurrence. However, the classic method was found to be more successful in restoring apical prolapse.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committe (Date:26.12.2022, Decision No: 368).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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FGF-21 Level is higher in patients with breast cancer, a candidate for a new biomarker?

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ABSTRACT

Aims: Fibroblast Growth Factor 21 (FGF-21) is a member of the FGF family involved in biological processes such as embryonic development. cell growth. morphogenesis. tissue repair. tumour growth and invasion. with mitogenic and cytogenetic activity at 19q13.33.Breast cancer is a deadly and increasing disease in women. and recent studies have shown a relationship between some cancers. including breast cancer. and hormones secreted from adipose tissue.The aim of the present study was the measurement of FGF-21 levels in patients with breast cancer and its association with breast cancer.

Methods: The study included 39 patients with newly diagnosed breast cancer and 39 healthy controls. During the patients' routine blood tests. a venous blood sample was taken and the serum levels of FGF-21 were determined by ELISA.

Results: Demographic and laboratory data were compared between the newly diagnosed breast cancer group and the control group. The control group consisted of 39 participants with a mean age of 52.49 ± 7.02 years. In the patient group. 39 participants with a mean age of 52.15 ± 6.21 years were included in the study. there was no statistical difference regarding age($p>0.05$).In the control group. the mean FGF-21 level was 121.35 ± 88.4 pg/ml. while the mean FGF-21 level in the patient group was 171 ± 117.45 pg/ml. a statistically significant difference was detected(p value=0.036).

Conclusion: FGF-21 is thought to have significant and beneficial effects on glucose. lipid and energy metabolism. as well as slowing the growth of cancer cells. and may later be used as a biological marker for breast cancer.

Keywords: FGF-21, breast cancer, obesity

INTRODUCTION

Breast cancer is the most common malignancy in women and the most common cause of cancer-related death after lung cancer in women. In recent years. there has been an increase in the incidence of breast cancer. and as well as metabolic syndrome. especially in industrialized countries. with the spread of obesity.[1] As a result of that it brought to mind the question of whether there is a relationship between metabolic syndrome and breast cancer.

Metabolic syndrome is characterised by a cluster of metabolic disorders that may be risk factors for diabetes mellitus. coronary heart disease. peripheral vascular disease and cerebrovascular.[2] Metabolic syndrome is thought to be associated with an increased risk of many cancers. including breast cancer.[3] Several hormonal. metabolic and inflammatory mechanisms are known to play a role in the development and progression of breast cancer.[4] Adipocytokines as a carcinogen are being tried to be defined whether there is another link between obesity and cancer. Falk Libby E. et al.[5] investigated the effect of adiponectin on tumor cell proliferation in early stage breast cancer. The effect of different adiponectin isoforms on breast cancer cells was examined and the results of the present study suggested that a spesifik AdipoQ isoform may enhance breast cancerinvasion.possibly via autophagic induction.

Fibroblast Growth Factor (FGF-21) is a member of the FGF family involved in biological processes such as embryonic development, cell growth, morphogenesis, tissue repair, and tumor growth and invasion.[6] If there is no adiponectin in

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the environment; it has been shown that FGF-21 is unable to upregulate glucose uptake alone into the adipocytes. It is known that adiponectin protects against chronic illnesses such as diabetes, obesity and cancer through its anti-inflammatory properties.[7] A few years ago, it was assumed that fatty tissue cells (brown fat tissue), which had been found, converted to energetic heat through mitochondria, leading to weight loss.[8] In 2013; Luo Y et al.,[9] reported that although liver and muscle have received the most attention so far as the two main organs that send FGF21 as a stress signal, other organs may also use the same mechanism to recruit adipocytes in large fat depots or the microenvironment of various tissues. In the microenvironment of tissues containing ectopic or interspersed adipose tissue or adipocytes, such as the breast, bone marrow, and perirenal and epicardial regions, FGF21 serves to alter adipocyte signaling affecting parenchymal cell functions through a paracrine mechanism, and in stressed adipose tissues composed predominantly of adipocytes, by both paracrine and autocrine mechanisms. becomes active.

In line with these findings FGF-21 has significant and positive metabolic effects and anti-carcinogenic properties on breast cancer. In this study we aimed to measure FGF-21 levels in patients with breast cancer and to show their association with metabolic parameters in patients with cancer and healty control group.

METHODS

The study was carried out with the permission of Ankara Abdurrahman Yurtaslan Oncology Hospital Research and Training Center Ethics Committee (Date: 04.05.2016. Decision No: 2016- 5378). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This study was conducted between newly diagnosed stage 1-2 breast cancer patients who applied to Ankara Abdurrahman Yurtaslan Oncology Hospital between January 2016 and August 2016, and a control group of the same age group without a diagnosis of cancer who applied to the internal medicine outpatient clinics of Ankara Training and Research Hospital. Thirty-nine patients aged between 40-70 years who were diagnosed with breast cancer stage 1 and 2 and 39 healthy volunteer female patients were included in the study.

Demographic and charactheristic features including age. body mass index (BMI). waist and arm circumference of the all participants were gathered. Arm circumference was measured. Participants were evaluated with detailed physical examination and laboratory findings were collected. From all patients 5 cc blood was taken after eight hours of fasting in the morning hours. Blood obtained was centrifuged at 3000 rpm for 10-20 minutes after clotting was anticipated. Glucose. blood urea nitrogen (BUN). creatinine. uric acid. albumin. sodium(Na). potassium(K). calcium(Ca). phosphorus(P). aspartate aminotransferase (AST). alanine aminotransferase (ALT). gamma glutamyl transferase (GGT). alkaline phosphatase (ALP). bilirubin. Total cholesterol. High Density Lipoprotein (HDL-C). Low Density Lipoprotein (LDL-C). triglyceride(TG). complete blood count (CBC). thyroid function tests (TFT). anti-TPO. high sensitivity C- reactive protein (hs-CRP). erythrocyte sedimentation rate (ESR) levels were studied in the biochemistry laboratory of our hospital on the Beckman Coulter LH780 device by enzymatic colorimetric method (Cobas c501. Roche. Japon). Serum FGF-21 level was determined by enzyme-linked immunosorbent assay (ELISA) method using Biovendor Research and Diagnostic Products (antibody coated 96-well plate human FGF-21) ELISA kit. Biomedical Technologies Inc. Absorbance measurements were performed at 450 nm on a USA ELx800 (Biotek Instruments. INC.) Microplate reader. According to the ELISA kit prospectus; for the measurement of FGF-21 levels. serum samples were diluted 1: 2 by buffer dilution prior to analysis. The standard curve range for analysis was 30 1920 pg / ml. sensitivity 7 pg / ml. intraassay and interassay change were 3.0-4.1% and 3.6-3.9%. respectively.

Stastistical Analysis

The data were analysed using SPSS 22.0 (Statistical Packages for Social Sciences). Arithmetic mean. standard deviation (SD). number and percentage (%) were used as descriptive statistical parameters of the central criteria. The kolmogorov-simirnov test was used to check the normal distribution of the data. If the difference between the breast cancer group and the control group was appropriate with normal distribution. the independent student T test was performed for the continuous variables. chi-squared test or fisher's exact test was used to compare the two categorical variables. In the groups with and without breast cancer. dietary fat. physical activity, menopausal status and frequency distributions of categorical data were used, and the chi-squared test was used between groups. Correlation analysis was performed using the pearson correlation rank test. The significance level was accepted as p-value <0.05.

RESULTS

The demographic and laboratory data of the newly diagnosed breast cancer patient group and the control group were compared. The patient group was evaluated preoperatively. The control group consisted of 39 participants with a mean age of 52.49±7.02 years. In the patient group. 39 participants with the mean age of 52.15±6.21 years were included in the study. No statistical difference was observed regarding age between these two groups (p>0.05). In the control group. the mean FGF-21 level was 121.35±88.4 pg / ml. while the mean FGF-21 level in the patient group was 171±117.45 pg / ml and statistically significant difference was detected (p value=0.036). In Figure it was shown the changes of the FGF-21 levels in the patient and the control group. Arm circumference measurements were 34.15±6.11 cms in the control group and 31.38±3.65 cms in the patient group and it was found significantly different (p value =0.018). BMI and waist circumferences of control and patient groups were similar(p>0.05).

Total cholesterol, uric acid, LDL, TG, TSH, total bilirubin. ESR levels were also similar and there were no statistical difference (p>0.05). Whereas no significant difference was found for white blood cell. platelet count. and hemoglobin

levels (p>0.05). On the other hand creatinin,ALT, HDL, C albumin, free thyroxin, direct bilirubin, CRP and arm circumference measurements were significantly different between the patient and control group (p<0.05). All these finding were detaild in the Table .

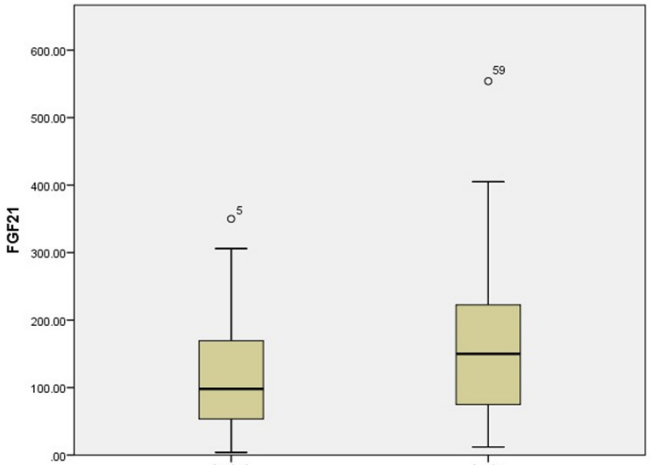

Figure. Serum FGF-21 levels in the patient and control group

Table . Demographic laboratory charactheristics and body measurements of the study population

Mean±S	Patient Group (n=39)	Control Group (n=39)	P Value
Age,year	52.15±6.21	52.49 ±7.02	0.825
BMI, kg/m^2	28.81±5.17	30.44 ±4.11	0.128
Fasting glucose. mg/dl	107±28.69	103 ±9.21	0.386
Creatinin. mg/dl	0.69 ±0.12	0.77 ±0.11	0.001
ALT, u/l	17.66 ±8.69	29.97 ±25.30	0.005
Uric acid, mg/dl	4.52 ±1.23	4.72 ±1.78	0.568
Total cholesterol, mg/dl	201.53 ±42.07	214.46 ±35.77	0.148
LDL-C, mg/dl	127.30 ±34.54	130.38 ±30.10	0.676
HDL-C, mg/dl	44.53 ±9.34	54.58 ±13	<0.001
TG, mg/dl	141.58 ±67.40	156.97 ±86.71	0.384
Calcium, mg/dl	9.40 ±0.71	9.71 ±0.47	0.026
Albumin, g/dl	4.03 ±0.74	4.42 ±0.30	0.003
TSH, mIU/L	1.65 ±1.11	2.02 ±1.12	0.155
ST4, ng/dl	1.06 ±0.30	0.82 ±0.17	<0.001
Total bilirubin, mg/dl	0.65 ±0.39	0.58 ±0.29	0.381
Direct bilirubin, mg/dl	0.25 ±0.19	0.12 ±0.07	<0.001
CRP, mg/L	4.47 ±5.64	0.70 ±0.55	<0.001
ESR,mm/hour	18.74 ±15.40	17.38 ±9.49	0.640
White blood cell,10^3/mm^3	7.36 ±2.38	7.44 ±2.05	0.867
Platelet count,10^3/mm^3	299.74 ±53.14	309.33 ±59.99	0.457
Hemoglobin, g/dl	13.32 ±1.28	12.98 ±1.52	0.285
Waist circumference, cm	98.20 ±12.44	95.38 ±6.38	0.212
Arm circumference, cm	31.38 ±3.65	34.15 ±6.11	0.018
FGF-21, pg/ml	171 ±117.45	121.35 ±88.43	0.036

* Variables were presented as n (%). mean ± SD or median [Q1-Q3]
BMI. Body Mass Index; ALT. LDL-C. Low Density Lipoprotein-Cholesterol; HDL-C. High Density Lipoprotein-Cholesterol; TG. Triglyceride; TSH. Thyroid Stimulating Hormone; FT4. Free thyroid hormone4; CRP. C-Reactive protein ; ESR. Erythrocyte Sedimentation Rate; FGF-21. Fibroblast growth factor 21, pg/ml. picogram/ml;kg/m^2 .kilogram/square meter; mg/l. milligram/litre; mm. millimeter; cm. centimeter

DISCUSSION

Breast cancer is the most commonly diagnosed cancer in women worldwide, with more than 2 million new cases in 2020.[11] Many genetic, reproductive and environmental factors are effective on the development of breast cancer. One of the most important of these factors is the metabolic syndrome. The prevalence of the metabolic syndrome is rapidly increasing all over the world, parallel to that the incidence of breast cancer is also rising.[12] FGF-21 is expressed in the adipose tissue, pancreas, and mainly in the liver. FGF-21 is a powerful regulator of metabolism. It regulates energy balance as well as specific effects on glucose and lipid metabolism. Pharmacological studies in primates and rats have shown that FGF-21 promotes a wide metabolic activity, increases insulin sensitivity, reduces plasma glucose, insulin, lipid levels, promotes the use of fat and energy consumption, and causes weight loss, therefore it has been suggested that this polypeptide may be a promising agent for the treatment of metabolic disorders associated with diabetes and obesity.[13]

It has recently been determined that some members of FGFs, including FGF-15, FGF-19, FGF-21, and FGF-23 play important metabolic roles.14 FGF 21, FGF19 affect glucose, lipid and energy metabolism via KLB and FGFR tyrosine kinase in fat cells and hepatocytes, in addition, obesity and metabolic abnormalities are factors contributing to the progression of breast tumor. Studies on FGFR4 in the liver reveal endocrine FGF21 signaling roles in both metabolic and cellular homeostasis.

In a study, very important results were obtained; it was shown that in obese or diabetic mice; FGF-21 administration decreased glucose, glucagon, lipids, visceral fat, tissue and body weight via increasing insulin sensitivity without changes in movement and diet. Free fatty acids, glucose uptake, HDL have been found to increase. Recombinant therapeutic application of FGF21 has been shown to lower blood sugar, triglyceride levels in diabetic and obese mice, reverse hepatic fat storing, and increase insulin sensitivity.[12] In a study by Zhang et al.,[13] there was a positive correlation between FGF-21 level and the parameters of obesity such as BMI, waist circumference and body fat ratio. FGF-21 concentration was closely related to body weight and amount of adipose tissue. A study provides evidence that increased expression of hepatic FGF21 in lean liver disease promotes breast cancer progression by increasing the anti-apoptotic abilities of breast cancer cells. Similar to our study, we observed overexpression of FGF21 in breast cancer tissues and patients with high FGF21 levels have poorer prognoses. shows. These findings highlight the clinical importance of FGF21 as both a prognostic indicator and a potential target for the treatment of breast cancer.[14]

Cancer-associated fibroblasts are activated fibroblasts that serve as a key component of the tumor microenvironment; FGF-19, FGF-21 and FGF-23 are endocrine FGFs that bind to Klotho and FGF receptors. FGFR1 is often overexpressed in breast and lung cancer, Promoter hypermethylation correlates with poorer survival of patients with gastric cancer, making it an independent prognosis factor.[15,16]

In our study, data such as age, BMI, waist and arm circumference, diet and exercise information, menopause status, comorbidities and medications were used. Our findings showed that FGF-21 levels were significantly higher in patients with early stage (1-2) breast cancer compared to the control group (p:0.036). Creatinine, ALT, HDL, calcium, albumin, fT4, direct bilirubin and CRP levels showed significant differences between the patient and control groups.

In similar studies in the literature, the positive correlation between FGF-21 and obesity, high blood sugar and LDL elevation was not found to be significant in our study. The average BMI of our patient group, in which FGF-21 was found to be significantly elevated, was determined to be overweight as 25.8 kg/m^2.

The strength of our study is that FGF-21 can be used as a biomarker for breast cancer in the future due to its significant and positive effect on glucose, lipid and energy metabolism, as well as its ability to stimulate the growth of cancer cells and cause breast cancer.

When its relationship with stage and treatment response is examined, it is predicted that it can be used as a useful agent in follow-up and treatment.

Limitations

Limitations of the study include a small patient population and the inclusion of only early-stage (stage 1-2) breast cancer patients.

CONCLUSION

It is believed that FGF-21 could be used in the future as a biological marker for breast cancer. as it has a significant and positive effect on glucose. lipid and energy metabolism. as well as slowing the growth of cancer cells. and as breast cancer is considered a metabolic cancer. It is predicted that when the relationship with stage and treatment response is studied. it can be used as a useful agent in follow-up and treatment. Larger randomised controlled trials are needed to clarify our findings.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara Abdurrahman Yurtaslan Oncology Hospital Research and Training Center Ethics Committee (Date: 04.05.2016. Decision No: 2016- 5378).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design. execution. and analysis of the paper. and that they have approved the final version.

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Original Article

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Predictors of ejection fraction recovery and baseline differences in patients with peripartum cardiomyopathy and dilated cardiomyopathy

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ABSTRACT

Aims: Dilated cardiomyopathy (DCM) and peripartum cardiomyopathy (PPCM) are heart failure conditions with similar clinical, morphological and pathophysiological features but different underlying pathways. In PPCM and DCM patients, improvement in left ventricular ejection fraction (LVEF) varies depending on a number of factors. In this study, we aimed to determine the main differences between DCM and PPCM patients and the predictors of LVEF recovery in these patients.

Methods: This cross-sectional, observational study included 33 consecutive female patients, 10 with PPCM and 23 with DCM, attending a tertiary cardiac center between March 2020 and April 2023. We performed a retrospective analysis of some clinical data and LVEF measurements. The main outcome was accepted as EF improvement at a follow-up of at least 12 months. Binary logistic analysis was conducted to assess predictive factors linked to LVEF recovery. This involved using binary logistic regression analysis to figure out odds ratio (OR) and 95% confidence interval (CI).

Results: The PPCM group had a higher mean follow-up LVEF and LVEF value increase ($p<0.001$). A total of 10 patients (30%), 4 (17%) in the DCM group, and 6 (60%) in the PPCM group revealed evidence of LVEF recovery. Left atrium anteroposterior (LA-AP) diameter emerged as an independent predictor of EF recovery in the multivariate analysis (OR:0.566, 95 CI%; 0.322-0.995, $p=0.048$). Furthermore, the receiver operating characteristic (ROC) curve analysis identified a cutoff value of <37.5 mm for LA-AP diameter as the optimal threshold for predicting EF recovery, with 80% sensitivity and 78% specificity.

Conclusion: LA-AP diameter was a significant indicator of LVEF recovery in patients with DCM and PPCM.

Keywords: Dilated cardiomyopathy, ejection fraction recovery, peripartum cardiomyopathy

INTROUCTION

Dilated cardiomyopathy (DCM) is a heart muscle disease characterized by a decrease in systolic function, dilation in the heart chambers, and arrhythmia.[1] Various causes are implicated in the a etiology of dilated cardiomyopathy, including viral infections, genetic factors, systemic diseases, and toxic agents (alcohol or chemotherapy).[1-3] A large number of DCM patients referred to as idiopathic DCM, do not have an identifiable a etiological cause.[1,4] Furthermore, patients with coronary artery disease, valvular diseases, congenital heart diseases, hypertension, and abnormal loading conditions are excluded from this characterization, and therefore, in some sources, are also referred to as non-ischemic DCM.[1,4]

Peripartum cardiomyopathy (PPCM) is a clinical condition that reveals in late pregnancy or early postnatal period in the absence of a known pre-existing cardiac dysfunction, has a diverse clinical presentation and shares similar morphological findings with DCM, including ventricular dilatation and impaired systolic function.[1,5,6] Data on the pathophysiology of PPCM are limited and underlying risk factors include advanced age, history of pre-eclampsia, malnutrition, smoking, African ethnicity, diabetes, multiparity and teenage pregnancy.[1,5,6,7]

Due to the similar clinical, morphological and pathophysiological features of DCM and PPCM, it has been assumed that PPCM is DCM with a pregnancy-onset.[5,6,8] Nonetheless, fundamental variations in underlying pathways highlight significant differences between the two cardiomyopathies.[6-8] PPCM is diagnosed in the absence of other a etiological causes of DCM.[5,7] There are currently limited data

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regarding prognosis, response to medical care, and variations in both diseases' morphological and clinical features. More than half of PPCM patients have an improvement in left ventricular ejection fraction (LVEF) within the first 6 months, whereas this rate varies in DCM patients depending on a number of factors such as age, gender and baseline EF.[1,3,5-7] The main objectives of this study were to identify the key distinctions between DCM and PPCM patients and the predictors of LVEF recovery in these patients.

METHODS

The study was carried out with the permission of Ethical Committe of Faculty of Başakşehir Çam Sakura City Hospital Research Ethics (Date: 24.04.2024, Decision No: 272). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In the study by Zhang et al.[9] analyzing ejection fraction (EF) recovery, EF recovery rate was found to be 24.5%. The minimum sample size was determined to be 31 individuals in a power analysis (logistic regression model) with an OR of 0.099 obtained from this study, an α=0.1, and a power of 95%.[10] Based on this result, our cross-sectional, observational study included 33 consecutive female patients, 10 with PPCM and 23 with DCM, admitted to a tertiary cardiac center between March 2020 and April 2023. Exclusion criteria were as follows: baseline EF > 40%, male gender, ischemic cardiomyopathy, acute myocarditis, infiltrative myocardial disease, neuromuscular disease, moderate or severe primary valvular stenosis and regurgitation, congenital heart disease, general systemic disease, and stage III-V renal failure. Laboratory and clinical data, as well as demographic data, were gathered utilizing the hospital's medical database. Additionally, phone interviews were used to gather follow-up data. The study population was divided into two groups to compare peripartum and dilated cardiomyopathy patients. Informed consent was obtained from the patients. Artificial intelligence-enabled technologies including chatbots, image generators, and large language models weren't implemented in this study.

The main outcome was LVEF improvement at a follow-up of at least 12 months. DCM and PPCM were defined on the basis of the current European and American guidelines on heart failure (HF), cardiomyopathy and cardiac diseases in pregnant women as mentioned above.[1,3,5,6] According to the expert panel's recommendations, the improvement in ejection fraction was determined on the basis of documented LVEF, <40% at baseline, ≥10% absolute improvement in LVEF, and a second LVEF measurement >40%.[11] Blood samples were obtained from all patients upon admission to the hospital, in order to measure the complete blood count (using the Beckman Coulter LH 750 in Fullerton, California, USA) and various biochemical variables, such as N- terminal pro-brain natriuretic peptide (NT-proBNP), glucose, creatinine, lipid profile, albumin, and others, using the Cobas Integra 800 Roche Diagnostic Basel, Switzerland. The patient's baseline EF and supplementary echocardiographic parameters were measured at the time of the patient's initial diagnosis of cardiomyopathy. The 12-month follow-up EF was determined as the highest value in repeated measurements. The New York Heart Association (NYHA) classification, Kansas City Cardiomyopathy Questionnaire and six minute walk test were used to assess the patients' social, functional, and physical capacity.[2,3] According to the American Society of Echocardiography recommendations, licensed physicians at the study clinic performed echocardiographic evaluations.[12] A Philips ultrasound cardiovascular system, Affiniti CVx, United States of America (USA) was used with a X51 transducer. LVEF was measured by modified bi-plane Simpson method in the apical 4-chamber and 2-chamber view.

Statistical Analysis

The statistical analysis was conducted using the SPSS 22.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA). The normality of the distribution was evaluated using the kolmogorov–smirnov test. Quantitative variables with a normal distribution were previewed as mean±standard deviation, while variables with non-normal distribution were represented as median (interquartile range). Categorical variables were expressed as percentages. The Independent Samples t-test was utilized to match quantitative variable groups, while the chi-square test was handled for categorical variables. In addition to the variables that were statistically significant between the groups, we created a model by analyzing parameters that could be predictive in preliminary studies and our clinical experience. Binary logistic analysis was conducted to assess predictive factors linked to LVEF recovery. This involved using binary logistic regression analysis to figure out OR and 95% confidence interval (CI). Potential confounding factors were assessed using univariate regression analysis, and any confounders with a p-value less than 0.25 were included in the multivariate analysis. The Hosmer-Lemeshow goodness-of-fit test was applied to this multivariate logistic regression model. An analysis using the receiver operating characteristic (ROC) curve was performed to determine the area under the curve for predicting improvement in ejection fraction. The Youden index was utilized to identify the ideal threshold and sensitivity and specificity values for the significant parameters in the ROC analysis. A p-value less than 0.05 was accepted statistically significant. Moreover, post hoc power analysis was also performed to evaluate the statistical power of our study. The power of the study was calculated as 85% with an α=0.1 and a sample size of 33. This analysis supports that our study results were statistically significant and reliable.

RESULTS

The study population consisted of total 33 female patients with a mean age of 44.39 ±13.69 years. Patients were categorized as PPCM (n=10) and DCM (n=23) group. PPCM patients were younger (p<0.001). Other demographic characteristics and comorbidities were comparable between the groups (Table 1). Cardiac resynchronization therapy (CRT-D) and implantable cardioverter defibrillator (ICD) were implanted in 3 and 5 patients, respectively, all of whom were in the DCM group. Metoprolol was the most commonly prescribed beta-blocker in PPCM patients, whereas carvedilol was more common in DCM patients (p=0.014). Sixty-one per cent of DCM patients were receiving sodium-glucose cotransporter -2 inhibitor therapy (p=0.003). Prescription of other medical treatments

was similar in both groups. The total number of patients under the guideline-recommended quadruple therapy for HF with reduced LVEF was 15 (45%). Functional, social and physical capacity assessments of both groups were similar (Table 1).

Table 1. Demographic and clinical characteristics of patients with PPCM and DCM

Parameter	DCM (n: 23)	PPCM (n: 10)	Total (n: 33)	p value
Demographic features				
Age, years	50.08 (± 11.37)	31.30 (± 8.76)	44.39 (± 13.69)	<0.001
DM, n(%)	7 (30%)	1 (10%)	8 (24%)	0.203
HT, n(%)	11 (48%)	2 (20%)	13 (39%)	0.133
COPD, n(%)	3 (13%)	1 (10%)	4 (12%)	0.806
Smoking, n(%)	7 (30 %)	0 (0%)	7 (30%)	0.145
Alcohol, n(%)	1 (4%)	0 (0%)	1 (3%)	0.503
Hyperlipidemia, n(%)	1 (4%)	0 (0%)	1 (3%)	0.503
Hypothyroidism, n(%)	2 (9%)	1 (10%)	3 (9%)	0.905
Weight, kg	74.64 (± 15.79)	73.30 (± 14.15)	74.23 (± 15.10)	0.818
SBP, mmHg	124.95 (± 22.24)	119.50 (± 18.02)	123.30 (± 20.92)	0.500
DBP, mmHg	73.74 (± 14.77)	76.10 (± 7.59)	74.45 (± 12.94)	0.638
CRT-D, n(%)	3 (13%)	0 (0%)	3 (9%)	0.231
ICD, n(%)	5 (22%)	0 (0%)	5 (15%)	0.109
Medical treatment				
Beta-blocker				0.014
Metoprolol, n(%)	6 (26%)	8 (80%)	14 (42%)	
Carvedilol, n(%)	13 (57%)	2 (20%)	15 (45%)	
Bisoprolol, n(%)	4 (17%)	0 (0%)	4 (12%)	
ACE-I	0 (0%)	0 (0%)	0 (0%)	0.266
Ramipril, n(%)	10 (43%)	8 (80%)	18 (55%)	
Enalapril, n(%)	1 (4%)	0 (0%)	1 (3%)	
Perindopril, n(%)	4 (17%)	1 (10%)	5 (15%)	
ARB	0 (0%)	0 (0%)	0 (0%)	0.633
Valsartan, n(%)	1 (4%)	1 (10%)	2 (6%)	
Candesartan, n(%)	2 (9%)	0 (0%)	2 (6%)	
Losartan, n(%)	1 (4%)	0 (0%)	1 (3%)	
ARNI, n(%)	3 (13%)	0 (0%)	3 (9%)	0.231
MRA, n(%)	18 (78%)	7 (70%)	25 (85%)	0.673
Furosemide, n(%)	20 (86%)	8 (80%)	28(0%)	0.578
HCT, n(%)	3 (13%)	1 (10%)	4 (12%)	0.806
SGLT-2 inhibitor, n(%)	14 (61%)	1 (10%)	15 (45%)	0.003
Digoxin, n(%)	1 (4%)	0 (0%)	1 (3%)	0.503
Ivabradine, n(%)	6 (26%)	2 (20%)	8 (24%)	0.708
Warfarin, n(%)	4 (17%)	0 (0%)	4 (12%)	0.159
NOAC, n(%)	3 (13%)	0 (0%)	3 (9%)	0.231
ASA, n(%)	11 (48%)	2 (20%)	13 (39%)	0.133
P2Y12 inhibitor, n(%)	2 (9%)	0 (0%)	2 (6%)	0.336
Functional, social and physical capacity				
NYHA class, n(%)				0.799
I	5 (22%)	3 (30%)	8 (24%)	
II	14 (61%)	6 (60%)	20 (61%)	
III	4 (17%)	1 (10%)	5 (15%)	
6 MWT, m	326.26 ± 104.81	393.40 ± 50.67	346.60 ± 96.21	0.064
Kansas Score (Summary)	68.38 ± 18.18	74.17± 17.07	70.14 ± 17.79	0.399

ASA; acetylsalicylic acid, ACEI: angiotensin-converting enzyme inhibitör, ARB; angiotensin receptor blocker, ARNI; angiotensin receptor/neprilysin inhibitör, DBP; diastolic blood pressure, DCM; dilated cardiomyopathy, DM; diabetes mellitus, HCT; hydrochlorothiazide, HT; hypertension, COPD; chronic obstructive pulmonary disease, CRT; cardiac resynchronization therapy, MRA; mineralocorticoid receptor antagonist, NOAC; non–vitamin K antagonist oral anticoagulant, NYHA; New York Heart Association, ICD; implantable cardioverter defibrillator, MRA: Mineralocorticoid Receptor Antagonist, PPCM; peripartum cardiomyopathy, SBP; systolic blood pressure, SGLT-2: sodium-glucose cotransporter -2, 6 MWT; six minute walking test

Left bundle branch block (LBBB) was detected in 5 patients and atrial fibrillation in 4 patients. Baseline electrocardiographic findings were comparable between the groups. Left atrium anteroposterior (LA-AP) diameter, right atrium area (RAA), basal right ventricular end-diastolic diameter (RVEDD) were larger and estimated systolic pulmonary artery pressure was higher in DCM patients. Other echocardiographic findings were similar in both groups (Table 2).

Table 2. ECG, echocardiography and follow up features of the study population

Parameter	DCM (n: 23)	PPCM (n: 10)	Total (n: 33)	p value
ECG features				
AF, n(%)	4 (17%)	0 (0%)	4 (12%)	0.159
LBBB, n(%)	4 (17%)	1 (10%)	5 (15%)	0.586
RBBB, n(%)	2 (9%)	0 (0%)	2 (6%)	0.336
QRS Width, ms	111.78 ± 25.10	103.00 ± 22.67	109.12 ± 24.38	0.350
Heart Rate, bpm	70.60 ± 10.24	71.40 ± 11.64	70.84 ± 10.50	0.846
Echocardiographic measurements				
LVDD, mm	57.52 ± 4.64	53.80 ± 9.35	56.39 ± 6.51	0.134
LVSD, mm	46.04 ± 6.13	44.50 ± 6.67	45.57 ± 6.23	0.522
EF,%	28.52 ± 5.30	31.97 ± 4.63	29.57 ± 5.28	0.085
LA-AP diameter, mm	40.87 ± 6.34	36.30 ± 3.62	39.48 ± 5.99	0.042
LA-SI diameter, mm	51.00 ± 7.60	46.20 ± 5.65	49.54 ± 7.33	0.084
RAA, cm^2	14.73 ± 4.82	10.75 ± 2.84	13.52 ± 4.66	0.022
TAPSE, mm	20.40 ± 6.41	21.65 ± 3.00	20.78 ± 5.57	0.564
RV S',cm/s	10.76 ± 2.99	12.91 ± 2.60	11.41 ± 3.01	0.059
sPAP, mmHg	32.65 ± 12.90	22.900± 5.89	29.69 ± 12.03	0.030
RVEDD (basal), mm	36.78 ± 6.45	31.70 ± 5.98	35.24 ± 6.65	0.042
Mitral regurgitation				0.792
Grade 1, n(%)	14 (61%)	7 (70%)	21 (64%)	
Grade 2, n(%)	5 (22%)	1 (10%)	6 (18%)	
Grade 3, n(%)	3 (13%)	1 (10%)	4 (12%)	
Tricuspid regurgitation				0.146
Grade 1, n(%)	14 (61%)	10 (100%)	24 (73%)	
Grade 2, n(%)	4 (17%)	0 (0%)	4 (12%)	
Grade 3, n(%)	3 (13%)	0 (0%)	3 (9%)	
Grade 4, n(%)	2 (9%)	0 (0%)	2 (6%)	
Aortic regurgitation				0.696
Grade 1, n(%)	8 (35%)	2 (20%)	10 (30%)	
Grade 2, n(%)	2 (9%)	1 (10%)	3 (9%)	
Follow up				
Follow-up Time, months	23.09 ± 16.92	23.70 ± 11.43	23.27 ± 15.28	0.918
Re-hospitalization, n(%)	9 (39%)	2 (20%)	11 (33%)	0.284
Follow-up EF, %	33.92 ± 8.55	48.300 ± 7.50	38.28 ± 10.54	<0.001
Increase in EF value, Median+IQR	0 (0-10)	15.5 (13.7-20.6)	8 (0-16.5)	0.010

AF; atrial fibrillation, QTc; corrected QT interval, DCM; dilated cardiomyopathy, EF; ejection fraction, LA- AP; left atrium anterior-posterior, LA-SI; left atrium superior-inferior, LBBB; left bundle branch block, LVDD; left ventricle diastolic diameter, LVSD; left ventricle systolic diameter, PPCM; peripartum cardiomyopathy, RAA; right atrium area, RBBB; right bundle branch block, RVEDD; right ventricle end-diastolic diameter, RV S'; right ventricle S', sPAP; systolic pulmonary pressure, TAPSE; Tricuspid annular plane systolic excursion.

The PPCM group had higher mean follow-up LVEF (p<0.001) and LVEF value increase (p=0.010). A total of 10 patients (30%), 4 (17%) in the DCM group, and 6(60%) in the PPCM group revealed evidence of LVEF recovery. During a follow-up of 23.27± 15.28 months, no deaths occurred, 11(33%) patients were re-hospitalized. In the DCM group, mean potassium level was higher and glomerular filtration rate was lower. Serum iron, ferritin and thyroxine levels were lower and total iron binding capacity was higher in PPCM patients (Table 3). A total of 24 (72%) patients, including all PPCM patients, were diagnosed with iron deficiency.

Table 3. Laboratory parameters of the study population

Parameter	DCM (n: 23)	PPCM (n: 10)	Total (n: 33)	p value
Laboratory measurements				
Glucose, mg/dl	102.73 ± 16.61	98.30 ± 18.40	101.39 ± 17.00	0.499
Creatinine, mg/dl	0.84 ± 0.27	0.66 ± 0.16	0.79 ± 0.25	0.056
GFR, mL/min/1.73m²	85.08 ± 25.35	114.50 ± 19.50	94.00 ± 27.15	0.003
Sodium, mEq/L	139.08 ± 2.69	138.70 ± 1.33	138.97 ± 2.35	0.671
Potassium, mEq/L	4.51 ± 0.43	4.18 ± 0.27	4.41 ± 0.42	0.038
Calcium, mg/dl	9.08 ± 0.49	9.19± 0.64	9.11 ± 0.53	0.577
AST, U/L	20.52 ± 14.28	14.90 ± 4.70	18.81 ± 12.38	0.237
ALT, U/L	16.73 ± 8.02	14.70 ± 9.11	16.12 ± 8.27	0.524
LDH, U/L	207.43 ± 47.08	162.00 ± 20.02	193.66 ± 45.67	0.007
Total Cholesterol, mg/dl	176.26 ± 60.33	172.60 ± 23.20	175.15 ± 51.54	0.855
LDL –C, mg/dl	110.95 ± 54.80	103.80 ± 22.93	108.78 ± 47.15	0.695
HDL –C, mg/dl	43.78 ± 11.41	47.70 ± 8.16	44.97 ± 10.56	0.336
Triglycerides, mg/dl	110.17 ± 40.29	105.80 ± 52.02	108.84 ± 43.37	0.795
TSH, µIU/mL	3.15 ± 6.46	6.54 ± 13.83	4.17 ± 9.22	0.339
Thyroxine, µg/dl	1.35 ± 0.29	1.06 ± 0.31	1.26 ± 0.32	0.018
Serum Iron, µg/dl	71.47 ± 26.76	48.40 ± 29.29	64.48 ± 29.15	0.034
TIBC, µg/dl	328.34 ± 44.57	364.60 ± 43.54	339.33 ± 46.75	0.039
Ferritin, ng/ml	137.39 ± 118.65	35.30 ± 26.94	106.45 ± 110.24	0.012
Folate, ng/mL	10.73 ± 7.81	5.89 ± 4.01	9.26 ± 7.18	0.074
Vitamin B12, pg/ml	344.91 ± 107.17	268.80 ± 116.19	321.8 ± 113.82	0.077
Lowest NT-pro BNP, pmol/L	770.4 ± 1715.3	177.1 ± 302.6	590.7 ± 1457.8	0.290
Highest NT-pro BNP, pmol/L	4332.5 ± 5324.4	6465.4 ± 11300.6	4978.8 ± 7509.8	0.462
CRP, mg/L	5.13 ± 4.32	6.31 ± 10.36	5.48 ± 6.58	0.644
Total Protein, g/dl	56.55 ± 27.24	64.70 ± 10.06	59.02 ± 23.52	0.369
Albumin, g/dl	39.29 ± 11.52	43.60 ± 6.78	40.59 ± 10.40	0.281
Hemoglobin, g/dl	13.17 ± 1.81	12.45 ± 1.55	12.95 ± 1.74	0.284
Hematocrit (%)	39.23 ± 5.15	37.85 ± 4.72	38.81 ± 4.99	0.474
Platelets, 109/L	254.34 ± 76.36	318.20 ± 66.91	273.69 ± 78.46	0.029

ALT; alanine transaminase, AST; aspartate transaminase, CRP; C-reactive protein, DCM; dilated cardiomyopathy, HDL-C; high- density lipoprotein cholesterol LDH; lactate dehydrogenase, LDL-C; low-density lipoprotein cholesterol, PPCM; peripartum cardiomyopathy, TIBC; total iron binding capacity, TSH; thyroid-stimulating hormone

Table 4. Univariate and multivariate logistic regression analysis for predicting EF recovery

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age, years	0.936	(0.880-0.997)	0.039	1.049	(0.930-1.184)	0.435
Beta blocker treatment	0.730	(0.234-2.273)	0.578			
SGLT-2 inhibitor treatment	0.388	(0.086-1.748)	0.218	0.425	(0.024-7.618)	0.561
LVDD, mm	0.887	(0.769-1.023)	0.100	1.067	(0.881-1.293)	0.508
Basline EF, %	1.098	(0.944-1.277)	0.226			0.354
Follow-up EF, %	4.956	(0.139-176.22)	0.380			
LA-AP diameter, mm	0.700	(0.539-0.909)	0.007	0.656	(0.449-0.959)	0.029
RAA, cm2	0.685	(0.505-0.930)	0.015	1.144	(0.571-2.293)	0.704
RVEDD, mm	0.826	(0.699-0.975)	0.024	0.828	(0.609-1.126)	0.229
sPAP, mmHg	0.878	(0.763-1.010)	0.068	1.012	(0.843-1.215)	0.896
Highest BNP, pmol/L	1.000	(1.000-1.000)	0.883			
CMP type	7.125	(1.352-37.558)	0.021	6.126	(0.104-362.960)	0.384

Hosmer-Lemeshow Goodness-of-Fit Test: $\chi^2 = 9.238$, df = 8, p = 0.323. CMP; cardiomyopathy, EF; ejection fraction , LA-AP; left atrium anterior-posterior, LVDD; left ventricle diastolic diameter, RAA; right atrium area, RVEDD; right ventricle end-diastolic diameter, SGLT-2: sodium-glucose cotransporter -2, sPAP; systolic pulmonary pressure.

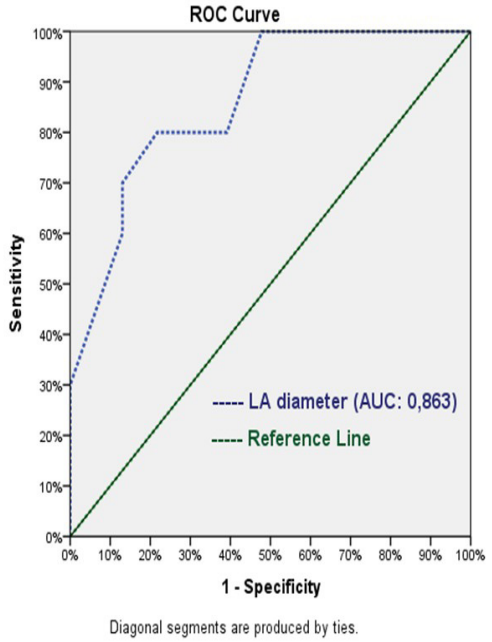

Figure. ROC analysis of LA diameter as a predictor of EF improvement. (AUC:0.863, 80% sensitivity, 78% specificity, with a cut- off 37.5 mm)

The statistical examination utilized multivariable logistic regression to establish a predictive model. Within this analytical framework, LA-AP diameter emerged as an independent predictor of EF recovery, exhibiting an OR:0.566, 95 CI%; 0.322-0.995, p=0.048 in the multivariate analysis (Table 4). The prognostic performance of LA-AP diameter for LVEF recovery was assessed through ROC curve analysis. The calculated area under the curve (AUC) for LA-AP diameter was 0.863 (95 CI%; 0.734-0.992, p-value=0.001), indicating statistical significance. Furthermore, the ROC curve analysis identified a cutoff value of <37.5 mm for LA-AP diameter as the optimal threshold for predicting LVEF recovery, with 80% sensitivity and 78% specificity (Figure). In contrast, when evaluating PPCM as a determinant of LVEF recovery, its significance was solely evident in univariate analysis and did not maintain significance in multivariate analysis. ROC curve analysis also revealed no statistically significant difference in terms of predicting LVEF recovery (AUC:0.713, 95 CI%;0.508-0.919, p=0.055).

DISCUSSION

The main findings of this study were as follows: i) LA-AP diameter was a reliable predictor of LVEF recovery, ii) In PPCM patients, LVEF value increase at follow-up and mean LVEF at follow-up were higher than in DCM patients, iii) Iron deficiency was more common in PPCM patients than in DCM patients, iv) Only about half of the patients received the quadruple medical therapy recommended by the guidelines, and a significant proportion of these individuals had DCM.

PPCM is an uncommon and idiopathic form of systolic HF, and its incidence varies widely around the world, ranging from a high of 1 in 96 births in parts of Nigeria to a low of 1 in 20,000 births in Japan.[6,13-15] Although the precise cause of PPCM is uncertain, theories include pregnancy-related alterations in hormones and hemodynamics, autoimmune diseases, ççk, classic symptoms and signs of HF.[5-6] However, in pregnancy, the diagnosis of PPCM is rather challenging and often misdiagnosed, as some of these symptoms are associated with physiological changes experienced during pregnancy

and other a etiological causes.[5-7] Approximately 50% to 80% of patients reveal improvement in systolic function, mostly in the first 6 months.[6,7,15,21] PPCM is also associated with serious conditions such as cardiogenic shock, arrhythmias and thromboembolism, and in some women cardiac function never fully recovers.[5-7,15,21] Moreover, even if complete recovery occurs in some patients, relapse may occur in subsequent pregnancies.[5-6] In this study, recovery of systolic function was observed in 6(60%) of 10 PPCM patients. There were no serious complications and no relapse during follow-up.

Although the precise underlying pathways are different, patients with DCM and PPCM experience comparable pathophysiological processes, including as impaired microvasculature and sarcomere integrity, increased oxidative stress, and underlying genetic abnormalities.[1,3,4,7] Cardiac remodeling is observed as a part of these processes in both patient groups.[1,3,5] In DCM patients, as well as in PPCM patients, improvement in LVEF has been reported, ranging from approximately 7.3% to 70%, although the definition of LVEF recovery has led to differences in reported rates.[9,11,22-25] In a study by Cho et al.,[27] LVEF recovery was defined as LVEF > 50% on follow-up echocardiography, with an improvement rate of 30.9%. However, when LVEF recovery was defined as an increase in LVEF > 10%, the improvement rate increased to 70%.[26] In another study focusing on changes in left ventricle (LV) diameter and fractional shortening, an improvement rate of 37% in systolic functions was reported. In this study, while the LVEF recovery was 17% in isolated DCM patients, it was 30% in the entire group. Furthermore, although LVEF improvement in PPCM patients was relatively higher than in DCM patients, LV systolic function improved markedly in both DCM and PPCM groups.

Several studies have identified certain demographic, clinical, and echocardiographic features contribute to LVEF recovery.[23-29] Young age, female gender, shorter duration of HF symptoms, absence of LBBB, basal LVEF, basal LVDD, LA diameter, NT-pro BNP, and troponin levels constituted a significant portion of major predictors of LVEF recovery.[3,11,22-29] Interestingly, while LBBB was a strong predictor of LVEF improvement after CRT implantation, it did not maintain this value in patients receiving only medical treatment.[25,30] In this study, age, LA-AP diameter, RAA, basal RVEDD and presence of PPCM were found to be good predictors for LVEF recovery in univariate analysis, with LA-AP diameter being identified as a major predictor in multivariate analysis. Additionally, the relatively young age of the study population has been considered as a reason for the lack of significant age as a predictor, unlike other studies.

Until recently, the role of the LA in the development of HF was not clearly understood. Traditionally, focus was on impaired LV function and remodeling in HF patients, and the role of the LA was overlooked. Classically, the LA in HF patients was thought to modulate LV filling and cardiac output.[31,32] Recent research has revealed that the LA also has endocrine and regulatory roles in HF patients, in addition to mechanical function.[31-34] In response to elevated LV filling pressures in HF patients, the LA undergoes remodeling, which involves myosin isoform expression, collagen matrix transformation, reduced intrinsic contractility, necrosis, fibrosis, and apoptosis.[31,32] This process manifests as more eccentric LA remodeling in patients with DCM and increased LA stiffness in patients with HF and preserved EF.[31-33] In the early stages of HF, the LA acts as an effective pump, maintaining LV filling and contractile function through the Frank-Starling mechanism.[31] However, in the later stages, structural and functional changes render this effect inadequate.[31-33] It has been reported that LA diameters are larger in patients with chronic HF and atrial AF.[28,33,34] Furthermore, LA dilation has been identified as a prognostic marker in HF patients, indicating mortality and the need for heart transplantation.[26-28,33,34] In our study, we found that patients with smaller LA-AP diameters showed greater improvements in LV function.

In patients with HF, a diagnosis of iron deficiency was made in the presence of low transferrin saturation (<20%) or low serum ferritin concentration (<100 µg/L) criteria.[2,3] Based on these diagnostic criteria, the prevalence of iron deficiency in HF patients varies between 55% and 80% depending on the HF presentation.[35] According to recent studies, intravenous iron supplementation is suggested by current guidelines to reduce HF symptoms, improve quality of life, and reduce hospitalization risk in patients with low LVEF or mildly reduced LVEF and iron deficiency.[2,3,35-38] In this study, iron deficiency was present in approximately 72% of patients and was observed in all PPCM patients. The greater likelihood of iron deficiency in PPCM patients was explained by the physiological changes of pregnancy and the postpartum period, together with HF. These facts highlight the importance of careful evaluation for the diagnosis and treatment of iron deficiency in PPCM patients.

Some limitations of this study existed. Firstly, this study was an observational evaluation of a single, tertiary referral center record with relatively small numbers. Furthermore, the likelihood of doing accurate and reliable multivariate analyses was hampered by the very low number of clinical events that were discovered during follow-up. Secondly, considering the retrospective nature of the study, selection bias was inevitable. Thirdly, given that the study required the inclusion of patients who had two transthoracic echocardiography at least 6 months apart and the initial echocardiography obtained might not have been the first evaluation for HF diagnosis, we could not exclude potential temporal bias. The inclusion of only patients with LVEF <40% was another limitation of the study. Fourthly, due to limitations in echocardiographic data, volumetric measurements were not included to evaluate improvement in LVEF. Nevertheless, since the study group consisted of DCM and PPCM patients with global LV dysfunction, the calculated LVEF and diameter indices represented a rough estimate of systolic function. Finally, the lack of genetic analysis and cardiac magnetic resonance imaging findings of the patients were other limitations.

CONCLUSION

DCM and PPCM patients were similar to each other with many clinical and morphological features. In both patient groups, there was a possibility of improvement in cardiac function. LA-AP diameter was a significant indicator of improved heart function in these individuals.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Faculty of Başakşehir Çam and Sakura City Hospital Research Ethics Committe (Date: 24.04.2024, Decision No: 272).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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