Clinical Medicine & Research
Volume 24, Number 3: 100-105
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clinmedres.org

Original Research

Association of Iron Deficiency Anemia with Outcomes in Atrial Fibrillation: A Nationwide Analysis

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Background: Patients with atrial fibrillation (AF) frequently have iron deficiency anemia (IDA), but the mechanism by which this condition affects clinical outcomes is not well understood. The purpose of this study was to assess whether IDA is associated with mortality in patients with AF.

Methods: Data from the National Inpatient Sample (NIS) for 2021–2022 examined IDA and inpatient outcomes in a nationally representative cohort of hospitalized adults diagnosed with AF. Patients were categorized by IDA status. The factors assessed were mortality, hospital and intensive care unit (ICU) length of stay, thromboembolic and cardiovascular complications, and overall hospital expenses. Hospital, clinical, and demographic factors were included in multivariable logistic and linear regression models.

Results: Of the 8.35 million AF hospitalizations, 7.1% had associated IDA. IDA was linked to multiple comorbidities along with increased risk of hypotension (OR: 1.15, 95% CI 1.12-1.17, *P*<0.001), acute kidney injury (OR: 1.25, 95% CI 1.23-1.27, *P*<0.001), and heart failure (Adjusted Odds Ratio [AOR]: 1.29, 95% CI 1.27-1.31, *P*<0.001). Ironically, IDA was linked independently to decreased risks of cardiac arrest (AOR: 0.70, 95% CI 0.66-0.73, *P*<0.001), transient ischemic attack (AOR: 0.58, 95% CI 0.53-0.63, *P*<0.001), stroke (OR: 0.49,95% CI 0.47-0.51, *P*<0.001), and in-hospital mortality (OR: 0.66, 95% CI 0.64-0.68, *P*<0.001). IDA was also associated with increased hospital expenses and increased LOS (*P*<0.001).

Conclusion: IDA was linked to higher morbidity and healthcare use in those with AF admitted to the hospital, but there was a decrease in mortality and thromboembolic events. These results suggest the possibility of tailored iron therapy and imply a complex interaction between IDA and AF-related outcomes.

Keywords: Iron deficiency anemia; Atrial fibrillation; National inpatient sample (NIS)

Atrial fibrillation (AF) is one of the most common sustained cardiac arrhythmias that affects millions of patients worldwide. It is associated with increased morbidity, mortality, and utilization of significant healthcare. The burden of AF continues to rise, especially with aging populations, and it could lead to increased cardiovascular risk factors, making it crucial for interventions to reduce hospitalizations and complications.[1,2]

Iron deficiency anemia (IDA) is recognized as a prevalent and clinically significant comorbidity among patients with cardiovascular diseases like AF. Patients with IDA often experience poor clinical outcomes, including increased severity of symptoms, frequency of hospitalization, and poor quality of life.[2,3] Recent studies have highlighted the rise of hospitalization trends among patients diagnosed with AF who had coexistent IDA.[3]

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Received: May 17, 2025
Revised: January 25, 2026
Accepted: February 2, 2026

doi:10.3121/cmr.2026.2040

Table 1. Baseline characteristics stratified by iron deficiency in patients with atrial fibrillation

Variable	No Iron Deficiency (%)	Iron Deficiency (%)	*P* value
Age (years), mean (95% CI)	74.9 [74.8–74.9]	75.4 [75.3–75.5]	<0.001
Female Sex	45.7%	51.4%	<0.001
Race			<0.001
White	78.9%	75.9%	
Black	10.3%	13.4%	
Hispanic	6.3%	6.2%	
Asian/Pacific Islander	2.2%	2.1%	
Native American	0.4%	0.4%	
Other	2.0%	2.0%	
Median Household Income Quartile			<0.001
Quartile 1 (lowest)	27.1%	28.2%	
Quartile 2	26.2%	26.1%	
Quartile 3	24.9%	24.9%	
Quartile 4 (highest)	21.8%	20.8%	
Hospital Region			<0.001
Northeast	19.4%	20.0%	
Midwest	23.4%	26.8%	
South	39.1%	37.0%	
West	18.1%	16.2%	
Hospital Teaching Status			<0.001
Rural	9.3%	8.8%	
Urban Non-teaching	18.3%	17.2%	
Urban Teaching	72.4%	74.1%	
Hospital Bed Size			0.0134
Small	23.4%	23.2%	
Medium	29.4%	28.7%	
Large	47.2%	48.1%	
Charlson Comorbidity Index Category			<0.001
0	8.17%	4.27%	
1	15.54%	10.94%	
2	17.65%	15.16%	
≥ 3	58.63%	69.63%	
Acute Kidney Injury (AKI)	32.2%	39.2%	<0.001
Heart Failure (HF)	52.4%	62.9%	<0.001
Pulmonary Edema	1.16%	1.12%	0.1580
TIA	0.75%	0.46%	<0.001
Stroke	4.34%	2.45%	<0.001
Acute Respiratory Failure	30.0%	31.6%	<0.001
Cardiogenic Shock	3.92%	3.67%	<0.001
Hypotension	10.8%	12.5%	<0.001
Pulmonary Embolism	1.84%	1.69%	<0.001
Cardiac Arrest	2.12%	1.49%	<0.001
Length of Stay (days)	6.42	7.32	<0.001
Total Hospitalization Charge (USD)	85,728	88,494	<0.001

Abnormalities in iron metabolism may specifically contribute to the pathophysiology of AF, potentially influencing clinical outcomes beyond anemia-related complications.[6] Ongoing clinical trials emphasize therapeutic interventions targeting iron deficiency in AF patients to improve outcomes and optimize resource utilization.[4] Despite these developments, the existing literature provides limited insights into the exact impact of IDA on hospital outcomes, including mortality, stroke incidence, acute kidney injury, and length of hospital stay, particularly in nationally representative cohorts.[5] Therefore, the primary objective of this study was to examine the association of IDA with in-hospital mortality. The secondary outcomes were in-hospital complications, length of hospital stay, and total hospitalization charges.

Methods

This retrospective observational study data were obtained from the National Inpatient Sample (NIS) from 2021–2022, which is part of the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ). NIS is the largest publicly available inpatient all-payer healthcare database in the United States and includes a 20% stratified sample of all discharges from U.S. community hospitals. This excludes the rehabilitation and long-term acute care facilities.

We included adults (≥18 years) who were hospitalized with a diagnosis of AF. AF was identified using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. Patients were further categorized based on the presence or absence of IDA by using the ICD-10-CM codes. Those with missing data were excluded from the analysis.

The primary exposure was the presence of IDA among those hospitalized with AF. The covariates included were age, sex, race, median household income quartile, Charlson Comorbidity Index (CCI), hospital region, bed size, and teaching status. The primary outcome was in-hospital mortality. The CCI was a score which included all the comorbidities. The score was categorized as 0,1-2, and ≥ 3 to determine the comorbid

burden. Secondary outcomes included acute kidney injury, heart failure, transient ischemic attack, stroke, cardiogenic shock, pulmonary embolism, hypotension, cardiac arrest, acute respiratory failure, pulmonary edema, hospital length of stay, and total hospitalization charges (in U.S. dollars). The statistical analysis of categorical variables used Chi-square tests, and continuous variables were compared using t-tests or Wilcoxon rank-sum tests, as appropriate.

To evaluate the association between IDA and outcomes, multivariable logistic regression models were used for binary variables, and linear regression models were used for continuous variables. The regression model includes patient demographics, median household income, CCI, and hospital characteristics (region, bed size, and teaching status). A P value <0.05 was considered statistically significant. The NIS database did not reveal any patient identity or publicly available data; therefore, this study was exempted from Institutional Review Board (IRB) approval and informed consent requirements in accordance with the guidelines of the U.S. Department of Health and Human Services.

Results

We identified about 8.35 million adults (≥18 years) who were admitted with a diagnosis of AF. Among these, 0.59 million (7.1%) had IDA, while 7.75 million (92.9%) did not. Patients with IDA were slightly older, with a mean age of about 75.4 years (95% CI 75.3–75.5, P<0.001), and were predominantly female (51.4%). There were significant differences in baseline characteristics like race, household income quartiles, hospital region, teaching status, and bed size (P<0.05). There were also more patients with IDA who had a CCI ≥3 (69.6% vs. 58.6%; P<0.001), reflecting a greater comorbidity burden.

Table 1 summarizes baseline characteristics stratified by IDA status. It demonstrates notable demographic differences, such as age, sex, race, and socioeconomic factors, as well as significant variation in hospital-level factors. This table also depicts that patients with IDA were more likely to be admitted to urban teaching hospitals with large-bed facilities and were disproportionately affected by multiple comorbidities.

In unadjusted analyses, patients with IDA had higher rates of acute kidney injury (AKI), heart failure, acute respiratory failure, and hypotension in comparison to those without IDA (P<0.001). Alternatively, there were lower rates of stroke, transient ischemic attack (TIA), cardiogenic shock, pulmonary embolism, and cardiac arrest observed in the IDA group (P<0.001). Patients with IDA also experienced longer hospital stays (7.32 vs. 6.42 days; P< 0.001) and incurred higher total hospitalization charges ($88,494 vs. $85,728; P<0.001).

Table 2 demonstrates the outcomes after adjusting for demographics, hospital characteristics, and comorbidities. IDA remained significantly associated with reduced odds of mortality (AOR: 0.66; 95% CI: 0.64–0.68; P<0.001). Although IDA was independently associated with increased odds of AKI (OR: 1.25; 95% CI: 1.23–1.27, P<0.001), heart failure (OR: 1.29; 95% CI: 1.27–1.31, P<0.001), and hypotension (OR: 1.15; 95% CI: 1.12–1.17, P<0.001). IDA was also associated with significantly lower odds of stroke (OR: 0.49; 95% CI: 0.47–0.51, P<0.001), TIA (OR: 0.58; 95% CI: 0.53–0.63, P<0.001), cardiogenic shock (OR: 0.89; 95% CI: 0.86–0.93, P<0.001), pulmonary embolism (OR: 0.94; 95% CI: 0.90–0.98; P=0.007), and cardiac arrest (OR: 0.70; 95% CI: 0.66–0.73; P<0.001). There were no significant associations found for pulmonary complications like acute respiratory failure (OR: 1.00; 95% CI: 0.99–1.02; P=0.507) or pulmonary edema (OR: 0.96; 95% CI: 0.91–1.02; P=0.152) (Figure 1).

Table 2 presents adjusted associations between IDA and clinical outcomes. This reinforces that IDA is associated with increased heart failure and kidney injury. Moreover, IDA was associated with a longer mean length of stay by 0.73 days (95% CI: 0.68–0.79; P<0.001) along with an increase in total hospitalization charges of $2,569.85 (95% CI: $1,451.67–$3,688.03; P<0.001) per admission (Figures 2 & 3).

Table 2. Adjusted outcomes associated with iron deficiency

Outcomes	Adjusted OR or Coefficient (95% CI)	*P* value
Mortality (Died)	0.66 [0.64–0.68]	<0.001
Acute Kidney Injury (AKI)	1.25 [1.23–1.27]	<0.001
Heart Failure	1.29 [1.27–1.31]	<0.001
Pulmonary Edema	0.96 [0.91–1.02]	0.152
Transient Ischemic Attack (TIA)	0.58 [0.53–0.63]	<0.001
Stroke	0.49 [0.47–0.51]	<0.001
Acute Respiratory Failure (ARF)	1.00 [0.99–1.02]	0.507
Cardiogenic Shock	0.89 [0.86–0.93]	<0.001
Hypotension	1.15 [1.12–1.17]	<0.001
Pulmonary Embolism	0.94 [0.90–0.98]	0.007
Cardiac Arrest	0.70 [0.66–0.73]	<0.001
Length of Stay (days) †	+0.73 days (0.68–0.79)	<0.001
Total Charges ($) †	+$2569.85 ($1451.67–$3688.03)	<0.001

Discussion

Our findings of increased comorbidity burden among AF patients with IDA aligns with previous reports, such as from Hanna-Rivero et al.,[1] who demonstrated IDA is prevalent among AF patients and often coexists with other chronic conditions such as heart failure and chronic kidney disease. The elevated risk of heart failure and AKI in the

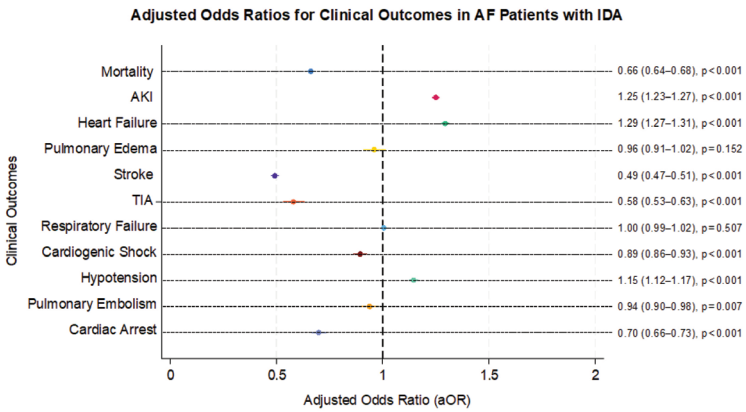


Figure 1. Adjusted Odds Ratio for Clinical Outcomes in AF Patients with IDA.

IDA group further reinforces these associations. Similarly, Savarese et al.[2] emphasized that iron deficiency adversely impacts myocardial energy metabolism and oxygen delivery, predisposing patients to cardiovascular complications. These results are also supported by the observations of Alharbi et al.,[7] who found that IDA in heart failure was associated with worse outcomes, including readmissions and higher total healthcare charges.

The increased length of hospital stay and total hospitalization charges among IDA patients are consistent with the literature, which indicates IDA contributes to higher healthcare resource utilization, especially in cardiovascular populations.[3,7,9] Interestingly, despite these adverse events, IDA was associated with a lower risk of mortality and other complications such as stroke and cardiac arrest. This could be due to more aggressive monitoring and management due to their anticipated vulnerability.[3,8,10] Minhas et al.[3] also reported patients with both AF and IDA had higher comorbidity burdens and longer hospital stays, even though mortality outcomes were not consistently unfavorable. Our study supports and extends these observations, showing that mortality may not be worse even with worse clinical profiles.

There was a lower risk of stroke and TIA in our IDA cohort, which is intriguing. One explanation is that anemia may reduce blood viscosity and platelet aggregation, potentially

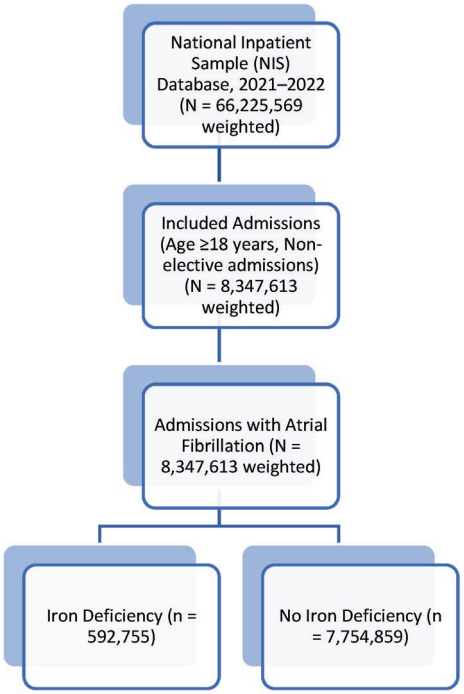
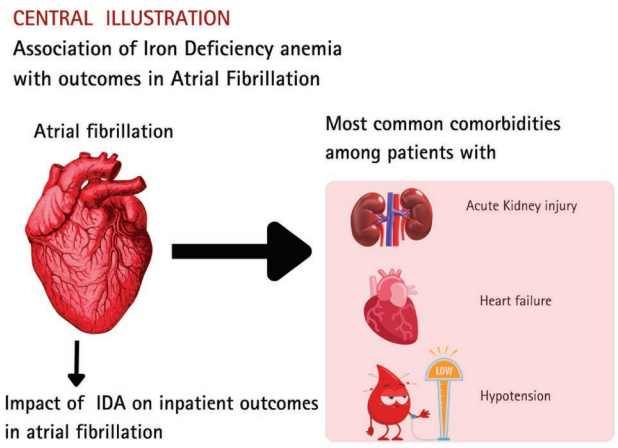


Figure 2. Flowchart illustrating selection of study cohort from the National Inpatient Sample (NIS) Database (2021–2022).



Adjusted Odds	Odds Ratio
Hospital Mortality	0.66 (0.64-0.68)
Stroke	0.49 (0.47-0.51)
TIA	0.58 (0.53-0.63)
AKI	1.25 (1.23-1.27)
Heart Failure	1.29 (1.27-1.31)
Hypotension	1.15 (1.12-1.17)
Pulmonary Embolism	0.94 (0.90-0.98)
Cardiac arrest	0.70 (0.66-0.73)

Figure 3. Central illustration- Association of Iron deficiency anemia with outcomes in Atrial fibrillation.

lowering the risk of embolic events. Alternatively, as suggested by Kamihara et al.,[6] specific iron kinetics in AF patients with IDA may modulate coagulation pathways differently. This hypothesis is also supported by Paolillo et al.,[5] who emphasized the various influences of anemia and iron deficiency on the interplay between thrombosis and cardiac function in heart failure and AF.

Other studies have explored the importance of early diagnosis and correction of iron deficiency to reduce atrial remodeling and arrhythmias, as suggested by Silverberg et al.[11] Recent findings by Mordi et al.[12] also emphasized that iron repletion can improve exercise capacity, thereby reducing hospitalization in patients with concurrent cardiac conditions. This suggests a potential therapeutic benefit in AF cohorts as well.

The IRON-AF study, a prospective randomized trial, investigated intravenous iron supplementation in patients with AF and iron deficiency. Our findings in this study add to the growing evidence suggesting that IDA is not merely a marker of illness severity but also a potential therapeutic target.[4]

Limitations

The study has multiple limitations related to the retrospective analysis conducted using administrative databases. NIS is a large dataset, and ICD-10-CM codes were used to identify atrial fibrillation; IDA could have been misclassified, which may raise concern about type II error. This study confirmed IDA based on hemoglobin or ferritin status; therefore, the severity of IDA was not assessed. Furthermore, iron supplementation, anticoagulation, or rhythm-control strategies were not assessed. Lastly, since this is a cross-sectional study, causality between IDA and clinical outcomes in atrial fibrillation cannot be stated.

Conclusion

This study emphasizes the importance of identifying IDA in patients hospitalized with AF. IDA is associated with an increase in comorbidities along with higher rates of complications such as heart failure and AKI. These findings raise important clinical questions regarding the pathophysiological impact of iron status in AF and suggest IDA may be both a risk marker and a modifiable factor in patient management. Future prospective trials would be essential to determine whether replenishing iron could improve outcomes in this unique, high-risk population.

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