Research Article

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In-hospital mortality in amyloid light chain amyloidosis: analysis of the Premier Healthcare Database

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Aim: Describe the clinical and economic burden of hospitalizations for amyloid light chain (AL) amyloidosis. **Materials & methods:** This retrospective analysis used nationally representative hospital discharge data (2017–2020) to report discharge status, resource use and costs for hospitalizations among patients with AL amyloidosis. **Results:** Of 1341 patients identified, 92% were discharged alive and 8% experienced in-hospital death. Compared with the average US hospital stay during 2017–2019 (4.7 days, mean costs of $13,046 and mean charges of $54,496), hospital stays for AL amyloidosis were longer and costlier (9.7 days, $27,098.61, $111,233.91), especially in patients with in-hospital death (12.2 days, $44,966, $182,338.18). **Conclusion:** AL amyloidosis is associated with significant clinical and economic burden.

Plain language summary:

What is this article about?: Delayed amyloid light chain (AL) amyloidosis diagnosis is common and associated with poor prognosis and increased healthcare utilization and costs due to disease progression. The study objective was to examine mortality, hospitalization and associated costs.

What were the results?: About 8% of patients hospitalized with amyloid light chain (AL) amyloidosis died in the hospital, of these, 80% had both cardiac and renal involvement versus 54% of patients discharged alive. Compared with the average US hospital stay, the average AL amyloidosis hospitalization is twice as costly and for individuals who died in hospital it is three-times as much.

What do the results of the study mean?: Results suggest that there is still a need for increased awareness of the disease, which may lead to earlier treatment and reduced costs.

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Keywords: AL amyloidosis • hospitalization • mortality

Systemic amyloid light chain (AL) amyloidosis is a rare, progressive and fatal disease where clonal plasma cells overproduce light chain proteins that misfold, aggregate and deposit as amyloid in vital organs [1–4]. It is the most common and severe form of systemic amyloidosis [1]. Diagnosis of this condition is complicated since there is no solitary diagnostic test value [5]. Furthermore, as multiple organs (e.g., kidney, heart and liver) can be impacted by amyloid accumulation, diagnosis is often delayed due to overlapping symptoms that mimic common conditions [1–3,5–9].

Survival is poor with disease progression, as most organ damage is irreversible, and mortality is primarily driven by cardiac failure [1–3,5–8,10]. The goal of treatment is to recover organ function by targeting the abnormal plasma cell clone as quickly as possible, with most regimens derived from those used to treat multiple myeloma [6,11]. Untreated, survival is less than 1 year [1,2,5,6,8]. And while overall survival has improved with increasing disease awareness and number of treatment options and clinical advents [6,10,12], mortality is still high among patients with AL amyloidosis, especially among subpopulations such as older adults and patients with Mayo stage 4 disease [10,12].

Poor prognosis further hindered by delayed diagnosis makes AL amyloidosis especially burdensome both clinically and economically. Previous studies have examined healthcare utilization and costs among patients with AL amyloidosis, but available information is still limited [13]. Past studies are based on data from individual treatment centers (rather than nationally representative data) or utilize older real-world data and had to rely on algorithms to identify patients with AL amyloidosis rather than the more recently introduced (2017) AL amyloidosis-specific International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) diagnosis code (E85.81) [13–16]. To add to the limited research on disease and economic burden among patients with AL amyloidosis, we used a nationally, representative claims database and specific AL amyloidosis coding to examine mortality, hospitalization and associated costs.

Materials & methods

This was a retrospective claims analysis of the Premier® Healthcare Database (PHD) (Premier, Inc., NC, USA). Premier contains complete clinical coding, hospital cost and patient billing data from more than 1041 hospitals throughout the USA. The database covers 25% of US hospital discharges. Data are at the admission level, and patients admitted more than once are considered separate admissions. In this study, the terms admission and patient are used interchangeably for simplicity. Both charge and cost data are available for each hospitalization. Charges are amounts billed to the payer. In contrast, costs represent payment for services and include variable expenses (those related directly to the activity of the relevant department such as supplies and direct patient care) and fixed expenses (including depreciation, management, repair and maintenance and overhead). Costs are reported by Premier based on a combination of information from individual hospital cost-accounting systems and calculations using Medicare costs to charges ratios. Reported costs do not include professional fees for services by physicians and other independent practitioners [17]. Premier data are deidentified, compliant with the Health Insurance Portability and Accountability Act (HIPAA) and consistent with 45 CFR 46.101(b)(4) making it exempt from Institutional Review Board oversight.

Adult patients with AL amyloidosis were identified by the presence of at least one inpatient claim for AL amyloidosis (ICD-10-CM diagnosis code: E85.81) in any diagnosis field during the study period (1 October 2017–31 December 2020). This period was selected because the specific code for AL amyloidosis (ICD-10-CM: E85.81) was not available until 1 October 2017. If patients had multiple qualified inpatients claims during the study period, only the first hospitalization was included.

Of the above identified patients, those having any of the following diseases during the same hospitalization(s) were excluded if they had a diagnosis for other types of amyloidosis (ICD-10-CM codes: E85.0x-E85.3x), chronic inflammatory disease (e.g., rheumatoid arthritis [ICD-10-CM: M05.40-M06.9]), inflammatory bowel diseases (Crohn's disease [ICD-10-CM: K50.xx], ulcerative colitis [ICD-10-CM: K51.xx]), bronchiectasis (ICD-10-CM: J47.xx, Q33.4) or chronic osteomyelitis (ICD-10-CM: A02.24, H05.02x; M86.xx).

Demographic characteristics, comorbidities (e.g., Charlson Comorbidity Index [CCI]) and admission characteristics, including admission type, most frequent admitting or primary diagnoses, severity of disease (all patient refined diagnosis related groups [APR-DRG] severity of illness: minor, moderate, major, extreme), cardiac or renal involvement (calculated based on presence of relevant diagnostic codes) and discharge status, were measured. Healthcare utilization (e.g., length of stay [LOS], emergency department visits, in-patient services) and costs were also measured. All costs were inflated to 2020 USD using the medical care component of the Consumer Price Index [18]. Utilization measures were identified based on diagnosis and procedure codes while cost measures were based on hospital billing records. Total hospital associated costs included the total cost to treat the patient during the hospital encounter (e.g., supplies, labor, depreciation of equipment), as well as variable and fixed expenses. Variable expenses included expenses that relate directly to or vary with the activity (volume) of the department (e.g., supplies and hands on patient care); fixed expenses included those that do not relate directly to or vary with the activity (volume) of the department (e.g., depreciation, management, repair and maintenance and overhead). The total costs did not include professional fees for the services received in hospitals by physicians and other skilled healthcare professionals licensed for independent practice.

Patients were stratified between those with an in-hospital death and those discharged alive. Descriptive statistics including mean, standard deviations (SD) and relative frequencies and percentages for continuous and categorical data, respectively, were reported. To compare between diagnostic versus other hospitalizations, t-test and χ^2 (or exact χ^2) test were performed for continuous and categorical variables, respectively. The exact χ^2 test was used

Table 1. Demographics of hospitalized amyloid light chain amyloidosis patients, stratified by discharge status.

	Discharge status		Adult AL amyloidosis patients n (%) = 1341 (100%)	p-value
	In-hospital death n (%) = 107 (8.0%)	Discharged alive n (%) = 1234 (92.0%)		
Age, years, mean (SD) [median]	66.4 (10.1) [67]	67.3 (11.3) [68]	67.2 (11.2) [68]	0.441
Age group, years, n (%)				0.511
18–34	0 (0)	7 (0.6)	7 (0.5)	
35–54	12 (11.2)	151 (12.2)	163 (12.2)	
55–64	34 (31.8)	319 (25.9)	353 (26.3)	
65 or older	61 (57.0)	757 (61.3)	818 (61.0)	
Female, n (%)	45 (42.1)	547 (44.3)	592 (44.1)	0.650
Race, n (%)				0.965
White	67 (62.6)	795 (64.4)	862 (64.3)	
African–American	26 (24.3)	280 (22.7)	306 (22.8)	
Other	9 (8.4)	115 (9.3)	124 (9.2)	
Asian	2 (1.9)	17 (1.4)	19 (1.4)	
Unable to determine	3 (2.8)	27 (2.2)	30 (2.2)	
Primary payer type, n (%)				0.051
Medicare	60 (56.1)	777 (63.0)	837 (62.4)	
Medicaid	12 (11.2)	116 (9.4)	128 (9.5)	
Commercial	12 (11.2)	88 (7.1)	100 (7.5)	
Self-pay	4 (3.7)	11 (0.9)	15 (1.1)	
Managed care	17 (15.9)	202 (16.4)	219 (16.3)	
Other	2 (1.9)	40 (3.2)	42 (3.1)	
Year of hospitalization, n (%)				0.860
2017[†]	5 (4.7)	75 (6.1)	80 (6.0)	
2018	33 (30.8)	352 (28.5)	385 (28.7)	
2019	35 (32.7)	434 (35.2)	469 (35.0)	
2020	34 (31.8)	373 (30.2)	407 (30.4)	

[†]ICD-10-CM code E85.81 for light chain (AL) amyloidosis was not available until 1 October 2017.
AL: Systemic amyloid light chain; SD: Standard deviation.

Table 2. Charlson Comorbidity Index, stratified by discharge status.

	Discharge status		Adult AL amyloidosis patients n (%) = 1341 (100%)	p-value
	In-hospital death n (%) = 107 (8.0%)	Discharged alive n (%) = 1234 (92.0%)		
Charlson Comorbidity Index, mean (SD) [median]	4.5 (2.2) [4]	3.9 (2.3) [4]	3.9 (2.3) [4]	0.008

AL: Systemic amyloid light chain; SD: Standard deviation.

when one of the cell counts was less than 5. All data transformations and statistical analyses were performed using SAS© version 9.4 (SAS Institute Inc., NC, USA).

Results

Among the 1419 adult patients with a diagnosis of AL amyloidosis between 1 October 2017 and 31 December 2020, 60 were excluded for having a diagnosis code for another type of amyloidosis and 18 for having a diagnosis code for a chronic inflammatory disease, which left a final sample of 1341. Table 1 provides demographic characteristics for the study cohort. The mean (SD) age of the overall sample was 67.2 (11.2) years, with the majority of patients being 65 years or older in age (61%), 44.1% were female, 64.3% were White and Medicare was the primary payer type (62.4%). Patients were quite ill with a mean CCI score of 3.9 and APR-DRG severity of illness classification of major (56.9%) or extreme (27.5%) (Table 2). Hospitalizations were primarily urgent/emergent (87.6%) and occurred in the South (42.1%) and in teaching hospitals (62.4%) (Table 3). The main source of admission was

Table 3. Hospital characteristics, stratified by discharge status.

	Discharge status		Adult AL amyloidosis patients n (%) = 1341 (100%)	p-value
	In-hospital death n (%) = 107 (8.0%)	Discharged alive n (%) = 1234 (92.0%)		
Admission type, n (%)				<0.001
Elective	1 (0.9)	165 (13.4)	166 (12.4)	
Urgent/emergent	106 (99.1)	1069 (86.6)	1175 (87.6)	
Hospital region, n (%)				0.379
Northeast	29 (27.1)	272 (22.0)	301 (22.4)	
Midwest	20 (18.7)	305 (24.7)	325 (24.2)	
West	14 (13.1)	137 (11.1)	151 (11.3)	
South	44 (41.1)	520 (42.1)	564 (42.1)	
Hospital type, n (%)				0.504
Teaching	70 (65.4)	767 (62.2)	837 (62.4)	
Non teaching	37 (34.6)	467 (37.8)	504 (37.6)	
Hospital location, n (%)				0.883
Rural	9 (8.4)	109 (8.8)	118 (8.8)	
Urban	98 (91.6)	1125 (91.2)	1223 (91.2)	
Hospital bed size, n (%)				0.022
0–199	11 (10.3)	142 (11.5)	153 (11.4)	
200–499	30 (28.0)	498 (40.4)	528 (39.4)	
500+	66 (61.7)	594 (48.1)	660 (49.2)	
Admission source, n (%)				<0.001
Clinic	7 (6.5)	158 (12.8)	165 (12.3)	
Nonhealthcare facility	71 (66.4)	929 (75.3)	1000 (74.6)	
Transfer from hospital, SNF or other facility	29 (27.1)	139 (11.3)	168 (12.5)	
Other	0 (0)	8 (0.6)	8 (0.6)	

AL: Systemic amyloid light chain; SD: Standard deviation; SNF: Skilled nursing facility.

nonhealthcare facilities (74.6%). Most patients were discharged home or home with nursing care (66.4%) (Table 3) and had an overall LOS of 9.7 days (Table 4).

Of the 1341 patients, 8% had an in-hospital death (defined as discharge status of death) (Table 4). Demographic characteristics (age, gender, race, primary payer type) for this subgroup were similar to the overall cohort. Patients who died at the hospital had a higher comorbidity burden compared with those discharged alive (CCI: 4.5 vs 3.9; p = 0.008), as well as more severe disease on the APR-DRG scale (extreme: 77.6 vs 23.2%). Nearly 80% of patients who died in the hospital had an admission with cardiac or renal involvement compared with 50% of those discharged alive (Table 5). The most frequent admitting and primary diagnoses were similar between groups; however, sepsis was a frequent diagnosis only among those who died in the hospital (Table 5). Hematopoietic stem cell transplant was more frequent in patients discharged alive than in those who died in the hospital (6.4 vs 0.9%; p = 0.017).

For the overall cohort, mean (SD) total costs were $27,098.61 ($34,849.13) and total charges were $111,233.91 ($144,852.70) (Figure 1). In terms of resource use and costs, a significant difference was found between patients who died in the hospital and those discharged alive. The mean LOS was 12.2 days for patients who died in the hospital compared with 9.2 days for patients who were discharged alive (p = 0.024). Total costs and charges were also significantly higher among the first group when compared with the second ($44,965.97 [$60,813.82] vs $25,549.33 [$31,173.79]; p < 0.001) and $182,338.18 [$230,288.49] vs $105,068.46 [$133,293.58]; p = 0.001).

Discussion

While AL amyloidosis is the most common form of systemic amyloidosis, little is known about the economic burden associated with AL amyloidosis hospitalizations. The present study adds to the limited real-world data on hospital utilization and cost in AL amyloidosis, while also comparing these characteristics between patients with different outcomes post-hospitalization – those with an in-hospital death versus those discharged alive.

Table 4. Discharge status and healthcare utilization, stratified by discharge status.

	Discharge status		Adult AL amyloidosis patients n (%) = 1341 (100%)	p-value
	In-hospital death n (%) = 107 (8.0%)	Discharged alive n (%) = 1234 (92.0%)		
Discharge status, n (%)				n/a
Home or home with nursing care	0 (0)	891 (72.2)	891 (66.4)	
Transferred to hospice, rehabilitation center or nursing home	0 (0)	269 (21.8)	269 (20.1)	
Death during hospitalization	107 (100.0)	0 (0)	107 (8.0)	
Other/unknown	0 (0)	74 (6.0)	74 (5.5)	
Overall length of stay (days), mean (SD) (median)	12.2 (13.0) [9.0]	9.2 (9.4) [6.0]	9.5 (9.7) [6.0]	0.024
Intensive care unit (ICU),† n (%)	53 (49.5)	216 (17.5)	269 (20.1)	<0.001
Length of ICU stay among utilizers, mean (SD) (median)	7.2 (7.1) [5.0]	6.3 (7.8) [3.0]	6.5 (7.6) [3.0]	0.479
ED,† n (%)	74 (69.2)	841 (68.2)	915 (68.2)	0.830
Length of ED stay among utilizers, mean (SD) (median)	1.2 (0.9) [1.0]	1.3 (3.1) [1.0]	1.3 (3.0) [1.0]	0.581
Coronary care unit,† n (%)	15 (14.0)	43 (3.5)	58 (4.3)	<0.001
Length of coronary care unit stay among utilizers, mean (SD) (median)	7.5 (6.4) [6.0]	5.7 (4.6) [4.0]	6.1 (5.1) [4.5]	0.241
Oncology ward,† n (%)	3 (2.8)	72 (5.8)	75 (5.6)	0.191
Length of oncology ward stay among utilizers, mean (SD) (median)	2.3 (0.6) [2.0]	9.5 (9.4) [7.0]	9.3 (9.3) [7.0]	<0.001
Hospice,† n (%)	0 (0.0)	0 (0.0)	0 (0.0)	n/a

†Care units identified through hospital billing records, based on any charge for room and board.
AL: Systemic amyloid light chain; ED: Emergency department; ICU: Intensive care unit; SD: Standard deviation.

Table 5. Cardiac or renal involvement and most frequent diagnosis (admitting and primary), stratified by discharge status.

	Discharge status		Adult AL amyloidosis patients n (%) = 1341 (100%)	p-value
	In-hospital death n (%) = 107 (8.0%)	Discharged alive n (%) = 1234 (92.0%)		
Cardiac or renal involvement, n (Col%) (Row%)				<0.001
Cardiac and renal	85 (79.4) [11.6]	649 (52.6) [88.4]	734 (54.7) [100.0]	
Cardiac only	7 (6.5) [4.0]	169 (13.7) [96.0]	176 (13.1) [100.0]	
Renal only	13 (12.1) [4.2]	296 (24.0) [95.8]	309 (23.0) [100.0]	
No cardiac or renal involvement	2 (1.9) [1.6]	120 (9.7) [98.4]	122 (9.1) [100.0]	
Most frequent admitting diagnosis, by cohort, n (%)				
Unknown	8 (7.5)	125 (10.1)	–	–
Shortness of breath	10 (9.4)	98 (7.9)	–	–
Sepsis, unspecified organisms	9 (8.4)	–	–	–
Light chain (AL) amyloidosis	–	72 (5.8)	–	–
Acute kidney failure, unspecified	–	65 (5.3)	–	–
Most frequent primary diagnosis, by cohort, n (%)				–
Light chain (AL) amyloidosis	18 (16.8)	222 (18.0)	–	–
Sepsis, unspecified organisms	12 (11.2)	–	–	–
Hypertensive heart and CKD w/HF and stage 1–4 CKD or unspecified CKD	11 (10.3)	73 (5.9)	–	–
Acute kidney failure, unspecified	6 (5.6)	70 (5.7)	–	–
Organ-limited amyloidosis	6 (5.6)	–	–	–
MM not having achieved remission	–	67 (5.4)	–	–

AL: Systemic amyloid light chain; CKD: Chronic kidney disease; HF: Heart failure; MM: Multiple myeloma; SD: Standard deviation.

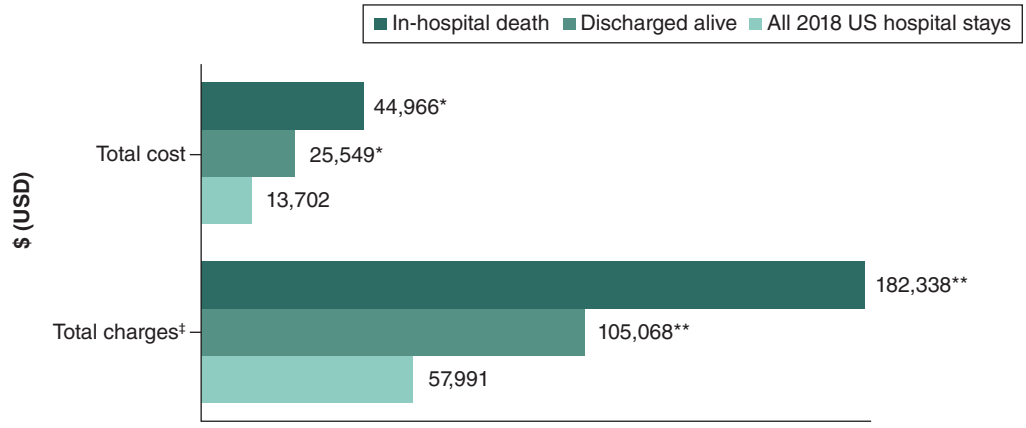

Figure 1. Hospital-associated costs† of in-hospital deaths, adjusted to 2020 USD.
†Total costs and charges do not include professional fees for the services received in hospitals by physicians and other skilled healthcare professionals licensed for independent practice.
‡Determined by the hospital billing records, not by procedure codes.
*$p < 0.001$.
**$p = 0.001$.

This retrospective analysis of hospital records found a mean cost of $27,099 for AL amyloidosis hospitalizations. In-hospital mortality among patients hospitalized with AL amyloidosis was 8%. Examining resource use and costs associated with AL amyloidosis hospitalizations by discharge status showed that patients who died in the hospital had higher costs and longer stays than those discharged alive ($44,966 vs $25,549; $p < 0.001$ and 12.2 vs 9.4 days; $p = 0.024$).

For additional context, the average US hospital stays during 2017–2019 had a mean cost of $13,046 and mean charge of $54,496, while its LOS was 4.7 days. Thus, the average AL amyloidosis hospitalization is twice as costly as the average US hospital stay. Furthermore, costs associated with stays for individuals who died during a hospitalization are three-times as much as the costs of the average US stay.

Past research has shown that cardiac and renal involvement is common in AL amyloidosis, with cardiac involvement being a primary driver of mortality in patients with AL amyloidosis [9,13,14,19,20]. We found that among the patients with AL amyloidosis who died in hospital, 80% had both cardiac and renal involvement compared with 53% of patients who were discharged alive. Costs related to end of life heart failure and renal disease are high in the general population [13], but have not been directly examined in AL amyloidosis. We did not stratify costs by cardiac and renal involvement, but this involvement is likely to have impacted the cost difference among patients with AL amyloidosis with an in-hospital death compared with those discharged alive.

As the specific diagnosis code for AL amyloidosis was not introduced until 2017, our results may not be directly comparable to prior research. A 2018 study using commercial insurance claims data from 2007–2015 estimated the LOS at 10.2 days and inpatient cost at just under $37,909 per year, but patients were identified through an algorithm that relied on a more general code plus the use of specific medications [15]. A 2019 study using the same database as the current study but focusing on cardiac amyloidosis from all subtypes found an average LOS of 8.3 days and a cost of $20,584 [14]. Similarly to our findings, a 2019 study of patients with amyloidosis in the 2005–2014 National Inpatient Sample found that hospitalized patients with amyloidosis had a longer LOS, lower likelihood of being discharged home, and higher likelihood of dying in the hospital compared with a matched cohort without amyloidosis [20]. Additionally, a concomitant diagnosis of heart failure was associated with more comorbidity and mortality [20].

Rates of hospital admissions in patients with amyloidosis are increasing [20], thus, characterizing hospitalizations and possibly identifying areas for cost savings and unmet need among this population is key for future research, as well as clinical management of AL amyloidosis. Diagnostic delay is still common for a number of reasons, including the overlapping and non specific nature of symptoms and lack of familiarity of the disease among patients and physicians, which leads to poorer outcomes and greater disease burden [7,9,21]. This was evident in our study as the majority of patients had emergency department visits (69.2% of patients with an in-hospital death and 68.2% of patients discharged alive). Patients who died in the hospital were also more likely to be seen in the ICU than those

discharged alive (49.5 vs 17.5%; $p < 0.001$). Untreated patients with AL amyloidosis and cardiac involvement have a median survival of less than 1 year [4,8,22]. In an analysis of survival trends and primary causes of death among a population of patients with AL amyloidosis, Staron *et al.* found that while survival rates among those with cardiac involvement had generally improved, in older patients (>70 years), this was not the case [12]. The mean age in our study was 67.2 years. Older patients had the highest rate of mortality due to factors such as poor tolerance to treatment and comorbidity burden along with multiorgan involvement, highlighting the need for earlier diagnosis in this population [7,12].

This study has several limitations. While the Premier database covers 25% of US hospital discharges, it does not include federally funded (e.g., US Department of Veterans Affairs) or closed panel health maintenance organization facilities. In addition, because it primarily includes information relevant to payment for services, miscoding is possible. Relying on diagnosis codes, rather than clinical information (e.g., lab values), did not allow us to use Mayo staging for disease severity or examine the impact on outcomes. This lack of lab values also hindered us from examining whether patients with in-hospital death had any lab markers that may have predicted cardiac involvement earlier or later in their clinical journey, timing of which could have impacted prognosis [4,10,23]. Additionally, all data pertained to only the hospital admission of interest. This, coupled with the fact that results were only descriptive, meant that we also did not examine any long-term factors, such as early or late diagnosis or healthcare journey prior to index, or control for differences between the stratified groups (patients with in-hospital death and patients discharged alive) that could have impacted outcomes.

Conclusion

This is the first real-world study to use an AL amyloidosis-specific ICD diagnostic code to characterize in-hospital mortality among patients with the disease. While all AL amyloidosis hospitalizations are associated with greater resource use and higher costs than the average US hospitalization, the clinical and economic burden is especially severe corresponding to AL amyloidosis patients who died during a hospitalization. Cardiac and renal involvement is found in a higher proportion of patients with AL amyloidosis who died in the hospital compared with those discharged alive. Adding to what little is known about the clinical and hospitalization characteristics among this population may increase awareness and knowledge of the disease, leading to earlier treatment and possibly reduced costs.

Summary points

- Diagnosing systematic amyloid light chain (AL) amyloidosis is challenging as there is no solitary diagnostic test to detect this disease and the condition is associated with symptoms that mimic common conditions.
- Delayed diagnosis impacts survival, as disease progression is associated with irreversible organ damage.
- This retrospective cohort study used 2017–2020 hospital discharge data from the Premier® Healthcare Database.
- Between 2017 and 2020, 1419 hospitalizations included at least one inpatient claim with a diagnosis for AL amyloidosis. After applying additional study criteria, the final sample included 1341 patients.
- Of the 1341 patients, 8% died in-hospital.
- Among those who died in the hospital, nearly 80% had an admission with cardiac or renal involvement compared with 50% of those discharged alive.
- Patients with an in-hospital death had longer hospital stays and higher total costs and charges compared with those discharged alive.
- Characterizing the hospitalizations and clinical outcomes of these patients may increase awareness of the disease and improve early diagnosis.

Financial & competing interests disclosure

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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