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ORIGINAL ARTICLE

Association between atrial fibrillation and elevated risk of gastroesophageal reflux disease and complications in individuals under 50 years of age

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ABSTRACT

Background: Atrial fibrillation (Afib) and gastroesophageal reflux disease (GERD) are common conditions in hospitalized patients, yet there is limited evidence suggesting a direct relationship between them. This study aims to explore the correlation between Afib and GERD, as well as GERD-related complications such as esophageal strictures, Barrett's esophagus, and esophageal cancer, with age as a key factor of reference. **Methods:** A population-based analysis was performed using data from the National Inpatient Sample (NIS) from 2017 to 2019. Patients diagnosed with GERD were divided into groups based on whether they had a concurrent diagnosis of Afib or not and were compared with patients without GERD. Age was identified as a common risk factor for both Afib and GERD, leading to the substratification of the cohort into two age groups, using 50 years as a reference point. Other risk factors, such as obesity, smoking, hiatal hernia, race, and gender, were accounted for using ICD10 codes, and these factors were included in the analysis. **Results:** The results of the study revealed a clear predisposition for an increased risk of GERD and its related complications in younger patients with Afib. The prevalence of GERD was significantly higher in patients with Afib compared to those without (24.9% *vs.* 16.0%), with similar trends in both paroxysmal Afib (PAF) and persistent Afib (PerAF) subtypes. However, the overall risk of developing GERD did not increase significantly in older patients with Afib. In patients under 50, the prevalence of GERD (17.9% *vs.* 6.8%) and GERD phenotypes, such as nonerosive reflux disease (NERD) and erosive esophagitis (EE), was notably higher in Afib patients than in those without Afib. Patients under 50 with PAF had higher odds of developing GERD (1.213) and NERD (1.218) than those without Afib. Younger Afib patients also exhibited higher rates of reflux-related complications. These included esophageal strictures (21.8 *vs.* 7.3 per 10,000), Barrett's esophagus without dysplasia (32.8 *vs.* 8.4 per 10,000), and esophageal cancer (10.3 *vs.* 1.8 per 10,000), particularly in those with PAF and PerAF. Afib patients with PAF under 50 demonstrated significantly higher odds of developing Barrett's esophagus without dysplasia (1.532), while those with PerAF had a higher risk of esophageal cancer (1.543). **Conclusion:** In conclusion, Afib in patients under 50 is associated with a significantly higher risk of developing GERD and its related complications, highlighting the role of age in disease progression.

Key words: atrial fibrillation, younger patients, gastroesophageal reflux disease, esophageal strictures, Barrett's esophagus, esophageal cancer

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INTRODUCTION

Atrial fibrillation (Afib) is one of the most commonly encountered cardiac arrhythmia in routine practice, affecting approximately 1%–2% of the general population.[1,2] Clinical presentation can vary, and it includes palpitations, shortness of breath, and chest pain; there is also a significant subset of incidental diagnoses of Afib in asymptomatic patients. Diagnosis is dependent on the interpretation of an electrocardiogram.[3] The prevalence of Afib has been shown to increase with age and in those with cardiovascular disorders, such as heart failure, hypertension, ischemic heart disease, and diabetes mellitus. Other factors, including sleep apnea, obesity, and systemic inflammation/infection, have also been suggested as contributors to Afib.[4] The prevalence of Afib is projected to increase by 200%–300% over the next few decades. This rise is attributed to the availability of more treatment options, which are improving survival rates for cardiac complications, as well as suboptimal management of Afib risk factors.[5] Afib can have a significant impact on quality of life, and it is associated with an increased healthcare burden.[6]

Gastroesophageal reflux disease (GERD) affects approximately 20% of the general population. Clinically, it can present with heartburn and reflux, driven by the regurgitation of gastric content into the distal esophagus. The prevalence of GERD in the US has continued to rise due to increased rates of associated risk factors, such as metabolic syndrome, obesity, and predisposing dietary habits.[7–9] It is commonly associated with obesity, sleep apnea, hiatal hernia, and tobacco use.[10,11]

Both Afib and GERD are multifactorial in etiology, with significant overlap in shared predisposing risk factors. The potential relationship between these two conditions has been previously suggested.[12,13] One example is Roemhold gastrocardiac syndrome.[14] However, with the exception of possible neurogenic interplay driven by shared sensory pathways no potential underlying mechanism has been discerned. The role of impaired autonomic nervous system innervation has been postulated in prior studies, which could be attributed to common intercrossing nerve innervation between the heart and esophagus.[15] A study by Tougas *et al.* demonstrated that mechanical and electrical stimulation of the distal esophagus conducted while monitoring the range of the power spectrum of beat-to-beat heart rate variability elicited a lower heart rate response, with a concurrent drop in the low-frequency power component and a contrasting rise in the high-frequency power component.[16] This evidence was further evaluated in a study of 30 patients with Afib undergoing cardiac ablation, where it was noted that more patients with preexisting gastrointestinal symptoms suggestive of GERD reported Afib compared to asymptomatic patients.[17] Finally, Cuomo *et al.* showed a significant correlation between heart rate variation (monitored by sympathetic modulation/vagal modulation ratio) following a downward trend in esophageal pH, which was countered by regular use of proton pump inhibitors; this resulted in a significant reduction in cardiac symptoms.[18]

This study investigated whether Afib is associated with an increased risk of developing GERD and the rise in its prevalence by using a large nationwide database. We also assessed the potential relationship between Afib and GERD complications, including esophageal strictures (ES), Barrett's esophagus (BE) with or without dysplasia, and esophageal cancer (EC).

MATERIALS AND METHODS

Database

This retrospective, population-based cohort study utilized the National Inpatient Sample (NIS) database for the period 2017–2019. This database was developed by the Healthcare Cost and Utilization Project, A partnership between federal, state, and industry entities, sponsored by the Agency for Healthcare Research and Quality (AHRQ). The NIS is the largest US publicly available all-payer inpatient healthcare database that estimates inpatient utilization, access, cost, quality, and outcomes; it contains unweighted data from around seven million hospital stays annually. The NIS approximates a 20% stratified sample of all discharges from US community hospitals, excluding rehabilitation and long-term acute care hospitals.

Data collection and outcomes

We used the NIS to access a comprehensive dataset containing the essential variables that were pertinent to our study. We included data spanning three years to use the most up-to-date information available. Data extraction was replicated for each variable to ensure consistent and reproducible data handling.

A total of 12,174,068 patients admitted to hospitals during 2017–2019 were included in this study. Patients diagnosed with GERD (ICD-10-CM K21.9 and K21.0) with and without Afib (ICD-10-CM I48.0, I48.1, I48.2, and I48.91) were extracted and substratified into two groups based on age (above or below 50 years). These two groups were then matched against their comparable counterparts without GERD. The decision to divide the patient population by age was dictated by our preliminary findings. Initial data analysis showed a specific trend highlighting age as a pivotal variable in patients younger than 50. The rationale behind choosing

this time frame was to utilize the most recent dataset available at the time and provide an adequate timeline before the establishment of the diagnosis of interest, while allowing for a sufficient duration of exposure to allow for potential complications to develop.

The risk factors of Afib and GERD integrated into our study were hiatal hernia, smoking, and obesity. Further risk factor identification through sociodemographic data extraction involved age, race, gender, obesity, controlled type 2 diabetes (T2DM), hiatal hernia, and hypertension.

Two subtypes of GERD were factored into our analysis: nonerosive reflux disease (NERD) and erosive esophagitis (EE). Two subtypes of Afib were incorporated: paroxysmal Afib (PAF) and persistent Afib (PerAF). The diagnosis of GERD was based on reflux testing or endoscopic upper gastrointestinal luminal evaluation with histopathology.[12] The diagnosis of Afib was based on the use of an electrocardiogram or Holter monitor.

The GERD-related complications considered in our analysis were ES, BE with and without dysplasia, and EC. To assess the odds of developing GERD and GERD-related complications in patients with Afib, we measured Afib patients with GERD and GERD-related complications (cases) against Afib patients without this disease and its complications (controls).

We excluded patients with histories of foregut surgery, uncontrolled T2DM (ICD-10-CM E11.65), eosinophilic esophagitis (ICD-10-CM K20.0), infective esophagitis (ICD-10-CM K20.8), and atrial flutter (ICD-10-CM I48.92). We used the following ICD-10-CM codes to extract the relevant data: ICD-10-CM K21.9 and K21.0 for GERD and ICD-10-CM I48.0, I48.1, I48.2, and I48.91 for Afib. All the diagnoses included or excluded from this study were selected by screening the ICD-10-CM codes (Figure 1).

Ethical considerations

This study was conducted in compliance with the ethical standards outlined in the Declaration of Helsinki. As the NIS database contains de-identified patient data, our study was exempt from the requirement to obtain institutional review board approval.

Statistical analysis

All the demographic and risk factor data in this study were categorical; they are thus presented as cases and percentages. Chi-squared analysis was used to analyze the association between GERD and Afib and investigate the association between GERD complications in patients with and without Afib. More specifically, the prevalence of GERD, as well as NERD/EE, was examined in patients with and without Afib. The patients were then stratified by age, and the prevalence within each group was calculated using chi-squared analysis. Multivariate logistic regression was used to assess the risks (in the form of odds ratios [ORs]) of GERD and GERD-related complications with and without Afib (PAF and PerAF). Initially, we used multivariate logistic regression to investigate the risk of GERD and GERD-related complications in patients with Afib, accounting for possible confounding factors associated with both GERD and Afib. These confounding factors included age, gender, race, smoking status, hiatal hernia, and obesity. Subsequently, the patients were divided into two subgroups based on age (50 years), and the analysis was repeated with similar confounding factors. A two-sample test for equal proportions was conducted, with a P value of < 0.05 considered statistically significant. IBM SPSS Statistics version 28.0.1.1 was used for statistical analysis.

RESULTS

A total of 12,018,275 hospitalized patients of all age groups were included in our study, covering the period 2017–2019. Of these patients, 2,051,965 who had been diagnosed with GERD were identified, including those with and without Afib (362,839 and 1,689,126, respectively). Overall, the patients with GERD and Afib were older than those without Afib (75.1 ± 0.1 years *vs.* 61.8 ± 0.1 years, respectively; $P < 0.05$). There were more female patients than male ones in the GERD group regardless of concurrent, or lack of, Afib diagnosis. Concerning the risk factor stratification, there were significantly fewer patients with a history of smoking in the GERD with Afib group than in the GERD-only group (7.9% *vs.* 16.4%, respectively; $P < 0.05$). The prevalence of hiatal hernia, controlled T2DM, and obesity showed no significant difference in the patients with both GERD and Afib compared to their counterparts with only GERD (Table 1).

Regarding the prevalence and risk of developing GERD, the patients with Afib exhibited a higher prevalence of GERD compared to those without Afib (24.9% *vs.* 16.0%, respectively; $P < 0.01$). This finding was consistent across the two subtypes of Afib (PAF [26.9%] and PerAF [23.7%]; Figure 1A). Further analysis of the different subtypes of Afib revealed an increased prevalence of GERD in both PAF (19.6%) and PerAF (17.6%) compared to patients without Afib ($P < 0.01$; Figure 1A). However, no significant increased risk of GERD was identified in Afib patients after adjusting for confounding factors, including age, gender, race, and other comorbidities (Odds Ratio [OR]: 0.86, 95% Confidence Interval [CI]: 0.856–1.025, $P > 0.05$), even when accounting for both subtypes (PAF and PerAF,

Table 1: Demographic classification, risk factors, and comorbidities between Afib with and without GERD

Items		GERD with Afib	GERD without Afib	*P* value
Age		75.1 ± 0.1	61.8 ± 0.1	< 0.05
Sex	Female	193,718 (53.4%)	1,008,902 (59.7%)	< 0.05
	Male	169,110 (46.6%)	680,123 (40.3%)	< 0.01
Race	White	300,792 (82.9%)	1,229,788 (72.8%)	> 0.05
	Black	29,541 (8.1%)	235,690 (14.0%)	< 0.05
	Hispanic	13,031 (3.6%)	107,042 (6.3%)	< 0.05
	Asian	3,726 (1.0%)	22,969 (1.4%)	< 0.05
Risk factors	Contr. T2DM	45,362 (12.5%)	211,570 (12.5%)	> 0.05
	Obesity	68,532 (18.9%)	357,002 (21.1%)	> 0.05
	Smoking	28,490 (7.9%)	277,030 (16.4%)	< 0.05
	Hiatal hernia	18,579 (5.1%)	92,540 (5.5%)	> 0.05
	Hypertension	75.1 ± 0.1	61.8 ± 0.1	< 0.05

GERD, gastroesophageal reflux disease; Afib, atrial fibrillation; T2DM, type 2 diabetes.

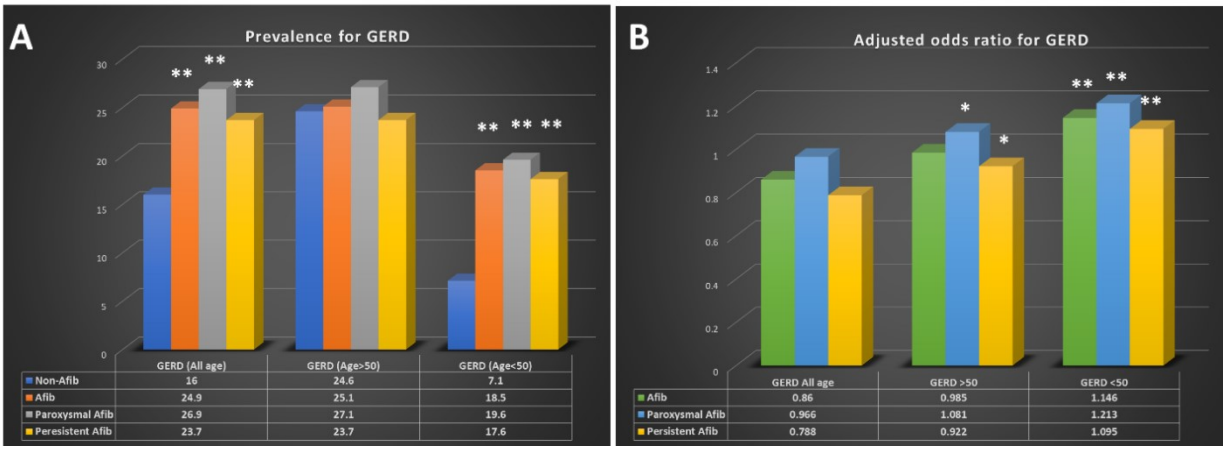

Figure 1. Bar graph of prevalence and odds ratios for the Afib patients with GERD, adjusted for age, sex, race, obesity, hiatal hernia, and history of smoking. (A) The prevalence of GERD in patients with Afib and different types of Afib based on the age. (B) The adjusted odds ratio of GERD in different age groups of patients with Afib and different types of Afib. $^{*}P < 0.05$. $^{**}P < 0.01$. GERD, gastroesophageal reflux disease; Afib, atrial fibrillation.

Figure 1B and Table 2).

When subclassified into different age groups, there was no significant difference in the prevalence of GERD among the patients with Afib who were older than 50 compared to the patients without Afib (25.1% *vs.* 24.6%, respectively; $P > 0.05$), regardless of Afib subtype (PAF [27.1%] and PerAF [23.7%]; $P > 0.05$; Figure 1A and Table 2). Furthermore, after adjusting for confounding factors, there was no significant rise in the combined risk of GERD in the Afib patients aged above 50 (OR: 0.985, 95% CI: 0.950–1.042, $P > 0.05$; Figure 1A and Table 2). However, there was a statistically significant increased risk of GERD in the patients with the PAF subtype (OR: 1.081, 95% CI: 1.074–1.081, $P < 0.05$; Figure 1B and Table 2).

In contrast, the patients who were aged below 50 were found to exhibit a statistically significant rise in the prevalence of GERD in both cumulative Afib (18.50%, $P < 0.01$) and the subcohorts of Afib subtypes (PAF [19.60%] and PerAF [17.60%]), with a higher predisposition among the patients with PAF to develop GERD (OR: 1.213, 95% CI: 1.179–1.249, $P < 0.01$) compared to those with PerAF (OR: 1.095, 95% CI: 1.068–1.024, $P < 0.01$; Figure 1B and Table 2).

Regarding the prevalence and likelihood of developing GERD-related complications, we found an inherent increased risk of developing NERD among the patients with Afib compared to those without Afib (OR 1.151, 95% CI: 1.129–1.173, $P < 0.01$; Figure 2B and Table 3), which resulted in an increased prevalence of NERD in this patient population (17.9%) compared to that in the population without Afib (6.8%, $P < 0.01$; Figure 2A). The patients with PAF were found to be at higher risk

Table 2: Prevalence and odds ratios for Afib patients of different ages with GERD

Afib patients		Cases	Prevalence	Cases per 10,000	*P* value	Adjusted OR	95% CI	*P* value
Afib all	Yes	362,839	24.90%	-	< 0.01	0.860	0.856–1.025	> 0.05
	No	1,689,126	16.00%	-	-	-	-	-
	PAF	135,257	26.90%	-	< 0.01	0.966	0.959–1.050	> 0.05
	PerAF	216,289	23.70%	-	< 0.01	0.851	0.784–1.025	> 0.05
Afib > 50 y/o	Yes	355,488	-	25.1	> 0.05	0.985	0.950–1.042	> 0.05
	No	1,330,397	-	24.6	-	-	-	-
	PAF	132,177	-	27.1	> 0.05	1.081	1.074–1.089	< 0.05
	PerAF	216,289	-	23.7	> 0.05	0.922	0.917–0.928	< 0.05
Afib < 50 y/o	Yes	14,610	-	18.5	< 0.01	1.146	1.125–1.168	< 0.01
	No	653,592	-	7.1	-	-	-	
	PAF	6,268	-	19.6	< 0.01	1.213	1.179–1.249	< 0.01
	PerAF	8,037	-	17.6	< 0.01	1.095	1.068–1.024	< 0.01

Top four rows: Afib patients of all ages. Adjusted for age, race, gender, obesity, smoking history, and hiatal hernia. Afib, atrial fibrillation; GERD, gastroesophageal reflux disease; PAF, paroxysmal atrial fibrillation; PerAF, persistent atrial fibrillation; OR, odds ratio; CI, confidence interval.

Table 3: Prevalence and odds ratios for Afib patients below 50 y/o with NERD, EE, and GERD-related complications, adjusted for age, race, gender, obesity, smoking history, and hiatal hernia

Items	Afib	Cases	Prevalence	Cases per 10,000	*P* value	Adjusted OR	95% CI	*P* value
Nonerosive reflux disease	Yes	14,062	17.90%	-	< 0.01	1.151	1.129–1.173	< 0.01
	No	626,485	6.80%	-	-	-	-	-
	PAF	6,037	19.00%	-	< 0.01	1.218	1.183–1.254	< 0.01
	PerAF	7,732	17.10%	-	< 0.01	1.100	1.072–1.129	< 0.01
Erosive esophagitis	Yes	531	-	0.8	< 0.01	0.992	0.906–1.086	> 0.05
	No	26,463	-	0.3	-	-	-	-
	PAF	222	-	0.9	< 0.01	1.044	0.909–1.198	> 0.05
	PerAF	297	-	0.8	< 0.01	0.952	0.844–1.074	> 0.05
Esophageal strictures	Yes	141	-	21.8	< 0.01	1.188	1.001–1.411	< 0.05
	No	6,327	-	7.3	-	-	-	-
	PAF	60	-	23.2	< 0.01	1.268	0.976–1.647	> 0.05
	PerAF	80	-	21.3	< 0.01	1.159	0.925–1.452	> 0.05
Barrett's esophagus without dysplasia	YES	212	-	32.8	< 0.01	0.999	0.898–1.150	> 0.05
	NO	7,257	-	8.4	-	-	-	-
	PAF	108	-	41.8	< 0.01	1.532	1.454–1.613	< 0.01
	PerAF	101	-	26.9	< 0.01	0.813	0.665–0.995	< 0.05
Barrett's esophagus with dysplasia	Yes	2	-	0.3	> 0.05	0.449	0.110–1.822	> 0.05
	No	140	-	0.1	-	-	-	-
	PAF	1	-	0.3	> 0.05	0.385	0.054–2.765	> 0.05
	PerAF	1	-	0.2	> 0.05	0.572	0.080–4.107	> 0.05
Esophageal cancer	Yes	67	-	10.3	< 0.01	1.240	0.696–1.587	> 0.05
	No	1,514	-	1.8	-	-	-	-
	PAF	19	-	7.3	< 0.01	0.866	0.550–1.363	> 0.05
	PerAF	48	-	12.8	< 0.01	1.543	1.155–2.060	< 0.01

Afib, atrial fibrillation; PAF, paroxysmal atrial fibrillation; PerAF, persistent atrial fibrillation; OR, odds ratio; CI, confidence interval.

of developing NERD (OR 1.218, 95% CI: 1.183–1.254, $P < 0.01$) compared to the patients with PerAF (OR 1.10, 95% CI: 1.072–1.129, $P < 0.01$; Figure 2B and Table 3). The prevalence of NERD followed suit and was equivocally elevated across both Afib subtypes, with a higher predisposition in PAF than PerAF (19.0% *vs.* 17.1%, respectively; $P < 0.001$; Figure 2A and Table 3).

EE was also found to be more prevalent among patients with Afib compared to those without Afib (0.8% *vs.*

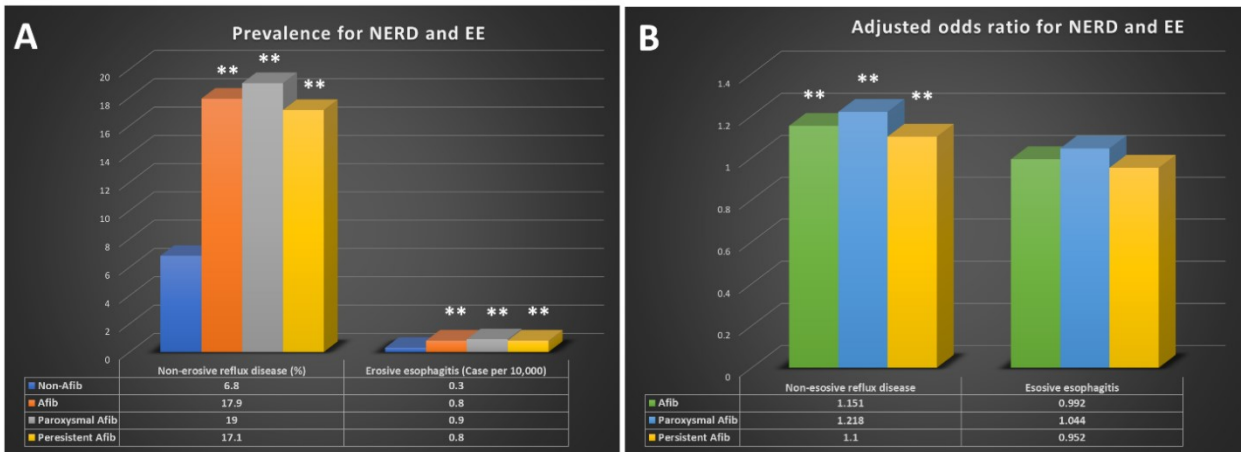

Figure 2. Bar graph of prevalence and odds ratios for Afib patients with NERD, EE, and GERD-related complications, adjusted for age, sex, race, obesity, hiatal hernia, and history of smoking. (A) The prevalence of subtypes of GERD (NERD and EE) in young patients (Age < 50 y/o) with Afib and different types of Afib. (B) The adjusted odds ratio of NERD and EE in younger patients (Age < 50 y/o) with Afib and different types of Afib. $^{*}P < 0.05$. $^{**}P < 0.01$. GERD, gastroesophageal reflux disease; Afib, atrial fibrillation; NERD, nonerosive reflux disease; EE, erosive esophagitis.

0.3%, respectively; $P < 0.01$; Figure 2A and Table 3). However, no significant change in the risk of EE was detected among patients with Afib compared to their counterparts without Afib (OR: 0.992, 95% CI: 0.906–1.086, $P > 0.05$; Figure 2B and Table 3). Concerning the Afib subtypes, despite a rise in the prevalence of EE among the patients with both subtypes (PAF [0.9%] and PerAF [0.8%]) compared to the patients without Afib (0.3%, $P < 0.01$; Figure 2A and Table 3), there was no increased risk of developing EE among the patients with PAF (OR: 1.044, 95% CI: 0.909–1.198, $P > 0.05$) and those with PerAF (OR: 0.952, 95% CI: 0.844–1.074, $P > 0.05$; Figure 2B and Table 3).

The risk of developing ES was elevated in patients with Afib (OR 1.188, 95% CI: 1.001–1.441, $P < 0.001$; Figure 3A and Table 3), with a rise in prevalence in this population (21.8 cases per 10,000) compared to that without Afib (7.3 cases per 10,000, $P < 0.01$; Table 3 and Figure 3). This pattern was consistent across the subtypes of Afib (PAF [23.2 cases per 10,000] and PerAF [21.3 cases per 10,000]). However, after controlling for possible confounders, there was no corresponding rise in the individualized risk of developing ES in either patient cohort (PAF [OR: 1.268, 95% CI: 0.976–1.674, $P > 0.05$] and PerAF [OR: 1.159, 95% CI: 0.925–1.452, $P > 0.05$]; Table 3 and Figure 3B).

The patients with Afib were found to have an increased prevalence of BE without dysplasia (32.8 cases per 10,000) compared to those without Afib (8.4 cases per 10,000, $P < 0.01$; Table 3 and Figure 3A). This prevalence was consistent regardless of the Afib subtype (PAF [41.8 cases per 10,000] and PerAF [26.9 cases per 10,000]). However, the patients with PAF were significantly more likely to develop BE without dysplasia (OR 1.532, 95% CI: 1.454–1.631, $P < 0.001$) compared to those with PerAF (OR: 0.813, 95% CI: 0.665–0.995, $P < 0.05$) and those without Afib (Table 3 and Figure 3B).

The patients with Afib were also found to have an increased prevalence of BE with dysplasia (0.3 cases per 10,000) compared to those without Afib (0.1 cases per 10, 000) ($P > 0.05$; Table 3 and Figure 3A). However, there was no attributable risk of developing BE with dysplasia among patients with Afib (Table 3 and Figure 3).

Finally, there was an increased prevalence of EC in the patients with Afib (10.3 cases per 10,000 patients) compared to those without Afib (1.8 cases per 10,000; $P < 0.01$; Table 3 and Figure 3A). Further analysis of the two Afib subtypes showed matching trends in patients with PAF (7.3 cases per 10,000) and PerAF (12.8 cases per 10,000, $P < 0.01$; Table 3 and Figure 3A). Despite this, only the patients with PerAF were at a significantly higher risk of EC (OR 1.543, 95% CI: 1.155–2.060, $P < 0.01$; Table 3 and Figure 3B).

DISCUSSION

The primary outcome of our study is the evidence concerning the significantly increased risk and prevalence of GERD and its complications in patients with Afib compared to those without Afib, even when adjusting for several possible confounders, such as obesity, smoking, male gender, and hypertension. It is also crucial to note that this association was only present in patients aged below 50. This study is the first of its kind to account for the chronological element as a variable when analyzing a comprehensive inpatient database for the association between GERD and Afib,

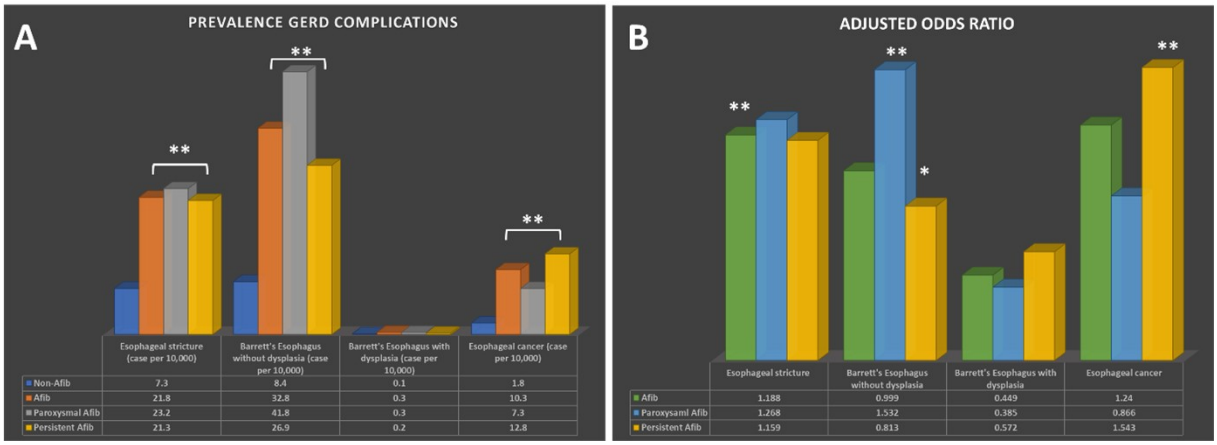

Figure 3. Bar graph of prevalence and odds ratios for Afib patients with GERD-related complications, adjusted for age, sex, race, obesity, hiatal hernia, and history of smoking. (A) The prevalence of of GERD complications in young patients (Age < 50 y/o) with Afib and different types of Afib. (B) The adjusted odds ratio of GERD complications in younger patients (Age < 50 y/o) with Afib and different types of Afib. $^{*}P < 0.05$. $^{**}P < 0.01$. GERD, gastroesophageal reflux disease; Afib, atrial fibrillation.

spanning over three years.

We also obtained several interesting findings by analyzing different subtypes of GERD and Afib. First, the patients with Afib were associated with a high risk of NERD but not EE. Second, the subjects with PAF were found to have a higher risk and prevalence of BE without dysplasia than those with PerAF. Third, the patients with PerAF were found to have a significantly higher risk and prevalence of EC than those with PAF.

Our results hold particular significance as the abovementioned correlation was identified only among younger patients. The literature has underscored age as a pivotal risk factor in the onset of Afib.[19,20] In our preliminary analysis, we observed a heightened prevalence of GERD and GERD-related complications in Afib patients across all age groups. However, upon adjusting for confounding factors, no significant risk association was discerned with advancing age. Subsequently, we conducted a focused examination of Afib risk based on age categories and concluded that the prevalence of Afib was not significantly influenced by age in individuals under 50. Consequently, we decided to exclude Afib patients aged 50 and above from our study. This exclusion made our study more intriguing, as it suggested the potential benefits of early upper endoscopy screening for younger Afib patients exhibiting signs of GERD.

Several previous small studies have demonstrated similar correlations. In a study involving 188 subjects, Afib significantly correlated with self-reported GERD but not with hypertension or gender.[21] These findings were echoed in a retrospective, case–control study from South Korea involving 3224 subjects. By using endoscopic examination or pH monitoring, the authors of this study found that patients with Afib had a higher prevalence of GERD as they were more predisposed to developing this disease (hazard ratio: 1.37).[22] In their case–control study, which encompassed only nonvalvular Afib patients, Kubota *et al.* reported the prevalence of GERD to be significantly higher in PerAF patients compared to PAF patients; PAF was also not correlated with Afib risk factors, such as hypertension or diabetes[23], which contradicts our findings.

Another significant result of our study is that several GERD-associated complications, such as ES, BE, and EC, impacted patients with Afib more frequently than those without the condition. This risk association was found to be much higher in the patients with PAF than their counterparts with PerAF. The patients with PAF had a higher risk (greater than 50%) of developing ES and BE without dysplasia. In the PerAF patients, the risk of having these GERD complications was estimated to be around 30%.

More importantly, we found that the patients with PAF had a higher risk of developing BE with dysplasia than those with PerAF (48% *vs.* 32%, respectively). Both subclasses of Afib had a heightened risk of 55% for EC compared to those without Afib, potentially suggesting that Afib, regardless of subtype, could be an independent risk factor for this kind of cancer, which would prompt more attention. Despite the lack of a direct pathophysiological mechanism linking Afib and these complications, this pattern has been recognized in several previous studies. Jiang *et al.*, for example, found that patients with BE and Afib exhibited a high prevalence of hyperlipidemia and chronic pulmonary disease, with a low prevalence of acute heart failure and hospital mortality.[24] In another study involving 29 patients who underwent pulmonary vein isolation to

treat Afib, endoscopic examinations revealed a high prevalence of structural changes in the esophageal wall after ablation in patients with Afib.[25] Several cases have reported the association between Afib and EC or treatment for such cancer.

Three mechanisms might drive the increased prevalence and risk of GERD in patients with Afib. The first one is the possible mass effect, with direct anatomical compression, of the distal esophageal wall by the left atrium due to its anatomical proximity,[26,27] as the two parts are only separated by a thin layer of connective tissue, usually less than five millimeters in thickness.[28,29] This mechanism might be compounded by the eventual development of an enlarged left atrium, specifically in those with PerAF, which would lead the hypothesized mass effect to be the driving factor behind this correlation and further impact the function of the lower esophageal sphincter (LES). Kubota *et al.* found that symptoms indicative of GERD was more frequently exhibited by patients with PerAF compared to those with PAF.[23] However, relevant data remains scarce due to the lack of a large, cross-validated inpatient cohort study.[26,27]

The second mechanism concerns the sympathetic and parasympathetic arms of the autonomic nervous system, which play an essential role in influencing the course of Afib.[30,31] Both the LES and the posterior aspect of the left atrium have unique anatomic profiles with extensive neurogenic networks of innervation.[32,33] Abnormal parasympathetic nervous system activity in patients with Afib could potentially affect the bordering parts of the lower esophagus and LES. Notably, vagal reflexes have been elicited during cardiac ablation procedures near the pulmonary vein.[34] This finding has been validated by the blunting of said reflexes after cardiac ablation of the left atrium.[35] Younger patients with no evidence of pathological structural heart disease or PAF were found to be at an increased risk of becoming symptomatic, underscoring a previously established predominance of vagal stimulation in this patient population.[36] Potentially, this corroborates our findings regarding a higher risk and prevalence of developing GERD in patients with PAF compared to those with PerAF.

The third mechanism concerns the systemic and localized proinflammatory responses that have been shown to be associated with increased prevalence of Afib and are considered independent risk factors. It is believed that circulating proinflammatory mediators, specifically interleukins and C-reactive protein, as well as concurrent oxidative stress, can trigger Afib.[37,38] Similarly, both systemic and local proinflammatory responses can predispose to the development of GERD. In one study, biopsies of the lower esophageal mucosa in patients with NERD revealed an increased expression of proinflammatory markers, such as interleukin-6 and interleukin-8.[39] Only a slight neutrophilic infiltration was evident in the esophageal mucosa in approximately 50% of patients with NERD, which implies an underlying role of even the mildest proinflammatory response in leading to pathophysiological changes of the esophageal mucosa. This is consistent with our findings that link a mild proinflammatory state in patients with Afib with NERD but not EE.

Our study has several limitations. First, the NIS, despite being a comprehensive nationwide inpatient database, lacks pertinent outpatient information, including patient therapeutics (*e.g.*, proton pump inhibitors, rate and rhythm control therapy for Afib, and related cardiac interventions). These elements can account for a considerable part of patients' overall outcomes. Second, the diagnosis of GERD and its complications and outcomes was based on the ICD-10-CM codes from different hospital systems and electronic medical records. It was assumed that the diagnosis of each complication of GERD, including ES, BE, and EC, was based on images, endoscopy, and pathology. However, further retrospective or prospective studies are required to extrapolate our findings if closer clinical and interventional monitoring, such as luminal evaluation by endoscopy, is warranted. The risk factors of GERD, including smoking, diabetes, and hiatal hernia, were also determined *via* ICD-10-CM codes, but no timeline for such risk factor exposure or degree of exposure could be identified or incorporated into our analysis. Further research is needed to address these limitations and advance the literature to mitigate potentially irreversible complications that carry significant morbidity and mortality.

CONCLUSION

The main clinical implication of our study is that patients with Afib, specifically those aged below 50, with a concurrent diagnosis of GERD (or expressing signs and symptoms suggestive of this disease), should be investigated for GERD-related complications, especially BE with dysplasia and EC (or for GERD, if not already established). To prevent GERD complications, early treatment with antacids or upper endoscopy screening for patients with Afib should be considered.

DECLARATION

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Author contributions
Wang XL: Conceptualization, investigation, data curation, data analysis, visualization, drafting the

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Data availability statement
The Marshall University School of Medicine, Institutional Review Board, has deemed studies using the NIS database as exempt from requiring IRB approval due to the de-identified and aggregated nature of the data in the database. The Case Western Reserve University/ Metrohealth Medical Center Institutional Review Board has deemed studies using the NIS database as exempt from requiring IRB approval due to the de-identified and aggregated nature of the data in the database at the standard defined in Section 164.514 (a) of the HIPAA Privacy Rule.

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