Increasing Rate of Hospital Admissions in Patients With Amyloidosis (from the National Inpatient Sample)

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Cardiac amyloidosis is an increasingly recognized cause of heart failure with preserved or mildly reduced ejection fraction with emerging treatment options. We sought to analyze the temporal trends and impact of hospital admissions in patients with amyloidosis. The National Inpatient Sample was queried to identify patients from 2005 to 2014 who were hospitalized with a diagnosis of amyloidosis using ICD9 codes. Trends over time of prevalence, demographics, co-morbidities, and outcomes were described. Propensity-matching was used to assess the impact of amyloidosis on in-hospital outcomes, including mortality. A total of 156,914 admissions in patients with amyloidosis (age 69.86 +/− 12.33 years, 45.7% female, 68.5% Caucasian) were identified. Hospitalizations more than doubled with a peak of 21,740 per year and 62 per 100,000 admissions in 2014. Over time, patients admitted with amyloidosis were older and more likely to have co-morbid medical conditions. A diagnosis of heart failure was present in 34.7% of patients, increased over time (p = 0.001), and was associated with further morbidity and mortality. In a propensity-matched analysis, patients admitted with amyloidosis had a longer length of stay (7.5 vs 6.2 days), were less likely to be discharged home (43.6% vs 48.7%), and were more likely to die during the hospitalization (7.4% vs 4.9%, p <0.001 for all). In conclusion, inpatient hospitalizations in the United States in patients with amyloidosis have increased over time and are associated with high morbidity and mortality, particularly when there is concomitant heart failure. **(Am J Cardiol 2019;124:1765−1769)**

Cardiac amyloidosis is an increasingly recognized cause of heart failure, often with preserved or mildly reduced ejection fraction. Cardiac involvement in amyloidosis primarily occurs as a result of deposition of one of 2 distinct proteins: immunoglobulin light chains (AL) or transthyretin (ATTR). In AL amyloidosis, clonal plasma cells secrete immunoglobulin light chains (kappa or lambda) which pathologically misfold and aggregate as amyloid fibrils. In ATTR, the wild-type or mutated transthyretin protein made in the liver dissociates into misfolded monomers, then oligomers, which then aggregate to form amyloid fibrils. Although there are some data regarding the incidence and prevalence of AL amyloidosis,[1,2] the estimates for ATTR are less certain. It is presumed that the incidence and prevalence of cardiac amyloidosis are increasing due to an increased awareness of the disease, improved noninvasive diagnostic imaging modalities,[3] and novel treatment options which improve symptoms, quality of life, and mortality.[4] However, the impact and temporal trends of hospital admissions in patients with amyloidosis are unclear. To address these gaps in knowledge, we sought to evaluate trends in hospitalizations and in-hospital mortality over time in patients with cardiac amyloidosis.

Methods

The National Inpatient Sample (NIS) is a publicly available database available online at https://www.distributor.hcup-us.ahrq.gov. Additional information on the data, analytic methods, and study materials are available from the corresponding author to support replication of the results. The NIS is a stratified sample of 20% of discharges from United States hospitals and includes almost 8 million hospital discharges per year. It represents more than 95% of the United States hospitalizations from 44 states participating in the Healthcare Cost and Utilization Project. To enable national estimates, discharge weights provided by the Agency for Healthcare Research and Quality were applied.[5] For this analysis, patients were included between 2005 and 2014.

The NIS was queried using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Baseline patient covariates were queried using Elixhauser co-morbidities to integrate covariates associated with in-hospital mortality and 30-day readmissions.[6] Codes 277.30 and 277.39 were used to capture patients with amyloidosis in the primary or secondary diagnosis fields. Additional ICD9 codes for the study are listed in the Supplemental Methods.

Categorical data are shown as frequencies and percents and were compared with the Cochran Armitage trend test across years of our study. Continuous data are presented as mean ± standard deviation and tested with linear trend tests. Because the NIS represents a random 20% sample of hospital discharges, we used the available weights to produce national

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estimates. Because the NIS went through a sampling change in 2012 from a clustered random sample to a completely random sample, we used the updated trend weights to mimic a consistent weighting scheme across the years. We then used the full NIS denominator to define amyloid admissions per 100,000 overall admissions. Next, to compare outcomes with the amyloid cohort, we performed propensity matching to other inpatient admissions in the same year and same hospital based on multiple covariates: age, sex, race, all 29 Elixhauser co-morbidity variables, history of pacemaker, and history of arrhythmia. From this matched cohort, we compared inpatient mortality and other outcome variables. Statistical analyses were performed using SAS 9.4 (Cary, North Carolina) with a p value of 0.05 marking statistical significance. The study was reviewed by the Institutional Review Board and approval was not required.

Results

Over the 10-year time period from 2005 through 2014, there were 156,914 total hospitalizations and 41 hospitalizations per 100,000 in patients with a diagnosis of amyloidosis; 45.7% of the patients admitted were female and 68.5% were Caucasian. Mean age was 69.86 +/− 13.22 years and 69.7% of patients had Medicare insurance. Patients were predominantly admitted to large (68.9%) and urban teaching (65.4%) hospitals. A diagnosis of heart failure was present in 34.7% of the overall cohort; other demographics and co-morbidities are listed in Table 1.

Trends in hospital admissions over time are seen in Figure 1. There was a more than doubling of the overall number of hospital admissions in patients with amyloidosis (from 9,296 in 2005 to 21,740 in 2014; p <0.001) and admissions for amyloidosis per 100,000 admissions (from 23.7 in 2005 to 61.5 in 2014; p <0.001) over the study period. The average age of patients admitted with amyloidosis increased from 65.9 to 71.1 years, along with the number with Medicare insurance (p <0.001 for both). Co-morbidities including anemia, chronic pulmonary disease, depression, diabetes, hypertension, hypothyroidism, electrolyte disorders, neuropathy, obesity, renal failure, and weight loss, all increased over time (p <0.001 for all).

A diagnosis of heart failure increased over time (from 30.3% in 2005 to 36.8% in 2014; p = 0.001). Multiple myeloma was present in 13.7% of patients and slightly decreased over time (p = 0.017). The prevalence of peripheral neuropathy, cardiac arrhythmia (both atrial and ventricular), heart block, and pulmonary hypertension also increased over time (p = 0.001, <0.001, and 0.004, respectively). A larger proportion of patients were admitted to urban teaching hospitals over time. The percentage of admissions for African Americans as well as those in the Southern states increased to a greater degree as compared with other populations.

In the overall cohort, 7.5% of patients died during hospitalization with no significant trend over time (p = 0.05, Table 2). Less patients with amyloidosis were discharged home over the course of the study period (p <0.001, Figure 2). Length of stay was 7.56 +/− 9.26 days and remained stable over time (p = 0.153). Patients with a diagnosis of amyloidosis who died or had a cardiac arrest in the hospital were more likely to be older and have co-morbid diagnoses of heart failure, coagulopathy, liver disease, fluid/electrolyte disturbances, weight loss, or arrhythmias (p <0.001 for all).

Patients with a concomitant diagnosis of heart failure were more likely to undergo right heart catheterization, endomyocardial biopsy, or have a pacemaker or defibrillator implanted during the hospitalization (p <0.001 for all). The rates of inpatient right heart catheterization and endomyocardial biopsy increased over time in the overall amyloidosis population (p <0.001 and 0.021, respectively). There were 209 patients who received heart transplantation. Patients with heart failure were less likely to be discharged home and more likely to die in the hospital (p <0.001 for both) than those without heart failure (Table 2).

The propensity matched analysis is found in the Supplemental Table and revealed excellent matching (standardized difference <11% for all covariates). Importantly, within these well-matched patients, those admitted with a diagnosis of amyloidosis were more likely to die during the hospitalization (7.4% vs 4.9%, p <0.001) as compared with patients without a concomitant diagnosis of amyloidosis. Patients with amyloidosis also had a longer length of stay (7.5 +/− 9.2 days vs 6.2 +/− 8.1 days, p <0.001) and were less likely to be discharged home (43.6% vs 48.7%, p <0.001).

Discussion

In this national, epidemiologic description of the trends and outcomes of admissions for patients with amyloidosis, there was a steady increase in hospital admissions in patients with amyloidosis over a 10-year period with now over 20,000 hospitalizations per year. Patients with amyloidosis were found to have a longer length of stay, a lower likelihood of being discharged home, and a greater likelihood of dying in the hospital as compared with a propensity-matched cohort without amyloidosis. Over the study period, patients admitted with amyloidosis were older and more likely to have co-morbid medical conditions. Concomitant amyloid-associated diagnoses such as heart failure, peripheral neuropathy, cardiac arrhythmia, and heart block also increased over time and the rates of admission increased for African American patients. A concomitant diagnosis of heart failure portended more co-morbidity and mortality.

Previous studies of the incidence and prevalence of amyloidosis are sparse. A monoclonal gammopathy of uncertain significance is the typical precursor of AL amyloidosis, which occurs in 3.2% of persons 50 years of age or older and 5.3% of persons 70 years of age or older.[7] The rate of progression of monoclonal gammopathy of uncertain significance to AL amyloidosis has been estimated at 1% per year,[8] yielding an incidence of 3000 to 5000 cases/year in the United States.[1,2,9] Regarding ATTR amyloidosis, the most common genetic variant in the United States is V122I which is estimated to be present in 3.5% of all African Americans and typically causes a cardiomyopathy.[10] Although there is variable penetrance, this puts nearly 1.7 million African American at risk for developing the disease. The global prevalence estimate of ATTR polyneuropathy is 10,000 to 40,000.[11] The true prevalence of wild type ATTR is unclear, though 25% of patients over 85 years old were found to have myocardial wild type TTR deposits at the time of autopsy.[12]

Table 1
Baseline variables

Variable	Overall cohort (n = 156,914)	Heart failure		p Value
		Yes (n = 54,428)	No (n = 102,485)	
Age, (years)	69.86 ± 13.22	71.36 ± 12.25	69.06 ± 13.64	<0.001
Women	45.7%	41.2%	48.0%	<0.001
White*	68.5%	62.6%	71.6%	<0.001
Black*	19.5%	27.1%	15.4%	
Primary insurance				
Medicare	69.7%	71.8%	68.6%	<0.001
Medicaid	5.6%	5.6%	5.6%	
Private	21.3%	19.7%	22.2%	
Median household income national quartile of patient's ZIP Code				
1	23.1%	24.5%	22.4%	<0.001
2	23.0%	22.7%	23.2%	
3	25.0%	24.7%	25.2%	
4	28.8%	28.1%	29.1%	
Bed size of hospital				
Small	10.3%	10.9%	9.9%	0.245
Medium	20.9%	20.3%	21.2%	
Large	68.9%	68.8%	68.9%	
Location/teaching status of hospital				
Rural	6.6%	6.9%	6.5%	0.919
Urban nonteaching	28.0%	27.5%	28.2%	
Urban teaching	65.4%	65.6%	65.3%	
Region of hospital				
Northeast	25.6%	26.6%	25.1%	<0.001
Midwest	23.7%	25.5%	22.7%	
South	31.1%	30.5%	31.4%	
West	19.6%	17.4%	20.7%	
Non-AHRQ comorbidities				
Multiple myeloma	13.7%	17.0%	11.9%	<0.001
Pulmonary hypertension	6.4%	14.0%	2.3%	<0.001
Pacemaker	3.7%	6.1%	2.4%	<0.001
Defibrillator	2.2%	4.8%	0.8%	<0.001
Arrhythmia	31.3%	49.3%	21.7%	<0.001
AHRQ comorbidities†				
Deficiency anemias	26.4%	30.3%	24.4%	<0.001
Chronic blood loss anemia	1.1%	1.1%	1.1%	0.571
Chronic pulmonary disease	15.1%	19.9%	12.6%	<0.001
Coagulopathy	10.3%	11.8%	9.4%	<0.001
Depression	9.6%	8.0%	10.4%	<0.001
Diabetes, uncomplicated	14.8%	15.7%	14.3%	0.001
Diabetes with complications	4.1%	5.4%	3.4%	<0.001
Hypertension	58.6%	55.7%	60.1%	<0.001
Hypothyroidism	14.7%	15.8%	14.1%	<0.001
Liver disease	4.2%	4.4%	4.1%	0.101
Lymphoma	13.5%	17.2%	11.6%	<0.001
Fluid and electrolyte disorders	35.2%	39.1%	33.1%	<0.001
Other neurological disorders	8.5%	6.5%	9.5%	<0.001
Obesity	4.7%	5.7%	4.2%	<0.001
Peripheral vascular disorders	5.7%	6.6%	5.2%	<0.001
Pulmonary circulation disorders	4.6%	8.1%	2.7%	<0.001
Renal failure	34.7%	46.4%	28.5%	<0.001
Valvular disease	6.8%	9.6%	5.3%	<0.001
Weight loss	9.5%	10.1%	9.2%	0.009

AHRQ = Agency for Healthcare Research and Quality.

* Of the 88% of patients who identified race in the cohort.

† AHRQ variables for acquired immunodeficiency syndrome, alcohol abuse, rheumatoid arthritis, drug abuse, metastatic cancer, paralysis, psychoses, solid tumor without metastases, and peptic ulcer disease were removed from the table but included in the propensity match.

The explanation for the more than doubling of the rate of hospitalization in those with amyloidosis is likely multifaceted. One possibility is that the incidence and prevalence of amyloidosis are increasing due to a growing awareness of the disease, in part driven by new and evolving diagnostic testing[3] and treatments.[4] Alternatively, the aging of the population may contribute to these observed trends. The increasing prevalence of patients in southern states and in

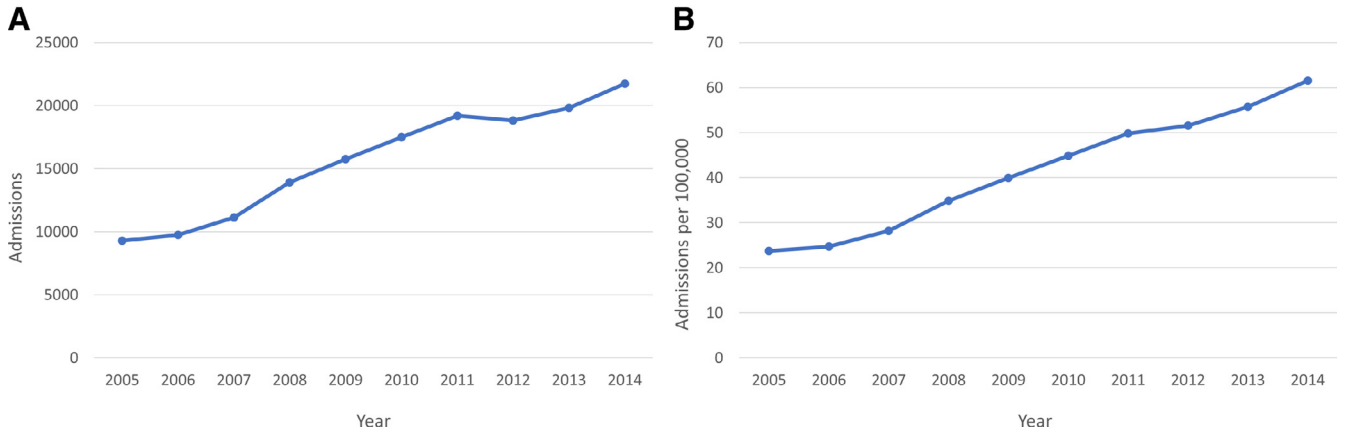

Figure 1. Overall admissions and admissions per 100,000 for amyloidosis. Overall admissions (*A*) and admissions per 100,000 admissions (*B*) in patients with amyloidosis have increased over time.

Table 2
Outcomes

Variable	Overall cohort (n = 156,914)	Heart failure		p Value
		Yes (n = 54,428)	No (n = 102,485)	
Cardiac arrest during hospitalization	1.3%	2.2%	0.8%	<0.001
Length of stay	7.56 ± 9.26	8.03 ± 9.92	7.31 ± 8.88	< 0.001
Disposition of patient				
Routine	43.5%	42.1%	44.2%	<0.001
Transfer to Short Term Hospital	3.3%	3.3%	3.2%	
Transfer to Skilled Nursing Facility	27.0%	22.0%	29.7%	
Home health care	18.2%	23.1%	15.6%	
Died during hospitalization	7.5%	9.0%	6.6%	

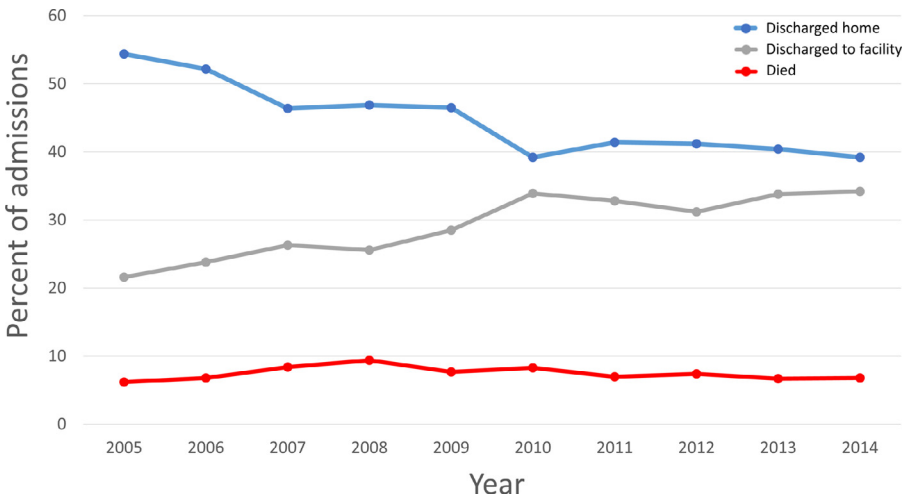

Figure 2. Disposition after hospitalization. Disposition of patients with amyloidosis after hospitalization. Discharges home decreased from 54.4% to 39.2% from 2005 to 2014 (*blue line*). Discharge to a facility increased over this time period from 21.6% to 34.2% (*gray line*), and inpatient death remained stable from 6.2% to 6.8% (*red line*). (Color version of figure is available online.)

African Americans likely reflects the identification of patients with hereditary ATTR amyloidosis from the V122I mutation which is found in 3% to 4% of the African American population.[10]

Unfortunately, it is not possible to differentiate AL versus ATTR amyloidosis in the NIS. However, it seems likely that ATTR is contributing to this trend given the increase in older patients and African Americans over time with a decrease in concomitant multiple myeloma. Moreover, AL amyloidosis has shown a fairly stable diagnosis rate over the past 7 decades,[1] while the prevalence has increased (from 15.5 to 40.5 cases per million), likely due to patients living longer with the disease.[2] Additionally, the trend of outpatient initiation of therapy for multiple myeloma suggests that this increase in hospitalization is more driven by ATTR.

The relatively stable inpatient mortality noted in this study is in contrast to the increase in overall age-adjusted mortality detailed in a study using the National Vital Statistics System over a longer time period from 1970 to 2015.[13] That study noted the highest mortality rates in African American patients. Interestingly, the lowest mortality for amyloidosis was noted in southern states which have higher African American populations, potentially due to underdiagnosis.

The co-morbidities seen in this study shed light onto the inpatient population of patients with amyloidosis. Organ failure that may be attributed to amyloidosis was most prevalent in the heart and kidneys, with concomitant diagnoses of heart failure and renal failure each being found in a third of the cohort. Neurologic disorders were less common (8.5%). Data regarding orthopedic manifestations of amyloidosis (carpal tunnel syndrome, biceps tendon rupture, trigger finger, and spinal stenosis[14]) are not typically documented with ICD9 codes for inpatients and were not included in this analysis. Interestingly, hypertension was noted in 58% of patients. The classic teaching is that patients with cardiac amyloidosis have an increased left ventricular wall thickness without a diagnosis of hypertension. It is important to recognize that a concomitant diagnosis of hypertension should not dissuade the provider from considering amyloidosis.

There are a broad spectrum of treatment options for AL amyloidosis[15,16] and an emerging foundation of treatments for ATTR.[4] In addition, novel treatments for both diseases are on the horizon in preclinical and clinical trials. Understanding the prevalence and temporal trends in amyloidosis can serve as a foundation for improved diagnostic algorithms and better strategies to offer treatment to those patients most likely to benefit.

As with all NIS studies, administrative data is limited due to the accuracy of coding and potentially lacks some clinically-important details. A second limitation is that ICD9 codes cannot specify which type of amyloidosis is present (i.e., AL or ATTR), limiting the epidemiologic analysis of the true prevalence and specification of the disease subtypes using such data sets. The NIS is not reliable enough over the study period to quantify what percentage of hospitalization was for amyloidosis as the primary problem versus a secondary co-morbidity. Additionally, classification of disease acuity in ICD9 codes (i.e., acute systolic heart failure versus congestive heart failure not otherwise specified) was not included in this analysis as the definitions and incentives related to these coding patterns changed over the study period.

In conclusion, inpatient hospitalizations in the United States for patients with amyloidosis have increased over time and now number over 20,000 per year. In recent years, patients admitted with amyloidosis are more likely to be older, have more co-morbid conditions including heart failure, and be discharged to facilities or with home health. Patients with amyloidosis were found to have a longer length of stay, lower likelihood of being discharged home, and higher likelihood of dying in the hospital as compared with a matched cohort without amyloidosis. A concomitant diagnosis of heart failure is associated with more co-morbidity and mortality. Given the increasing prevalence of hospitalizations in patients with amyloidosis, enhanced diagnostic and treatment options have the potential to improve care for a growing population of patients.

Disclosures

BWS is a consultant for Alnylam. MH has served on the advisory board for Pfizer, Alnylam, Akcea, and Eidos.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.08.045.

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