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# Clinical outcomes of atrial fibrillation with hyperthyroidism

Muhammad Zubair Khan MBBS[1] | Ashwani Gupta MD, FACC, FHRS[2] | Jordesha Hodge MD[1] | Kirtenkumar Patel MD[3] | Krunalkumar Patel MD[1] | Muhammad Samsoor Zarak MD[4] | Sona Franklin MD[1] | Harsh Patel MD[5] | Shruti Jesani MD[6] | Sejal Savani MPH[7] | Vraj Shah MBBS[8] | Vincent M. Figueredo MD, FACC[2] | Arvind R. Cavale MD, FACE, PCEO[9] | Steven Kutalek MD, FACC, FAHA, FHRS[10]

[1]Department of Internal Medicine, St. Mary Medical Center, Langhorne, PA, USA

[2]Division of Cardiology, St. Mary Medical Center, Langhorne, PA, USA

[3]Department of Cardiology, North Shore University Hospital, Manhasset, NY, USA

[4]Post Doc Research Fellow, West Virginia University of Medicine, Morgantown, WV, USA

[5]Department of Internal Medicine, Louis A Weiss Memorial Hospital, Chicago, IL, USA

[6]Department of Internal Medicine, Trinitas Regional Medical Center, Elizabeth, NJ, USA

[7]NYU College of Dentistry, New York, NY, USA

[8]Division of Cardiology, Medical College of Baroda, Vadodara, India

[9]Department of Medicine, St. Mary Medical Center, Langhorne, PA, USA

[10]Department of Cardiology, Drexel University College of Medicine, Philadelphia, PA, USA

**Correspondence**
Steven Kutalek, St Mary Medical Center, 1201 Langhorne-Newtown Road, Langhorne, PA 19047, USA.
Email: Kutaleks@aol.com

## Abstract

**Background:** Atrial fibrillation (Afib) is a common cardiac manifestation of hyperthyroidism. The data regarding outcomes of Afib with and without hyperthyroidism are lacking.

**Hypothesis:** We hypothesized that patients with Afib and hyperthyroidism have better clinical outcomes, compared with Afib patients without hyperthyroidism.

**Methods:** We queried the National Inpatient Sample database for years 2015-2017 using Validated ICD-10-CM codes for Afib and hyperthyroidism. Patients were separated into two groups, Afib with hyperthyroidism and without hyperthyroidism.

**Results:** The study was conducted with 68 095 278 patients. A total of 9 727 295 Afib patients were identified, 90 635 (0.9%) had hyperthyroidism. The prevalence of hyperthyroidism was higher in patients with Afib (0.9% vs 0.4%, $P < .001$), compared with patients without Afib. Using multivariate regression analysis adjusting for various confounding factors, the odds ratio of Afib with hyperthyroidism was 2.08 (CI 2.07-2.10; $P < .0001$). Afib patients with hyperthyroidism were younger (71 vs 75 years, $P < .0001$) and more likely to be female (64% vs 47%; $P < .0001$) as compared with Afib patients without hyperthyroidism. Afib patients with hyperthyroidism had lower prevalence of CAD (36% vs 44%, $P < .0001$), cardiomyopathy (24.1% vs 25.9%, $P < .0001$), valvular disease (6.9% vs 7.4%, $P < .0001$), hypertension (60.7% vs 64.4%, $P < .0001$), diabetes mellitus (29% vs 32%, $P < .0001$) and obstructive sleep apnea (10.5% vs 12.2%, $P < .0001$). Afib with hyperthyroidism had lower hospitalization cost ($14 968 ± 21 871 vs $15 955 ± 22 233, $P < .0001$), shorter mean length of stay (5.7 ± 6.6 vs 5.9 ± 6.6 days, $P < .0001$) and lower in-hospital mortality (3.3% vs 4.8%, $P < .0001$. The disposition to home was higher in Afib with hyperthyroidism patients (51% vs 42; $P < .0001$).

**Conclusion:** Hyperthyroidism is associated with Afib in both univariate and multivariate analysis. Afib patients with hyperthyroidism have better clinical outcomes, compared with Afib patients without hyperthyroidism.

**KEYWORDS**
arrhythmia, atrial fibrillation, hyperthyroidism

## 1 | INTRODUCTION

Atrial fibrillation (Afib) is the most common arrhythmia in the United States.[1] Studies have reported that two thirds of Afib patients who visit the emergency department are admitted to the hospital; this results in higher healthcare costs compared to patients who experience other types of arrhythmias.[2,3] Hyperthyroidism, coronary arterial disease, congestive heart failure, valvular disease, chronic pulmonary disease, hypertension, diabetes mellitus, obstructive sleep apnea, obesity, RA/collagen vascular disease, and old age are risk factors for Afib.[4–9] Each risk factor has varying effects on the clinical outcomes, such as hospitalization cost, length of stay, in-hospital mortality, and discharge disposition for Afib patients. Our study examines the clinical outcomes of Afib patients with hyperthyroidism. The association of Afib and hyperthyroidism is well known; however, the clinical outcomes as mentioned above have not been reported.

## 2 | METHODS

This study was conducted using the National Inpatient Sample (NIS) database from October 2015 to December 2017. NIS is the largest inpatient care database in the United States that was developed by the Healthcare Cost and Utilization Project (HCUP) and is the sponsored Agency for Healthcare Research. It represents more than 95% of the US population from 47 states and consists of a 20% stratified sample of all inpatient discharges from US hospitals excluding rehabilitations and long-term acute care hospitals. The self-weighting design used has the advantage of producing stable and precise data. Its principle of inclusivity, such as incorporating all-payers (Medicare, Medicaid, primary payers and uninsured), allows for estimates on trends for more than 36 million inpatient hospital stays nationally. Each admission contains information on patient demographics, primary and secondary diagnosis, comorbidities, length of stay, hospital costs, hospital characteristics, and discharge disposition.[10,11]

The study cohort was derived from a de-identified and publicly available database; therefore, it qualified for exemption from formal approval of the Institutional Review Board (IRB). The International Classification of Disease, 10th revision, Clinical Modification (ICD 10-CM) codes were used to identify the relevant diagnoses for our study in the NIS database which are list in Table 1. The primary outcome was to determine the hospitalization cost, length of stay, in-hospital mortality, and discharge disposition for Afib patients due to hyperthyroidism. Our study included patients 18 years and older. The baseline characteristics, namely, age, gender, and race, were obtained using ICD-10-CM codes. The individual comorbidities were obtained from the Elixhauser comorbidity software.

**TABLE 1** ICD 10 codes

| | |
|---|---|
| Atrial fibrillation | I48.0, I48.1, I48.2, I48.91 |
| Coronary arterial disease | I20, I21, I22, I24.0, I24.8, I24.9, I25.1 |
| OSA | G47.33 |
| Hyperthyroidism | |
| Thyrotoxicosis with diffuse goiter | E05.0 |
| Thyrotoxicosis with toxic single thyroid nodule | E05.1 |
| Thyrotoxicosis with toxic multinodular goiter | E05.2 |
| Thyrotoxicosis from ectopic thyroid tissue | E05.3 |
| Thyrotoxicosis factitia | E05.4 |
| Other thyrotoxicosis | E05.8 |
| Thyrotoxicosis, unspecified | E05.9 |
| Cardiomyopathy | I42.0, I42.1, I42.2, I42.5, I42.6, I42.7, I42.8, I42.9, I43 |
| Myocarditis | I40, I41 |

## 3 | STATISTICAL ANALYSIS

The data analysis and extraction were done using SAS statistical software version 9.4. All continuous variables, such as length of stay, in-hospital mortality, and hospitalization cost were compared using Student's *t* test. These variables were presented as a mean and standard deviation (SD) for normally distributed variables, while median and interquartile ranges were used for non-Gaussian distributed variables. On the other hand, categorical variables were analyzed using the Pearson chi-square test. These variables were presented as a weighted frequency in percentages. A $P < .05$ was considered statistically significant. The propensity score matching method, as demonstrated in Table 4, was used to adjust for cofounders and aid in assessment of the clinical outcomes of patients with AF with and without hyperthyroidism.

## 4 | RESULTS

This study included data from the NIS database for patient hospital admissions for the years 2015 to 2017. After excluding patients <18 years of age, the total number of patients included in the study was 68 095 278. Patients were first divided into two groups, Afib and no Afib; 9 727 295 patients were in the Afib group and 58 367 983 patients were in the no Afib group. The overall incidence of Afib was 14.3% (shown in Figure 1). An extensive comparison of baseline patient-level characteristics between patients with Afib and patients without AFib is shown in Table 2. Patients with Afib were older with a mean age of 75.1 and more likely to be male (52.3 vs

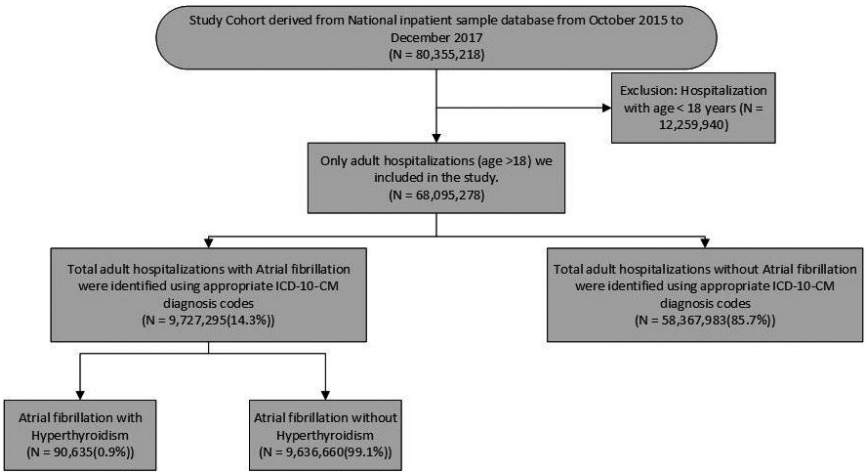


**FIGURE 1** The flow chart of the sample included in the study

**TABLE 2** Clinical characteristics of Afib versus without Afib in 2015q4-2017 patients

| Characteristics | Afib | No Afib | *P* value |
|---|---|---|---|
| N = 68 095 278 | N = 9 727 295 (14.3%) | N = 58 367 983 (85.7%) | |
| Age | | | |
| Mean years (SD) | 75.1 ± 11.8 | 54.8 ± 19.9 | <.0001 |
| Gender | | | |
| Male | 5 084 493 (52.3%) | 23 503 849 (40.3%) | <.0001 |
| Female | 4 640 263 (47.7%) | 34 842 419 (59.7%) | |
| *Missing—24 255 | | | |
| Age groups | | | |
| 18-34 | 45 890 (0.5%) | 13 005 590 (22.3%) | <.0001 |
| 35-49 | 236 730 (2.4%) | 9 611 285 (16.5%) | |
| 50-64 | 1 484 909 (15.3%) | 14 771 668 (25.3%) | |
| 65-79 | 3 917 873 (40.3%) | 13 930 404 (23.9%) | |
| ≥80 | 4 041 893 (41.5%) | 7 049 036 (12.1%) | |
| Race | | | |
| Caucasians | 7 630 781 (78.4%) | 36 527 564 (62.6%) | <.0001 |
| African-Americans | 840 265 (8.6%) | 9 090 433 (15.6%) | |
| Others | 1 256 139 (12.9%) | 12 748 826 (21.8%) | |
| *Missing—1270 | | | |
| Elixhauser comorbidities | | | |
| Coronary arterial disease | 4 251 598 (43.7%) | 9 786 820 (16.8%) | <.0001 |
| Cardiomyopathy | 2 526 689 (25.9%) | 3 948 298 (6.8%) | <.0001 |
| Valvular disease | 717 565 (7.4%) | 1 261 254 (2.2%) | <.0001 |
| Cardiomyopathy | 951 130 (9.8%) | 1 318 200 (2.3%) | <.0001 |
| Chronic pulmonary disease | 2 575 969 (26.5%) | 9 842 246 (16.9%) | <.0001 |
| Hypertension | 6 258 432 (64.3%) | 26 191 277 (44.9%) | <.0001 |
| Diabetes mellitus | 3 090 659 (31.8%) | 12 682 714 (21.7%) | <.0001 |
| Hyperthyroidism | 90 635 (0.9%) | 252 270 (0.4%) | <.0001 |
| Obesity | 1 443 189 (14.8%) | 7 980 097 (13.7%) | <.0001 |
| Alcohol abuse | 260 575 (2.7%) | 2 755 463 (4.7%) | <.0001 |
| Collagen vascular disease | 291 975 (3%) | 1 497 259 (2.6%) | <.0001 |
| Obstructive sleep apnea | 1 186 890 (12.2%) | 3 285 019 (5.6%) | <.0001 |

Abbreviations: Afib, atrial fibrillation; BMI, body mass index; SD, standard deviation.

40.3, $P < .001$), when compared to patients without Afib. The prevalence of hyperthyroidism in patients with Afib was 0.9%, whereas, in patients without Afib, it was 0.4%, $P < .001$. In addition, Table 2 showed that other comorbidities such as, coronary arterial disease, congestive heart failure, valvular disease, chronic pulmonary disease, hypertension, obstructive sleep apnea, obesity and rheumatic/collagen vascular disease were more prevalent in patients with Afib compared to patients without Afib. The association of Afib and hyperthyroidism was further assessed using multivariate regression analysis (Table 3). After adjusting for all other comorbidities, hyperthyroidism association with Afib remained statistically significant (odds ratio 2.08, CI 2.07-2.10, $P < .001$).

The Afib group was further divided into two groups; with hyperthyroidism and without hyperthyroidism, to assess the impact of the presence of hyperthyroidism. Mean hospitalization cost, length of stay, in-hospital mortality, were lower in Afib patients with hyperthyroidism compared to patients with Afib related to other comorbidities (Table 4). Afib patients with hyperthyroidism had a higher discharge disposition to home compared to patients with Afib related to the comorbidities listed above (50.6 vs 41.8, $P < .0001$). The data in Table 4 also demonstrated that Afib patients without hyperthyroidism tend to have a higher prevalence of other comorbidities such as coronary arterial disease, congestive heart failure, valvular disease, chronic pulmonary disease, hypertension, diabetes mellitus, obstructive sleep apnea, obesity and rheumatic/collagen vascular disease compared to Afib patients with hyperthyroidism. Pateints with Afib and hyperthyroidism were younger as shown in Table 4.

The annual trends of mean hospitalization cost, length of stay and in-hospital mortality were compared between Afib with hyperthyroidism and Afib without hyperthyroidism, as shown in Figures 2-4, respectively. Overall, Afib with hyperthyroidism had lower hospitalization cost, length of stay and in-hospital mortality when compared to Afib without hyperthyroidism. The percent mortality for Afib with and without hyperthyroidism decreased from 2015 to 2017. However, for periods 2016 and 2017, the mortality in Afib patients with hyperthyroidism was significantly lower than Afib patients without hyperthyroidism as shown in Figure 4.

**TABLE 3** Multiple regression analysis of Atrial fibrillation with all of below risk factors in the table

| | ODDS ratio | 95% Wald confidence limits | *P* value |
|---|---|---|---|
| Hyperthyroidism | 2.23 | 2.21–2.25 | <.0001 |
| Coronary artery disease (CAD) | 1.83 | 1.82–1.84 | <.0001 |
| Cardiomyopathy | 3.61 | 3.60–3.63 | <.0001 |
| Valvular disease | 1.76 | 1.75–1.77 | <.0001 |
| Hypertension (HTN) | 1.97 | 1.96–1.98 | <.0001 |
| Diabetes mellitus (DM) | 1.04 | 1.03–1.06 | <.0001 |
| OSA(Obstructive sleep apnea) | 1.92 | 1.90–1.92 | <.0001 |
| Collagen vascular disease | 0.92 | 0.0.91–0.93 | <.0001 |
| Chronic pulmonary disease | 1.26 | 1.25–1.27 | <.0001 |
| Alcohol abuse | 1.12 | 1.11–1.13 | <.0001 |
| Age | 1.07 | 1.05–1.08 | <.0001 |

## 5 | DISCUSSION

There was an association between Afib and hyperthyroidism in a large patient sample size after multivariate regression analysis. The prevalence of hyperthyroidism in Afib was higher when compared to patients without Afib. The study demonstrated that hospitalization costs, mean length of stay and in-hospital mortality were lower in Afib patients with hyperthyroidism compared with Afib patients without hyperthyroidism. We also found that the disposition to home was higher in Afib with hyperthyroidism patients compared with Afib patients without hyperthyroidism.

The pathophysiology of Afib in hyperthyroid patients is related to the effect of triiodothyronine (T3), which is the biologically active form of thyroid hormone, directly on atrial myocytes, or indirectly by altering peripheral vascular resistance, or by influencing the sympathoadrenergic system.[12] T3 results in increased sarcoplasmic calcium ATPase, myosin heavy chain α, voltage gated potassium channels, sodium channels and β1 adrenergic receptors. These cause increased heart rate, systolic blood pressure, ventricular contractility and cardiac hypertrophy.[12,13] There are a few proposed mechanisms by which thyroid hormones increase the risk of atrial fibrillation, including, shortening of the action potential duration, activation of arrhythmogenic foci, increasing the left atrial pressure due to increased left ventricular mass and impaired relaxation, and ischemia secondary to increased resting heart rate.[12–17]

Risk factors for Afib include, but are not limited to, coronary arterial disease, congestive heart failure, valvular disease, chronic pulmonary disease, hypertension, diabetes mellitus, obstructive sleep apnea, obesity, rheumatic/collagen vascular diseases and old age.[4–9] From our analysis, we identified that Afib patients with hyperthyroidism had a low prevalence of these coexisting comorbidities (Table 4). Afib patients with hyperthyroidism were younger and more likely to be female compared with Afib patients without hyperthyroidism. The increased prevalence in females supports the finding that thyroid diseases are more common in women, which may be related to the increased prevalence of autoimmune diseases, as well as greater hormonal fluctuations (menstruation, pregnancy) in women.[18,19]

Hospitalization cost, mean length of stay and in-hospital mortality were consistently lower in Afib patients with hyperthyroidism compared with Afib patients without hyperthyroidism over the period of 2015 to 2017, as shown in Figures 2-4, respectively. These findings are likely due to the reversibility of the underlying disease. A higher percentage of these patients were able to be discharged home when compared to Afib patients without hyperthyroidism.

Anti-thyroid medications such as carbimazole/methimazole, propylthiouracil or radio-iodine are used to achieve a euthyroid state,

**TABLE 4** Clinical characteristics of Afib with hyperthyroidism versus Afib without Hyperthyroidism in 2015q4-2017 patients

| Characteristics | Afib with hyperthyroidism | Afib without hyperthyroidism | *P* value |
|---|---|---|---|
| N = 9 727 295 | N = 90 635 (0.9%) | N = 9 636 660 (99.1%) | |
| Age | | | |
| Mean years (SD) | 70.9 ± 14 | 75.1 ± 11.8 | <.0001 |
| Gender | | | |
| Male | 32 730 (36.1%) | 5 051 763 (52.4%) | <.0001 |
| Female | 57 885 (63.9%) | 4 582 378 (47.6%) | |
| *Missing—2540 | | | |
| Age groups | | | |
| 18-34 | 1500 (1.6%) | 44 390 (0.5%) | <.0001 |
| 35-49 | 5750 (6.3%) | 230 980 (2.4%) | |
| 50-64 | 19 630 (21.7%) | 1 465 279 (15.2%) | |
| 65-79 | 34 900 (38.5%) | 3 882 973 (40.3%) | |
| ≥80 | 28 855 (31.8%) | 4 013 038 (41.6%) | |
| Race | | | |
| Caucasians | 61 625 (68%) | 7 569 156 (78.5%) | <.0001 |
| African-Americans | 15 070 (16.6%) | 825 195 (8.6%) | |
| Others | 13 935 (15.4%) | 1 242 204 (12.9%) | |
| *Missing—110 | | | |
| Elixhauser comorbidities | | | |
| Coronary arterial disease | 33 015 (36.4%) | 4 218 583 (43.8%) | <.0001 |
| Cardiomyopathy | 21 805 (24.1%) | 2 504 884 (25.9%) | <.0001 |
| Valvular disease | 6250 (6.9%) | 711 315 (7.4%) | <.0001 |
| Chronic pulmonary disease | 23 360 (25.8%) | 2 552 609 (26.5%) | <.0001 |
| Hypertension | 55 025 (60.7%) | 6 203 407 (64.4%) | <.0001 |
| Diabetes mellitus | 26 240 (28.9%) | 3 064 419 (31.8%) | <.0001 |
| Obesity | 12 800 (14.1%) | 1 430 389 (14.8%) | <.0001 |
| Collagen vascular disease | 2605 (2.9%) | 289 370 (3%) | <.02 |
| Obstructive sleep apnea | 9535 (10.5%) | 1 177 355 (12.2%) | <.0001 |
| Outcomes | | | |
| In-hospital mortality | 3035 (3.3%) | 466 990 (4.8%) | <.0001 |
| *Missing—8085 | | | <.0001 |
| Length of stay, days, median (IQR) | 5.7 ± 6.6 | 5.9 ± 6.6 | <.0001 |
| Total hospitalization costs, $, median (IQR) | 14 968 ± 21 871 | 15 955 ± 22 233 | <.0001 |
| Disposition | | | |
| Discharge to home | 45 810 (50.6%) | 4 023 383 (41.8%) | <.0001 |
| Transfer other: includes skilled Nursing Facility (SNF), Intermediate Care Facility (ICF), and another type of facility | 21 675 (23.9%) | 2 835 168 (29.4%) | |
| Home health care | 16 755 (18.5%) | 1 978 349 (20.5%) | |
| Against medical advice (AMA) | 885 (0.9%) | 66 195 (0.7%) | |
| *Missing—8085 | | | |

Abbreviations: A. fib, atrial fibrillation; IQR, interquartile range; SD, standard deviation.

subsequently, thyroidectomy is performed as definitive treatment.[20] Until a euthyroid state is achieved, beta blockers are used to control heart rate and reduce cardiac failure.[21,22] Up to two-third of patients who are treated for hyperthyroidism convert to sinus rhythm.[13] The ease of conversion to sinus rhythm is also likely higher due to a lower prevalence of coexisting risk factors in Afib patients with hyperthyroidism (Table 4). Studies have shown that Afib patients with other risk factors, such as coronary artery disease, hypertension and

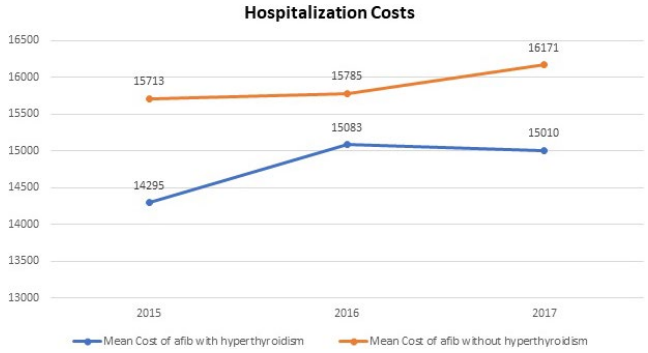


**FIGURE 2** Comparison of the mean cost of hospitalization costs between patients with Afib and hyperthyroidism and Afib patients without hyperthyroidism

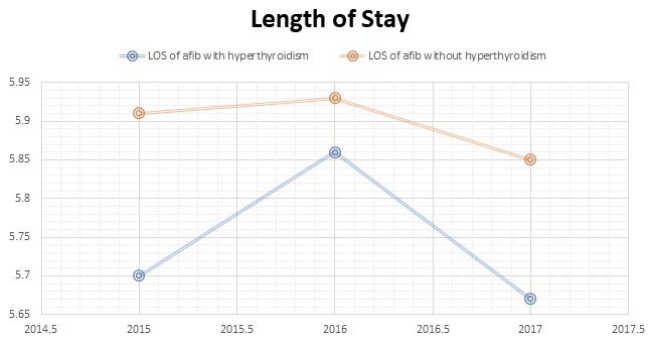


**FIGURE 3** Comparison of length of stay (LOS) between patients with Afib and hyperthyroidism and Afib without hyperthyroidism

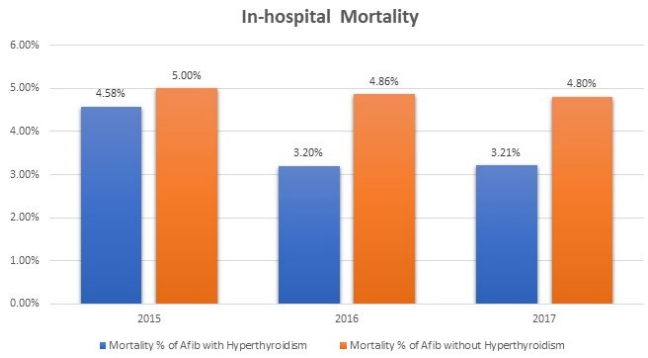


**FIGURE 4** Depiction of in-hospital mortality among patients with Afib and hyperthyroidism and Afib patients without hyperthyroidism

cardiomyopathy have worse clinical outcomes, including increased mortality.[23–25]

## 6 | LIMITATIONS

Our study sample size is large and representative of 95% of hospitals in the US. However, there are limitations to this study. We were not able to discern whether patients developed Afib before or after the development of the hyperthyroidism given the nature of the database. We relied primarily on diagnosis codes for hyperthyroidism and Afib, which could potentially lead to exposure and outcome misclassification. We did not investigate disease severity, which could affect the development of Afib.

## 7 | CONCLUSION

From our study, it was determined that patients with Afib and hyperthyroidism have reduced hospitalization costs, shorter length of stay and lower in-hospital mortality when compared to Afib without hyperthyroidism. We also found that patients with hyperthyroidism have a 3-fold increased risk of Afib compared to those without hyperthyroidism. Given the potential for reversibility of this condition, this may account for the better clinical outcomes observed in these patients.

### CONFLICT OF INTEREST

The authors declare no conflict of interests for this article.

### ORCID

*Muhammad Zubair Khan* https://orcid.org/0000-0002-8884-3146
*Kirtenkumar Patel* https://orcid.org/0000-0002-3289-6003
*Krunalkumar Patel* https://orcid.org/0000-0002-0636-6498

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