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Research paper

Trends in incidence and clinical outcome of non-ST elevation myocardial infarction in patients with amyloidosis in the United States, 2010–2020

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ABSTRACT

Study objective: To assess temporal changes in clinical profile and in-hospital outcome of patients with amyloidosis presenting with non-ST elevation myocardial infarction, NSTEMI.
Design/setting: We conducted a retrospective observational study using the National Inpatient Sample (NIS) database from January 1, 2010, to December 31, 2020.
Main outcomes: Primary outcome of interest was trend in adjusted in-hospital mortality in patients with amyloidosis presenting with NSTEMI from 2010 to 2020. Our secondary outcomes were trend in rate of coronary revascularization, and trend in duration of hospitalization.
Results: We identified 272,896 hospitalizations for amyloidosis. There was a temporal increase in incidence of NSTEMI among patients aged 18-44 years from 15.5 % to 28.0 %, a reverse trend was observed in 45–64 years: 22.1 % to 17.7 %, $p = 0.043$. There was no statistically significant difference in rate of coronary revascularization from 2010 to 2020; 16.3 % to 14.2 %, $p = 0.86$. We observed an increased odds of all-cause in-hospital mortality in patients with NSTEMI compared to those without NSTEMI (aOR = 2.2, 95 % CI: 1.9–2.6, $p < 0.001$) but there was a decrease trend in mortality from 21.5 % to 11.3 %, $p = 0.013$ for trend. Hospitalization duration was also observed to decreased from 14.1 days to 10.9 days during the study period ($p = 0.055$ for trend).
Conclusion: In patients with amyloidosis presenting with NSTEMI, there was increased incidence of NSTEMI among young adults, a steady trend in coronary revascularization, and a decreasing trend of adjusted all-cause in-hospital mortality and length of hospitalization from 2010 to 2020 in the United States.

1. Introduction

Systemic Amyloidosis is a disorder of misfolded insoluble fibril protein depositions in multiple organ systems. Cardiac involvement is a poor prognostic indicator and mostly due to the deposition of either monoclonal immunoglobulin light chain (AL) or transthyretin (ATTR) protein leading to biventricular hypertrophy, conduction abnormalities, valvular disease, and heart failure [1,2]. In patients with cardiac amyloidosis, histopathology reports have described cardiac coronary artery microvasculature disease associated with myocardial ischemia and microinfarction [3–5], however, data on clinical coronary ischemic events is limited. Few case reports have described acute coronary events in patients with amyloidosis [6,7]. Uddin et al. large data study reported on ST elevation myocardial infarction (STEMI) in 4252 patients with cardiac amyloidosis and found a STEMI incidence of 10.3 % [8]. To the best of our knowledge, no contemporary report exists on the incidence, characteristics, and clinical outcome of non-ST elevation myocardial infarction (NSTEMI) in amyloidosis. We sought to assess the temporal changes in clinical profile and in-hospital outcome of patients with amyloidosis presenting with NSTEMI.

2. Methods

We conducted a retrospective observational study using the National

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Inpatient Sample (NIS) database from January 1, 2010, to December 31, 2020. The NIS is part of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP) database. It is the largest publicly available all-payer inpatient database that produce national estimates of inpatient clinical outcomes, healthcare utilization, and cost in the United States. The database is generated from participating States and covers >97 % of the US population. The NIS is updated annually and estimates about 35 million hospitalizations each year [9]. The database is de-identified and contains information on patients' hospitalization, demographics, clinical conditions organized into primary and secondary diagnoses and procedures using International Classification of Diseases (ICD) codes. To accurately estimate trends using NIS datasets, trend weight files were merged to the original NIS files by year and hospital identification number. For years before 2012, the trend weight was used to create national estimates for trend analysis. For 2012 and after, the regular discharge weight was used. To also account for the transition from ICD-9 to ICD-10 diagnoses and procedure codes in 2015, both ICD-9 and ICD-10 codes were used to extract data from the 2015 NIS database. These are consistent with the redesigned NIS trend analysis [10] and have been previously used in other studies [11–13]. The NIS database has been extensively used to study independently trends in amyloidosis, acute myocardial infarction, and coronary revascularization in the United States [12,14,15]. Study met Howard University Institutional Review Board (IRB) exempt criteria as NIS databases are de-identified publicly available data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [16].

Patients aged 18 years and older with diagnosis of amyloidosis were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10-CM) codes; ICD-9-CM: 277.30, 277.39, and ICD-10-CM: E85.XX (see Supplement material). Among patients with amyloidosis, patients with non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI) were identified. 1149 STEMI hospitalizations identified were excluded from analyses to minimize selection bias. Baseline patient characteristics included age, sex, race, and insurance type. Comorbidities included hypertension, diabetes mellitus, heart failure, atrial fibrillation/flutter, prior history of myocardial infarction, prior history of percutaneous coronary intervention or coronary artery bypass graft, stroke, peripheral vascular disease, COPD, liver disease, hyperlipidemia, and tobacco use. Charlson comorbidity index [17,18] which is used to generate morbidity score that reflect mortality risk was also examined. Hospital characteristics included hospital teaching status.

Our primary outcome of interest was trend in adjusted in-hospital mortality in patients with amyloidosis presenting with NSTEMI from 2010 to 2020. Our secondary outcomes were trend in rate of coronary revascularization, and trend in duration of hospitalization. Coronary revascularization was defined as patient who received percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Trends in demographic profile and comorbidities were also investigated in different eras (2010–2012, 2013–2015, 2016–2018, 2019–2020). These eras were selected to illustrate aggregated demographics and comorbid characteristics and not the year-to-year change in profile as used in previous trend studies [12].

Weighted data was used for all statistical analyses. Categorical variables are presented as percentage and were compared with the Cochran Armitage trend test across year periods. Continuous data were presented as mean ± standard deviation and were tested with linear trend test. To estimate the effect of time on in-hospital mortality and coronary revascularization in study population over the study period, logistic regression models were constructed to estimate odds ratios and 95 % CIs using 2010 calendar year as the reference year, predictive margin was used to estimate the actual mean value of outcome for each level of the predictor. For estimation of trend for length of hospitalization, a linear regression was used. Because of the changing demographics over the years, outcomes were adjusted for adjust for age, sex, and race using multivariate logic regression. p values for trend were estimated with a regression model evaluating calendar year as a continuous variable. A 2-sided p value of < 0.05 was considered statistically significant. Stata version 17.0 (Stata Corp, College Station, TX, USA) was used for all data analyses.

3. Results

We identified 272,896 hospitalizations for amyloidosis, of whom 2.9 % presented with NSTEMI: mean age was 72.7 ± 12 years, 62.5 % were males. Majority of patients were non-Hispanic Whites, Blacks accounted for 29.3 % of study population. Among patients with amyloidosis, high incidence of NSTEMI was observed in year 2014; 42 per 1000 admissions for amyloidosis (Fig. 1 and Table 2). In patients with amyloidosis, there was a temporal increase in incidence of NSTEMI among age 18-44 years from 15.5 % to 28.0 % from 2010–2012 to 2019–2020, a reverse trend was observed in patients aged 45-64 years; 22.1 % to 17.7 %, $p = 0.043$.

Across eras, we observed an increasing concomitance of heart failure, 60.4 % (2010−2012) to 73.0 % (2019–2020), $p < 0.001$. There was also an increased in atrial fibrillation/flutter diagnosis; 33.1 % (2010–2012) to 42.7 % (2019–2020), $p = 0.037$ (Fig. 2). There was a statistically significant increase in percentage of patients with Charlson comorbidity index ≥5 from 2010–2012 to 2019–2020; 38.4 % to 55.6 %, $p < 0.001$. Table 1 illustrates the baseline clinical characteristics of the study population.

Among our study population, we observed overall coronary revascularization rate of 8.5 % (95 % CI: 7.7 %–10.0 %) for NSTEMI in amyloidosis, Table 3 in Supplementary tables illustrates temporal trends in crude and adjusted revascularization rates. After adjusting for age, sex, and race, from 2010 to 2020, there was no statistically significant difference in trend of coronary revascularization in patients with amyloidosis presenting with NSTEMI across the years; 16.3 % to 14.2 %, $p = 0.93$ (Fig. 3).

We observed increased odds of all-cause in-hospital mortality in patients with NSTEMI compared to those without NSTEMI (aOR = 2.2, 95 % CI: 1.9–2.6, $p < 0.001$). However, from 2010 to 2020, there was a decrease trend in mortality from 21.5 % to 11.3 %, $p = 0.013$ for trend (Fig. 3), crude and adjusted in-hospital mortality rates elaborated in Table 4 in Supplementary tables.

Hospitalization duration was also observed to decreased from 14.1 days to 10.9 days during the study period (14.1 days to 10.9 days, $p = 0.055$ for trend) (Table 5 in Supplementary tables).

4. Discussion

This study demonstrates 3 major findings; 1. In patients with systemic amyloidosis, there was an increased trend of NSTEMI hospitalization in those aged 18-44 yrs. in the United States. 2. We found a stable trend in rate of coronary revascularization in our study population. 3. A temporal decrease in all-cause in-hospital mortality and length of hospitalization were observed.

In patients without prespecified disease, multiple studies have established an increasing trend of coronary ischemic events in young adult population [19–23]. The Atherosclerosis Risk in Communities (ARIC) Surveillance study which looked at young adult patients aged 35–54 years reported an increased trend of acute myocardial infarction from 27 % to 32 % between 1995–1999 and 2010–2014 eras [19]. Wu et al., in 2020 established in their review of acute MI in young adults that, despite the decreasing trend of myocardial infarction in older population, among young adult there is either an increasing or steady trend [22]. The proposed mechanism of the increasing coronary ischemic events is believe to be due to increasing modifiable cardiovascular risk factors and subsequent epicardial coronary atherosclerotic

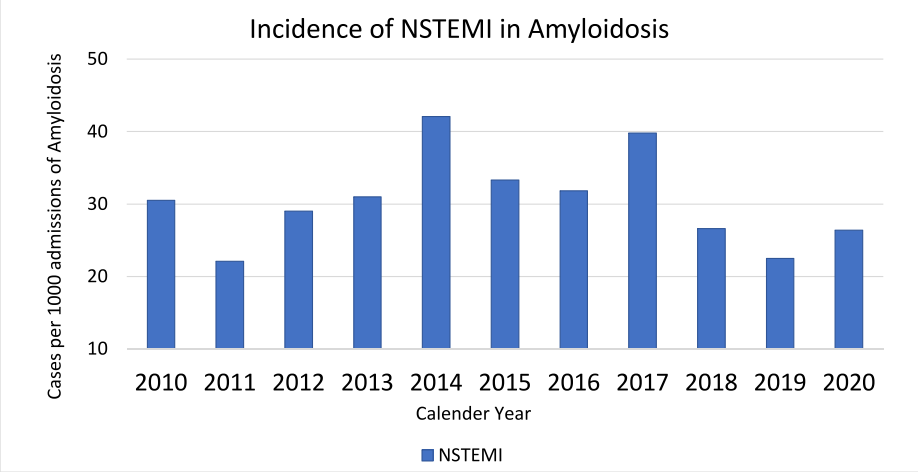

Fig. 1. Temporal trends in volume of NSTEMI in patients with amyloidosis.

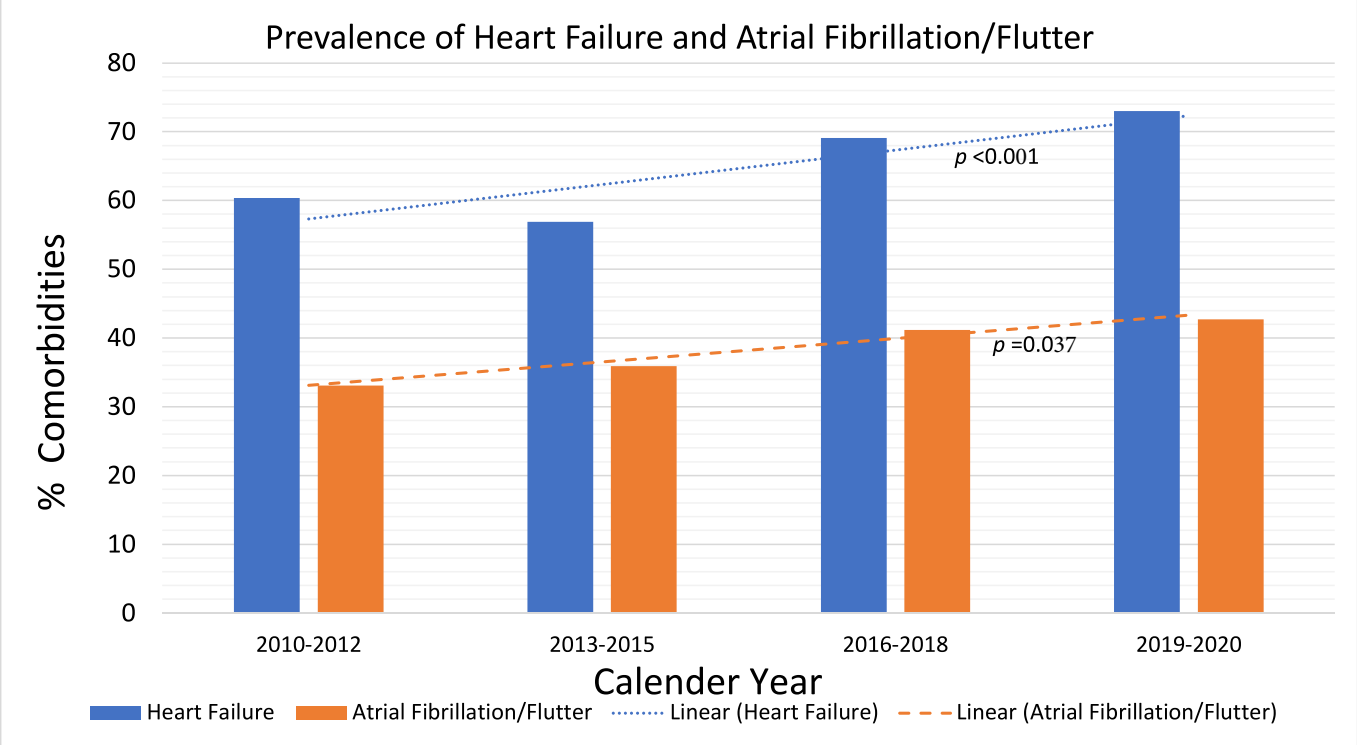

Fig. 2. Prevalence of heart failure and atrial fibrillation/flutter in amyloidosis.

changes in young patients [24]. However, in patients with amyloidosis presenting with symptomatic ischemic coronary artery disease, we cautiously argue that atherosclerosis may not be the primary or only culprit, this is because even in older patients with systemic amyloidosis who experienced coronary ischemic events, studies have rarely identified epicardial coronary atherosclerotic obstruction; obstructive intramural coronary has been implicated in symptomatic ischemic heart disease in systemic amyloidosis [25,26]. Wittich et al., upon review of pathology specimen of 58 patients with amyloidosis, found that in 97 % of the specimen there was amyloid deposition in epicardial coronary arteries, but no intraluminal obstruction was observed in any of the patients [27]. Soma et al., in their report also discussed a 49-year-old man who presented with STEMI with baseline angiography showing patent coronaries, biopsy revealed amyloidosis after coronary artery angiography suggested vascular endothelial dysfunction in response to acetylcholine and coronary flow reserve in response to papaverine [28]. These underscores previously described coronary microvascular dysfunction mechanisms described in patients with cardiac amyloidosis presenting with angina symptoms [29].

Previous studies have established decreasing and steady trend of coronary revascularization in the United States [12,30,31], the reason for this trend was hypothesized to be due to influential clinical trials that showed PCI can safely be deferred in patients with stable CAD provided an effective medical therapy is initiated [32,33], and the applications of appropriate use criteria for coronary revascularization to address potential overuse [34,35]. However, given older age at diagnosis of amyloidosis and increased in cardiovascular comorbidities as observed in our study population, it is reasonable to assume that patients with amyloidosis presenting with NSTEMI would have high risk stratification profile and hence higher invasive approach with intent for

Table 1
Temporal changes in demographic and clinical characteristics in amyloidosis patients presenting with non-ST elevation myocardial infarction, N = 7977.

Characteristics	2010–2012 n = 1443	2013–2015 n = 2099	2016–2018 n = 2655	2019–2020 n = 1780	
	(%)	(%)	(%)	(%)	*p* value
Age group (years)					0.043
18–44	15.5	19.0	32.0	28.0	
45–64	22.1	23.6	20.7	17.7	
65–84	63.2	60.5	55.6	60.1	
85 and older	13.1	14.1	20.5	18.5	
Males	56.5	62.6	65.4	63.2	0.10
Race					0.09
Non-Hispanic White	64.3	68.5	63.9	56.5	
Black	28.5	25.5	29.4	34.3	
Hispanic	7.2	6.0	6.7	9.3	
Insurance					0.57
Medicare	78.1	74.6	76.6	78.2	
Medicaid	6.9	6.3	7.7	7.3	
Private	14.0	17.8	13.9	11.6	
Uninsured	1.0	1.2	1.7	1.7	
Comorbidities					
Hypertension	26.5	26.2	17.9	11.2	<0.001
Diabetes	28.8	23.3	29.2	32.8	0.033
Heart failure	60.4	56.9	69.1	73.0	<0.001
A-fib/A-flutter	33.1	35.9	41.2	42.7	0.037
Prior MI	6.5	9.0	11.9	13.8	0.012
Prior PCI	7.4	10.9	9.2	11.8	0.24
Prior CABG	5.3	5.2	5.3	7.9	0.35
Stroke	5.0	6.4	8.3	8.4	0.28
PVD	5.4	5.5	4.0	4.2	0.64
COPD	17.1	19.5	19.8	18.8	0.81
Liver disease	3.0	1.7	9.0	8.2	<0.001
CKD	49.2	49.8	56.3	53.3	0.12
Hyperlipidemia	40.7	45.9	48.2	59.2	<0.001
Tobacco use	4.7	8.3	7.9	10.9	0.036
Charlson comorbidity index					<0.001
≤2	22.5	30.5	12.1	15.5	
3–4	39.1	34.8	37.7	28.9	
≥5	38.4	34.8	50.3	55.6	
Average LOS (days)	10.1	9.0	8.7	8.5	0.075
Teaching hospital	60.6	75.5	81.5	82.3	<0.001

A-fib/A-flutter: Atrial fibrillation and Atrial Flutter.
COPD: chronic obstructive pulmonary disease.
CKD: chronic kidney disease.
LOS: Length of stay in days.
Prior CABG: prior history of coronary artery bypass graft.
Prior MI: Prior history of myocardial infarction.
Prior PCI: Prior history of percutaneous coronary intervention.
PVD: peripheral vascular disease.

Table 2
Temporal trends in volume of NSTEMI in patients with amyloidosis.

Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Amyloidosis	16,702	18,459	18,805	19,810	21,750	23,060	23,455	27,365	30,860	35,735	36,895
NSTEMI	509	408	545	614	915	767	745	1090	820	805	975
NSTEMI[a]	30.5	22.1	29.0	31.0	42.1	33.3	31.8	39.8	26.6	22.5	26.4

NSTEMI: non-ST segment Elevation Myocardial Infarction.
[a] NSTEMI per 1000 admissions for amyloidosis.

revascularization based on current guidelines [36]. Our study found relatively lower rates of revascularization in patients presenting with NSTEMI in the setting of amyloidosis compared to the general population [37,38] and a steady trend over the study period. This observation can be explained by the non-obstruction of epicardial coronary arteries in the pathogenesis of angina in amyloidosis and the overall increase in effective medical therapy in patient with stable CAD. However, given this is only an observational study, further prospective studies are needed to assess coronary revascularization characteristics in patients with amyloidosis.

In the general population, mortality for patients with amyloidosis has been stable over the years in the United States [14]. Patients with cardiac amyloidosis, however, are experiencing improved clinical outcome, Westin et al. demonstrated a decrease in 1-year mortality from 74 % in 1998–2002 to 39 % in 2013–2017 in patients with cardiac amyloidosis using the Danish National registry database [39]. In our study, we also observed a decrease from 21 % to 11 % of all-cause in-hospital mortality from 2010 to 2020 in the United States in patients with amyloidosis who presented with NSTEMI, despite increased odds of in-hospital mortality in amyloidosis and NSTEMI compared with amyloidosis without NSTEMI. Limited studies have examined ACS among patients with amyloidosis, Uddin et al., again assessed mortality

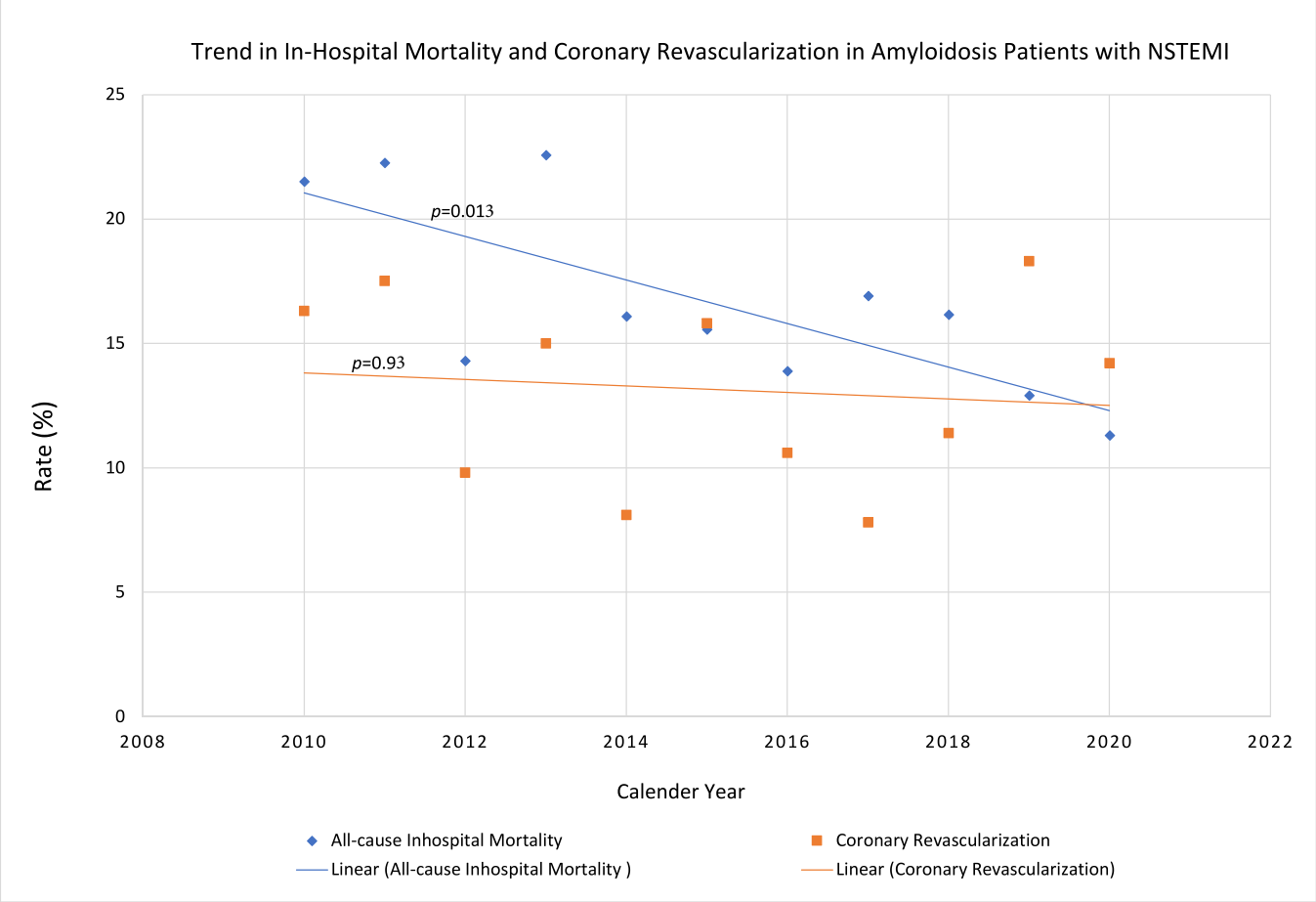

Fig. 3. Trend in all-cause in-hospital mortality and coronary revascularization rates in amyloidosis patients presenting with NSTEMI.

trend in STEMI patients with cardiac amyloidosis from 2014 to 2018 in the United States and found a steady trend over the study period [8]. Notwithstanding the large sample size of their study, the study period may have been short to detect changes in mortality trend given the relative rare diagnosis of amyloidosis. To the best of our knowledge, our study is the first large data study examining NSTEMI mortality trend in patients with amyloidosis. Though more prospective studies are required to evaluate outcome of coronary ischemic events in patients with amyloidosis, we hypothesis that the improvement in mortality and length of hospitalization over the study period is attributable to the advancement in medical treatment of ACS [32,38,40] and evaluation and treatment for amyloidosis especially cardiac amyloidosis [41–43]. It is worth mentioning that the noted trend of NSTEMI in young patients with amyloidosis observed in this study provides a reasonable premise for clinicians to consider evaluation for cardiac amyloidosis in patients presenting with ACS with no identifiable etiology especially when coronary angiogram reveals patent coronary arteries. This may provide opportunity for early diagnosis and treatment of cardiac amyloidosis.

5. Study limitations

This a retrospective study based on an administrative claim-based database that uses International Classification of Diseases (ICD) codes for classifying disease and procedures. The definition of the NSTEMI, PCI, CABG and comorbidities are based on these codes which are subjection to errors and selection bias. However, multiple studies have validated and used the same codes to estimate national trends of amyloidosis, STEMI, NSTEMI and coronary revascularization independently [12–14]. The NIS database does not provide inpatient laboratory results, EKG findings, coronary angiogram findings or list of medical therapy instituted while patient is hospitalized. This raises concerns for multiple confounding factors that cannot be assessed and accounted for. That notwithstanding, the database provides a large sample size that have been widely used in national estimate of hospitalizations and procedures outcome.

In patients with amyloidosis presenting with NSTEMI, we found significant changes in demographics and clinical characteristics over the study period. There was increased incidence of NSTEMI among young adults, a steady trend in coronary revascularization, and a decreasing trend of adjusted all-cause in-hospital mortality between 2010 and 2020 in the United States. These findings call for consideration for evaluation of cardiac amyloidosis in young adults presenting with acute coronary ischemic events in the absence of threatening imminent identifiable etiology. Study also highlights improvement in management of NSTEMI and amyloidosis over the years.

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CRediT authorship contribution statement

John Gharbin: Conceptualization, Methodology, Software, Writing - Original Draft, **Adwoa Winful**: Conceptualization, Methodology, Software, Writing - Original Draft, **Pamela Alebna**: Data curation, Result compilation, Writing - Original Draft, **Niyati Grewal:** Data curation, Result compilation, Reviewing and Editing, **Ahmed Brgdar**: Writing original draft preparation. **Suchelis Rhodd**: Writing original draft preparation. **Mohammed Taha**: Writing original draft preparation, **Urooj Fatima:** Supervision, Reviewing and Editing **Prafulla Mehrotra:**

Supervision, Reviewing and Editing **Anekwe Onwuanyi:** Supervision, Reviewing and Editing.

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Ethical statement

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed (correct citation).
7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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