Short Communication

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Diagnostic amyloid light chain amyloidosis hospitalizations associated with high acuity and cost: analysis of the Premier Healthcare Database

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Aim: Estimate the frequency and costs of diagnostic admissions among hospitalized patients with amyloid light chain (AL) amyloidosis. **Materials & methods:** This retrospective analysis used nationally representative hospital discharge data from 2017 to 2020 to report resource use and cost for hospitalizations during which AL amyloidosis was diagnosed. **Results:** Of 1341 admissions, 17.6% were diagnostic. Bone marrow (79.5%) and kidney (44.9%) biopsies were the most common qualifying biopsies. Diagnostic hospitalizations had longer length of stay (14.5 vs 8.4 days; $p < 0.001$) and higher cost ($40,052 [USD] vs $24,360; $p < 0.001$) than nondiagnostic ones. **Conclusion:** Diagnostic admissions are more likely to be urgent/emergent, require longer stays and have higher costs compared with hospitalizations in known AL amyloidosis patients. Improved diagnostic pathways toward early diagnosis are needed.

Plain language summary: What is this article about? Diagnosing amyloid light chain (AL) amyloidosis is challenging and may occur during an acute admission, which may be resource intensive and costly. The objective of the study was to estimate the frequency of diagnostic admissions among hospitalized patients with AL amyloidosis and the associated healthcare utilization and costs. What were the results? About 17.6% of hospital admissions for patients with AL amyloidosis were identified as a diagnostic encounter. Patients with AL amyloidosis diagnosed in the hospital have longer hospital stays and higher costs than other AL amyloidosis hospitalizations. What do the results of the study mean? Results suggest that continued effort is needed to improve diagnostic pathways toward early diagnosis of this multisystem disease.

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Systemic amyloid light chain (AL) amyloidosis is a plasma cell disorder associated with multiorgan dysfunction secondary to insoluble fibril deposition into multiple organs (e.g., kidneys, liver, heart and nerves). It is the most common and severe type of systemic amyloidosis with an estimated 8–12 cases per million persons per year [1–3], approximately 30,000–45,000 patients live with AL amyloidosis in the USA and the EU [4]. As is true for many rare diseases, data on the cost of care for this condition is limited, both because of the small population size and because, in this disease specifically, until recently it did not have its own International Classification of Disease (ICD) code. In 2017; however, an International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code specific to AL amyloidosis was introduced, making it feasible to more accurately estimate cost and utilization using claims data.

We aimed to use this newly introduced code to add to estimates of the economic burden of the condition. In addition, diagnosing AL amyloidosis is challenging and patients have multiple rounds of inconclusive testing over

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months or years [5]. Patients may be diagnosed as part of a workup for severe organ dysfunction. We hypothesized that these workups might occur during an acute admission and would be resource intensive and costly. Therefore, we also aimed to estimate the frequency of diagnostic admissions among hospitalized patients with AL amyloidosis and the associated healthcare utilization and costs.

Materials & methods

This retrospective cohort study used 2017–2020 data from the Premier® Healthcare Database (Premier, Inc., NC, USA), which contains clinical coding, hospital cost and patient billing data from approximately 25% of all US hospital discharges. The database contains a record of all billed items including medications, laboratory, diagnostic and therapeutic services. Diagnosis fields include admitting and primary diagnosis, with the latter defined by the Uniform Hospital Discharge Data Set as the condition chiefly responsible for the admission. The charge and cost for each hospitalization is available. 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 reported by the Premier Healthcare Database are 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 [6]. Patients can be tracked across hospitalizations if they are readmitted to the same hospital. Data are at the admission level, and patients admitted more than once are considered separate admissions. The terms admission and patient are used interchangeably for simplicity.

The study population included hospitalized patients aged ≥18 years with ≥1 inpatient claim containing the ICD-10-CM for AL amyloidosis (E85.81) during the study period of 1 October 2017–31 December 2020. This period was selected because the code E85.81 specific for AL amyloidosis was not available before October 2017. Patients 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 disease (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). When more than one qualifying hospitalization for a patient existed, only the first one was included. We reported data on patient socio-demographics, payer type, comorbidities, discharge status, hospital characteristics, length of stay (LOS), intensive care unit (ICU) use, mortality and hospitalization costs. Patients were stratified into diagnostic and other hospitalization. A diagnostic hospitalization was one where the patient had a code for bone marrow, kidney, liver, abdominal fat pad, salivary gland, gingival or endomyocardial biopsy during the stay. In addition, hospitalizations were not considered diagnostic if they included evidence of a solid organ or hematopoietic cell transplant.

Descriptive statistics including means with standard deviations (SD) and relative frequencies with percentages for continuous and categorical data, respectively, were calculated. To compare between diagnostic versus other hospitalizations, t-test and χ^2 test were performed for continuous and categorical variables respectively. Costs were inflated to 2020 USD using the medical care component of the Consumer Price Index [7]. For context, we compared costs to the most recent national averages calculated from the 2018 National Inpatient Sample and inflated to 2020 USD. Statistical analyses were performed using SAS© version 9.4.

Results

Between 2017 and 2020, 1419 hospitalizations included ≥1 inpatient claim for AL amyloidosis. Of these, 60 were excluded for having codes consistent with other amyloidosis subtypes and 18 for having codes for comorbid chronic inflammatory conditions, leaving 1,341 patients in the study sample (Table 1). The mean (SD) age at admission was 67.2 (11.2) years. Male patients made up 65.9% of the sample. Most (64.3%) were White with 22.8% Black, 1.4% Asian and 11.4% other or undetermined. Medicare was the primary payer for 62.4% of admission, followed by managed care at 16.3%, Medicaid at 9.5% and commercial indemnity plans at 7.5%. Admissions were relatively evenly distributed across years 2018–2020 (28.7, 35.0 and 30.4%, respectively) with 6.0% from 2017 (the ICD code for AL amyloidosis became available in October 2017). Most admissions were to teaching hospitals (62.4%) in urban areas (91.2%; results not shown). The mean (SD) (median) LOS was 9.5 (9.7) (6.0) days. During the hospital stay, 20.1% of patients were admitted to the ICU and had a mean (SD) ICU LOS of 6.5 (7.6) days. A total of 107 (8%, 95% CI: 6.5–9.4%) patients died in the hospital. The mean (SD) total hospitalization cost was $27,099 ($34,849) for hospitalized patients with AL amyloidosis. In comparison, the mean cost for all US hospital

Table 1. Demographics of hospitalized amyloid light chain amyloidosis patients, hospital characteristics and physician specialty, stratified by type of hospitalization.

	Type of hospitalization		All adult AL amyloidosis hospitalization	p-value
	Diagnostic‡	Other		
n (%)	234 (17.4)	1,107 (82.6)	1,341 (100.0)	
Age, mean (SD) (median)	67.7 (11.1) [68]	67.1 (11.2) [67]	67.2 (11.2) [68]	0.490
Female, n (%)	114 (48.7)	478 (43.2)	592 (44.1)	0.121
Race, n (%)				0.570
White	147 (62.8)	715 (64.6)	862 (64.3)	
African–American	50 (21.4)	256 (23.1)	306 (22.8)	
Other	25 (10.7)	99 (8.9)	124 (9.2)	
Asian	4 (1.7)	15 (1.4)	19 (1.4)	
Unable to determine	8 (3.4)	22 (2.0)	30 (2.2)	
Primary payer type, n (%)				0.623
Medicare	154 (65.8)	683 (61.7)	837 (62.4)	
Medicaid	23 (9.8)	105 (9.5)	128 (9.5)	
Commercial	14 (6.0)	86 (7.8)	100 (7.5)	
Self-pay	4 (1.7)	11 (1.0)	15 (1.1)	
Managed care	32 (13.7)	187 (16.9)	219 (16.3)	
Other	7 (3.0)	35 (3.2)	42 (3.1)	
Year of hospitalization80, n (%)				0.317
2017†	20 (8.5)	60 (5.4)	80† (6.0)	
2018	63 (26.9)	322 (29.1)	385 (28.7)	
2019	80 (34.2)	389 (35.1)	469 (35.0)	
2020	71 (30.3)	336 (30.4)	407 (30.4)	
Admission type, n (%)				0.050
Elective	20 (8.5)	146 (13.2)	166 (12.4)	
Urgent/emergent	214 (91.5)	961 (86.8)	1,175 (87.6)	
Hospital type, n (%)				0.547
Teaching	142 (60.7)	695 (62.8)	837 (62.4)	
Non-teaching	92 (39.3)	412 (37.2)	504 (37.6)	
Any diagnostic biopsies, n (%)	234 (100.0)	2 (0.2)	236 (17.6)	<0.001
Bone marrow biopsy	186 (79.5)	2 (0.2)§	188 (14.0)	<0.001
Salivary gland biopsy	0 (0.0)	0 (0.0)	0 (0.0)	n/a
Abdominal fat pad biopsy	4 (1.7)	0 (0.0)	4 (0.3)	<0.001
Liver biopsy	3 (1.3)	0 (0.0)	3 (0.2)	0.005
Gingival biopsy	0 (0.0)	0 (0.0)	0 (0.0)	n/a
Kidney biopsy	105 (44.9)	0 (0.0)	105 (7.8)	<0.001
Endomyocardial biopsy	5 (2.1)	0 (0.0)	5 (0.4)	<0.001

†ICD-10-CM code E85.81 for light chain (AL) amyloidosis not available until 1 October 2017.
‡Defined as presence of bone marrow, kidney, liver, abdominal fat pad, salivary gland, gingival or endomyocardial biopsy and absence of solid organ or hematopoietic stem cell transplant.
§These patients had stem cell transplantation during the episode thus their episode was not considered diagnostic.
AL: Amyloid light chain.

stays was $14,661 ($129) (based on 2018 data inflated to 2020 USD) [8], and the mean cost for all US hospital stays with a principal diagnosis of cancer was $23,249 (2017 data inflated to 2020) [9].

Of 1341 hospital admissions, 236 (17.6%) were considered diagnostic (Table 1). Patient demographics, payer type, year of admission and teaching hospital status did not differ between diagnostic and other admissions. Bone marrow and kidney biopsies were the most common types of biopsies performed during diagnostic hospitalization (79.5 and 44.9%, respectively), while only five cases of endomyocardial biopsy – typically, an outpatient procedure – were performed among these admissions. Diagnostic hospitalizations had longer LOS (mean [SD] 14.5 [11.7] vs 8.4 [8.9] days; $p < 0.001$), higher cost ($40,052 vs $24,360; $p < 0.001$) and higher total charges ($161,526 vs $104,129; $p < 0.001$) than nondiagnostic ones, but mortality was similar between the two groups (Figure 1).

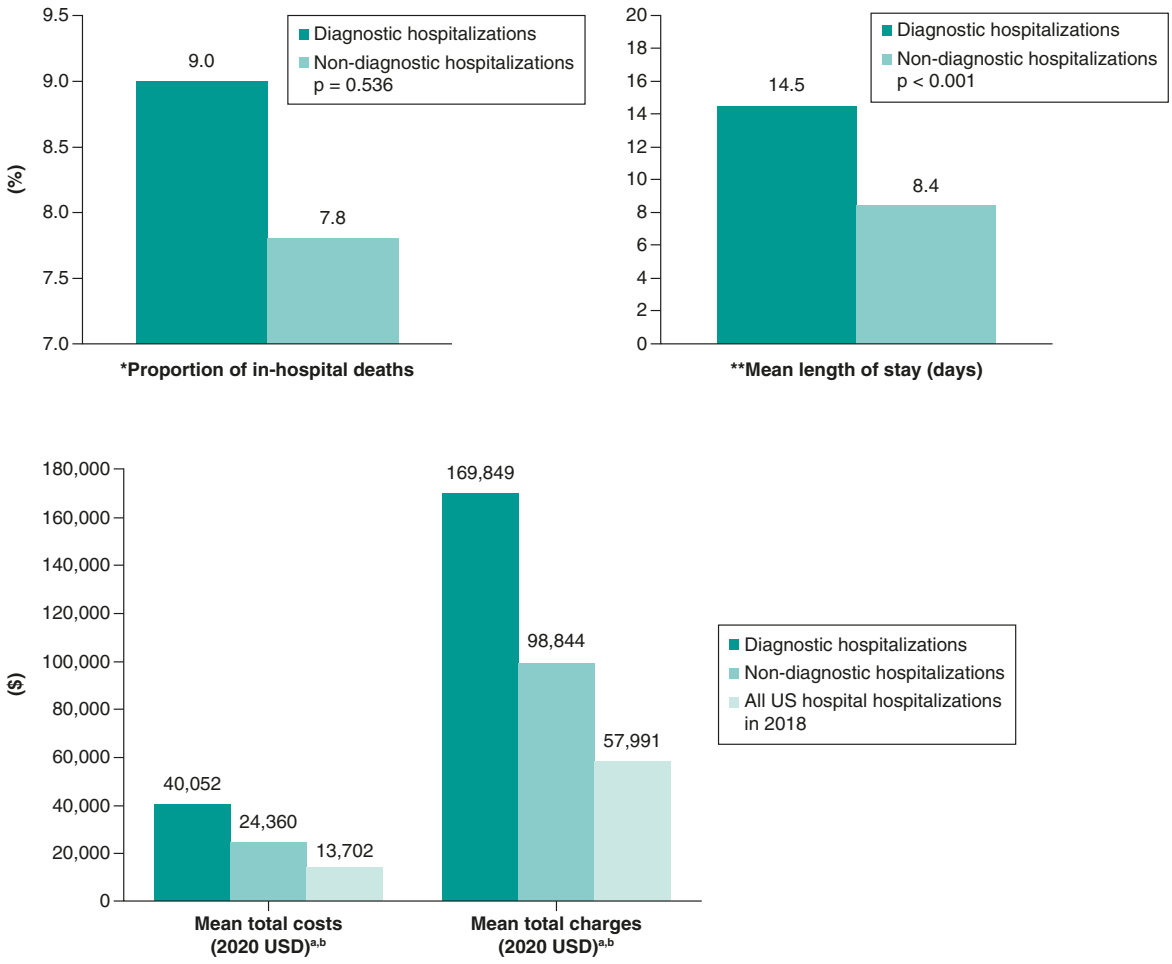

Figure 1. In-hospital death, length of stay and hospital costs and charges, stratified by type of hospitalization.
***Difference in cost and charges for diagnostic hospitalization and nondiagnostic hospitalization ($p < 0.001$). ****Total costs and charges do not include professional fees for the services received in hospitals by physicians and other skilled healthcare professionals licensed for independent practice.

Discussion

AL amyloidosis often presents a diagnostic challenge. Patients with nonspecific symptoms like fatigue or symptoms typical of other conditions, like shortness of breath, often have multiple rounds of inconclusive testing over months or years [5]. Our analysis provides several novel insights into hospitalizations among patients with AL amyloidosis. Approximately one in six hospitalizations with AL amyloidosis is associated with the initial diagnosis of the disease. Of diagnostic admissions, one in five spent time in the ICU and one in 13 died before discharge. Diagnostic admissions are more likely to be urgent or emergent, require longer hospital stays and have substantially higher costs compared with hospitalizations in patients with known AL amyloidosis. To better understand the drivers of the cost gap between diagnostic and other admissions, we compared daily costs as well as average costs in various cost categories between these groups. Diagnostic hospitalizations were less costly per day than other hospitalizations ($2775 vs $3164; $p = 0.005$), while mean costs for different procedures were not significantly different between the two groups. Therefore, varying utilization of diagnostic and therapeutic services and varying LOS are likely to be the main drivers of cost differences. Notably, there are intrinsic differences in utilization among the two groups; diagnostic admissions have biopsy procedures while transplants only happen in other admissions.

Limited data exist on hospital utilization and cost in AL amyloidosis. A 2018 study using commercial insurance claims data from 2007 to 2015 estimated the LOS at 10.2 days and inpatient cost at just under $37,909 per year, but, as there was no ICD code specific for AL amyloidosis available at the time of that study, the authors relied on a more general code plus the use of specific medications to identify individuals with the disease [10]. 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 [11].

Our study is limited on the reliance for specific biopsies to identify patients having had a diagnostic admission. This could have led to exclusion of patients whose diagnosis was made in the hospital on the basis of other findings and inclusion of patients whose diagnosis was previously known but had biopsies for other reasons. This would be unlikely as the diagnosis of AL amyloidosis relies on tissue confirmation. Some tissue sites (e.g., fat pad) are specific to AL amyloidosis. It would also be unlikely that a patient with confirmed AL amyloidosis would undergo a subsequent bone marrow biopsy during hospitalization. The Premier database, while widely used for research, includes primarily information relevant to payment for services and miscoding is possible. It does not include data from federally funded hospitals (e.g., Veterans Affairs).

Conclusion

In conclusion, for the first time, AL amyloidosis specific codes to study hospitalizations in a large, nationally representative database provide data on diagnostic hospitalizations in the disease. Patients with AL amyloidosis are quite ill, with 20% spending time in the ICU and 8% dying in the hospital. Those diagnosed in the hospital have longer stays and higher costs than other AL amyloidosis hospitalizations. Continued effort is needed to improve diagnostic pathways toward early diagnosis of this multisystem disease.

Summary points

- Diagnosing systemic amyloid light chain amyloid light chain (AL) amyloidosis is challenging and might occur during an acute admission.
- This is the first analysis to use AL amyloidosis specific codes in a nationally representative database to provide data on hospital admissions for this disease.
- 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 study sample included 1341 patients.
- AL amyloidosis patients admitted to hospital are acutely ill. One in five patients are admitted to the intensive care unit during their stay, and one in 12 patients died in hospital.
- During the study period, 17.6% of hospital admissions for patients with AL amyloidosis were identified as the encounter during which the disease was diagnosed.
- Diagnostic admissions for AL amyloidosis cost almost twice as much as the average hospitalization in the USA.
- Continued effort is needed to improve early diagnosis of this multisystem disease.

Financial & competing interests disclosure

This analysis was supported by Prothena Biosciences Ltd., Dublin, Ireland, a member of the Prothena Corporation PLC group. TP Quock is an employee of Prothena Biosciences Inc. and holds stock in Prothena Corporation PLC group. A D'Souza is an employee of the Medical College of WI, USA and was paid by Prothena Biosciences Inc. to consult as a subject matter expert. E Chang, K Bognar, MS Broder and MH Tarbox are employees of PHAR, which received funding from Prothena to conduct the research described in this manuscript. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

The Premier data are de-identified, compliant with the Health Insurance Portability and Accountability Act (HIPAA) and thus consisted with 45 CFR 46.101(b)(4) and exempt from Institutional Review Board oversight.

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• **Provides one of the few estimates of healthcare resource utilization and costs among patients with amyloid light chain amyloidosis; however, patients were identified by a general amyloidosis code plus the use of specific medications.**

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• **Provides one of the few estimates of healthcare resource utilization and cost among patients with cardiac amyloidosis.**