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Increased inpatient mortality in patients hospitalized for atrial fibrillation and atrial flutter with concomitant amyloidosis: Insight from National Inpatient Sample (NIS) 2016–2017

Asim Kichloo^{a, b}, Shakeel Jamal^a, Michael Albosta^a, Muhammad Zia Khan^c, Michael Aljadah^d, Ehizogie Edigin^e, Rawan Amir^f, Farah Wani^b, Ehtesham Ul-Haq^g, Khalil Kanjwal^{h, *}

^a Central Michigan University College of Medicine, Saginaw, MI, USA

^b Samaritan Medical Center, Watertown, NY, USA

^c West Virginia University School of Medicine, Morgantown, WV, USA

^d Medical College of Wisconsin, Milwaukee, WI, USA

^e John H. Stroger, Jr. Hospital of Cook County, Chicago, USA

^f University of Maryland School of Medicine, Baltimore, MD, USA

^g University of Kentucky College of Medicine, Bowling Green, KY, USA

^h Michigan State University McLaren Greater Lansing Hospital, Lansing, MI, USA

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ABSTRACT

Purpose: Using National Inpatient Database (NIS), comparison of clinical outcomes for patients primarily admitted for atrial fibrillation/flutter with and without a secondary diagnosis of amyloidosis was done. Inpatient mortality was the primary outcome and hospital length of stay (LOS), mean total hospital charges, odds of undergoing cardiac ablation, pharmacologic cardioversion, having a secondary discharge diagnosis of heart block, cardiogenic shock and cardiac arrest were secondary outcomes.

Methods: NIS database of 2016, 2017 was used for only adult hospitalizations with atrial fibrillation/flutter as principal diagnosis with and without amyloidosis as secondary diagnosis using ICD-10 codes. Multivariate logistic with linear regression analysis was used to adjust for confounders.

Results: 932,054 hospitalizations were for adult patients with a principal discharge diagnosis of atrial fibrillation/flutter. 830 (0.09%) of these hospitalizations had amyloidosis.

Atrial fibrillation/flutter hospitalizations with co-existing amyloidosis have higher inpatient mortality (4.22% vs 0.88%, AOR: 3.92, 95% CI 1.81–8.51, $p = 0.001$) and likelihood of having a secondary discharge diagnosis of cardiac arrest (2.40% vs 0.51%, AOR: 4.80, 95% CI 1.89–12.20, $p = 0.001$) compared to those without amyloidosis.

Conclusions: Hospitalizations of atrial fibrillation/flutter with co-existing amyloidosis have higher inpatient mortality and odds of having a secondary discharge diagnosis of cardiac arrest compared to those without amyloidosis. However, LOS, total hospital charges, likelihood of undergoing cardiac ablation, pharmacologic cardioversion, having a secondary discharge diagnosis of heart block and cardiogenic shock were similar between both groups.

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* Corresponding author. Medicine Michigan State University Director of Electrophysiology McLaren Greater Lansing Hospital, Lansing, MI, 48901, USA.

E-mail addresses: Kichlooasim@gmail.com (A. Kichloo), Jamal1sm@cmich.edu (S. Jamal), albos1ms@cmich.edu (M. Albosta), ziaulislam87@gmail.com (M.Z. Khan), maljadah@mcw.edu (M. Aljadah), ehizogie.edigin@cookcountyhhs.org (E. Edigin), ra.amir793@gmail.com (R. Amir), farahwani04@gmail.com (F. Wani), ehtesham136@gmail.com (E. Ul-Haq), khalilkanjwal@yahoo.com (K. Kanjwal).

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1. Introduction

Amyloidosis refers to a disease process in which misfolded proteins aggregate into oligomers and polymers, and subsequently deposit in organs and tissues [1] While there has been limited data quantifying the incidence of amyloidosis in the United States, one study estimated that from 1990 to 2015 the incidence of AL amyloidosis was approximately 1.2/100,000 person-years [2].

Amyloid deposition can occur in nearly any organ system, including the cardiac system, gastrointestinal tract, pancreas, liver, kidneys, eyes and central nervous system (CNS) leading to significant morbidity and mortality [1]. Deposition of amyloid into extracellular cardiac tissue (atria, ventricles, conduction tissues, coronaries and valves) can result in myocardial cell toxicity leading to stiffening of the ventricles and causing symptoms of heart failure including dyspnea on exertion, orthopnea, abdominal distention and edema [3]. Involvement of the cardiac conduction system can lead to a number of rhythm abnormalities, the most common of which is atrial fibrillation [3,4]. Atrial arrhythmias occur in about 10–15% of patients with amyloidosis with cardiac involvement. Cardiac involvement in amyloidosis is known to be leading cause of morbidity and mortality in amyloidosis [5]. The purpose of this study is to evaluate the effect of amyloidosis on clinical outcomes in patients who are hospitalized for atrial fibrillation/flutter. We conducted a cross-sectional analysis using data from the National Inpatient Sample (NIS) database.

2. Methods

2.1. Data source

We performed a retrospective study of hospitalizations for two consecutive years of 2016 and 2017 using principal diagnosis of atrial fibrillation/flutter with and without a secondary diagnosis of amyloidosis inpatient setting across the United States. Hospitalizations were selected from the NIS database, which is the largest publicly available all-payer inpatient database in the United States of America (USA). It has been designed as a stratified probability sample and represents, all nonfederal acute care hospitals nationwide. In this database, principal diagnosis and secondary diagnoses were reviewed. A principal diagnosis is the main ICD-10 code related to the hospitalization. Secondary diagnoses were any ICD-10 code other than the principal diagnosis. As information in this database are de-identified and available to the public, no institutional review board approval is required.

2.2. Inclusion criteria and study variables

The population for this study consisted of all acute care hospitalizations noted in the NIS in years 2016 and 2017. The variables for this study included gender, race, age, medical comorbidities, primary and secondary outcomes (outlined below). Hospitalizations and clinical outcomes of interest were identified, and ICD-10 codes were used for that (supplementary table 1). Atrial fibrillation/flutter hospitalization with and without amyloidosis were reviewed for outcomes and base line characteristics.

2.3. Outcomes

The primary outcome of our interest was inpatient mortality. Mean total hospital charges, Hospital length of stay (LOS), odds of having cardiac ablation, pharmacologic cardioversion, having a secondary discharge diagnosis of heart block, cardiogenic shock and cardiac arrest were secondary outcomes of interest.

Also, atrial fibrillation/flutter Hospitalizations with ablation were extracted by using ICD procedure codes (all 0258 codes) for “destruction of conduction system of the heart”, and those with electrical cardioversion were extracted using ICD 10 procedure codes (5A2204Z) for “restoration of cardiac rhythm”.

2.4. Statistical analysis

STATA, version 16 (StataCorp, Texas, USA) was used to analyze

the data. A univariate logistic regression analysis using all variables and co-morbidities in Table 1 was used to calculate unadjusted odds ratios (ORs) for the primary outcome. All variables with P-values <0.1 were included in a multivariate logistic regression model. P-values <0.05 were designated significant in the multivariate analysis. Confounders were also selected from literature review. Charlson index was utilized to adjust for comorbidity burden. Multivariate logistic and linear regression model with all variables and co-morbidities in Table 1 were used to adjust for confounders for the secondary outcomes.

3. Results

71 million discharges in 2016 and 2017 database were noted. 932,054 inpatient hospitalizations were for adult patients, with a principal discharge diagnosis of Atrial fibrillation/flutter. 830 (0.09%) of these hospitalizations had amyloidosis as a secondary billing diagnosis, while 931,224 (99.91%) hospitalizations did not have amyloidosis as a secondary diagnosis. Baseline characteristics of atrial fibrillation/flutter hospitalizations with and without co-existing amyloidosis are presented below in Table 1. Patients with co-existing amyloidosis were older (72.44 vs 70.45 years, $p = 0.029$) and less were female (38.55% vs 49.62%, $p = 0.0037$). Additionally, patients with co-existing amyloidosis were more often African American (22.78% vs 8.44%, $p = 0.0027$). Using the Charlson comorbidity index, which is a score used to estimate risk of death from comorbid disease, we found that patients with co-existing amyloidosis most frequently had scores ≥ 3 (63.25% vs 30.79%, $p < 0.0001$). It was also found that patients with coexisting amyloidosis were more frequently admitted to large hospitals (60.24% vs 50.04%, $p = 0.0308$) as well as teaching hospitals (81.33% vs 62.77%, $p < 0.0001$) located in urban areas. Finally, patients with coexisting amyloidosis more often had CHF (66.27% vs. 37.63%, $p < 0.0001$), CKD (41.57% vs 18.25%, $p < 0.0001$), anemia (23.49% vs 15.67%, $p < 0.0059$) or were requiring maintenance hemodialysis (9.64% vs 2.19%, $p < 0.0001$).

When considering the primary outcome of in-hospital mortality, we found that rates are higher in atrial fibrillation/flutter hospitalizations with co-existing amyloidosis (4.22% vs 0.88%, AOR: 3.92, 95% CI 1.81–8.51, $p = 0.001$). Secondary outcomes were significant for an increased likelihood of having a secondary discharge diagnosis of cardiac arrest (2.40% vs 0.51%, AOR: 4.80, 95% CI 1.89–12.20, $p = 0.001$) compared to those without coexisting amyloidosis. Patients with coexisting amyloidosis were also more likely to have had pharmacologic cardioversion, heart block, and cardiogenic shock although these values did not achieve statistical significance. In addition, atrial fibrillation/flutter hospitalizations with coexisting amyloidosis were found to have higher mean length of stay and total cost, however these measures also failed to achieve statistical significance. Table 2 describes the clinical outcomes of atrial fibrillation/flutter hospitalizations with and without amyloidosis.

4. Discussion

Our analysis demonstrated that patients hospitalized with atrial fibrillation/flutter and coexisting amyloidosis were more likely to be older, African American, and with a higher Charlson comorbidity index. As mentioned previously, increasing age is an independent risk factor for the development of atrial fibrillation/flutter as well as amyloidosis [2,6]. Furthermore, the presence of an increased number of comorbidities is likely associated with the development of chronic, low-level inflammation, and this can likely explain the increased incidence of amyloidosis seen in these patients admitted for atrial fibrillation/flutter with higher comorbidity burden.

Table 1
Baseline characteristics of atrial fibrillation/flutter hospitalizations with and without Amyloidosis.

	AF (n = 932,054)		p-value
	Without AL (n = 931,224)	With AL (n = 830)	
Age (years)	70.45	72.44	0.029
Female	49.62%	38.55%	0.004
Race			0.003
White	81.74%	70.89%	
Black	8.44%	22.78%	
Hispanic	5.93%	4.43%	
Asians	1.51%	0%	
Native Americans	0.35%	0%	
Others	2.03%	1.90%	
Charlson comorbidity index			<0.0001
0	23.80%	1.81%	
1	26.08%	21.08%	
2	19.33%	13.86%	
≥3	30.79%	63.25%	
Hospital bed size			0.031
Small	19.70%	13.25%	
Medium	30.26%	26.51%	
Large	50.04%	60.24%	
Hospital teaching status			<0.0001
Nonteaching	37.23%	18.67%	
Teaching	62.77%	81.33%	
Hospital location			0.003
Rural	10.86%	3.61%	
Urban	89.14%	96.39%	
Expected primary payer			0.077
Medicare	69.92%	77.64%	
Medicaid	6.39%	3.11%	
Private	21.3%	18.63%	
Self-pay	2.39%	0.62%	
Median household income(quarter)			0.164
1st (0–25th)	27.51%	24.1%	
2nd (26th–50th)	27.04%	22.29%	
3rd (51st–75th)	24.75%	27.11%	
4th (76th–100th)	20.7%	26.51%	
Hospital region			0.010
Northeast	20.26%	31.33%	
Midwest	24.26%	23.49%	
South	40.37%	31.33%	
West	15.12%	13.86%	
Dyslipidemia	50.33%	47.59%	0.486
History of MI	8.45%	5.42%	0.161
History of PCI	1.13%	2.41%	0.122
History of CABG	7.67%	5.42%	0.281
Baseline pacemaker	5.36%	5.42%	0.972
AICD	0.27%	1.20%	0.020
COPD	19.73%	12.05%	0.013
Carotid artery disease	1.31%	1.81%	0.571
History of stroke	9.77%	12.05%	0.311
HTN	48.02%	28.31%	<0.0001
Peripheral vessel disease	4.21%	2.41%	0.249
Hypothyroidism	16.98%	17.47%	0.873
DM type 1&2	28.32%	24.7%	0.283
Obesity	19.80%	7.23%	0.0001
CHF	37.63%	66.27%	<0.0001
CKD	18.25%	41.57%	<0.0001
Liver disease	3.04%	5.42%	0.065
Electrolyte derangement	18.53%	22.89%	0.144
Maintenance hemodialysis	2.19%	9.64%	<0.0001
O2 dependence	3.51%	2.41%	0.439
Smoking	27.90%	25.90%	0.557
Anemia	15.67%	23.49%	0.006
On anticoagulation	29.53%	34.34%	0.158
CAD	29.53%	24.10%	0.127

Abbreviations: AF: Atrial fibrillation/flutter, AL: Amyloidosis, MI: Myocardial infarction, PCI: percutaneous coronary intervention, CABG: Coronary artery bypass graft, COPD: Chronic obstructive pulmonary disease, HTN: Hypertension, DM: Diabetes Mellitus, CHF: Chronic congestive heart failure, CKD: Chronic kidney disease, O2: oxygen, AICD: presence of Automated implantable cardioverter defibrillator, median household income: median household income for patient's Zip code, CAD: Coronary artery disease that is known but includes patients with and without a prior history of MI.

Table 2
Clinical outcomes of atrial fibrillation/flutter hospitalizations with and without amyloidosis.

	AF with Amyloidosis (n = 830)	AF without Amyloidosis (n = 931,224)	Adjusted Odds Ratio (AOR)	p-value
	%	%	(95% CI)	
Primary outcome				
In-hospital mortality	4.22	0.88	3.92 (1.81-8.51)	0.001*
Secondary outcomes				
Ablation	3.01	5.25	0.44 (0.17-1.10)	0.077
Pharmacologic cardioversion	0.60	0.38	1.47 (0.20-10.96)	0.709
Heart block	10.24	7.58	1.02 (0.60-1.74)	0.928
Cardiogenic shock	2.40	0.51	2.07 (0.63-6.80)	0.232
Cardiac arrest	3.01	0.40	4.80 (1.89-12.20)	0.001*
			Adjusted mean difference	
LOS, mean, days	5.88	3.39	0.63 ([-0.09]-1.34)	0.087
Total charge, mean, USD	58,105	40,181	-1,915 ([-10,274]-6,445)	0.653

Abbreviations: AF: Atrial fibrillation/flutter, LOS: Hospital length of stay, C.I: Confidence Interval, USD: United states dollars, * Statistically significant.

Patients with atrial fibrillation/flutter and coexisting amyloidosis more often had congestive heart failure (CHF), chronic kidney disease (CKD), anemia and required maintenance hemodialysis. While amyloidosis has been shown to affect nearly every organ system, the cardiac and renal systems are two of the most commonly afflicted. For example, immunoglobulin light chain (AL) amyloidosis, the most common of the systemic amyloidosis types, involves the heart in approximately 80% of patients, while involving the kidney in approximately two-thirds of those affected [7]. Of the patients with cardiac involvement, the presentation is most commonly as heart failure with preserved ejection fraction [7]. On the contrary, the other most common type of amyloidosis, AA amyloidosis, most commonly affects the kidneys. In fact, in a study by Lachmann et al., of 374 patients with AA amyloidosis 97% had proteinuria greater than 500 mg/day or serum creatinine levels greater than 1.5 mg/dL [8]. Over time, this amyloid deposition in the kidneys likely results in the culmination of chronic kidney disease. Lastly, hereditary transthyretin amyloidosis is being increasingly recognized as a cause of heart failure in elderly patients, and cardiac involvement in patients inheriting the mutated allele nears 100% [9]. Like the more common wild-type transthyretin amyloidosis, patients with this hereditary disorder suffer from heart failure with preserved ejection fraction, however conduction system dysfunction and arrhythmic disorders are often seen in these individuals as well [9].

Patients suffering from atrial fibrillation/flutter and coexisting amyloidosis had higher rates of in-hospital mortality and cardiac arrest. Cardiac arrest is a likely consequence of the deposition of amyloid fibrils into the cardiac muscle and conduction system which may result in both bradyarrhythmias, tachyarrhythmias, and heart blocks [3]. When amyloid fibrils infiltrate the cardiac tissue, the ventricles become thick and fibrotic. This leads to decreased ventricular compliance ultimately manifesting as diastolic dysfunction [3]. It is well known that patients with heart failure are prone to the development of ventricular arrhythmias and eventually, cardiac arrest. With an increased risk of conduction system abnormalities, it is not unreasonable to suspect increased length of stay and higher total cost utilization during hospitalizations, even though these findings did not achieve statistical significance.

It should be noted our findings resonate with Isath et al. who also reported an increased prevalence of cardiac arrhythmias in cardiac amyloidosis that worsened in-patient clinical outcomes [10]. The authors of that study reported an increased length and cost of hospital stay in patients with cardiac arrhythmias and underlying cardiac amyloidosis [10]. Moreover, Thakkar et al. used 2016 and 2017 NIS database and reported that cardiac arrhythmias with cardiac amyloidosis hospitalizations have worse in-patient clinical outcomes [11]. They reported higher mortality in

hospitalizations for cardiac amyloidosis with arrhythmias when compared to without arrhythmias. They also reported an increase in length and cost of stay for patients with cardiac arrhythmia with cardiac amyloidosis. All arrhythmias were taken into consideration in both studies [11].

4.1. Limitations

This paper is not without limitations. Incident and rate ratios could not be determined because of the inherent nature of cross-sectional data. Another limitation to the study was that stratified analysis could not be performed due to the limited number of cases in the study groups. As an example, when using ICD-10 codes for Transthyretin (ATTR) cardiomyopathy, a single case with a primary diagnosis of transthyretin cardiomyopathy during years 2016 and 2017 had not been documented and lead to the limitation of not being able to do a subgroup analyses with patients with transthyretin cardiomyopathy. Furthermore, the NIS database has an inherent limitation of not being able to distinguish between new and chronic diagnoses, comorbidities, and complications [12,13]. The NIS database also relies on the accuracy of the ICD coding system. We used the validated codes which have been used in prior studies to minimize error. But it cannot be determined if a patient was in normal sinus rhythm or actively in atrial fibrillation/flutter rhythm during the hospitalization. NIS does not discern if the complications occurred during the hospitalization or prior to presenting to the hospital.

5. Conclusion

Atrial fibrillation/flutter hospitalizations with coexisting amyloidosis were found to have a higher inpatient mortality and odds of having a secondary discharge diagnosis of cardiac arrest compared to those without amyloidosis. However, LOS, total hospital charges, likelihood of undergoing cardiac ablation, pharmacologic cardioversion, having a secondary discharge diagnosis of heart block and cardiogenic shock were similar in both groups.

Ethics approval

The involved institutions do not require ethical approval for literature reviews.

Informed consent

Informed consent was not required for literature reviews.

Funding sources

None.

Availability of data and materials

We used and/or analyzed the NIS database 2016 & 2017, available online at <http://www.hcup-us.ahrq.gov>. The NIS is a large publicly available all-payer inpatient care database in the United States, containing data on more than seven million hospital stays yearly. Its large sample size is ideal for developing national and regional estimates and enables analyses of rare conditions, uncommon treatments, and special populations.

Authorship statement

Asim Kichloo and Shakeel Jamal are credited with substantial contribution to the design of the work, acquisition and interpretation of the data, drafting the manuscript, revision of important intellectual content, final approval of the version published, and agreement of accountability for all aspects of the work. Michael Albosta is credited with substantial contribution to interpretation of data, literature review of all sections discussed, drafting of the manuscript, final approval of the version published, and agreement of accountability for all aspects of the work. Michael Aljadah and Ehizogie Edigin are credited with substantial contribution to acquisition, analysis, and interpretation of the data, revision of critically important intellectual content, final approval of the version to be published, and agreement of accountability for all aspects of the work. Muhammad Zia Khan, Farah Wani, and Rawan Amir are credited with interpretation of the data, literature review of all sections, revision of important intellectual content, final approval of the version published, and agreement of accountability for all aspects of the work. Ehtesham Ul-Haq and Khalil Kanjwal are credited with interpretation of data, literature review, specifically for the discussion section, revision of the work for critically important intellectual content, final approval of the version published, and agreement of accountability for all aspects of the work.

Declaration of competing interest

Authors declare no Conflict of Interests for this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ipej.2021.06.005>.

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