

## ORIGINAL RESEARCH

# Amyloidosis and 30-Day Outcomes Among Patients With Heart Failure

## A Nationwide Readmissions Database Study



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## ABSTRACT

**BACKGROUND** The burden of amyloidosis among hospitalized patients is increasing over time. However, amyloidosis remains an underdiagnosed cause of heart failure (HF) hospitalization among older adults.

**OBJECTIVES** We investigated the prevalence and prognostic implications of amyloidosis among patients hospitalized with HF.

**METHODS** All hospitalizations for primary diagnosis of HF between January 1, 2010, and August 31, 2015, identified in the Nationwide Readmissions Database were categorized into those with and without a secondary diagnosis of amyloidosis. HF hospitalizations with amyloidosis were then matched in a 3:1 fashion to HF hospitalizations without amyloidosis using the year of admission, discharge quarter, age, sex, and Charlson comorbidity index. Primary outcomes were inpatient mortality and 30-day readmission. Multivariable logistic regression was used to estimate the association between HF with amyloidosis and clinical outcomes.

**RESULTS** Of 1,593,360 HF hospitalizations that met inclusion criteria, 2,846 (0.18%) had HF with a secondary diagnosis of amyloidosis and were matched to 8,515 hospitalizations for HF without amyloidosis. Hospitalizations for HF with amyloidosis were associated with higher prevalence of kidney disease (56% vs. 45%), malignancy (20% vs. 4%), and higher inpatient mortality (6% vs. 3%) as compared with HF without amyloidosis. In adjusted analyses, HF with amyloidosis was associated with higher odds of in-hospital mortality (odds ratio: 1.46; 95% confidence interval [CI]: 1.17 to 1.82), 30-day readmission (odds ratio: 1.17; 95% CI: 1.05 to 1.31), and longer mean length of stay (least-squares mean difference: 1.46; 95% CI: 1.12 to 1.80).

**CONCLUSIONS** In patients hospitalized with decompensated HF, presence of amyloidosis was associated with higher risk of inpatient mortality and 30-day readmission. (J Am Coll Cardiol CardioOnc 2020;2:710-8) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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Cardiac amyloidosis is associated with biventricular hypertrophy, conduction abnormalities, valvular disease, and heart failure (HF) (1,2). Recent studies have demonstrated that the prevalence of amyloidosis in patients with HF is higher than previously anticipated, with evidence of amyloidosis in 5% to 20% of patients with HF (3-6). Although previously thought to be incurable, recent advances in the diagnosis and treatment of cardiac amyloidosis now offer hope, particularly in light-chain amyloidosis (2,7,8) and transthyretin amyloidosis (ATTR) in both the acquired wild-type or hereditary variant forms (2,9-12). Several diagnostic techniques such as bone scintigraphy (13), speckle-tracking echocardiography, cardiac magnetic resonance, and T1 mapping techniques (14) are evolving and have contributed to greater recognition of this disease in clinical practice.

Our current understanding of the prevalence and prognostic implications of amyloidosis in patients with HF is largely based on small, single-center studies that have prospectively screened patients for amyloid deposition. These studies have either focused on the outpatient population or were underpowered to evaluate the impact of amyloidosis on clinical outcomes in patients with HF (4,5,15,16). In this study, we used a large national sample to estimate the prevalence of amyloidosis in decompensated HF and investigate its association with patient outcomes.

## METHODS

**STUDY DESIGN AND POPULATION.** Hospitalizations for HF were identified using the Nationwide Readmissions Database (NRD). The NRD is a constituent of the Healthcare Cost and Utilization Project family of health care databases developed through a federal-state-industry partnership and sponsored by the Agency for Healthcare Research and Quality. The NRD is an all-payer database that includes over 15 million discharges from 22 states and accounts for 51% of the total U.S. resident population and 49% of all U.S. hospitalizations (17). Importantly, the NRD contains verified patient linkage numbers, meaning patients can be tracked across hospitals within a state, each year, allowing capture of in-state readmissions. Healthcare Cost and Utilization Project datasets, including the NRD, conform to the

definition of a limited dataset and institutional board review is not required (18).

All hospitalizations with a primary diagnosis of HF (International Classification of Diseases-9th Revision-Clinical Modification [ICD-9-CM] 428 to 428.9) between January 1, 2010, and August 31, 2015, and were residents of the state were eligible for inclusion. For the present analysis, only the first HF hospitalization event for a particular patient within each year was included. Hospitalizations with discharges in December were excluded, as they were unable to have complete 30-day follow-up, given how the NRD assigns linked patient identification codes; similarly, hospitalizations from September 2015 were not included, as their 30-day follow-up period would include time after October 1, 2015, when ICD-10th Revision-Clinical Modification codes were implemented. Consistent with prior literature, secondary diagnoses for amyloidosis were identified using ICD-9-CM codes 277.3 to 277.39 (19-21). The ICD-9-CM codes for amyloidosis are not specific to the type of amyloidosis, and the data for the sensitivity and specificity of these codes are not yet available.

**STATISTICAL METHODS.** Hospitalizations of patients with HF and amyloidosis were matched to hospitalizations of patients with HF without amyloidosis using the year of admission, discharge quarter, age, sex, and Charlson comorbidity index (CCI). CCI was estimated using the Deyo et al. (22) coding scheme; however, HF was excluded when calculating scores (because all patients were required to have a primary diagnosis of HF to be included). HF hospitalizations with amyloidosis could be matched to more than 1 HF hospitalization event without amyloidosis. Up to 3 HF hospitalization matches were included in the final cohort; if >3 matches were identified, then 3 were randomly selected for inclusion. We chose traditional matching over propensity matching for the present analysis to evaluate the association between presence of amyloidosis with risk of adverse outcomes in patients with HF, given that the intent of the present analysis was not to estimate the causal effects of the observational data or the comparative effectiveness of therapeutic strategies. If no matches were identified, matching criteria were expanded to age  $\pm 2$  years and CCI  $\pm 1$  point.

## ABBREVIATIONS AND ACRONYMS

<b>ATTR</b>	= transthyretin amyloidosis
<b>CCI</b>	= Charlson comorbidity index
<b>CI</b>	= confidence interval
<b>CV</b>	= cardiovascular
<b>HF</b>	= heart failure
<b>ICD-9-CM</b>	= International Classification of Diseases-9th Revision-Clinical Modification
<b>LOS</b>	= length of stay
<b>NRD</b>	= Nationwide Readmissions Database
<b>OR</b>	= odds ratio

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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Primary outcomes of interest for our study were in-hospital mortality and the first readmission within 30-day follow up that were determined based on the NRD follow-up data. After a patient's HF hospitalization was identified, all hospitalizations with this patient's unique identifier in the same year were captured. The NRD assigns a timing variable to each patient, and subsequent hospitalizations that were within 30 days after the timing variable at index HF hospitalization discharge were retained. The secondary outcome of interest was the length of stay (LOS) during the index hospitalization. Baseline characteristics and outcomes across the matched cohorts (HF hospitalizations with vs. without a secondary diagnosis of amyloidosis) are displayed as median (interquartile range) for continuous variables and proportions for categorical variables. Standardized mean differences (SMDs) were used to compare the distribution of matched and unmatched characteristics across HF patients with and without amyloidosis. An absolute difference  $>0.20$  was considered meaningfully different.

Adjusted association between secondary diagnosis of amyloidosis among HF hospitalizations and the clinical outcomes of interest were assessed using multivariable logistic (for in-hospital mortality and 30-day readmission) and linear (for LOS) regression analysis. These models were adjusted for primary insurance type, median household income for the patient's zip code, secondary diagnoses of atrial fibrillation (ICD-9-CM 427.31 and 427.31), coronary artery disease (ICD-9-CM 414.00 to 414.07), hypertension (ICD-9-CM 401.0 to 405.99), obesity (ICD-9-CM 278.0 to 278.8), and hospital characteristics (teaching status, size). Generalized estimating equations were used to calculate standard errors after accounting for clustering by matched groups. Patients who died during their index hospitalization were excluded from readmission analyses. Readmission was further classified as cardiovascular (CV) related and non-CV-related readmissions using ICD-9-CM codes 390 to 459.9. Among hospitalizations with amyloidosis, CV readmissions were further categorized as HF, ischemic heart disease, cerebrovascular, dysrhythmia, and others, and non-CV readmission as those primarily due to amyloidosis, renal causes, bleeding, and infectious and other causes. Deaths outside of hospitalizations were not available and could not be used as a competing event when assessing readmissions. Model results are presented as odds ratio (OR) with 95% confidence interval (CI). A  $p$  value  $<0.05$  was used to determine statistical significance. Cumulative incidence function and log-rank test were used to assess and compare the

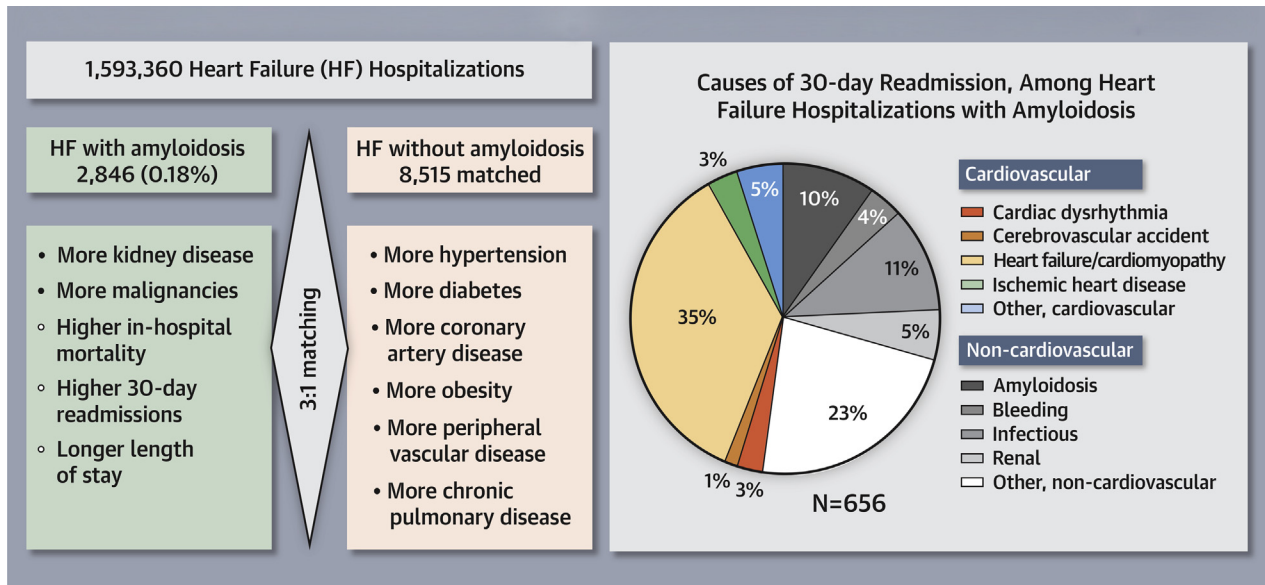
timing of 30-day readmission across the 2 groups. Poisson regression was used to assess temporal trends in patient outcomes; time (year of diagnosis) was treated as linear in these analyses. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

## RESULTS

There were 1,593,360 HF hospitalizations between 2010 and 2015 that met inclusion criteria, of which 2,846 (0.18%) had a secondary diagnosis of amyloidosis (**Central Illustration**). This approximated closely to the prevalence of coexisting diagnosis of amyloidosis and HF without respect to the position of these diagnoses in the cohort (0.15%). Baseline characteristics of all HF hospitalizations stratified by the secondary diagnosis of amyloidosis are described in **Table 1**. Of those, 2,834 ( $>99\%$ ) hospitalizations matched with at least 1 HF hospitalization on discharge quarter, exact age, sex, and exact CCI (median 143 [interquartile range: 1 to 2,563] matches). The 12 hospitalizations with amyloidosis that did not match were either for relatively young patients ( $<25$  years of age) or had high CCIs (range 6 to 12); however, after expanding matching criteria to age  $\pm 2$  years and CCI  $\pm 1$  point for those patients, all were able to be matched (median 7 [interquartile range: 2 to 31] matches).

After matching, 11,361 hospitalizations were included (2,846 HF with amyloidosis and 8,515 HF without amyloidosis hospitalizations), and  $>99\%$  ( $n = 2,833$ ) of HF with amyloidosis hospitalizations had 3 matches included. Among the matched hospitalizations, 63% were men and the median age was 75 (interquartile range: 66 to 82) years. HF with amyloidosis had a higher prevalence of malignancy (20% vs. 4%; SMD = 0.48), and kidney disease (56% vs. 45%; SMD = 0.22) compared with HF without amyloidosis. A total of 80% of malignancies in the HF with amyloidosis group were multiple myeloma, compared with only 9% in the HF alone group ( $p < 0.001$ ). The HF with amyloidosis group had a lower prevalence of chronic pulmonary disease (20% vs. 37%; SMD = -0.37), diabetes mellitus (26% vs. 46%; SMD = -0.42), history of myocardial infarction (8% vs. 14%; SMD = -0.22), peripheral vascular disease (5% vs. 11%; SMD = -0.21), coronary artery disease (32% vs. 51%; SMD = -0.39), hypertension (68% vs. 79%; SMD = -0.28), and obesity (8% vs. 19%; SMD = -0.31) but more commonly belonged to the highest income group (31% vs. 20%; SMD = 0.26) and were treated at teaching hospitals (70% vs. 48%; SMD = 0.45) (**Table 1**).

**CENTRAL ILLUSTRATION Association of Amyloidosis With In-Hospital and 30-Day Outcomes Among Patients Hospitalized with HF: An Analysis From the Nationwide Readmissions Database**



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Of 1,593,360 heart failure (HF) hospitalizations, 2,846 (0.18%) had HF with a secondary diagnosis of amyloidosis. Hospitalizations with HF and amyloidosis had a higher prevalence of renal disease and malignancy. Furthermore, HF with amyloidosis was associated with higher odds of in-hospital mortality, 30-day readmission, and a longer length of stay. HF was the most common primary readmission diagnosis in HF patients with amyloidosis.

In the entire matched cohort, there were 4% inpatient deaths, and 22% had a readmission event within 30-days post-discharge. In unadjusted analysis, HF hospitalization with (vs. without) secondary diagnosis of amyloidosis was associated with a 2-fold higher risk of inpatient mortality (6% vs. 3%;  $p < 0.001$ ). Thirty-day readmission was also higher following HF hospitalization with (vs. without) secondary diagnosis amyloidosis (24% vs. 21%;  $p < 0.001$ ), largely driven by differences in readmissions in the latter part of 30-day post-discharge follow-up period (log-rank test,  $p = 0.004$ ) (Figure 1). In the HF hospitalization with amyloidosis group, the readmission events related to CV versus non-CV-related causes were not significantly different (48% and 52%, respectively), with decompensated HF being the most common primary readmission diagnosis, constituting 35% of all readmissions (Figure 2). The rates of CV and non-CV-related readmissions were also comparable in the HF without amyloidosis group (51% vs. 49%) (Table 2). In temporal trends analysis, the risk of inpatient mortality and 30-day readmission did not change significantly over time during the study period for either HF hospitalizations with or without amyloidosis (Figure 3). For inpatient mortality and 30-day

readmission outcomes, the exponentiated regression coefficient for 1-year increase in time for HF hospitalizations without amyloidosis was 0.96 (95% CI: 0.89 to 1.03) and 1.00 (95% CI: 0.97 to 1.03) respectively. Similarly, the exponentiated regression coefficient for 1-year increase in time for HF hospitalizations with amyloidosis was 0.94 (95% CI: 0.86 to 1.03) for inpatient mortality and 0.98 (95% CI: 0.93 to 1.02) for 30-day readmission outcome. HF with amyloidosis had a longer median LOS (5 days vs. 4 days;  $p < 0.001$ ) (Table 2).

In adjusted analysis, HF hospitalization with (vs. without [reference group]) a secondary diagnosis of amyloidosis was significantly associated with a higher likelihood of inpatient mortality (OR: 1.46; 95% CI: 1.17 to 1.82) and 30-day readmission (OR: 1.17; 95% CI: 1.05 to 1.31). This was largely driven by a higher likelihood of readmission for non-CV causes (OR: 1.19; 95% CI: 1.03 to 1.38). In contrast, the likelihood of readmission for CV causes was not significantly different between the 2 groups (OR: 1.15; 95% CI: 1.00 to 1.34) (Table 2). The LOS was also significantly higher in HF hospitalizations with (vs. without [reference group]) a secondary diagnosis of amyloidosis (Table 2).

**TABLE 1** Baseline Characteristics of Patients Admitted With HF, Stratified by Presence or Absence of Amyloidosis

	HF With Amyloidosis (n = 2,846)	HF Without Amyloidosis		SMD*
		All Hospitalizations (N = 1,590,514)	Matched Hospitalizations (n = 8,515)	
<b>Matched characteristics</b>				
Male	1,792 (63)	799,551 (50)	5,360 (63)	0.0005
Age, yrs	75 (66-82)	76 (64-85)	75 (66-82)	0.004
CCI	2 (1-3)	2 (1-3)	2 (1-3)	0.009
<b>CCI component†</b>				
Cerebrovascular disease	80 (3)	45,456 (3)	239 (3)	0.0002
Chronic pulmonary disease	570 (20)	577,178 (36)	3,186 (37)	0.37
Diabetes mellitus	733 (26)	697,753 (44)	3,931 (46)	0.42
History of MI	226 (8)	214,573 (13)	1,203 (14)	0.22
Liver disease	84 (3)	30,838 (2)	175 (2)	0.07
Malignancy‡	561 (20)	70,154 (4)	368 (4)	0.48
Peripheral vascular disease	146 (5)	143,766 (9)	897 (11)	0.21
Renal disease	1,598 (56)	656,664 (41)	3,811 (45)	0.22
<b>Unmatched characteristics</b>				
<b>Primary insurance</b>				
Medicaid/Medicare	2,325 (82)	1,337,168 (85)	7,285 (86)	0.12
Private	432 (15)	167,087 (11)	844 (10)	0.17
Other/self-pay	79 (3)	78,278 (5)	349 (4)	0.07
<b>Median household income§</b>				
Low	705 (25)	501,014 (32)	2,649 (32)	0.17
Medium	597 (21)	392,249 (25)	2,084 (25)	0.08
High	635 (23)	364,308 (23)	2,002 (24)	0.01
Highest	866 (31)	310,209 (20)	1,649 (20)	0.26
<b>Other comorbidities</b>				
Atrial fibrillation	1,354 (48)	652,576 (41)	3,582 (42)	0.10
Coronary artery disease	910 (32)	745,027 (47)	4,365 (51)	0.39
Hypertension	1,921 (68)	1,246,316 (78)	6,728 (79)	0.28
Obesity	225 (8)	288,716 (18)	1,611 (19)	0.31
Elective admission	210 (7)	92,843 (6)	503 (6)	0.04
Teaching hospital	1,985 (70)	749,922 (47)	4,118 (48)	0.45
<b>Hospital bed size  </b>				
Small	312 (11)	205,767 (13)	1,100 (13)	0.05
Medium	603 (21)	427,331 (27)	2,323 (27)	0.14
Large	1,931 (68)	957,416 (60)	5,092 (60)	0.16

Values are n (%) or median (interquartile range). \*SMD comparing patients with amyloidosis with the matched cohort of those with only HF; an absolute difference in SMD >0.20 was considered meaningfully different. †Although hospitalizations were matched on CCI score, individual components were not specifically matched. ‡Includes diagnoses of nonmetastatic tumors, metastatic tumors, lymphoma, and leukemia; multiple myeloma was 80% of all cancer diagnoses in patients with amyloidosis, compared with only 9% in HF only ( $p < 0.001$ ). §Estimated median household income for the patient's zip code, stratified into quartiles each year. ||Hospital size is based on the number of hospital beds; cutpoints were chosen within each region and hospital type strata so that approximately one-third of hospitals would appear in each category.

CCI = Charlson comorbidity index; HF = heart failure; MI = myocardial infarction; SMD = standardized mean difference.

In sensitivity analysis with additional adjustment for the presence of multiple myeloma, the patterns of association between HF hospitalization with (vs. without [reference group]) amyloidosis and the likelihood of inpatient mortality and 30-day readmission were consistent with that observed in the

primary analysis (for inpatient mortality, OR: 1.30; 95% CI: 1.02 to 1.64; for 30-day readmission, OR: 1.13; 95% CI: 1.01 to 1.27). Furthermore, the association between HF hospitalization with (vs. without [reference group]) amyloidosis and short-term outcomes was not modified by the teaching status of the hospital ( $p$  interaction for inpatient mortality = 0.73;  $p$  interaction for 30-day readmission = 0.83).

## DISCUSSION

In this large multistate sample of HF hospitalizations in the United States, the estimated prevalence of a secondary diagnosis of amyloidosis was 0.18%. After matching for age, sex, and CCI, HF hospitalization with (vs. without) amyloidosis was associated with a higher prevalence of kidney disease and malignancy. HF hospitalization with (vs. without) amyloidosis was also associated with a higher likelihood of in-hospital mortality and 30-day readmission, largely driven by the higher rates of non-CV readmissions.

Prior studies have estimated the prevalence of ATTR amyloidosis in HF, as detected by imaging or myocardial biopsy, to be between 5% and 20% (3-6). In the present study, the overall prevalence of clinical diagnosis of amyloidosis among decompensated HF hospitalizations was significantly lower. Consistent with our observations, previous studies from administrative datasets have also demonstrated a markedly lower prevalence of amyloidosis in hospitalized patients (19-21). Our study adds to the existing literature by evaluating the burden and prognostic implications of amyloidosis in patients hospitalized with a primary diagnosis of HF. This is particularly relevant because HF is one of the key clinical manifestations of cardiac amyloidosis (19,21). The low prevalence of amyloidosis observed in large, contemporary cohorts of hospitalized patients in the United States is largely driven by underdiagnosis of amyloidosis in otherwise higher-risk patients and suggests a potential gap in detection in clinical practice. In a recent study, Gilstrap et al. (19) demonstrated that despite an overall low prevalence, the burden of coexisting amyloidosis and HF among hospitalized Medicare beneficiaries is increasing over time. Similarly, Sperry et al. (21) demonstrated a temporal increase in the diagnosis of HF among patients with amyloidosis. Future studies are needed to determine if the increase in the prevalence of HF with amyloidosis is related to increasing awareness and improving detection of the amyloidosis or is more reflective of an evolution of its natural epidemiology.

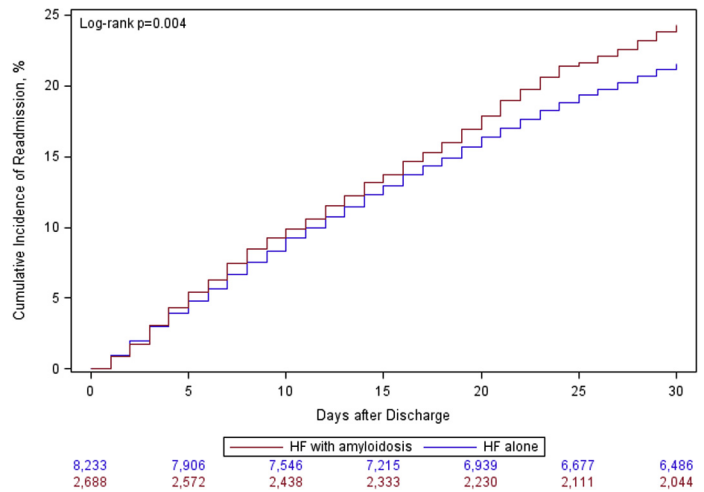
Consistent with prior literature, HF with amyloidosis had a higher prevalence of kidney disease and

cancer (23,24). We also observed a lower burden of chronic pulmonary disease as well as traditional HF risk factors such as hypertension, diabetes mellitus, coronary artery disease, peripheral vascular disease, and obesity in HF with amyloidosis. These findings suggest that the progression and development of HF in patients with amyloidosis may not be entirely driven by traditional HF risk factor-mediated pathways. Future studies are needed to understand the causal role of amyloidosis in the pathogenesis of HF.

We also observed that HF hospitalizations with (vs. without) amyloidosis were more prevalent at teaching hospitals and belong to the highest studied income group. Although it would be expected that patients with a rare diagnosis are more likely to receive care at teaching hospitals due to potential referral bias, these findings could also reflect the disparities in resource availability or diagnostic disparities due to awareness. It is plausible that patients hospitalized at teaching hospitals or with more resources to pursue specialized care are more likely to be diagnosed with amyloidosis. Geographic variability in amyloidosis mortality with greater reporting near amyloidosis centers has previously been observed, underscoring the possibility of underdiagnoses of amyloidosis in other areas (25). It is noteworthy that we found no differences in the association of a secondary diagnosis of amyloidosis with inpatient mortality or 30-day readmissions across the teaching or nonteaching hospitals. These findings suggest that care quality and outcomes associated with HF hospitalizations in patients with amyloidosis may not differ significantly between teaching versus nonteaching hospitals.

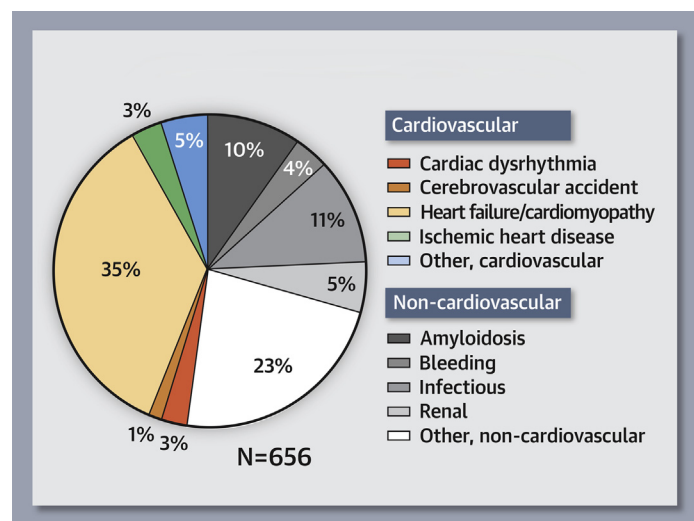
We observed that HF hospitalizations with (vs. without) amyloidosis were associated with significantly higher likelihood of inpatient mortality and 30-day readmission. This is largely consistent with the high morbidity and mortality associated with the presence of amyloidosis in other cohorts (21,26). The higher risk of adverse clinical outcomes in patients with HF and amyloidosis is particularly relevant in light of the effective therapies available for amyloid light-chain cardiac amyloidosis (7,27,28). Furthermore, newer therapies such as Tafamidis, a transthyretin-stabilizing molecule, was recently shown to significantly lower the risk of mortality and CV hospitalizations among patients with ATTR amyloid cardiomyopathy (9), and Patisiran has been shown to slow the progression of structural and functional abnormalities in patients with ATTR-hereditary subtype amyloidosis (12). Future studies

**FIGURE 1** Cumulative Event Rate of 30-Day Readmission Among Patients Admitted With HF, Stratified by Presence or Absence of Amyloidosis



The cumulative rate of readmission over the 30-day follow-up period was higher in the heart failure (HF) with amyloidosis group (24% vs. 21%;  $p < 0.001$ ) as determined by cumulative incidence function (log-rank test,  $p = 0.004$ ).

**FIGURE 2** Causes of 30-Day Readmission Among Heart Failure Hospitalizations With Amyloidosis



The proportion of readmissions related to cardiovascular versus noncardiovascular causes were similar (48% and 52%, respectively) in the heart failure with amyloidosis group. Heart failure was the most common primary readmission diagnosis, constituting 35% of all readmissions.

**TABLE 2** Incidence and Adjusted Patient Outcomes Associated With Hospitalizations for HF With Secondary Diagnosis of Amyloidosis Matched to HF Hospitalizations Without Amyloidosis Using the Year of Admission, Discharge Quarter, Age, Sex, and CCI

	Incidence		OR/LSM (95% CI)*	p Value
	Amyloidosis	No Amyloidosis		
Discharge disposition				
Routine/home health	2,169 (76)	6,579 (77)	1.00 (ref)	—
Transfer, short term	33 (1)	113 (1)	1.13 (0.75-1.69)†	0.57
Transfer, skilled facility	470 (17)	1,460 (17)	0.99 (0.88-1.12)†	0.93
Death	158 (6)	244 (3)	1.46 (1.17-1.82)†	<0.001
30-day readmission‡				
Any readmission	656 (24)	1,761 (21)	1.17 (1.05-1.31)†	0.005
CV related	313 (12)	898 (11)	1.15 (1.00-1.34)†	0.06
Non-CV related	343 (13)	863 (10)	1.19 (1.03-1.38)†	0.02
No readmission	2,032 (76)	6,754 (79)	1.00 (ref)	—
Length of stay, days	5 (3-9)	4 (2-6)	1.46 (1.12-1.80)§	<0.001

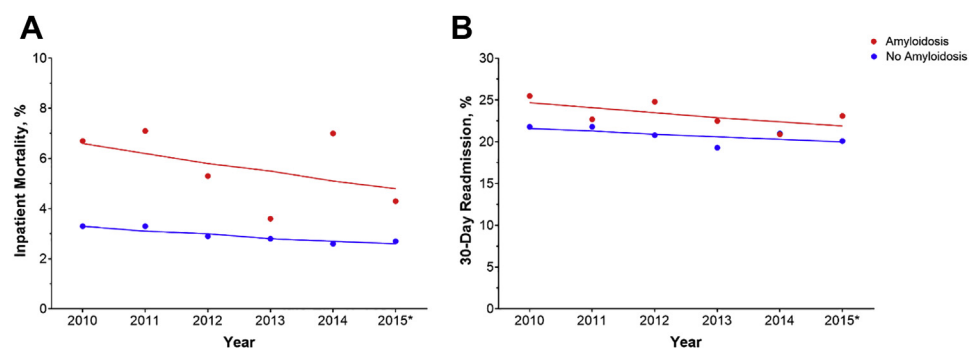
Values are n (%), unless otherwise indicated. \*Adjusted for primary insurance type, median household income for the patient's zip code, comorbidities not captured in the CCI (atrial fibrillation, coronary artery disease, hypertension, and obesity), hospital teaching status, and hospital size; length of stay was modeled using generalized linear regression. †OR. ‡Among hospitalizations resulting in patients being discharged alive only (n = 10,959). §LSM.

CI = confidence interval; CV = cardiovascular; LSM = least-squares mean difference; OR = odds ratio; other abbreviations as in Table 1.

focused on developing a multicomponent screening strategy that incorporates clinical risk assessment followed by evaluation for amyloidosis are needed to identify patients with HF who have subtypes that may benefit from these promising therapies for particular forms of amyloidosis (7,29,30).

**STUDY LIMITATIONS.** First, owing to the observational nature of our study design, there is potential for

residual confounding that may underlie the observed association between presence of amyloidosis and risk of adverse outcomes. Thus, our observations do not establish a causal association between amyloidosis and risk of adverse outcomes among patients with HF. Although we matched on CCI, the actual comorbidities in patients with and without amyloidosis were different; therefore, matching on CCI would not fully account for these differences and bias could exist if different comorbidities had different impacts on patient outcomes in HF. However, after adjusting for multiple myeloma, similar results were seen for inpatient mortality and 30-day readmission. Second, the NRD is a database of linked inpatient discharge records, so we were unable to capture mortality outside of hospitalizations and could not account for the competing risk of deaths outside of the hospitals when calculating readmissions. Third, we only evaluated the association between diagnosis of amyloidosis and risk of first hospitalization within 30 days. This is consistent with the rehospitalization outcome assessed in most claims-based studies and HF clinical trials. The competing risk of non-CV or CV hospitalization for the other type of hospitalization was not accounted for in this study. However, the rates of recurrent hospitalization within a 30-day period is low, and thus the competing risk would have a modest effect on the observed associations. Fourth, as only hospitalizations within the same state would be linked, we would have missed all readmissions that occurred outside of the state of index hospitalization. However, we restricted our cohort to those that were

**FIGURE 3** Trends in Inpatient Mortality and 30-Day Readmission in Heart Failure Hospitalizations, Stratified by Secondary Amyloidosis Diagnosis

\* Only includes hospitalizations between January and September 2015

The risk of (A) inpatient mortality and (B) 30-day readmission did not change significantly over time during the study period for either heart failure hospitalizations with or without amyloidosis. For inpatient mortality and 30-day readmission outcomes, the exponentiated regression coefficient for 1-year increase in time for heart failure hospitalizations without amyloidosis was 0.96 (95% confidence interval [CI]: 0.89 to 1.03) and 1.00 (95% CI: 0.97 to 1.03), respectively. The exponentiated regression coefficient for 1-year increase in time for heart failure hospitalizations with amyloidosis was 0.94 (95% CI: 0.86 to 1.03) for inpatient mortality and 0.98 (95% CI: 0.93 to 1.02) for 30-day readmission outcome. \*Only includes hospitalizations between January and September 2015.

residents of the state that they were initially treated in to minimize this limitation of the database. Fifth, we could not assess whether patients with HF and amyloidosis had amyloidosis with cardiac involvement or determine the type(s) or genetic mutations of amyloidosis, given how the diseases are captured in ICD-9-CM codes. Furthermore, lack of data on disease severity, both for amyloidosis (extent of multisystem involvement) and HF (ejection fraction, New York Heart Association functional class, cardiac biomarkers) as well as details of any treatment for both diseases precludes us from adjusting for those critical factors in the model as well. Sixth, there was also a potential for coding errors and differences in coding practices across the hospitals included in the database. Although the sensitivity and specificity of the ICD-9-CM codes for the diagnosis of amyloidosis are not available, the ICD-9-CM codes used to identify amyloidosis are consistent with those reported previously in the literature (19–21). Coding errors and missing codes could have caused us to underestimate the presence of amyloidosis and other comorbidities across the groups; however, we expect this misclassification (e.g., classifying HF with amyloidosis as HF alone due to the absence of an amyloidosis diagnosis from the discharge records) to bias results toward the null (i.e., no effect). Last, we were unable to study the effect of race or geographic location, as that information is not available in the NRD.

## CONCLUSIONS

In our analysis of HF hospitalizations from a large national U.S. database, a secondary diagnosis of amyloidosis was present in 0.18% and represents a cohort with a higher prevalence of kidney disease and cancer and a lower burden of traditional cardiovascular risk factors, compared with a cohort without amyloidosis. Furthermore, HF hospitalization with amyloidosis was associated with a significantly higher risk of inpatient mortality and 30-day readmission, highlighting the poor prognosis of this patient population. With the advent of new life-prolonging therapies for cardiac amyloidosis, these results emphasize the need to develop more effective screening strategies to facilitate early diagnosis of amyloidosis in HF patients.

## AUTHOR DISCLOSURES

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Hospitalizations for HF with amyloidosis are associated with higher inpatient mortality and 30-day readmissions than those without amyloidosis.

**TRANSLATIONAL OUTLOOK:** Future studies are needed to determine if recent advancements in therapies for amyloidosis may improve the clinical outcomes among these high-risk patients with HF and amyloidosis.

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