CLINICAL INVESTIGATION

Ethnic/racial differences in risk factors and clinical outcomes among patients with amyloidosis

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ABSTRACT

Background: Cardiac amyloidosis is caused by abnormal extracellular deposition of insoluble fibrils in cardiac tissue. It can be fatal when untreated and is often underdiagnosed. Understanding the ethnic/racial differences in risk factors is critical for early diagnosis and treatment to improve clinical outcomes.

Methods: We performed a retrospective cross-sectional study utilizing the National Inpatient Sample database from 2015 to 2018 using ICD-10-CM codes. The primary variables of interest were race/ethnicity and amyloidosis subtypes, while the primary outcomes were in-hospital mortality, gastrointestinal bleeding, renal failure, and hospital length-of-stay.

Results: Amyloidosis was reported in 0.17% of all hospitalizations (N = 19,678,415). Of these, 0.09% were non-Hispanic whites, 0.04% were non-Hispanic blacks, and 0.02% were Hispanic. Hospitalizations with ATTR amyloidosis subtype were frequently observed in older individuals and males with coronary artery disease, whereas AL amyloidosis subtype was associated with non-Hispanic whites, congestive heart failure, and longer hospital length of stay. Renal failure was associated with non-Hispanic blacks (adjusted relative risk [RR] = 1.31, $p < 0.001$), Hispanics (RR = 1.08, $p = 0.028$) and had an increased risk of mortality. Similarly, the hospital length of stay was longer with non-Hispanic blacks (RR = 1.19, $p < 0.001$) and Hispanics (RR = 1.05, $p = 0.03$) compared to non-Hispanic whites. Hispanics had a reduced risk of mortality (RR = 0.77, $p = 0.028$) compared to non-Hispanic whites and non-Hispanic blacks, and no significant difference in mortality was seen between non-Hispanic whites and non-Hispanic blacks (RR = 1.00, $p = 0.963$).

Conclusions: Our findings highlight significant ethnic/racial differences in risk factors and outcomes among amyloidosis-related US hospitalizations that can possibly be used for early detection, treatment, and better clinical outcomes.

Key Indexing Terms: Amyloidosis, Racial differences; Heart failure; Renal failure; Gastrointestinal bleeding; Cardiac amyloidosis. **[Am J Med Sci 2022;■(■):1–10.]**

INTRODUCTION

Amyloidosis is a rare and life-threatening disease that results from pathologic protein aggregation and abnormal extracellular deposition of insoluble fibrils causing multi-organ dysfunction due to disruption of tissue architecture by amyloid deposits.[1–4] Cardiac amyloidosis (CA) is due to an abnormal extracellular deposition of insoluble amyloid fibrils in the myocardium, stiffening the heart and leading to myocardial restriction and dysfunction.[5–7] CA is an increasingly recognized form of infiltrative cardiomyopathies leading to heart failure.[5,8–11] Although the exact prevalence of CA remains unknown, there is recognition that this condition is more common than previously believed due to an increased number of referrals for suspicion of CA and autopsy findings.[7,12] A study looking at geographic disparities in amyloidosis mortality reported in the United States observed that non-Hispanic blacks were overrepresented in amyloidosis mortality, while simultaneously finding a lack of higher reported mortality rates in those states with a greater proportion of black residents, suggesting possible underdiagnoses of amyloidosis, including CA, in many areas of the United States (US).[13] However, there is no recent estimate available for amyloidosis in the US by ethnic/racial groups.

There are more than 30 human amyloid proteins that have been identified, of which amyloid light-chain immunoglobulins (AL) and hepatic-derived transthyretin (ATTR) are two of the most common subtypes worldwide. The AL subtype is associated with plasma cell dyscrasia and recognized as the most common form of systemic amyloidosis whereas the ATTR subtype is associated with normal or mutated transthyretin and older age and recognized as the most common hereditary amyloidosis worldwide.[3,14,15] Around 2,000 new cases of AL amyloidosis occur in the US per year with approximately half having significant cardiac involvement.[15–17] Cardiac infiltration with AL or ATTR subtypes typically manifests with symptoms of heart failure and/or arrhythmias with some patients presenting with atrioventricular (AV) block, restrictive cardiomyopathy, and heart failure.[5,6,12] The burden of cardiac involvement is the main prognostic factor in patients with AL amyloidosis, being the most important predictor of the treatment outcome and overall survival.[8,18] Untreated CA is fatal with a reported median survival of less than 1 year for AL involvement and 4 years for ATTR, with an even lower median survival of around 6 months from onset of heart failure.[7,13,19–21] One study using healthcare claims databases found a significant increase in AL amyloidosis prevalence between 2007 and 2015.[18] Although the incidences of cardiac events and related mortality greatly differ by ethnicity/race, the ethnic/racial differences of amyloidosis have not been systemically studied in the US population.

While the factors that determine the organ distribution of amyloid deposits are not well understood, there is continued evidence that CA is part of a systemic disease rather than an isolated condition.[4,7] In addition to cardiac involvement, amyloid most commonly affects the kidneys, nerves, vasculature, the liver and gastrointestinal tract, and soft tissues.[4,7,17,22] Systemic amyloidosis can also present with carpal tunnel syndrome, orthostatic hypotension, and periorbital purpura.[17,23,24] It has been suggested that small periorbital bruises in the setting of heart failure (HF) are pathognomonic for AL amyloidosis.[7] Without treatment, amyloidosis-associated kidney disease usually progresses to end-stage renal disease (ESRD).[4] Additionally, upper and lower gastrointestinal (GI) bleeding can occur due to gastric amyloidosis pathophysiology such as ischemia, infarction and lesions caused by amyloid infiltration.[25–27] Improved responses to appropriate amyloidosis therapy initiation have been shown to depend on early diagnosis and accurate typing of amyloid deposits, which is often delayed due to these varied presentations.[17] Given the fatal outcomes associated with amyloidosis if untreated, and with advancements in the therapeutic management of amyloidosis, particularly the ATTR subtype, it is critical to better understand the epidemiological differences in amyloidosis and associated outcomes for timely identification and appropriate therapy. Specifically, understanding factors associated with GI bleeding and renal failure (RF) in amyloidosis is necessary for developing individualized care. Moreover, ethnic/racial differences may persist in outcomes of amyloidosis due to differences in clinical presentation. However, the distribution of GI bleeding, RF, and ESRD has not been studied according to ethnicity/race and amyloidosis subtypes.

Because amyloidosis is relatively a rare disease, National Inpatient Sample (NIS) data may be a powerful tool to study the ethnic/racial epidemiology of amyloidosis. We aimed to determine the prevalence of amyloidosis in US hospitalizations and sought to determine the differences in risk factors and outcomes according to ethnicity/race and amyloidosis subtypes among US hospitalizations.

METHODS

We performed a retrospective study utilizing the NIS database from 2015 to 2018 including hospitalizations with a diagnosis of CA based on the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes to identify amyloidosis, GI bleeding, and renal failure (RF). The ICD-10-CM codes used to identify each of these diagnoses and comorbidities are listed in Supplementary Tables 1 and 2. Specifically the following ICD 10 codes were used to diagnose amyloidosis and types;

E85 Amyloidosis
E85.0 Non-neuropathic heredofamilial amyloidosis
E85.1 Neuropathic heredofamilial amyloidosis
E85.2 Heredofamilial amyloidosis, unspecified
E85.3 Secondary systemic amyloidosis
E85.4 Organ-limited amyloidosis
E85.8 Other amyloidosis
E85.81 Light chain (AL) amyloidosis
E85.82 Wild-type transthyretin-related (ATTR) amyloidosis
E85.89 Other amyloidosis
E85.9 Amyloidosis, unspecified

We selected the study period to capture all amyloidosis and its subtypes, using ICD-10-CM codes, and to avoid any misclassification during the study period.

The NIS is the largest publicly available all-player, inpatient database in the United States by the Healthcare Cost and Utilization Project (HCUP) developed through a Federal-State-Industry partnership and sponsored by the Agency for Healthcare Research and Quality (AHRQ).[28] Its large sample size is ideal for developing national and regional estimates and enables analyses of rare conditions, uncommon treatments, and special populations.[29] Due to the nature of this study having deidentified hospitalizations, it did not require approval from the institutional review board. We included all the adult (age $\geq$ 18 years) hospitalizations reported in the NIS database during the study period for estimating CA-related hospitalizations by ethnic/racial groups. For demographics, we included age (years), gender (male/female), and ethnicity/race (non-Hispanic white, non-

Hispanic black, Hispanic, and others). Additionally, we collected data on the presence or absence of diabetes mellitus (DM), hypertension (HTN), congestive heart failure (CHF), liver disease, pulmonary disease, coronary artery disease (CAD), RF, and GI bleed in a retrospective manner using the NIS database based on ICD codes (Supplementary Table 1).

The primary outcomes in this study were renal failure, GI bleed, hospital length of stay (HLOS) and in-hospital mortality. Of note, a fraction of patients might have had preexistent ESRD at the time of hospitalization unrelated to Amyloidosis. The primary variables of interest were ethnicity/race and the AL and ATTR subtypes of amyloidosis. Accordingly, hospital characteristics, comorbidities, and outcomes were compared by ethnic/racial groups (non-Hispanic whites, non-Hispanic blacks, Hispanic and others) and amyloidosis subtypes (AL, ATTR and others).

STATISTICAL ANALYSIS

Appropriate weight-adjusted analyses were performed in this study as per the NIS documentation.[29] Initially, we estimated the prevalence of CA in the entire cohort and by ethnic/racial groups using survey-weighted exact binomial distribution and reported along with a 95% confidence interval (CI). All the variables were presented with frequency and percentage except for age and hospital length of stay which were summarized with mean and standard deviation (SD). The quantitative and categorized variables were compared between ethnic/racial groups using either survey generalized linear model (GLM) with log link and Poisson distribution or normal distribution with the identity link function. The distributions of all the variables were also compared by GI bleeding, RF, type of amyloidosis, and mortality status using survey GLM models. The adjusted associations of ethnicity with primary binary outcomes were determined using survey GLM with log link and Poisson distribution. In addition, a survey GLM with gamma distribution and a log link function was used for determining the adjusted association of ethnicity with HLOS. The results of survey GLM regression analyses were summarized with risk ratio (RR) and 95% CI. Age was standardized in all the regression analyses. All the considered risk factors including age, sex, amyloidosis type, DM, HTN, hyperlipidemia, CHF, liver disease, thyroid disorder, pulmonary disease, and CAD were adjusted in the multivariable analyses. All the statistical analyses were performed using STATA 17. P-values less than 5% were considered statistically significant results.

RESULTS

Ethnic/racial differences in risk factors and outcomes

Of the total population (N = 19,678,415), the prevalence of amyloidosis was 0.17% (N = 34,894) in all US hospitalizations during this time period. The prevalence of amyloidosis was estimated to be 0.09% (95% CI: 0.094%, 0.097%) in non-Hispanic whites (NHW), 0.04% (95% CI: 0.043%, 0.045%) in non-Hispanic blacks (NHB) and 0.02% (95% CI: 0.0182%, 0.019%) among Hispanics. Table 1 provides the unadjusted comparisons of hospitalizations related to amyloidosis. Hispanics (51.5 $\pm$ 20.1) and NHB (54.4 $\pm$ 20.0) were younger than NHW (66.7 $\pm$ 17.2). NHB (65%) and Hispanics with amyloidosis (67%) were more likely to be females relative to NHW (52%). All the comorbidities (HTN, pulmonary disease, CAD, thyroid disorder, hyperlipidemia) were found to be higher in NHW compared to NHB and Hispanics except for DM which was higher in NHB than NHW and CHF which was similarly observed in NHW and NHB but higher than Hispanics. In terms of outcomes, there were no differences in GI bleeding across ethnic/racial groups. However, RF and ESRD was seen significantly more in NHB (26.7%, 11.8%) followed by Hispanics (23.5%, 10.9%), others (22%, 8.7%) and NHW (20%, 6.9%), respectively. The mortality was significantly higher among NH Whites (4.4%) compared to NH Blacks (3.2%) and Hispanics (2.2%). However, the average HLOS was longer in NHB (7.33 days) compared to NHW (6.33 days) and Hispanics (6.37 days).

Amyloidosis differences in risk factors and outcomes

Of total amyloidosis, 733 hospitalizations were AL(+), 118 ATTR(+), and 34,043 were AL/ATTR(-). AL(+) subtype was prevalent in NHW (2.5%) compared to NHB (1.6%) and Hispanics (1.3%) whereas ATTR(+) subtype was relatively higher in NHB and NHW than in Hispanics (Table 2). AL(+) subtype of amyloidosis had more HTN, CHF and females than ATTR(+), whereas CAD was commonly observed in the ATTR(+) subtype. Although AL(+) subtype (65.6 $\pm$ 11.4) had younger individuals than ATTR (+) (77.6 $\pm$ 11.2), it was significantly different than the AL/ATTR(-) subtypes (60.9 $\pm$ 19.7). Any RF was more commonly observed in ATTR(+) subtype whereas the frequency of ESRD (19.4% vs 2.54%, $p < 0.001$), mortality (6.6% vs 5.9%, $p = 0.0003$) and longer HLOS (8.9 $\pm$ 11.8 vs. 7.1 $\pm$ 6.23, $p < 0.001$) were associated with AL(+) type than ATTR(+). Hospitalized individuals with AL/ATTR(-) subtypes were significantly younger with more females and HTN than AL(+) and ATTR(+) (Table 2).

Unadjusted factors associated with gastrointestinal bleeding and renal failure

Of total hospitalizations with amyloidosis, 2.93% (n = 1022) had GI bleeding and 41.7% (n = 14574) had RF. The distributions of all the characteristics were found to be different according to RF status and some with GI bleeding (Table 3). GI bleeds related to amyloidosis were more likely to be observed in older individuals (63.86 vs. 60.94 years, $p = <.0001$), males (51.85 vs. 42.04, $p = <.0001$) and with CHF (17.6% vs. 10.0%, $p < .0001$). RF in hospitalized patients with amyloidosis was statistically more common in older individuals, NHB and those

Table 1. Characteristics and outcomes by race/ethnicity.

	NHW N = 18900 N (%)	NHB N = 8648 N (%)	Hispanic N = 3715 N (%)	Other N = 3631 N (%)	P-value
Age, mean (SD)	66.68 (17.17)	54.42 (20.03)	51.45 (20.12)	57.14 (20.27)	<.0001
Sex-female	9908 (52.43)	5620 (65.01)	2494 (67.17)	2098 (57.78)	<.0001
Amyloidosis type					0.0006
AL/ATTR (-)	18364 (97.16)	8472 (97.96)	3663 (98.60)	3544 (97.60)	
AL (+)	467 (2.47)	139 (1.61)	49 (1.32)	78 (2.15)	
ATTR (+)	69 (0.37)	37 (0.43)	#	#	
Risk factors					
Diabetes	2719 (14.39)	1681 (19.44)	613 (16.5)	593 (16.41)	<.0001
HTN	6508 (34.43)	2702 (31.24)	118 (30.09)	1162 (32)	<.0001
CHF	2105 (11.14)	894 (10.34)	246 (6.62)	335 (9.23)	<.0001
Liver disease	218 (1.15)	109 (1.26)	45 (1.51)	51 (1.4)	0.270
Thyroid disease	3480 (18.41)	650 (7.52)	488 (13.14)	494 (13.61)	<.0001
Hyperlipidemia	6204 (32.83)	2204 (25.49)	792 (21.32)	934 (25.72)	<.0001
Pulmonary disease	2109 (11.16)	731 (8.45)	213 (5.73)	220 (6.06)	<.0001
CAD	3658 (19.35)	1158 (13.39)	351 (9.45)	460 (12.67)	<.0001
Outcomes					
GI bleeding	553 (2.93)	258 (2.98)	106 (2.85)	105 (2.89)	0.933
Renal Failure	3772 (19.96)	2308 (26.7)	873 (23.5)	799 (22.0)	<.0001
ESRD	1320 (6.9)	1022 (11.8)	406 (10.9)	316 (8.7)	<.0001
Mortality	838 (4.44)	280 (3.24)	83 (2.23)	136 (3.75)	<.0001
HLOS, mean (SD)	6.33 (7.88)	7.33 (10.14)	6.37 (7.76)^	6.60 (7.25)	<.0001 *

*Log transformed variable; ^ = Not significantly different from NHW.
#signifies values less than 11, NIS HCUP Data Use Agreement (DUA) has small cell size restriction. Reporting small numbers of observations increases the risk for individual identification and is a violation of the HCUP DUA.
NHW = non-Hispanic white; NHB = non-Hispanic black; AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; HTN = hypertension; CHF = congestive heart failure; CAD = coronary artery disease; GI = gastrointestinal; ESRD = end-stage renal disease; HLOS = hospital length of stay; SD = standard deviation.

with certain comorbid conditions: DM, HTN, CHF, pulmonary disease, thyroid disorder, hyperlipidemia, CAD, and GI bleeding (Table 3). GI bleeding was also more frequent among hospitalized individuals with RF. Both GI bleeding and RF had significantly higher mortality rates and extended HLOS (Table 3).

Adjusted factors associated with gastrointestinal bleeding, renal failure, and mortality

In the adjusted analyses (Table 4), RF was associated with NHB (RR = 1.31, $p < 0.001$) and Hispanics (RR = 1.08, $p = 0.028$) compared to NHW. Although the GI bleeding was higher in NHB (RR = 1.14, $p = 0.087$) and Hispanics (RR = 1.15, $p = 0.189$) compared to NHW, the associations were not statistically significant. NHB was not significantly associated with mortality compared to NHW (RR = 1.00, p-value = 0.963). However, in-hospital mortality related to amyloidosis was significantly lower in Hispanics (RR = 0.77, $p = 0.028$) compared to NHW in adjusted analyses. Higher age, male gender, AL(+) subtype and CHF were consistently associated with RF, GI bleeding and mortality. Compared to the AL/ATTR(-) subtypes, AL(+) was associated with an increased risk of RF (RR = 1.32, $p < 0.001$), GI bleeding (RR = 1.74, $p < 0.001$) and mortality (RR = 1.43, $p = 0.019$). In addition, ATTR(+) (RR = 1.15, $p = 0.025$), DM (RR = 1.31, $p < .0001$), hyperlipidemia (RR = 1.16, $p < .0001$) and CAD (RR = 1.14, $p < .0001$) were associated with increased prevalence of RF only. In contrast, HTN was inversely associated with a higher prevalence of RF (RR = 0.29, $p < 0.001$), GI bleeding (RR = 0.61, $p < 0.001$) and mortality (RR = 0.61, $p < 0.001$). Both GI bleeding (RR = 2.09, $p < 0.001$) and RF (RR = 2.07, $p < 0.001$) had significantly higher in-hospital mortality rates in adjusted analyses.

Adjusted factors associated with hospital length of stay

Longer HLOS was noticed in NHB (RR = 1.19, $p < 0.001$) and Hispanics (RR = 1.05, $p = 0.03$) compared to NHW in the adjusted analysis. In addition, AL(+) subtype (RR = 1.31, $p < 0.001$), male gender (RR = 1.10, $p < 0.001$) and increasing age (RR = 1.06, $p < 0.001$) were also associated with extended HLOS among amyloidosis admissions. HTN, CHF and hyperlipidemia were inversely associated with HLOS (Table 5).

DISCUSSION

In our study, the prevalence of amyloidosis hospitalization was higher in NHW, compared to NHB and Hispanics, with whites being older than in other ethnic/racial

Table 2. Differences in risk factors and outcomes by amyloidosis type.

	AL (+) N = 733 N (%)	ATTR (+) N = 118 N (%)	AL/ATTR (-) N = 34043 N (%)	P-value
Age, mean (SD)	65.62 (11.4)	77.6 (11.17)	60.87 (19.74)	<.0001+
Sex-female	318 (43.38)	33 (27.97)	19769 (58.08)	<.0001+
White	467 (63.71)	69 (58.47)	18364 (53.94)	0.0006
Black	139 (18.94)	37 (31.36)	8472 (24.89)	0.0006
Hispanic	49 (6.68)	#	3663 (10.76)	0.0006
Other	78 (10.63)	#	3544 (10.41)	0.0005
Diabetes	127 (17.3)	17 (14.41)	5465 (16.05)	0.631
HTN	110 (15.0)	#	11371 (33.4)	<.0001+
CHF	144 (19.65)	16 (13.56)	3420 (10.05)	<.0001
Liver disease	13 (1.77)	#	421 (1.24)	0.319
Thyroid disease	120 (16.37)	11 (9.32)	4981 (14.63)	0.148
Hyperlipidemia	262 (35.74)	46 (38.98)	9826 (28.86)	<.0001
Pulmonary disease	69 (9.4)	#	3194 (9.38)	0.947
CAD	123 (16.78)	36 (30.51)	5468 (16.06)	0.0002+
GI Bleeding	45 (6.14)	#	971 (2.85)	<.0001
Renal Failure	354 (48.29)	27 (22.88)	7371 (21.65)	<.0001+
ESRD	142 (19.37)	#	2919 (8.57)	<.0001+
Mortality	48 (6.55)	#	1282 (3.77)	0.0003
HLOS, mean (SD)	8.88 (11.76)	7.14 (6.23)	6.56 (8.35)	<.0001+,*

+Significantly different between AL + and ATTR + groups.
*Log transformed variable was analyzed.
#signifies values less than 11, NIS HCUP Data Use Agreement (DUA) has small cell size restriction. Reporting small numbers of observations increases the risk for individual identification and is a violation of the HCUP DUA.
AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; SD = standard deviation; HTN = hypertension; CHF = congestive heart failure; CAD = coronary artery disease; GI = gastrointestinal; ESRD = end-stage renal disease; HLOS = hospital length of stay.

Table 3. Differences in risk factors and outcomes by GI bleeding and renal failure status.

	GI Bleeding (-) N = 33872 N (%)	GI Bleeding (+) N = 1022 N (%)	P-value	Renal failure (-) N = 20320 N (%)	Renal failure (+) N = 14574 N (%)	P-value
Age, mean (SD)	60.94 (19.66)	63.86 (17.42)	<.0001	59.36 (20.09)	63.35 (18.67)	<.0001
Sex-females	19628 (57.96)	492 (48.14)		12953 (63.76)	7167 (49.18)	<.0001
Diabetes	5421 (16)	188 (18.4)	0.055	2301 (11.32)	3308 (22.7)	<.0001
HTN	11268 (33.27)	222 (21.72)	<.0001	9672 (47.6)	1818 (12.47)	<.0001
CHF	3400 (10.04)	180 (17.61)	<.0001	1369 (6.74)	2211 (15.17)	<.0001
Liver disease	409 (1.21)	25 (2.45)	NA	207 (1.02)	227 (1.56)	NA
Thyroid	4950 (14.61)	162 (15.85)	0.283	2784 (13.70)	2328 (15.97)	<.0001
Hyperlipidemia	9835 (29.04)	299 (29.26)	0.882	5263 (25.90)	4871 (33.42)	<.0001
Pulmonary disease	3159 (9.33)	114 (11.15)	0.064	1814 (8.93)	1459 (10.01)	0.004
CAD	5439 (16.06)	188 (18.4)	0.053	2494 (12.27)	3133 (21.5)	<.0001
Renal failure/GI bleeding	13934 (41.14)	640 (62.62)	<.0001	382 (1.88)	640 (4.39)	<.0001
Mortality	1237 (3.65)	100 (9.78)	<.0001	484 (2.38)	853 (5.85)	<.0001
HLOS, mean (SD) *	6.47 (7.92)	11.20 (18.14)	<.0001	5.76 (7.13)	7.79 (9.86)	<.0001

*Log transformed variable was analyzed.
GI = gastrointestinal; SD = standard deviation; HTN = hypertension; CHF = congestive heart failure; CAD = coronary artery disease; HLOS = hospital length of stay.

groups. Only a few epidemiological data have been published for amyloidosis. The first study of AL amyloidosis, conducted in the United States, had an all-White sample population with an incidence rate of 9 cases per million person-years.[1,30,31] The median age at presentation was 55 to 60 with the mean age of AL amyloidosis patients being 63 years.[17,18] While there are some studies that evaluate age and gender, currently, little is known about

Table 4. Adjusted associations of race/ethnicity and amyloidosis type on outcomes.

	Renal failure				GI Bleeding				Mortality			
	RR	95% CI		p-value	RR	95% CI		p-value	RR	95% CI		p-value
Race/Ethnicity												
NHW (ref)												
NHB	1.31	1.24	1.38	<.0001	1.14	0.98	1.34	0.087	1.00	0.87	1.15	0.963
Hispanic	1.08	1.01	1.16	0.028	1.15	0.93	1.42	0.189	0.77	0.62	0.97	0.028
Other	1.03	0.97	1.09	0.318	1.07	0.87	1.33	0.490	1.07	0.91	1.28	0.396
Age (Standardized)	1.11	1.08	1.13	<.0001	1.15	1.07	1.23	<.0001	1.93	1.81	2.06	<.0001
Female (ref: Male)	0.80	1.08	1.13	<.0001	0.73	0.64	0.83	<.0001	0.80	0.72	0.89	<.0001
Amyloidosis type												
AL -/ATTR – (ref)												
AL+	1.32	1.24	1.39	<.0001	1.74	1.29	2.34	<.0001	1.43	1.06	1.92	0.019
ATTR +	1.15	1.02	1.28	0.025	1.28	0.58	2.81	0.532	0.83	0.42	1.65	0.594
Diabetes	1.31	1.27	1.34	<.0001	1.05	1.29	2.34	<.0001	0.91	0.78	1.06	0.217
HTN	0.29	0.27	0.31	<.0001	0.61	0.58	2.81	0.532	0.61	0.53	0.69	<.0001
CHF	1.14	1.10	1.18	<.0001	1.55	1.31	1.83	<.0001	1.21	1.04	1.40	0.014
Thyroid	1.10	1.06	1.15	<.0001	1.09	0.92	1.30	0.308	0.86	0.74	0.99	0.046
Hyperlipidemia	1.16	1.13	1.19	<.0001	0.92	0.79	1.07	0.289	0.69	0.61	0.78	<.0001
Pulmonary disease	0.97	0.93	1.01	0.154	1.12	0.91	1.37	0.275	0.97	0.82	1.15	0.748
CAD	1.14	1.11	1.17	<.0001	0.96	0.81	1.14	0.630	1.01	0.88	1.15	0.925
Year												
2015-2016 (ref)												
2017	0.95	0.88	1.03	0.240	0.96	0.81	1.13	0.609	1.13	0.98	1.30	0.078
2018	0.96	0.89	1.04	0.342	1.05	0.89	1.23	0.537	1.12	0.97	1.28	0.122

GI = gastrointestinal; RR = relative risk; CI = confidence interval; NHW = non-Hispanic white; NHB = non-Hispanic black; ref = in reference to; AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; HTN = hypertension; CHF = congestive heart failure; CAD = coronary artery disease.

disease features of systemic amyloidosis and outcomes in ethnic/racial minorities.[32] Consistent with our study, one study found both younger onset of disease by 4-6 years and a more aggressive disease phenotype in minority groups.[32] We observed more RF, ESRD and longer HLOS in NHB and Hispanics than in NHW. This is probably due to a higher frequency of DM in NHB and Hispanics; DM is known to be disproportionally higher in blacks and Hispanics compared to whites. Presence of DM in individuals with amyloidosis may worsen poor prognosis during hospitalizations, particularly among blacks and Hispanics. However, HTN was inversely associated with a higher prevalence of RF, GI bleeding and in-hospital mortality. This suggests that some therapeutic interventions related to HTN may yield protection against amyloidosis.

Consistent with previous studies, we also observed that NHB individuals, older age and male sex were more often associated with ATTR amyloidosis.[13,33] ATTR cardiomyopathy is responsible for a significant heart failure burden in black individuals and has been reported as the fourth leading cause of heart failure in individuals of African descent.[13] Though we observed CAD being more prevalent in the ATTR subtype, AL had more frequent and severe complications including CHF, RF and higher mortality. The AL subtype is one of the most common, predominant causes of renal amyloidosis cases, contributing to progressive renal insufficiency and ESRD if diagnosed late.[34] Similar to our study findings, clinical observations have suggested that the severity of heart failure in AL amyloidosis is likely higher than in ATTR amyloidosis.[7]

Among patients with amyloidosis and GI involvement, weight loss, heartburn and GI bleeding are reported to be the most common symptoms.[21] Our study found that among hospitalizations with amyloidosis, GI bleeding was more common in males, older individuals, and those with RF, DM, CHF and liver disease. Hospitalizations with amyloidosis and GI bleeds had significantly higher mortality with longer HLOS than those without GI bleeding in our study. Additionally, in this study, we show that RF in amyloidosis was associated with older age, black race, longer HLOS, and overall higher mortality. Our study observed that older age, male gender and CHF were consistently associated with poorer outcomes in hospitalizations with amyloidosis. This suggests that CHF patients of older age or male gender should be prioritized for amyloidosis screening and treatment.

Despite whites presenting at older ages and having significantly higher comorbidities i.e., more CHF, pulmonary disease, CAD, thyroid disorder, hyperlipidemia and HTN - and risk factors, such as AL subtype, we identified poorer outcomes and higher prevalence of RF and ESRD among blacks and Hispanics, including longer HLOS in blacks compared to white patients among all hospitalizations related to amyloidosis. However, in-hospital mortality was favorable in Hispanics (2.23%) and blacks

Table 5. Adjusted associations of race/ethnicity and amyloidosis type with hospital length of stay.

	HLOS			
	RR	**95% CI**	**p-value**	
Race/Ethnicity				
White (ref)				
Black	1.19	1.15	1.24	<.0001
Hispanic	1.05	1.01	1.11	0.03
Other	1.07	1.03	1.12	0.001
Age (Standardized)	1.06	1.05	1.08	<.0001
Female (ref: Male)	0.91	0.88	0.94	<.0001
Amyloidosis type				
AL -/ATTR – (ref)				
AL+	1.31	1.18	1.45	<.0001
ATTR +	0.96	0.83	1.12	0.645
Diabetes	0.99	0.96	1.03	0.914
HTN	0.88	0.86	0.92	<.0001
CHF	0.99	0.95	1.05	0.900
Thyroid	0.98	0.95	1.02	0.395
Hyperlipidemia	0.95	0.92	0.98	0.003
Pulmonary disease	0.97	0.92	1.01	0.217
CAD	0.91	0.91	0.98	0.003
Year				
2015/2016 (ref)				
2017	1.003	0.96	1.04	0.877
2018	1.01	0.96	1.05	0.700

HLOS = hospital length of stay; RR = relative risk; CI = confidence interval; ref = in reference to; AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; HTN = hypertension; CHF = congestive heart failure; CAD = coronary artery disease.

(3.24%), without any statistically significant difference between NHB and NHW (4.44%). White patients had highest in-hospital mortality compared to Hispanics; this finding could be due to presenting differences in the characteristics of white patients such as older age at presentation with more males and more adverse risk factors such as CAD, CHF and pulmonary disease compared to Hispanics. In-hospital mortality has been associated with older age, male gender, AL or ATTR amyloid subtypes and these comorbid diseases in other studies.[35] However, no adjusted differences in mortality were observed between white and black patients. This is mainly due to the highest frequency of RF and ESRD, and a similar frequency of CHF, among black patients compared to white patients. Our findings clearly suggest importance of early diagnosis and treatment of amyloidosis, particularly among hospitalized individuals with CHF and RF. Screening and early, accurate diagnosis and typing of amyloid protein are required in CHF and RF, including patients with ESRD, for correct management and appropriate treatment.

Our findings also reflect significant complications associated with amyloidosis in NHB and Hispanics despite lower mortality. Systemic barriers in health care access such as inequitable access to diagnostic testing and fewer referrals to specialized treatment centers within minority groups may be contributing factors.[32] It has been suggested that reported rising death rates with CA most likely represent increased disease recognition rather than increased lethality, but there still remains an underdiagnosis of amyloidosis in locations with less access to specialized amyloidosis care.[13] Our study estimates a low prevalence of amyloidosis among US hospitalizations with worse clinical outcomes in those with RF and ESRD among amyloidosis admissions. Finally, this study suggests significant ethnic/racial differences in baseline characteristics and outcomes for hospitalized patients with amyloidosis.

There are several limitations of our study due to the deficiencies and limitations of administrative databases. First, the NIS database is an administrative claim-based database that uses ICD codes and is susceptible to miscoding with diagnoses and procedural codes and possible underreporting of amyloidosis cases in the NIS database. This may have led to underreporting or over reporting cases of cardiac amyloidosis and the different amyloid types (AL, ATTR) types may have been underreported if appropriate workup to delineate type was not performed. Also, regarding renal failure, a fraction of patients might have had preexistent ESRD at the time of hospitalization unrelated to Amyloidosis which may inflate renal failure prevalence. With regard to ATTR, a history of hypertension may not be apparent in the data set at the time of hospitalization because of orthostasis related to neuropathy or progression of heart failure with volume depletion and may have been underreported. Of note, the large AL/ATTR (-) category likely includes some AL and ATTR+ patients related to administrative data coding issues as well as inadequate phenotyping and genotyping workup. Secondly, the NIS database is based on in-hospital outcomes and thus does not include data after discharge so long-term outcomes could not be assessed. Third, NIS collects data on encounters, and not individual patients, therefore patients may be represented more than once in case of repeated admissions. Fourth, the small number of patients for certain subgroups, such as with ATTR is a limitation and finally the study period was before the approval of tafamidis which may impact both hospitalization and outcomes. Hospitalization numbers and trends may likely change after 2018. Despite these limitations, our study provides useful information on the epidemiology of amyloidosis by race/ethnicity with nationally representative data utilizing the validated NIS database with a large sample size and analytical data with clinical and demographic information from across the US, allowing for greater power and generalization of data.

The NIS database has previously looked at other aspects of amyloidosis including coexisting atrial fibrillation and outcomes,[36] and overall increase in hospitalization.[37,38] Kichloo et al compared clinical outcomes for patients primarily admitted for atrial fibrillation/flutter with and without a secondary diagnosis of amyloidosis using the NIS database.[39] They reported that

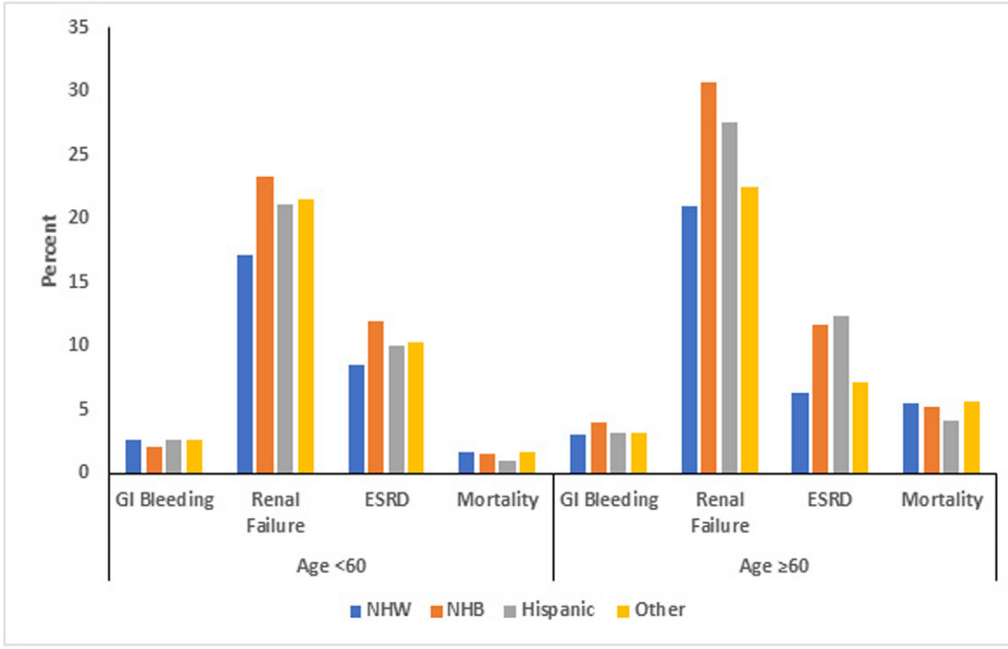

FIG. 1. Prevalence of GI bleeding, Renal failure, ESRD, and death in amyloidosis patients by ethnicity and age category
NHW = non-Hispanic white; NHB = non-Hispanic black GI = gastrointestinal; ESRD = end-stage renal disease.

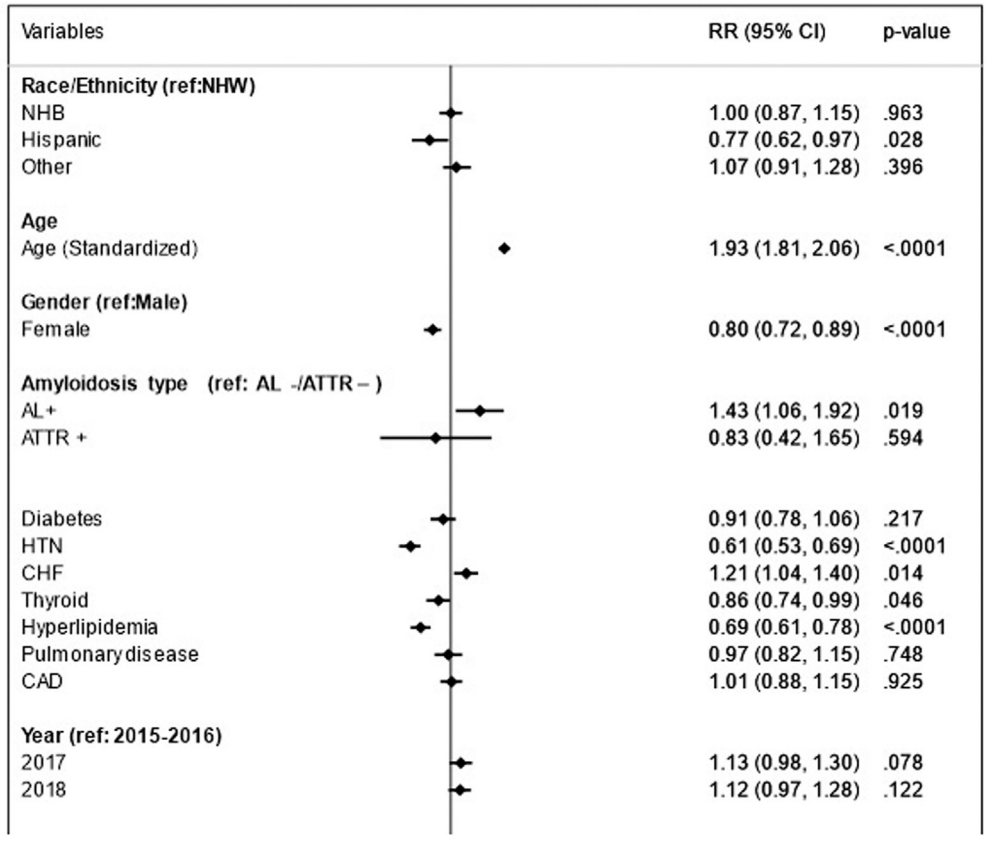

FIG. 2. Adjusted associations of ethnicity and amyloidosis type on mortality
RR = relative risk; CI = confidence interval; NHW = non-Hispanic white; NHB = non-Hispanic black AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; HTN = hypertension; CHF = congestive heart failure; CAD = coronary artery disease.

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.[39] Thakkar et al compared patient characteristics, outcomes, and hospitalization costs between cardiac amyloidosis patients with and without documented arrhythmias and reported that the primary outcome of all-cause mortality was significantly higher in cardiac amyloidosis patients with arrhythmia than without(13.9% vs 5.3%, p-value <0.001).[40] Oladarin et al assessed the prevalence, trends of hospitalization, and outcomes of cardiovascular manifestations in amyloidosis using the NIS database and showed that hospitalizations of amyloidosis have increased considerably over the past decades with a concurrent decline in in-hospital mortality.[41] However, despite this decline and after adjusting for other factors, amyloidosis hospitalization with cardiovascular manifestations was still associated with higher in-hospital mortality suggesting need for identifying amyloidosis in patients with cardiovascular manifestations.[41] Abe at al investigated the temporal trends in the prevalence and prognostic implication of atrial fibrillation in patient with light-chain cardiac amyloidosis (AL-CA) and reported that while acute on chronic heart failure was significantly higher in patients with AL-CA and AF, compared with those with AL-CA alone (55.6% vs. 48.3%; P < 0.0001), there was no difference in in-hospital mortality (7.5% vs. 7.5%; P = 0.9), stroke (2.0% vs. 2.5%; P = 0.5), median LOS (5 [3-9] vs. 5 [3-8]; P = 0.3), and median total hospital cost $42,469 ([$21,309-$92,855] vs. $44,008 [$22,889-$94,200]; P = 0.6) in patients with AL-CA and AF.[42] Isath et al evaluated the burden of arrhythmias in cardiac amyloidosis, their predictors, and impact on in-hospital outcomes and showed that cardiac arrhythmias are common in patients with cardiac amyloidosis and are associated with worse in-hospital outcomes, increased length of stay, and cost of hospitalization.[43] Another analysis from NIS data presented at American Society of Hematology meeting as an abstract reported disparities in AL amyloidosis care for black patients and Hispanics compared to white patients, noting lower utilization of palliative care services in blacks.[44] Of note, apart from the study by Abe et al,[42] none of the other studies using the NIS database characterized amyloidosis subtypes. Our study despite limitations of NIS database coding does provide some unique insight on characteristics of different amyloid phenotypes. Fig 1 and 2.

CONCLUSIONS

Our data adds to the existing literature highlighting significant heterogeneity in amyloidosis subtype, complications and clinical outcomes, including mortality, across race and ethnicity in amyloidosis. Understanding ethnic/racial characteristics and outcomes for patients with amyloidosis may help clinicians identify those at highest risk and target such individuals with aggressive therapies to improve outcomes. Of note, the large AL/ATTR (-) category likely includes some AL and ATTR+ patients related to both administrative data coding issues as well as possible inadequate phenotyping and genotyping workup. This highlights the need for clinicians to perform adequate work up to accurately identify type of amyloidosis since this has significant therapeutic implications. Amyloidosis often tends to be diagnosed late due to low prevalence, nonspecific presentation and lack of clinician awareness. Considering these associations may help in earlier clinical diagnosis and treatment, which may lead to better clinical outcomes and, in some cases, possible complete/prolonged remission.

CONFLICT OF INTEREST STATEMENT/ DISCLOSURES

The author has no financial or other conflicts of interest to disclose.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjms.2022.12.009.

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