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Characterization of Cardiac Fat in Atrial Fibrillation Patients Prior to Ablation Treatment

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Featured Application: This study demonstrated the impact that heart fat can have in atrial fibrillation patients and its association with fibrillation recurrence after ablation treatment.

Abstract: Epicardial adipose tissue (EAT) and pericardial adipose tissue (PAT) contribute to the development of left atrial fibrillation (AF). The purpose of this study is to determine the factors influencing cardiac fat, evaluate its impact on heart function, and evaluate its role in the recurrence of AF. Cardiac MRI exams of n = 198 patients with paroxysmal AF were retrospectively analyzed to quantify EAT and PAT. Body mass index (BMI) showed significant associations with increased EAT, PAT, and total cardiac fat, particularly with the total end-systolic area ($p < 0.001$). Males were associated with increased PAT (r = −0.331, $p < 0.001$) and EAT (r = −0.168, $p = 0.019$). Increased PAT end-diastolic volume was also associated with an increase in LV mass (r = 0.249, $p < 0.01$). An inverse relationship between EAT end-systolic area and cardiac index (r = −0.220, $p < 0.01$) was observed. Although BMI did not significantly affect AF recurrence, overweight patients (36%) experienced slightly more AF recurrence than obese patients (33%). Obesity is substantially associated with an increase in EAT and PAT, while sex appears to play a greater role in PAT than EAT and decreased cardiac function.

Keywords: epicardial adipose tissue; pericardial adipose tissue; cardiac magnetic resonance; atrial fibrillation; machine learning

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1. Introduction

Atrial fibrillation (AF), as a sustained and growing epidemic, is the most common arrhythmia among adults, leading to an increase in mortality and morbidity [1]. The pathophysiology of AF is caused by asynchronous excitation of the atria, leading to irregularities in both the atrial and ventricular contractions [2]. Age [2] and various comorbidities including obesity [3], type 2 diabetes [4] obstructive sleep apnea [5], and alcohol consumption [6] are recognized as risk factors.

Obesity, which refers to the distribution of total body fat and is measured using body mass index (BMI), is a well-established risk factor for AF [7]. Excessive body fat, particularly metabolically active visceral fat, increases inflammatory and oxidative stress on the heart, leading to atrial enlargement and electrical instability, predisposing to AF [8–11]. Obesity-related expansion of epicardial adipose tissue (EAT), a visceral fat deposit located between the myocardium and epicardium, causes microvascular dysfunction and fibrosis of the underlying myocardium, resulting in atrial myopathy that can lead to AF [12]. Epicardial fat

thickness is associated with metabolic syndromes and an increased risk of cardiovascular diseases [13]. In-vivo and ex-vivo studies suggest that the accumulation of EAT can also potentially impact the left ventricle (LV) diastolic function [14–16]. Moreover, pericardial adipose tissue (PAT), which refers to fat deposits outside the epicardium, causes cardiovascular dysfunction [17]. An increment in PAT has been linked to a rise in the incidence, severity, and recurrence of AF seen in obesity [18]. The impact of the fat around the heart and AF remains unclear. Thus, quantifying EAT and PAT are important parameters that can help identify patients who may be at risk for cardiovascular events.

Different imaging modalities can measure cardiac fat deposits, such as cardiac computed tomography (CCT), which was proposed as a gold standard for quantifying the EAT volume. However, due to the significant amount of ionizing radiation, CCT poses a potential health risk to the patient [19]. This limitation was surmounted by the introduction of cardiac magnetic resonance imaging (MRI), which can measure cardiac function, morphology, perfusion, and myocardial tissue in a single exam with minimal, if any, impact on patients' health. In the current study, therefore, we aim to assess the factors that influence EAT and PAT fat in AF using cardiac MRI.

The study's hypotheses are: (1) an increase in BMI and subsequent obesity will be associated with increased cardiac fat deposition; (2) an increase in cardiac fat will have a functional impact on the heart, i.e., LV deterioration; and (3) there will be an increased incidence of AF recurrence in patients with higher cardiac fat deposits. The specific objectives of the study are: (1) to characterize parameters that influence cardiac fat; (2) to assess the effect of cardiac fat on the functional parameters of the heart; and (3) to assess the role of cardiac fat in AF recurrence.

2. Materials and Methods

2.1. Study Population

In this retrospective study, a total of 198 patients with a history of paroxysmal AF with normal systolic function, scanned between 2016 and 2021 with a standardized cardiac MRI exam, were retrospectively included from the Cardiovascular Imaging Registry of Calgary (CIROC) database. All patients were required to have a 1st referral for a cardiac MRI exam within 3 months prior to ablation procedure by their electrophysiologist. Patients with significant mitral or aortic valve disease, inappropriate/incomplete image quality (motion artifacts due to arrythmia event/incomplete acquisition), indication for re-ablation procedure, incomplete exams, or arrythmia events during the MRI examination were excluded. Those members of the study population that were found to have a normal BMI were used as the controls in this investigation, and the reference population to which the results strictly apply is therefore adults with a history of paroxysmal AF that were referred for ablation treatment and were found at the time of examination to have a normal BMI. The study utilized intakeDI^{TM} (Cohesic Inc., Calgary, AB, Canada), to coordinate and capture routine patient informed consent and self-reported health quality of life questionnaires and for standardized collection of MRI-related variables. CIROC provides access to medication prescription and usage, laboratory results, diagnostic and procedural information, device interrogation, 12-lead ECG and Holter data, vital statistics, and major cardiovascular outcomes. AF recurrence was assessed using 12-lead ECG and Holter monitoring following the ablation procedure. The most recent CIROC update output was obtained in October 2022. This study was approved by the University of Calgary's Conjoint Health Research Ethics Board, and all subjects gave written informed consent. All research activities were in accordance with the Declaration of Helsinki.

2.2. Cardiac Magnetic Resonace Imaging Acquisition

All subjects were required to exhibit sinus rhythm during the CMR examination. Patients underwent an identical standardized MRI protocol using 3T MRI scanners Skyra/Prisma (Siemens, Erlangen, Germany) inclusive of multiplanar steady-state free-precession (SSFP) cine imaging of the 4-chamber, 3-chamber, 2-chamber, and short axis of the LV at end-expiration.

Additionally, 3D magnetic resonance angiography (MRA) of the LA was performed using the administration of 0.2 mmol/kg gadolinium contrast (Gadovist®, Bayer Inc., Mississauga, ON, Canada) [20].

2.3. Standard Cardiac Magnetic Resonace Imaging Assessment

A commercial software (cvi42 v5.11, Circle Cardiovascular Imaging Inc., Calgary, AB, Canada) was used to analyze heart function from standard ECG-gated cine images. The short-axis cine images were used to measure LV end-diastolic volume (EDV), LV end-systolic volume (ESV), LV stroke volume (SV), LV mass, LV cardiac output (CO), LVEDV indexed to body surface area (BSA), LVESV indexed to BSA, LV mass indexed to BSA, and LV ejection fraction (LVEF). LA volume and LA volume indexed to BSA were measured using the bi-plane area-length method in 2- and 4-chamber views [20].

2.4. Epicardial and Pericardial Fat Assessment

An expert reader was provided with a complete series of 4-chamber images and performed blinded segmentation of the epicardial (EAT) and pericardial (PAT) adipose tissue. EAT was defined as the hyperintense signal within the pericardium surrounding the ventricles. PAT was defined as the fat adjacent but outside the pericardium. The segmentation was performed using an automate pipeline developed and validated by Daude et al. [19]. The end-systolic (ES) and end-diastolic (ED) frames were used for the quantification of EAT and PAT.

2.5. Statistical Analysis

The statistical analysis was performed using SPSS version 29.0 with statistical significance set to a p-value of 0.05. Normality of the data was assessed by the Kolmogorov–Smirnov test. If data were not normally distributed, non-parametric tests were used. The descriptive statistics of the study population and functional parameters of the heart were stratified by body mass index (BMI). Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as absolute numbers and percentages. Differences among BMI groups for the variables were assessed by one-way ANOVA or Kruskal–Wallis H test and corrected using Bonferroni adjustment. Intergroup comparisons were performed by T-tests for parametric data and Mann–Whitney U test for non-parametric data. Spearman's and Pearson's correlations were used to assess the correlation between the different cardiac fat parameters and functional parameters of the heart, as well as correlate cardiac fat to demographic variables like sex and age.

3. Results

3.1. Demographics

Table 1 compares the demographic and clinical features of the AF patients across normal (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), and obese (>30 kg/m^2) BMI categories. This study included 198 patients, ranging in age from 22 to 83 years. Obese patients were generally younger (57.4 ± 10.4 years) than overweight patients (60.0 ± 9.5 years), despite having a higher BMI and body surface area (34.0 ± 3.2 kg/m^2, 2.3 ± 0.2 m^2) relative to overweight patients (27.2 ± 1.5 kg/m^2, 2.1 ± 0.2 m^2). Comorbid conditions such as diabetes (75% and 25%), hypertension (34.6% and 49.1%), and hypercholesterolemia (42.3% and 50%) were more common in overweight and obese patients, respectively. Interestingly, there was no significant difference in stroke risk (p = 0.059) between BMI groups, with the most prevalent CHA_2DS_2-VASc score of 1 indicating moderate risk for all BMI categories. Obese patients were more likely to be using anticoagulants (30%), beta blockers (21.5%), and antiarrhythmic drugs (21.5%), but overall medication consumption was highest in overweight patients.

Table 1. Demographic and clinical characteristics of atrial fibrillation patients in relation to BMI.

BMI	Normal (n = 45)	Overweight (n = 79)	Obese (n = 74)	*p*-Value
Demographics				
Age (years)	56.1 (±12.1)	60.0 (±9.5)	57.4 (±10.4)	0.071
Sex n (% men)	31 (15.5%)	56 (28.0%)	57 (28.5%)	0.187
Sex n (% women)	14 (7.0%)	23 (11.5%)	17 (8.5%)	
Height (cm)	178.6 (±8.5)	177.3 (±10.2)	177.4 (±9.8)	0.265
Weight (Kg)	73.4 (±8.1) †	85.9 (±10.7) ‡	107.1 (±15.3) #	<0.001 **
Body Mass Index, BMI (kg/m^2)	23.0 (±1.4) †	27.2 (±1.5) ‡	34.0 (±3.2) #	<0.001 **
Body Surface Area, BSA (m^2) [a]	1.9 (±0.1) †	2.1 (±0.2) ‡	2.3 (±0.2) #	<0.001 **
Smoke [b]	1 (±1)	1 (±1)	2 (±1)	0.327
Caffeine [c]	3 (±1)	4 (±1)	4 (±1)	0.111
Alcohol [d]	3 (±1)	3 (±1)	3 (±1)	0.069
Comorbidities				
Diabetes	0	3 (75%)	1 (25%)	0.333
Hypertension [e]	3 (5.5%	19 (34.6%)	27 (49.1%)	0.086
Hypercholesteremia	1 (3.9%) †	11 (42.3%)	13 (50%) #	0.001 *
Stroke Risk Score				
CHA_2DS_2-VASc Score	1.4 (±0.9)	1.7 (±1.0)	1.8 (±1.01)	0.059
Score 0 (n)	6	6	6	
Score 1 (n)	20	29	29	
Score 2 (n)	14	27	22	
Score 3 (n)	4	12	11	
Score 4 (n)	1	4	5	
Score 5 (n)	0	1	1	
Medications				
Anti-arrhythmic	15 (7.5%) †	47 (23.5%)	43 (21.5%) #	0.004 *
Anti-coagulant	37 (18.5%)	69 (34.5%)	60 (30%)	0.182
Beta-blocker	26 (13%)	47 (23.5%)	45 (22.5%)	0.316
ACE inhibitor or ARB	7 (3.5%)	20 (10%)	29 (14.5%) #	0.005 *
Statins	8 (4%)	22 (11%)	19 (9.5%)	0.149
Non-dihydropyridine calcium channel blocker	5 (2.5%)	20 (10%) ‡	7 (3.5%)	0.006 *
Lab results				
Total cholesterol (mmol/L)	4.5 (±0.9)	4.7 (±1.3)	4.6 (±1.1)	0.314
Low-density lipoprotein, LDL (mmol/L)	2.4 (±0.6)	2.7 (±1.0)	2.7 (±0.9)	0.233
High-density lipoprotein, HDL (mmol/L)	1.5 (±0.4)	1.3 (±0.5)	1.2 (±0.3) #	0.038 *
Triglycerides, TG (mmol/L)	1.3 (±0.6)	1.7 (±0.8)	1.6 (±0.7)	0.129

Continuous variables are expressed as mean ± SD and categorical variables as absolute numbers and percentages. Percentages are of each BMI group. * p-value < 0.05 assessed by Kruskal–Wallis H test and adjusted using Bonferroni adjustment for multiple comparisons; ** $p < 0.001$; [a] measured by Mosteller equation; [b] Smoked or vaped nicotine products within the past 10 years, 1, no products; 2, ≤1 products per day; 3, 1–10 products per day; 4, >10 per day; [c] Past 3-months (on average) caffeine (coffee, tea, or other caffeinated drinks), 1, none; 2, 1 cup per month; 3, 1–2 cups per week; 4, 1–2 per day; [d] Past 3-months (on average) alcohol, 1, none; 2, 1–3 per month; 3, 1–2 per week; 4, 1–2 per day; [e] both treated and untreated hypertension were considered; †, difference between group 1 and 2, $p < 0.05$; ‡, difference between group 2 and 3, $p < 0.05$; #, difference between group 1 and 3, $p < 0.05$. Intergroup comparisons were performed by T-tests for parametric data and Mann–Whitney U test for non-parametric data.

3.2. Factors Influencing Different Cardiac Fat Parameters

Table 2 highlights a significant increase in both the end-systolic and end-diastolic phases of all EAT, PAT, and total cardiac fat areas with obesity. The end-diastolic fat area was found to be less than the end-systolic area in all cardiac fat parameters, which can be attributed to the compression effect of the myocardium on the fat during ventricular diastole. BMI, age, and sex's correlation with EAT, PAT, and total cardiac fat areas is demonstrated in Table 3. BMI exhibited a significant association with all parameters, particularly with total end-systolic area (r = 0.458, $p < 0.001$). Male sex had a higher

association to PAT and total cardiac fat area, most notably with PAT area in 4-chamber view (r = −0.331, $p < 0.001$). Age weakly correlated with EAT end-systolic (r = 0.172, $p = 0.016$) and EAT end-diastolic (r = 0.19, $p = 0.008$) areas, but not with PAT. A higher PAT area in end-systolic and end-diastolic phases in males than females was observed across all BMI groups (see green brackets in Figure 1c–e). However, a larger total cardiac fat area was observed in males than females only across overweight and obese patients but not in normal-weight patients (see green bracket in Figure 1f,g). In normal-weight patients (yellow box plot in Figure 2), the area of EAT, PAT, and total cardiac fat in end-systolic phase is significantly higher in >60 years age group than 40 to 50 years age group (see green brackets in Figure 2a,c,f, $p < 0.05$). Similar results were obtained with the areas of EAT and PAT in end-diastolic phase (top upper green bracket in Figure 2b,d) but not with total cardiac fat (Figure 2g). This may suggest that cardiac fat parameters increase with age in normal weighted patients with paroxysmal AF. In overweight patients, there were larger EAT areas in end-diastolic phase in the age group 50 to 60 years compared with age group 40 to 50 years (see lower green bracket Figure 2b, $p < 0.05$). In obese patients, we observed an apparent trend of the EAT areas in the end-systolic and end-diastolic phases increasing with age until 60 years, at which point there showed a slight drop, although not statistically significant (Figure 2a,b). Notably, EAT and PAT were not associated with CHA_2DS_2-VASc stroke-risk score, suggesting that cardiac fat may be an independent marker of AF.

Table 2. Cardiac fat parameters in relation to BMI.

	Normal (n = 45)	Overweight (n = 79)	Obese (n = 74)	*p*-Value
Epicardial Adipose Tissue (EAT)				
EAT End-systolic area (cm^2)	10.8 (±4.5) †	14.7 (±5.7) ‡	17.6 (±5.1) #	<0.001 **
EAT End-diastolic area (cm^2)	10.4 (±4.8) †	13.9 (±5.7) ‡	16.5 (±4.9) #	<0.001 **
Pericardial Adipose Tissue (PAT)				
PAT Area in 4-Chamber view (cm^2)	24.9 (±17.6) †	35.2 (±16.6) ‡	48.1 (±21.7) #	<0.001 **
PAT End-systolic area (cm^2)	12.8 (±9.8) †	18.9 (±10.7) ‡	25.6 (±12.2) #	<0.001 **
PAT End-diastolic area (cm^2)	11.8 (±9.8) †	17.7 (±9.6) ‡	24.5 (±11.5) #	<0.001 **
Total cardiac fat (EAT + PAT)				
Total end-systolic area (cm^2)	23.6 (±13.8) †	33.6 (±15.6) ‡	43.1 (±16.2) #	<0.001 **
Total end-diastolic area (cm^2)	22.1 (±14.12) †	31.6 (±14.5) ‡	40.9 (±15.2) #	<0.001 **

Variables are expressed as mean ± SD. ** $p < 0.001$ assessed by Kruskal–Wallis H test and adjusted using Bonferroni adjustment for multiple comparisons; †, difference between group 1 and 2, $p < 0.05$; ‡, difference between group 2 and 3, $p < 0.05$; and #, difference between group 1 and 3, $p < 0.05$.

Table 3. Correlation between cardiac fat parameters and demographic characteristics.

	BMI	Age Ranges [a]	Sex [b]
Epicardial Adipose Tissue (EAT)			
EAT End-systolic area (cm^2)	0.389 **, <0.001	0.172 *, 0.016	−0.167 *, 0.20
EAT End-diastolic area (cm^2)	0.429 **, <0.001	0.190 **, 0.008	−0.168 *, 0.019
Pericardial Adipose Tissue (PAT)			
PAT Area in 4-Chamber view (cm^2)	0.434 **, <0.001	NS	−0.331 **, <0.001
PAT End-systolic area (cm^2)	0.434 **, <0.001	NS	−0.296 **, <0.001
PAT End-diastolic area (cm^2)	0.432 **, <0.001	NS	−0.282 **, <0.001
Total cardiac fat (EAT + PAT)			
Total end-systolic area (cm^2)	0.458 **, <0.001	NS	−0.267 **, <0.001
Total end-diastolic area (cm^2)	0.443 **, <0.001	0.145 *, 0.043	−0.258 **, <0.001

Pearson's correlation was performed for parametric data, and Spearman's correlation was conducted for non-parametric data. All variables are expressed as correlation coefficient r, *p*-value. * Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed). [a] 5 age ranges were considered: less than 30, between 30 and 40, between 40 and 50, between 50 and 60, and older than 60; [b] male sex was assigned a value of 1 and female of 2. Age ranges were considered a continuous variable. A negative correlation indicates tendency towards males. BMI, Body mass index; NS, Not significant $p > 0.05$.

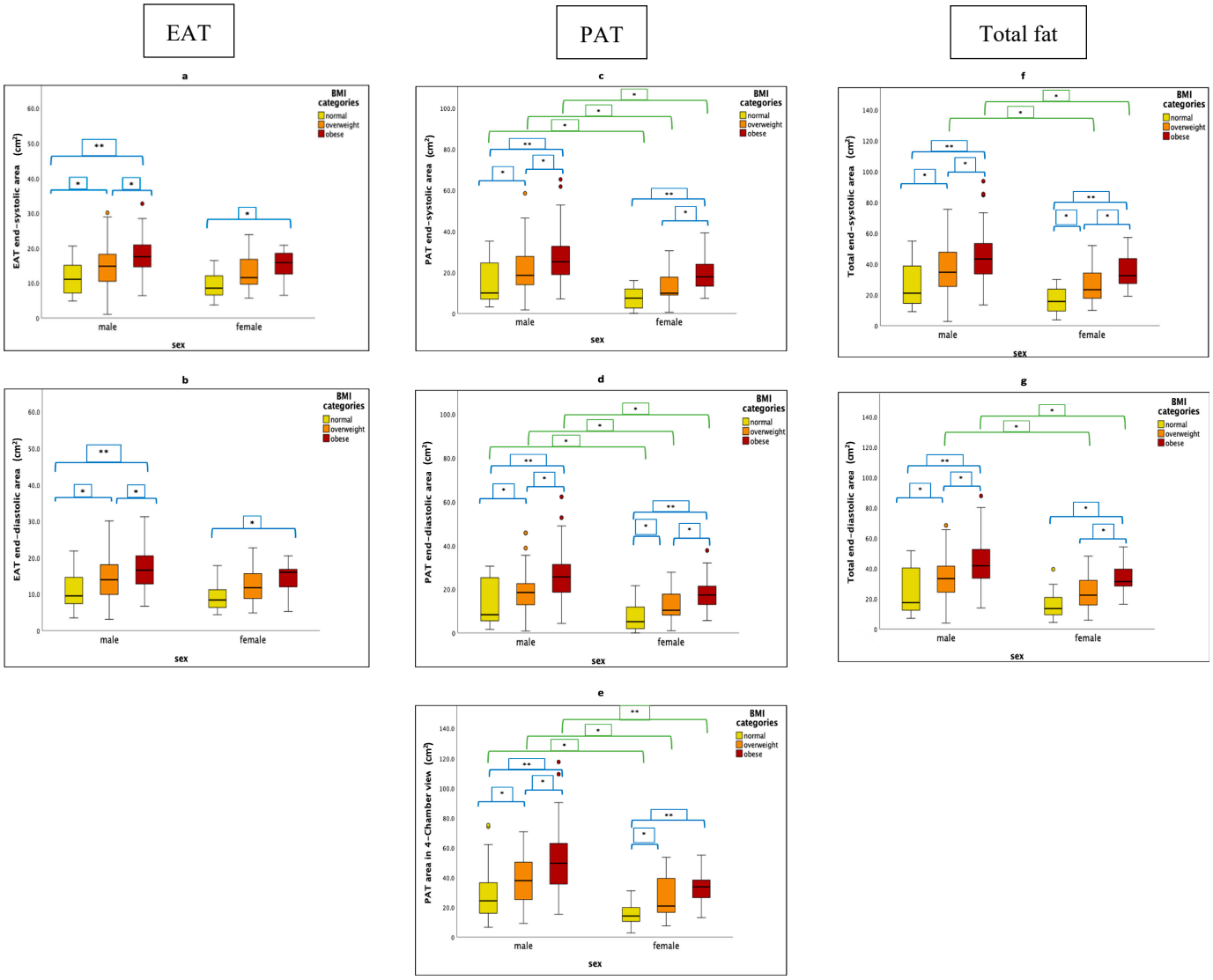

Figure 1. Area of EAT, PAT, and total cardiac fat stratified by sex and BMI, suggesting that sex may play more of a role in PAT than EAT, with higher deposition in males across all BMI groups. (**a**,**c**,**f**) illustrates the respective fat parameter within end-systolic phase, and (**b**,**d**,**g**) within end-diastolic phase. (**e**) illustrates PAT area in 4-chamber view. The box plots were generated by SPSS using the areas for EAT, PAT, and total cardiac fat with respect to sex and BMI. Within each sex group (male and female), box plots are colored according to BMI categories (normal, overweight, and obese, as shown in the top-left legend). Blue brackets on top of the box plots represent differences in EAT, PAT, and total cardiac fat within BMI categories in each sex group, whereas the green brackets represent differences in cardiac fat across sex within the same BMI group. * within the box represents $p < 0.05$ as measured by one-way ANOVA, independent samples T-test or Mann–Whitney U test; ** indicates $p < 0.001$; EAT, Epicardial adipose tissue; and PAT, pericardial adipose tissue.

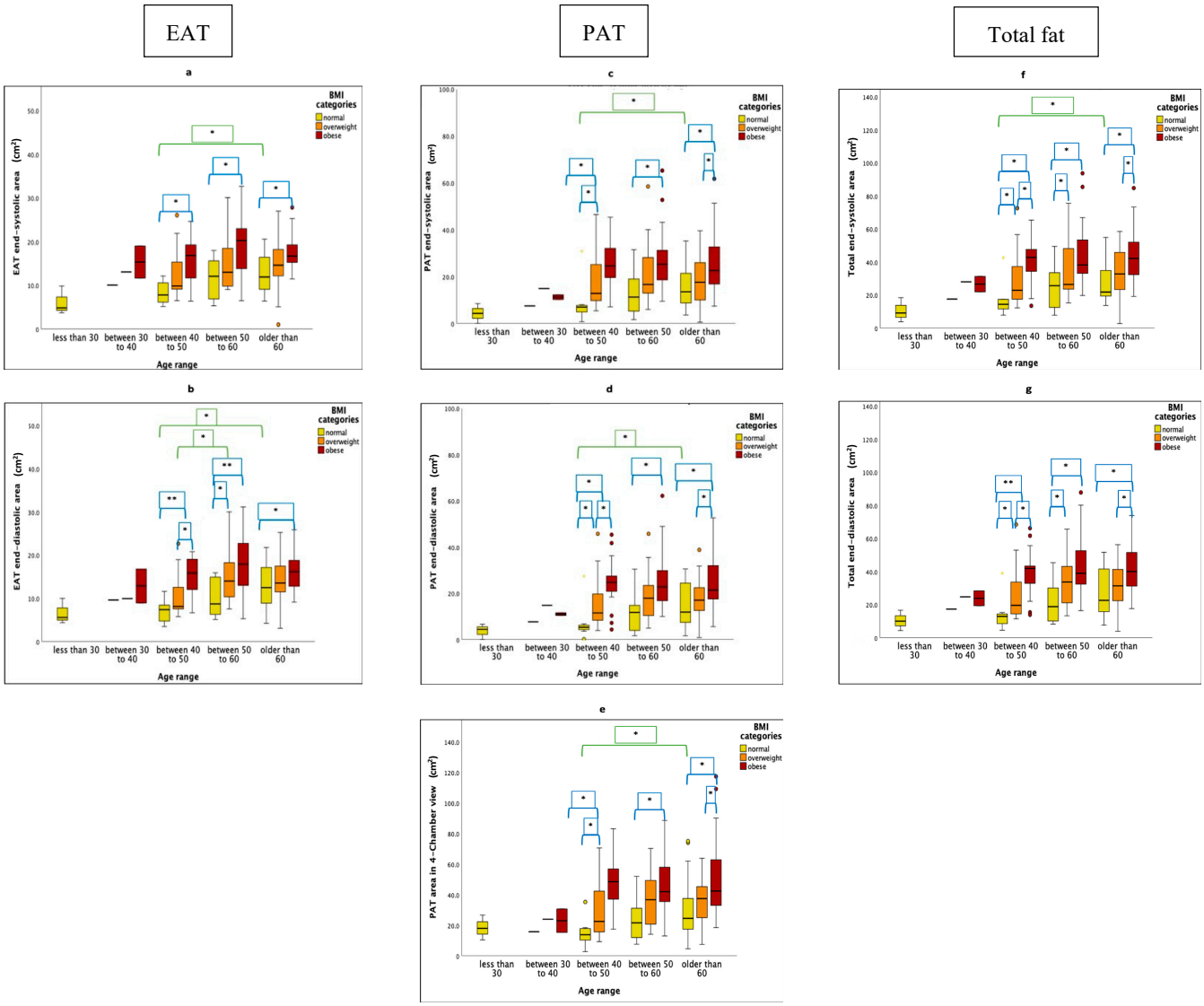

Figure 2. Area of EAT, PAT, and total cardiac fat stratified by age groups and BMI. Cardiac fat parameters may increase with age in normal-weight patients with paroxysmal AF. (**a**,**c**,**f**) illustrates the respective fat parameter within the end-systolic phase, and (**b**,**d**,**g**) within the end-diastolic phase. (**e**) illustrates PAT area in 4-chamber view. The box plots were generated by SPSS using the areas for EAT, PAT, and total cardiac fat with respect to five age groups (<30, 30–40, 40–50, 50–60, and >60 years) and BMI. Within each age group, box plots are colored according to BMI categories. Blue brackets on top of the box plots represent differences in EAT, PAT, and total cardiac fat within BMI categories in each age group, whereas the green brackets represent differences in cardiac fat across different ages within the same BMI group. * within the box represents $p < 0.05$ as measured by one-way ANOVA or Mann–Whitney U test; ** indicates $p < 0.001$; EAT, Epicardial adipose tissue; PAT, pericardial adipose tissue; and BMI, body mass index.

3.3. Functional Parameters and Cardiac Fat

Table 4 summarizes the anatomical and functional characteristics of the heart in our patient population in relation to BMI groups. The LA volume increased with BMI for both patient and indexed values. In the left and right ventricles, patient EDV and ESV also increased with BMI. However, when indexed to account for BSA, ventricular volumes decreased, indicating reduced heart functionality with increased body fat. Similarly, patients' LV mass significantly increased with obesity (126.2 ± 32.6 g); however, indexed values revealed a decrease in mass in obese patients (55.1 ± 11.8 g/m^2) compared to nor-

mal patients (56.0 ± 9.8 g/m^2). Obese patients exhibited a significantly reduced cardiac index (2.9 ± 0.6 L/min/m^2) compared to normal patients (3.2 ± 0.6 L/min/m^2), but no significant decrease in left and right ventricular ejection fraction (EF) across BMI was noted. Table 5 illustrates the association between cardiac fat and functional parameters. A positive correlation between LV mass and PAT areas was evident, with the PAT area in 4-chamber view displaying the highest association (r = 0.279, $p < 0.01$). Conversely, a negative correlation was observed between EAT end-systolic area and cardiac index (r = −0.220, $p < 0.01$), suggesting that an increase in EAT may be associated with a decreased functional capacity of the heart. Scatter plots for these correlations are shown in Figure 3.

Table 4. Anatomical and functional characteristics of the heart in atrial fibrillation patients in relation to BMI.

BMI	Normal (n = 45)	Overweight (n = 79)	Obese (n = 74)	*p*-Value
Left Ventricle (LV)				
LV-EDV (mL)	161.7 (±31.8)	161.7 (±30.5) ‡	177.4 (±38.0) #	<0.001 **
LV-ESV (mL)	62.9 (±17.8)	65.2 (±18.7) ‡	71.8 (±20.5) #	0.01 *
LV-Mass (g)	107.0 (±21.8)	107.6 (±26.6) ‡	126.2 (±32.6) #	<0.001 **
LV-EF (%)	61.0 (±8.3)	59.9 (±7.1)	59.5 (±8.0)	0.14
Indexed LV-EDV (mL/m^2) [a]	84.5 (±14.0) †	78.3 (±11.9)	77.3 (±12.9) #	<0.001 **
Indexed LV-ESV (mL/m^2) [a]	32.8 (±8.3)	31.5 (±7.8)	31.3 (±8.0)	0.21
Indexed LV-Mass (g/m^2) [a]	56.0 (±9.8) †	51.8 (±10.3)	55.1 (±11.8)	0.03 *
LV-Cardiac Index (L/min/m^2) [a]	3.2 (±0.6) †	2.7 (±0.4)	2.9 (±0.6) #	<0.001 **
Left Atrium (LA)				
LA-Volume (mL)	73.0 (±20.8) †	88.2 (±32.4) ‡	100.1 (±30.7) #	<0.001 **
Indexed LA-Volume (mL/m^2) [a]	38.3 (±11.4)	43.1 (±16.5)	43.9 (±13.1) #	0.04 *
Right Ventricle (RV)				
Patient RV-EDV (mL)	178.5 (±47.0)	174.6 (±41.3) ‡	191.0 (±48.6)	0.03 *
Patient RV-ESV (mL)	80.1 (±26.5)	78.9 (±26.4)	86.3 (±27.5)	0.09
RV-EF (%)	55.3 (±7.7)	55.5 (±7.5)	55.1 (±6.6)	0.32
Indexed RV-EDV (mL/m^2) [a]	92.9 (±20.4) †	84.3 (±16.4)	83.0 (±17.4) #	0.01 *
Indexed RV-ESV (mL/m^2) [a]	41.6 (±11.8)	37.9 (±11.1)	37.4 (±10.2) #	0.04 *

All variables are expressed as mean ± SD. * p-value < 0.05 assessed by Kruskal–Wallis H test and adjusted using Bonferroni adjustment for multiple comparisons; ** $p < 0.001$; [a] parameter was indexed by body surface area (BSA); EDV: End-diastolic volume; ESV: End-systolic volume; EF: Ejection Fraction. †, difference between group 1 and 2, $p < 0.05$; ‡, difference between group 2 and 3, $p < 0.05$; and #, difference between group 1 and 3, $p < 0.05$.

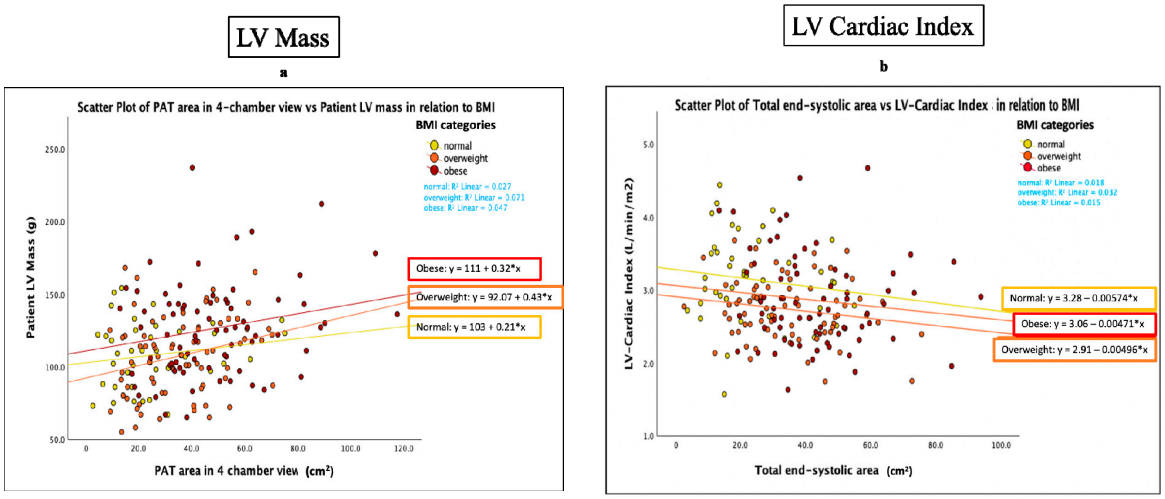

Figure 3. Scatter plots of cardiac fat vs cardiac function stratified by BMI. (**a**) An increase in PAT area in 4-chamber view is associated with an increase in LV mass, particularly in overweight and obese patients. (**b**) An increase in total fat area is correlated to a decrease in cardiac index, most notably in overweight patients. PAT: pericardial adipose tissue; LV: Left ventricle; and BMI: body mass index.

Table 5. Correlation of cardiac fat parameters with structural and functional characteristics of the heart.

	Indexed LV-EDV [a]	LV-EDV	LV-ESV	LV-Cardiac Index [a]	LV-Mass	Indexed RV-EDV [a]	LA-Volume
Epicardial Adipose Tissue (EAT)							
EAT End-systolic area (cm^2)	−0.166 *, 0.02	NS	NS	−0.220 **, <0.01	0.188 **, 0.01	−0.173 *, 0.02	NS
EAT End-diastolic area (cm^2)	−0.183 *, 0.01	NS	NS	−0.211 **, <0.01	0.157 *, 0.03	−0.168 *, 0.02	NS
Pericardial Adipose Tissue (PAT)							
PAT Area in 4 Chamber view (cm^2)	NS	0.159 *, 0.03	0.179 *, 0.01	NS	0.279 **, <0.01	NS	0.156 *, 0.04
PAT End-systolic area (cm^2)	−0.146 *, 0.04	NS	0.164 *, 0.02	−0.207 **, <0.01	0.224 **, <0.01	NS	NS
PAT End-diastolic area (cm^2)	NS	0.176 *, 0.02	0.194 **, 0.01	−0.163 *, 0.03	0.249 **, <0.01	NS	0.174 *, 0.02
Total cardiac fat (EAT + PAT)							
Total end-systolic area (cm^2)	−0.174 *, 0.02	NS	NS	−0.213 **, <0.01	0.217 **, <0.01	−0.154 *, 0.03	NS
Total end-diastolic area (cm^2)	NS	NS	0.156 *, 0.03	−0.184 *, 0.01	0.224 **, 0.01	NS	0.164 *, 0.03

Pearson's correlation was performed for parametric data, and Spearman's Correlation was conducted for non-parametric data. All variables are expressed as correlation coefficient r, *p*-value. * Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed). [a] parameter was indexed by body surface area (BSA). LV: Left Ventricle; EDV: End-diastolic volume; ESV: End-systolic volume; and NS: Not significant $p > 0.05$.

3.4. Obesity and AF Reccurrence

Table 6 demonstrates that the frequency of AF recurrence was highest in overweight patients (36.4%), followed by obese (33.3%) and normal-weight patients (20.2%). However, there was no significant difference in AF recurrence rates among the groups ($p = 0.298$). Obese patients had the longest days until recurrence (80.1 ± 131.1 days), followed by normal-weight (69.0 ± 86.7 days) and overweight patients (53.3 ± 59.3 days). The Kaplan–Meier graph in Figure 4 also illustrates this concept, showing a trend of longer time to AF recurrence in obese patients compared to normal and overweight patients. Subjects with recurrence demonstrated increased, but not significant, EAT (EAT end-systolic: 14.94 ± 5.61 cm^2 vs. 14.84 ± 7.42 cm^2, $p = 0.945$; EAT end-diastolic: 14.22 ± 5.64 cm^2 vs. 12.9 ± 5.86 cm^2, $p = 0.337$).

Table 6. Atrial fibrillation recurrence in relation to BMI.

BMI	Normal (n = 45)	Overweight (n = 79)	Obese (n = 74)	*p*-Value *
Frequency of recurrence n(%)	40 (20.2%)	72 (36.4%)	66 (33.3%)	0.298
Days until recurrence	69.0 (±86.7)	53.3 (±59.3)	80.1 (±131.1)	0.321

Continuous variables are expressed as mean ± SD and categorical variables as absolute number and percentage. * *p*-value was assessed by Kruskal–Wallis H test and adjusted using Bonferroni adjustment for multiple comparisons.

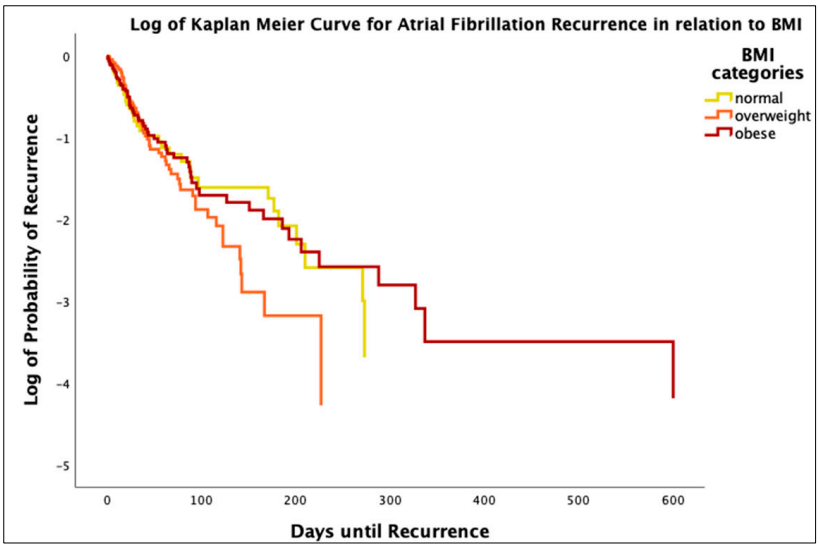

Figure 4. Kaplan–Meier survival analysis curve for atrial fibrillation recurrence in relation to BMI. The Log Rank (Mantel-Cox) *p*-value for overall comparison is 0.552.

4. Discussion

Our findings indicate that obesity and its subsequent deposition of cardiac fat significantly impacts both the anatomical and functional characteristics of the heart, predisposing to atrial fibrillation. All cardiac fat parameters, including EAT, PAT, and total cardiac fat area, are substantially associated with an increase in BMI. Moreover, an increase in BMI was also associated with a decrease in functionality, as indicated by reduced cardiac indices in obese patients.

Our findings demonstrate that BMI is significantly associated with EAT, PAT, and total cardiac fat area, making obesity pivotal in atrial fibrillation. In the context of cardiovascular diseases, including AF, EAT has been shown to have a direct relationship with obesity and BMI [21,22]. The relationship stems from the shared embryological origin of EAT with the epicardial layer of the myocardium, resulting in no connective tissue layer separating the two [22]. Therefore, excessive deposition of EAT causes direct fibrofatty infiltration and the release of inflammatory mediators such as interleukin-1-beta, interleukin-6, tumor necrosis factor-alpha, and monocyte chemoattractant protein-1 that, via paracrine mechanism, cause atrial fibrosis and AF [21].

Furthermore, EAT contains abundant ganglionated plexi that might contribute to the recurrence of AF [23–26]. In our study, overweight and obese AF patients showed higher recurrence compared to normal. EAT inflammatory activity has been reported as being higher in patients with AF than in controls, and it was shown to be greater in the left main artery than in the subcutaneous or visceral thoracic tissue [23]. An increased EAT could affect the ganglia function and impact the atrial substrate remodeling, and thereby, the maintenance of AF [25]. The association of the regional distribution of fat was not evaluated in the current study. However, regional EAT increment may be associated with AF nesting [25]. The latter remains an important question to address in future studies.

Our study also reveals an association between PAT and BMI in the setting of paroxysmal AF. On the other hand, Wong et al. demonstrated significant associations of PAT with AF presence, severity, and post-ablation outcomes, independent of systemic adiposity measures like BMI and BSA, suggesting that PAT may be a possible independent biomarker of AF [27]. However, this might be attributable to the use of volume measurements compared to area measurements in our study.

Sex and age also impact cardiac fat and AF. Our findings reveal slight sex differences for EAT and PAT deposition, with male sex having a stronger correlation to PAT area than EAT. In fact, across all BMI groups, males had significantly higher PAT areas compared to females. Men tend to have higher visceral fat deposition, which includes EAT and PAT,

whereas women have more subcutaneous fat deposits [28]. Gill et al. also illustrated that PAT volume is positively associated with BMI and is significantly higher in men than in women. However, in the context of metabolic syndrome and other cardiometabolic risk measures that are similar for various cardiovascular diseases including AF, the association of PAT was found to be stronger in women compared to men [29]. Nonetheless, sex seems to play less of a role in EAT than PAT, as in our study, there was no significant difference between the area of EAT in the hearts of normal, overweight, or obese males and their female counterparts. Conversely, Zhu et al. demonstrated higher total EAT volume in male AF patients and higher peri-atrial/total EAT ratio in post-menopausal females, alongside a greater rate of post-ablation AF recurrence [30]. Further exploration into sex differences in cardiac fat deposition is needed.

Advancing age, a well-established AF risk factor, may affect cardiac fat dynamics [2]. Our results demonstrate significant EAT and PAT area differences in normal-weight patients between age groups 40 and 50 years and over 60 years, suggesting that epicardial fat naturally increases with age. Indeed, previous studies have found EAT to be 22% thicker in patients aged 65 years and older, corroborating the notion of age-related increase [22,31]. This could be partially attributed to the hormonal changes that come with aging or to medications that manage comorbid conditions.

With respect to anatomical and functional parameters, we observed that patients' LV mass significantly increased with obesity and was positively correlated with EAT and PAT. However, when indexed by BSA, LV mass was reduced among obese patients and had no association with cardiac fat. Our data suggest eccentric and not concentric LV changes, indicating increased preload rather than afterload, which might be consistent with increased BMI. This implies that the relationship between LV mass and cardiac fat is influenced by body size adjustment, suggesting that LV mass may be linked to larger body size rather than solely cardiac hypertrophy. This aligns with findings by Nerker et al. and Fox et al., who propose that in the context of CAD, the influence of obesity on cardiac remodeling may overcome the local consequences of both EAT and PAT [32,33]. The central obesity and visceral adipose tissue may raise LV afterload, eventually resulting in LV remodeling as a compensatory mechanism, which comprises an increase in LV diameter, volume, and mass [32]. Thus, it seems that obesity's impact on LV mass and cardiac structure may extend beyond local cardiac fat deposits.

EAT and PAT in our patient population also exhibited negative correlations with functional aspects such as LV-Cardiac Index (CI), which reflects cardiac output (CO) adjusted by BSA [34]. Although, to our knowledge, no clear EAT/PAT-CI relationship in the setting of AF has been established, it is recognized that higher BMI is associated with an enlarged left atrium, subsequently increasing stroke volume and CO [3]. Prolonged elevated output leads to LV enlargement and hypertrophy, eventually resulting in diastolic dysfunction and systolic impairment [3]. Indeed, AF is known to increase the risk of heart failure along with EAT [15,16,35].

Obese patients with AF tend to be younger than patients with a normal BMI, which was also the case in our patient population. The impact of age may explain our findings, given that age is a key predictor of all-cause mortality in AF [3]. Moreover, obese patients tend to have more comorbidities, warranting stricter treatment strategies for rhythm control and anticoagulation, potentially influencing their outcomes [3]. Thus, the roots of the obesity paradox likely stem from the complex interactions of several contributing factors, requiring further exploration in future studies. In our study, EAT did not show an association with AF recurrence. However, other studies have demonstrated that EAT can be associated with AF recurrence [36].

Our study has certain limitations that warrant consideration. Firstly, this was a single-center investigation, and our findings may not fully represent broader populations. We were limited to the records captured by our local registry. The normal BMI group served as a control group and reference for other BMI groups. An appropriate control match was not conducted. We focused solely on area measurements of EAT and PAT and did not consider

volume measurements. The automate machine learning model is only able to quantify EAT and PAT following similar patterns to those used in the training dataset. The latter limited our capacity to define and quantify regions not included in the model. Additionally, due to the constraints of our available data, we were unable to analyze the potential effects of underweight individuals (BMI < 18.5). Although BMI is acknowledged as a significant cardiovascular risk indicator, it must be noted that it is limited in predicting total adiposity due to the contribution of subcutaneous adipose mass [37].

5. Conclusions

Our findings indicate that obesity, and its subsequent cardiac fat deposition, has a significant impact on the anatomical and functional characteristics of the heart, predisposing to AF. Significant correlations were found between cardiac fat parameters EAT, PAT, and total cardiac fat area, and higher BMI levels. An increased BMI was also associated with a decrease in functionality, as indicated by reduced cardiac indices in obese patients.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Conjoint Health Research Ethics Board of the University of Calgary (REB13-0902 was approved on 18 June 2014).

Informed Consent Statement: Written informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The anonymized data presented in this study are available upon request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

Conflicts of Interest: The authors declare no conflict of interest.

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