



The relationship between lung involvement in rheumatoid arthritis and sarcopenia

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■ MAIN POINTS

- Lung involvement of Rheumatoid Arthritis affects the quality of muscle.
- Computed tomography density is a valuable method for determining muscle quality.
- The muscle density/ aortic density ratio allows assessment of muscle quality without being influenced by acquisition parameters.

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■ ABSTRACT

Aim: This study investigated the effect of lung involvement in Rheumatoid Arthritis (RA) on sarcopenia.

Materials and Methods: A retrospective analysis was conducted on patients with RA diagnosed between January 2020 and January 2024. Patients with non-contrast thoracic CT scans available in the hospital database were included. A control group consisting of individuals without any inflammatory diseases was also selected. Muscle area (MA) and muscle-to-aorta density (M/A density) ratio were compared between the RA and control groups, as well as between RA patients with and without pulmonary involvement.

Results: A total of 187 individuals (156 women, 31 men) were included in the study, comprising 84 patients in the RA group and 103 in the control group. The M/A density ratio was significantly lower in the RA group ($p < 0.001$). Among RA patients, 30 (36%) had pulmonary involvement. The M/A density ratio was significantly lower in RA patients with lung involvement compared to those without ($p = 0.016$). However, the muscle area showed no significant difference among the groups ($p = 0.683$).

Conclusion: This study found that RA lung involvement may be associated with increased muscle adiposity. Prospective studies with large populations are needed to confirm this association.

Keywords: Rheumatoid Arthritis (RA), Lung involvement, Sarcopenia, Muscle density, Computed Tomography (CT)

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■ INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects the joints. The prevalence of rheumatoid arthritis varies worldwide, ranging from 0.25% to 1%. Women are affected more [1]. Proinflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and interleukin-1 (IL-1) play a key role in the pathogenesis of RA [2]. In approximately half of the patients with RA, concomitant extraarticular findings can be present. The respiratory system is involved in 60-80% of RA patients, which is the most common extraarticular involvement [3].

Sarcopenia is a disease that reduces muscle strength, mass, and function. Usually, it occurs later in life [2]. A revised criteria system, developed by the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) in 2018, updated the

definition of sarcopenia. EWGSOP2 defined two types of sarcopenia: primary sarcopenia associated with aging in adults over 40 years old, and secondary sarcopenia related to chronic inflammation, inactivity, or malnutrition. EWGSOP2 has also identified Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) as the most suitable diagnostic imaging methods for measuring muscle area [4]. In primary sarcopenia, various factors, including physical inactivity, inflammation, and hormonal changes, contribute. These causes are also effective in rheumatoid sarcopenia. Proinflammatory cytokines in RA may accelerate muscle loss, leading to the progression of rheumatoid sarcopenia. Additionally, decreased physical activity further increases this risk [5].

In the RA population, the number of studies using CT to evaluate the muscle area or density of the RA is very scarce.

Although the effect of RA on muscle tissue has been examined in the literature, the relationship between lung involvement in RA and its relation with muscle density has not been previously evaluated. This study is one of the first to examine how muscle density is affected in patients with RA lung involvement. For these reasons, this study aimed to investigate the relationship between sarcopenia and pulmonary involvement in RA, which is common in the Turkish population, by measuring the paraspinal muscle area on CT.

MATERIALS AND METHODS

Study design

This retrospective, observational case-control study was conducted according to the STROBE guidelines.

Sampling method

A non-probability purposive sampling method was employed to include RA patients with thoracic CT scans available between January 2020 and January 2024. After obtaining ethics committee approval, patients diagnosed with RA in our hospital were retrospectively screened. Among these patients, those with non-contrast Thorax CT were included in the study. Age- and sex-matched controls without inflammatory diseases were selected using simple random sampling from the hospital database. The control group was selected from pre-diagnoses without widespread systemic effects such as trauma or nodule follow-up. In both groups, a diagnosis of cancer, a history of chronic diseases known to affect muscle health (e.g., chronic kidney disease, liver disease, malabsorption syndromes), or pregnancy was excluded. In addition, those whose CT images had artifacts that were enough to affect the evaluation were also excluded from the study. CRP, RF, and anti-CCP values of patients with RA were also examined. Thorax CTs were evaluated for rheumatoid arthritis lung involvement in the group diagnosed with RA. Lung involvement patterns were determined as usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), bronchiolitis obliterans (BO), rheumatoid nodule (RN), isolated bronchiectasis, and lymphoid interstitial pneumonia (LIP) [6].

Sample size

Due to the retrospective design, sample size was determined by the availability of suitable patients and controls within the hospital records. Sample size calculation was performed.

Measurement methods

Paraspinal muscle area (MA) was manually measured on axial thoracic CT images at the level of the 12th thoracic vertebra using the Sectra PACS (IDS7, Sweden) software. A region of interest (ROI) was carefully drawn to encompass the outer margin of the paraspinal muscles bilaterally. The aortic density was measured by placing an ROI over the aorta at the same

level, using the widest circular area that fully enclosed the lumen without including surrounding tissues. In addition, the degree of muscle adiposity was determined by the ratio of the mean density of the muscle to the aortic density (M/A density) (Figure 1). This ratio eliminated density differences that may arise from shooting parameters. MA and M/A density ratio values were compared between the patient and control groups. In addition, those with and without parenchymal lung involvement in the RA group were compared. All measurements were performed with Sectra Workstation software (PACS, Sectra Workstation IDS7, Sweden). Radiological measurements were independently performed by two experienced radiologists who were blinded to the participants' clinical status and group assignment.



Figure 1. Measurement of muscle area, muscle density, and aortic density.

Since the patient's BMI was unknown, the area of subcutaneous adipose tissue was measured instead (Figure 2). Subcutaneous adipose tissue was evaluated by automatic measurement on the Aquarius iNtuition Viewer (V4.4.13, Terarecon) workstation.

The CT scan was performed using a 128-detector scanner (GE Revolution EVO, Milwaukee, USA). Slices were taken from the lung apices to the bottom. The scan parameters are 0.625mm slice, 100 kV, auto mA (min 80 - max 250), large FOV, 40mm coverage, rotation time 0,6 s, pitch 1,375. The slice thickness was 2.5 mm.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was evaluated using Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed continuous variables were expressed as mean $\pm$ standard deviation; non-normally distributed variables were presented as median (min–max). Categorical variables were reported as

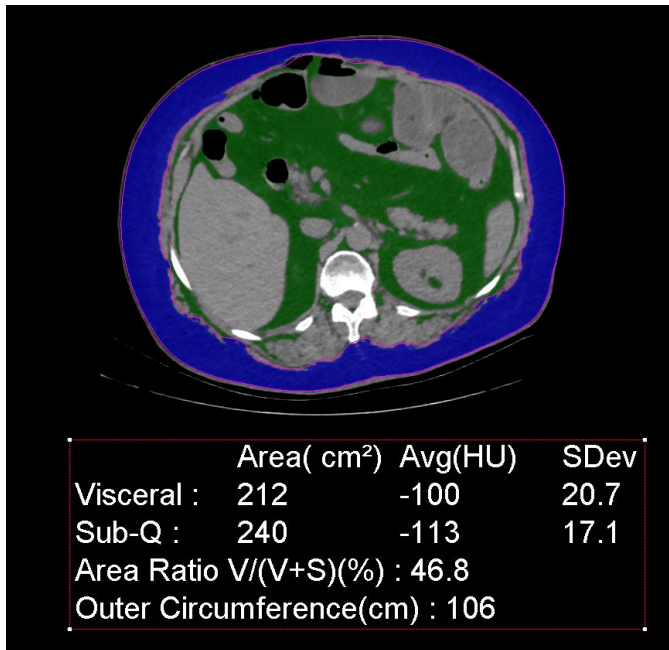


Figure 2. Automatic measurement of subcutaneous fat tissue via workstation.

frequency and percentage. The intraclass correlation coefficient (ICC) was used to assess the interobserver agreement of the MA and M/A density ratio.

For hypothesis testing, the Student's t-test was performed for normally distributed variables, and the Mann-Whitney U test was used for non-normally distributed variables. Spearman correlation analysis was used to assess relationships between continuous variables. Multiple linear regression was used to model the relationship between lung involvement status (dummy-coded) and each muscle outcome, with the control group as the reference category. A p-value < 0.05 was considered statistically significant.

■ RESULTS

This study included 187 people; 156 (83%) were female and 31 (17%) were male. The patient group consisted of 84 individuals, comprising 71 women (85%) and 13 males (15%). The control group consisted of 103 people, including 85 women (83%) and 18 males (17%). There was no significant difference between the two groups in the gender comparison ($p = 0.867$). The interobserver ICC values were 0.970 (95% CI, 0.93–0.98) and 0.991 (95% CI, 0.97–0.99) for MA and the M/A density ratio, respectively.

Comparison of data between groups

CRP values were available in 84 in the RA group and 73 in the control group. Age, CRP, MA, and M/A density ratio data did not follow normal distribution in both groups. Therefore, they were compared with non-parametric tests, and the results are shown in Table 1. Although the median muscle area was higher in the control group and the median CRP in the RA group, no statistical difference was observed

($p=0.180$, $p=0.851$, respectively). M/A density ratio value was significantly lower in the RA group ($p<0.001$) (Figure 3). Subcutaneous fat tissue was normally distributed in both groups. There was no significant difference between the normal and RA groups ($p = 0.088$, as determined by a student t-test).

Table 1. Comparison of the MA and M/A density ratio between the RA group and the control group.

	RA Median (min-max)	Control Median (min-max)	p
Age (year)	60 (26-78)	60 (26-78)	0.952
CRP (mg/dL)	5 (1-215)	5 (1-215)	0.851
MA (mm²)	3260.5 (1090-5347)	3260.5 (1090-5347)	0.180
M/A density ratio	0.52 (-1.60-1.60)	0.52 (-1.60-1.60)	<0.001

p was obtained from the Mann-Whitney U test.

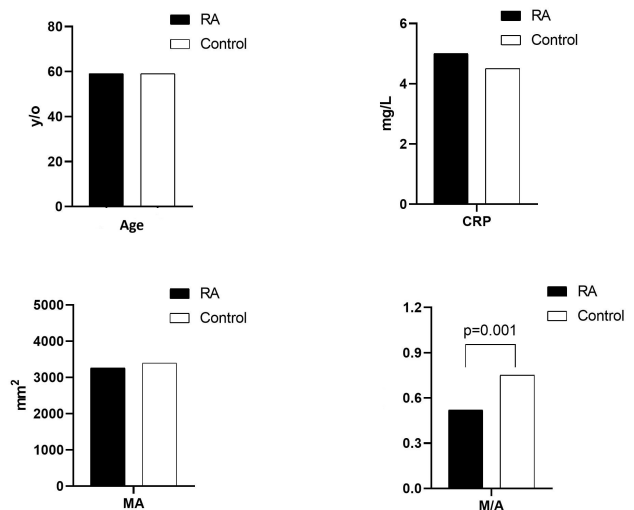


Figure 3. Graphical comparison of RA and control group.

In the RA group, 82 people had Anti-CCP values and median=16 (min=0.5, max=500), 82 had RF values and median=20 (min=1, max=240). 30 (36%) people had lung involvement, and 54 (64%) had no. The involvement pattern was 3 UIP, 9 NSIP, 9 BO, 2 RN, 6 isolated bronchiectasis, and 1 LIP. Isolated emphysema was observed in 2 individuals and was not considered as lung involvement. The patient group was divided into two groups according to lung involvement and compared. RF, CRP, anti-CCP, M/A density, and age were not normally distributed in the patient group. The muscle area and subcutaneous fat tissue followed a normal distribution. There was no significant difference between the groups in terms of gender comparison ($p = 1.000$). There was no significant difference between the patient subgroups when comparing MA and subcutaneous fat tissue using the Student's t-test ($p = 0.683$, $p = 0.779$, respectively). The parameters of the patient sub-group comparison that do not follow a normal distribution are shown in Table 2. In the comparison between those with and without lung involvement,

the M/A density ratio was found to be significantly lower in those with lung involvement ($p < 0.05$) (Figure 4).

Table 2. Comparison of non-normally distributed data of those with and without lung involvement.

	Lung involvement		p
	Yes Median (min-max)	No Median (min-max)	
Age (year)	64 (26-78)	59 (26-74)	0.064
CRP (mg/dL)	4.5 (1-215)	5 (1-116)	0.683
RF (IU/mL)	25 (6-240)	20 (1-159)	0.125
Anti-CCP (EU/ml)	70 (0.5-500)	8.5 (0.5-500)	0.123
M/A density ratio	0.337 (-1.60-1.11)	0.551 (-0.84-1.60)	0.016

p was obtained from the Mann-Whitney U test.

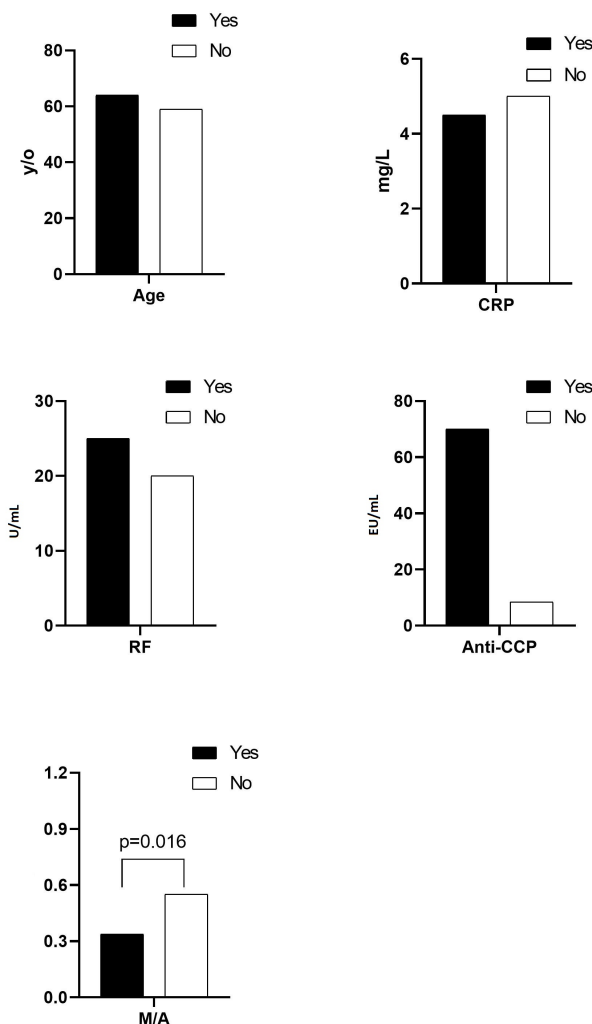


Figure 4. Comparison of groups according to the presence and absence of lung involvement.

When gender was compared, the MA and M/A density ratio were significantly higher in men; however, no significant difference was observed in age ($p = 0.001$, $p = 0.019$, $p = 0.996$, respectively). The findings are summarized in Table 3.

Significance of the model with regression analysis

To further investigate the impact of lung involvement on muscle characteristics, two separate multiple linear regression analyses were conducted. In the first model, muscle area (MA) was entered as the dependent variable, and lung involvement status was coded using two dummy variables: "lung involvement = yes" and "lung involvement = no," with the control group (healthy individuals) as the reference category. The overall model was not statistically significant, $F(2, 184) = 1.315$, $p = 0.271$, indicating that lung involvement status did not significantly predict muscle area. The model explained only 1.4% of the total variance ($R^2 = 0.014$; Adjusted $R^2 = 0.003$). In terms of individual predictors, neither RA patients without lung involvement ($B = -181.61$, $p = 0.117$) nor those with lung involvement ($B = -115.01$, $p = 0.420$) showed a statistically significant difference in muscle area compared to the control group.

In the second model, the M/A density ratio was used as the dependent variable to evaluate changes in muscle quality. Again, the predictor variables were the two dummy-coded lung involvement groups, with the control group as reference. This model was statistically significant, $F(2, 184) = 15.684$, $p < 0.001$, explaining 14.6% of the variance in the M/A density ratio ($R^2 = 0.146$; Adjusted $R^2 = 0.136$), which is a moderate effect size in clinical research.

In terms of regression coefficients, RA patients without lung involvement had significantly lower M/A density ratio than controls ($B = -0.175$, $p = 0.011$), suggesting a moderate decrease in muscle quality. RA patients with lung involvement showed an even more pronounced reduction ($B = -0.462$, $p < 0.001$), highlighting the potential additive or synergistic effect of pulmonary involvement on intramuscular fat infiltration. These findings indicate that while muscle mass (area) may not differ significantly across groups, muscle quality, as reflected by M/A density ratio, is significantly reduced in RA patients, especially in those with pulmonary manifestations. The detailed coefficients and significance values are presented in Table 4.

Correlation analysis between data

The data were analyzed using the Spearman correlation test. MA and M/A density ratio correlation was statistically insignificant ($p = 0.402$).

No association between age and MA ($p = 0.289$). A high negative correlation was observed between the M/A density ratio and age ($p < 0.001$, $\rho = -0.489$).

DISCUSSION

Sarcopenia is a significant comorbidity and extraarticular finding in rheumatoid arthritis (RA), affecting about 25% of individuals with the disease [7]. While lung involvement is the most common extraarticular manifestation of RA [6], the relationship between RA pulmonary involvement and sarcopenia

Table 3. Comparison of muscle area, muscle density, M/A density ratio, and age between genders.

	Muscle Area (mm ²)			Muscle Density (HU)			M/A Density Ratio			Age (year)		
	Median	Minimum	Maximum	Median	Minimum	Maximum	Median	Minimum	Maximum	Median	Minimum	Maximum
Male	3753	2467	5425	25	-40	55	0.75	0.05	1.43	61	21	86
Female	3280	1090	5300	30	2	52	0.60	-1.60	1.60	59	18	88
p-value	0.001			0.090			0.019			0.996		

p was obtained from the Mann-Whitney U test.

Table 4. Regression analysis predicting muscle area and M/A density ratio.

Dependent variable	Predictor	B	SE	β	t	p
Muscle Area (Adjusted R ² = 0.003, p = 0.271)	(Constant)	3467.61	67.60	--	51.30	<0.001
	Lung involvement = no	-181.61	115.26	-0.12	-1.58	0.117
	Lung involvement = yes	-115.01	142.33	-0.06	-0.81	0.420
M/A Density Ratio (Adjusted R ² = 0.136, p < 0.001)	(Constant)	0.709	0.040	--	17.76	<0.001
	Lung involvement = no	-0.175	0.068	-0.183	-2.57	0.011
	Lung involvement = yes	-0.462	0.084	-0.390	-5.50	<0.001

p-values are based on t-tests within the regression model.

nia has not been widely studied. To the best of our knowledge, this study is the first to investigate this link.

Muscle quality can be evaluated by muscle density obtained from CT, which indicates myocellular lipid content and fatty infiltration [8]. In this study, we assessed muscle mass and quality using CT, a widely accepted technique. To overcome potential density variations caused by imaging parameters, we calculated the ratio of muscle density to aortic density. This approach ensures more precise measurements by eliminating technical differences.

Measuring muscle mass and density via CT is particularly useful in RA because, unlike muscle strength tests, it is not affected by joint inflammation [4]. Our findings support the work of Khoja et al. [9], who demonstrated that skeletal muscle fat infiltration increases in RA patients compared to age-matched controls. We also found that this condition was more pronounced in patients with lung involvement.

Skeletal muscle fat is associated with disease activity and negatively impacts muscle strength, physical performance, and disability, independent of muscle mass [9–11]. Our results align with two studies involving over 100 participants, which found that higher muscle density was associated with less disability (measured by the Health Assessment Questionnaire (HAQ)) and greater physical function (measured by the Short Physical Performance Battery (SPPB)) [11, 12]. Furthermore, studies on non-RA patients have shown that low muscle density is linked to adverse outcomes, including increased weakness, mobility limitations, and a higher risk of hip fractures and hospitalization [11]. The relationship between muscle density and strength is also stronger in RA patients compared to healthy controls [12]. Consistent with the existing literature, our findings suggest that pulmonary involvement in RA may impact muscle quality and contribute to these comorbidities. Although our regression model was statistically significant in predicting the muscle-to-aorta (M/A) density ratio, the ex-

plained variance was modest (Adjusted R² = 0.136). This suggests that other unmeasured factors may contribute to muscle adiposity in RA patients. Important covariates such as BMI, metabolic disorders (e.g., diabetes mellitus, hyperlipidemia), insulin resistance, and physical activity levels were not available due to the study’s retrospective nature. The absence of these variables may have limited the explanatory power of our models. Future prospective studies with comprehensive clinical and metabolic profiling are warranted to better understand the multifactorial nature of muscle fat infiltration in RA.

The accumulation of intramuscular fat in RA patients can be caused by chronic systemic inflammation, physical inactivity, excessive total and visceral adiposity, and the use of medications such as glucocorticoids [11]. Inflammatory cytokines, such as IL-6 and tumor necrosis factor, have been associated with decreased muscle density [13]. A study found that muscle concentrations of IL-6 protein were significantly higher in RA patients compared to controls [14]. When these findings are considered together, it is clear that RA-related inflammation is a significant factor in muscle fat infiltration.

Similar to the study by Baker et al. [15], we observed low muscle density in the RA group. While muscle area was lower in our RA group, this difference was not statistically significant. This supports the findings of Kramer et al., who showed that thigh muscle density, but not area, was associated with less disability and greater physical functioning [11]. In our study, RA and RA-related lung involvement significantly affected muscle density, but not muscle area, suggesting a link to greater disability and reduced physical activity.

Baker et al. found no significant relationship between muscle density and BMI in RA patients, suggesting that BMI may be a limited indicator for assessing muscle density [15]. Consistent with this, our study did not find a difference in subcutaneous adipose tissue area between the groups. However,

our study found a positive correlation between the area of the psoas major muscle and abdominal subcutaneous and visceral fat, which consistent with the literature [16], as well as a negative correlation between the M/A density ratio and subcutaneous fat area. This contradicts the idea that subcutaneous adipose tissue reduces sarcopenia. Consistent with the literature, our study found that the paraspinal muscle area was significantly lower in women [17]. While we found no significant difference in muscle density between men and women, the M/A ratio was significantly lower in women. This suggests that the ratio is a more precise measurement, unaffected by imaging parameters [18]. Unlike cadaveric studies [19], our study found no significant correlation between muscle area and age. This may be because sarcopenia is influenced by factors beyond age, such as inactivity, diseases, and medications. However, consistent with existing literature, we did find a significant negative correlation between M/A density and age.

The absence of a statistical difference in CRP values between the patient and control groups may seem like a negative result at first glance. However, this can be considered a factor increasing the study's statistical power. In this way, more homogeneity was provided for the groups. The fact that there was no significant difference between the groups in terms of CRP values is thought to be due to increased CRP secondary to trauma in the individuals in the control group included in the study [20].

The findings of this study suggest that evaluating muscle density using CT in RA patients, particularly those with pulmonary involvement, may provide a valuable non-invasive tool for early identification of sarcopenia risk. This could guide clinicians in initiating nutritional, physical activity, or pharmacological interventions to mitigate muscle quality deterioration.

Limitations

This study has several limitations. First, due to its retrospective design, BMI, physical activity levels, and metabolic comorbidities could not be included in the analysis. Second, the sample size was limited by the number of available CT scans that met the inclusion criteria. Third, the high proportion of female patients in our study may be explained by the fact that RA is more common in women. However, this may restrict the generalization of the findings to male patients.

CONCLUSION

In this study, unlike the existing literature, we found that RA lung involvement may also lead to increased muscle adiposity. We believe that the primary reason for this is the increase in inflammation. However, immobility and medications used due to lung involvement can also cause this. To better understand this relationship, larger prospective studies investigating the effects of RA-related lung involvement on muscles are needed.

Ethics Committee Approval: This study was approved by Sivas Cumhuriyet University Non-Interventional Clinical Research Ethics Committee (date:19-12-2024, decision number:2024-12/58).

Informed Consent: This retrospective study was approved by the institutional ethics committee. Since the data were collected from existing medical records and anonymized, informed consent was not required.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No author of this paper has a conflict of interest, including specific financial interests, relationships, and affiliations relevant to the subject matter or materials included in this manuscript.

Author Contributions: EG: Conception, Design, Analysis and Interpretation, Data Collection and Preprocessing, Literature Review, Writing, AS: Conception, Materials, Data Collection and Preprocessing, IA: Analysis and Interpretation, Literature Review, Critical Review, SA: Analysis and Interpretation, Literature Review, Critical Review.

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