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Determination of the timing for thoracic imaging prior to pulmonary metastasectomy: an analysis on surgical planning and lesion detection

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ABSTRACT

Aims: The aim of this study is to reveal the relationship between the timing of thoracic computed tomography (CT) imaging conducted prior to surgery and the pre-surgical period in patients planned for pulmonary metastasectomy (PM), and to determine a safe pre-surgical timing for thoracic CT.

Methods: This study is a retrospective cohort study examining the data of patients who underwent pulmonary metastasectomy (PM). The research includes 96 patients who underwent PM between January 2017 and July 2022. Patients' demographic data, primary malignancy diagnoses, type of operation, sizes of masses requiring anatomical resection, the number of lesions detected in thoracic CT, the number of lesions identified during surgery, and the timing of thoracic tomography were recorded. The timing of thoracic CT imaging was compared with the number of lesions detected preoperatively and postoperatively.

Results: The study included 96 patients, comprising 49 females and 47 males. The most common primary pathological diagnosis was colon cancer at 36.5%, followed by breast cancer at 12.5%. 66.6% of the patients were operated on with thoracotomy, 29.1% with video-assisted thoracoscopic surgery (VATS), and 4.2% with rethoracotomy. The average number of lesions detected in preoperative thoracic tomography was 1.67±0.96, while the average number of lesions detected during surgery was 2.03±1.41. In patient groups where thoracic CT was performed 10 days or less before the operation, no significant difference was found between the number of lesions detected during surgery and the number of lesions in the CT. However, in patients where thoracic CT was performed more than 10 days before the operation, the number of lesions detected during surgery was significantly higher than the number of lesions detected in the CT.

Conclusion: In this research, it was concluded that for patients planned for PM, repeating thoracic CT after the 10th day following the initial detection of metastases in the pre-surgical phase may contribute to the detection of more lesions.

Keywords: Pulmonary metastasectomy, thoracic computed tomography, number of lesions, metastatic disease

INTRODUCTION

Cancer is characterized by the uncontrolled growth and spread of certain cells to other body parts. According to the World Health Organization (WHO) 2020 report, cancer is a leading cause of death globally, accounting for approximately 10 million deaths in 2020.[1] About 30% of patients with malignant diseases develop pulmonary metastasis, which is the spread of cancer cells from the primary tumor to distant organs, significantly contributing to cancer morbidity and mortality.[2-5] Pulmonary metastases commonly originate from colon, rectum, kidney, breast, prostate, and oropharyngeal carcinomas, among others.

The management of pulmonary metastases includes various strategies such as surgery, radiotherapy, and chemotherapy, with surgery recommended for patients in the oligometastatic stage who can tolerate the procedure.[6] Pulmonary metastasectomy (PM) has been established as a treatment that can prolong survival in patients with metastatic lung cancer from various primary solid tumors.[7] However, the decision to proceed with metastasectomy is influenced by several factors including the ability to completely resect metastatic disease and the number of pulmonary metastases.[8] Preoperative assessment with thoracic computed tomography (CT) is crucial for operation planning, aiming to minimize residual disease post-surgery.[9] The timing of thoracic CT imaging prior to surgery is pivotal, as earlier detection of metastases can lead to

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more comprehensive resection and potentially improved long-term outcomes.[10]

This study aims to explore the relationship between the timing of thoracic CT imaging conducted prior to surgery and the outcomes in patients planned for PM, seeking to establish a safe pre-surgical timing for thoracic imaging.

METHODS

Ethical approval for this study was obtained from Kartal Dr. Lütfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 27.04.2023, Decision No: 2023/514/248/14), adhering to the ethical guidelines of the Declaration of Helsinki for medical research involving human subjects.

This retrospective cohort study analyzed patients who underwent PM surgery in the thoracic surgery clinic of Kartal Dr. Lütfi Kırdar City Hospital from January 2017 to July 2022. Inclusion criteria were patients above the age of 18 who had undergone PM, while exclusion criteria included patients with incomplete medical records, and patients with contraindications to thoracic surgery due to other health conditions.

Data were meticulously gathered from hospital records and medical files, encompassing demographic details (age, gender), clinical parameters (CT scan dates, number of lesions detected), and surgical techniques employed. Specific attention was given to documenting the thoracic CT technical criteria, including scan resolution, contrast use, and slice thickness, ensuring a standardized approach across all patients.

The thoracic CT imaging, as depicted in Figure, is instrumental in our preoperative assessment, providing high-resolution insights into the number, location, and characteristics of pulmonary nodules. Thoracic CT scans were interpreted by a radiologist who experience in thoracic imaging, ensuring consistency and accuracy in identifying metastatic nodules. The radiological appearance of metastatic nodules was defined based on size, density, and contrast enhancement patterns, aiming to differentiate metastatic lesions from benign nodules.

Statistical Analysis

In the descriptive statistics of the data, mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used. The distribution of variables was measured with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for the analysis of quantitative independent data. The Wilcoxon test was used for the analysis of dependent quantitative data. Spearman's correlation analysis was used for correlation analysis. SPSS 28.0 (Version 29, Chicago, IL, USA) software was used for the analyses. Results were considered statistically significant for $p<0.05$.

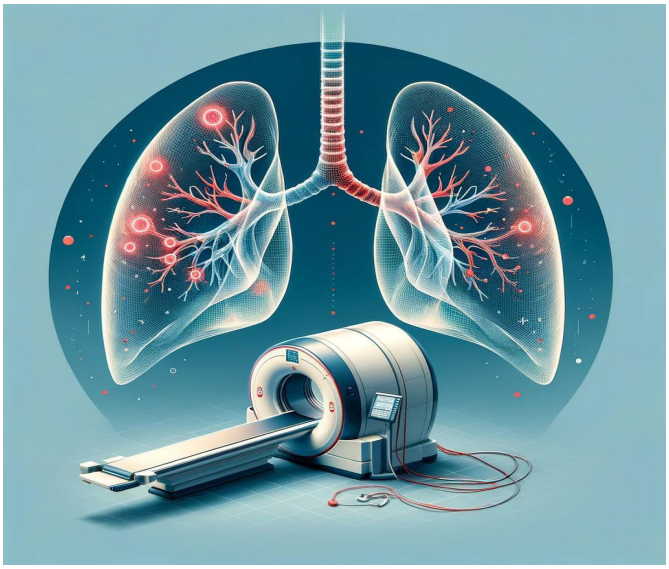

Figure. Illustration of thoracic CT imaging in pulmonary metastasectomy assessment

RESULTS

In this study, the primary malignancies of patients undergoing PM surgery were examined in detail. The total number of patients is n=96. The ages of the patients in our study range from 6.0 to 79.0 years, with a median age of 56.0. This reflects a heterogeneous age distribution prior to surgical intervention. The gender distribution of patients is balanced, with 51.0% females and 49.0% males. The dates of patients' thoracic CT scans are spread over a wide range (1.0-30.0 days), with a median CT date of 10.0 days. This indicates that patients were assessed at different times for medical imaging. There is a statistically significant increase in the number of lesions during the operative period ($p<0.05$) (Table 1).

Table 1. General characteristics of the patients

Variables	Min-Max	Median	Mean±sd/n-%
Age	6.0 - 79.0	56.0	55.3 ± 13.2
Gender Woman			49 51.0%
Time between thoracic CT and operation (days)	1.0 - 30.0	10.0	11.4 ± 8.5
CT lesion count	1.0 - 6.0	1.0	1.7 ± 1.0
Operative lesion count	1.0 - 8.0	1.0	2.0 ± 1.4
Increase in lesion count	0.0 - 3.0	0.0	0.4 ± 0.7
Mass size (mm)	2.0 - 8.0	3.0	3.9 ± 1.4

CT: Computed tomography

According to the findings, the most common histopathological type of primary tumor in 36.5% (n=35) of these patients is colon cancer. Breast cancer is

the second most frequent, accounting for 12.5% (n=12) of cases. Other common malignancy types include 7.3% (n=7) renal cell carcinoma (RCC), 8.3% (n=8) rectum cancer, and 5.2% (n=5) osteosarcoma. Among the rare types are mandibular malignant melanoma, mesenchymal tumor, stomach cancer, pancreatic cancer, uterine sarcoma, and ureteral carcinoma, each constituting 1.0% (n=1) of cases. These results show a heterogeneous distribution of primary malignancies in patients undergoing pulmonary metastasectomy. Data on surgical techniques used for metastasectomy interventions in a total of 82 patients are as follows: Video-assisted thoracoscopic surgery (VATS) was the method of choice in 35.4% (n=34) of all interventions. Thoracotomy emerged as a surgical technique used in 60.4% (n=58) of patients. Rethoracotomy was used in 4.2% (n=4) of the total interventions.

The procedures performed were 75.0% (n=72) wedge resections, 5.2% (n=5) lower left lobectomies, 3.1% (n=3) lower lobe superior segmentectomies, 2.1% (n=2 each) upper lobe anterior segmentectomies and upper lobe posterior segmentectomies, and 1.0% (n=1 each) for lower lobe basal segmentectomy, lower lobe posterior segmentectomy, apical segmentectomy, apicoposterior segmentectomy, right lower bilobectomy, right middle lobectomy, right upper lobectomy, and left upper lobectomy. These results indicate that the wedge resection technique is commonly preferred for the removal of metastatic lesions, with other specific lobectomy types being used at lower rates (Table 2).

In the study, the Wilcoxon test was used to evaluate the differences between the number of lesions in thoracic CT and the number of lesions during surgery. It was found that the difference between the CT lesion count and the operative lesion count was statistically significant ($p<0.05$). The Wilcoxon test indicates that these changes signify an increase in the number of lesions from the CT period to the operative period. The number of lesions during the operative period showed a significant increase ($p<0.05$) compared to the CT period. No significant difference ($p>0.05$) was observed in the number of lesions during the CT period between the groups with <10 days post-CT and >10 days post-CT. No significant difference ($p>0.05$) was observed in the number of lesions on the day of surgery between the groups with <10 days post-CT and >10 days post-CT. In the group with <10 days post-CT, the number of lesions during the operative period showed a significant increase ($p<0.05$) compared to the CT period. In the group with >10 days post-CT, the number of lesions during the operative period showed a significant increase ($p<0.05$) compared to the CT period. The increase in the number of lesions in the group with >10 days post-CT was significantly ($p<0.05$) higher than in the group with <10 days post-CT (Table 3).

Table 2. Types of surgical operations performed on patients

Variables	Surgical methods	n	%
Implemented intervention	VATS	34	35.4%
	Thoracotomy	58	60.4%
	Rethoracotomy	4	4.2%
Types of lobectomies	Lower lobe basal segmentegtomy	2	2.1%
	Lower lobe posterior segmentegtomy	1	1.0%
	Lower lobe superior segmentegtomy	3	3.1%
	Apical segmentegtomy	2	2.1%
	Apiko posterior segmentegtomy	1	1.0%
	Right lower bilobectomy	1	1.0%
	Right middle lobectomy	1	1.0%
	Right upper lobectomy	2	2.1%
	Left lower bilobectomy	1	1.0%
	Left lower lobectomy	5	5.2%
	Left upper lobectomy	1	1.0%
	Upper lobe anterior segmentegtomy	2	2.1%
	Upper lobe posterior segmentegtomy	2	2.1%
	Wedge resection	72	75.0%

VATS: Video-assisted thoracoscopic surgery

Table 3. Timing of thoracic tomography in pulmonary metastases

Number of lesions	After thorax CT <10 day			After thorax CT >10 day			p	
	Mean±sd		Median	Mean±sd		Median		
Detected on preoperative thoracic CT	1.70	1.13	1.00	1.62	0.63	2.00	0.422	m
Detected during surgery	1.95	1.56	1.00	2.15	1.16	2.00	0.078	m
Increase in the number of lesions	0.25	0.66	0.00	0.54	0.76	0.00	0.006	m
Intra-group variation		0.010	W		0.000	w		

m: Mann whitney u test, w: Wilcoxon test, CT: Computed tomography

DISCUSSION

According to the findings of this study, in patient groups where thoracic CT was performed 10 days or less before the surgery, no significant difference was observed between the number of lesions detected during surgery and the number of lesions in the thoracic CT. However, in patients where thoracic CT was performed more than 10 days before the surgery, the number of lesions detected during surgery was significantly higher than the number of lesions detected in the thoracic CT. This suggests that the time elapsed before pulmonary metastasectomy may influence the number of lesions detected during surgery, and thoracic CT taken a longer time before could contribute to detecting more lesions. This important observation should be considered in clinical decision-making and operation planning.

Looking at recent developments in many types of cancer, aggressive pulmonary resection, R0 resection, or curative resection in lung metastases arising in these patients has become a standard strategy for addressing pulmonary metastasis when it can be achieved in addition to systemic chemotherapy and surgical treatment.[11,12]

When examining recommendations, for patients undergoing PM, a longer disease-free interval between the treatment of the primary tumor and the emergence of metastatic disease is desired, and there is no absolute time frame, including the synchronous presentation of metastatic disease, that is considered too short to contemplate PM.[13,14] However, especially for the detection of synchronous metastases, it is recommended to repeat lung CT six to eight weeks after the recognition of pulmonary metastases, to ensure that no additional target lesions (or too many target lesions) have emerged.[15] Yet, in our literature review, we did not find any specific recommendations on how long before surgery thoracic CT imaging should be performed in patients with planned primary operations. Nevertheless, the decision-making process for PM is dynamic and requires close follow-up.[16]

In our research, when examining the demographic data of patients undergoing PM, we found it to be consistent with the literature.[17] Similar to our study, many authors have also found no statistically significant difference in long-term survival between male and female patients after pulmonary metastasectomy.[18,19] Research has shown that accurate preoperative assessment and operation planning with sectional imaging can reliably detect nodules as small as 2 to 3 mm.[20] In this research, similarly, nodules as small as 2 mm were detected, with an average size of 3.9 mm. Among the poor prognostic factors identified through multivariate analysis using a broad cohort are the number and size of tumors.[21] Studies particularly investigating the relationship between tumor sizes and recurrence stand out, with research showing that recurrences are more frequent in metastases larger than 2 mm.[21,22] Similarly, the inverse relationship between the number of metastases and survival is likely due to multiple factors. As the number of pulmonary metastases increases, the likelihood of incomplete resection, the burden of widespread occult disease in the lungs, and the probability of recurrence in the lung are higher.[23,24] Consistent with the literature, in this research, the number of nodules is between 1-2.[21] Outcomes are better with fewer metastases. However, among thoracic surgeons, there is no consensus on what burden of disease constitutes an insurmountable barrier for patients with multiple metastases. The important factor is not the absolute number of metastases, but the feasibility of resecting all disease areas.

Colon malignancies are the most common primary tumors in patients undergoing PM, followed by RCC, breast cancer, ENT (ear, nose, and throat) cancers, and uterine malignancies.[25] Consistent with these data, our study also found that the most frequent primary malignancy was colon malignancy.

In PM, several standard lung resection techniques characterized by the amount of lung tissue removed (e.g., wedge resection, segmentectomy, lobectomy) can be used to resect pulmonary metastases, either through an open thoracotomy incision (anterior thoracotomy, posterior thoracotomy) or using minimally invasive techniques. The choice between VATS or open thoracotomy approach depends on the characteristics of the metastases, including their locations, numbers, and sizes, as well as lesion stability assessed in thoracic CT scans.[26] Open thoracotomy has traditionally been the standard for the resection of pulmonary metastases to allow for bimanual palpation of the lungs. However, VATS is gaining popularity with advanced imaging techniques that can more accurately detect smaller lesions.[27] In our study as well, thoracotomy has an advantage over VATS. Similarly, in our research, nearly all patients were aimed for complete resection using both methods. This is thought to be due to the ongoing debate over the safety of VATS in PMs.[28] Despite advancements in imaging technology, occult lesions continue to be a source of concern.[29] The method used for PM in the patients included in the study is Wedge Resection. Wedge resection for pulmonary metastasis is now considered an appropriate procedure due to its reduced invasiveness and ability to preserve lung function.[7] Therefore, it is the most commonly used procedure for resecting pulmonary metastases from various types of malignancies.[30]

There is no direct evidence addressing how soon before metastasectomy a chest CT scan should be performed.[9] Limited data suggest that patients with tumor doubling

times of <20 to 40 days have poor outcomes after metastasectomy and are less likely to be considered realistic candidates for metastasectomy.[31] Similarly, a study found better survival in patients with metastatic colorectal carcinoma resected within a month compared to those who had resection more than a month after the initial detection of isolated pulmonary metastases.[32] Therefore, although the data are limited, some studies suggest that delaying resection after the discovery of a metastasis offers no significant benefit and recommend proceeding with metastasectomy as soon as patient assessment is complete, based on well-designed comparative series that directly address the question.[9] Hence, in this study, the boundary for thoracic imaging was set at 10 days, comparing two groups, and it was considered that thoracic CT imaging within 10 days prior to surgery could affect the number of lesions detected during surgery, and thoracic CT taken a longer time before could contribute to detecting more lesions. Similarly, it was thought that performing a new thoracic imaging 10 days after the first detection of a metastasis could be appropriate, akin to the recommendation of conducting a CT scan within 4 weeks post-metastasectomy unless the tumor doubling time is exceptionally short or long.

Limitations

This study has some limitations. The retrospective analysis of data carries the risk of missing or erroneous information. The patient sample used in the study is limited, which could restrict the generalizability of the findings. The research is based on data obtained from a single center, which may limit the level of representation of the general population. Future studies involving larger participant groups, prospective designs, and data collection from different clinical settings could help to mitigate these limitations.

CONCLUSION

In this research, it was concluded that for patients planned for PM, repeating thoracic CT after the 10th day following the initial detection of metastases in the pre-surgical phase may contribute to the detection of more lesions.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Kartal Dr. Lütfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 27.04.2023, Decision No: 2023/514/248/14).

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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Impact of obstructive sleep apnea risk on prognosis and treatment responses of lung cancer

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ABSTRACT

Aims: Obstructive sleep apnea (OSA) may affect oncogenic processes in a specific way for each tumor type. This study was conducted to reveal the relationship between OSA risk and prognosis and treatment responses in patients with lung cancer.

Methods: This prospective study included stage III and IV lung cancer patients aged between 18 and 75 years. Patients with poor performance status, cranial metastasis, congestive heart failure, surgery history, and positive airway pressure device use were excluded. STOP-BANG questionnaire was used to assess the OSA risk. The primary end-point was the differences in the survival and treatment responses of patients at intermediate/high risk of OSA compared with those at low OSA risk. Data from the patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) were analyzed separately.

Results: Ninety-eight patients (34 SCLC and 64 NSCLC), mostly male (85.7%), with a mean age of 59.3±8 were included in the analysis. Overall survival was similar in the groups. However, in the SCLC group, those at low OSA risk had a shorter progression-free survival (PFS) than those at intermediate/high risk (105±31.8 days, vs 272±16.2 days, p=0.001). Cox regression analysis showed that low OSA risk was an independent risk factor for PFS in only the SCLC group (HR:4.9 CI:1.6-14.7, p=0.005).

Conclusion: Our results showed that low OSA risk was an independent poor prognostic factor for PFS in SCLC regardless of the tumor stage.

Keywords: Lung cancer, obstructive sleep apnea, overall survival, progression-free survival, STOP-BANG questionnaire

INTRODUCTION

There has been an increased research interest in the relationship between obstructive sleep apnea (OSA) and cancer recently.[1] However, it is difficult to clarify this relationship because of the established risk factors such as age and obesity.[2] Intermittent hypoxia (IH), the characteristic feature of OSA, has an important role in carcinogenesis.[3] After the carcinogenic effects of IH were demonstrated in cell culture and animal studies.[1,3] Human studies of the OSA-cancer link gained momentum. In addition to its local effect on tumor cells, IH causes an increase in the release of inflammatory and angiogenic molecules and accelerates oncogenic processes systemically.[3,4] In addition, OSA-associated IH is believed to be responsible for resistance to cancer therapy.[5] Sleep disruptions, immune deregulation, and circadian rhythm changes caused by OSA were also shown as important factors in tumorigenesis.[6,7]

However, some epidemiological studies revealed conflicting results with the aforementioned animal studies.[8,9] Additionally, it has been revealed that the oncogenic effect of IH decreases with aging and obesity.[10,11] These oncogenic properties of OSA may also vary according to the tumor cell type. Some evidence suggests that the incidence of breast, rectum, prostate, and colon cancer decreases with OSA.[12] In a large cohort including various types of cancer, the incident and prevalent cancers were not associated with OSA severity in terms of apnea-hypopnea index (AHI) and sleep time spent with oxygen saturation <90%. The cancer incidence was associated with nocturnal oxygen desaturation in only smoking-related cancers.[8]

The studies about the lung cancer-OSA relationship mostly include non-small cell lung cancer (NSCLC) patients. In a study conducted on a hospital database containing mostly adenocarcinoma cases, it was seen that the overall survival (OS) was shorter in moderate-to-severe OSA patients than in the mild OSA group.[13] Current evidence indicates that OSA can have differential effects on different histological

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cancer types. The impact of OSA risk on each type of lung cancer needs to be evaluated. This study was conducted to show the impact of OSA risk on prognosis and treatment responses in patients with NSCLC and small cell lung cancer (SCLC) separately.

METHODS

This prospective observational study comprised lung cancer patients at locally advanced or metastatic stages aged between 18-75 years. Data of the patients who were admitted to our pulmonology clinics between 1.6.2019 and 31.12.2020 before or during the first-line standard chemotherapy and agreed to participate in the study were collected. The study was approved by the Ankara Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.05.2019, Decision No: 1905). The study protocol was registered at ClinicalTrials.gov with protocol number 1905 (ClinicalTrials.gov Identifier: NCT04003961). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The exclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status ≥2, cranial metastasis, congestive heart failure (ejection fraction≤%50), surgery history, treatment refusal, incomplete treatment (≤2 cycles), and the use of positive airway pressure device. The clinical data from 10 patients who were followed up by another hospital and 4 patients who did not complete the questionnaires were missing. Four patients enrolled in the other studies for immunotherapy drugs were also excluded (Figure 1). As general health insurance in Turkiye does not reimburse immunotherapy for the first-line treatment of lung cancer, all the patients enrolled in the study were on platinum-doublet systemic chemotherapy or concurrent/sequential chemoradiotherapy. The patients were assessed for the risk of obstructive sleep apnea (OSA) with the STOP-BANG questionnaire and excessive daytime sleepiness (EDS) with the Epworth sleepiness scale (ESS).

The 8th tumor node metastasis (TNM) staging system of the International Association for the Study of Lung Cancer (IASLC) was used for staging NSCLC.[14] For the staging of SCLC, a two-stage (limited/extensive) staging scheme belonging to the "Veterans' Administration Lung Study Group (VALSG)", which has been used in clinical practice since the 1950s, was used.[15]

Demographic and clinical data of the patients grouped according to OSA risk, overall/progression-free survival, and treatment side effects were evaluated comparatively. The variables included in the data set can be listed as: 1-Demographic information of the patients (age, gender, smoking history), anthropometric measurements (body mass index, neck circumference), 2-clinical information

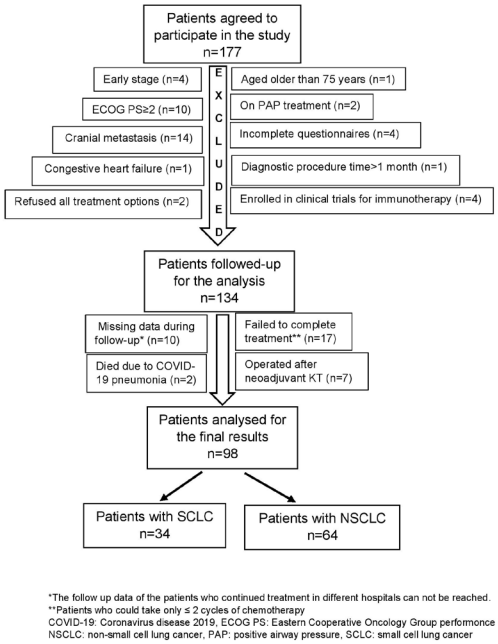

Figure 1. Flowchart of the study

(radiological TNM stages, diagnosis method, date of diagnosis, Patients' general medical condition, treatment outcomes, albumin, lactate dehydrogenase level, complete blood count results, and the results of Epworth sleepiness scale and STOP-BANG questionnaires) The radiotherapy related side effects (esophagitis and/or radiation pneumonia) were also recorded. The systemic inflammatory index (SII) value was calculated from the absolute neutrophil, lymphocyte, and platelet counts (NxP/L) in the complete blood count at the time of diagnosis.[16] The risk for OSA was assessed according to the results of the STOP-BANG survey as stated below.[17]

Evaluation of the STOP-BANG Survey Results

OSA-low risk: 0-2 positive responses to questions

OSA-intermediate risk: 3-4 positive responses to questions

OSA-high risk: 5-8 positive responses to questions or yes to at least 2 of 4 STOP questions and yes to at least 2 of 4 STOP questions and male patients, BMI≥35 kg/m^2 or neck circumference ≥43 cm for men, ≥41 cm for women.

In the follow-ups performed at 3-month periods after the treatment (please rephrase), the radiological response evaluation criteria in solid tumors (RECIST guideline version 1.1 criteria) was used to determine progression.[18] The patients with progression according to RECIST 1.1 in the first follow-up were considered as the early progression group. This study was conducted in accordance with the Declaration of Helsinki. The patients who approved informed consent for the usage of their data were included.

The primary endpoint of this study is to reveal the impact of OSA risk on the prognosis and treatment responses in

patients with lung cancer. To address prognosis, overall survival (OS) and Progression-free survival (PFS) were used. OS was calculated as the time (in days) from the date of pathological diagnosis to the date of death or the end of the study (31.12.2021). PFS was calculated as the time (in days) between the date of pathological diagnosis and the date of progression, date of death, or date of study termination.

As a secondary endpoint, the impact of OSA risk on radiotherapy-related side effects was investigated.

Statistical Analysis

SPSS 21 for Windows was used for data analysis. Descriptive statistics were stated as mean±standard deviation for normally distributed variables, median [IQR] for non-normally distributed variables, and the number of cases and (%) for nominal variables.

The t-test and Mann-Whitney U test were used to test differences in normally distributed and non-normally distributed variables, respectively. The ratios were compared using the 'Pearson Chi-Square or Fisher Exact test'.

The Kaplan-Meier survival estimates were calculated. The effect of the variables on survival was investigated using the log-rank test. The univariate analysis revealed OSA risk, smoking history, stage, and neck circumference as the possible risk factors for survival. OSA risk was highly correlated with neck circumference. The parameters including OSA risk, smoking history, and stage were entered into the Cox regression analysis with the Backward selection method to determine independent predictors of survival. Schoenfeld and Martingale analysis was used to assess the proportional hazards assumption and model fit. The results were considered statistically significant when the p-value is <0.05.

RESULTS

Out of 177 patients who agreed to participate in the study, 98 patients were included in the final analyses. The participants were mostly male, with a mean age of 59.3±8. The SCLC group included 34 and the NSCLC group included 64 patients. The flowchart for exclusion criteria is illustrated in Figure 1. The patients were divided into 2 groups according to the STOP-BANG score: low OSA risk and intermediate-high OSA risk. An endobronchial fine needle biopsy was performed in 24 patients (24.5%). Fiberoptic bronchoscopy was performed in 46 patients (46.9%). Computed tomography-guided transthoracic fine needle aspiration biopsy was performed in 23 patients (23.5%), cryobiopsy in 3 patients (3.1%), cell block cytology of pleural effusion in one patient (1%), and pleural biopsy in one patient (1%).

The statistical analysis was performed in SCLC and NSCLC groups separately. Five patients (14.7%) with SCLC and 23 (35.9%) patients in the NSCLC group were at low risk for OSA according to the STOP-BANG score. In both SCLC and NSCLC patients, the low-risk and intermediate/high-risk groups were similar for age, gender, comorbidities, active smoking percentage, Epworth sleepiness score, stage, and treatment. Laboratory values including systemic inflammatory index, white blood cell count, and lactate dehydrogenase at the time of diagnosis were also similar in the two groups. The components of the STOP-BANG score including neck circumference and BMI values were higher in the intermediate/high-risk group. Unlike the SCLC group, the albumin value was lower in the low OSA risk group among NSCLC patients (Table 1, 2).

All patients underwent platinum-based doublet chemotherapy regimens. While 67.3% (n=23) of the patients with SCLC received etoposide-cisplatin chemotherapy, the remaining 11 (32.7%) were treated with the etoposide-carboplatin regimen. The majority of the patients in the NSCLC group (n=48, 75%) were treated with a paclitaxel carboplatin regimen. The other treatment regimens given to the NSCLC group were as follows: Paclitaxel-cisplatin for 6 patients (9.4%), pemetrexed-cisplatin for 6 patients (9.4%), gemcitabine-cisplatin for 3 patients (4.7%), and docetaxel carboplatin for 1 patient (1.6%).

The SCLC patients with limited stage (n=17) and extensive stage who responded to the first-line chemotherapy (n=5) received sequential/concurrent radiotherapy. Among this study population with SCLC, radiotherapy-induced esophagitis and/or radiation pneumonia developed in 5 patients with intermediate/high OSA risk. In the low-risk group, no patient reported RT-related side effects. However, this difference was not statistically significant (0% vs 26.3%, p=1.000). The rate of early progression (progression in the first 3 months) was statistically higher in patients with low OSA risk in the SCLC group (80% vs 17.2%, p=0.012).

In the NSCLC group, 9 out of 30 patients who received sequential/concurrent chemoradiotherapy were at low risk for OSA. In this group, only 1 patient (11.1%) developed esophagitis due to radiotherapy. Radiotherapy-induced esophagitis and/or radiation pneumonia were recorded in 5 patients (23.8%) among 21 NSCLC patients with moderate-high risk of OSA (p=0.64). The low and intermediate/high OSA risk groups were similar for early progression rates in NSCLC patients (Table 2).

Table 1. Demographic and clinical characteristics of the patients with SCLC

	OSA RISK		
	Low n=5	Medium-High n=29	p-value
Age, years, mean±SD	54.6±13.9	60.1±7.4	0.435
Gender, male, % (n)	60 (3)	89.7 (26)	0.146
Smoking, active, % (n)	(n=5) 40 (2)	(n=23) 65.2 (15)	0.353
BMI, kg/m², median (IQR)	23.4 (3)	26.1 (4.4)	0.010
Neck circumference (cm)	38 (3)	41 (3)	0.001
Comorbidity, % (n) Asthma/COPD	0	20.7 (6)	0.556
DM	20 (1)	6.9 (2)	0.400
HT	20 (1)	31.0 (9)	1.000
CVD/arrhythmia	0	10.3 (3)	1.000
Stage, % (n)			
Limited	40 (2)	51.7 (15)	1.000
Extensive	60 (3)	48.3 (14)	
Treatment, % (n)			
CT	40 (2)	34.5 (10)	1.000
CRT	60 (3)	65.5 (19)	1.000
Early progression, % (n)	80 (4)	17.2 (5)	0.012
RT-related side effects, % (n)	(n=3) 0	(n=19) 26.3 (5)	1.000
WBC (x10count/L), median (IQR)	6990 (3495)	9430 (4165)	0.296
SII (cells/L), median (IQR)	882 (864)	848.5 (1434)	0.942
Hg (g/dl), mean±SD	13.9±1.8	14.5±1.8	0.452
Albumin (g/dl), mean±SD	(n=5) 38.4±3.3	(n=22) 39.8±4.9	0.548
LDH (U/L), median (IQR)	(n=5) 298 (169)	(n=22) 254 (138)	0.492
ESS Score, median (IQR)	6 (4)	2 (4)	0.065

SCLC: Small cell lung cancer, OSA: Obstructive sleep apnea, BMI: Body-mass index, IQR: interquartile range COPD: Chronic obstructive pulmonary disease, DM: diabetes mellitus, HT: Hypertension, CVD: cardiovascular disease, CT: chemotherapy, CRT: chemoradio-therapy, RT:radiotherapy, WBC: White blood cell count, SII: Systemic inflammatory index, Hg:Hemoglobin, LDH: Lactate dehydrogenase, ESS: Epworth sleepiness scale

Table 2. Demographic and clinical characteristics of the patients with NSCLC

	OSA RISK		
	Low n=23	Medium-High n=41	p-value
Age, mean±SD	56.8±8.9	60.8±7.1	0.053
Gender, male, % (n)	87 (20)	85.4 (35)	1.000
Smoking, active, % (n)	(n=19) 47.4 (9)	(n=29) 44.8 (13)	1.000
BMI, median (IQR)	(n=23) 23.5 (4)	(n=40) 27.9 (6)	0.001
Neck circumference (cm), median (IQR)	38 (3)	40 (5)	0.001
Comorbidity, % (n)			
Asthma/COPD	13 (3)	9 (22)	0.510
DM	13 (3)	24.4 (10)	0.342
HT	13 (3)	34.1 (14)	0.059
CVD/ arrhythmia	8.7 (2)	12.2 (5)	1.000
Stage, % (n)			
Locally advanced	43.5 (10)	56.1 (23)	0.332
Metastatic	56.5 (13)	43.9 (18)	
Treatment, % (n)			
CT	60.9 (14)	48.8 (20)	0.409
CRT	39.1 (9)	51.2 (21)	
RT-related side effects, % (n)	(n=9) 11.1 (1)	(n=21) 23.8 (5)	0.640
Early progression, % (n)	43.5 (10)	35 (14)	0.505
WBC (x10 count/L), median (IQR)	9590 (3080)	9340 (2275)	0.386
SII, median (IQR)	1028.8 (1186)	996.7 (928)	0.471
Hg, g/dl, mean±SD	13.6±1.6	14.1±1.5	0.182
Albumin, g/dl, mean±SD	(n=19) 34.6±3.3	(n=32) 37.3±4	0.018
LDH, U/L, median (IQR)	(n=18) 247 (119)	(n=32) 208 (86)	0.656
ESS Score, median (IQR)	1 (3)	2 (5)	0.052

NSCLC: non-small cell lung cancer, OSA: Obstructive sleep apnea, BMI: Body-mass index, IQR: interquartile range COPD: Chronic obstructive pulmonary disease, DM: diabetes mellitus, HT: Hypertension, CVD: cardiovascular disease, CT: chemotherapy, CRT: chemoradio-therapy, RT:radiotherapy WBC: White blood cell count, SII: Systemic inflammatory index, Hg:Hemoglobin, LDH: Lactate dehydrogenase, ESS: Epworth sleepiness scale

In the Cox regression analysis including disease stage and OSA risk, PFS was shorter in patients with SCLC having low OSA risk (Table 3). In log-rank analysis, the median PFS for the low-risk group with SCLC patients was 105±31.8 days, while it was 272±16.2 days in the medium/high-risk group (p=0.001, Figure 2). On the other hand, the groups were similar in terms of OS. Cox regression analysis in the NSCLC group showed that the advanced stage was a poor prognostic factor for both PFS and OS, regardless of OSA risk and albumin levels (Table 3).

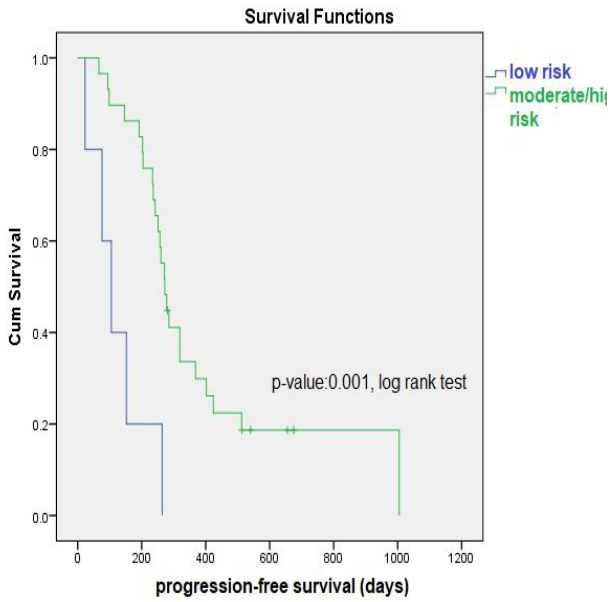

Figure 2. Graphs of Kaplan Meier analysis for progression-free survival of the patients with SCLC

Table 3. Cox regression analysis for survival (days)

OS for SCLC	**RR**	**95% CI**	**p-value**
Stage (extensive vs limited)	1.89	0.82-4.32	0.133
OSA risk (medium/high vs low)	0.59	0.19-1.82	0.361
PFS for SCLC	**RR**	**95% CI**	**p-value**
Stage (extensive vs limited)	1.63	0.42-6.44	0.480
OSA risk (medium/high vs low)	0.09	0.02-0.36	0.001
OS for NSCLC	**RR**	**95% CI**	**p-value**
Stage (advanced vs locally advanced)	2.95	(1.36-6.39)	0.006
OSA risk (medium/high vs low)	0.87	(0.41-1.83)	0.715
Albumin	0.95	(0.85-1.05)	0.280
PFS for NSCLC	**RR**	**95% CI**	**p-value**
Stage (advanced vs locally advanced)	2.49	(1.3-4.76)	0.006
OSA risk (medium/high vs low)	0.93	(0.49-1.78)	0.835
Albumin	0.99	(0.91-1.08)	0.879

OS: overall survival, RR: relative risk, SCLC: Small cell lung cancer, OSA: Obstructive sleep apnea, PFS: Progression-free survival, NSCLC: Non-small cell lung cancer,

DISCUSSION

This study reveals that PFS was shorter and the rate of early progression was higher among SCLC patients with low-OSA risk compared with intermediate/high OSA risk. On the other hand, we showed that OSA risk did not affect the prognosis of NSCLC patients. These results suggest that the effects of OSA may differ depending on histological type. Although not statistically significant, the result showing that RT-related adverse events were observed in only one patient in the low OSA risk group may prompt further research on this topic.

Current research on the OSA-cancer relationship includes animal experiments, cell culture studies, and human studies from non-specific databases. However, the results obtained so far are scientifically contradictory. In animal studies, mice are exposed to a model of IH in which the nadir of oxyhemoglobin saturation was reduced to the range of 65-72% by applying a 6% fraction of inspired oxygen (FiO_2) for 90 seconds, 20 times per hour, for 12 hours/day for 5 weeks.[19] This model represents a more severe and long-lasting form of IH than in many OSA patients. Besides, contrary to 5 week-period of IH in animal models, it is not possible to determine the exact onset of OSA in humans. Nonetheless, animal experiments showed that tumor growth is accelerated by intermittent hypoxia in melanoma, lung, renal, breast cancers, and myeloma.[3,20-23] Most of the animal experiments have defined tumor growth as the primary endpoint. However, only a few studies evaluated metastasis and invasion. Although rarely mentioned in these studies, another hallmark of OSA, sleep fragmentation, has been reported to promote cancer progression.[3,6]

Human studies have been made using databases or records of the general population that are not specific to OSA. In these analyses, the severity of IH, confounding factors, and the effects of OSA treatment were not fully assessed. Study populations typically included all cancer types, but specific analyses for single cancer types were lacking. The incidence of cancer in some studies was also too low to yield solid evidence.[24] Christensen et al.[25] found that those with OSA-related symptoms had a higher incidence of smoking-related cancers. In studies reporting polysomnographic or polygraphic data, the percentage of night-time with SpO^2<90% (Tsat90%) was associated with high incidence in all cancer types and cancer-related mortality.[10] This effect was even more pronounced when positive airway pressure (PAP) therapy-compliant patients were excluded.[26,27] The previous studies also showed that the association between cancer incidence/mortality and OSA was stronger for males, younger (aged <65 years), leaner, and less sleepy patients.[11,26] Our study population includes only PAP therapy-naïve patients with smoking-related cancer and the majority of participants were male. The median BMI of our study group was below 30 kg/m^2 and the median ESS score was below 10. These clinical characteristics of our study population may lead to an expectation for a strong effect of OSA risk for poor prognosis in lung cancer patients. However, we revealed a negative effect of intermediate/high OSA risk on the PFS of the patients with SCLC.

Only a few studies have focussed on the relationship between an individual tumor type and OSA so far.

The first human study on melanoma was published by Martínez-García et al.[28] The authors demonstrated a correlation between aggressiveness factors of melanoma (such as the Breslow index, presence of ulceration, and mitotic index), AHI, and oxygen desaturation index. It was reported that the incidence of head and neck tumors and histological aggressiveness of renal tumors were higher in OSA patients.[20,29,30] There is also a growing body of evidence for the OSA-lung cancer relationship. A meta-analysis including four studies revealed a 30% increase in the incidence of lung cancer for patients with OSA.[31] In a murine lung cancer model, IH was shown to be a factor that increases tumor growth and metastatic processes.[32] Recent studies including mostly NSCLC patients have pointed out that IH aggravated the proliferation, invasion, migration, and drug resistance of tumor cells.[33] Unlike previous studies SCLC patients of our study population were analyzed separately.

In another study of 23 cases from the Asian population, severe OSA was found to increase cancer-related mortality in lung cancer patients with stages 3 and 4.[34] On the other hand, in an analysis comparing 7 patients with lung cancer and comorbid OSA and 45 patients with lung cancer and no OSA, no significant correlation was reported between mortality rate and OSA.[35] These conflicting results may be related to the severity of OSA or histologic type of lung cancer. Similarly, Gozal et al.[12] provided epidemiological evidence from a nationwide cohort including 5.6 million individuals proving that the effect of OSA depends on cancer type and lacks any associations with an increased risk of metastatic cancer or cancer-related deaths. In this study, it was found that the incidence of lung cancer was lower in OSA patients when compared to the non-OSA group. Despite the correlations between the hypoxia-inducible factor (HIF) signaling pathway and tumorigenesis and therapy resistance, variations in recruiting this pathway may lead to divergent results in different types of cancer. It was shown that HIF activity may vary in cancer cell lines under the same level of hypoxia.[36] Furthermore, it was found that hypoxia does not effect etoposide-induced apoptosis in lung cancer cell lines while it reduces p53 activity in hepatoma cells.[37] These findings and our results suggest the existence of cancer-type specific intrinsic reactions to hypoxia.

In our study, the groups defined by OSA risk were similar in terms of confounding factors such as age, smoking rate, treatment modality WBC, SII, hemoglobulin, and LDH levels. Therefore, we performed comparisons in homogenous groups with a specific histologic type of cancer. Additionally, the STOP-BANG questionnaire provides more concrete evidence of OSA risk compared to a symptom-based study.[25] Nevertheless, the lack of polysomnographic data is the major limitation of our study. On the other hand, the sensitivity of the STOP-BANG test for patients with AHI>5 is 0.93.[38] Considering its high sensitivity, our results can be regarded as a basis for future studies. In 2019, Marhuenda et al.[39] published a remarkable study in which they exposed NSCLC cell cultures with different oncogenic mutations to different severity (moderate and severe) and types (intermittent vs sustained) of hypoxia. The authors reported that epithelial cell adhesion molecule and cell proliferation were not changed in some cell types when compared with normoxic cultures, and different results were obtained according to the type of IH. Likewise, our analysis yielded different results for NSCLC and SCLC. The poor PFS in the low-risk group with SCLC patients may be associated with the genetic and epigenetic characteristics of the tumor and the severity of OSA, which could not be determined in the current study.

CONCLUSION

This study shows that each histological subtype of lung cancer may have a unique response to OSA risk. OSA risk may also alter the side effects of cancer treatment. Larger future studies that include polysomnographic and genetic data to explore the metastatic processes, treatment responses, and side effects in the OSA-SCLC overlap are warranted.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.05.2019, Decision No: 1905).

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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Pan-immune inflammatory value a new diagnostic biomarker in postmenopausal osteoporosis

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ABSTRACT

Aims: Postmenopausal osteoporosis (PMOP) is one of the most common bone diseases. We aimed to investigate the relationship between pan-immune inflammatory value and decreased bone mineral density in postmenopausal women.

Methods: This prospective cross-sectional study was composed of 186 postmenopausal women. Osteoporosis was diagnosed with dual-energy X-ray absorptiometry (DEXA) results according to World Health Organization (WHO) recommendations and patients were separated into 3 groups; 1. control group with a T-score >-1; 2. group osteopenia with a T-score between -1.0 and -2.5; 3. group osteoporosis with a T-score ≤-2.5. After the physical examinations of all patients, venous blood samples were collected and the pan-immune inflammation value (PIV) was calculated. The parameters were evaluated statistically with the PIV value between the groups.

Results: Groups are similar in terms of age, menopausal age, education, and occupation. PIV was significantly higher in postmenopausal women with osteoporosis than women with osteopenia and the control group ($p<0.001$, $p<0.001$). PIV was significantly higher in postmenopausal women with osteopenia than the control group ($p<0.001$). Distinguishing between osteoporosis and osteopenia, PIV≥306.20 was 72.6% sensitivity, 69.4% specificity, and 71.7% negative predictive value. Distinguishing between osteopenia and control, PIV≥152.02 was 85.5% sensitivity, 56.5% specificity, 66.3% positive predictive value, and 79.5% negative predictive value.

Conclusion: In our study, we found that the PIV was statistically higher in PMOP, it was also statistically higher in postmenopausal women with osteopenia compared to healthy controls. We believe that PIV can be a cheap, easy, and reliable evaluation parameter for determining the risk of osteoporosis and osteopenia in women with PMOP.

Keywords: Pan-immune-inflammatory value, postmenopausal osteoporosis, osteopenia

INTRODUCTION

Osteoporosis is a skeletal system disease, characterized by low bone mineral mass and impaired microarchitecture of bone tissue.[1] Osteoporosis is one of the most common chronic diseases in humans.[2] The World Health Organization (WHO) defines osteoporosis as a bone mineral density (BMD) less than 2.5 standard deviations lower than that of normal young adults.[3] Decreased bone mass results in decreased bone strength and increased risk of fractures. Osteoporosis is also the most common bone disease worldwide, affecting one in three women and one in five men over the age of 50[4] and with increasing aging, both the prevalence of osteoporosis and the prevalence of osteoporosis-related fragility fractures increase. Osteoporosis has become an important public health problem as the elderly population increases. Postmenopausal osteoporosis (PMOP) is characterized by mainly trabecular bone loss due to endogenous estrogen deficiency after menopause. It is estimated that at least 40% of postmenopausal women will develop a fracture at some point in their lives.[5] Therefore, the evaluation of osteoporosis in patients is important not only for the treatment of osteoporosis but also for preventing complications related to osteoporosis, reducing the risk of fractures, and decreasing mortality.[6]

Previous studies have shown a relationship between bone loss, the immune system, and systemic inflammation. In postmenopausal women, estrogen loss leads to T cell activation and the release of proinflammatory cytokines such as interleukin (IL) 17-A and tumor necrosing factor (TNF).[7,8] IL 17-A increases bone destruction.[9] However, TNF-alpha also stimulates osteoclastogenesis directly through osteoclasts.[10] As a result of all this, PMOP develops.

Bone mineral density measurements support and confirm the diagnosis of osteoporosis, assessment of

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fracture risk, and evaluation of the patient's treatment plan are among the methods used during the diagnosis and post-treatment follow-up.[11] Dual-energy X-ray absorptiometry (DEXA) is the most common measurement for the diagnosis of PMOP. However, DEXA is not available everywhere. Also, there is no definitive biomarker for which a patient should be referred for a DEXA scan. For this reason, some inexpensive and rapid blood parameters that can assess the risk of osteoporosis in outpatient clinic conditions are being studied. Neutrophil and lymphocyte ratio (NLR),[12] monocyte lymphocyte ratio (MLR),[13] platelet lymphocyte ratio (PLR),[14] systemic immune-inflammation index (SII)[15] have been studied at osteoporosis.

Pan-immune inflammatory value (PIV) is a new diagnostic biomarker. PIV is calculated from a complete blood count that includes neutrophils, platelets, monocytes, and lymphocytes. Each of these immune cells plays a role in inflammation. PIV has been previously studied in inflammatory diseases such as colorectal cancer, melanoma, rheumatoid arthritis, and vasculitis.[16-19]

In this study, we aimed to investigate the relationship between PIV and decreased bone mineral density in postmenopausal women.

METHODS

This prospective cross-sectional study was composed of 186 postmenopausal women over 45. Participants who applied to physical medicine and rehabilitation outpatient clinics between October 2023 and February 2024, and who had been in natural menopause for the last 1 year were included. Participants with endocrinologic or rheumatic diseases such as diabetes mellitus, rheumatism, thyroid diseases, parathyroid diseases, or hepatorenal insufficiency, malignancy, presence of acute and chronic infection, use of medication associated with osteoporosis such as corticosteroids, calcium medications or chemotherapy drugs, use of hematopoietic drugs that affect blood parameters, surgical menopause or those with a metal prosthesis that will obstacle DEXA examination were excluded. The study was carried out according to the principles of the Declaration of Helsinki, and written informed consent was obtained from all patients. Hitit University Clinical Researches Ethics Committee approved the study (Date: 26.12.2023, Decision No: 2023-170).

Patients were asked about their education, occupation, age at menopause, chronic diseases, medications, and smoking status. After the physical examinations of all patients, venous blood samples were collected and the complete blood cell parameters; monocyte counts (10^9/L), neutrophil counts (10^9/L), lymphocyte counts (10^9/L), and platelet counts (10^9/L) were noted. Pan-immune inflammation value (PIV) was calculated with the formula: (neutrophil count×platelet count×monocyte count)/lymphocyte count.[16]

Before DEXA measurement, the height of the patients was measured with a tape measure in centimeters and weight was measured with a scale in kilograms, and body mass index (BMI) kg/m^2 was calculated. Bone mineral density was measured at three sites: femoral neck, total femur, and total lumbal (lumbal 1-4 vertebrae) using the Horizon bone densitometry system (MAN-04871). In the light of WHO osteoporosis diagnostic criteria, patients were categorized into 3 groups; control, osteopenia, and osteoporosis, according to DEXA results.[3] 1. Group control group with a T-score >-1; 2. group osteopenia with a T-score between -1,0 and -2.5; 3. group osteoporosis with a T-score ≤-2.5.

In the light of the previous study, the effect size for the ANOVA test (followed by the t-test) was found to be approximately 0.243, and in the a priori power analysis performed with a statistical significance of 0.05 and a statistical power of 0.80, the total sample size of the 3 groups was found to be 168 people, consisting of 3 groups of 56 participants in each group, so that significance could be achieved in the pair group analysis between the groups.[20]

Statistical Analysis

This study was designed prospectively. All statistical analyses were conducted using IBM SPSS Statistics for Windows software (version 26; IBM Corp., Armonk, N.Y., USA). The normal distribution of data was assessed using the Shapiro-Wilks test. Correlations between variables were evaluated using Pearson and Spearman correlation coefficients, depending on the data distribution. Comparison of numerical measurements between independent groups according to research groups, such as age, height, weight, menopausal age, neutrophil, monocyte, lymphocyte counts, femur neck T score, femur total T score, lumbar total T score, and PIV, was assessed using the Mann-Whitney U test and Kruskal-Wallis Test for post-hoc tests, in accordance with the distribution of the data. An ANOVA test was done for the assessment of the difference between means of platelet counts between groups. Categorical variables such as educational status, current occupation, and smoking history were evaluated for ratio comparisons between research groups using the Chi-square test. Receiver Operating Characteristic (ROC) curves were utilized to demonstrate the discriminative ability of statistically significant variables. Cut-off values for these markers were determined using the area under the curve and the Youden index. Sensitivity, specificity, positive

predictive value (PPV), negative predictive value (NPV), and accuracy values were calculated based on these cut-off values. Odds ratio values were computed for these cut-off points. A significance level of p<0.05 was considered statistically significant.

RESULTS

Of the total 186 female patients in the entire group, the median age was found to be 62.5 (46-83) years. Patients were categorized into three groups: control (n=62), osteopenic (n=62), and osteoporotic (n=62). When assessed in terms of mean ages, the median age in the control group was 61 years; in the osteopenic group, it was 63.5 years; and in the osteoporotic group, it was 63 years; however, no statistically significant difference was observed (p=0.056). There was no difference in terms of height, menopausal age, education, and occupation between groups (p=0.280, p=0.297, p=0.845, and p=0.052, respectively). The median weight of osteoporotic patients was lower than control and osteopenic patients (p<0.001 for control vs osteoporotic and p=0.007 for osteopenic vs osteoporotic) (Table 1). While evaluating the smoking history of the groups, osteoporotic patients were found to have a higher ratio of smokers at 38.71%, indicating a statistically significant difference compared to other groups (p<0.001 against control participants, p<0.001 against osteopenic patients (Table 1).

The comparisons between hematological laboratory values between groups and radiological indices of osteoporosis are extensively detailed in Table 1, including post-hoc test results. When examining the PIV of patients in the groups, the median PIV for the control group was 143.91, while the median PIV for the osteopenic patients was 245.49, and the median PIV for the osteoporotic patients was higher with 441.90, indicating a statistically significant difference between all groups (p<0.001 for Kruskal-Wallis and all post-hoc tests) (Table 1, Figure 1 and Figure 2).

To assess the optimal cut-off point of PIV for distinguishing between control and osteopenia groups, the area under the curve and the Youden index were employed in ROC analysis. For the diagnosis of osteopenia, the most suitable PIV cut-off value was determined to be ≥152.02 with 85.5% sensitivity, 56.5% specificity, 66.3% positive predictive value, 79.5% negative predictive value, and 70.96% test accuracy (OR 7.634, 95% CI 3.208-18.163, p<0.001). A PIV of or exceeding 152.02 increased the likelihood of osteopenia by 6.634 times (Table 2, Figure 3).

Table 1. Descriptive variables of all participants. comparisons between groups and results of post-hoc comparisons

Variables		All participants (n=186)	Control (n=62)	Osteopenic (n=62)	Osteoporotic (n=62)	Statistical significance	Control vs osteopenic	Control vs osteoporotic	Osteopenic vs osteoporotic
Age		62.5 (46-83)	61 (46-78)	63.5 (48-80)	63 (46-83)	0.056			
Height		152 (51-170)	153 (144-165)	152 (90-168)	151.5 (51-170)	0.280			
Weight		71 (7-147)	76.5 (53-113)	73.5 (7-146)	68.5 (38-147)	<0.001	0.356	<0.001	0.007
Menopausal age		47 (29-162)	47 (35-56)	48 (36-55)	45.5 (29-162)	0.297			
Education	Primary shool	165 (88.71%)	54 (87.1%)	57 (91.94%)	54 (87.1%)	0.845			
	High school	14 (7.53%)	5 (8.06%)	3 (4.84%)	6 (9.68%)				
	University	7 (3.76%)	3 (4.84%)	2 (3.23%)	2 (3.23%)				
Occupation	Housewife	168 (90.32%)	53 (85.48%)	60 (96.77%)	55 (88.71%)	0.052			
	Working	8 (4.3%)	2 (3.23%)	1 (1.61%)	5 (8.06%)				
	Retired	10 (5.38%)	7 (11.29%)	1 (1.61%)	2 (3.23%)				
Smoking History	Non-smoker	151 (81.18%)	56 (90.32%)	57 (91.94%)	38 (61.29%)	<0.001	0.752	<0.001	<0.001
	Smoker	35 (18.82%)	6 (9.68%)	5 (8.06%)	24 (38.71%)				
Neutrophil count		3.98 (1.36-8.43)	3.16 (1.36-6.47)	3.75 (2.12-8.43)	4.92 (3.1-7.42)	<0.001	0.009	<0.001	<0.001
Monocyte count		0.49 (0.21-1.57)	0.51 (0.31-1.57)	0.49 (0.21-1.16)	0.49 (0.26-1.2)	0.657			
Lymphocyte count		2.29 (1.09-5.54)	2.7 (1.51-5.54)	2.13 (1.1-3.92)	2.05 (1.09-4.06)	<0.001	<0.001	<0.001	0.292
Platelet count		271.49±52.33	240.77±38.56	262.79±52.8	310.9±37.63	<0.001	0.016	<0.001	<0.001
Femur neck T score		-1.1 (-3-2.3)	0 (-1.5-2.3)	-1.35 (-2.3-1.9)	-1.7 (-3-1.9)	<0.001	<0.001	<0.001	0.025
Femur total T score		-0.7 (-2.8-5)	0.55 (-1.2-2.8)	-1 (-2.3-5)	-1.4 (-2.8-1.6)	<0.001	<0.001	<0.001	0.056
Lumbar total T score		-1.8 (-4.2-2.6)	-0.35 (-3-2.4)	-1.9 (-2.6--0.7)	-3 (-4.2-2.6)	<0.001	<0.001	<0.001	<0.001
PIV		248.65 (35.04-2238.82)	143.91 (35.04-485.10)	245.49 (70.18-749.58)	441.90 (147.11-2238.82)	<0.001	<0.001	<0.001	<0.001

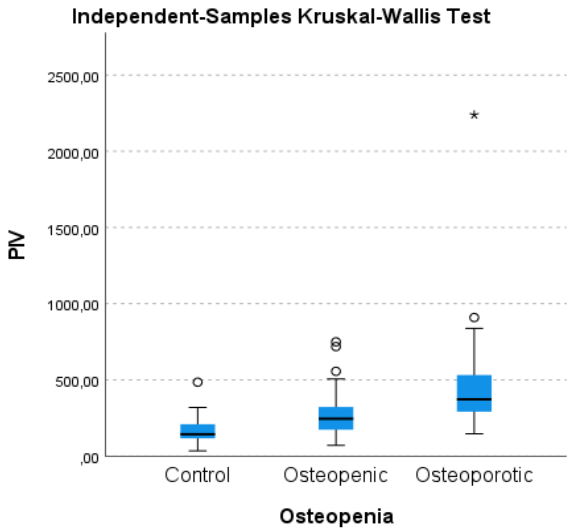

Figure 1. Boxplot diagrams of pan-immune inflammation values between groups

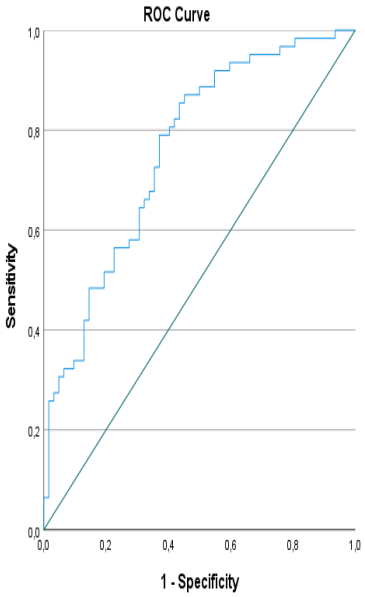

Figure 3. Receiver Operating Curve of PIV for the distinction between control and osteopenic groups

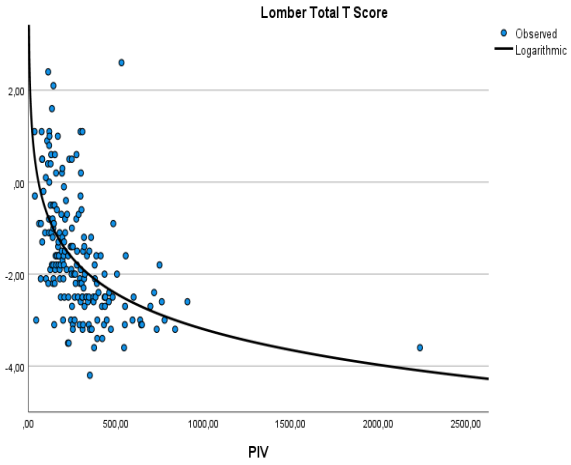

Figure 2. Logarithmic curve estimation of PIV and Lomber Total T Score

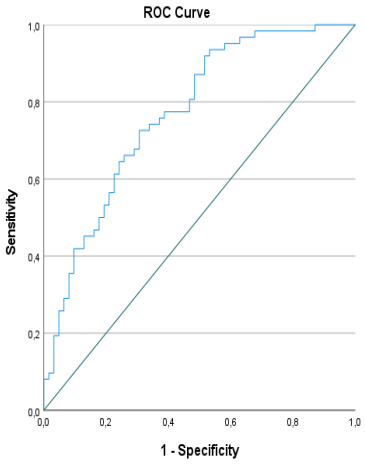

Figure 4. Receiver Operating Curve of PIV for the distinction between osteopenic and osteoporotic groups

Similarly, another ROC analysis was done for the assessment between osteopenic and osteoporotic groups. For the diagnosis of osteoporosis, the optimal PIV cut-off point was found to be ≥306.20 with 72.6% sensitivity, 69.4% specificity, 70.3% positive predictive value, 71.7% negative predictive value, and 70.96% test accuracy (OR 5.991, 95% CI 2.756-13.022, p<0.001). A PIV of or exceeding 306.20 increased the likelihood of osteoporosis by 4.991 times (Table 2, Figure 4).

DISCUSSION

To our knowledge, this is the first study investigating the relationship between PIV and BMD in women with PMOP. We found that high PIV levels were associated with low BMD and PIV was found to be significant both in differentiating healthy patients and those with osteoporosis, and in differentiating osteoporosis and osteopenia.

Table 2. Cut-off points and diagnostic values of variables for distinction between non-appendicitis patients and appendicitis patients

Variables	Cut-Off	Diagnostic values					ROC curve			Odds ratio		
		Sensitivity	Specificity	PPV	NPV	Accuracy	Area (SE)	95%CI	p	Odds ratio	95%CI	p
Control vs osteopenic	≥152.02	85.5%	56.5%	66.3%	79.5%	70.96%	0.758 (0.043)	0.675-0.842	<0.001	7.634	3.208-18.163	<0.001
Osteoporotic vs osteopenic	≥306.20	72.6%	69.4%	70.3%	71.7%	70.96%	0.770 (0.042)	0.688-0.852	<0.001	5.991	2.756-13.022	<0.001

PMOP is a common chronic disease. At least 40% of postmenopausal women are predicted to develop a fracture at some point in their lives.[5] As a result of fracture development due to PMOP, chronic pain, deformity, reduced independence due to physical limitation, psychosocial difficulties, deterioration in quality of life, disability, and even fracture-related deaths can be observed.[21] With the increase in the elderly population, both osteoporosis and related fractures are increasing day by day and are becoming a serious public health problem.[22] Therefore it is important to understand osteoporosis and blood parameters associated with osteoporosis.

In previous studies, it was found that some blood parameters were associated with bone hemostasis. In a study on mice, T and B lymphocytes have been shown to be effective in bone homeostasis. osteoprotogenin, which regulates bone resorption, was shown to be driven by B cells.[23] T cells have also been shown to be activated in PMOP due to decreased estrogen levels and to produce inflammatory cytokines involved in bone destruction such as receptor activator of nuclear factor kappa-B ligand (RANKL) and TNF alfa.[24] In the presence of inflammation, neutrophils have been shown to destroy bone tissue by releasing chemokines that summon T17 cells.[25] Circulating platelet levels also increase inflammation and osteoclastogenesis is triggered.[26] Monocytes in the blood turn into osteoclasts in case of estrogen deficiency and inflammation and increase bone destruction.[27] In our study, we aimed to find out whether there is a relationship between BMD and complete blood count parameters, which are frequently evaluated in outpatient clinics. There are several studies investigating complete blood count parameters in PMOP. Kale demonstrated that MLR and PLR were significantly higher in PMOP.[28] Another study conducted on Chinese women found a strong relationship between NLR and BMD.[12] Du et al.[29] evaluated a relationship between high SII levels and low BMD.When the research in the literature is evaluated, it is thought that there is a relationship between immune system cells and PMOP. We wanted to use PIV, a more comprehensive assessment tool that includes all these immune cells; neutrophils platelets monocytes, and lymphocytes. In our study, an inverse relationship was found between PIV and BMD values. PIV was even significant in differentiating osteoporosis and osteopenia. PIV was statistically higher in PMOP, and also higher in women with osteopenia than healthy individuals. According to Fang et al.[15] SII was not only found to be associated with BMD but also found to be effective in determining the risk of fractures in PMOP. However, we did not investigate the relationship between fracture risk and PIV in our study. It will be useful to conduct studies in which this relationship is investigated in the future.

If we can distinguish patients with osteopenia in the postmenopausal period, we can start their treatment early and reduce the risk of complications. In our study, PIV was also found effective in making this distinction. In differentiating healthy individuals from patients with osteopenia PIV was a 66.3% positive predictive value and in osteopenic and osteoporotic groups PIV was a 70.3% positive predictive value.

Smoking is an independent risk factor for osteoporosis. According to Weng et al.[30] in their review, it was also discussed that there is a negative relationship between smoking and BMD values of the femoral and lumbar vertebrae. Trevisan et al.[31] In patients with PMOP, they found a greater decrease in femoral BMD in smokers than in non-smokers at the end of 2 years. In our study, BMD values were also found to be lower in smokers both in the femur and lumbar vertebrae, but we could not determine the rate of change over the years because we did not follow the patients.

Currently, new potential therapeutic agents such as denosumab, IL-1 receptor antagonist, and TNF-α antibody are being developed for the treatment of osteoporosis secondary to inflammation. This shows the importance of understanding the relationship between the immune system and osteoporosis both in diagnosis and treatment. Since our study is a cross-sectional study, we evaluated the patients once. It would be useful to follow up on patients with PMOP and investigate the change in PIV values after treatment.

Limitations

Since we planned a cross-sectional study, we evaluated the patients once. We did not evaluate other parameters that may be associated with osteoporosis. We did not measure other blood values that may be associated with bone turnover.

Studies in larger groups of patients, taking into account other parameters that may be associated with osteoporosis, are needed.

CONCLUSION

Osteoporosis is a significant global public health problem with rising prevalence due to increasing morbidity, fracture-related mortality risk, and high treatment costs. Although DEXA is the most commonly used diagnostic method, it is not available in all areas. Therefore, the determination of new biomarkers that are easily accessible and cost-effective has gained prominence. In our study, we found that the PIV was statistically higher in PMOP, it was also statistically higher in

postmenopausal women with osteopenia compared to healthy controls. We believe that PIV can be a cheap, easy, and reliable evaluation parameter for determining the risk of osteoporosis and osteopenia in women with PMOP.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by Hitit University Clinical Researches Ethics Committee (Date: 26.12.2023, Decision No: 2023-170).

Informed Consent

In this study, each patient provided informed consent prior to participation.

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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Comparison of the results of early and elective endoscopic retrograde cholangiopancreatography in patients with mild cholangitis

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ABSTRACT

Aims: The optimal duration of endoscopic retrograde cholangiopancreatography (ERCP) in patients with mild cholangitis and when it should be performed is unclear. This study aimed to compare the results of patients with mild cholangitis who underwent early and elective ERCP.

Methods: This study was designed as a retrospective study to compare the results of elective (time from admission to ERCP>72 h) and early (time from admission to ERCP≤72 h) ERCP in patients with mild cholangitis according to the Tocyo 18 (TC18) guideline. The study included patients with naive papillae and mild cholangitis who underwent ERCP between February 2019 and 2023 at a single tertiary center's gastroenterology clinic.

Results: A total of 432 mild cholangitis patients were included in our study. The mean age and ASA score of the elective ERCP group was slightly higher than the other group (respectively, p=0.039 and p=0.025). No significant difference was found between the two groups in terms of technical and clinical success, mortality, ERCP-related adverse events, organ failure and intensive care unit admission. Length of hospital stay (LHS) was significantly (p<0.001) higher in the elective group compared to the early group.

Conclusion: Our study showed that in patients with mild cholangitis with uncertain optimal ERCP time, ERCP in the early or elective period had no significant effect on mortality and other adverse outcomes, but ERCP in the early period shortened the patients' LHS duration.

Keywords: ERCP, mild cholangitis, mortality, pancreatitis

INTRODUCTION

Acute cholangitis is a medical condition caused by obstruction of the bile ducts for various reasons.[1] Although causes such as stricture, malignancy and parasites are involved in the etiology, the most common cause is bile duct stones.[2] Acute cholangitis is fatal in 5-10% of cases if not diagnosed and treated in time.[3]

Depending on the severity of the disease, treatment for acute cholangitis consists mainly of antimicrobial therapy and biliary decompression.[4] Biliary decompression is performed by endoscopic retrograde cholangiopancreatography (ERCP) or interventional radiological drainage. The optimal duration of ERCP in patients with acute cholangitis is still unclear. In a study investigating the optimal duration of ERCP in patients with acute cholangitis, it was reported that the duration of hospitalisation increased and some additional adverse outcomes occurred in patients undergoing ERCP after 48 hours.[5] Another study suggested that there was no significant difference in adverse outcomes in patients with non-severe acute cholangitis who underwent emergency or elective biliary drainage.[6] The most comprehensive guideline on this topic is the Tokyo (TC) 18 guideline revised in 2018.[7] According to this guideline, the diagnosis of acute cholangitis is based on systemic inflammation, cholestasis and imaging findings and is divided into 3 categories as severe, moderate and mild. While urgent biliary drainage is recommended for patients with severe cholangitis and early biliary drainage is recommended for patients with moderate cholangitis, antibiotic treatment or biliary drainage is recommended for patients with mild cholangitis. However, in this guideline, it is unclear when biliary drainage should be performed in patients with mild cholangitis.[7]

In the literature, studies that included patients with mild to moderate cholangitis have evaluated the optimal duration of ERCP[8] but we could not find studies that included patients with mild cholangitis only. In this

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study, we aimed to compare the results of patients with mild cholangitis who underwent early and elective ERCP.

METHODS

Ethics

Ethical approval was obtained from the Yıldırım Beyazıt University Faculty of Medicine Clinical Researches Ethics Committee (Date: 26.05.2021, Decision No: 56) and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

Study Design and Patients

This study was designed as a retrospective study to compare the results of elective (time from admission to ERCP>72 h) and early (time from admission to ERCP≤72 h) ERCP in patients with mild cholangitis. The study included patients with naive papillae and mild cholangitis who underwent ERCP between February 2019 and 2023 at a single tertiary center's gastroenterology clinic. Using electronic medical records and the endoscopy database, we retrospectively analysed data from consecutive patients who underwent ERCP for mild cholangitis. Except for the diagnosis of mild cholangitis, patients with surgically altered anatomy (Billroth 2 gastrectomy or Roux-en-Y anastomosis), those under 18 years of age, those who had undergone sphincterotomy were excluded from the study. Patients with missing records and data were also excluded from the study.

ERCP Procedures

Antibiotic treatment and fluid resuscitation were given to all enrolled patients before the procedure. All ERCPs were performed using a lateral scope (TJF 190; Olympus Optical, Tokyo, Japan) by an experienced endoscopist who performs >800 therapeutic ERCPs per year. Patients were sedated with propofol and midazolam by anestegiologist. Standard biliary cannulation was performed using a guide wire and sphincterotome. Alternative techniques such as double guidewire and precut were used when selective biliary cannulation could not be achieved with this method. All patients were hospitalised for at least 24 hours after the procedure.

Definitons

Acute cholangitis was diagnosed and graded according to the TG18 guidelines for acute cholangitis[9]. Patients who underwent ERCP within 72 hours of admission were classified as having undergone an "early period", while patients who underwent ERCP beyond 72 hours of admission were classified as having undergone an "elective period". Comorbidity scores were calculated for the patients in the study using the Charlson Comorbidity Index (CCI)[10]. American Society of Anesthesiologists' Physical Status (ASA-PS) score[11] was divided into two groups: below and above 2 points. Weekends were defined as Saturday, Sunday and public holidays in Turkey. Night time was defined as 5 pm to 8 am, during which time there was no outpatient service in our hospital. Technical success was defined as successful decompression of the bile duct. Clinical success was defined as improvement in symptoms of cholangitis and laboratory findings such as CRP and white blood cell count improved within 7 days of ERCP. ERCP-related adverse events (AEs) in all patients after the procedure were defined according to international consensus criteria.[12] Organ failure was defined as hypotension requiring vasopressors, need for mechanical ventilation, or acute kidney injury (1.5-fold increase in serum creatinine from baseline or need for dialysis) persisting for more than 48 hours.[13]

Study Outcomes

The primary outcomes included technical success, clinical success, in-hospital mortality, intensive care unit (ICU) admission, organ failure and early adverse events associated with ERCP. The secondary outcome of this study was the length of hospital stay (LHS) between the two groups.

Statistical Analysis

In our study, the data were analysed using SPSS 25 (Armonk, NY: IBM Corp.) software. Mean, standard deviation, median (quartiles), frequency and percentage statistics were used to express numerical variables. Normality assessment was performed with Kolmogorov-Smirnov and Shapiro-Wilk tests. Student-t and Mann Whitney U tests were used to analyse numerical variables. Chi-square (Pearson, Yates and Fisher's) tests were used to analyse categorical variables. In the analyses of the relationship between numerical variables and ERCP groups, two-tailed correlation coefficients and phi coefficients were used for categorical variables. The significance level was set at 0.05 for all analysis.

RESULTS

A total of 432 mild cholangitis patients were included in our study. Although the age of the elective ERCP group was slightly higher than the other group (p=0.039), the gender distribution was similar between both groups (p=0.824). The high number of patients with Charlson index greater than two in the elective patient group did not lead to a significant result (p=0.168), whereas the high number of patients with ASA score greater than two led to a significant result (p=0.025) in this group. Time of hospital admission was concentrated during working hours in the early ERCP group (60.6%), while in the elective ERCP group it was mostly (37.6%) during holidays (p<0.001). Other variables and detailed results of the variables are presented in Table 1.

Table 1. Basic characteristics

Variables	All cases	Early ERCP (≤72 hours, n=203)	Elective ERCP (72 hours<, n=229)	p
Age	62.1±16.2	60.4±17.2	63. 6±15	0.039
Sex				
Male	211 (48.8)	98 (48.3)	113 (49.3)	0.824
Female	221 (51.2)	105 (51.7)	116 (50.7)	
Charlson comorbidity index				
<=2	221 (51.2)	111 (54.7)	110 (48)	0.168
>2	211 (48.8)	92 (45.3)	119 (52)	
ASA-PS score				0.025
<=2	351 (81.3)	174 (85.7)	177 (77.3)	
>2	81 (18.8)	29 (14.3)	52 (22.7)	
History of cholecystectomy	61 (14.1)	31 (15.3)	30 (13.1)	0.518
Time of hospital admission				
Working hours	188 (43.5)	123 (60.6)	65 (28.4)	<0.001
Night time	155 (35.9)	77 (37.9)	78 (34.1)	
Weekends	89 (20.6)	3 (1.5)	86 (37.6)	
Etiology of acute cholangitis				0.227
Bile duct stones	368 (85.2)	177 (87.2)	191 (83.4)	
Malignancy	22 (5.1)	14 (6.9)	12 (5.2)	
Benign structure	17 (3.9)	6 (3)	14 (6.1)	
Others	25 (5.8)	6 (3)	12 (5.2)	
Laboratory datas				
WBC	9.5 (7.26 - 12.1)	9.5 (7.17 - 12.1)	9.3 (7.3 - 11.9)	0.989
Crp	29.4 (13.8 - 78.2)	29 (13.2 - 74.3)	31.8 (14.1 - 82)	0.667
Tbil	3.6 (2.1 - 5.4)	3.7 (2.3 - 5.6)	3.5 (1.9 - 4.9)	0.061
GGT	449 (249.5 - 684)	446 (267 - 699)	457 (235 - 681)	0.736

Numerical variables with normal distribution are presented as mean±standard deviation, skewed distributions as median (Q1-Q3), and categorical variables as n(%).

It was concluded that technical and clinical success did not vary according to the duration of ERCP (p=0.455 and p=0.872 respectively) and that adverse events were not related to the duration of ERCP. ICU admission increased slightly in the elective ERCP group, but did not reach significance (p=1.00). Median LHS was significantly (p<0.001) higher in the elective group compared to the early group, while hospital stay after ERCP was almost significantly lower in the elective group (p=0.057). The results of the analyses are presented in Table 2.

The associations of variables with categorised ERCP duration were also analysed. Especially LHS was observed to increase in the elective ERCP group (rpb=0.449 and p<0.001). However, similar relationships to the results of univariable analyses were observed for other variables (Figure 1, Figure 2).

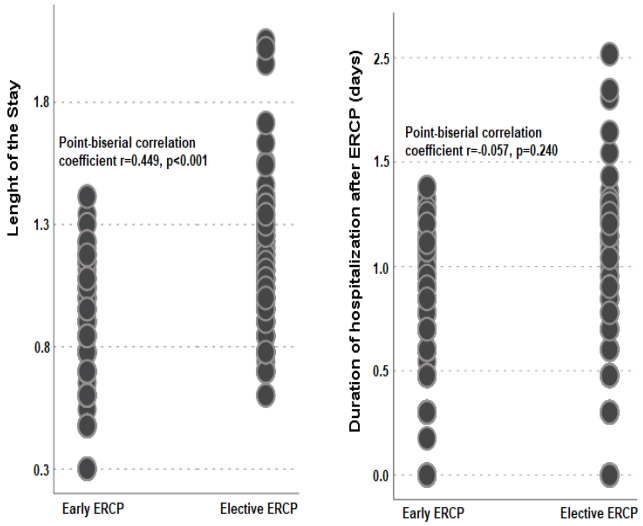

Figure 1. Scatter of logarithmic values of length of stay and duration of hospitalization after ercp variables with ercp duration

Table 2. Analysis of variables according to ERCP time

Variables	Early ERCP (≤72 hours, n=203)	Elective ERCP (72 hours<, n=229)	p
Technical success	201 (99)	224 (97.8)	0.455*
Clinical success	188 (92.6)	213 (93)	0.872
Adverse events associated with ERCP			
Pancreatitis	26 (12.8)	35 (15.3)	0.461
Bleeding	7 (3.4)	6 (2.6)	0.825**
Perforation	0 (0)	4 (1.7)	0.126*
Organ failure	2 (1)	2 (1)	1.00*
Admission to intensive care unit	5 (2.5)	6 (2.6)	1.00**
In-hospital mortality	2 (1)	2 (1)	1.00*
Length of stay, days	6 (4-6)	9.5 (7-13)	<0.001
Duration of hospitalization after ERCP, days	4 (2-6)	3 (1-5)	0.057

Variables are presented as n (%). *: Fisher Exact test, **: Yates correction

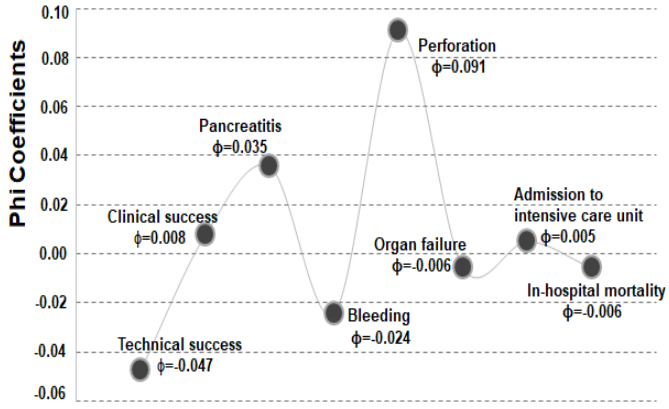

Figure 2. Scatter of phi coefficients between ERCP duration and categorical variables

DISCUSSION

This study showed that there was no significant difference between early (first 72 hours) and elective ERCP (after 72 hours) in terms of mortality, organ failure, intensive care unit stay, ERCP-related complications, technical and clinical success in patients with mild cholangitis. Another important finding of the study is that patients with mild cholangitis who underwent early ERCP had a significantly shorter LHS.

The controversy surrounding the optimal duration of ERCP in patients with acute cholangitis is still ongoing. In a retrospective study published in 2017, the duration of ERCP in patients with acute cholangitis was divided into two groups according to the time before and after 48 hours. ICU admission and LHS were significantly more common in patients who underwent late ERCP. When the same study evaluated the groups according to 72-hour duration, hypotension requiring vasopressors was also found significantly more frequently in the late group patients. However, this study included all grades of acute cholangitis together.[5] The findings and hypotheses of a recent retrospective study by Huang et al.[14] are interesting. In this study, subgroup analyses were performed in all patients with severe, moderate and mild cholangitis. There was no significant difference in 30-day mortality and ICU admission rates in patients with mild cholangitis when evaluated in both the 24-hour and 48-hour groups, whereas LHS was found to be significantly shorter in the early groups.[14] In another study, patients with non-severe cholangitis were defined and compared as emergency and elective groups according to the first 12 hours and beyond. According to this study, no significant difference was found between the groups in any parameter including mortality, organ failure, ICU admission and LHS.[6] A review of published guidelines, in addition to studies in the literature, shows that the optimal duration of ERCP is controversial. The American Society of Gastrointestinal Endoscopy (ASGE) guideline 2021 evaluated the association of acute cholangitis with adverse outcomes, primarily in patients with severe and moderate cholangitis, and suggested that ERCP performed within the first 48 hours significantly reduced 30-day mortality and length of hospital stay.[15] The European Society of Gastrointestinal Endoscopy (ESGE) recommended that severe cholangitis patients should be performed within the first 12 hours, moderate cholangitis patients should be performed within 48-72 hours, while no time recommendation was made for patients with mild cholangitis and elective ERCP was recommended.[16] The results of three recent meta-analyses show that the discussion about the optimal timing of ERCP is mainly focused on 24 hours and 48 hours, based on data analysis of significant outcomes in their respective time frames. However, these three trials reported that the optimal timing of ERCP did not affect survival outcomes in patients with acute cholangitis of different severity - mild, moderate and severe.[17-19] We think that patients with acute cholangitis should be analysed in separate groups according to the severity of cholangitis in order to investigate the optimal duration of ERCP. In addition, the common finding of all these studies is that the LHS of patients who underwent ERCP in the early period is shorter.[17-19] In our study, LHS was found to be significantly shorter in patients who underwent ERCP in the early period, which is similar to the literature.

In our study, the fact that age and ASA score were significantly higher in the elective group, despite the small difference, suggests that these patients may be mainly due to prolonged preoperative anaesthetic

preparation. However, the fact that there was no significant difference in the primary outcome parameters between the elective group and the early group, despite the higher age and ASA score, is another notable finding of our study. There was no significant difference between the two groups in terms of ERCP-related complications, mortality, organ failure and admission to ICU. Perforation was seen in 4 patients in the elective group and only one of these patients was operated on and died in the follow-up due to prolonged ICU hospitalisation and non-cholangitis infection. In the other patients, a metal fully covered stent was placed during the procedure and the patients were discharged after follow-up. However, there was no significant statistical difference between the groups in this study.

Limitations

The most important limitation of our study is that it was retrospective and single-centre. Moreover, the relatively small number of patients included was a further limitation. Finally, the fact that only in-hospital mortality was assessed in the mortality factor and the lack of mortality data at 1 month or later can also be considered as a limiting aspect of the study.

CONCLUSION

Our study showed that in patients with mild cholangitis with uncertain optimal ERCP time, ERCP in the early or elective period had no significant effect on mortality and other adverse outcomes, but ERCP in the early period shortened the patients' LHS duration. However, large and multicentre studies are needed to clarify the definitions of duration in the literature and the optimal duration of ERCP in patients with mild cholangitis.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Yıldırım Beyazıt University Faculty of Medicine Clinical Researches Ethics Committee (Date: 27.05.2021, Decision No: 56).

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 Contrubitions

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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Persistent iatrogenic atrial septal defect after cryoballoon ablation for atrial fibrillation

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ABSTRACT

Aims: Pulmonary vein isolation (PVI) by cryoballoon ablation (CB) technology is effective and safe treatment option for atrial fibrillation (AF). CB is performed by large diameter, 15Fr (4.95mm) transseptal sheath that may lead to creation of iatrogenic atrial septal defect (iASD). The objective of this study was to assess the incidence of iASD in patients who had undergone CB.

Methods: Patients with AF having undergone Arctic Front® CB ablation and a subsequent transesophageal echocardiography (TEE) examination during post-ablation follow up period were consecutively enrolled. During all CB procedures, 15Fr transseptal sheath (Flex Cath, Medtronic, Minneapolis, MN) was utilized via single transseptal puncture (TsP).

Results: Twenty-eight patients (15 females, mean age 55.8+15.5) with paroxysmal (n=24) or persistent (n=4) AF formed study group. iASD was present 11 (39.3%) of them after mean follow-up time of 17.3+6.2 months. The procedural time is significantly longer in patient with iASD (119.0+8.8 minutes, p=0.01). No patients died or suffered from any clinically significant cerebral ischemic event. There was no sign of increase in systolic pulmonary arterial pressure (sPAP).

Conclusion: iASD after CB was found to be present in 39.3% of patient during a mean follow-up time of 17.3+6.2 months. The prolonged CB procedural time was the only factor that predicted iASD in our study. No adverse clinic events that might be related to iASD was observed during follow-up period.

Keywords: Iatrogenic atrial septal defect, cryoballoon ablation, pulmonary vein isolation, atrial fibrillation

INTRODUCTION

Pulmonary vein isolation (PVI) is an effective and safe treatment option in symptomatic paroxysmal atrial fibrillation.[1] In all catheter ablation procedures for atrial fibrillation (AF), transseptal puncture (TsP) is needed to gain access to left atrium (LA). One of the complications of TsP is residual iatrogenic atrial septal defect (iASD) which was first recognized after percutaneous mitral balloon valvuloplasty (PMBV) procedures.[2] Residual iASD is also observed after AF ablation procedures, but the literature is sparse on this topic.

Cryoballoon ablation (CBA) system is newly developed technology to make PVI more effective and feasible. The CBA procedure was found to be effective and safe method of pulmonary vein isolation for AF in the first clinical researches.[3,4] Because transseptal sheath with large outer diameter, 15 Fr (4.95mm), is used for delivery and manipulation of the cryoballoon catheter in the LA, risk of residual iASD is thought to increase. The objective of this study was to assess the prevalence of iASD in patients who had undergone CB.

METHODS

Ethics

This study protocol has been approved by Ankara University Faculty of Medicine Clinical Researches Ethics Committee (Date: 13.01.2014, Decision No: 01-06-14). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

Between December 2011 and November 2013, pulmonary vein isolation using Arctic Front cryoballoon was performed on 84 patients with persistent atrial fibrillation at our clinic. Among these patients, 28 individuals who underwent transesophageal echocardiography for any reason following the ablation procedure were included in the study. .patients with AF who were treated by Arctic Front® Cryoballoon between December 2011 and November 2013 and undergoing subsequent transesophageal echocardiography (TEE) examination for any reason after CBA were

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consecutively enrolled in our retrospective analysis. The indications of reperforming TEE, obtained from medical records were unexplained chest pain and dyspnea, further examination of mitral valve regurgitation and anatomy, suspicion of interatrial shunt and poor transthoracic ultrasound wave transmission. Exclusion criteria include previous LA ablation for AF or other transseptal puncture, second TsP during or after the index CB procedure for any reasons, and ASD, patent foramen ovale or other congenital heart disease prior to ablation.

Echocardiographic Examination

The preprocedural transthoracic/transesophageal echocardiography was performed in all patients. Pre-and post- procedural TTEs enabled assessment of diameter, diastolic and systolic function of left ventricle, right ventricle functions, left atrial diameter, anatomy and function of valves, atrial and ventricular septum. Ventricular systolic pressure was estimated from tricuspid valve regurgitation jet velocity by the modified Bernoulli equation and was considered equal to the systolic pulmonary artery pressure (sPAP). TEE was performed using pre and post commercial equipment (Vivid S5, GE Medical System, Milwaukee, MI, USA) and LA thrombus and anatomy, valves anatomy and function, interatrial septum with 2D and color doppler flow were examined from multiple views (Figure). iASD was defined as interatrial shunt confirmed by doppler flow beside the fossa ovalis but not fulfilling the criteria of patent foramen ovale (PFO).[5] In a case of confirmed iASD, the characteristic of transseptal flow was also examined thereafter injection of agitated saline before and after Valsalva maneuver.

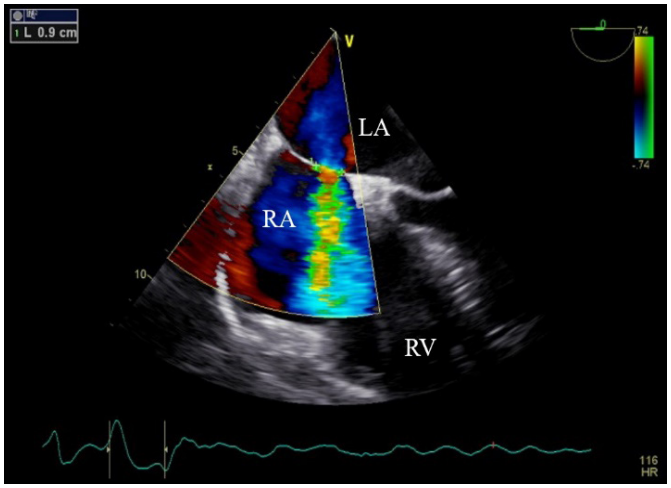

Figure. Mid esophageal view of interatrial septum with color flow doppler demonstrating left-to-right shunt across 0.9cm persistent iatrogenic septal defect. LA: left atrium, RA: Right atrium, RV: right ventricle

Transseptal Puncture and Cryoballoon Ablation Procedure

In our study all pulmonary vein ablation procedures were performed with Arctic Front® Cryoballoon Ablation System (Medtronic, Inc.). In all patients single TsP was performed by Brockenborough needle and 8F sheath (Mullins transseptal guiding introducer, St Jude Medical, Minnetonka, MN, USA). TsP was performed with guide of TEE and fluoroscopy. The 8F sheath was exchanged for 300cm 0.035inch J guidewire and then was utilized to left superior pulmonary vein. Then the outer diameter 15Fr, inner diameter 12Fr Ts catheter (Flex Cath, Medtronic, Minneapolis, MN) was introduced to LA along the guidewire. Inside the sheath the arctic front balloon was introduced to LA and the balloon was inflated. Once inflated and pushed against the pulmonary vein (PV) ostium, PV occlusion was evaluated by dye injection. After flushing the line with saline, N2O was pumping into balloon for freezing. After that, thawing, deflation of balloon and pulling back the system were performed in an order. Because in all patient single TsP was performed, the mapping catheter for evaluating the isolation PV could be introduced to LA only after arctic front system was pulled back. During the whole procedure activated clotting time was maintained above 300 seconds with supplement of heparin infusion as required. After CBA procedure all patients were in sinus rhythm. There was no acute complication during hospital stay.

Post Ablation Treatment And Follow-Up

After the day of CBA procedure all patient underwent TTE to evaluate the pericardial effusion. Oral anti-coagulant (OAC) and low molecular weight heparin (LMWH) therapy was started at the same day with CB. When the INR level reached the target[2,6], LMWH was stopped. OAC therapy was continued at least 3 months, and then anti-thrombotic therapy was decided according CHA2DS2 VASc risk assessment of individual patient. Anti-arrhythmic therapy was introduced at least 3 months following the procedure to all patients and discontinued thereafter if the patient was free of AF relapse.

During follow-up period, the information about whether the patient suffered or died from ischemic cerebrovascular event/transient ischemic attack was obtained from medical records and patients were examined for signs and symptoms of ischemic cerebral emboli.

Statistical Analysis

Continuous data are expressed as mean+standard deviation, categorical data as number and percentages. Comparisons of continuous variables were done with Student's t tests or Mann-Whitney as appropriate and binominal variables with chi-square or Fischer test. Two-tailed p values <0.05 were considered significant. Statistical analyses were conducted using SPSS software (SPSS v11.5 IBM Inc., Chicago, IL, USA).

RESULTS

Patients and Baseline Echocardiographic Characteristics

Twenty-eight patients (15 females, mean age 55.8+15.5) with paroxysmal (n=24) or persistent (n=4) AF formed study group. There were no left or right ventricle dilatation/dysfunction or severe heart valve dysfunction in pre-ablation echocardiography. The mean E/E′ ratio was 7.6+2.2 and there was no patient with E/E′ ratio more than 15 in our study population. The other clinical and baseline TTE characteristics are given in Table 1.

Table 1. Baseline characteristics

Number of patients	28
Women, n (%)	15 (53.6)
Age, year	55.8+15.5
BMI, kg/m^2	29.9+4.6
Creatinine clearance*, mL/min	106.5+40.4
HT, n (%)	13 (46.4)
DM, n (%)	5 (17.9)
CHA2DS2 VASc score	1.0 (0–5)
Paroxysmal AF, n (%)	24 (85.7)
OAC treatment during TEE, n (%)	10 (35.7)
LA diameter/BSA, cm/m^2	2.22+0.24
sPAP, mmHg	30 (20–55)
E/E′ ratio	7.6+2.2

BMI, body mass index; HT, hypertension; DM, diabetes mellitus; HL, hyperlipidemia; AF, atrial fibrillation; TEE, transesophageal echocardiography; OAC, oral anticoagulant; LA, left atrium; BSA, body surface area; sPAP, systolic pulmonary artery pressure
*estimated creatinine clearance that is calculated by Cockcroft-Gault formula [[(140-age) x weight/73 x serum creatinine] x if woman 0.85]

Post-Ablation Follow-Up

Mean follow-up was 17.3+6.2 months. In the post-procedural TEE, iASD was detected in 11 (39.3%) patients. In all patients with iASD, there were left to right shunt in color doppler examination. Clinic and echocardiographic characteristics of patients are given in Table 2. No significant difference in clinic and echocardiographic characteristics was identified between the patient with or without residual iASD. In study group, post-ablation change in sPAP was not significantly different between two groups (p=0.805).

In our study, the mean duration of CBA procedure was 106.9+20.1 minutes and the mean duration of fluoroscopy was 106.9+20.1 minutes. The comparison of duration of CBA, fluoroscopy and follow up period between the patients with and without iASD are given in Table 3. Procedural duration in patients with and without iASD was 119.0+8.8 and 92.9+21.0 minutes, in order. The mean procedural time was significantly longer in patients with iASD than the patients without iASD (p=0.010).

We divided the study population into two subgroups according date of procedure to evaluate the learning curve. No significant difference in procedural time or iASD prevalence was observed between the patients that CBA performed in the first 3 month (n=14) and after the first 3 months (n=14) (p=0.699 and p=0.220).

In our study, nobody suffered or died from cerebrovascular event or transient ischemic attack during follow up period.

Table 2. Comparison of clinical and echocardiographic parameters between patient with or without iASD

	with iASD	without iASD	p
Sex, women, n (%)	5 (45.5)	10 (58.9	0.488
Age, year	50.4+15.8	59.3+14.7	0.138
BMI, kg/m^2	29.4+4.2	30.2+4.9	0.647
Creatinine clearance*, mL/min	92.6 (54–216)	93 (71–194)	0.746
HT, n (%)	5 (45.5)	8 (47.1)	0.934
DM, n (%)	1 (9.1)	4 (23.5)	0.619
HL, n (%)	1 (9.1)	4 (23.5)	0.619
CHA_2DS_2 VASc score	1.0 (0–2)	1.0 (0–5)	0.285
Paroxysmal AF, n (%)	10 (90.9)	14(82.4)	1.00
OAC treatment during TEE, n (%)	3 (27.3)	7(41.2)	0.689
Baseline TTE characteristics			
LA diameter/BSA, cm/m^2	2.24 (1.65–2.32)	2.21 (1.81–2.88)	0.639
sPAP, mmHg	27.5 (20–35)	30 (25–55)	0.077
E/E′ ratio	6.96+1.75	8.19+2.57	0.304
Postprocedural TTE characteristic			
sPAP, mmHg	30 (25–50)	30 (25–35)	0.383

iASD, iatrogenic atrial septal defect; BMI, body mass index; HT, hypertension; DM, diabetes mellitus; HL, hyperlipidemia; AF, atrial fibrillation; TEE, transesophageal echocardiography; OAC, oral anticoagulant; LA, left atrium; BSA, body surface area; sPAP, systolic pulmonary artery pressure
*estimated creatinine clearance that is calculated by Cockcroft-Gault formula [[(140-age) x weight/73 x serum creatinine] x if woman 0.85]

Table 3. The comparison of procedural characteristics and follow up time

	Duration of CBA (min)	p	Fluoroscopy duration (min)	p	Time between CBA and TEE (months)	p
with iASD	119.0+8.8	0.010	46.6+ 14.1	0.804	15 (6.0–24.5)	0.134
Without iASD	92.9+21.0		44.8+21.9		21 (6.0–26.0)	

iASD, iatrogenic atrial septal defect; CBA, Cryoballoon ablation; TEE, transesophageal echocardiography; min, minute

DISCUSSION

In experienced hand, transseptal puncture can be performed with minimal complication; but acute procedure related ASDs are inevitable. This study assessed the prevalence of iASD in patients undergoing transseptal catheterization with 15F sheath during cryoballoon ablation. The main findings of this study are (1) iASD was found to be present in 39.3% of patients by TEE during a mean follow-up time of 17.3+6.2 months[2]; no significant relationship between baseline characteristics of patient and development of iASD[6]; Procedural time was found to be only predictor of iASD in our population (119+8.8 minutes, p=0.010).

A relatively recent trail on patients undergoing PVI with second generation CB reported that iASD prevalence was 8.4% after 15.5 months median follow-up[7] and Cronin et al.[8] detected iASD in the 17.6 % and 2.4% of patients respectively CBA group and RFA group at 118.2+40.7 days follow-up. TTE was performed to detect iASD in both aforementioned studies. There are many invasive and non-invasive methods that are used to detect ASD. These are oximetry method, indicator-dilution method, two-dimensional (2-D) TTE and TEE. TTE has high sensitivity and specificity in detection ASD.[9] Moreover, addition of harmonic imaging, color doppler and provocative maneuver to TTE examination increases its sensitivity.[10] But in the presence of small defect (<5mm) and/or poor ultrasound wave transmission, TEE is superior to TTE.[11] In our study, dimension of iASD is 2mm in two patients, 4.5mm in three, 5mm in one patient and 5-6mm in five patients. Consequently, using of more sensitive diagnostic tool is thought to be the reason of higher rate of iASD in our study.

In our knowledge first report on iASD in the electrophysiology era was published by Fitchet et al.[11] In this research there was no iASD at 3 months after ablation procedure with 8Fr catheter. Afterwards Hammerstingl et al.[12] investigated iASD among the 42 patients that were divided into two groups, one that two 8Fr transseptal catheter utilized through two separate TsP and in the other two 8Fr catheter through the same, single TsP into LA. Although iASD incidence was as high as 29.6% in single TsP, no iASD was detected in two TsP group.[11] Furthermore, Rillig et al.[13] observed low incidence of iASD (3.7%, n=1) after PVI procedures through double TsP. Moreover, the incidence of iASD following PVI was founded to be significantly higher in the CBA group, which larger Ts (15F) catheter was used, compared to RF ablation group.[8,14,15] In MitraClip system the 22Fr transseptal catheter is used to reach mitral valve and iASD was found up to 50% of sixty-six patients at 6 months by TEE.[16] As a result of above-mentioned articles, smaller Ts punctures although multiple have higher tendency to close. Large sheath through interatrial septum might cause more damage to septum than small outer diameter.

As mentioned before the outer diameter, 15Fr Ts sheath was used in CBA in our study. Similar outer diameter, 14Fr Ts sheath is used to left atrial appendix (LAA) closure procedures. The incidence iASD was found to be 7% by transesophageal echocardiography at 12 months after LAA closure procedure.[17] The other procedure that larger, 8.5+14 Fr sheaths are used with remote robotic navigation system (RNS) in PVI procedure. iASD was detected by TEE in 21.1% of patients undergoing PVI with RNS.[18] In these procedures the iASD incidence was lower than our study beside same or larger outer diameter Ts catheter using. An explanation for that finding might be that more extensive sheath manipulation needed in PVI than LAA closure procedure and the position of the outer artisan sheath (in Robotic Navigation System) remains rather stable throughout the procedure as mainly the inner sheath is used for catheter navigation. Torquing and bending the sheath in many directions to reach PV antra, especially right lower PV, might cause higher level of shear stress and damage to septum. The intense of maneuvering might be more important factor of septum damage rather than overall diameter of sheath.

The first article directly reports the iASD after CB procedure in literature was published by Chan et al.[19] In that report the prevalence of iASD in the 9th month TEE after CB was 30%. Thereafter Sieira et al.[20] detected iASD by TEE in 20.5% of 39 patients at 11.7+8.2 months after CB procedures. Spontaneous closure of iASD with time was observed in previous researches.[13,17] No longer closure of iASD was observed after 3 years in patients with iASD undergoing CB ablation.[21] Davies et al.[22] observed presence of iASD in 7 out of 27 patients (26%) after median follow-up time of 553 days. Mugnai et al.[14] reported iASD prevalence was 22.5% of 127 patients at median 11.6 months. Yang et al.[15] detected iASD in 15.6 % of 141 patients at 1 year after CB operation. Linhart et al.[23] detected 37 iASD in 101 patients (37%) after median 2.9 years follow- up. Linhart et al.[23] reported nearest findings to our results. Different from all other study, patients who had PFO before intervention were included in Linhart's cohort. In our investigation the prevalence of iASD was at least 10% higher than in aforementioned articles except Linhart et al.'s[23] research. This inconsistency cannot be explained by methodology of echocardiography, difference in size or extent of manipulation of Ts sheath. The higher percentage of iASD in our study population might result from different patient characteristics or a statistical effect of small patient number in our trial.

Female sex, hypertension had been described as risk factors for iASD after CBA procedures[15,22]; but no demographic and baseline echocardiographic parameters was found to be predictor of iASD in our trail. Linhart et al.[23] reported that lower left atrial appendage flow velocity was associated with higher risk of persistence of iASD. In our study, left atrial appendage flow velocity was not measured before or after the procedure. In this study, CBA procedural time was found to be the only predictor of iASD. In some patients because of anatomic variation in LA the cannulation of PV antra, especially right inferior PV, is challenging. This challenge that increases in shear stress on septum is thought to be most likely one of the explanations of longer procedural time in patients with iASD. Consistent with our hypothesis, the atrial septal angle[7], left atrial operation time[15] and number of cryo-application[21] were described as iASD predictors. It might be speculated that experience of operator affects the procedural time and intense of sheath manipulation. We divided the study group into two according to date of CBA to evaluate the effect of learning curve on iASD incidence, but no significant difference in iASD rate and procedural time was detected between group. Low experience of operator (<25 procedures/year) and/or center (<50 procedures/year) were founded to increase in-hospital complications of AF ablation but chronic complication didn't search.[24] Despite we don't have acute complications in our study group, as result of prolongation of procedure duration the higher incidence of persistent iASD in our center where 28 cases were performed in 2 years might be the chronic complication of low operator experience.

The adverse clinical outcomes in patients with unrepaired congenital ASD include left-to-right shunt causing right ventricular volume overload, paradoxical embolism and atrial arrhythmias. iASD that required closure after CB PVI was reported 2 (1.9%) large size (10-10mm) by Chan et al.[21] and 2 (4.8%) Cronin et al.[8] Yang et al.[15] reported that the recurrence rate of in patients with iASD was significantly higher than patient without iASD (53.13vs.28.74%, P<0.05) and the analysis of CB and RF subgroup of the cohort was consistent with this finding. There was no significant difference in the 6-min walk test, new stroke and rehospitalization rate between iASD and non-iASD group. In our study population, no patient suffered from right ventricular failure or required closure of iASD, but recurrence AF rate was not searched. Large right to left shunt (RLS), atrial septal aneurysms, PFO size are known risk factors for paradoxical embolism and stroke[25] and long-term oral anticoagulation is recommended for patients with congenital ASD and AF[26]. In our study, RLS only in late cardiac cycle (>3 beats) was present in 4 (33.3%) patients. No patients died or suffered from any clinically significant cerebral ischemic event, during follow up period. Absence of high-risk criteria for paradoxical emboli, treatment with OAC at least 3 months, short-term follow-up period and small number of patients might be reasons that prevent clinically significant cerebral emboli in our study.

Limitations

The small number of patients and limited follow-up and retrospective design are the main limitations of our study. We did not perform immediate TEE which would have helped us to evaluate the closure rate or size of iASD in a different stage of follow-up. All patients were treated with OAC at least 3 months after CB procedure and then continued with anti-platelet or anti-coagulation therapy. This fact may affect the occurrence of systemic embolism. After AF ablation, cerebral emboli might be silent and could have been detected by specific imaging technique.[27] No specific imaging technique has been ruled out silent cerebral ischemia in our study.

CONCLUSION

In our study we investigate the residual iASD with TEE after CB procedures. iASD was detected by TEE in 11 (39.3%) patients at 17.3+6.2 months. Clinically significant cerebral ischemia or increase in sPAP that might be related to iASD was not observed during follow-up. CB procedural time was only predictor of iASD after TsP. this finding supports hypothesis that increase stress and damage might cause residual iASD. Further studies with larger population and longer follow-up might be required to confirm our findings.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara University Faculty of Medicine Clinical Researches Ethics Committee (Date: 13.01.2014, Decision No: 01-06-14).

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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Evaluation of metabolic parameters of microsatellites stable and instable colorectal cancer patients via PET/CT

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ABSTRACT

Aims: Microsatellite instability has been determined as an important indicator in selecting chemotherapy drugs in colorectal cancer. Within the scope of this research, we aimed to elucidate the pathology reports and determine whether the metabolic parameters detected by PET/CT differ in MSI-positive and negative patients.

Methods: A total of 35 patients were analyzed retrospectively. The patient population consisted of patients who applied to the Nuclear Medicine Department with a diagnosis of colon or rectum cancer, underwent PET/CT imaging for staging purposes, and were operated on.

Results: A total of 35 colon or rectum cancer patients were included in this retrospective analysis. When microsatellite instability was analyzed among the patients, it was found that female patients comprised 4 microsatellite instability-positive and 16 microsatellite instability-negative individuals. On the other hand, 5 of the males were microsatellite instability positive, and 10 were microsatellite instability negative. The mean SUVmax value was 16.4±8.2, SUVmean was 8.1±1.9, TLG was 392.4±520.8, and MTV was 26.5±25.4 in the microsatellite instability-positive individuals. On the other hand, the mean SUVmax value was 22.7±9.7, SUVmean was 5.2±2.2, TLG was 316.4±325.7, and MTV was 21.7±21.7 in the microsatellite instability-negative individuals.

Conclusion: With the advancement of image analysis technology, MTV, and TLG, volumetric indexes derived from 18F-FDG PET have been proposed for risk stratification of cancer patients. Regarding the outcomes of this research, the semiquantitative and metabolic parameters obtained by PET/CT are not different in colorectal cancer cases with instable and stable microsatellites.

Keywords: Colorectal cancer, microsatellite instability, positron emission tomography/computed tomography (PET/CT), mismatch repair genes (MMR), standardized uptake value (SUV)

INTRODUCTION

Colon Cancer is the third most common type of cancer among women and men worldwide. The average 5-year survival rate for colon cancer is 63%, and this rate is 90% in the early stage, 71% in the locally advanced stage, and 14% in the metastatic stage. In the current staging of colon cancer, Tumor size and depth, number of metastatic lymph nodes (LN), and the presence of distant organ metastases are used. The development of colorectal cancer (CRC) is thought to occur through 2 different mutational pathways called chromosomal instability or microsatellite instability.[1] Chromosomal instability is a common feature in 85% of colorectal cancers. The fact that it can be observed even in the smallest adenoma suggests that chromosomal instability occurs in the very early stages of colorectal cancer development. The microsatellite instability (MSI) pathway effectively develops 15-20% of colorectal cancers.[2] MSI is mainly caused by mutational inactivation of one of the four major mismatch repair (MMR) genes (MSH2, MLH1, MSH6, or PMS2).

Colon cancers with MSI features have different clinical and pathological features than microsatellite-stable ones. MSI has been defined as a positive prognostic factor in colorectal cancers. Tumors with high microsatellite instability (MSI-H) have less possibility of metastasis. It has been suggested that they have a better prognosis.[3]

MSI has been determined as an important indicator in selecting chemotherapy drugs in CRC.[4] Recent studies have shown that CRCs with MSI resist 5-fluorouracil (5-FU) chemotherapy and do not benefit from it.[5] MSI status is evaluated in the pathological sample after invasive

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surgery or biopsy. Therefore, noninvasive methods are needed to evaluate MSI status preoperatively and facilitate immunotherapy of CRC patients.[6]

The 2-[18F]fluoro-2-deoxy-Dglucose (FDG), a glucose analog, is used in Positron Emission Tomography/Computed Tomography (PET/CT). The combined use of PET and CT provides information about the tumor's anatomical and metabolic characteristics, thus enabling more precise staging. It is a noninvasive imaging method that allows diagnosis, staging, and prognosis determination with the metabolic parameters obtained during the study. Morphological changes in colorectal cancers have not yet been determined. The superiority of PET/CT over other radiological methods is that it can show the metabolic/functional changes in the tumor tissue in the early stages when it is not formed.[7] FDG PET/CT has proven useful in diagnosing, staging, detecting recurrence, and evaluating treatment response in CRCs. Response evaluation with PET/CT is performed by visual and/or semiquantitative standardized uptake value (SUV) measurement of glucose metabolism in addition to morphological imaging. It has an important place in determining prognosis.[8]

Previous studies compared metabolic parameters detected by PET/CT in patients with positive and negative MSI. Song et al.[9] found that MSI-H CRCs had higher Metabolic tumor volume (MTV), were younger than MSS types, and were mostly located in the right semicolon. Zhang et al.[10] stated that metabolic parameters obtained from 18F-FDG PET/CT can preoperatively predict the MSI status in CRC and show the best correlation with MTV50%. Li et al.[11] established the 18F-FDG PET/CT radionics prediction model, a noninvasive and objective mechanism for preoperatively diagnosing MSI status in patients with CRC.

Within the scope of this research, we aimed to elucidate the pathology reports and determine whether the metabolic parameters detected by PET/CT differ in MSI-positive and negative patients.

METHODS

A total of 35 patients were analyzed retrospectively. The patient population consisted of patients who applied to the Nuclear Medicine Department with a diagnosis of colon or rectum cancer, underwent PET/CT imaging for staging purposes, and were operated on. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from Dicle Universty Medical Faculty Ethics Committee for Nonınterventional Studies (Date: 20.12.2023, Decision No: 10).

Patients were required to fast for at least 6 h and have a blood glucose level of 140 mg/dL for the FDG PET/CT imaging. FDG at a dose of 0.1 mCI/kg was injected intravenously into the patients. After the injection, the patients were kept in a special lead-coated room for 1 hour for the medication to spread through the whole body, and a CT scan of the whole body (from vertex to knees) was performed. Subsequently, whole-body emission scanning was performed with PET. A 2016 model Siemens Horizon brand PET/CT device with 3D-TOF was used for imaging. The slice thickness of the device was 3 mm, and the images were created according to PET iterative and by the CT bp-LOR reconstruction processing method. The low-dose CT device used for anatomical detail and attenuation correction was adjusted to 80 mA and 120 kV (Siemens Healthcare, GmbH Henkestrasse 127, 91052 Erlangen, Germany). An ROI has been determined from the primary tumor location, and the SUVmax,SUVmean, MTV, and TLG have been calculated.

Pathological evaluation was made by immunohistochemical method. It was evaluated whether there was loss of expression. Preservation of expression was considered normal, and the presence of loss of expression was considered damage.

The MSS and MSI-positive cases were recorded regarding their pathology reports. A senior pathologist evaluated of resected specimens with Immuno-histochemical staining. Specifically, the general pathological types, differentiation grade, TNM stages, and the expression of MMR proteins (MLH1, PMS2, MSH2, and MSH6) were assessed.

Inclusion Criteria

Patients who applied to our institution with a diagnosis of colon or rectum cancer underwent PET/CT imaging for staging.

Exclusion Criteria

Patients with relapses who were previously operated on and individuals with another malignity.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 26.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data were given as descriptive values. For comparisons between groups, the "Kolmogorov Smirnov test" was used for two groups, and the "Pearson Chi-Square Test" was used to compare categorical variables. Student's t-test was utilized to compare SUV and other metabolic values of lesions. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

A total of 35 colon or rectum cancer patients were included in this retrospective analysis. The mean age of the patients was 56.2±13.4 years. Of the individuals, 57% (n=20) were female and 43% (n=15) were male. Microsatellite instability was detected in 9 patients, and in 26 patients, microsatellite instability was negative. The pathologic diagnosis was adenocarcinoma in 91% (n=32) of the individuals, while mucinous adenocarcinoma was observed in 9% (n=3). The baseline demographic characteristics of the study group are elaborated in Table 1.

Table 1. The baseline demographic characteristics of the study group

Age	56.2±13.4
Gender (Female/Male)	20/15
Microsatellite instability positive	9
Microsatellite instability negative	26
Pathologic diagnosis	Adenocarcinoma (n=32) Mucinous adenocarcinoma (n=3)

When microsatellite instability was analyzed among the patients, it was found that female patients comprised 4 microsatellite instability-positive and 16 microsatellite instability-negative individuals. On the other hand, 5 of the males were microsatellite instability positive, and 10 were microsatellite instability negative (Table 2).

The mean age of the microsatellite instability-positive patients was 64.2±12.4 years, and microsatellite instability-negative patients were 53.4±12.8 years (Table 2).

Table 2. Comparison of age, gender and metabolic parameters obtained from PET-CT imaging between microsatellite instability positive and negative groups

	Microsatellite instability positive (n=9)	Microsatellite instability negative (n=26)	P-Value
Gender (Female/Male)	4/5	16/10	p>0.05
Age (Year)	64.2±12.4	53.4±12.8	p>0.05
SUVmax	16.4±8.2	22.7±9.7	p>0.05
SUVmean	8.1±1.9	5.2±2.2	p>0.05
TLG	392.4±520.8	316.4±325.7	p>0.05
MTV	26.5±25.4	21.7±21.7	p>0.05

The mean SUVmax value was 16.4±8.2, SUVmean was 8.1±1.9, TLG was 392.4±520.8, and MTV was 26.5±25.4 in the microsatellite instability-positive individuals. On the other hand, the mean SUVmax value was 22.7±9.7, SUVmean was 5.2±2.2, TLG was 316.4± 325.7, and MTV was 21.7±21.7 in the microsatellite instability-negative individuals.

DISCUSSION

Microsatellites are repetitive DNA motifs closely associated with many important genes within the genome. These repetitive sequences consist of 1–6 nucleotides. Each microsatellite consists of two parts: a central core and peripheral flanks. The specificity of the microsatellite depends on the change in the number of repetitive units in the central nucleus. Microsatellites are much more distributed in the non-coding regions of genes. In addition, microsatellites are thought to play an important role in forming and rearranging chromosomal structures that may affect gene replication and expression.[12] Due to mutations or epigenetic changes in DNA mismatch repair (MMR) genes, the normal function of the DNA-MMR system is disrupted, and the number of microsatellite base pairs undergoes a change known as microsatellite instability (MSI). The normal tissue DNA repair system can correct DNA replication errors. However, the possibility of gene mutation increases due to the absence of MMR genes in tumor cells or errors in the replication repair process. MSI can be defined as a change in microsatellite length resulting from inserting or deleting a repeating unit, leading to new microsatellite alleles.[13]

According to the number of mutations of microsatellite regions, three different subtypes are formed: high levels of MSI (MSI-H), low levels of MSI (MSI-L), and stable microsatellite (MSS). Studies have shown that MSI plays an important role in the pathogenesis of malignant tumors and is closely related to the formation and prognosis of many malignancies. Most studies have revealed that patients with MSI-H levels have a better anti-tumor effect, the ability to inhibit tumor cell growth, and a better prognosis than those with MSI-L/MSS.[14]

MSI was first described in CRC. CRC can be divided into two, according to the different molecular mechanisms of MSI: CRC without a significant family genetic history and familial non-polyposis Lynch syndrome. Lynch syndrome is an autosomal dominant tumor syndrome caused by mutations in MMR strains, and 15% of CRC patients show DNA-MMR deficiency with MSI-H.[15] Most cases have MLH1 or MSH2 mutation or hypermethylation of the MLH1 promoter. Smyrk et al.[16] have shown that the tumors of people with MSI-H contain a high density of tumor-infiltrating lymphocytes, consisting of cytotoxic T lymphocytes, which can generate a specific anti-tumor immune response. Kim et al.[17] reported that patients with stage 1–3 MSI-H CRC

had a better clinical prognosis. Still, local recurrence and peritoneal metastasis were more common in these patients. Colon cancers with microsatellite instability show different clinical and pathological features. MSI is detected in more than 90% of patients with Hereditary Non-Polyposis Colorectal Cancer (HNPCC) and approximately 15% of sporadic colorectal cancers. Because sporadic colorectal cancers are much more common than hereditary forms, most tumors showing microsatellite instability are sporadic tumors.[18]

High-level microsatellite unstable (MSI-H) cancers are mostly located in the proximal colon. In 2/3 of HNPCC patients and more than 90% of patients with MSI-H sporadic colorectal cancer, the lesion is detected proximal to the splenic flexure.[19]

Although three methodologies have been utilized to determine MSI status: immunohistochemistry (IHC), polymerase chain reaction (PCR), and next-generation sequencing (NGS), due to their limitations, a non-invasive alternative is an unmet need. The heterogeneity of MSI-H status, poor DNA quality of biopsy samples, the invasive procedure, and the long duration period in their clinical application can be elaborated as downsides.[20,21] At this stage, FDG PET/CT may be positioned as a valuable molecular imaging modality that is less invasive.[22] Chung et al.[23] published that MSI status correlated with 18F-FDG uptake in gastric cancer.

Song et al.[9] used 18F-FDG PET/CT and demonstrated the relationship between MSI status and MTV in colorectal cancer. Their hypothesis that 18F-FDG PET/CT might be a helpful tool for noninvasively inferring MSI-H CRC patients was supported by their outcomes and confirmed with the results of Liu et al.[24] The 18F-FDG PET/CT reflected anatomic morphology and glucose metabolism, which contained lots of information about prognosis and treatment response. However, against these encouraging data, one should keep in mind that 18F-FDG PET/CT may have good prediction performance, but it cannot replace pathologic testing for examining MSI status.[25]

Jiang et al.[26] retrospectively analyzed the pretreatment parameters of PET and reported the highest diagnostic performance of MTV 3.0 and TLG 3.0 in predicting PD-L1 expression levels in CRC. Wu et al.[27] found that the quantitative imaging features derived from dual-energy computed tomography (DECT) achieved good predictive performance for MSI status in CRC patients. In addition, radiomics-based artificial intelligence, such as MRI-based deep learning models, also demonstrated optimal diagnostic capability for discriminating MSI from microsatellite stability. Wu et al.[27] stated that MTV with the percentage thresholds, rather than the fixed thresholds, showed better predictive performances of MSI. Liu et al.[24] reported that the metabolic parameters derived from 18F-FDG PET/CT could preoperatively predict the MSI status in CRC, with MTV 50% demonstrating the highest predictive performance and recommended using these parameters, the noninvasive evaluation of MSI can be achieved, and leverage immunotherapy in CRC patients.

In our study, we could not detect a significant difference in FDG uptake (SUVmax, SUVmean, MTV, and TLG) values between the microsatellite instability positive and microsatellite instability negative groups. Our findings do not fully coincide with the literature due to the small number of operabl CRC . Studies with larger series may provide a better understanding of the relationships between MSI status and FDG uptake values.

CONCLUSION

With the advancement of image analysis technology, MTV, and TLG, volumetric indexes derived from 18F-FDG PET have been proposed for risk stratification of cancer patients. Regarding the outcomes of this research, the semiquantitative and metabolic parameters obtained by PET/CT are not different in colorectal cancer cases with instable and stable microsatellites.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Dicle Universty Medical Faculty Ethics Committee for Non-interventional Studies (Date: 20.12.2023, Decision No: 10).

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.

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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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Data Availability
The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Original Article

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Assessment of biomarkers indicating activation of the complement system in pregnant women with fetal growth restriction

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ABSTRACT

Aims: To compare serum levels of sC5b-9, C3, C4, C1-INH, and CH50, which are indicators of complement system activation and regulatory processes, in pregnant women with and without fetal growth restriction (FGR).

Methods: This study enrolled eighty-six women with gestational age between 24 and 36 weeks. Maternal blood samples were obtained from 43 patients diagnosed with FGR and 43 from healthy pregnancies. Serum complement levels were measured using commercially available ELISA kits according to the manufacturer's instructions (SunRed, China).

Results: When the levels of complement activation biomarkers of pregnancies with FGR were compared with those of healthy pregnancies, the C1est level was significantly higher, C4 and CH50 levels were slightly lower, and Sc5b9 and C3 levels were similar.

Conclusion: While the exact role of complement activation in FGR remains fully elucidated, the elevated levels of C1-INH in women with FGR suggest a compensatory mechanism to mitigate thrombus formation and inflammation. This adaptive response may be a potential therapeutic target for improving placental function and pregnancy outcomes.

Keywords: Complement system, fetal growth restriction, pregnancy, placenta

INTRODUCTION

The complement system is an essential component of the innate immunity.[1] It acts as a bridge between innate and adaptive immunity and helps to clear immune complexes and apoptotic cells. Activation of the complement system is crucial for the immune system's ability to defend against pathogens; if it becomes excessive or targets the wrong areas, it can cause various disorders.[2,3] Studies have shown that the complement system is not only a defense mechanism against infection but is also involved in fundamental processes of pregnancy, such as placental angiogenesis and trophoblast invasion.[4-6] The complement system activity increases during pregnancy. However, complement inhibition is required at the implantation site during placental development and maintenance to maintain a normal placenta and ensure a healthy pregnancy. Abnormal or excessive activation of the complement system in the placenta is probably related to placental dysfunction, which can lead to pregnancy complications such as pre-eclampsia and fetal growth restriction (FGR).[7]

FGR is a significant obstetric condition affecting approximately 10% of pregnancies, in which the fetus does not achieve its full potential due to maternal, fetal, and placental factors. It is usually defined as a fetal abdominal circumference (AC) and estimated fetal weight (EFW) below the 10th percentile.[8] FGR increases the risk of perinatal morbidity and mortality and is associated with severe long-term health problems such as metabolic disorders and susceptibility to neurodevelopmental delays.[9,10] The placenta is vital during human pregnancy as it facilitates nutrient transfer, promotes immune tolerance, and adapts the mother's body to support the growing fetus.[11] Failure of deep placentation, underdevelopment of placental villi, reduced cytotrophoblast proliferation, and inadequate capillarization are common pathologies associated with FGR.[12,13]

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The complement system plays a crucial role in fetal growth restriction, as evidenced by various studies. Activation of the complement system, particularly through the C5a-C5aR interaction, has been identified as a key mediator of pregnancy loss and growth restriction.[14,15] In particular, soluble membrane attack complex (sC5b-9) complexes may directly affect placental functions by increasing cytokine synthesis and vascular permeability in endothelial cells.[16] Increased or decreased levels of C3 and C4 may indicate significant changes in the immune modulation capacity of trophoblast cells and the structural integrity of the placenta.[17] As C1-esterase inhibitor (C1-INH) is mainly involved in controlling the classical pathway of the complement system, abnormal changes in its levels may trigger abnormal complement activation at the maternal-fetal interface.[18,19] CH50, which reflects the total hemolytic complement activity in serum, is considered a general indicator of complement system activation.[20]

This study aimed to elucidate the role of the complement system in the pathogenesis of FGR and to provide new avenues for early diagnosis and management by comparing serum levels of sC5b-9, C3, C4, C1-INH, and CH50, which are indicators of complement system activation and regulatory processes, in pregnant women with and without FGR.

METHODS

In this prospective cross-sectional study conducted between 2021 and 2022, 86 singleton pregnant women participated, including 43 pregnant women with fetal growth restriction (FGR) and 43 healthy pregnant women, all between 24 and 36 weeks of gestation. All participants provided written informed consent after being informed of the study. This study was approved by the Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date: 26.05.2021, Decision No: 99). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Fetuses with congenital malformations or diagnosed genetic syndromes, multiple pregnancies, and pregnant women with chronic diseases (pre-existing diabetes, autoimmune disorders, current cancer diagnosis, human immunodeficiency virus, and hepatitis) were excluded.

In all women included in the study, gestational age was confirmed in the first trimester using ultrasound biometry based on crown-rump length and menstrual history. All fetuses underwent a complete anatomical scan and Doppler imaging. Estimated fetal weight (EFW) was calculated using a formula ithat included ultrasound measurements of biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL). The end-diastolic flow (EDF), resistive index (RI), pulsatility index (PI), systolic/diastolic velocity ratio (S/D), middle cerebral artery (MCA), ductus venous (DV), cerebroplacental ratio (MCA-PI/UA-PI), uterine artery pulsatility index were measured using Doppler velocimetry. All examinations were performed using an Arietta 850 ultrasound system (HITACHI, Tokyo, Japan).

The EFW was compared with the reference growth standard and evaluated as a percentile for gestational age. FGR was defined according to the following criteria: abdominal circumference (AC) and estimated fetal weight (FW) below the 3rd percentile, absence of umbilical artery (UA) end-diastolic flow (EDF), AC/estimated FW combination below the 10th percentile, and pulsatility index (PI) above the 95th percentile. In order to diagnose FGR, at least one of these parameters must be present before 32 weeks of gestation.[21] The control group comprised pregnant women without FGR.

Demographic and clinical data were obtained from the patients' medical files. Maternal factors analyzed included age, body mass index (BMI), gravidity/parity, miscarriage, and smoking. Perinatal outcomes such as mode of delivery, gestational age at delivery, indications for cesarean section, Apgar score, birth weight, neonatal sex, neonatal intensive care unit admission, neonatal morbidity, and mortality were analyzed.

Venous blood was collected from participants using heparinized tubes. Samples were centrifuged at 3000 RPM for 10 minutes to obtain serum. Serum samples were immediately frozen and stored at -80°C for subsequent analyses. Sc5b9, C3, C4, C1-INH, and CH50 levels were determined using commercially available ELISA kits according to the manufacturer's instructions (SunRed, China).

Statistical Analysis

G*Power version 3.1.9.7 was used for sample size estimation. According to Cohen's guidelines, it was calculated that 86 participants would be needed to detect significant differences between groups on the primary outcome measure with a medium effect size, an alpha value of 0.05, and a power value of 0.80. IBM SPSS v26 (USA) was used for the statistical analyses. Data are presented as medians and minimum and maximum values, numbers, and percentages as appropriate. The Kolmogorov-Smirnov test was used to determine the normal distribution of the numerical data. Where appropriate, The Mann-Whitney or chi-square test was used to compare numerical variables and proportions. The statistical significance level was set at $P<0.05$.

RESULTS

This study compared the serum concentrations of complement biomarkers between 43 women with healthy pregnancies in the control group and 43 women diagnosed with FGR. There were no significant differences in age, gravidity, parity, miscarriage, or BMI between the control and FGR groups (p>0.05) (Table 1). The FGR group exhibited lower gestational age, biparietal diameter, head circumference, abdominal circumference, femur length, estimated fetal weight, umbilical artery flow, and higher pulsatility index values in the uterine arteries than the control group (p<0.05). Fetal biometry and Doppler measurements are presented in Table 2.

Table 1. Maternal characteristics of the study groups

	Controls (n=43)	FGR (n=43)	Significance
Age (years)	29 (22-39)	29 (19-44)	0.726
Gravidity	2 (1-8)	2 (1-9)	0.704
Parity	1 (0-6)	1 (0-5)	0.332
Miscarriage	9 (20.9%)	10 (23.2%)	0.795
Smoking	3 (7%)	1 (2.3%)	0.306
BMI (kg/m²)	27.3 (21.1-39.7)	28.0 (18.4-40.0)	0.548

FGR: Fetal growth restriction, BMI: Body mass index
The Kolmogorov-Smirnov test was used to determine the normal distribution of the numerical data. Statistical significance was assessed using the Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. The statistical significance level was set at P<0.05.

The FGR group had lower Apgar scores, higher cesarean delivery and neonatal intensive care unit admission rates, and higher neonatal mortality and morbidity rates (P<0.05). Perinatal outcomes are presented in Table 3.

The median serum sC5b-9 concentration in the control group was 253.8 mg/L. In the FGR group, the median concentration was slightly lower at 251.6 mg/L. However, this difference was not statistically significant (p=0.431). Regarding C3 levels, both groups showed a median of 1.6 mg/L. The control group had a 1.2 to 2.5 mg/L range, while the FGR group was 0.3 to 2.0 mg/L, indicating no significant difference between the two groups (p=0.907).

Similarly, serum C4 levels were comparable between the two groups, with a median of 0.3 mg/L for controls (range 0.10 to 0.6 mg/L) and a slightly lower median of 0.2 mg/L for the FGR group (range 0.9 to 1.5 mg/L), which did not reach statistical significance (p=0.137).

Notably, the serum C1-INH concentration was significantly higher in the FGR group with a median of 83.4 mg/L (range 19.2 to 107.7 mg/L) compared to 68.4 mg/L (range 8.2 to 102.0 mg/L) in the control group (p=0.019). The CH50 levels were higher in the control group, with a median of 121 mg/L (range 13 to 179 mg/L), than in the FGR group, which had a median of 104 mg/L (range 65 to 133 mg/L). However, this difference was not statistically significant (p=0.083) (Table 4).

Table 2. Fetal biometry and Doppler parameters of study participants

	Controls (n=43)	Fetal growth restriction (n=43)	Significance
Gestational age by obstetric exam (w)	30 (24-35)	31 (25-37)	0.812
Gestational age by ultrasound exam (w)	31 (24-36)	27 (21-34)	0.001
Biparietal diameter (mm)	79 (59-90)	71 (51-85)	0.002
Head circumference (mm)	291 (217-332)	265 (199-311)	0.001
Abdominal circumference (AC) (mm)	269 (196-317)	225 (160-305)	0.000
AC percentile (%)	55 (6-90)	0 (0-8)	0.001
Femur length (mm)	58 (42-68)	50 (33-72)	0.003
Estimated fetal weight (EFW)	1700 (671-2762)	1016 (396-2570)	0.001
EFW percentile (%)	49 (9-98)	0 (0-9)	0.001
Absent end-diastolic flow	0	12 ()	
Umbilical artery pulsatility index (UA-PI)	0.9 (0.5-3.6)	1.1 (0.5-2.0)	0.001
Middle cerebral artery pulsatility index (MCA-PI)	2.0 (1.1-3.4)	1.5 (0.9-2.3)	0.001
Cerebroplacental ratio (MCA-PI/UA-PI)	2.1 (1.8-4.1)	1.4 (0.6-3.6)	0.001
Right uterine artery pulsatility index	0.8 (0.5-2.1)	1.5 (0.5-3.0)	0.001
Right uterine artery notch present	0 (0%)	17 (39.5%)	0.001
Left uterine artery pulsatility index	0.9 (0.4-1.7)	1.4 (0.6-4.0)	0.001
Left uterine artery notch present	0 (0%)	20 (46.5%)	0.001
Ductus venosus pulsatility index	0.6 (0.3-1.0)	0.6 (0.3-1.1)	0.318

Data are presented as number (%) or median (min-max). The Kolmogorov-Smirnov test was used to determine the normal distribution of the numerical data. Statistical significance was assessed using the Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. The statistical significance level was set at P<0.05.

Table 3. Perinatal outcomes of the study participants

	Controls (n=43)	Fetal growth restriction (n=43)	
Gestational age at delivery (weeks)	39 (33-41)	33 (25-37)	0.001
Mode of delivery			0.001
Vaginal	20 (46.5%)	6 (14%)	
Cesarean section	23 (53.5%)	37 (86%)	
Indications of cesarean section			
Fetal distress	6 (26.1%)	14 (38.9%)	
Previous cesarean section	11 (47.8%)	8 (22.2%)	
Abnormal labor	3 (13%)	1 (2.9%)	
Placental abruption	0 (0%)	4 (11.1%)	
The reverse flow of ductus venosus	0 (0%)	2 (5.6%)	
Preeclampsia	0 (0%)	4 (11.1%)	
Other	6 (12.9%)	3 (8.4%)	
Birth weight (g)	3190 (2390-4800)	1270 (440-2650)	0.001
Newborn gender			0.104
Female	18 (42.9)	26 (60.6)	
Male	24 (57.1%)	17 (39.5%)	
Apgar score at min 1	8 (1-9)	6 (0-8)	0.001
Apgar score at min 5	9 (2-10)	8 (0-9)	0.001
Admission to the neonatal intensive care unit	7 (16.3%)	35 (81.4%)	0.001
Neonatal mortality	1 (2.3%)	8 (18.6%)	
Neonatal morbidity	0 (0%)	3 (7%)	

Data are presented as number (%) or median (min-max). The Kolmogorov-Smirnov test was used to determine the normal distribution of the numerical data. Statistical significance was assessed using the Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. The statistical significance level was set at P<0.05.

Table 4. Studied complement biomarkers of the women with healthy pregnancy and FGR

	Controls (n=43)	FGR (n=43)	Significance
sC5b-9 (mg/L)	253.8 (171.9-2766.6)	251.6 (17.7-784.6)	0.431
C3 (mg/L)	1.6 (1.2-2.5)	1.6 (0.3-2.0)	0.907
C4 (mg/L)	0.3 (0.10-0.6)	0.2 (0.9-1.5)	0.137
C1-INH (mg/L)	68.4 (8.2-102.0)	83.4 (19.2-107.7)	0.019
CH50 (units/mL)	121 (13-179)	104 (65-133)	0.083

C1-INH: C1 esterase inhibitor, CH50: The total hemolytic complement, sC5b-9: Soluble membrane attack complex

DISCUSSION

Our study compared the serum levels of sC5b-9, C3, C4, C1-INH, and CH50 complement components between pregnant women with and without FGR. Our results showed that the serum C1-INH levels were significantly higher in women with FGR (p<0.05). C1-INH is mainly involved in controlling the classical pathway of the complement system, and abnormal changes in its levels may trigger abnormal complement activation at the maternal-fetal interface, leading to placental dysfunction and endothelial damage. C1-esterase inhibitor has been studied for its immunomodulatory effects, showing a reduction in proinflammatory cytokines and an increase in anti-inflammatory cytokines.[22] The literature shows that higher plasma levels of C1-inhibitor are associated with a lower risk of future venous thromboembolism.[23,24] In the case of FGR, higher levels of C1 esterase inhibitor may mean that the body is trying to stop thrombus formation and keep blood flow through the vessels open.C1-esterase inhibitor attenuates the inflammatory response during human endotoxemia.[25] In pregnant women with hereditary angioedema (HAE), a nanofiltered C1 esterase inhibitor was found to be safe and effective for managing HAE attacks during pregnancy, with a favorable risk-benefit profile and positive pregnancy outcomes.[26] Additionally, severe acute respiratory syndrome coronavirus-2 infection may lead to a deficiency in the C1 esterase inhibitor, potentially contributing to severe systemic abnormalities in patients with COVID-19.[27] These findings suggest that C1-esterase inhibitor modulates inflammatory responses and may affect fetal growth and development.

Complement system activity is increased during pregnancy. However, complement inhibition is required at the implantation site during placental development and maintenance to maintain a normal placenta and ensure a healthy pregnancy. Abnormal or excessive activation of the complement system in the placenta is

likely related to placental dysfunction, which can lead to pregnancy complications such as preeclampsia and FGR.[28]

Guillermina Girardi et al.[29] showed in their study of mice with spontaneous abortion and FGR that complement activation, especially C5a, is a crucial intermediate step in the development of antibody-independent placental and fetal damage. The study also suggested that complement activation may lead to an imbalance in the angiogenic factors necessary for proper placental development.

Lynch et al.[30] reported that increases in complement activation products in early pregnancy are associated with adverse pregnancy outcomes, including preeclampsia. The lack of a significant difference in serum C3 levels between our groups may suggest that alternative pathway activation may not be as critical in the etiology of FGR as other pregnancy complications. However, the consistency of C3 levels between both groups suggests that a basic level of complement activity is maintained during pregnancy and that it is essential to balance the protective and pathogenic roles of complement activation.

A mouse model was used in the study by Qu et al.[31] They demonstrated that deficiency of the C5 component provided a protective effect against fetal growth restriction and loss after unilateral uterine ischemia/reperfusion. These results suggest that C5 may be a potential vulnerability factor in these processes, and its deficiency may prevent adverse outcomes. In support of these findings, in a case described by Burwick and Feinberg[32], a patient with severe preeclampsia/HELLP syndrome at 26 weeks of gestation was treated with eculizumab targeting C5, resulting in a marked improvement in the clinical condition and complete normalization of laboratory parameters. Prolonged pregnancy treatment by 17 days. Inhibition of complement activation has shown promise in preventing angiogenesis failure and rescuing pregnancies affected by fetal loss and growth restriction.[33]

Derzsy et al.[2] emphasized that the C3a/C3 ratio and sC5b-9 levels are increased in preeclamptic pregnancies, indicating excessive complement activation. The fact that there was no significant difference in sC5b-9 levels between the control and FGR groups in our study suggests that the terminal pathway of complement activation indicated by sC5b-9 does not dominate FGR, unlike preeclampsia.

Limitations

The relatively small sample size, the use of a prospective cross-sectional design, and the examination of a limited number of complementary system components limit the generalizability of the findings and the establishment of causal relationships.

CONCLUSION

Although the exact role of complement activation in fetal growth restriction (FGR) remains fully elucidated, the elevated levels of C1-INH in women with FGR suggest a compensatory mechanism to mitigate thrombus formation and inflammation. This adaptive response may be a potential therapeutic target for improving placental function and improving pregnancy outcomes. Further research with a larger cohort and a comprehensive analysis of the complement system are necessary to confirm these findings and develop targeted interventions.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee. (Date: 26.05.2021, Decision No: 99).

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.

Availability of Data and Material

The data analyzed during the study are available from the corresponding author upon request.

Authors' 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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Pre-operative pulmonary risk assessment in surgery patients

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ABSTRACT

Aims: Postoperative pulmonary complications (PPC) that may develop after surgery are important causes of morbidity and mortality. PPCs cause a prolongation of hospital stays and an increase in hospitalization costs. The study aims to determine factors associated with PPCs to predict PPCs in surgical patients undergoing preoperative evaluation.

Methods: A retrospective cohort study was conducted at Şişli Hamidiye Etfal Training and Research Hospital using data from 200 patients referred for preoperative pulmonary evaluation from anesthesia and surgery clinics. This study analyzed the characteristics and outcomes of patients with PPC and those without PPC. The Canet pulmonary risk scores are used for PPC in all preoperative surgery patients. The study's primary endpoints are to determine the development of respiratory failure, bronchospasm/asthma, COPD exacerbation, atelectasis, pleural effusion, or pneumonia. The study also analyzed the effective respiratory function parameters for PPC development using a logistic regression model.

Results: The total study population included 200 patients with a median age of 53.5 years (aged between 19-88), 103 (51.5%) of whom were female. PPCs were observed in 38% (n=76) of the study group. There was a statistically significant difference between the patients in terms of the development of postoperative pulmonary complications according to gender (higher in males, p=0.001) and smoking (p=0.0001). Preoperative oxygen saturation (SpO2) and FEV1/FVC ratio were significant predictors of PPC development, and complications were more frequent in low-saturated patients (p=0.0001, p=0.013 respectively). The relationship between SpO2 and PPC was confirmed via logistic regression analysis. A one-unit increase in saturation reduced the occurrence of postoperative respiratory complications by 0.645-fold. The cut-off value for the saturation value was 97.5%, with a sensitivity of 46.8% and a specificity of 71.1% [p=0.0001, 95% CI, (0.521-0.798)].

Conclusion: In this study, the Canet (ARISCAT) score, a preoperative evaluation scale validated in Turkey that predicts postoperative pulmonary complications and mortality, was used. The Canet risk score is a simple risk score with moderate discriminatory performance for predicting PPCs. It may be useful in identifying individual patients at high risk of PPC and in the design of future studies to evaluate interventions to prevent these complications. However, a customized preoperative risk assessment system is needed for each patient.

Keywords: Preoperative pulmonary evaluation, postoperative pulmonary complication, surgical patients, pulmonary risk, Canet (ARISCAT) scoring

INTRODUCTION

Postoperative pulmonary complications (PPC) are important causes of morbidity and mortality. PPCs cause a prolongation of hospital stays and an increase in hospitalization costs.[1] Possible strategies to identify high-risk patients in the preoperative period, have been investigated. Modifiable risk factors should be evaluated to minimize postoperative complications. In the preoperative period anesthetic evaluation is aimed at detecting and treating patients at risk for the development of complications; hence, consultation with a pulmonologist will surely decrease morbidity and mortality.[2]

To pre-determine the risk of complications and mortality in patients who undergo surgery, preoperative evaluation should determine the factors that cause deterioration in pulmonary functions in the perioperative period. PPCs are usually the result of significant deterioration of pulmonary function due to surgery itself, anesthesia, or pharmacological applications.[3] The most important postoperative complications are respiratory failure, acute exacerbations of Chronic Obstructive Pulmonary Disease (COPD), pulmonary thromboembolism, pneumonia, prolonged mechanical ventilation, and atelectasis.[4]

Atelectasis, pneumonia, respiratory failure, and tracheobronchial infection can be listed among the main PPCs. The most common postoperative complication is atelectasis. The primary cause of mortality has been reported

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as pneumonia. In addition, revealing the potential risk factors for pulmonary complications enables the prediction of complications by determining preventive strategies for these patients. In previous studies, preoperative risk factors for the development of PPC were investigated for specific surgical groups, such as upper abdominal interventions[5], esophagectomy[6], and total knee arthroplasty.[7]

Pulmonary complications are frequently seen postoperatively in patients due to multifactorial causes. The surgical intervention, the anesthesia method, and the preoperative risk factors of the patients play an important role. The risk factors associated with demographic characteristics and anesthesia include obesity, smoking, age, comorbidities, and the effectiveness of postoperative pain treatment, as well as the type and duration of anesthesia. The surgical risk factors include the duration of the intervention, the surgical technique, and the size of the incision.

We used the Canet scoring system (Figure 1) and PFTs (pulmonary function tests) data in the Assessment of Respiratory Risk in Surgical Patients in our hospital. The factors in the Canet scoring system include age, preoperative arterial oxygen saturation in the air, acute respiratory infection in the previous month, preoperative anemia, upper abdominal or intrathoracic surgery, duration of surgery, and emergency surgical intervention.[9]

Independent predictors of risk for PPCs		Risk score
Age, years		
≤ 50		0
51–80		3
> 80		16
Preoperative SpO_2, %		
≥ 96%		0
91–95%		8
≤ 90%		24
Respiratory infection in the last month		
No		0
Yes		17
Preoperative anemia (HbO_2 ≤ 10 g/dl)		
No		0
Yes		11
Surgical incision		
Peripheral		0
Upper abdominal		15
Intrathoracic		24
Duration of surgery, hours		
≤ 2		0
2–3		16
> 3		23
Emergency procedure		
No		0
Yes		8
Risk class	Number of points in risk score	Pulmonary complications rates
Low risk	<26 points	1.6%
Intermediate risk	26–44 points	13.3%
High risk	≥45 points	42.1%

PPC postoperative pulmonary complications

Figure 1. ARISCAT (Canet) risk index[9]

Our study shows that gender, smoking status, comorbidities, respiratory symptoms like dyspnea, findings from respiratory exams like expiratory rhonchus, respiratory function exams (preoperative oxygen saturation, SpO2), and pulmonary function tests (PFT) can all help figure out if someone will have a PPC. The aim of the study is to show how accurate these tests can be.

Our study aims to identify all factors that may affect the development of PPCs in surgical patients and minimize pulmonary risk by predicting PPC during the preoperative period. Additionally, clinic also uses the Canet scoring system and respiratory system evaluation tests, like preoperative SpO2 and PFT parameters, to figure out the pulmonary risk before surgery in people who already have respiratory diseases or who have just been diagnosed with respiratory diseases. We aim to reduce the risk of PPC by implementing effective pulmonary improvement approaches.

METHODS

Ethical Considerations

All procedures were followed by the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval was granted from Şişli Hamidiye Etfal Training and Research Hospital Clinical Researches Ethics Committee (Date: 06.09.2022, Decision No: 2144). As this was retrospective research, no informed consent was obtained from participants.

Study Population

Between January 1, 2022, and August 1, 2022, our Chest Diseases outpatient clinic examined 200 patients who were referred for preoperative pulmonary evaluation from the anesthesia and surgical clinics at Health Sciences University Şişli Hamidiye Etfal Hospital.

Inclusion criteria: Patients over the age of 18, regardless of gender, male or female, who underwent surgical intervention or surgical treatment and who requested a preoperative pulmonary evaluation were included in the study.

Exclusion criteria: Patients under 18 years of age, patients who were not suitable for preoperative pulmonary evaluation, and patients with psychiatric diseases were not included in the study.

Study Design

A retrospective cohort study was conducted at Şişli Hamidiye Etfal Hospital using data from 200 patients who were referred for preoperative pulmonary evaluation from anesthesia and surgery clinics. The patients were divided into two groups for the study. Group 1 comprised individuals who did not develop any PPCs, while Group 2 comprised those who did. The analysis was carried out on patients with complete data files. As this was a retrospective study, we did not obtain any consent forms from the patients.

The postoperative period was considered to be 1 week. Canet pulmonary risk scores were used to evaluate the risk of PPCs in all preoperative surgery patients (Figure 1). The Canet scoring system factors that we use for the assessment

of respiratory risk in surgical patients in our hospital were recorded. The scores were obtained from the hospital's electronic database.

Data Collection

As part of this study, we analyzed the data of 200 patients who were assessed at the Şişli Hamidiye Etfal Training & Research Hospital Pulmonology Outpatient Clinic between January 1, 2022, and August 1, 2022. The data of patients is gathered from their files and also from the hospital's database. Information such as the patient's age, gender, chronic conditions, symptoms, duration, lab results, treatments, readmissions, ongoing symptoms, hospitalizations, ICU admissions, and mortality was documented in the case follow-up form.

The Canet pulmonary risk scores (low arterial oxygen saturation before surgery, recent acute respiratory infection, age, anemia before surgery, upper abdominal or intrathoracic surgery, surgery lasting at least 2 hours, and emergency surgery) and admissions to the intensive care unit were looked at in the past. The primary endpoint of the study was to evaluate PPC, which includes respiratory failure, bronchospasm or asthma, acute COPD exacerbation, atelectasis, pleural effusion, or pneumonia The study's secondary endpoints were comparisons of ICU admission rates and 1-month mortality rates between patients with and without PPCs. A prediction index was created that determines the respiratory function parameters (SpO2 and PFT) that are effective in predicting the development of PPC (logistic regression prediction model).

Statistical Analysis

The IBM SPSS 26.0 package program was used in the statistical analysis of the study. Descriptive statistics (frequency, percentage, mean, standard deviation, etc.) of the patients in the study were calculated. The Chi-square test was used for categorical data, the independent samples t-test, or the Mann-Whitney U test was used for continuous (numerical) data based on the normal distribution status. These tests were used to compare demographic data, clinical features, PFT results, and Canet risk classification results based on the status of having respiratory complications after surgery. Receiver Operating Characteristic (ROC) curves were used to evaluate the predictive ability of preoperative SpO2, Forced Vital Capacity (FVC), Forced Expiratory Volume in One Second (FEV1), and FEV1/FVC rates for postoperative PPCs in each diagnostic group. Logistic regression analysis was conducted to determine the factors influencing PPC development. Cut-off values were computed to identify the risk factors associated with each variable, including risk score, PFT results, and saturation levels, on PPCs. All statistical analyses were evaluated at the 95% confidence interval, and significance was evaluated at the $p<0.05$ level.

RESULTS

Basic Characteristics

The total study population included 200 patients. The demographic characteristics of patients are shown in Table 1. The mean age in Group 1 (PPC negative, n=124) was 59.4±15.4 years (range 19-85 years), and in Group 2 (PPC positive, n=76), mean age was 62.51±13.8 years (range 19-88 years). While the groups were similar in terms of age distribution and mean age ($p>0.05$). PPCs were not detected in 75 (60.5%) female patients in Group 1, whereas they were detected in 48 (63.2%) male patients in Group 2. The gender distribution between the groups with PPC (positive) and without PPC (negative) showed a statistically significant difference ($p<0.001$). Group 1 (PPC-negative) had a higher proportion of non-smokers (59 patients, 47.6%) compared to Group 2 (PPC-positive), and in Group 1 there are more ex-smokers (42 patients, 55.3%). This comparison suggests non-smoking is a significant factor in preventing PPCs. There was a difference in the prevalence of gastrointestinal (GI) disease between the groups, with 14 patients (11.3%) in Group 1 (PPC-negative) and 1 patient (1.3%) in Group 2 (PPC-positive). However, this difference was not statistically significant.

Table 1. The comparisons of the demographic characteristics of PPC (-) and PPC (+) groups

	Postoperative Pulmonary complication		p
	Group 1 PPC(-) (n=124)	Group 2 PPC(+) (n=76)	
Age	59.4±15.4	62.51±13.8	0.188
≤50	31 (25)	15 (19.7)	0.391
51-80	85 (68.5)	54 (71.1)	0.709
>80	8 (6.5)	7 (9.2)	0.472
Gender			
Male	49 (39.5)	48 (63.2)	0.001**
Female	75 (60.5)	28 (36.8)	0.001**
Smoking status			
Smoker	30 (24.2)	19 (25)	0.898
Non-smoker	59 (47.6)	15 (19.7)	0.0001**
Ex-smoker	35 (28.2)	42 (55.3)	0.0001**
Comorbidities disease			
No	6 (4.8)	5 (6.6)	0.6
Cancer	19 (15.3)	19 (25)	0.09
HT	17 (13.7)	7 (9.2)	0.342
HD	7 (5.6)	7 (9.2)	0.337
GISD	14 (11.3)	1 (1.3)	0.009**
COPD	14 (11.3)	16 (21.1)	0.061
Asthma	29 (23.4)	11 (14.5)	0.126
DM	3 (2.4)	1 (1.3)	1
Other	15 (12.1)	9 (11.8)	0.957

*:p<0.05; **: P<0.01, PPC: Postoperative pulmonary complications, PPC (-): Without Postoperative pulmonary complications, PPC (+): with Postoperative pulmonary complications, HT: Hypertension, HD: Heart disease, GISD: Gastrointestinal system Disease, COPD: Chronic Obstructive Pulmonary Disease, DM: Diabetes mellitus

The clinical features of patients are shown in Table 2. Preoperative respiratory symptoms were significantly more frequent in Group 2 (PPC positive) compared to Group 1 (PPC negative) (77.6% vs. 20.2%, p=0.002). Preoperative SpO2 was measured preoperatively, with an average of 96.78±1.7. The majority of patients (82.5%, n=165) had SpO2 levels at or above 96%. SpO2 reflects the oxygen level in your blood and can be an indicator of potential respiratory problems.

Table 2. The comparisons of the clinical features of PPC (-) and PPC (+) groups

	Postoperative Pulmonary complication		p
	Group 1 PPC(-) (n=124)	Group 2 PPC(+) (n=76)	
Respiratory symptoms			
Normal	25 (20.2)	4 (5.3)	0.004**
Dyspnea	70 (56.5)	59 (77.6)	0.002**
Chest pain	19 (15.3)	11 (14.5)	0.87
Cough	10 (8.1)	2 (2.6)	0.116
Physical examination findings			
Normal	26 (21)	0 (0)	0.0001**
Expiratory rhonchi	10 (8.1)	23 (30.3)	0.0001**
Expiration was prolonged	45 (36.3)	28 (36.8)	0.937
Breath sounds were coarse	41 (33.1)	21 (27.6)	0.42
Reduced breath sounds	2 (1.6)	4 (5.3)	0.203
Preoperative SPO2 (%)	97.2± 1.1	96.09± 2.2	0.0001**
<90%	0 (0)	5 (6.6)	0.007**
%91-95	10 (8.1)	20 (26.3)	0.0001**
≥96%	114 (91.9)	51 (67.1)	0.0001**
Preoperative anemia hemoglobin (g/dl)	12.65± 2	12.53± 2.4	0.904
≤10 g/dl	14 (11.3)	15 (19.7)	0.1
>10 g/dl	110 (88.7)	61 (80.3)	0.1
Prior diagnosis of pulmonary diseases			
Yes	47 (37.9)	48 (63.2)	0.001**
No	77 (62.1)	28 (36.8)	0.001**
Newly diagnosed pulmonary diseases			
Yes	34 (27.4)	46 (60.5)	0.0001**
No	90 (72.6)	30 (39.5)	0.0001**

**: p<0.01, PPC: Postoperative Pulmonary complications, Preoperative SPO2 (%): Preoperative oxygen saturation, PPC (-): Without Postoperative pulmonary complications, PPC (+): with Postoperative pulmonary complications

PPC patients are shown in Table 3. As you can see, respiratory failure was the most common PPC, affecting 34.2% (n=26) of patients with PPCs. Atelectasis (27.6%, n=21) and COPD/asthma attacks (21%, n=16) were also relatively frequent. Pneumonia (13%, n=10), bronchospasm (2.6%, n=2), and other complications (1.3%, n=1) were in group 2 patients. Overall, PPCs were observed in 76 out of 200 patients (38%).

Table 3. Distribution of PPCs for all patients

Variables (n=200)	n (%)
No	124 (62)
Atelectasis	21 (10.5)
Pneumonia	10 (5)
Respiratory failure	26 (13)
COPD or asthma attack	16 (8)
Bronchospasm	2 (1)
Other	1 (0.5)

COPD: Cronic Obstructive Pulmonary Disease, PPC: Postoperative Pulmonary complication

Table 4 shows PPCs according to PFT results. Preoperative SpO2 and the ratio of Forced Expiratory Volume in One Second (FEV1) to Forced Vital

Table 4. The comparisons of the PFT Results of PPC (-) and PPC (+) groups

PFT	Postoperative Pulmonary Complication		p
	Group 1 PPC(-) (n=117)	Group 2 PPC(+) (n=69)	
FVC	77.07±23.5	74±21.5	0.376
Normal (≥70%)	76 (65)	38 (55.1)	0.213
Abnormal (< 70)	41 (35)	31 (44.9)	
FEV1	76.33±25.3	70.12± 20.7	0.086
Normal (> 80)	54 (46.2)	22 (31.9)	0.146
Mild obstruction (60-80)	35 (29.9)	28 (40.6)	
Abnormal (<60)	28 (23.9)	19 (27.5)	
FEV1/FVC	81.1±12.2	77.25±12th	0.013*
Normal (≥70%)	102 (87.2)	51 (73.9)	0.029*
Abnormal (<70)	15 (12.8)	18 (26.1)	

*: p<0.05, PPC: Postoperative pulmonary complication, PFT: Pulmonary function test, FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, PPC (-): Without postoperative pulmonary complications, PPC (+): With postoperative pulmonary complications

Capacity (FVC) were also important indicators of PPC development. Complications were more common in people who were not fully saturated (p=0.0001, p=0.013, respectively). (FEV1: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity).

Table 5 shows PPCs according to the results of the Canet classification. Individuals with higher pulmonary risk scores (≥45) had an increased risk of PPC (p=0.0001).

Table 6 shows the effect of SpO2, FEV1/FVC ratio, and Canet risk score on PPC. Logistic regression analysis was

Table 5. The comparisons of risk factors for postoperative pulmonary complications PPCs between CANET classification PPC (-) and PPC (+) groups

	Postoperative Pulmonary Complication		p
	Group 1 PPC (-) (n=124)	Group 2 PPC (+) (n=76)	
Pulmonary risk score	29.57± 13.7	52.72± 12.4	0.0001**
Low (below 26 points)	47 (37.9)	0 (0)	
Medium (26-44 points)	64 (51.6)	16 (21.1)	0.0001**
High (45 points and above)	13 (10.5)	60 (78.9)	

**: p<0.01, PPC: Postoperative pulmonary complication, PPC (-): Without postoperative pulmonary complications, PPC (+): With postoperative pulmonary complications

used to find the risk factors (SpO2, FEV1/FVC ratio, and Canet risk score) that are effective in the development of PPCs. The relationship between SpO2 and PPC was confirmed through logistic regression analysis (p=0.0001). A one-unit increase in SpO2 reduced the risk of postoperative respiratory complications by 0.645 times result was confirmed via logistic regression analysis (95% CI, 0.645 (0.521 to 0.798; p=0.0001). A one-unit increase in the Canet risk score increases the risk of PPCs 1.143 fold (95% CI, 1.143 (1.101 to 1.185; p=0.0001). The relationship between the FEV1/FVC ratio and PPC was confirmed via logistic regression analysis (95% CI: 0.95-0.999; p=0.037), A one-unit increase in the FEV1/FVC value reduces the risk of PPCs by 0.974 times.

Table 7 shows the cut-off value for postoperative pulmonary complications of the Canet risk score, FEV1/FVC, and SpO_2 for postoperative respiratory complications. The cut-off value for the SpO2 value was 97.5%, with a sensitivity of 46.8% and a specificity of 71.1% (p=0.0001).The cut-off value for Canet risk score scores was 42.5, with a sensitivity of 81.6% and a specificity of 81.5%, which is statistically significant (p=0.0001). The cut-off value for the FEV1/FVC ratio was 81.5%, with a sensitivity of 55.6% and a specificity of 58.0%, achieving statistical significance (p=0.013).

DISCUSSION

Our study revealed that certain factors contribute to the development of PPCs, such as gender, smoking, and comorbid diseases (such as GIS disease). From our analysis of demographic data, shortness of breath emerged as a significant respiratory symptom, while expiratory rhonchi were highlighted as a key finding during the examination. Additionally, preoperative SpO2 values, as well as a previous diagnosis of respiratory system disease, were identified as potential risk factors for PPCs. In addition, our study showed that newly diagnosed respiratory system diseases can also increase the likelihood of developing PPCs.

Among the 200 patients, 38% (n=76) developed at least one PPC within the first month, with respiratory failure (13%, n=26) being the most common, followed by atelectasis (10.5%, n=21). Notably, 26 patients suffered from respiratory failure and 21 from atelectasis. We classified them separately because, even though atelectasis can contribute to respiratory failure, they are distinct conditions.

Table 6. The effect of CANET risk score, of FEV1/FVC, of SpO_2 on PPC

	χ^2	p (Model)	-2 Log likelihood		R^2	
Canet risk score	107.299	<0.0001**	158.327		0.565	
Postoperative pulmonary complication	**B**	**Standard Error**	**Wald**	**Sd**	**p**	**Exp(B) CI**
Risk score	0.133	0.019	50.838	1	0.0001**	1,143 (1,101-1,185)
Constant	-6.040	0.837	52.041	1	0.0001**	0.002
FEV1/FVC	4.343	0.037*	240.979		0.032	
Postoperative respiratory complication	**B**	**Standard Error**	**Wald**	**Sd**	**p**	**Exp(B) CI**
EV1/FVC	**-0.026**	**0.013**	**4.230**	**1**	**0.04***	**0,974 (0,95-0,999)**
Constant	**1.540**	**1.013**	**2.313**	**1**	**0.128**	**4.666**
Preoperative SpO_2	21.043	0.0001**	244.582		0.136	
Postoperative respiratory complication	B	Standard Error	Wald	Sd	p	**Exp(B) CI**
SpO_2	-0.439	0.109	16.190	1	0.0001**	0.645 (0,521-0,798)
Constant	41.992	10.565	15.797	1	0.0001**	1.725

PPC: Postoperative pulmonary complication, SpO2 (%): Preoperative oxygen saturation, FEV1: Forced Expiratory Volume in One Second, FVC: Forced Vital Capacity, Confidence Intervals (CI)

Table 7. The cut-off value for PPC of CANET risk score, of FEV1/FVC, of SpO2 on PPC

Risk Factor (PPC)	AUC (%)	Cut off	p	Sensitivity (%)	Specificity (%)
CANET risk score	0.892 (0.848;0.937)	42.5	0.0001**	81.6%	81.5%
FEV1/FVC	0.609 (0.525;0.693)	81.5	0.013*	55.6%	58.0%
Preoperative SpO_2	0.656 (0.576;0.736)	97.5	0.0001**	46.8%	71.1%

PPC: Postoperative pulmonary complication, SpO2 (%): Preoperative oxygen saturation, FEV1: Forced Expiratory Volume in One Second, FVC: Forced Vital Capacity

In a study conducted by Su H. et al.[10], the development of PPC was associated with prolonged hospital stays. These results may show that the development of PPC will prolong the length of stay in the hospital, as well as that prolonged hospitalization may lead to the development of PPC. Previous studies have shown that PPCs such as pulmonary embolism, atelectasis, pneumonia, and respiratory failure prolong the length of stay in the hospital. The results and PPCs obtained in our study are the results of the first 7 days after surgery.

PPCs like pneumonia and atelectasis are major concerns after surgery. They can significantly worsen a patient's condition by causing dyspnea, requiring additional oxygen support, and potentially leading to respiratory failure. This not only increases morbidity, or the likelihood of experiencing negative health effects, but can also raise mortality risk. Additionally, PPCs often necessitate extended hospital stays, placing a strain on healthcare resources and increasing costs.[11] Pulmonary complications increase the length of stay in the hospital, the need for prolonged mechanical ventilation, or a predisposition to secondary infections. Diaphragm movements are restricted, and bronchial mucociliary activities decrease during the intubated period of the patients. Petrar et al.[12] and Sogame et al.[13] reported that PPCs not only prolong the length of hospital stay but also increase the rate of patient admission to the intensive care unit. It has been reported that atelectasis is the most common postoperative pulmonary complication.[14]

Examination of postoperative complications reveals that pneumonia, respiratory failure (indicated by oxygen demand), bronchospasm, atelectasis, and pleural effusion are among the most frequent and concerning issues encountered. These complications can significantly prolong hospital stays, increase healthcare costs, and worsen patient outcomes. [15] In a study conducted by Ko E. et al.[15], the importance of pulmonary complaints in the preoperative period was proven to be similar to the data previously published in the literature. The risk of developing postoperative complications increases in patients with preoperative cough, sputum, and dyspnea complaints.

When the postoperative period (30 days) data were examined, the low, medium, and high-risk scoring system of Canet et al.[16] was applied in our study, and its usefulness was demonstrated. Preoperative smoking cessation has been shown to result in longer-term cessation at a higher rate than smoking cessation at other times.[17] In our study, gender (being male) and active smoking were found to have clinically significant effects on the risk of PPC.

Those who have had an upper respiratory tract infection in the last month before the operation are more likely to develop PPC. Perioperative smokers have an increased risk of major morbidity and mortality, including 30-day PPC, surgical site infection, ICU hospitalization, wound complications, neurological complications, and septic shock.[18,19] In the study by Bluman et al.[20], postoperative pulmonary complications were more common in smokers.

Two observational studies evaluating PPC rates using pulmonary function tests like FVC and the FEV1/FVC ratio found a significant correlation. Patients with lower FVC and FEV1/FVC had a higher incidence of PPCs. This suggests that lower pulmonary function might be a risk factor for developing PPCs[21,22] Wong et al.[23] investigated 105 patients undergoing cardiothoracic surgery with severe chronic obstructive pulmonary disease (defined as FEV1<1.2 L and FEV1/FVC ratio <75%). In their cohort, an FEV1/FVC ratio of less than 50% constituted one of the five independent risk factors. Three other independent factors (abdominal surgery, ASA class IV or V, and general anesthesia) provided higher odds ratios in the multivariate model.[24] In another study of 460 patients undergoing abdominal surgery, FEV1<61%, FEV1 between 61 and 79%, the presence of ischemic heart disease, undergoing cancer surgery, and age were each identified as independent risk factors. The strongest single factor is FEV1<61%.[25]

When the results of our study were examined, the FEV1/FVC ratio was an essential predictor of PPC development, and complications were higher in low-saturated patients (p=0.013). Table 6, Table 7, and Figure 2, Figure 3, and Figure 4 show the relationship between the FEV1/FVC ratio and PPC, which was confirmed via logistic regression analysis (p=0.037). A one-unit increase in FEV1/FVC value reduces the occurrence of PPCs by 0.974 fold.

This 10-year study at Lille University Hospital investigated ventilation parameters and their association

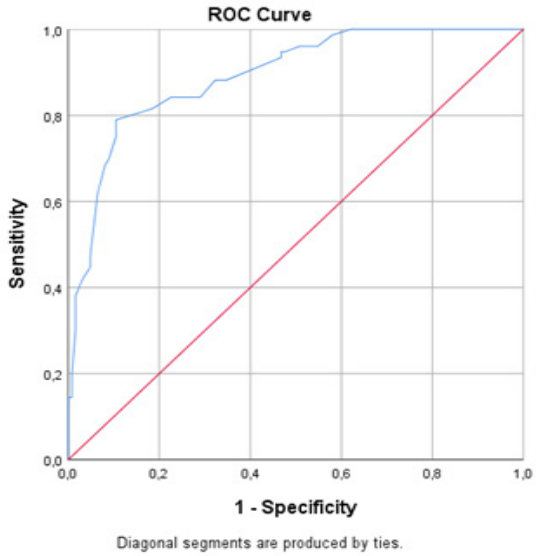

Figure 2. ROC curve CANET risk score on postoperative pulmonary complication (ROC Analyse)

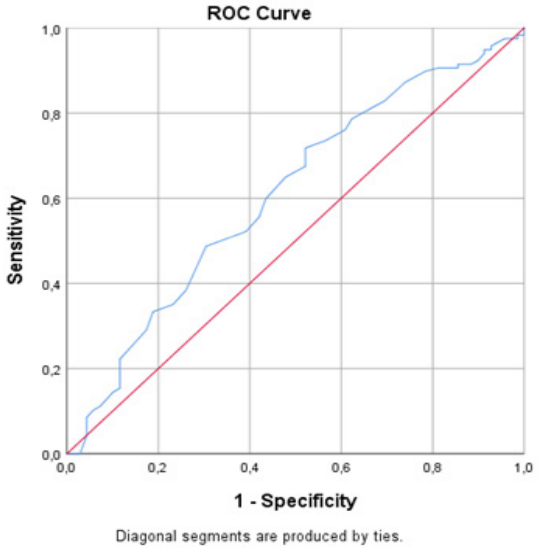

Figure 3. ROC curve value FEV1/FVC on postoperative pulmonary complication (ROC Analyse)

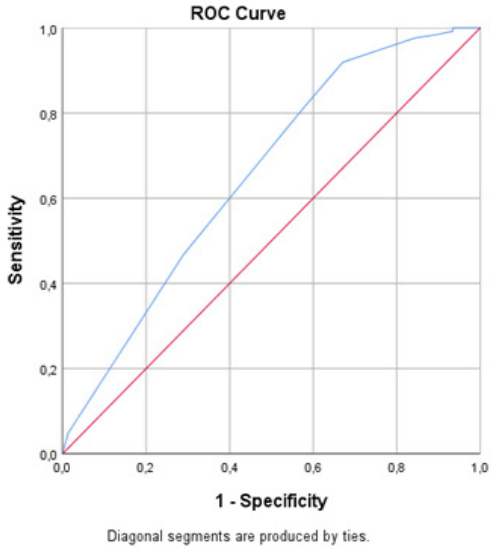

Figure 4. ROC curve value SpO2 on postoperative pulmonary complication (ROC Analyse)

with PPC development. These included lower estimated body weight, lower expiratory tidal volume (the amount of air exhaled with each breath during mechanical ventilation), reduced dynamic respiratory system compliance (the lungs' ability to expand and contract), and higher estimated mechanical power (likely referring to the work required by the ventilator to move air). Also, things that happened during surgery, like SpO2 levels below 96% and ETco2 levels dropping, were found to be independent predictors of PPCs.[26]

Limitations

The findings of our study have some limitations. Firstly, since our study was retrospective and observational, our study was designed with the data in the patient file. Therefore, no data other than these could be added to our study. Second, the sample size was insufficient, which may require a larger cohort for more robust statistical analyses. Thirdly, since there is no standard scoring and evaluation system for each pulmonologist in preoperative pulmonary evaluation, the potential for bias exists due to each expert's experience.

CONCLUSION

In our study, various factors such as gender, smoking status, comorbidities, respiratory symptoms (ex. dyspnea), respiratory examination findings (ex. expiratory rhonchus), prior diagnosis of pulmonary diseases, newly diagnosed pulmonary diseases, and respiratory function examinations (preoperative SpO2 and PFT measurements) are examined to determine how effective and reliable they can be in predicting PPCs.

At the same time, we used the Canet risk scoring method, which has been previously validated in Turkey, to estimate the risk of PPCs. This scoring system helps determine preoperative risks in patients who wish to receive treatment in Chest Disease outpatient clinics. Our study concluded that the Canet scoring method, using PFT parameters, is an effective tool for preoperative evaluation and risk prediction, especially in estimating the risk of PPC and mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Şişli Hamidiye Etfal Training and Research Hospital Clinical Researches Ethical Committee (Date: 06.09.2022, Decision No. 2144).

Informed Consent

As this was retrospective research, no informed consent was obtained from participants.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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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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Review

MEDICINE PALLIATIVE CARE

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Acute fibrinous and organizing pneumonia

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ABSTRACT

Acute fibrinous and organizing pneumonia (AFOP), first described histologically by Beasley et al.1 in 2002. AFOP occurs in a wide age range (38-78 age) and in a non-sexist spectrum of patients. Although idiopathic cases have been reported, case series in which the underlying etiology is known. The histologically specific pattern is the presence of organized intra-alveolar fibrin and is the essential parameter for diagnosis. There is no significant difference in the radiological pattern except for the halo finding in the comparison of AFOP and COP. In patients presenting with an acute and more fulminant picture, the clinic presents with rapidly worsening respiratory failure. The main complaints were fever, cough and chest pain respectively. Since AFOP is a diagnosis of exclusion, most patients are diagnosed with pneumonia that does not respond to treatment or has delayed resolution during follow up. Although the clinical presentations of the fulminant and subacute forms of AFOP are different, a clear distinction cannot be made for treatment due to the high mortality of the fulminant form. The prognosis is poor in acute fulminant cases.

Keywords: Organized pneumonia, interstitial lung disease, acute acute fibrinous

INTRODUCTION

Acute fibrinous and organizing pneumonia (AFOP), first described histologically by Beasley et al.[1] in 2002, has a specific histological pattern of its own and in 2022 American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JPS) and AssociacionLatinoamericana de Torax (ALAT) consensus is an idiopathic interstitial lung disease excluded from idiopathic pulmonary fibrosis (IPF).[2]

ETIOLOGY

AFOP occurs in a wide age range (38-78 age) and in a non-sexist spectrum of patients.[3] Although idiopathic cases have been reported, case series in which the underlying etiology is known and AFOP has been attributed to it has been published.[4-8] Basically, the most common condition is the diagnosis of AFOP with a tissue sample followed by a background rheumatologic disease, immunosuppressive comorbidities or drug use (Table).

In studies on COP patients, it was reported that those with intra-alveolar fibrin consistent with AFOP had a worse prognosis, but no significant radiological involvement difference was reported except for the halo finding.[4]For this reason, although it was thought to be a subtype of COP in the first evaluation, it has been accepted as a different interstitial lung disease in current guidelines due to its histological differences, and there is no consensus in favor of increased mortality or significant clinical difference in the co-occurrence of COP-AFOP compared to other etiologies.

Table. Probable etiologies in acute fibrinous and organizing pneumonia[5]

Autoimmune diseases	Polymyositis, dermatomyositis, ANCA-related vasculitides, rheumatoid arthritis, systemic sclerosis
Lung diseases	Cryptogenic organizing pneumonia, hypersensitivity pneumonia, acute and chronic eosinophilic pneumonias
Drug utilization	Statin, bleomycin, busulfan, abacavir, decitabine
Immunosuppressive conditions	Lung transplantation, myelodysplastic syndrome, monoclonal gammopathies, autologous bone marrow transplantation,
Infectious conditions	Human Immunodeficiency Virus, previous influenza, Pneumocystis carinii, Mycoplasma subtypes, history of fungal infection
Post-treatment conditions	Radiation pneumonitis
Hematological malignancies	Hodgkin lymphoma, acute myeloid leukemia, multiple myeloma
Other	Environmental exposure (Charcoal, hairspray), Idiopathic

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HISTOLOGY

The histologically specific pattern is the presence of organized intra-alveolar fibrin and is the essential parameter for diagnosis.[1] After the presence of fibrin, there are findings in favor of other organizing pneumonia, but the absence of histological involvement specific to other interstitial lung diseases (such as the presence of hyaline membrane and eosinophils) is required for the diagnosis of AFOP. Diagnosis of AFOP with these three elements (intra-alveolar fibrin, organizing pneumonia and other specific involvement exclusion) can be seen patchy in 90% of preparations in multiple biopsies or large tissue samples. Granulomatous infiltration, bronchopneumonia or abscess formation is also not seen in AFOP, which is performed with the presence of fibrin and patchy involvement to exclude from diffuse alveolar damage, and with the absence of eosinophils to exclude from eosinophilic pneumonia.[9]

CLINIC

In patients presenting with an acute and more fulminant picture, the clinic presents with rapidly worsening respiratory failure. In a single-center study conducted by Gomes et al.[5], in which mostly patients who applied in the form of subacute AFOP were evaluated; the main complaints were fever (69.2%), cough (46.2%) and chest pain (30.8%), respectively. Chills, fatigue, and weight loss can also be seen as nonpulmonary symptoms. Examination findings are mostly non-specific and can be summarized as auscultation findings consistent with pneumonia and the presence of desaturation that varies according to the clinic.

RADIOLOGY

In a study stating that there is no significant difference in the radiological pattern except for the halo finding in the comparison of AFOP and COP, Onishi et al.[4] argue that both the halo finding and the pathologic result are more significant in imaging and sampling performed at the early stage of the disease. Although there is a publication stating that a single nodule containing an air bronchogram in patients diagnosed at an early stage quickly turns into a common density, also in ground-glass, with multilobe involvement, there are studies that focus primarily on bilateral involvement of the lung basal progressively.[9] In most cases, the expected radiological appearance is consolidation in tomography sections in almost all patients and ground-glass accompanying consolidation, although it varies from study to study.[4,5,10]

DIAGNOSIS

Since AFOP is a diagnosis of exclusion, most patients are diagnosed with pneumonia that does not respond to treatment or has delayed resolution during followup. The role of laboratory results in diagnosis seems to be limited due to increased infective parameters in almost all patients.[5,9] In most cases, patients have increased C-reactive protein (CRP) levels either at the time of diagnosis or at follow-up, and CRP elevation is more pronounced in patients with AFOP than in other interstitial lung diseases.[5] Although different results were reported in studies evaluating the level of interleukin-6 (IL-6), they agreed that an increase was observed.[5,11] Pulmonary parenchyma biopsy is required for a definitive diagnosis, since the differential diagnosis cannot be made from the clinical presentation complaints of the patients and there may be a wide variety of diseases and exposure history in the background.

TREATMENT

Although the clinical presentations of the fulminant and subacute forms of AFOP are different, a clear distinction cannot be made for treatment due to the high mortality of the fulminant form. As seen in the literature, case reports are also seen in two general categories, like AFOP. In the first case, it is often not possible to prepare for the differential diagnosis in patients presenting with a very rapidly progressive clinic that cannot be differentiated from acute respiratory distress syndrome (ARDS). High-dose intravenous pulse methylprednisolone (1000 mg/day for 3 days) is used as a treatment in patient groups considered in favor of interstitial lung disease.[12] In the survivors of this group and in patients with slower clinical progression, mostly diagnosed with AFOP as a diagnosis of exclusion in the differential diagnosis, treatment protocols are mostly initiation of 1 mg/kg/day methylprednisolone as a maintenance steroidand 5-10 mg/day with weekly or biweekly titration. It consists of reducing the dose to methylprednisolone. As seen in the pulmonary vasculitis treatment protocols given for steroid sparing treatment and prevention of end organ damage, cases of AFOP using azathioprine, methotrexate, cyclophosphamide, tacrolimus and cyclosporine have been reported, but due to the number of treatment superiority and comparison, these additional treatment modalities have not been specified yet.[4,12]

It is known that the use of empirical antibiotics in acute fulminant cases is included in the treatment because ARDS and sepsis cannot be ruled out. There are no comparative studies on the role of adjunctive antibiotic therapy in these cases, with a group not given antibiotics. In the review of Kuza et al.[9], studies on both anti-biotherapy and steroid use were evaluated and although there is no definite treatment regimen, the steroid dose mentioned is appropriate in most patients, antibiotic therapy is started empirically by making a diagnosis of exclusion in subacute

patients, and non-steroid immunomodulatory agents are given, but mostly these patient groups are treated. It was stated that he currently has a rheumatological disease and, on the basis of this disease, the need for additional immunosuppressive therapy to steroids was decided.

Although the duration of total steroid use is not clearly known, there are studies that successfully indicate 3-month early titration regimens and long-term low-dose steroid use for up to 24 months.[13,14] Since the average steroid response is 90% or more in the publications, the current treatment should be steroid-based if there is no underlying rheumatological pathology, and if there is a life-threatening condition (such as ARDS), this steroid should be administered as an intravenous pulse of 1 g/day for at least three days. If it is not, it is given as 1 mg/kg/day or as a dose where treatment response is seen according to clinical experience. In maintenance, close follow-up with progressive dose reduction after clinical response is seen can be done on a weekly or biweekly dose titration schedule. In this follow-up or initial diagnosis, if additional immunosuppressive therapy is needed, it should be planned to reduce the total steroid dose with combined therapy, especially in elderly patients.

PROGNOSIS

Survival expectancy is high in fulminant cases that survive the acute condition and in patients with subacute follow-up, and in most case series, patients who meet this definition survived to study termination. The absence of mortality in subacute patients seen in the first description is consistent with case series with similar clinics. Studies also support the relatively good survival in patients presenting with subacute clinics.[5,10]

CONCLUSION

Acute fibrinous and organizing pneumonia (AFOP) is an uncommon histologic interstitial pneumonia form that is distinguished by intra-alveolar fibrin deposition and organized pneumonia. Although the clinical manifestations of the fulminant and subacute forms of AFOP are different, a clear differentiation cannot be made for treatment due to the significant mortality of the fulminant form.

ETHICAL DECLARATIONS

Referee Evaluation Process

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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Letter to Editor

MEDICINE PALLIATIVE CARE

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Entecavir induced gynecomastia-triggering factor or coincidence?

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Dear Editor,

Hepatitis B is still a viral infection agent that constitutes an important health problem all over the world. Despite widespread vaccination and innovations in treatment modalities, it still maintains its effectiveness. It is very important to diagnose this viral infection on time, to include the patient in the follow-up protocol, to determine the severity of the disease and then to plan the optimal treatment steps.[1-4] Entecavir is an important nucleoside analogue that plays a pivotal role in the treatment of HBV.[5] In this case report, it was aimed to present a case report regarding bilateral gynecomastia and mastodonia while receiving entecavir treatment.

A 52-year-old male patient who was followed up for chronic HBV was admitted to the hospital with complaint of painful enlargement in both breasts. He stated that his current complaints started about 15-20 days ago and that he had never encountered such a situation before. The patient had a known history of chronic HBV infection for 2 years and had been using 0.5 mg/day entecavir tablet therapy for HBV infection for the last 5 months. The patient stated that he did not use any medication other than entecavir treatment. He also declared that he did not use alcohol, cigarettes or other herbal medicines. None of the family members had such a disease or complaint. In physicial examination, his general condition was good, he was conscious and cooperative, and also he was overweight. Physical examination revealed no abnormal findings. In blood tests, serum aspartate aminotransferase was 45 IU/L and alanine aminotransferase levels was 50 IU/L, respectively. Serum direct bilirubin level was within normal range and total bilirubin level was 1.3 mg/dL. His creatinine level was 1.2 mg/dL and other routine biochemical tests were within normal range and HBV-DNA level was also negative. Ultrasonography imaginary revealed minimal splenomegaly with chronic liver disease appearance. On upper gastrointestinal endoscopy examination, esophageal varices were not noticed. Mammography and breast ultrasonography were performed and gynecomastia was confirmed. Follicle-stimulating hormone, luteinizing hormone, testosterone, TSH levels were within normal range.

According to patient's clinical picture, physical examination, biochemical tests, ultrasonography and endoscopic evaluation entecavir-induced gynecomastia was considered to be possible and entecavir treatment was stopped. After stopping entecavir, it was first considered to switch to tenofovir treatment, but this was not done due to the creatinine level being at the upper limit and the GFR value. After 2 weeks, entecavir treatment was restarted because the mastodinia was resolved and the clinical condition was stable. No recurrence of mastodynia was observed and gynecomastia did not progress.

The etiology of gynecomastia is multifactorial, however, in most cases, no demonstrable cause can be identified.[6] In fact, gynecomastia can occur due to physiological, pathological or pharmacological reasons. As a result, regardless of the situation that causes gynecomastia, the underlying pathophysiological mechanism of gynecomastia is increased estrogen levels, decrease in androgen levels, defect or insensitivity of androgen receptors.[6,7] Thus, gynecomastia develops as the ratio of hormonal levels changes. It is estimated that approximately 10-25% of all clinically detected gynecomastia cases are caused by various medications.[6] Entecavir is a nucleoside analog used in the treatment of chronic hepatitis B infection and reduces viral replication. It began to be widely used all over the world after it was approved by the US Food and Drug Administration in 2005.[8] The case of gynecomastia due to entecavir use has been reported very rarely in the literature. In the literature, the development of gynecomastia was first reported in a 55-year-old male patient using entecavir by Bayramıçlı et al.[9]

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As a result, patients treated with various agents during hepatitis B treatment should be closely monitored for treatment response and, of course, treatment side effects. Although the pathophysiological cause needs to be clarified, entecavir-induced gynecomastia may develop in patients. In this case, close monitoring of the patient and changing the treatment if the clinical situation requires it may be an appropriate approach.

ETHICAL DECLARRATIONS

Referee Evaluation Process
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