Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:195-201
DOI: 10.4274/BMJ.galenos.2022.2022.3-8

Research

May Hepatic Steatosis Be Associated with Gynecomastia and Epicardial Fat? A Retrospective Study of 599 Male Patients

Hepatik Steatoz Jinekomasti ve Epikardiyal Yağlanma ile İlişkili Olabilir mi? 599 Erkek Hastanın Retrospektif Analizi

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ABSTRACT

Objective: There is no study in the literature investigating the association of hepatic steatosis both gynecomastia and epicardial fat thickness together. We determined the correlations between hepatic steatosis through liver density, gynecomastia and epicardial fat thickness in patients undergoing computed tomography (CT) scans due to suspected coronavirus disease-2019 (COVID-19) symptoms.

Methods: A total of 599 male patients who underwent chest CT scans because of a presumed diagnosis of COVID-19 in our radiology clinic were included in the study. Patients' age, diameters of the subareolar glandular tissues of the right and left breasts, the right retroareolar fatty tissue, liver and spleen density, epicardial fat thickness and biochemical parameters were recorded and analyzed. Laboratory analyses were performed according to the standard methods.

Results: The mean age of the patients was 47.21±15.00 years. The left subareolar tissue thickness and the right retroareolar fatty tissue thickness that are used to indicate gynecomastia were significantly correlated with liver density in the negative direction ($r=-0.137$, $p<0.001$; $r=-0.172$, $p<0.001$; respectively). Epicardial fat thickness was statistically significantly correlated with right subareolar tissue thickness ($r=0.085$, $p=0.037$), left subareolar tissue thickness ($r=0.101$, $p=0.014$) and right retroareolar fatty tissue thickness ($r=0.148$, $p<0.001$).

Conclusion: The results of this study showed that gynecomastia was significantly correlated with both age and hepatic steatosis. Epicardial fat thickness is also associated with hepatic steatosis. We demonstrated the significant correlations between epicardial fat thickness and gynecomastia for the first time. Nevertheless, our results need to be confirmed by further comprehensive studies.

Keywords: Hepatic steatosis, gynecomastia, epicardial fat, computed tomography

ÖZ

Amaç: Literatürde hepatik steatozun hem jinekomasti hem de epikardiyal yağ kalınlığı ile ilişkisini araştıran bir çalışma bulunmamaktadır. Şüpheli koronavirüs hastalığı-2019 (COVID-19) semptomları nedeniyle bilgisayarlı tomografi (BT) taraması yapılan hastalarda karaciğer yoğunluğu, jinekomasti ve epikardiyal yağ kalınlığı ile hepatik steatoz arasındaki ilişkileri belirlemeyi amaçladık.

Gereç ve Yöntem: Radyoloji kliniğimizde COVID-19 ön tanısı ile akciğer tomografisi çekilen toplam 599 erkek hasta çalışmaya dahil edilmiştir. Hastaların yaşı, sağ ve sol meme subareolar glandüler doku çapları, sağ retroareolar yağ dokusu, karaciğer ve dalak yoğunluğu, epikardiyal yağ kalınlığı ve biyokimyasal parametreleri kaydedilerek analiz edilmiştir. Laboratuvar analizleri standart yöntemlere göre yapılmıştır.

Bulgular: Hastaların yaş ortalaması 47,21±15,00 yıldır. Jinekomasti varlığını belirtmek için kullanılan sol subareolar doku kalınlığı ve sağ retroareolar yağ dokusu kalınlığı negatif yönde karaciğer yoğunluğu ile anlamlı olarak ilişkili bulundu (sırasıyla $r=-0,137$, $p<0,001$; $r=-0,172$, $p<0,001$). Epikardiyal yağ kalınlığı, sağ subareolar doku kalınlığı ($r=0,085$, $p=0,037$), sol subareolar doku kalınlığı ($r=0,101$, $p=0,014$) ve sağ retroareolar yağ dokusu kalınlığı ($r=0,148$, $p<0,001$) ile istatistiksel olarak anlamlı korelasyon göstermiştir.

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Cite as: Aksoy SH, Aydın S, Yurdaışık I, Dalkılıç O. May Hepatic Steatosis Be Associated with Gynecomastia and Epicardial Fat? A Retrospective Study of 599 Male Patients. Med J Bakirkoy 2022;18:195-201

Received: 22.03.2022
Accepted: 19.04.2022

Sonuç: Bu çalışmanın sonuçları, jinekomastinin hem yaş hem de karaciğer yağlanması ile önemli ölçüde ilişkili olduğunu göstermiştir. Epikardiyal yağ kalınlığı da karaciğer yağlanması ile ilişkilidir. Epikardiyal yağ kalınlığı ile jinekomasti arasındaki anlamlı korelasyonu ilk kez gösterdik. Bununla birlikte, sonuçlarımızın daha kapsamlı çalışmalarla doğrulanması gerekmektedir.

Anahtar Kelimeler: Hepatik steatoz, jinekomasti, epikardiyal yağ, bilgisayarlı tomografi

INTRODUCTION

Hepatic steatosis, also known as fatty liver disease, refers to the accumulation of triglycerides within cytoplasmic vesicles of hepatocytes. Hepatic steatosis is associated with liver damage ranging from simple steatosis to liver fibrosis, cirrhosis and hepatocellular carcinoma (1). Numerous risk factors of developing hepatic steatosis have been identified, including diabetes mellitus, insulin resistance, obesity, dyslipidemia, hypertension and alcohol overuse (2). The prevalence of hepatic steatosis has been reported 3-39% due to variable and subjective diagnostic criteria (3,4). Several imaging modalities such as ultrasound, computed tomography (CT) and magnetic resonance imaging can show changes in hepatic steatosis in a non-invasive manner. CT can provide more objective measurement of liver density, thus hepatic steatosis (5). Non-contrast CT scan can detect hepatic steatosis with a sensitivity of 82% and specificity of 100% (6).

Gynecomastia is a benign proliferation of breast glandular tissue in men. It is the most common male breast abnormality and is thought to develop due to a hormonal imbalance through multiple mechanisms (7). Gynecomastia can be physically disturbing, causing psychological distress and may have negative effects on body image and self-confidence. Glandular tissue of ≥2 cm in the subareolar area is generally accepted as gynecomastia (8). The prevalence of gynecomastia has been reported to be between 32-65% depending on the diagnostic method, age and lifestyle (9). However, the actual incidence of gynecomastia in the general population is unclear because most of these patients are asymptomatic and breast screening is not routinely performed in men. The widespread use of CT for other indications results in gynecomastia to is reported commonly as an incidental finding on thoracic CT (10). Some studies have reported that hepatic liver disease is among the risk factors of developing gynecomastia (11). Patients with hepatic steatosis often have high estrogen and low testosterone levels that clinically manifest as testicular atrophy, palmar erythema and gynecomastia (12). However, the exact mechanism through which hepatic steatosis can contribute to the development of gynecomastia has yet to be clarified.

However, the severity of hepatic steatosis has been associated with epicardial fat thickness, which is a marker of visceral fat (13). Hepatic steatosis may coexist and interplay with epicardial fat. Quantification of epicardial fat thickness can be easily obtained using multislice CT. Measurement of the epicardial fat thickness on CT is performed using regions of interest on short axis views (14). To the best of our knowledge, there is no study in the literature investigating the association of hepatic steatosis with both gynecomastia and epicardial fat thickness. In this study, we determined the correlations between hepatic steatosis through liver density, gynecomastia and epicardial fat thickness in patients undergoing CT scans due to suspected coronavirus disease-2019 (COVID-19) symptoms.

METHODS

Before the beginning, the study protocol was approved by the local ethics committee of Istinye University with the 05/08/2021 dated and (2017-KAEK-120)/2/2021.G-111 numbered decision. The study was conducted in accordance with the ethical principles of 1964 Declaration of Helsinki and its later amendments.

A total of 599 male patients who underwent chest CT scans due to a presumed diagnosis of COVID-19 in our radiology clinic between 2018 and 2021 were included in the study. Female patients, those with established heart disease, hepatic failure, renal failure, active infection, malignancy, chronic systemic inflammatory disease and patients with missing data were excluded from the study. Patients' age, diameters of the subareolar glandular tissues of the right and left breasts, diameter of the right retroareolar fatty tissue, liver density, spleen density, epicardial fat thickness and biochemical parameters including fasting blood glucose, the levels of cholesterol, triglycerides, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase and gamma-glutamyltransferase were recorded and analyzed.

Blood samples were collected from the patients after a 12-h fasting for laboratory analysis of fasting blood glucose, cholesterol, triglycerides and liver enzymes. Laboratory analyses were performed according to the standard methods.

CT Examinations

All images were taken using a 160-slices 320-row area detector CT device (Aquilion Prime ONE 320, Toshiba Medical Systems). CT protocols were performed at 120 kV, 100-200 mA and reconstructed at a slice thickness of 1 mm. The diagnosis of gynecomastia was established as a glandular tissue diameter (long axis of the area showing increased density) ≥2 cm at the nipple level in the axial plane or a glandular tissue diameter between 1 and 2 cm accompanied by vertical growth consistent with gynecomastia. Measurements of axial diameters were made separately for both breasts (Figure 1). Hepatic steatosis was defined as a liver density at least 10 Hounsfield Units (HU) smaller than the spleen density or a liver density <40 HU as measured on CT images (Figure 2). Epicardial fat thickness was measured from the visceral epicardium to the outside of the myocardium, and perpendicular to the surface of the heart on the axial section in millimeters (Figure 3).

Statistical Analysis

All statistical analyses were performed using SPSS 25.0 (SPSS, Statistical Package for Social Sciences, IBM Inc., Armonk, NY, USA) software. Continuous variables were expressed as mean ± standard deviation, while categorical variables were given as frequency (n) and percentage (%). The normal distribution of the data was evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. Statistical correlations between hepatic steatosis, gynecomastia, epicardial fat and laboratory parameters were examined with Pearson's correlation analysis (r).

RESULTS

A total of 599 male patients with a diagnosis of gynecomastia were included in the study. The mean age of the patients was 47.21±15.00 years. The age distribution of the gynecomastia patients is shown in Figure 4.

When parameters of epicardial fat were examined; the mean diameter of right subareolar granular tissue was measured as 12.27±5.95 mm, the mean diameter of left subareolar granular tissue as 14.70±7.07 mm and the mean diameter of right retroareolar fatty tissue as 18.29±9.55 mm.

The mean liver density of the patients was measured as 51.03±10.85 HU and the mean spleen density as 48.12±8.06 HU. The mean epicardial fat thickness was measured as 5.91±3.88 mm. Laboratory findings of the biochemical parameters are shown in Table 1.

The correlations between gynecomastia, hepatic steatosis, epidural fat thickness and biochemical parameters were evaluated with Pearson's correlation analysis. Accordingly, age was positively correlated with the left subareolar glandular tissue diameter (r=0.113, p=0.05), and right retroareolar fatty tissue diameter (r=0.116, p=0.04), and epicardial fat thickness (r=0.189, p<0.001) and negatively correlated with spleen density (r=-0.125**, p=0.002). Statistically significant strong correlations were found between right subareolar tissue thickness, left subareolar tissue thickness, right retroareolar fatty tissue thickness, liver density, spleen density and epicardial fat thickness (Table 2).

However, liver density showed a strong positive correlation with cholesterol (r=0.262, p<0.00) and a strong negative correlation with triglycerides (r=-0.122, p=0.004), while spleen density was strongly correlated with cholesterol (r=0.194, p<0.001), AST (r=0.235, p<0.001) and ALT (r=0.232, p<0.001) in the positive direction. No statistically

Table 1. Biochemical parameters of the patients

Biochemical parameter	Mean	± SD
Cholesterol	122.13	33.59
Triglycerides	130.27	80.78
Fasting blood glucose	113.85	40.78
AST	37.37	268.74
ALT	50.45	310.62
ALP	88.51	147.88
GGT	66.30	112.73

AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyltransferase, SD: Standard deviation

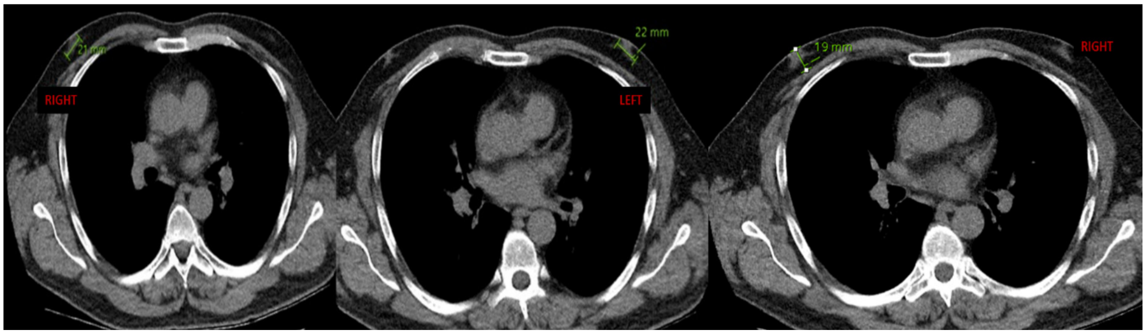

Figure 1. Measurements of gynecomastia parameters on CT sections: right subareolar glandular tissue diameter (left), left subareolar glandular tissue diameter (middle) and right retroareolar glandular tissue diameter (right)
CT: Computed tomography

Table 2. Correlations between the study parameters

		Right subareolar tissue thickness	Left subareolar tissue thickness	Right retroareolar fatty tissue thickness	Liver density	Spleen density	Epicardial fat thickness
Right subareolar tissue thickness	r	1	**0.524****	**0.304****	0.004	-0.032	**0.085***
	p	-	**<0.001**	**<0.001**	0.929	0.441	**0.037**
Left subareolar tissue thickness	r	**0.524****	1	-0.43	**-0.137****	-0.009	**0.101***
	p	**<0.001**	-	0.299	**0.001**	0.827	**0.014**
Right retroareolar fatty tissue thickness	r	**0.304****	-0.43	1	**-0.172****	-0.064	**0.148****
	p	**<0.001**	0.299	-	**<0.001**	0.116	**<0.001**
Liver density	r	0.004	**-0.137****	**-0.172****	1	**0.278****	**0.178****
	p	0.929	**0.001**	**<0.001**	-	**<0.001**	**<0.001**
Spleen density	r	-0.032	-0.009	-0.064	**0.278****	1	-0.003
	p	0.441	0.827	0.116	**<0.001**	-	0.947
Epicardial fat thickness	r	**0.085***	**0.101***	**0.148****	**0.178****	-0.003	1
	p	**0.037**	**0.014**	**<0.001**	**<0.001**	0.947	-

*Statistically significant, **Statistically highly significant

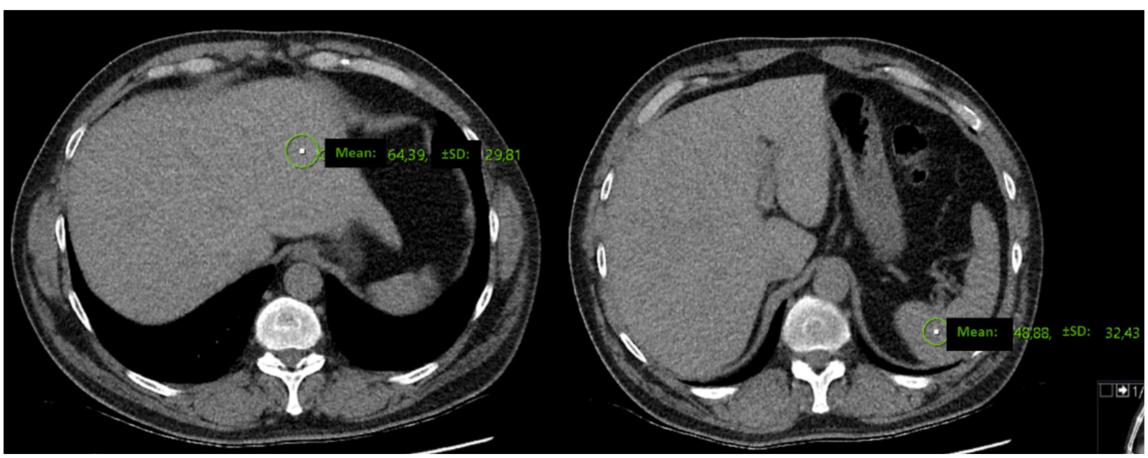

Figure 2. Measurements of hepatic steatosis parameters on CT images in Hounsfield Units: liver density (left), spleen density (right)
CT: Computed tomography

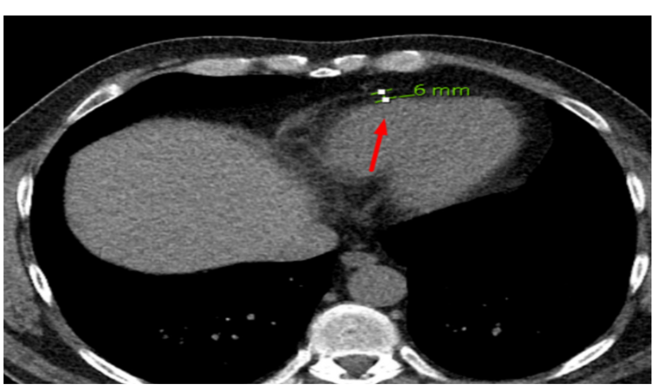

Figure 3. Measurement of epicardial fat thickness from the visceral epicardium to the outside of the myocardium

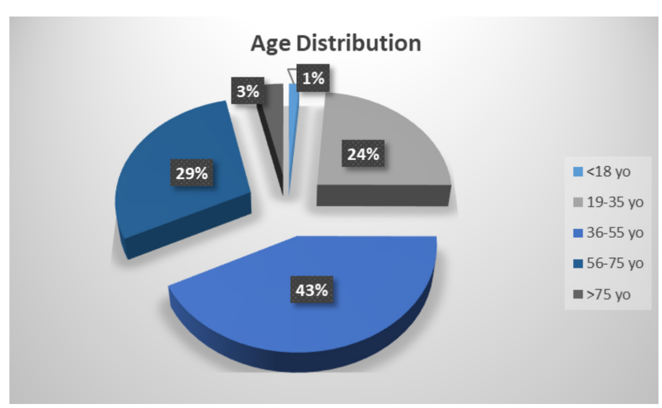

Figure 4. Distribution of the patients by age groups

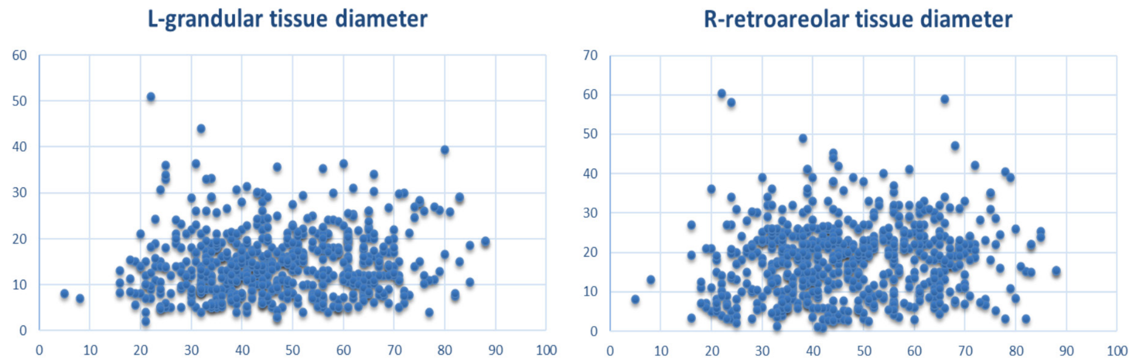

Figure 5. Correlations between age and glandular tissues of the left and right breasts

significant correlation was observed between the other study parameters.

DISCUSSION

The currently ongoing COVID-19 pandemic, has increased the number of CT scans performed due to a presumed diagnosis of pneumonia worldwide (8). This has caused various diseases and/or medical conditions to be noticed incidentally in CT examinations (15-17). However, this situation could be seen as an opportunity to retrospectively examine the relationships between various parameters through these CT scans with more objective measurements. In this study, we investigated the correlations between hepatic steatosis as determined on CT images of male patients who underwent chest imaging due to suspected COVID-19, gynecomastia, and epicardial fat thickness.

In this study, the mean age of patients with gynecomastia was found as 47.21 years. Kim et al. (9) reported the mean age as 56.99 years in 650 male patients with gynecomastia. Aslan et al. (8) reported the most common age group with gynecomastia as 30-39 years. This range was 36-55 years in our study, although age ranges were different between the two studies, general ranges were similar. Similar to our study, Aslan et al. examined CT images of male patients who were admitted during the COVID-19 pandemic to determine the prevalence of gynecomastia. The authors found significant correlations between age, right breast glandular tissue diameter ($r=0.235$, $p<0.001$) and left breast glandular tissue diameter ($r=0.219$, $p<0.001$) (8). In this study, age was positively correlated with the left subareolar glandular tissue diameter ($r=0.113$, $p=0.05$), and right retroareolar fatty tissue diameter ($r=0.116$, $p=0.04$) (Figure 5). These findings suggest a relationship between age and gynecomastia, possibly due to decreased testosterone levels with aging.

Studies investigating the relationship between liver disease and gynecomastia have reported conflicting results. Hepatic steatosis has been associated with low testosterone and high estrogen levels, diminished libido and gynecomastia, which is the most common benign condition characterized by enlargement of the male breast (18). Furthermore, there are studies reported that testosterone administration to cirrhotic patients has decreased the prevalence of gynecomastia (19). However, others could not find such a relationship and proposed that breast tissue sensitivity to a raised ratio of estrogen/testosterone is highly variable (11). In this study, the left subareolar tissue thickness and the right retroareolar fatty tissue thickness that are used indicate gynecomastia were significantly correlated with liver density in the negative direction ($r=-0.137$, $p<0.001$; $r=-0.172$, $p<0.001$; respectively) suggesting a relationship between hepatic steatosis and gynecomastia. Nevertheless, there is no sufficient data in the literature to draw a definitive conclusion on this issue and mechanisms of such a potential correlation are still to be clarified.

Epicardial fat accounts for 20% of heart weight and constitutes 80% of the heart's surface. Although it is a relatively neglected component of the heart, it has been proposed as a marker of cardiovascular risk (20,21). However, previous studies have reported the relationship between epicardial fat thickness and various diseases and medical conditions. Shemirani and Khoshavi (22) reported a correlation between epicardial fat thickness and the severity of coronary artery disease. Metwalley et al. (23) observed elevated epicardial fat thickness in pediatric patients with congenital adrenal hyperplasia. According to Petta et al. (13), in patients with non-alcoholic fatty liver disease, a higher epicardial fat thickness is associated with the severity of the disease. Iacobellis et al. (24) reported that epicardial fat thickness is a good indicator of hepatic steatosis in obese patients. Results of our study indicated a strong correlation between epicardial fat thickness and liver density, which is used to determine the presence of hepatic steatosis (r=0.178, p<0.01).

Although epicardial fat thickness is closely associated with fat deposition, no study could be found to investigate its correlation with fat proliferation in men's breasts, namely, gynecomastia. In this study, epicardial fat thickness was statistically significantly correlated with right subareolar tissue thickness (r=0.085, p=0.037), left subareolar tissue thickness (r=0.101, p=0.014) and right retroareolar fatty tissue thickness (r=0.148, p<0.001). However, the mechanisms underlying these correlations are yet to be clarified.

Study Limitations

The major limitations of this study include its retrospective design and being performed in a single center. Additionally, the same correlations could be investigated between obese and non-obese patients as epicardial fat thickness is closely associated with obesity. Finally, our results on the correlation between epicardial fat thickness and gynecomastia could not be compared due to the lack of similar studies. However, the number of our patients is relatively large and we examined the associations between hepatic steatosis, gynecomastia and epicardial fat thickness together, for the first time in the literature.

CONCLUSION

The results of this study showed that gynecomastia was significantly correlated with both age and hepatic steatosis. However, currently there is no clear data especially on the relationship between hepatic steatosis and gynecomastia. Additionally, epicardial fat thickness was also associated with hepatic steatosis. However, we demonstrated the significant correlations between epicardial fat thickness and gynecomastia for the first time. Nevertheless, our results need to be confirmed by further comprehensive multi-center studies with a larger series of patients.

Publication: This article has been published as pre-print on a website (researchsquare) as it can be seen in the similarity report. The link to the pre-print version is below: https://www.researchsquare.com/article/rs-1063300/v1

ETHICS

Ethics Committee Approval: Before the beginning, the study protocol was approved by the local ethics committee of Istinye University with the 05/08/2021 dated and (2017-KAEK-120)/2/2021.G-111 numbered decision.

Informed Consent: This was a retrospective study.

Authorship Contributions

Surgical and Medical Practices: S.H.A., S.A., I.Y., O.D., Concept: S.H.A., S.A., I.Y., O.D., Design: S.H.A., I.Y., Data Collection or Processing: S.H.A., O.D., Analysis or Interpretation: S.A., I.Y., Literature Search: S.H.A., S.A., O.D., Writing: S.H.A., I.Y.

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

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

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