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RESEARCH ARTICLE

The Impact of Sarcopenia on Post-COVID Pulmonary Sequelae

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Abstract

Introductıon: Following COVID-19 pneumonia, some patients experience symptoms such as weakness, fatigue, dyspnea, exertional dyspnea, and a persistent cough. This condition is defined as post-COVID-19 syndrome. Residual chest CT findings can be detected in some of these patients. Sarcopenia, a concept reflecting skeletal muscle mass loss, is a condition that occurs during the development of many diseases. This study aims to investigate the impact of sarcopenia on pulmonary sequelae following COVID-19 infection.

Methods: A total of 142 patients were included in our study. Among them, 73 patients had post-COVID sequelae on CT scans and served as the patient group, while 69 patients had no sequelae on CT scans and formed the control group. Muscle measurements derived from thoracic CT scans were manually obtained using PACS software. The areas and densities of the total pectoral muscles at the upper half level of the T4 vertebra and the paraspinal muscles at the lower half level of the T12 vertebra were recorded.

Results: There were no statistically significant differences in the mean values of T4 vertebra total pectoral muscle area, T12 vertebra paraspinal muscle area, T4 vertebra pectoral muscle density and T12 vertebra paraspinal muscle density between the groups. However, both the patient and control groups were sarcopenic according to reference values

Conclusion: In our study, we could not find an association between lung CT findings, respiratory symptoms of the patients, and sarcopenia, which was the main focus. We attributed this to the separate mechanisms and pathophysiological processes of sarcopenia and pulmonary sequelae.

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Introduction

Since its emergence in Wuhan, China, in December 2019, the virus known as SARS-CoV-2 has spread worldwide, leading to the deaths of more than 60 million people and infecting millions more as of 2023.[1] It is well known that the disease can manifest with either asymptomatic or mild symptoms, while approximately 20% of cases exhibit severe symptoms requiring hospitalization. The morbidity and mortality of COVID-19 are predominantly associated with acute viral pneumonia and subsequent acute respiratory distress syndrome (ARDS).[2] Some patients who have recovered from COVID-19 may experience symptoms such as prolonged weakness, fatigue, dyspnea, exertional dyspnea, and persistent cough weeks after the initial infection, leading them to seek care at post-COVID follow-up clinics. This condition is defined as long COVID if the infection persists for more than 4 weeks, and as post-COVID syndrome if it persists for more than 12 weeks, according to the guidance from The British Medical Journal.[3] Several studies have indicated that there is a high incidence of post-infectious complications, particularly pulmonary fibrosis, following severe COVID-19 infection. Acute COVID-19 infection can result in long-term sequelae such as organizing pneumonia.[4] In some studies, histological patterns such as usual interstitial pneumonia, desquamative interstitial pneumonia, and acute organizing pneumonia have been identified in patient groups with residual findings after COVID-19 pneumonia.[5]

Sarcopenia, a concept that reflects the loss of skeletal muscle mass, is a physiological change that occurs during the development of many diseases. Since the European Working Group on Sarcopenia in Older People proposed diagnostic criteria for sarcopenia based on muscle mass, muscle strength, and physical performance in 2010, it has been recognized as an important factor for not only the elderly but also many other diseases.[6] Therefore, the presence of sarcopenia is associated with poor prognosis for many medical conditions. Measurement of the cross-sectional skeletal muscle area (SMA) at the L3 vertebral level using computed tomography (CT) and the calculation of the SMA index (SMI) by dividing it by the square of the height play a significant role in the evaluation of sarcopenia.[7] Another important concept closely related to sarcopenia is muscle quality, which refers to microscopic and macroscopic changes in muscle structure and composition. Fat infiltration in skeletal muscles, also known as myosteatosis, is one of the commonly used indicators for assessing muscle quality.[8] Measurement of muscle density in Hounsfield Units (HU) using CT provides information about muscle quality.

The aim of our study is to investigate whether there is a difference in terms of sarcopenia between patients who still have symptoms and residual lung changes on CT after recovering from COVID-19, and patients whose lung findings completely resolved on follow-up CT after COVID-19. In this study, we examined the impact of sarcopenia on pulmonary sequelae following COVID-19 infection.

Material and Methods

Ethics approval and consent to participate

This study was conducted at Ankara City Hospital as an observational and retrospective. Permissions were obtained from the hospital ethics committee (file number: E2-23-3716) and the Ministry of Health of the Republic of Turkey. All procedures were in accordance with the Declaration of Helsinki. Written informed consent was not required, and verbal information and consent were sufficient.

Thoracic CT Imaging Technique

The imaging technique used for all patients was standard, and non-contrast-enhanced thoracic CT scans (GE Healthcare, Chicago, Illinois, USA). The scans were obtained in the supine position during inspiration. The imaging parameters were set as follows: tube voltage of 100 kV, tube current ranging from 50 to 399 mAs, and a slice thickness of 1.3 mm.

Evaluation of Thoracic CT

The evaluation of lung parenchyma on thoracic CT scans was performed separately by two radiologists with more than 5 years of experience in thoracic CT interpretation. The patients were classified into two groups based on the presence or absence of abnormal CT findings. In cases where there was a disagreement in the findings, a consensus was reached by consulting a third radiologist experienced in thoracic radiology. We assessed lung parenchymal findings for fibrosis/possible fibrosis. We looked for the following changes: ground-glass opacities (GGO), consolidation, subpleural irregular reticulation (SIR), traction bronchiectasis (TB), honeycombing, parenchymal bands, subpleural lines, and subsegment atelectasis. In the control group, none of these paren-

chymal findings were present. The measurements of muscle parameters were performed by two different radiologists at different times. Muscle measurements derived from thoracic CT scans were manually obtained using PACS software (GE Healthcare, Chicago, Illinois, USA) (Figure 1). The areas and densities of the total pectoralis muscles at the upper half level of the T4 vertebra and the paraspinal muscles at the lower half level of the T12 vertebra were recorded. Both pectoralis minor and pectoralis major muscles were included in the measurements of the pectoralis muscles area. The areas of muscle structures were recorded in cm^2 and their densities were recorded in HU, after using standard density threshold between -29 to +150 HU for excluding non-muscle structures.

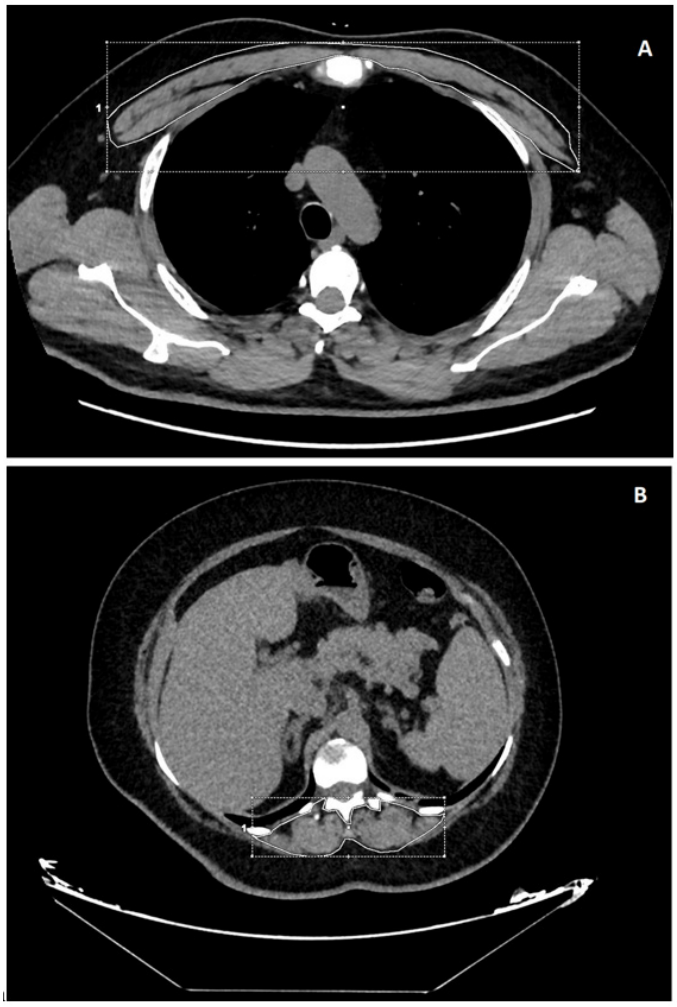

Figure 1 A: Region of interest (ROI) was circumscribed manually by two different radiologists for obtain PMA and PMD at the upper half level of T4 vertebra. B: PSMA and PSMD at the lower half level of T12 vertebra.

Case Selection, Demographic, and Clinical Data

Our study included adult patients (aged 18 years and older) who previously had COVID-19 infection and were being followed up at COVID-19 outpatient clinics. Many patients had ongoing complaints such as chest pain, shortness of breath, fatigue, and persistent cough. Most patients had undergone multiple thoracic CT scans after a negative PCR test for COVID-19. In our study, we considered the most recent CT scan performed after a minimum of 4 months following the negative test result. We included 150 patients in the study. Firstly, we divided them into two groups: those with abnormal lung CT findings (73 patients) and those with normal lung CT findings (69 patients) in the control group. Eight patients were excluded from the study due to positioning errors and artifacts that hindered proper measurements. Along with the demographic data of the patients, we evaluated comorbid conditions such as smoking history, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and heart disease, as well as hospitalization, intensive care unit admission, mechanical ventilation, and the use of steroid and antiviral treatments.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics Standard Concurrent User V26 (IBM Corp., Armonk, New York, USA) statistical software package. Descriptive statistics were presented as the number of units (n), percentage (%), mean (M), standard deviation (SD), median (Mdn), minimum (min), and maximum (max) values. The normal distribution of numerical variables was evaluated using the Shapiro-Wilk normality test. Differences between two dependent measurements were evaluated using the dependent samples t-test. Intra-class correlation coefficient (ICC) was examined to assess the agreement between evaluators. A correlation coefficient of 70% or higher is considered sufficient for reliability. The Cronbach's alpha and ICC coefficients were found to be above 0.70 for all items and total score, indicating sufficient reliability. Independent samples t-test was used to examine differences in numerical variables between study groups, and chi-square tests (Pearson chi-square/Fisher's exact test) were used to evaluate the relationships between categorical variables and groups. One-sample t-test was used to determine the differences between means and population means. A p-value of less than 0.05 was considered statistically significant.

Results

Clinical and Demographic Data of the Cases

A total of 142 patients were included in our study. Among them, 73 patients had post-COVID sequelae on CT scans and constituted the patient group, while 69 patients had no sequelae on CT scans and formed the control group. The mean age of the patient group was 64, and the mean age of the control group was 60. In the patient group, the CT scans were evaluated on average 6.5 months after the resolution of the disease, while in the control group, the CT scans were performed 6 months later. The patient and control groups were predominantly male, accounting for 74% and 58%, respectively. Females comprised 26% of the patient group and 42% of the control group. Additionally, we evaluated the patient and control groups based on their smoking history, hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), heart disease, as well as hospitalization, requirement for mechanical ventilation, and treatment methods (Table 1). The mean age of the patient group was statistically higher than that of the control group. Other characteristics were similar between the groups.

Table 1: Clinical and demographic data

Characteristics	Patient Group n=73	Control Group n=69	p-value
Age	64.84±8.98	59.99±9.13	**0.004**
Gender (male)	54 (%74)	40 (%58)	0.066
CT Scan after negative PCR (month)	6.59±3.13	6.14±2.07	0.977
Smoking	34 (%46.6)	32 (%46.4)	0.981
Hypertension	34 (%46.6)	23 (%33.3)	0.108
Diabetes Mellitus	13 (%17.8)	13 (%18.8)	0.874
Chronic obstructive pulmonary disease (COPD)	8 (%11)	2 (%2.9)	0.061
Heart Disease	16 (%21.9)	11 (%15.9)	0.364
Hospital History	67 (%91.8)	57 (%82.6)	0.101
Mechanical Ventilation	6 (%8.2)	1 (%1.4)	0.063
Antiviral Treatment	72 (%98.6)	69 (%100)	0.329
Steroid Treatment	63 (%86.3)	56 (%81.2)	0.406

Summary statistics presented as mean ± standard deviation (SD) and frequency (n) with percentage (%).

Evaluation of Lung Parenchymal Findings with CT

In our patient group, BCO was present in 66 patients (89.2%), subpleural reticulation was present in 64 patients (86.5%), traction bronchiectasis was detected in 44 patients, and consolidation was observed in 4 patients (5.4%) (59.5%) (Figure 2 and 3). Additionally, 7 patients (9.5%) exhibited honeycombing, 2 patients (2.7%) showed volume loss, 14 patients (18.9%) had parenchymal bands, 28 patients (37.8%) displayed subpleural lines, and 15 patients (20.3%) presented subsegment atelectasis (Table 2). None of these lung parenchyma findings were observed in our control group.

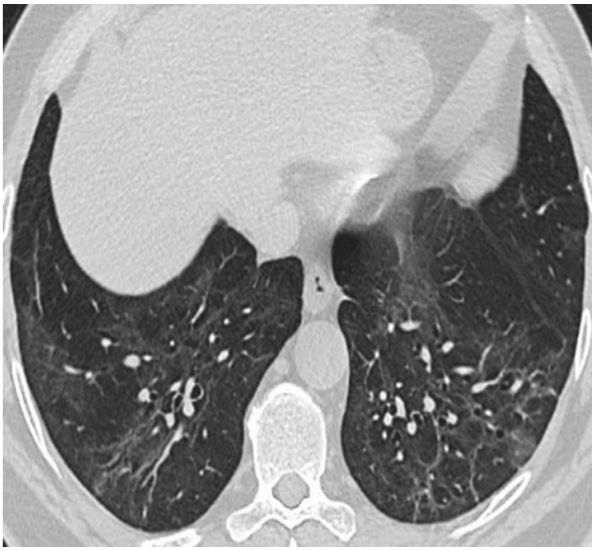

Figure 2: Post-COVID 9th month CT scan ground-glass opacities (GGO), subpleural irregular reticulation at bilateral lower lobes

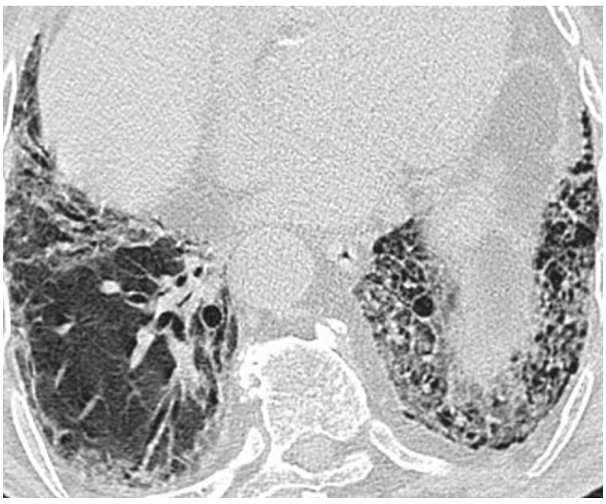

Figure 3: Post-COVID 14th month CT scan honeycombing and traction bronchiectasis at bilateral lower lobes

Table 2: Evaluation of Post-COVID Sequelae Changes by CT Scan

	n	%
Ground Glass Opacities (GGO)	66	89.2
Consolidation	4	5.4
Subpleural Reticular Pattern	64	86.5
Traction Bronchiectasis	44	59.5
Honeycomb	7	9.5
Parenchymal Bands	14	18.9
Subpleural Lines	28	37.8
Subsegmental Atelectasis	15	20.3

Evaluation of Thoracic Muscles with CT

In our study, the mean T4 vertebra pectoral muscle area (T4 PMA) was measured as 32.46 cm² and the T4 vertebra pectoral muscle density (T4 PMD) was 30.49 HU in the patient group. The mean T12 vertebra paraspinal muscle area (T12 PSMA) was determined as 40.91 cm², and T12 vertebra paraspinal muscle density (T12 PSMD) was 35.07 HU. In the control group, the mean T4 PMA was 31.66 cm², the T4 PMD was 31.42 HU, the mean T12 PSMA was 42.45 cm² and the T12 PSMD was 37.25 HU (Table3). There were no statistically significant differences between the groups in terms of T4 PMA, T12 PSMA, T4 PMD and T12 PSMD averages. When the agreement among the evaluators was examined, statistically significant excellent-level correlations were found (ICC-95% Confidence Interval).

Table 3: Muscle Analysis Results

		Patient Group (n=73)	Control Group (n=69)	Test Value	p
Evaluator 1	T4 PMA (cm²)	32.46±10.28	31.66±10.51	-0.909 *	0.363
	T4 PMD (HU)	30.49±10.35	31.42±10.91	-0.458 *	0.647
	T12 PSMA (cm²)	40.91±10.66	42.45±10.52	-0.821 *	0.412
	T12 PSMD (HU)	35.07±9.73	37.57±10.71	-1.753 *	0.080
Evaluator 2	T4 PMA (cm²)	32.2±9.95	31.72±10.52	0.704 *	0.481
	T4 PMD (HU)	30.4±10.2	31.28±10.77	-0.408 *	0.683
	T12 PSMA (cm²)	40.76±10.75	42.36±10.61	-0.967 *	0.333
	T12 PSMD (HU)	34.88±9.78	34.88±9.78	-1.743 *	0.081

*: Independent Samples t-Test (t); Summary statistics presented as mean ± standard deviation.
T4 PMA: T4 vertebra pectoral muscle area, T4 PMD: T4 vertebra pectoral muscle density, T12 PSMA: T12 vertebra paraspinal muscle area, T12 PSMD: T12 vertebra paraspinal muscle density, HU: Hounsfield Unit

In previous studies, the T4 PMA was reported as 41.6 cm² for males and 27.1 cm² for females,[9] while the T12 PSMA was stated as 56.0 cm² for males and 36.5 cm² for females.[10] Based on these values, we compared the measurements of our patient group. According to Table 4, both the first and second evaluators had similar average T12 paraspinal muscle measurements in females, but for other measurements, the study average was statistically lower than the population average.

Table 4: Comparison of muscle area measurements in the patient group compared to the previous average

		Gender	Mean±SD	Mean Value	Test Value	p
Evaluator 1	T4 PMA (cm²)	Male	36.77±7.66	41.6	-4.583	<0.001
		Female	20.43±6.31	27.1	-4.614	<0.001
	T12 PSMA (cm²)	Male	43.4±10.64	56.0	-8.615	<0.001
		Female	33.97±7.21	36.5	-0.984	0.383
Evaluator 2	T4 PMA (cm²)	Male	36.45±7.29	41.6	-5.091	<0.001
		Female	20.58±6.28	27.1	-4.529	<0.001
	T12 PSMA (cm²)	Male	43.21±10.82	56.0	-8.608	<0.001
		female	33.92±7.15	36.5	-1.023	0.320

One Sample t-test was used. SD: Standard deviation, T4 PMA: T4 vertebra pectoral muscle area, T4 PMD: T4 vertebra pectoral muscle density, T12 PSMA: T12 vertebra paraspinal muscle area, T12 PSMD: T12 vertebra paraspinal muscle density.

According to Table 5, the T12 muscle measurement taken from females in the study by the first evaluator was similar to the population average, but for other measurements, the study average was statistically lower than the population average. The same situation was applicable for the second evaluator as well.

Table 5: Comparison of muscle area measurements in the control group compared to the previous average

		Gender	Mean±SD	Mean Value	Test Value	p
Evaluator 1	T4 PMA (cm²)	Male	37.09±9.37	41.6	-3.048	0.004
		Female	22.69±6.79	27.1	-4.505	<0.001
	T12 PSMA (cm²)	Male	45.74±9.45	56.0	-6.866	<0.001
		Female	36.36±9.37	36.5	-0.105	0.917
Evaluator 2	T4 PMA (cm²)	Male	36.92±9.54	41.6	-3.107	0.004
		Female	22.98±7.00	27.1	-4.079	<0.001
	T12 PSMA (cm²)	Male	45.73±9.35	56.0	-6.866	<0.001
		female	36.21±9.51	36.5	-0.213	0.833

One Sample t-test was used. SD: Standard deviation, T4 PMA: T4 vertebra pectoral muscle area, T4 PMD: T4 vertebra pectoral muscle density, T12 PSMA: T12 vertebra paraspinal muscle area, T12 PSMD: T12 vertebra paraspinal muscle density.

Discussion

Sarcopenia is characterized by the progressive loss of skeletal muscle mass and quality associated with aging.[11] It is considered an independent negative prognostic factor in various diseases, including major surgeries, oncological, and cardiovascular diseases.[12-13] Sarcopenia can also affect respiratory muscles. As a result, it can impair the production of sufficient respiratory volume and the performance of high-force expiratory maneuvers.[14] One of the most current methods for evaluating sarcopenia is CT. It offers several advantages, such as providing detailed anatomical information, distinguishing between muscle, fat, and surrounding tissues, and easily calculating parameters such as muscle area and density. Some studies have shown that pectoral muscle analysis and segmentation derived from thoracic CT sections are associated with sarcopenia.[15]

Although the COVID-19 storm has ended, a process called post-COVID syndrome has emerged, particularly in patients who experienced severe pneumonia, lasting for weeks and manifesting with symptoms such as weakness, fatigue, myalgia, dyspnea or exertional dyspnea, and persistent cough.[16] In one-year follow-ups, it has been found that lung CT findings in these patients largely improve, but in some cases, residual lung changes such as ground-glass opacities, irregular reticulations, fibroatelectatic bands, air trapping areas, and even honeycombing persist.[17] .[16]These residual anomalies may be associated with respiratory complaints in patients following COVID-19 infection.

In our study, we included 142 patients with post-COVID symptoms. By examining their chest CT scans taken approximately 6 months after COVID-19 infection, we divided them into two groups. The first group consisted of patients with residual changes after COVID-19 infection in their chest CT scans, while the second group served as the control group, consisting of patients whose lung findings almost completely resolved on chest CT scans. We compared the muscle areas and muscle densities at the T4 and T12 levels between the two groups to assess sarcopenia. In our study, no significant differences were found in muscle areas and muscle densities at both the T4 and T12 levels. This indicates that there is no direct relationship between residual lung changes and sarcopenia. These results suggest that findings such as ground-glass opacities, irregular reticulation, and traction bronchiectasis, which can be detected even months after the disease on lung CT scans, may occur independently of sarcopenia, affecting respiratory muscles through different pathophysiological processes. This study may be the first to examine the relationship between post-COVID lung changes and sarcopenia, as we did not find a substantial amount of literature on this topic. Most studies focused on the impact of sarcopenia on the course of COVID-19 infection and its emergence in the post-COVID period. In conclusion, we can say that we did not find much information in the literature that would support or criticize our findings.

However, when comparing the measurements of muscle areas at T4 and T12 in both the patient group and the control group with the normal values gathered from previous studies, they were found to be significantly lower. This indicates that post-COVID syndrome may be associated with sarcopenia. In other words, although sarcopenia may not be directly related to residual lung anomalies in the pulmonary parenchyma, it may be associated with post-COVID syndrome.

In suspected sarcopenia cases, MRI and CT scans are recommended for measuring muscle quality and quantity, with CT scans at the L3 level being particularly useful for assessing body composition, though there is limited research on thoracic CT body composition in COVID-19 patients, who typically receive chest X-rays or thoracic CT scans. Molwitz et al. finds that fat and muscle measurements at T12 and L3 levels on CT scans are closely correlated. In COVID-19 patients who only have thoracic CT scans, T12 data can predict L3 values, which are commonly used for assessing sarcopenia and obesity. [18]

Antonarelli et al. conducted a study to investigate the prognostic effect of sarcopenia on patients infected with COVID-19, measuring the pectoral muscle area and density at the T4 level. The results showed no statistically significant differences in pectoral muscle area and density in relation to the severity and mortality of pneumonia assessed by the CT pneumonia severity score. However, the researchers found an association between sarcopenia and prolonged intensive care unit (ICU) stay and failed extubation.[12] In patients with low pneumonia severity score (less than 7), the pectoral muscle area was measured as 40.4±9.8 cm2 and muscle density as 29.2±5.9 HU, while in patients with high pneumonia severity score, the pectoral muscle area was measured as 38.9±7.8 cm2 and muscle density as 27.8±5.2 HU. The pecto-

ral muscle area measurements in both our patient and control groups were lower than these values (patient group: 32.2±9.95 cm2, control group: 31.72±10.52 cm2). The muscle density values of our patients were approximately similar. This suggests a potential association between COVID-19 infection and sarcopenia.

However, some researchers have argued that sarcopenia grading based on muscle analysis derived from CT can correlate with certain clinical outcomes related to COVID-19 infection. Of course, this aspect was not covered in our study, which focused on post-COVID pulmonary findings. Kim et al. concluded in their study that there might be a relationship between sarcopenia and death associated with COVID-19 infection.[19] Schiaffino et al. believe that sarcopenia is associated with longer ICU stays and mortality.[20] The same researchers measured the muscle area at the T12 level and found an average of 31 cm2 and muscle density of 37 HU. In our study, the T12 muscle area measurement was slightly higher (patient group: 40.76±10.75 cm2, control group: 42.36±10.61 cm2). The T12 muscle density was approximately similar (patient group: 34.88±9.78 HU, control group: 34.88±9.78 HU). Several studies have demonstrated the potential association of various clinical conditions with sarcopenia and COVID-19 infection.

In studies focusing on sarcopenia in lung diseases other than COVID-19, low muscle mass has been found to be associated with poor prognosis. For example, Kinsey et al. emphasized the association between low pectoral muscle mass and decreased overall survival in small cell lung cancer.[21] Moon et al. concluded that a decrease in thoracic muscle mass correlates with mortality in idiopathic pulmonary fibrosis.[22]

A study examining the frequency of sarcopenia and its relationship with clinical course in the post-COVID period found sarcopenia in 41% of the total 92 patients. However, the same study stated that there was no relationship between clinical course, disease severity, and sarcopenia.[23]

Muscle weakness and exercise intolerance are prominent symptoms in patients with post-acute sequelae of Covid-19, potentially resulting from muscle atrophy, reduced neural activation, and disruptions in metabolic function and blood flow. These symptoms are influenced by various factors like systemic inflammation, viral infection, inactivity, and comorbid conditions, with some patients reporting persistent symptoms for up to a year after infection. [24]

Research on COVID-19 infection and sarcopenia has indicated that musculoskeletal system involvement may occur during COVID-19 infection, as a result of medications used in infection treatment, or as part of post-COVID syndrome.[25-26] In our study, both the patient group and the control group had measurements indicating low muscle mass. This could be due to the factors mentioned above, or simply a natural process of aging. Our data on this matter is limited, and we believe that more detailed clinical research is needed.

There were several limitations to our study. First, it was a retrospective study conducted at a single center with a relatively small number of patients. Additionally, we were unable to calculate the Skeletal Muscle Index (SMI), by normalizing muscle mass to the square of the patient's height (cm^2/m^2) for many patients, because we did not have access to their height information.

According to Table 5, the T12 muscle measurement taken from females in the study by the first evaluator was similar to the population average, but for other measurements, the study average was statistically lower than the population average. The same situation was applicable for the second evaluator as well.

Conclusion

Numerous studies have been conducted on the relationship between sarcopenia and COVID-19 infection and its clinical course, which has been a popular research topic in recent years. While some studies have found no correlation with disease severity and progression, others have highlighted correlations in various aspects such as prolonged ICU stay, ease of extubation, and even mortality. However, one fact stands out in all studies, which is the association between COVID-19 infection and sarcopenia, particularly in elderly patients, regardless of whether it correlates with clinical course and conditions. More research and knowledge accumulation are needed in this regard. In our study, which primarily focused on lung CT findings and their association with the patient's respiratory symptoms, we did not identify a relationship with sarcopenia. We attributed this to the possibility of separate mechanisms and pathophysiological processes for sarcopenia and sequelae in the lungs.

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RESEARCH ARTICLE

Bladder Exstrophy Reconstruction Without Osteotomy; Evaluation of 50 Cases

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Abstract

Introductıon: To evaluate the outcome of our patients who underwent BE (bladder exstrophy)repair without osteotomy and to determine whether they are continent, upper urinary system functions, and complication rates.

Methods: The data of 50 patients who applied to our clinic due to bladder exstrophy between 2010 and 2022 were analyzed retrospectively. The gender of the patients, the age of the operation, the surgical interventions, the complications detected, whether they were continent or not, and their upper urinary system functions were recorded.

Results: The data of the 50 patients diagnosed with classical bladder exstrophy were evaluated and included in the study. Nine of these patients were female, and 41 were male. The patients' mean age was 71.2 months(6-264 months). The mean follow-up period was determined to be 70.8 months. Bladder closure was performed in 13 of 50 patients, bladder closure + bladder neck repair + epispadias repair was performed in 29 patients, and augmentation was performed for eight patients. Augmentation was recommended for five patients in the follow-up, but patients did not accept it. Skin dehiscence occurred in 2 patients, and a primary suture was performed for them. Three patients were reoperated for bladder dehiscence. During the follow-ups, cystolithotripsy was performed in 3 patients,and csytolitotomy was performed in 2 patients. Bladder dehiscence developed in 1 patient after csytolitotomy, and he was operated on.25 of the 50 patients included in the study were under five years of age. The continence status of the remaining 25 patients was evaluated. Fifteen (60%) of 25 patients were found to be continent.

Conclusion: Although strong advocates of bladder exstrophy repair with osteotomy exist, we recommend repair without osteotomy as an easy-to-apply and low-complication approach.

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Introduction

Bladder exstrophy (BE) is a congenital developmental disorder of the bladder. The anterior bladder wall is undeveloped, and the posterior bladder wall protrudes from the anterior abdominal wall.[1] The prevalence is about 2 in 100,000 births.[2] The condition is seen two times more frequently in boys than girls. However, some studies have also shown a very high male preponderance, with male to female = 6 to 1.[3]

Surgical treatment of patients with bladder exstrophy is still controversial. Some surgeons, particularly in males, recommend a single-stage repair in the neonatal period. Conversely, other surgeons advocate limiting neonatal surgery to bladder closure and postponing epispadias repair until later in life, usually between 6 months and 2 years.[4,5] It is also controversial whether osteotomy should be performed during bladder closure. The use of pelvic osteotomy to close bladder exstrophy has a long medical history. It is widely accepted, except in the first period of neonatal life (less than 72 hours), when osteotomies may not be required due to the malleability of the bones in early life.[6]

The primary aims of bladder exstrophy repair are to achieve urinary continence and to ensure the long-term preservation of the upper urinary tracts. There is considerable variation in the surgical techniques employed in BE reconstruction. It is regrettable that, despite the considerable technical advances made over the years, the effective management of this condition continues to present a significant challenge. The role of osteotomy in initial bladder closure remains a topic of significant debate and investigation. Some authors especially emphasize that osteotomy should be added to repair bladder exstrophy after the first 72 hours of life.[7] Some authors suggest that the success rate concerning closure in the repair of bladder exstrophy without osteotomy is similar to the series with osteotomy.[8] In our clinic, the repair of our bladder exstrophy cases is performed by approximating the pubic bones without osteotomy in the neonatal period. After the neonatal period, the repair is provided without osteotomy and approximating the pelvic ring.

This study seeks to evaluate patients who have had bladder exstrophy repair to establish whether they are continent, to determine the functionality of the upper urinary system, and to identify any complication rates who did not undergo osteotomy (pelvic ring approximated and nonapproached).

Material and Methods

After obtaining approval from the institutional ethics committee, we retrospectively analyzed the data of all patients who presented to our clinic with bladder exstrophy between 2010 and 2022. Patients with a follow-up period of fewer than six months who were operated on for duplicated bladder exstrophy and underwent ureterosigmoidostomy were excluded from the study. Patients were followed up every three months. It was recorded whether the patients were continent or not, how many hours they stayed dry if they had continent, whether they had fever urinary tract infection, used prophylactic antibiotics, used anticholinergics, used a clean intermittent catheter, or not. After physical examination, biochemistry, urinalysis, and ultrason are performed, bladder capacity measurement is performed once a year, and control urodynamics is performed when necessary. The patient's gender, age at the time of surgery, surgical procedures, complication rates, continence success rate, and upper urinary system functions were documented. Although continence is defined differently in many studies, daytime urinary continence was evaluated by the age of five years in our study. Patients were considered continent if completely dry for ≥3 hours, with or without a clean intermittent catheterization. [9] The patients were divided into three groups: those who had the first surgery in our clinic in the first 3 postnatal days, those who had the first surgery in our clinic after the third postnatal day, and those whose first surgery was performed in another center and was unsuccessful and underwent secondary closure by us. We performed the surgeries of all our patients using modern staged repair of bladder exstrophy techniques (MSRE).[10] Primary closure was performed in the newborn, epispadias correction at 12 months of age, and bladder neck reconstruction (BNR) at 4-5 years of age. Bladder augmentation (BA) was recommended and performed in patients with low bladder compliance and incontinence.

Statistical analysis

All statistical analyses were performed using SPSS version 25 (IBM Corporation, NY, USA). The chi-square test was used for categorical comparisons. Mann-Whitney U and Kruskal-Wallis tests were used to analyze independent variables. A p-value <0.05 was considered to be statistically significant.

Results

Three patients who were operated on for duplicated bladder exstrophy and three patients who underwent ureterosigmoidostomy operation were excluded from the study. Fifty patients operated on for classic bladder exstrophy were included in the study without gender discrimination. Nine of these patients were female and 41 were male. The mean age of the patients was calculated as 71.2 months (6-264 months) SD: 65.516. The mean follow-up period was 70.8 months (6-264 months) SD: 65.057. Primary operations were performed in 13 patients in the first three days of newborns, and 5 patients after the first 3 days of newborns due to bladder exstrophy in our clinic. Secondary bladder closure and complementary surgeries were performed in 32 patients whose first operations were performed in other centers.

Bladder closure was performed in 13 of 50 patients, bladder closure + bladder neck repair + epispadias repair in 29 patients (augmentation was recommended for 5 patients in the follow-up, but patients did not accept), and augmentation was performed for 8 patients (2 girls, 6 boys). Skin dehiscence occurred in 2 (4%) patients, and a primary suture was performed for them. Three patients (6%) were reoperated for bladder dehiscence. During the follow-ups, cystolithotripsy was performed in 3 patients (6%), cystolitotomy was performed in 2 (4%) patients (bladder dehiscence developed in 1 patient after cystolitotomy, and he was operated on.), and stone excision from the urethral diverticulum was performed in a patient. Bladder closure with the staged approach is expected to reach the appropriate age for the planned surgical interventions in thirteen patients. 25 of the 50 patients included in the study were under five years of age. The continence status of the remaining 25 patients was evaluated. 15 (60%) of the patients were found to be continent, and 10 (40%) were found to be incontinent. Of the 15 continent patients, 8 were augmented bladder patients. All patients who underwent augmentation were observed to be dry. When augmented patients were excluded, 7 (%41) of the remaining 17 patients were found to be continent. There was no significant difference in terms of continence between those who had only bladder closure and those who had epispadias repair in addition to bladder closure (p = 0.79).

Expected bladder capacity for age was normal or above normal in only two patients. The mean bladder capacity for age was -90 cc. The distribution of the ratio of the current bladder capacity of the patients to the expected bladder capacity by age is as in Table 1, and its median value was calculated as 55 percent.

Table 1. Bladder capacity of the patients to the expected bladder capacity by age

Bladder capacity	Frequency	Percent
<%10	2	% 4
%10-%25	7	% 14
%25-%50	14	% 28
%50-%75	15	% 30
>%75	12	% 24
Total	50	% 100

Discussion

Trendelenburg said that "All the patients of exstrophy are born with the potential of continence." at 1906.[11] Woodhouse and Kellett said that "All the patients of exstrophy bladder are born with the potential for fertility and continence." at 2006.[12]

The primary objectives of bladder exstrophy repair are to achieve urinary continence and to ensure the long-term preservation of the upper urinary tracts. There is considerable variability in the surgical techniques employed in the reconstruction of bladder exstrophy.

It is regrettable that, despite the considerable technical advances that have been made over the years, the management of this condition remains a significant challenge. Patients frequently report a lack of satisfaction and a sense of profound frustration. The outcomes of bladder exstrophy repair are often suboptimal, necessitating multiple specialized surgeries and frequent hospital admissions. In traditional reconstructive surgery for exstrophy bladder, the defect in the anterior abdominal wall can be repaired either with or without osteotomy, following bladder closure and epispadias repair.

A variety of osteotomy techniques have been described that facilitate the approximation of the pubic bones to the midline, thereby providing efficient protection of the closed bladder.[13] Additionally, osteotomy assists in the restoration of the transformation of the urogenital diaphragm from a rectangular to a triangular shape, which in turn facilitates the increase in corporal length following corporoplasty.

The role of osteotomy continues to be an im-

portant subject in bladder closure. The preference for osteotomy over non-osteotomy methods is based on several factors. Firstly, the closed bladder is secured within the reconstructed pelvic ring, ensuring stability. Secondly, the levator ani base is positioned to support the bladder base. Thirdly, the length of the corpora is not lost in corporoplasty, which is an important consideration. The prevailing view is that osteotomy is not required as an adjunct to bladder exstrophy closure performed within 72 hours of life due to the relatively malleable nature of the pelvic bone. After 72 hours of life, osteotomy is strongly recommended by most of the authors. There are also studies indicating that there is no difference in the success rate of bladder closures.[3,8,14-16] Nevertheless, symphysis diastasis is commonly seen to recur after the pelvic closure methods used.[17] In addition, due to complication rates, technical difficulties, and the need for postoperative immobilization, methods without osteotomy have begun to be preferred.

Özcan et al. demonstrated that a notable proportion of patients who underwent anterior diagonal iliac osteotomy exhibited a recurrence of diastasis of the pubic bones at a mean follow-up period of 34 months.[18]

Only a few studies investigate pubic diastasis following different pelvic osteotomy procedures with adequate follow-up.[19-22] Castagnetti et al. compared prospectively patients with and without osteotomy after initial closure. The mean recurrent pubic diastasis distance does not show a significant difference in the long term patients with and without osteotomy.[23]

During long-term follow-up, there were no significant differences observed in the width of pubic diastasis, the number of surgeries related to exstrophy, incontinence rates, or the need for clean intermittent catheterization for bladder emptying.[23]

According to Kertai et al., despite the hip morphology specific to bladder exstrophy, long-term hip function in adolescent adults was not impacted after symphysis approximation without osteotomy in infancy. The recurrence of symphysis diastasis after this procedure was in line with the long-term results seen after osteotomy.[17]

According to a case series by Mushtaq et al., 70 out of 74 patients (95%) achieved successful bladder closure through primary closure without osteotomy and postoperative immobilization.[14]

The data of 29 patients were evaluated in the study of J. S. Ellison et al. Continence was achieved in 3 out of 10 patients with osteotomy and 8 out of 17 patients without osteotomy (osteotomy status unknown in 2 patients); no significant correlation was found between osteotomy and continence status.[8] Ahmed et al.'s study, the continence rates were determined as 78.7%, spontaneous voided continence 17.0%. In our clinic, the continence rates were determined to be 41% in patients who did not undergo osteotomy, which is consistent with the literature.[24]

In the study of Marco Castagnetti et al., the data of 14 exstrophy patients were examined. Osteotomy was performed on eight patients, and 4 of these eight patients were found to be continent. Six patients did not undergo osteotomy, and 3 of these six patients were found to be continent. No difference was found in continence status in patients with and without osteotomy ($p=0.07$).[23]

In the study by Preeya et al. 286 bladder exstrophy patients, 186 of whom were in the neonatal period, were operated on by osteotomy. In 23 of the patients who were operated on during the neonatal period and in 3 of the patients who were operated out of the neonatal period; bladder dehiscence was observed in 26 (9%) of 286 patients who were operated on by osteotomy.[25] In the study by Hofmann et al., bladder dehiscence was not observed in 66 patients who underwent extrophy repair without osteotomy.[26] In our series, our bladder dehiscence rate was 6%, which is correlated with the literature.

Pelvic ring closure without osteotomy was accomplished in all infants with classical BE under one week of age in our department. We do pubic approximation in children older than one week.

Conclusion

In conclusion, despite the presence of Exstrophy Epispadias Complex-specific hip morphology, long-term hip function is preserved in adult and adolescent patients after symphyseal approximation without osteotomy in infancy. The pubic approximation is significantly less invasive and more straightforward than pelvic osteotomy.

Studies have shown that osteotomy does not affect continence and bladder dehiscence. In our study, we found that our results were consistent with the literature regarding continence, bladder dehiscence rate, and the preservation of upper urinary system functions, all of which are crucial for patients with bladder exstrophy. We argue that successful bladder exstrophy repair can be performed without osteotomy.

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RESEARCH ARTICLE

Investigation of Prohibitin Levels in Preeclampsia Cases: A Case Control Study from a Tertiary Hospital

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Abstract

Introductıon: To evaluate the relationship between the effects of prohibitin at the cellular level and the pathophysiology of preeclampsia.

Methods: This study included a total of 120 patients who presented to our clinic at 20–41 weeks of gestation. The participants were divided into three groups: 40 pregnant women with preeclampsia with severe features, 40 pregnant women with preeclampsia, and 40 healthy pregnant women. To measure serum prohibitin levels, 10 cc of venous blood was collected from each participant, and comparisons were made between the groups.

Results: Serum prohibitin levels were significantly higher in pregnant women with preeclampsia with severe features and preeclampsia compared to the control group ($p<0.001$ for both).

Conclusion: Prohibitin levels were found to be significantly increased in pregnant women with preeclampsia with severe features and those with preeclampsia compared to healthy pregnant women, suggesting that prohibitin may serve as a marker of preeclampsia.

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Introduction

Preeclampsia is among the most significant complications encountered in obstetrics, affecting approximately 2–7% of all pregnancies.[1] Defined as hypertension and proteinuria occurring after the 20th week of pregnancy, preeclampsia is, in fact, a multisystemic and complex syndrome that extends beyond hypertension and proteinuria, affecting the entire body.[2] Annually, approximately 50,000 maternal and 900,000 infant deaths globally are attributed to preeclampsia and its complications, accounting for around 12% of all maternal fatalities.[3] The onset and clinical course of the disease are unpredictable; therefore, robust tools are needed for accurate diagnosis and treatment. Preeclampsia with severe features characterized by severe hypertension, symptoms of central nervous system dysfunction, new onset headache unresponsive to medication,hepatocellular injury, thrombocytopenia, renal insuffiency, pulmonary edema, and cerebrovascular events.[4]

PHB is a pleiotropic protein belonging to the SPFH (stomatins, flotillins and HflK/C) protein family, sharing the SPFH domain that plays a role in both adipocytes and immune cells.[5] It derives its name from prohibitin, which was found in a search for anti-proliferative genes. Later, a homologous protein with almost 50% sequence homology to PHB was identified as a repressor of estrogen activity (REA, also known as PHB2). After the discovery of PHB2, PHB received the alternative name PHB1.[6,7]

Prohibitins have been reported to perform numerous functions across various cellular localizations and cell types. The functions attributed to prohibitins include their roles in nuclear transcription, their presence as lipid skeleton proteins in the plasma membrane, their function as mitochondrial morphogenesis proteins within mitochondria, and their regulation of apoptosis.[8] Furthermore, induced oxidative stress has been associated with prohibitin expression.[9] In endothelial cells, down-regulation of prohibitin has been shown to result in increased production of mitochondrial reactive oxygen species (ROS) and cellular aging.[10,11] Given the sequence of activities undertaken by prohibitin proteins, they have been identified as promising therapeutic targets in diverse disease states, including inflammation, obesity, and cancer, although a deeper understanding of their cell-specific functions remains essential.[12]

Considering the pathophysiology of preeclampsia and the cellular-level effects of prohibitin, prohibitin has been found noteworthy in elucidating the pathophysiology of preeclampsia. This study aimed to investigate prohibitin (PHB1) levels in cases of preeclampsia-complicated pregnancies and preeclampsia with severe features as compared to healthy pregnancies.

Material and Methods

Following approval from the local ethics committee (meeting number: 12, decision number: 21, date: August 1, 2019), the study was conducted with a total of 120 pregnant women who presented to the Obstetrics and Gynecology Clinic of Fırat University Medical Faculty Hospital. The study was designed as a prospective case control study, with participants selected using quota sampling. During blood sample collection, medical consent was obtained from all participants in accordance with the ethical guidelines of the Declaration of Helsinki. The participants were at gestational ages ranging from 20 to 41 weeks and were divided into three groups for evaluation: 40 patients with preeclampsia with severe features, 40 patients with preeclampsia, and 40 healthy pregnant women.

The preeclamptic patient group included individuals with blood pressure measurements of 140/90 mmHg or higher recorded at least twice with intervals of six hours or more, along with proteinuria of 300 mg/24 hours or higher, or a dipstick reading of +1 or greater. Preeclamptic patients were further evaluated in two subgroups according to the severity of preeclampsia based on the criteria specified in the introduction section. The control group included normotensive pregnancies with no significant pathology in their obstetric history (e.g., placenta previa, intrauterine growth restriction, or placental abruption) in both their current and previous pregnancies. Pregnant women with a history of diabetes mellitus, chronic hypertension, thromboembolism, thrombophilia, liver or renal disease, fetal anomalies, or multiple gestations were excluded from the study.

Detailed medical histories and obstetric evaluations were obtained for all participants. Data recorded included maternal age, body mass index (BMI), gravidity, parity gestational week, gestational week at birth, systolic/diastolic blood pressure and mean arterial pressure (MAP) measurements.

For the determination of serum prohibitin (PHB1) levels, 10 cc of venous blood was collected

in plain tubes. After the diagnosis of preeclampsia with severe features or preeclampsia, 10 cc of venous blood was taken from the patients, centrifuged at 5,000 rpm for 10 minutes, and stored at -86°C in Eppendorf tubes until analysis. Healthy pregnancies were verified through the absence of elevated blood pressure on routine examination cards, and further blood pressure measurements were taken before blood samples were collected and appropriately prepared for storage. Serum prohibitin levels were subsequently measured using the human prohibitin enzyme-linked immunosorbent assay kit [Shanghai Sunredbio Technology Co. Ltd., Catalog No.: 201-12-2131, China], following the kit instructions. Absorbance values were read spectrophotometrically at 450 nm using the Multiskan FC Microplate Photometer [Thermo Scientific, USA], and test results were reported in ng/ml, with a sensitivity of 0.0724 ng/ml and a measurement range of 0.1-30 ng/ml.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics version 22.0. Categorical variables were summarized as numbers and percentages, while continuous variables were presented as means and standard deviations. The Kolmogorov-Smirnov test was used to assess whether continuous variables met the normal distribution assumption. A one-way analysis of variance was used for the general comparison of continuous measures among more than two groups. The statistical significance level was accepted as 0.05 for all tests.

Results

The study included a total of 120 pregnant women, aged 18–44 years, comprising 40 women with preeclampsia with severe features, 40 with preeclampsia, and 40 healthy controls. There were no statistically significant differences in maternal age, body mass index, or mean gestational age between the three groups ($p > 0.05$). However, systolic, diastolic, and mean arterial blood pressure values were statistically significantly higher in the preeclampsia with severe features group compared to the preeclampsia and control groups ($p < 0.001$ and $p < 0.05$, respectively). Additionally, there were significant differences in systolic, diastolic, and mean arterial blood pressure values between the preeclampsia and control groups [Table 1].

Table1. Demographic and obstetric data of the study groups

	Group			
	Preeclampsia with severe features (n=40)	**Preeclampsia (n=40)**	**Control (n=40)**	**p-value**
Maternal age	30.7 ± 6.8	30.8 ± 5.7	30.1 ± 5.1	>0.05
BMI	28.9 ± 4.1	30.9± 4.0	29.3 ±4.3	>0.05
Gravidity	1 ± 1	2 ± 2	2 ± 2	0.417
Parity	1 ± 1	1 ± 1	2 ± 1	0.289
Gestational week	29 ± 4	29.5 ± 5	30 ± 4	0.216
Gestational week at birth	32.83 ± 4.27	35.11 ± 3.84	38 ± 2	<0.001
Systolic BP[mmHg]	168.46 ±12.88	141.87 ±7.90	107.5±11.93	<0.001
Diastolic BP[mmHg]	113.20 ± 6.73	92.12 ± 5.97	71.36 ± 7.42	<0.001
MAP[mmHg]	132.85 ±7.7	109.1 ± 4.2	82.86 ± 8.4	<0.001

Values are given as mean ± standard deviation.
n: number, BMI: body mass index, BP: blood pressure, MAP: mean arterial pressure

When comparing serum prohibitin levels across groups, the preeclampsia with severe features group showed statistically significantly higher levels compared to the control group [$p < 0.001$]. Similarly, prohibitin levels in the preeclampsia group were significantly elevated compared to the control group [$p < 0.001$]. However, no statistically significant difference was observed between the preeclampsia with severe features and preeclampsia groups ($p > 0.05$) [Table 2].

Table2. Comparison of the laboratory test results and prohibitin values between the study groups

	Prohibitin(ng/ml)	**Min**	**Max**	**p-value***
Preeclampsia with severe featuresa (n=40)	5.3988 ± 7.63748	.10	26.50	>0.05 a-b
Preeclampsiab (n=40)	5.0051 ± 6.59079	.59	30.00	
Contr (n=40)	2.6079 ± 2.35926	.10	9.95	<0.001 a-c b-c
Total [n=120]	4.3373 ± 6.05898	.10	30.00	

*One-way analysis of variance. Values are given as mean ± standard deviation.
n: number, min: minimum, max: maximum.

Discussion

This study showed that pregnant women with preeclampsia with severe features and preeclampsia had higher serum prohibitin levels than healthy pregnant women. The underlying biological mechanisms linking organ dysfunction in preeclampsia are not yet clear, and as a result, preeclampsia remains a disease of theories. While the precise cause of hypertensive disorders in pregnancy remains unclear, several hypotheses suggest that issues in placental implantation and trophoblastic invasion are key contributors to the disease.[13,14] The initial step are inadequate or abnormal trophoblastic invasion of the uterine decidua and spiral arteries during early pregnancy is generally considered a primary etiological factor in the development of preeclampsia and restriction of intrauterine growth. Predisposing genetic, immunological and preexisting maternal risk factors may affect this abnormal placentation.[15] As stated in many studies, impaired placental vascularity causes inadequate placental perfusion, which in turn causes the release of antiangiogenic factors into the systemic circulation and endothelial dysfunction occurs.[16] There is no curative treatment for PE, except the delivery of the placenta. As a result, management protocols for PE are supportive, including hypertension management, seizure prophylaxis, delivery at the optimal time, prevention of maternal and fetal mortality/morbidity due to the disease.[17] In the current study, the preeclampsia with severe features and preeclampsia group had significantly higher negative perinatal outcomes, such as preterm birth and maternal systolic, diastolic and mean blood pressures.

Apoptosis, although essential for normal placental development, can also play a role in pathological conditions of the placenta. The presence of these cells is associated with various stages of placental development, such as trophoblast attachment and invasion, trophoblast differentiation and cycle, spiral artery transformation, and parturition.[18,19] Furthermore, apoptosis has been shown to be essential in establishing maternal immune tolerance to paternal antigens expressed by trophoblasts.[20,21] Complicated pregnancies, such as those with preeclampsia or intrauterine growth restriction, show a high incidence of trophoblast apoptosis. Changes in the regulation of trophoblast apoptosis may contribute to the pathophysiology of these disorders.[22,23]

It has been reported that prohibitins have multiple functions, including roles in nuclear transcription across various cellular localizations and cell types, anti-oxidation, anti-inflammation, functioning as a lipid cytoskeletal protein within the plasma membrane, acting as a mitochondrial morphogenesis protein within the mitochondria, and serving as a regulatory protein in apoptosis.[24] Prohibitin expression has also been associated with induced oxidative stress. Nuell et al. reported that the downregulation of prohibitin in endothelial cells resulted in increased production of mitochondrial reactive oxygen species (ROS) and led to cellular senescence.[25] Under normal conditions, low ROS concentrations play essential roles in cell signaling and homeostasis.[26] However, oxidative stress can occur when the balance between ROS formation and the detoxification actions of antioxidant proteins is disrupted. The overproduction of reactive oxygen molecules as a result of placental oxidative stress in preeclampsia has an effect on endothelial dysfunction.[27] This data supports the idea that prohibitin is a factor of oxidative stress.

Mishra et al. determined that prohibitin protected cells and tissues against the induction of apoptosis.[28] Thus, it is plausible that increased levels of prohibitin in preeclampsia may function to prevent trophoblast apoptosis. In a study by Allaire et al., trophoblast apoptosis was shown to be elevated in pregnancies complicated by preeclampsia.[29]

The association of prohibitin with oxidative stress was further investigated by Jupe et al., who observed that prohibitin overexpression in intestinal epithelial cells reduced oxidative stress in inflammatory bowel disease.[30] In another study undertaken by Rusterholz et al., inflammation was found to be markedly increased in preeclampsia, and factors triggering inflammatory responses [such as infections and rheumatic diseases] were suggested to raise the likelihood of developing preeclampsia.[31] While this finding may contradict our results, it is possible that elevated prohibitin levels in our study reflect a compensatory mechanism to mitigate oxidative stress.

Studies showing that prohibitin expression is increased in autoimmune diseases.[32] It has been shown that preeclamptic pregnant women have autoantibodies that activate the angiotensin receptor and that autoantibody-mediated receptor activation contributes to the pathophysiology associated with

preeclampsia. This pathophysiology strengthens the possibility that preeclampsia is a pregnancy-related autoimmune disease.[33] Similarly, in the current study, the serum prohibitin level was found to be higher in the preeclampsia with severe features and preeclampsia group than in the control group and it was statistically significant. High serum prohibitin levels in preeclampsia patients suggest that there is a relationship between prohibitin and angiotensin reseptor systems, and this finding is in agreement with the literature.

Conclusion

To our knowledge, this is the first study to evaluate serum prohibitin levels in pregnant women with preeclampsia. This study revealed that prohibitin levels were significantly elevated in the severe preeclampsia and preeclampsia groups compared to the control group, highlighting prohibitin as a noteworthy biomarker. This novel biomarker appears to hold potential for managing pregnant women with preeclampsia. The relatively low number of cases and single-center experience can be considered as the major limitations of the research. To elucidate the role of prohibitin levels in the prediction of preeclampsia, as well as to evaluate their potential as a biomarker for clinical practice, it is essential to conduct studies with large patient cohorts.

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RESEARCH ARTICLE

The value of the second trimester glucose-to-lymphocyte ratio in predicting fetal loss at late preterm and term pregnancies

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Abstract

Introductıon: This study aimed to determine whether the second-trimester glucose-to-lymphocyte ratio (GLR) can predict intrauterine fetal demise (IUFD) at late preterm and term gestations.

Methods: A retrospective cross-sectional design was employed. Pregnant women aged 18–45 who delivered at our tertiary hospital between January 2023 and December 2024 were screened. Those diagnosed with IUFD at or beyond 34 weeks of gestation comprised the case group, while two healthy pregnant women of similar age and body mass index for each case served as the control group. Laboratory parameters from the 20th–24th weeks, including hemoglobin, white blood cell (WBC) count, neutrophil count, lymphocyte count, random blood glucose, and GLR, were analyzed.

Results: Data from 105 patients (35 IUFD, 70 controls) were included. The IUFD group had significantly lower WBC, neutrophil, and lymphocyte counts but higher glucose and GLR than controls ($p<0.01$). Receiver operating characteristic analysis showed an area under the curve of 0.876 ($p<0.01$) for GLR, with 80% sensitivity and 79% specificity at a cutoff of 0.604.

Conclusion: Elevated GLR in the second trimester may reflect subclinical inflammation and serve as a practical, cost-effective predictor of IUFD. Further large-scale studies are warranted to validate these findings.

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Introduction

Intrauterine fetal demise (IUFD) is defined as the cessation of fetal cardiac activity after the 20th week of gestation and prior to delivery.[1] It is one of the most dramatic complications of pregnancy, occurring in approximately 5 per 1000 births in developed countries, whereas the incidence is considerably higher in developing nations.[2] Although many risk factors have been identified, such as maternal diseases, fetal genetic or structural anomalies, or intrauterine infections, IUFD is not always confined to high-risk pregnancies.

An association between increased maternal inflammatory response in early pregnancy and fetal loss has been suggested. In acute or chronic inflammatory conditions, cells such as macrophages and neutrophils require a hyperglycemic environment to meet their elevated energy demands.[3] Furthermore, lymphopenia is a component of the acute severe inflammatory response, driven by corticosteroid-induced lymphocyte apoptosis and migration, along with the movement of lymphocytes to the inflammation site and the action of cytokines such as TNF-α.[4] While lymphopenia is more frequent and severe in acute inflammation, it may also occur in chronic inflammation due to suppressed lymphocyte production and prolonged consumption.

The glucose-to-lymphocyte ratio (GLR) has recently been proposed as a novel index reflecting this hyperglycemia and lymphopenia observed in inflammatory states. Its clinical utility in detecting inflammation and monitoring therapeutic response has been highlighted in various disorders.

Based on the hypothesis that subclinical inflammation in the second trimester is related to the subsequent development of IUFD, this study aimed to investigate the utility of the second-trimester GLR in predicting IUFD at term.

Material and Methods

This retrospective cross-sectional study included pregnant women aged 18–45 who were admitted to our tertiary training and research hospital between January 2023 and December 2024 with a diagnosis of IUFD at or beyond 37 weeks of gestation. Data were obtained from the hospital's electronic medical records and patient files. The study was approved by the local ethics committee under the approval number TABED-2-25-916.

Inclusion criteria required that all prenatal follow-ups and deliveries had taken place at our center, and that complete blood count (CBC) and biochemical tests had been performed between the 20th and 24th weeks of gestation. Patients diagnosed with IUFD after 34 weeks of gestation comprised the case group. The following criteria guided the selection of subjects for the control group: From the birth registry, for each patient in the case group, the first two patients of similar age, BMI, and gestational age who delivered live births subsequent to her were selected.

Patients were excluded if they met any of the following criteria: multiple pregnancies, chronic inflammatory disease, suspected or established malignancy, fetal genetic or major structural anomalies, any history of smoking, alcohol, or substance abuse, congenital infections, pregestational or gestational diabetes mellitus, chronic hypertension, or placental abruption.

The two groups were compared regarding age, gravidity, parity, number of abortions, BMI; and laboratory parameters obtained between the 20th and 24th weeks of gestation: hemoglobin, white blood cell count (WBC), neutrophil count, lymphocyte count, monocyte count, random blood glucose level, and the glucose/lymphocyte ratio (GLR).

Kolmogorov–Smirnov and Shapiro–Wilk tests were used to assess the normality of data distribution. Continuous variables without normal distribution were presented as median (interquartile range, IQR), and comparisons between groups were made using the Mann–Whitney U or Kruskal–Wallis tests. A receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive power of GLR, and the cut-off value that provided the highest sensitivity and specificity was calculated. Youden's index was used to determine the optimal cut-off value. Statistical significance was accepted as $p<0.05$. All analyses were performed using SPSS software (version 24, IBM Corp., Armonk, NY).

Results

A total of 105 patients (35 IUFD, 70 controls) were included. There was no significant difference between the groups regarding age, gravidity, parity, number of abortions, BMI, hemoglobin, and monocyte count.

In the IUFD group, WBC, neutrophil count, and lymphocyte count were significantly lower than in the control group ($p=0.03$, $p=0.02$, and $p<0.01$, respectively). The median values for glucose and GLR were significantly higher in the IUFD group ($p<0.01$,

p<0.01). Table 1 presents the clinical and laboratory characteristics of both groups.

Table 1. Comparison of clinical characteristics, laboratory results, birth outcomes, and combined inflammatory indices between IUFD and control groups

Variable	Control (n: 70) Median (IQR)	IUFD (n:35) Median (IQR)	p-value
Age (years)	29 (7)	27 (9)	0.05
Gravidity	2 (2)	2 (2)	0.40
Parity	1 (2)	1 (2)	0.91
Abortus	0 (1)	0 (0)	0.09
BMI	28.4 (12)	29.6 (14.1)	0.36
Hemoglobin (g/dL)	12 (2)	12.3 (2)	0.06
WBC (x109/L)	9.27 (2.5)	7.81 (3.2)	0.03
Neutrophil count (x109/L)	6.63 (2.3)	5.49 (2.5)	0.02
Lymphocyte count (x109/L)	1.79 (0.59)	1.35 (0.93)	<0.01
Monocyte Count (x109/L)	0.45 (0.17)	0.36 (0.23)	0.15
Glucose (mg/dL)	82.5 (17)	111 (16)	<0.01
GLR	0.048 (0.024)	0.083 (0.068)	<0.01

IUFD: intra uterine fetal demise, IQR: interquartile range, WBC: white blood cells, GLR: glucose-lymphocyte ratio, p values less than 0.05 accepted as statistically significant

ROC curve analysis for GLR in predicting IUFD showed an area under the curve (AUC) of 0.876 (95% CI: 0.802–0.949, p<0.01). The cut-off value for GLR providing optimal sensitivity and specificity was determined to be 0.604 (80% sensitivity, 79% specificity). Figure 1 and Table 2 show the ROC analysis results.

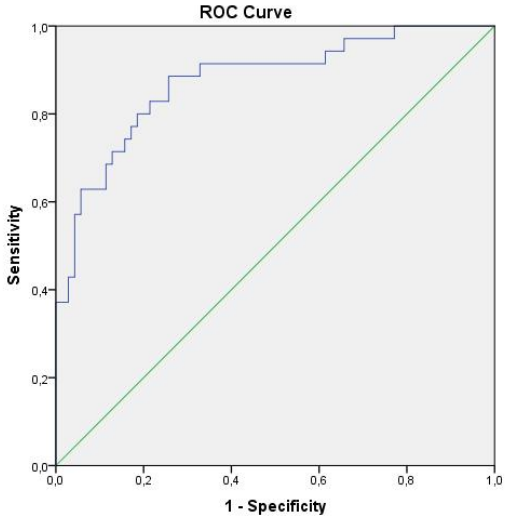

Figure 1

Table 2. Predictive Performance of GLR for IUFD Based on ROC Curve Analysis

Variable	AUC	95% CI	Cut-off value	Sensitivity	Specificity	p-value
GLR	0.876	0.802-0.949	0.604	80%	79%	<0.01

GLR: glucose-lymhocyte ratio, AUC: area under the curve, CI: confidence interval, p<0.05 accepted as statistically significant

Discussion

Numerous factors have been implicated in the etiology of IUFD, such as antepartum hemorrhage, fetal chromosomal or structural anomalies, intrauterine infections, fetal growth restriction, and preeclampsia-related placental insufficiency.[5] Several mechanisms have been proposed in its pathophysiology, among which acute or chronic fetal hypoxia is the most recognized. Evidence also suggests a strong link between inflammation and fetal demise.[6,7]

The relationship between IUFD and inflammation arises from the balanced functioning of maternal and fetal immune systems. Inflammation can compromise the intrauterine environment through maternal infections and proinflammatory responses. During maternal infections, proinflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) can alter placental vasculature, reducing uteroplacental blood flow and leading to fetal hypoxia.[8] These cytokines may also induce oxidative stress and apoptotic pathways in fetal tissues, causing direct fetal damage. At the placental level, an inflammatory response can hinder trophoblast invasion and result in placental insufficiency, potentially culminating in fetal growth restriction or death.[9] Moreover, hyperactivation of the maternal immune system may recognize the fetus as a foreign antigen and mount an immunologic attack.[10] Together, these mechanisms underscore the critical role of poorly regulated inflammation in IUFD.

GLR reflects the hyperglycemic environment in inflammatory states and the lymphopenia observed particularly during acute inflammation. Its use as a sensitive marker to diagnose inflammation and monitor therapeutic response is increasingly recognized in various clinical scenarios. Elevated GLR levels have been linked to higher mortality rates in septic patients admitted to intensive care units.[11] Similarly, in a large-scale retrospective study on adult patients with respiratory distress syndrome, an elevated GLR was identified as a readily accessible predictor of morta-

lity. [12] This marker has also attracted attention in malignancies characterized by increased inflammation, with studies suggesting that GLR is a cost-effective, useful prognostic indicator in pancreatic and breast cancers.[13–15] Furthermore, GLR has been associated with prognostic outcomes in acute conditions such as myocardial infarction and hemorrhagic cerebrovascular events.[16,17]

In obstetrics, reduced pregnancy-associated plasma protein-A (PAPP-A) and human chorionic gonadotropin (hCG), along with increased nuchal translucency in first-trimester aneuploidy screening, have been linked to a higher fetal demise risk, even in the absence of aneuploidy.[18] Additionally, combined inflammatory markers such as the systemic immune-inflammation index (SII) and the neutrophil-to-lymphocyte ratio (NLR) have been associated with conditions related to placental insufficiency and fetal death, including fetal growth restriction and severe preeclampsia.[19,20]

The findings of this study indicate that GLR, an emerging prognostic marker in various inflammatory diseases, could also be beneficial in predicting IUFD—a condition intimately related to inflammation. Specifically, elevated GLR levels in otherwise uncomplicated pregnancies at 20–24 weeks could predict IUFD with a promising sensitivity (80%) and specificity (79%). These results not only strengthen the association between inflammation and IUFD but also highlight GLR as a potential early warning marker.

The limitations of this study include its retrospective design and single-center data. Its strength lies in being, to our knowledge, the first study in the literature to investigate the association between GLR and IUFD.

Conclusion

Inflammation plays a pivotal role in the pathophysiology of late-onset IUFD, one of the most devastating pregnancy complications. GLR, a recently identified prognostic marker for several inflammatory conditions, has the potential to serve as a practical, cost-effective tool for early prediction of this unexpected obstetric complication. Recognizing inflammation early and implementing appropriate interventions could be beneficial. However, further large-scale studies are needed to substantiate these findings.

Statements & Declarations

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Declaration of Conflict Interests

The authors have no competing interests to declare.

Ethics approval

The study protocol was approved by the Ankara City Hospital Clinical Research Ethics Department and was performed in line with the Declaration of Helsinki. The ethics committee approval was obtained with the decision number TABED-2-25-916.

Author Contribution

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by OOO, DS. The first draft of the manuscript was written by OOO and DS commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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RESEARCH ARTICLE

Traces of Inflammation in Acute Appendicitis, Cholecystitis, and Diverticulitis: The Role of Biomarkers in Diagnosis

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Abstract

Introduction: Acute appendicitis, acute cholecystitis, and acute diverticulitis are among the most common causes of acute abdominal pain, requiring early diagnosis and rapid treatment. Although imaging modalities such as ultrasonography and computed tomography play a crucial role in diagnosis, access to these methods may be limited in certain situations. Inflammatory biomarkers, including C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and delta neutrophil index (DNI), have been suggested as potential tools for differential diagnosis. This study aims to evaluate the diagnostic value of these biomarkers.

Methods: This retrospective study included 171 patients diagnosed with acute appendicitis (n=62), acute diverticulitis (n=56), and acute cholecystitis (n=53). White blood cell (WBC), neutrophil, lymphocyte, and eosinophil counts, as well as NLR, DNI, and CRP levels, were compared. Statistical analyses and ROC analysis were performed to assess the diagnostic performance of these biomarkers.

Results: CRP and lymphocyte levels were found to be significantly higher in the acute diverticulitis group ($p < 0.05$). Although DNI, NLR, WBC, and neutrophil levels were elevated in all three groups, no statistically significant difference was observed between them ($p > 0.05$). ROC analysis demonstrated that DNI has a moderate diagnostic potential for all three diseases, but none of the biomarkers provided high specificity.

Conclusion: Inflammatory biomarkers alone are not sufficient as a diagnostic tool for differentiating acute appendicitis, acute cholecystitis, and acute diverticulitis. However, CRP may be useful in assessing disease severity in patients with diverticulitis. Particularly in settings where access to imaging modalities is limited or unavailable, biomarkers such as CRP, DNI, and NLR may serve as supportive tools for diagnosis. Nevertheless, large-scale, multicenter studies are required to better define the role of inflammatory response and biomarkers in differential diagnosis and prognosis.

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Introduction

Acute abdominal pain is a common clinical presentation that accounts for a significant proportion of emergency department visits and requires prompt diagnosis and management.[1] The most important cause of acute abdominal pain in the emergency setting is intra-abdominal infections. The term "intra-abdominal infections" encompasses a wide range of pathological conditions, from uncomplicated appendicitis to widespread fecal peritonitis.[2] The most common cause of intra-abdominal infections is acute appendicitis, followed by acute cholecystitis and acute diverticulitis.[3] These three conditions may present with similar clinical manifestations; however, due to differences in their pathophysiological mechanisms, the severity of inflammation and its systemic effects may vary.

Acute appendicitis is characterized by bacterial proliferation, mucosal ischemia, and transmural inflammation following obstruction of the appendiceal lümen.[4] Acute cholecystitis typically begins with edema and inflammation due to cystic duct obstruction and may progress to necrosis and suppuration in advanced stages.[5] Acute diverticulitis is a clinical condition triggered by fecal stasis and mucosal inflammation, often accompanied by micro- or macro-perforation and abscess formation.[6] In advanced stages of these diseases, necrosis, perforation, and peritonitis may develop, leading to an exacerbation of systemic inflammatory response and serious complications.

These three conditions can generally be distinguished through clinical findings and imaging modalities; however, diagnosis may be challenging in some cases. Atypical symptoms, inflammation occurring outside classical anatomical locations, and presentations in special patient groups such as the elderly, children, or pregnant individuals can complicate differential diagnosis. Ultrasonography (USG) and contrast-enhanced computed tomography (CT) are the most frequently used imaging techniques for definitive diagnosis. CT is generally considered the most reliable modality; however, it may not be feasible in cases where radiation exposure or contrast administration is contraindicated, such as in patients with renal failure, contrast allergies, pregnancy, or pediatric patients. USG, on the other hand, may be limited by bowel gas interference, obesity, operator dependency, and technical inadequacies, making it less reliable in some cases. Additionally, limited access to advanced imaging techniques in peripheral hospitals may delay diagnosis.[7] Under such circumstances, the use of inflammatory biomarkers in clinical evaluation and diagnostic processes becomes increasingly important.

Hematological and biochemical markers such as C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and delta neutrophil index (DNI) are widely used parameters for assessing systemic inflammatory response. CRP is an acute-phase reactant secreted by hepatocytes in response to pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), and it serves as a crucial indicator of disease severity.[8] NLR reflects the ratio between neutrophil elevation and lymphocyte reduction during inflammation, thereby providing insights into the severity of the inflammatory process.[9] DNI quantifies the proportion of circulating immature granulocytes, aiding in the detection of bacterial infections and assessment of the degree of inflammation.[10]

The use of inflammatory biomarkers not only supports diagnosis but also provides valuable information regarding disease prognosis and treatment decision-making. However, the extent to which these biomarkers differentiate between acute appendicitis, acute cholecystitis, and acute diverticulitis, and their reliability in diagnosis and differential diagnosis, remains unclear.

In this study, we aimed to compare the inflammatory response among patients with acute appendicitis, acute cholecystitis, and acute diverticulitis to evaluate the potential role of biomarkers in differential diagnosis. Furthermore, we sought to investigate the utility of these biomarkers in predicting disease prognosis and guiding clinical decision-making, particularly in settings with limited imaging availability, to determine whether they contribute to the diagnostic and therapeutic process.

Material and Methods

This retrospective study was conducted with adults aged ≥18 years who were treated in the general surgery clinic with a diagnosis of acute appendicitis, acute cholecystitis, or acute colonic diverticulitis between February 2019 and November 2020. A total of 1.198 case files were retrospectively screened. Patients younger than 18 years, those with diabetes mellitus, malignancies, immunodeficiency, severe heart failure, liver or kidney failure, a history of or-

gan transplantation, absence of a radiologically confirmed diagnosis, or cases where study criteria were not assessed at the time of presentation were excluded from the study.

The total white blood cell (WBC) count, neutrophil count, lymphocyte count, eosinophil count, neutrophil-to-lymphocyte ratio (NLR), delta neutrophil index (DNI), and C-reactive protein (CRP) levels were compared among the three groups. These parameters were assessed using the initial blood samples obtained in the emergency department. Hematological parameters were measured with the Siemens ADVIA 2120i Hematology Analyzer (Ireland, Dublin,2019). Leukocytosis and leukopenia were defined as WBC > 10.6 × 10^9/L and WBC < 3.5 × 10^9/L, respectively, based on the reference values provided by the laboratory medicine department of our hospital. The reference values of neutrophil, lymphocyte and eosinophil were taken as 1.5-7.7 (× 10 ^ 9)/L, 1.1-4 (× 10 ^ 9)/L and 0.02-0.5 (× 10 ^ 9)/L, respectively. CRP was measured using the Siemens Adria Chemistry XPT (Japan, Tokyo, 2018) device, taking 0-5 mg/dl as reference. The neutrophil-to-lymphocyte ratio (NLR) was automatically calculated as the ratio of the neutrophil count to the lymphocyte count using the ADVIA 2120i Hematology Analyzer.

Statistical Analysis

The patients' characteristics were summarized using descriptive statistics. Numerical parameters were presented as mean, standard deviation, minimum, and maximum values, with 95% confidence intervals provided where applicable. Non-numerical parameters were reported as frequencies and percentages. For secondary analyses, the Kolmogorov-Smirnov test was employed to assess the distribution of all variable groups. Parametric tests were applied to normally distributed variables, while non-parametric tests were used for variables with non-normal distributions. Analysis of variance (ANOVA) was performed for parameters with a normal distribution. The threshold for statistical significance (p-value) was set at 0.05. All statistical analyses were carried out using SPSS version 22.0.

Parameters that did not show normal distribution were compared using the Kruskal-Wallis test. Significant results from these analyses were further investigated using the Mann-Whitney U test. The chi-square test was employed for the comparison of categorical data. It was observed that age, WBC and neutrophil values showed normal distribution while the other values did not show normal distribution. Finally, receiver operating characteristic (ROC) analysis was conducted to determine the sensitivity, specificity, and recommended cut-off value of DNI for each group. For this analysis, DNI values from 51 cases with a homogeneous age and gender distribution, consisting of healthy individuals who visited the check-up outpatient clinic of our hospital, were utilized.

Results

A total of 1.198 case files were screened, and 62 appendicitis, 56 colonic diverticulitis and 53 calculus cholecystitis cases were included in the study. All pathologies had been radiologically confirmed by ultrasonography or computed tomography. The general datas of the study are given tables 1.

Table 1: General data of the patient groups

Parameter	Acute appendicitis	Acute diverticulitis	Acute cholecystitis	p	
WBC	12.290.48±4.475.40	13.117.50±3.933.07	12.995.85±5.443.67	0.577	*
Neutrophil count	9.739.52±4.107.08	10,223.75±3,770.14	10.386.60±4.893.01	0.695	*
Lymphocyte count	1.555 (400-5070)	1,920 (220-4,420)	1390 (220-4.420)	0.024	**
Eosinophil count	95 (10-460)	115 (10-470)	90 (0-950)	0.187	**
NLR	6.06 (1.40-30.27)	5.82 (1.32-26.41)	6.07 (1.71-30.84)	0.614	**
DNI	0.09 (0.01-11.7)	0.08 (0.01-7.8)	0.09 (0.01-13.5)	0.833	**
CRP	38.9 (2-258)	75.75 (6.25-303)	48 (2-354)	0.011	**

*ANOVA **Kruskal-Wallis test

WBC :White blood cell, NLR: Neutrophil Lymphocyte Ratio, DNI:Delta neutrophil index, CRP:C-reactive protein

The mean WBC and neutrophil counts were elevated in all three groups, although no statistically significant differences were observed between them. The mean lymphocyte counts fell within the reference ranges for all three groups; however, a significant difference was noted in the diverticulitis group (appendicitis-diverticulitis, p = 0.037; cholecystitis-diverticulitis, p = 0.011). No statistically significant differences were found in the mean eosinophil values among the three groups. The NLR and DNI were elevated in all three groups, but no statistically significant differences were observed.

The DNI values for all three groups were evaluated using ROC analysis. For acute appendicitis, the area under the curve (AUC) was calculated

as 0.771 ($p < 0.01$), with a DNI cut-off value of 1 yielding a sensitivity of 0.532 and a specificity of 0.925. For acute diverticulitis, the AUC was 0.742 ($p < 0.01$), with a sensitivity of 0.589 and specificity of 0.81 for a DNI cut-off value of 1. For acute cholecystitis, the AUC was calculated as 0.758 ($p < 0.01$), and a DNI value of 1 demonstrated a sensitivity of 0.547 and specificity of 0.929 (Figure 1).

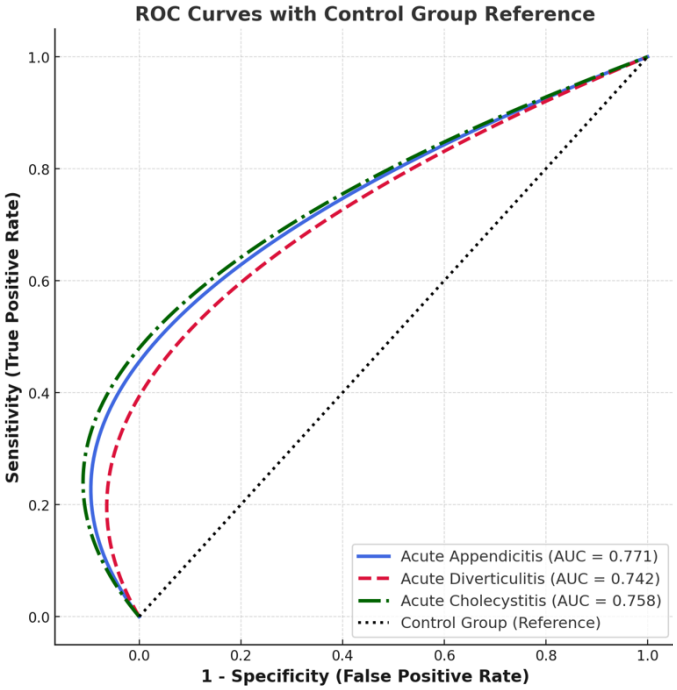

Figure 1: DNI ROC curves values for the three diagnoses

A significant difference was observed among the groups in terms of CRP and lymphocyte values, as determined by the Kruskal-Wallis test ($p < 0.05$). The Mann-Whitney U test, used to identify the group(s) responsible for the significant difference, revealed that the difference in CRP was attributed to the acute diverticulitis group (appendicitis vs diverticulitis, $p = 0.004$; cholecystitis vs diverticulitis, $p = 0.022$). Both CRP and lymphocyte values were significantly higher in the acute diverticulitis group.

The mean age of patients in the appendicitis group was statistically lower than that of the other two groups (appendicitis vs diverticulitis, $p = 0.012$; appendicitis vs cholecystitis, $p < 0.001$) (Table 2). No statistically significant differences were observed between the three groups regarding gender distribution (Table 3).

Table 2: Age distribution of the cases

Parameter	Acute appendicitis	Acute diverticlitis	Acute cholecystitis	p
Age	45.85±11.08	53.35±16.22	57.49±14.79	<0.001

Table 3: Muscle Analysis Results

Group		Female	Male	p
Acute appendicitis	Count	23	39	0.165
	% within the group	62.9%	37.1%	
Acute diverticulitis	Count	30	26	
	% within the group	53.6%	46.4%	
Acute cholecystitis	Count	24	29	
	% within the group	45.3%	54.7%	

Discussion

In this study, we aimed to investigate how the acute inflammatory response differs among patients with acute appendicitis, acute cholecystitis, and acute diverticulitis, as well as the role of inflammatory biomarkers in differential diagnosis. Our findings indicate that CRP and lymphocyte levels were significantly higher in the acute diverticulitis group ($p<0.05$), whereas DNI, NLR, WBC, and neutrophil levels were elevated in all three patient groups but did not show significant differences between them ($p>0.05$).

These differences suggest that the inflammatory process varies depending on the pathophysiological mechanisms of each disease, and the severity and systemic implications of inflammation may differ accordingly. The significantly higher CRP levels in acute diverticulitis patients may indicate that this condition is associated with more severe or prolonged inflammation. The elevated lymphocyte levels in this group may be related to the chronic inflammatory component of acute diverticulitis.

The observed increases in CRP and lymphocyte levels should not be regarded as specific tools for differential diagnosis; rather, they should be considered supportive parameters that may contribute to the diagnostic process when evaluated together with clinical and other laboratory findings.

CRP is a crucial component of the systemic response to acute inflammation and is secreted by hepatocytes in response to pro-inflammatory cytokines such as IL-6, IL-1, and TNF-α.[11–13] In our study, CRP levels were significantly higher in the acute diverticulitis group compared to the acute appendicitis and acute cholecystitis groups.

This finding is consistent with some studies in the literature. A review including 21 studies on diver-

ticulitis reported that CRP levels were significantly elevated in patients with complicated diverticulitis, and CRP levels above 150–200 mg/L were helpful in predicting perforation and the need for surgical intervention.[14–15] Additionally, CRP levels below 50 mg/L were associated with a lower likelihood of perforation, highlighting CRP as a potential marker for risk stratification.

A recent meta-analysis of 17 studies identified CRP as the most important laboratory biomarker for diagnosing diverticulitis, with particularly high negative predictive value.[16] These findings suggest that the inflammatory response in acute diverticulitis may be more severe or prolonged due to the nature of colonic pathology, delayed presentation, or microbial composition.

The neutrophil-to-lymphocyte ratio (NLR) is a hematological biomarker that reflects the dynamic balance between innate immunity (neutrophils) and adaptive immunity (lymphocytes). It is widely used in the assessment of inflammation, infection, stress, and cancer prognosis.[17] Clinical studies have shown that NLR has high sensitivity in diagnosing and classifying systemic infections, sepsis, and bacteremia, making it a valuable prognostic marker.[18]

A study involving 799 patients with histologically confirmed appendicitis found that NLR was significantly higher in cases of complicated appendicitis, with an area under the curve (AUC) value of 0.727 and a cutoff value of 6.96, suggesting its potential use as a biomarker for disease severity.[19]

In our study, NLR levels were found to be elevated in patients with acute appendicitis, acute cholecystitis, and acute diverticulitis; however, no statistically significant differences were observed between the groups. This suggests that while NLR is a sensitive marker for intra-abdominal inflammation, it may not be sufficiently specific for differential diagnosis.
DNI, which measures the proportion of immature granulocytes in peripheral circulation, is gaining increasing attention as a marker of infection severity.[20] It has been reported to be associated with sepsis, bacterial infections, and acute inflammatory conditions.[21–22]

Our ROC analysis demonstrated that DNI values were significantly elevated across all patient groups, with strong diagnostic potential as indicated by AUC values.However, no significant differences were found between the disease groups. This suggests that although DNI is a reliable marker for detecting acute inflammation, it has limited specificity in distinguishing between appendicitis, diverticulitis, and cholecystitis.

In our study, WBC and neutrophil levels were elevated in all three patient groups, but no significant differences were observed between them. This finding indicates that while these parameters are useful in identifying the inflammatory process, they are not sufficient for differentiating between different etiologies.[23–25]

The results of this study suggest that inflammatory biomarkers alone are not sufficient for differential diagnosis but are effective in identifying intra-abdominal infections. Particularly in peripheral hospitals or settings with limited imaging availability, inflammatory biomarkers may contribute to diagnosis and assist in patient management.

This study has certain limitations. Being a single-center, retrospective study may limit the generalizability of the results. Additionally, the relatively small sample size may have prevented the identification of potential differences between inflammatory biomarkers in a larger cohort. The study only evaluated biomarker levels at the time of presentation, without assessing changes over time. Moreover, precise diagnostic cutoff values for these biomarkers were not determined, and their correlations with imaging modalities were not analyzed in detail.

Intra-abdominal infections have distinct pathophysiological mechanisms, making it natural for inflammatory biomarkers to exhibit disease-specific variability. A better understanding of these mechanisms may enhance the role of inflammatory biomarkers in clinical evaluation. Our findings should be validated in larger patient cohorts through prospective studies, and further research should explore the effectiveness of combining inflammatory biomarkers in the diagnostic process.

Conclusion

This study aimed to evaluate the differences in inflammatory responses among patients with acute appendicitis, acute cholecystitis, and acute diverticulitis, as well as the potential role of biomarkers in differential diagnosis. Our findings indicate that CRP and lymphocyte levels were significantly elevated in patients with acute diverticulitis. However, while DNI, NLR, WBC, and neutrophil levels were elevated in all three groups, no statistically significant differences were observed between them.

The markedly higher CRP levels in diverticulitis suggest that the inflammatory process in this condi-

tion may be more prolonged and pronounced. However, despite the increased levels of biomarkers such as DNI and NLR across all patient groups, they were not sufficiently specific for differential diagnosis.

These results indicate that inflammatory biomarkers may be valuable in detecting intra-abdominal infections but may not be sufficient for definitive diagnosis on their own. Particularly in settings with limited imaging availability, these biomarkers may contribute to clinical assessment and serve as supportive diagnostic tools.

Nevertheless, further large-scale, prospective, and multicenter studies are required to enhance our understanding of inflammatory processes in these conditions. In particular, the mechanisms underlying the significant increase in CRP levels in diverticulitis and its potential diagnostic and prognostic implications should be explored in greater detail.

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CASE REPORT

A rare case of subacute thyroiditis presenting as severe neck pain and otalgia

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Abstract

Introduction: Subacute thyroiditis (de Quervain's thyroiditis) is a clinical disorder characterized by inflammation of the thyroid tissue. It is the most common cause of painful thyroid disease. Although its etiology is not fully understood, it is mainly caused by viral infections.

Case: A 41-year-old male patient presented to the internal medicine outpatient clinic complaining of severe pain on the left side of the face and ear a few weeks after an upper respiratory tract infection. The pain started in the neck and spread to the jaw and ear. It was continuous and seemed to increase with head movements and chewing. On physical examination, the thyroid gland was palpable and several cervical lymph nodes less than 1 cm in diameter were found. In addition, all other findings on systemic physical examination and vital signs were normal.Laboratory data revealed the following: TSH level 0.02 mIU/L (N: 0.34-5.60mIU/L), free T4 level: 2.53 ng/dL (N: 0.61-1.48 ng/dL), free T3 level 6.42 ng/L (N: 2.3-4.2 ng/L), erythrocyte sedimentation rate (ESR) 67 mm/h (N: 0-20 mm/h), C-reactive protein level (CRP) 13.6 mg/dL (0-0.8 mg/dL). Thyroid ultrasonography was non-specific. Scintigraphic examination reported a marked decrease in thyroid activity, loss of contour clarity and lack of involvement of the thyroid parenchyma. Tc99m pertechnetate showed no uptake in the thyroid gland, and scintigraphic examination revealed subacute thyroiditis. Based on the patient's physical examination and the laboratory and imaging studies performed on him, a diagnosis of subacute thyroiditis was made. Methylprednisolone was prescribed at a dose of 32 mg, which was gradually (The dose is reduced by half at one-week intervals) reduced and then discontinued at weekly follow-up visits after diagnosis. During th e follow-up period, notable improvement was observed in the patient's laboratory values.

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Introduction

Subacute granulomatous thyroiditis (de-Quervain thyroiditis) is a self-limiting, inflammatory and painful thyroid disease with severe pain after a possible viral infection of the thyroid gland.[1] Subacute granulomatous thyroiditis is a common cause of thyrotoxicosis and painful thyroiditis. There are several clinical symptoms associated with subacute granulomatous thyroiditis, including recent viral illness, swollen and inflamed thyroid glands, tenderness, thyrotoxicosis, reflex pain in the parietal, occipital, ear, jaw or throat, increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and a decrease in iodine uptake. Less common concomitant symptoms of de Quervain's thyroiditis include weakness, fatigue, arthralgia, low-grade fever, anemia, heterogeneous parenchymal changes on ultrasound (USG), and sometimes a decrease in blood flow signals on Doppler USG.[2] The pain usually starts in a single lobe and quickly spreads to the entire thyroid tissue and may radiate to the jaw and ears. Radiation, infection, trauma and subacute granulomatous thyroiditis are all causes of painful thyroiditis. Subacute granulomatous thyroiditis typically begins with thyrotoxicosis, followed by hypothyroidism and euthyroidism. This painful process usually resolves within a few weeks, but can sometimes take up to several months.

Case

A 41-year-old male patient presented to the internal medicine outpatient clinic complaining of severe pain on the left side of the face and ear a few weeks after an upper respiratory tract infection. The pain started in the neck and spread to the jaw and ear. It was continuous and seemed to increase with head movements and chewing. On physical examination, the thyroid gland was palpable and several cervical lymph nodes less than 1 cm in diameter were found. In addition, all other findings on systemic physical examination and vital signs were normal. At the time of his visit to our outpatient clinic, the patient had no known chronic illnesses and had not taken any medication in the past, but he had consumed several boxes of antibiotics prior to his appointment. A comprehensive review of our laboratory data revealed the following: TSH level 0.02 mIU/L (N: 0.34-5.60mIU/L), free T4 level: 2.53 ng/dL (N: 0.61-1.48 ng/dL), free T3 level 6.42 ng/L (N: 2.3-4.2 ng/L), erythrocyte sedimentation rate (ESR) 67 mm/h (N: 0-20 mm/h), C-reactive protein level (CRP) 13.6 mg/dL (0-0.8 mg/dL). Thyroid ultrasonography was non-specific (Figure 1). However, several lymphadenopathies smaller than 1 cm in diameter were located in the neck and reactive lymphadenopathies were found in the paratrecheal, submandibular, and parapharyngeal regions of the neck. Scintigraphic examination reported a marked decrease in thyroid activity, loss of contour clarity and lack of involvement of the thyroid parenchyma (Figure 2). Tc99m pertechnetate showed no uptake in the thyroid gland, and scintigraphic examination revealed subacute thyroiditis. Based on the patient's physical examination and the laboratory and imaging studies performed on him, a diagnosis of subacute thyroiditis was made. Methylprednisolone was prescribed at a dose of 32 mg, which was gradually (The dose is reduced by half at one-week intervals) reduced and then discontinued at weekly follow-up visits after diagnosis. During th e follow-up period, notable improvement was observed in the patient's laboratory values.

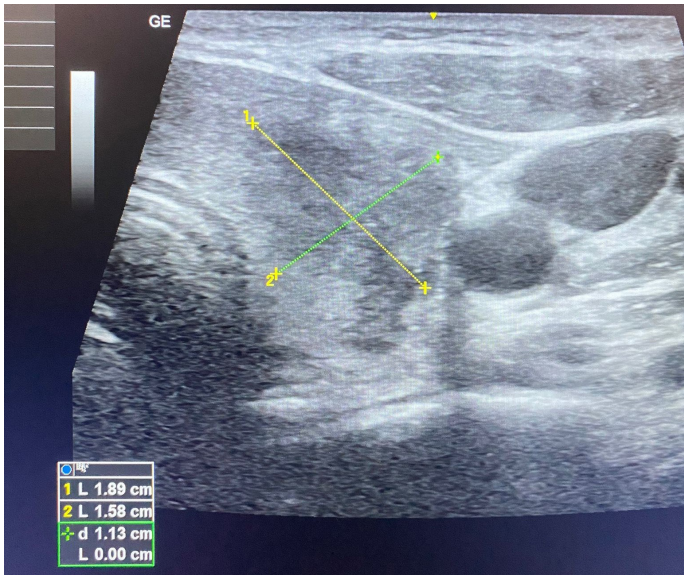

Figure 1: Ultrasonographic image of the case.

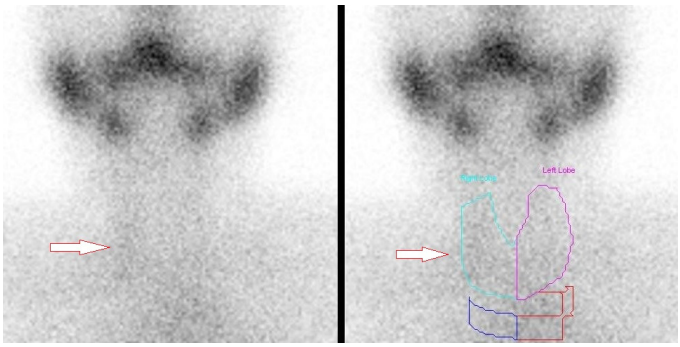

Figure 2: Scintigraphic image of the case. Arrow signs indicate the thyroid gland. Here it is seen that the thyroid gland does not retain any radioactive iodine.

Discussion

Subacute granulomatous thyroiditis occurs in 12 out of 100,000 people and is 3 to 5 times more common in women than in men.[3] It is a self-limiting disease. Although most patients are symptomatic, there is a risk of recurrence. It is known that the disease has a viral origin.[4] The pathogenesis consists of the destruction of the thyroid follicles by the attack of acute inflammatory cells and histiocytes, which are pseudogranulocytes, on the thyroid tissue. In the early phase of the disease, both T4 and T3 levels are elevated. There may be an increase in plasma thyroglobulin and ESR.[5] Technetium-99 uptake from the thyroid gland is low due to the destruction of the parenchyma. In the thyroid USG, the thyroid lobe appears hypoechoic and irregular.[6]

Many patients go through three different stages of the disease. First, the hyperthyroid phase of subacute granulomatous thyroiditis lasts until the colloid previously produced in the gland is depleted. This leads to a temporary hypothyroid phase, as no new thyroid hormone biosynthesis can take place after depletion. During the healing phase, thyroid functions gradually increase and return to normal, but some patients may develop permanent hypothyroidism. The following factors are thought to favour the development of permanent hypothyroidism: high-dose glucocorticoid therapy, female sex, positive antibodies, postpartum development and administration of ibuprofen alone.[7-9]

The differential diagnosis includes several diseases with a similar clinical picture. These; hashitoxicosis, acute pyogenic fungal and bacterial thyroiditis, acute hemorrhagic degeneration of thyroid nodules (haemorrhage in the nodules), diffuse infiltration of malignancies and anaplastic thyroid carcinoma can be confused with SAT.[10-12]

While subacute thyroiditis can typically be identified through anamnesis and physical examination, accurately diagnosing this condition may prove challenging. However, with proper diagnosis and treatment, patients can experience significant improvement in their clinical condition during the early stages of the disease and maintain a normal lifestyle. Steroids and NSAIDs are commonly employed for treatment.[13] For most patients, NSAIDs alone provide sufficient pain relief. However, a subset of patients does not respond to NSAIDs, necessitating the initiation of prednisolone at a dosage of 20-40 mg/day. Symptomatic improvement is typically observed in the majority of patients with this treatment regimen. It is crucial to gradually reduce the dosage of steroid therapy to avoid the development of adrenal insufficiency upon discontinuation. Notably, about 20% of patients experience a relapse following steroid discontinuation, requiring reinitiation of steroid therapy. In the thyrotoxic phase, propranolol is recommended. Consequently, approximately 90% of patients achieve complete recovery and resume their lives in a euthyroid state. Conversely, approximately 10% of patients develop persistent hypothyroidism later in life, necessitating lifelong levothyroxine replacement therapy.

Conclusion

In our case, Subacute Granulomatous Thyroiditis was triggered by a viral upper respiratory tract infection. The patient was initiated on methylprednisolone at a dosage of 32 mg, which was gradually tapered during weekly follow-ups. Laboratory values exhibited complete improvement during subsequent assessments.

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LETTER TO THE EDITOR

The Importance of Etiological Cause in Patients Admitted to The Intensive Care Unit with Acute Respiratory Distress Syndrome

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There are many underlying etiologic causes in patients admitted to the emergency department with pulmonary edema and acute respiratory distress syndrome (ARDS).[1] While the most common cause of pulmonary edema is cardiogenic problems, ARDS has non-cardiogenic pulmonary edema and viral and bacterial pulmonary infections are the most common causes of ARDS.[2] Here, we report a case that illustrates the importance of identifying treatable underlying causes, including severe valvular disease and viral infection, in a patient presenting with ARDS.

A 47-year-old male was admitted to the emergency room with acute respiratory distress, chest pain, and mild confusion. On arrival, he was tachypneic (respiratory rate: 34/min), hypoxic (SpO_2: 82% on room air), tachycardic (HR: 110 bpm), and normotensive (BP: 130/85 mmHg). He rapidly deteriorated, necessitating intubation. The patient has no known diseases and no history of smoking, alcohol, or drug use. In his family history, his father only has primary hypertension. Initial laboratory and imaging studies revealed elevated acute-phase reactants (CRP: 185 mg/L, ferritin: 420 ng/mL), and chest X-ray showed bilateral ground-glass appearance, infiltrative findings and diffuse pulmonary edema. Arterial blood gas revealed a PaO_2/FiO_2 ratio < 100. APACHE II score on admission was 18.

The patient was hospitalized in the level 3 intensive care unit with a prediagnosis of viral pneumonia and ARDS. In the intensive care unit, the patient is placed in the prone position and given positive pressure ventilator support. Diuretic, broad-spectrum antibiotic and oseltamivir treatment was started. Deep tracheal aspirate culture was negative. Upon detection of Influenza A in the upper respiratory tract panel, antibiotic treatment was narrowed and the diagnosis of ARDS secondary to viral pneumonia was confirmed. Forty-eight hours after intubation, blood gases improved (PaO_2/FiO_2 > 250), and and extubation was performed at the 72nd hour with effective diuresis. At this stage, echocardiographic assessment demonstrated severe stenosis of both the aortic and mitral valves (mitral valve area: 0.9 cm^2, mean gradient: 14 mmHg; aortic valve area: 0.7 cm^2, mean gradient: 40 mmHg), for which the cardiology recommended valve replacement. The patient was admitted to the ward five days after intensive care and two weeks after the completion of infection treatment, the patient underwent aortic and mitral valve replacement by the cardiovascular surgeon. And our patient resumed his social life in a short time.

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This case underlines the complex interplay between infectious and structural cardiac causes in ARDS. While viral pneumonia (Influenza A) likely triggered the acute deterioration, underlying unrecognized valvular disease significantly contributed to pulmonary edema.[3] In our case, both ARDS and pulmonary edema due to valvular heart pathologies were present and there were limitations in making an accurate definition. Although cardiovascular, atherosclerotic diseases, hypervolemia, renal failure or infectious agents are usually involved, it is necessary to determine the triggering factor correctly. Because if the triggering clinical picture is a correctable cause, we can prevent the patient from re-entering a mortal picture such as ARDS or pulmonary edema. As in our case, in a patient with aortic and mitral stenosis due to acute rheumatic fever, valve replacement can reduce the risk of sudden cardiac death and pulmonary edema.

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