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The relationship of atherogenic index of plasma with endothelial dysfunction biomarkers in patients with metabolic associated fatty liver disease

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ABSTRACT

Aims: The atherogenic index of plasma (AIP) is a marker used to predict atherosclerosis and cardiovascular disease (CVD). In this study, we examined the relationship of AIP with markers of endothelial dysfunction (ED) [asymmetric dimethylarginine (ADMA) and adiponectin] and early atherosclerosis [high-sensitivity C-reactive protein (hs-CRP)] in patients with metabolic associated fatty liver disease (MAFLD).

Methods: This was a cross-sectional study with retrospective enrollment. AIP was defined as the logarithmically transformed ratio of triglyceride to high-density lipoprotein cholesterol. All patients were divided into two groups according to whether they had steatohepatitis or fibrosis and were compared. Mean differences between two independent groups were assessed using the independent Student's t-test and Mann-Whitney U test as appropriate.

Results: A total of 129 male subjects with biopsy-proven MAFLD were enrolled. There were no significant differences regarding AIP (0.64±0.039 vs. 0.62±0.033, p=0.773) between patients with steatohepatitis (n=54) and without steatohepatitis (n=75). Additionally, similar findings were observed among subjects with fibrosis (n=84) and without fibrosis (n=45). However, there was no association of AIP with ADMA, adiponectin, hs-CRP, insulin and HOMA-IR levels (p=0.176, p=0.636, p=0.810, p=0.068, and p=0.126, respectively).

Conclusion: The lack of association between AIP and the biomarkers of ED or early atherosclerosis implies that this index may not be a significant predictor of CVD in MAFLD.

Introduction

Non-alcoholic fatty liver (FL) disease (NAFLD) is the most common chronic liver disease both in Türkiye and in the world. Recently, it was recommended that the disease be named and defined as metabolic associated FL disease (MAFLD) (1). The pathogenesis of MAFLD starts with hepatic fat accumulation, in association with peripheral insulin resistance (2,3). MAFLD is considered the liver component of metabolic syndrome (MetS) and is strongly associated with obesity, hypertension, type 2 diabetes mellitus (T2DM), and dyslipidemia (4,5). Overall, the combination of metabolic disorders leads to a significant increase in cardiovascular disease (CVD) risk. Ultimately, it has been reported that MAFLD confers an independent risk of CVD, apart from MetS and traditional cardiovascular risk factors (6-8).

Endothelial dysfunction (ED) plays an important role in the pathogenesis of the initial stage of atherosclerosis and is also a key factor in predicting future CVD (9,10). Multiple factors take part in the pathogenesis of ED, including increased oxidative stress, elevated asymmetric dimethylarginine (ADMA), angiotensin 2 and homocysteine, and decreased adiponectin levels (11-13). ADMA, an analog of L-arginine is a biomarker that decreases nitric oxide synthesis and therefore is associated with ED and CVD (14). Simultaneously, adiponectin is an important peptide secreted by adipocytes and is measured at low levels in obesity, MetS, T2DM, and CVD (15). Both ADMA and adiponectin are well-known biomarkers of ED and atherosclerosis (14,16). However, high-sensitivity C-reactive protein (hs-CRP), a systemic inflammatory marker connected with ED and atherosclerosis, is directly related to the risk of CVD (17).

The atherogenic index of plasma (AIP), a logarithmically transformed ratio of molar concentrations of triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C), is positively and strongly associated with obesity, T2DM, and MetS (18). Therefore, it has been reported to be associated with atherosclerosis and suggested as a novel biomarker for future risk of atherosclerosis and CVD (19). There are few studies in the current literature investigating the role of AIP in patients with MAFLD (20,21). However, the role of AIP in the prediction of increased CVD in MAFLD is unclear. To the best of our knowledge, the association of AIP with ED and atherosclerosis biomarkers has not been previously investigated in subjects with MAFLD. Therefore, this study examined the associations of AIP with cardiometabolic risk factors, and especially the relationship of AIP with ED or atherosclerosis in patients with MAFLD.

Methods

Study design and population

This retrospective study was performed using a previously obtained dataset of routine patient follow-up at the Gastroenterology Department, Gülhane Faculty of Medicine, Ankara, Türkiye (22,23). The participants were asymptomatic men who had undergone evaluation for elevated transaminases. Blood tests and liver biopsy were performed as part of the clinical algorithm. Patients with hypertension, T2DM, or those on medications that may affect the glucose or lipid metabolism (e.g., fibrates, statins) were excluded. The current study was approved by the Local Ethics Committee of Balikesir University Faculty of Medicine (approval no: 2020/164, date: 23.09.2020) and the study protocol conforms to the Helsinki Declaration.

MAFLD was diagnosed by the presence of one of the specific clinical conditions (overweight, obesity, T2DM, or evidence of metabolic dysregulation) in NAFLD patients. The metabolic dysregulation was defined by the presence of two of the criteria (24); 1) waist circumference (WC) ≥102 cm for men; 2) TG ≥150 mg/dL; 3) blood pressure ≥130/85 mmHg; 4) HDL-C <40 mg/dL for men; 5) prediabetes [e.g., glycated hemoglobin 5.7-6.4%, fasting plasma glucose (FPG) 100 to 125 mg/dL, or 2 h glucose levels 140 to 199 mg/dL]; 6) hs-CRP >2 mg/L; and 7) homeostasis model assessment of insulin resistance (HOMA-IR) index ≥2.5.

Anthropometric measurements

Clinical and laboratory data were collected at the time of the liver biopsy. Height, weight, and WC of all patients were measured after 8 h of fasting. WC was measured as the midway between the lowest rib and the level of the anterior superior iliac crests. Body mass index (BMI) was calculated as body weight (kg)/height^2 (m^2). Blood pressure was measured in a seated position three times, and mean blood pressure was determined. The diagnostic criteria for hypertension were systolic and diastolic blood pressure ≥140/90 mmHg.

Biochemical analyses

FPG, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, uric acid, bilirubin, gamma-glutamyl transpeptidase (GGT), total cholesterol (TC), TG, and HDL-C levels were evaluated by the enzymatic colorimetric method (Olympus Diagnostics Hamburg, Germany). Low-density lipoprotein cholesterol was calculated by following Friedewald's formula [TC-(TG/5+HDL-C)] (25). Basal insulin levels of the patients were measured by the chemiluminescence method (Roche Diagnostics GmbH, Mannheim, Germany). Insulin resistance [HOMA-IR=Fasting insulin (μU/mL) × FPG (mg/dL)/405] was measured using a formula correlated with the euglycemic-hyperinsulinemic clamp method (26).

Plasma ADMA levels were measured by ELISA (ADMA direct ELISA kit, Immunodiagnostic AG, Bensheim, Germany) (detection limit of ADMA assay=0.04 μmol/L). Intra-assay CV ranged from 5.8% to 7.9%, while inter-assay CV ranged from 7.6% to 10.8% for the ADMA assay. Measurements were

performed using an ELISA BioTek Synergy HT plate reader (BioTek Instruments Inc., Winooski, VT, USA). Serum levels of adiponectin were also measured using the ELISA (Human Adiponectin ELISA Kit, Cat. No: E09; Reutlingen, Germany). Intra-assay CV ranged from 2.35% to 4.66%, while inter-assay CV ranged from 5.7% to 6.72% for adiponectin. The minimum detectable concentration of adiponectin was 0.6 ng/mL. Measurements were implemented using an ELISA BioTek Synergy HT plate reader (BioTek Instruments Inc., Winooski, VT, USA). Serum hs-CRP levels were measured using the immune turbidimetric-fixed rate method with a biochemical auto-analyzer (Olympus AU 2700, Olympus Diagnostics, Hamburg, Germany). Intra-assay CV and inter-assay CV were 5.8% and 3.1%, respectively. The minimum detectable concentration for hs-CRP was 0.07 mg/L.

Assessment of AIP

The AIP was calculated as the logarithmic transformation of TG to HDL-C ratio [AIP=Log (TG/HDL-C)].

Liver histology

An experienced hepatopathologist blinded to subjects' details reviewed the histology slides to search for inflammation and/or fibrosis using the classification of Kleiner et al. (27). NAFLD activity score (NAS) was calculated as the unweighted sum of steatosis [none, mild, moderate, and severe (0-3)], lobular inflammation [inflammatory foci per 200× field (0 is no foci; 1 is <2 foci per 200× field, 2 is 2-4 foci per 200× field, 3 is >4 foci per 200× field)], and hepatocellular ballooning [none, few balloon cells, and many cells/prominent ballooning (0-2)] scores. As a result, the subjects were classified into three groups namely simple steatosis [SS, (NAS=0-2)], borderline steatohepatitis [BSH, (NAS=3-4)] and definite steatohepatitis (DSH) [DSH, (NAS ≥5)]. The fibrosis score was assessed using a 6-point scale [1a, b=mild (1a) / moderate (1b) zone 3 perisinusoidal fibrosis; 1c=portal fibrosis only; 2=zone 3 and portal/periportal fibrosis; 3=bridging fibrosis; 4=cirrhosis].

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 22.0 package program (IBM, Corp., Armonk, NY, USA). Normality assumptions were tested via Shapiro-Wilk analysis. Variables were expressed as mean±standard error (SE) when normally distributed and as median (25^{th}-75^{th} percentiles) when non-normally distributed. Mean differences between two independent groups were assessed using the independent samples t-test and Mann-Whitney U test as appropriate. We performed a one-way ANOVA test to determine mean differences between more than two groups. The correlation between numerical parameters was tested by the Pearson or Spearman methods. Differences and correlations were considered significant at $p<0.05$.

Results

The study included 129 patients with MAFLD (age, mean±SE: 32.1±0.5 years). Anthropometric, clinical, and laboratory data are shown in Table 1. Most patients were in the range of overweight or obesity. The distribution of histopathological parameters is shown in Table 2. Patients with SS and BSH were combined in one group described as non-DSH (n=75), with a mean±SE age of 32.7±0.7 years and DSH (n=54), with mean±SE age of 31.2±0.8 years. Fibrosis (F1-F3) was observed in 84 of 129 patients (65.1%). ALT and AST values were significantly higher in patients with fibrosis or steatohepatitis ($p<0.05$, for both). However, there was no significant difference in other parameters such as BMI, WC, glucose, insulin, HOMA-IR index, and lipid parameters. Additionally, there were also no significant differences in AIP, ADMA, adiponectin, and hs-CRP levels between the two groups. However, similar findings were observed among subjects with (n=84) and without fibrosis (n=45) except for insulin (p=0.007) and HOMA-IR (p=0.008) (Tables 3, 4).

Table 1. Anthropometric and laboratory data of the study population

	Values
Age (year)	32.08±0.53*
BMI (kg/m²)	28.2 (26.45-30.25)**
WC (cm)	100 (96-104)**
FPG (mg/dL)	93.67±0.95*
TC (mg/dL)	204±3.89*
TG (mg/dL)	166 (117-256)**
HDL-C (mg/dL)	40 (35-45)**
LDL-C (mg/dL)	124.76±3.07*
AST (U/L)	48 (37.5-58.5)**
ALT (U/L)	101 (74.5-130.5)**
GGT (U/L)	56 (44-76.75)**
UA (mg/dL)	6.6 (5.75-7.16)**
DBil (mg/dL)	0.16 (0.11-0.21)**
IBil (mg/dL)	0.6 (0.41-0.84)**
Insulin (mIU/L)	13.82 (10.11-19.79)**
Adiponectin (µg/mL)	3.94 (2.93-5.26)**
ADMA (µmol/L)	0.4 (0.33-0.49)**
hs-CRP (mg/L)	2.04 (1.19-3.26)**
HOMA-IR	2.98 (2.14-4.73)**
AIP	0.63±0.03*

*Mean±S.E., **Median (25^{th}-75^{th} percentiles). BMI: Body mass index, WC: Waist circumference, FPG: Fasting plasma glucose, TC: Total cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, UA: Uric acid, DBil: Direct bilirubin, IBil: Indirect bilirubin, ADMA: asymmetric dimethylarginine, hs-CRP: High-sensitive C-reactive protein, HOMA-IR: Homeostatic model assessment of insulin resistance, AIP: Atherogenic index of plasma

Table 2. Histopathological findings in the study population		
	n	%
Fibrosis		
0	45	34.9
1	76	58.9
2	6	4.7
3	2	1.6
Steatosis		
0	8	6.2
1	42	32.6
2	45	34.9
3	34	26.4
Lobular inflammation		
0	11	8.5
1	81	62.8
2	37	28.7
Hepatocellular ballooning		
0	28	21.7
1	83	64.3
2	18	14.0

AIP was positively correlated with GGT level (r=0.366, p<0.001) and, negatively correlated with direct bilirubin level (r=-0.487, p<0.001). However, there was no association of AIP with ADMA, adiponectin, hs-CRP, insulin and HOMA-IR levels (p=0.176, p=0.636, p=0.810, p=0.068, and p=0.126, respectively). Moreover, analysis of the AIP with the histological findings (including steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis scores) also showed no association between these parameters (p=0.505, p=0.388, p=0.599 and p=0.849, respectively).

Discussion

The results of this study show that the AIP calculated in patients with MAFLD was not related to inflammation or fibrosis nor the surrogate markers of ED and atherosclerosis. To the best of our knowledge, this is the first study searching for the relationship between AIP and inflammation or ED or liver histology in patients with MAFLD (below, the implications of these findings will be discussed in detail).

However, there are limited data regarding the relationship of AIP with NAFLD. Wang et al. (20) evaluated 538 subjects with ultrasonographically diagnosed NAFLD. They found a strong association of AIP with NAFLD in the multivariable logistic

Table 3. Demographic and laboratory characteristics of patients with DSH and non-DSH			
Variable	**Non-DSH (n=75)**	**DSH (n=54)**	**p-value**
Age (year)	32.71±0.732	31.2±0.76	0.165
BMI (kg/m²)	28.4 (27-31)	28.15 (26.15-29.5)	0.238
WC (cm)	99 (96-104.08)	100 (97-103.88)	0.764
FPG (mg/dL)	93.18±1.257	94.35±1.443	0.541
TC (mg/dL)	206.33±5.142	201.26±5.979	0.522
TG (mg/dL)	167 (110-255)	149.5 (122-258.5)	0.854
HDL-C (mg/dL)	41 (36-46)	38.5 (35-44.25)	0.211
LDL-C (mg/dL)	128.27±4.088	119.87±4.584	0.178
AST (U/L)	42 (34-53)	56 (41.75-65.25)	**<0.001**
ALT (U/L)	89 (63-112)	120 (93.75-163.25)	**<0.001**
GGT (U/L)	56 (41-83)	58 (45-76.5)	0.740
UA (mg/dL)	6.58 (5.69-7.1)	6.67 (5.92-7.26)	0.344
DBil (mg/dL)	0.15 (0.11-0.2)	0.16 (0.12-0.25)	0.292
IBil (mg/dL)	0.57 (0.4-0.77)	0.7 (0.46-0.9)	0.059
Insulin (mIU/L)	12.16 (9.56-19.78)	14.45 (10.36-20.71)	0.287
Adiponectin (µg/mL)	4 (2.85-5.61)	3.79 (3.04-4.84)	0.635
ADMA (µmol/L)	0.41 (0.34-0.48)	0.4 (0.33-0.56)	0.630
hs-CRP (mg/L)	2.04 (1.18-3.47)	2.06 (1.17-3.06)	0.660
HOMA-IR	2.78 (2.09-4.62)	3.39 (2.34-4.81)	0.351
AIP	0.62±0.033	0.64±0.039	0.773

Data are expressed as the mean±SE, and median (25^{th}-75^{th} interquartile range).
BMI: Body mass index, WC: Waist circumference, FPG: Fasting plasma glucose, TC: Total cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, UA: Uric acid, DBil: Direct bilirubin, IBil: Indirect bilirubin, ADMA: Asymmetric dimethylarginine, hs-CRP: High-sensitive C-reactive protein, HOMA-IR: Homeostatic model assessment of insulin resistance, AIP: Atherogenic index of plasma, DSH: Definite steatohepatitis

Table 4. Demographic and laboratory characteristics of patients with and without fibrosis

Variable	Without fibrosis (F0) (n=45)	With fibrosis (F1-F3) (n=84)	p-value
Age (year)	31.4±0.8	32.4±0.7	0.354
BMI (kg/m²)	28.2 (26.9-30.0)	28.3 (26.3-30.5)	0.884
WC (cm)	98.0 (97.0-103.4)	100.0 (96.0-104.8)	0.680
FPG (mg/dL)	92.7±1.8	94.2±1.1	0.451
TC (mg/dL)	206.3±5.7	203.1±5.2	0.700
TG (mg/dL)	169.0 (122.5-264.0)	166.0 (115.3-255.5)	0.729
HDL-C (mg/dL)	40 (34.5-43.5)	40.5 (36.0-46.8)	0.198
LDL-C (mg/dL)	127.1±4.1	123.5±4.2	0.580
AST (U/L)	40 (34-51.5)	51.5 (39.3-64.0)	**0.001**
ALT (U/L)	84 (66.5-114.0)	108.5 (85-140.8)	**0.012**
GGT (U/L)	56 (42.5-86.5)	56 (44.0-76.0)	0.855
UA (mg/dL)	6.4 (5.6-7.2)	6.6 (6.07-7.2)	0.243
DBil (mg/dL)	0.2 (0.1-0.2)	0.2 (0.1-0.2)	0.735
IBil (mg/dL)	0.6 (0.4-0.8)	0.6 (0.4-0.9)	0.349
Insulin (mIU/L)	11.2 (9.29-15.6)	15.38 (10.28-23.55)	**0.007**
Adiponectin (µg/mL)	3.72 (2.77-5.01)	3.96 (3.04-5.38)	0.577
ADMA (µmol/L)	0.41 (0.33-0.51)	0.4 (0.33-0.48)	0.780
hs-CRP (mg/L)	1.75 (1.07-2.99)	2.11 (1.30-3.37)	0.249
HOMA-IR	2.45 (2.07-3.70)	3.66 (2.36-5.36)	**0.008**
AIP	0.64±0.044	0.62±0.031	0.596

Data are expressed as the mean±SE, and median (25^{th}-75^{th} interquartile range). p values were calculated using Student's t-test and Mann-Whitney U test as appropriate. BMI: Body mass index, WC: Waist circumference, FPG: Fasting plasma glucose, TC: Total cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, UA: Uric acid, DBil: Direct bilirubin, IBil: Indirect bilirubin, ADMA: Asymmetric dimethylarginine, hs-CRP: High-sensitive C-reactive protein, HOMA-IR: Homeostatic model assessment of insulin resistance, AIP: Atherogenic index of plasma

regression analysis. Additionally, among the other metabolic factors, such as BMI, WC, and lipid profile, AIP was the best predictor of NAFLD in this study. In another study, Dong et al. (21) analyzed the relationship between AIP and ultrasonographically diagnosed NAFLD in non-obese subjects. AIP was significantly and positively correlated with NAFLD. Moreover, in univariate and multivariate regression analysis, AIP is an independent risk factor for NAFLD. In another cross-sectional study conducted by Xie et al. (28), 7,838 subjects were involved in evaluating the association between AIP and FL and assessing the predictive ability of AIP for FL. AIP was significantly higher in the FL group than in the non-FL group. Additionally, a significantly elevated risk of FL was observed in the higher quartile of AIP compared with that in the lowest quartile following adjustment of gender and age. As far as we know, this is the first study in the literature to investigate the role of AIP in patients with MAFLD. However, no significant difference was observed between the groups with and without DSH in terms of the AIP levels and between patients with and without fibrosis. In correlation analysis, AIP was related to direct bilirubin and GGT levels. However, all histological findings, especially fibrosis, were not significantly associated with AIP levels in subjects with MAFLD. As mentioned above, all the studies that investigated the association of AIP with NAFLD were conducted in subjects with ultrasonographically diagnosed FL. Although it is widely used in the evaluation of FL in clinical practice, liver ultrasonography lacks sufficient sensitivity and specificity to detect liver inflammation and fibrosis. Therefore, the major strength of our study was the use of liver biopsy to diagnose NAFLD, the gold standard method for evaluating liver histology. Considering our findings, we suggest that AIP is not a useful index for predicting MAFLD in routine clinical practice.

A large body of evidence suggests that NAFLD is associated with an increased risk of atherosclerosis and CVD, independently of classical risk factors and components of the MetS (29,30). Several key clinical paradigms are relevant concerning atherosclerosis and CVD formation in patients with NAFLD. For example, atherogenic dyslipidemia, oxidative stress, chronic subclinical inflammation, and dysregulation of adipokines, especially insulin resistance, are the main ones of these parameters (31,32). Recently, a growing body of evidence has indicated that AIP is a good predictor of atherosclerosis and a highly sensitive marker for predicting the risk of future CVD (33,34). Hence, it has been reported that AIP is significantly and positively associated with carotid artery intima-media

thickness, a surrogate marker of early atherosclerosis (35). Additionally, a large case-control study reported that elevated AIP was significantly associated with coronary artery disease (36). However, to the best of our knowledge, no study has investigated the role of AIP in the prediction of ED or atherosclerosis in subjects with NAFLD. In our work, we did not find any significant association between AIP and surrogate biomarkers of ED and early atherosclerosis, namely, ADMA, adiponectin, and hs-CRP levels. It has been reported that AIP is strongly associated with insulin resistance, obesity, and the risk of T2DM (37-40). Additionally, other studies revealed that elevated AIP is a risk factor for developing MetS independent of any components of MetS (41). As mentioned above, due to the small number of subjects with MetS, we couldn't perform an analysis to investigate the association of AIP with MetS in our study population. Because of the well-known relationship between ED with hypertension and T2DM, patients with these metabolic diseases were excluded from this study. Moreover, circulating markers of ED and atherosclerosis are affected by these metabolic confounders (42). Therefore, we believe that the study design by excluding confounding factors is important in terms of its results. After all, we think that the lack of relationship between AIP and ED observed in our study might be related to the absence of MetS in the study population. Considering these data, we suggest that AIP may not be a good predictor of ED in NAFLD and it contributes to the prediction of CVD by acting in concert with other metabolic abnormalities. Hence, there are conflicting reports in the literature regarding the relationship of AIP with CVD. In a cross-sectional study conducted among postmenopausal women, elevated AIP was not associated with the risk of CVD (43). Otherwise, in a prospective cohort study, a low AIP level in contrast with a high AIP level was an independent predictor of all-cause mortality in patients with acute coronary syndrome (44).

To our knowledge, this is the first study to investigate the role of AIP in the prediction of ED or atherosclerosis in patients with MAFLD. However, our study has several limitations. Firstly, the cross-sectional nature of the study precluded any determination of the role of AIP in the prediction of ED or atherosclerosis. For this reason, further prospective studies should be conducted to evaluate the significance of AIP in clinical practice. Secondly, the number of patients decreased because of the strict inclusion criteria. However, we believe that the study design was necessary to achieve the main objective. Thirdly, since the patient population consists of males, these results need to be studied and confirmed in women as well. Lastly, although it is widely used for estimating beta cell function and IR, the HOMA-IR index cannot be as accurate as the euglycemic hyperinsulinemic clamp method, which is the gold standard for assessing insulin sensitivity in humans.

Conclusion

In conclusion, AIP was not associated with either liver histopathology (hepatic inflammation or fibrosis) or surrogate markers of ED and atherosclerosis in the MAFLD patients. Further research is needed to better understand the role of AIP in predicting the clinical severity of MAFLD and the risk of CVD in this clinically relevant condition.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Balikesir University Faculty of Medicine (approval no: 2020/164, date: 23.09.2020) and the study protocol conforms to the Helsinki Declaration.

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Gü., H.G., G.Ç., S.T., A.F.Ç., Concept: A.K., A.S., T.D., Design: A.S., C.N.E., Data Collection or Processing: H.Gü., H.G., G.Ç., S.T., A.F.Ç., Analysis or Interpretation: A.C.Y., S.T., Literature Search: A.K., A.S., T.D., C.N.E., Writing: A.K., T.D.

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