Research Article

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# Healthcare resource utilization and costs in amyloid light-chain amyloidosis: a real-world study using US claims data

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**Aim:** To estimate healthcare utilization and costs in amyloid light-chain (AL) amyloidosis. **Patients & methods:** AL amyloidosis patients were identified in 2007–2015 claims databases if they had ≥1 inpatient/≥2 outpatient claims consistent with AL amyloidosis and received ≥1 AL-specific treatment. Descriptive statistics were reported. **Results:** 50.1% (n = 3670) were admitted ≥1 time during the year, 11.3% (n = 827) ≥3 times. From 2007 to 2015, bortezomib use increased from 4.6 to 25.3%; melphalan use decreased from 18.9 to 2.0%; costs increased from 92,866 to $114,030. Among incident patients with at least 2 years of follow-up, healthcare utilization and costs decreased from first to second year post-diagnosis. **Conclusion:** AL chemotherapy-based prescribing practices changed. Total annual healthcare costs increased over time among AL amyloidosis patients.

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**Keywords:** AL amyloidosis • healthcare costs • healthcare resource utilization

The amyloidoses refer to a group of rare disorders of protein folding characterized by extracellular tissue deposition of misfolded and aggregated autologous proteins as β-pleated sheet fibrils [1]. The most common and severe type of systemic amyloidosis is amyloid light-chain (AL) amyloidosis. In AL amyloidosis, amyloid fibrils are derived from κ or λ monoclonal light chains which are synthesized by a clonal population of plasma cells in the bone marrow [2]. With the exception of the CNS, the toxic monoclonal light chain proteins in AL can damage virtually all organs, most frequently the heart and kidneys. Cardiac involvement commonly manifests as heart failure. Renal involvement usually presents as nephrotic syndrome with progressive worsening of renal functions. [3].

Patients with AL amyloidosis have a poor prognosis with an estimated median survival ranging from 6 months to 3 years depending on the patient population and data used [4–7]. Eradication of the monoclonal plasma cell population and suppression of the pathologic light chains is the goal of the AL treatment [3]. To date, among treatments used for AL amyloidosis – most of which were derived from multiple myeloma treatment – none are deemed optimal due to insufficient data [8]. High-dose melphalan followed by autologous hematopoietic stem cell transplant (HSCT) is one treatment option included in the National Comprehensive Cancer Network guidelines, but this method of treatment is associated with significant side morbidity and mortality; therefore only about 20% of patients are eligible [9,10]. Among patients who are ineligible for HSCT; melphalan, dexamethasone and the bortezomib-based regimens are recommended [11]. Currently, there are no US FDA- or EMA-approved therapies for AL amyloidosis.

The disease burden of AL amyloidosis from an economic perspective has not been well characterized in the literature. AL amyloidosis patients with cardiac involvement (50–70% of AL amyloidosis cases [12,13]) have a high rate of heart failure-related hospitalization and heart transplant. Those with renal involvement may require dialysis and/or kidney transplant, which is both costly and entails high resource utilization. Most studies have examined healthcare utilization and costs of treatment components common in AL amyloidosis (e.g., dialysis

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and/or heart transplant) using data collected on patients with other diseases, such as multiple myeloma [14]. According to a study conducted by Teitelbaum *et al.*, the average cost associated with multiple myeloma treatment is US$118,353.50 [15]. HSCT and its associated complications are costly; one review of cost studies found that costs associated with HSCT ranged from $36,000 to $204,000 in 2012 dollars, depending on patient characteristics, transplant center experience, graft type, duration of hospitalization and transplantation complications [16].

In a formal literature search on PubMed using no date or language limits and the following terms: 'amyloidosis (Medical Subject Heading)'; 'healthcare utilization'; and 'healthcare cost', we found no studies that examined healthcare utilization and costs associated with AL amyloidosis. As a result, we sought to examine healthcare utilization and costs associated with the disease in the USA using real-world, nationally representative health insurance claims data. We employed a mixed method approach with cross-sectional and longitudinal analyses of two separate patient populations: prevalent; and incident AL amyloidosis patients, respectively. This information on AL amyloidosis is vital to understand the current burden on the healthcare system of this life-threatening disease, and provides a baseline against which to monitor trends.

## Patients & methods

### Data sources

We used data from the Truven MarketScan® Commercial and Medicare Supplement Databases (Truven Health Analytics, MI, USA) from 1 January 2007 to 31 December 2015 to estimate the annual healthcare utilization and costs among AL amyloidosis patients.

These claims data provide a unique opportunity to examine this rare disease because it include a sufficient sample of patients. The MarketScan Commercial and Medicare Supplemental Databases are Health Insurance Portability and Accountability Act-compliant administrative claims databases. The commercial data included medical encounters from approximately 65 million individuals and their dependents insured by employer-sponsored plans (i.e., non-Medicare eligible). Coverage was provided under a variety of fee-for-service, fully capitated and partially capitated health plans, including preferred provider organizations, point of service plans, indemnity plans and health maintenance organizations. The Medicare supplemental data included about 5.3 million Medicare-eligible retired employees and their spouses with employer-sponsored Medicare supplemental plans. Given the deidentified nature of the data used in the present study, informed consent was not required by Health Insurance Portability and Accountability Act rules.

### Study population

As there is no diagnosis code specific to AL amyloidosis, adults ≥18 years old with AL amyloidosis were identified if they had: at least one inpatient claim or at least two outpatient claims consistent with AL amyloidosis (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes: 277.30 [amyloidosis, unspecified] or 277.39 [Other amyloidosis]; International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM] codes: E85.4x [organ-limited amyloidosis], E85.8x [other amyloidosis] or E85.9x [amyloidosis, unspecified]) in any diagnosis field; and received one AL-specific treatment (e.g., chemotherapy and HSCT) on or after the first amyloidosis diagnosis in the study period. We identified two separate groups of patients – prevalent and incident-as described below.

### Prevalent AL amyloidosis patients

Adult patients ≥18 years old with prevalent or incident AL amyloidosis were identified in each calendar year during the study period between 1 January 2007 and 31 December 2015 (Figure 1). Full-year enrollment was not required after exploratory analysis suggested most patients with partial year enrollment likely died during the year. As illustrated in Figure 1, prevalent patients could be included in multiple calendar years.

### Incident AL amyloidosis patients

To identify incident AL amyloidosis, patients with AL amyloidosis were identified during the identification period between 1 January 2008 and 31 December 2014 (Figure 2). The first observed AL amyloidosis diagnosis date was the index date. To ensure that all patients were newly diagnosed with AL amyloidosis, they were excluded if they had a diagnosis of AL amyloidosis during the 1 year prior to the index date (1-year baseline period). Patients were also required to have continuous enrollment during the 1 year before the index date (1-year baseline period). The follow-up period was from the index date until the end of enrollment.

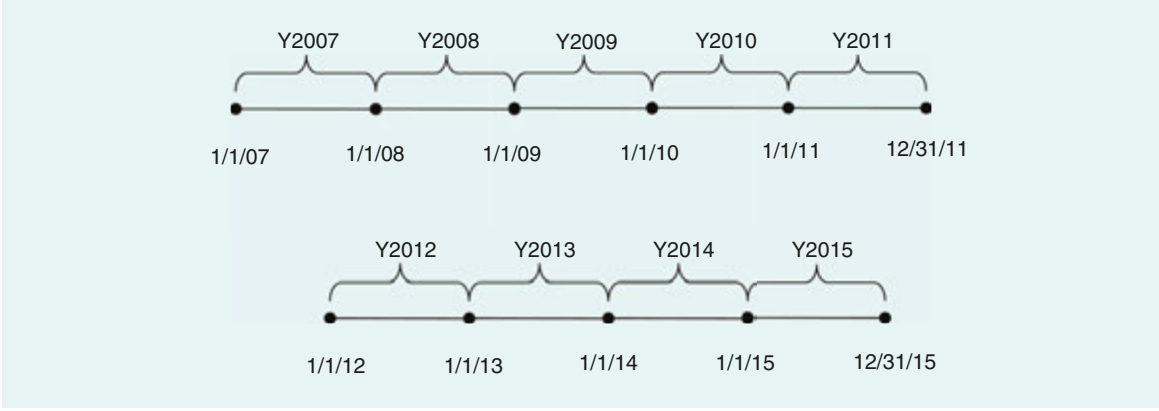


**Figure 1. Study timeline for prevalence analysis.**

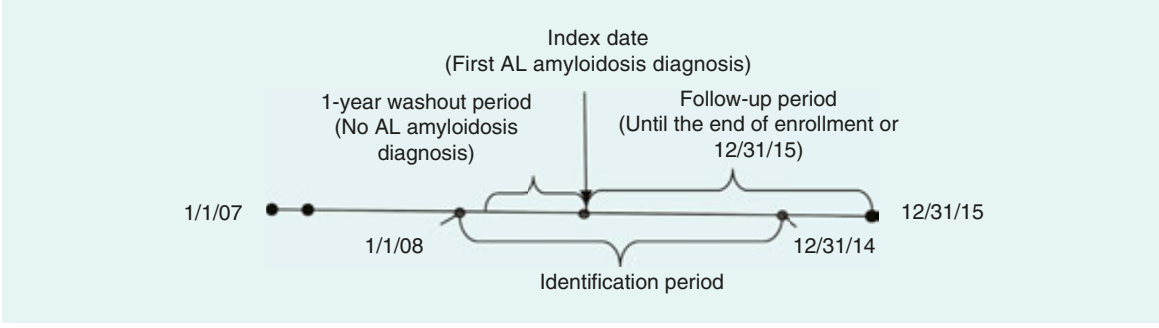


**Figure 2. Study timeline for incidence analysis.**

### Study measures & statistical analysis

For prevalent patients, we reported the following patient demographic, clinical characteristics and all-cause healthcare utilization and costs in each calendar year. For patients with incident AL amyloidosis, we reported the patient demographic and clinical measures during baseline (1-year period prior to the index date) and the healthcare resource utilization and cost measures based on follow-up enrollment lengths. Specifically, for patients with a follow-up length $\leq$12 months, we reported their actual healthcare utilization and costs without annualization. For a subgroup of patients who had follow-up length $\geq$24 months, we reported their annualized healthcare utilization and costs in each follow-up year.

## Patient demographic & clinical characteristics

Patient demographic and clinical characteristics included age, gender, geographic region, Charlson comorbidity index (CCI) [17], presence of multiple myeloma (ICD-9-CM: 203.0x; ICD-10-CM: C90.0x), monoclonal gammopathy of undetermined significance (ICD-9-CM: 273.1X; ICD-10-CM: D47.2x), hypothyroidism (ICD-9-CM: 244.0x, 244.1x, 244.8x, 244.9x; ICD-10-CM: E03.1x, E03.8x, E03.9x, E89.0x), Waldenström's macroglobulinemia (ICD-9-CM: 273.3x; ICD-10-CM: C88.0x) and carpal tunnel syndrome (ICD-9-CM: 354.0x; ICD-10-CM: G56.00, G56.01, G56.02, G56.03). Presence of these clinical characteristics was determined based upon having at least one claim with a relevant ICD-9/ICD-10 code.

## Healthcare resource utilization & costs

All-cause healthcare utilization included inpatient hospitalizations, emergency department (ED) visits, non-ED outpatient service visits and any pharmacy utilization. With regard to pharmacy utilization, patients were reported as using any treatment if they had at least one claim with a relevant ICD-9/ICD-10 code. Therefore, some treatments may have been used as part of combination therapy.

Table 1. Patient demographic characteristics and comorbidities for all prevalent patients combined all incident patients and incident patients with two or more years of follow-up.

| | All prevalent patients | All incident patients | Incident patients with 24+ months |
|---|---|---|---|
| N | 7326 | 2018 | 887 |
| Age, year, mean (SD): | 63.6 (12.1) | 63.8 (12.8) | 63.3 (13.6) |
| – 18–34 | 89 (1.2) | 28 (1.4) | 17 (1.9) |
| – 35–54 | 1449 (19.8) | 419 (20.8) | 206 (23.2) |
| – 55–64 | 2617 (35.7) | 660 (32.7) | 253 (28.5) |
| – 65+ | 3171 (43.3) | 911 (45.1) | 411 (46.3) |
| Female, n (%) | 3300 (45.0) | 926 (45.9) | 426 (48.0) |
| Region, n (%): | | | |
| – Midwest | 1950 (26.6) | 554 (27.5) | 252 (28.4) |
| – Northeast | 1619 (22.1) | 416 (20.6) | 188 (21.2) |
| – South | 2464 (33.6) | 703 (34.8) | 292 (32.9) |
| – West | 1293 (17.6) | 345 (17.1) | 155 (17.5) |
| Database, n (%): | | | |
| – Commercial | 4254 (58.1) | 1112 (55.1) | 469 (52.9) |
| – Medicare supplemental | 3072 (41.9) | 906 (44.9) | 418 (47.1) |
| CCI, mean (SD) [range]: | 4.3 (3.2) [0–19] | 3.3 (2.9) [0–19] | 2.8 (2.7) [0–17] |
| – Congestive heart failure | 2435 (33.2) | 466 (23.1) | 154 (17.4) |
| – Renal disease | 2878 (39.3) | 533 (26.4) | 134 (21.7) |
| – Moderate or severe liver disease | 2096 (28.6) | 510 (25.3) | 182 (20.5) |
| Multiple myeloma, n (%) | 2848 (38.9) | 312 (15.5) | 120 (13.5) |
| MGUS, n (%) | 1438 (19.6) | 318 (15.8) | 125 (14.1) |
| Hypothyroidism, n (%) | 1297 (17.7) | 327 (16.2) | 143 (16.1) |
| WM, n (%) | 179 (2.4) | 28 (1.4) | 13 (1.5) |
| Carpal tunnel syndrome, n (%) | 274 (3.7) | 101 (5.0) | 50 (5.6) |

CCI: Charlson comorbidity index; MGUS: Monoclonal gammopathy of undetermined significance; SD: Standard deviation; WM: Waldenström's macroglobulinemia.

Total all-cause healthcare costs were calculated by adding up all medical costs, which included inpatient hospitalization costs, ED service costs, non-ED outpatient service costs and pharmacy costs. Costs were for insurance-covered healthcare costs from fully adjudicated and paid claims, and included both patient and plan portions of each claim for all medical services utilized during the study period. Services provided 'out-of-network' or not covered by insurance were not included.

## Statistical analysis

Descriptive statistics including means, standard deviations (SD) and relative frequencies and percentages for continuous and categorical data, respectively, were reported. The mean healthcare utilization and costs were reported per-patient-per-year. Cost estimates were converted to 2015 (the final year of the study) US dollars using the Consumer Price Index to adjust for inflation. All data transformations and statistical analyses were performed using SAS© version 9.4.

## Results

### Patient demographic characteristics & comorbidities

In our claims databases, there were 7326 patients identified overall (27.5% [n = 2018] had incident AL amyloidosis), with a mean (SD) age 63.6 (12.1), 45% of whom were female. All US regions were represented, and the majority of patients had commercial insurance (Table 1).

Individuals with AL amyloidosis had a substantial burden of comorbidities or concurrent conditions, as determined by having at least one claim with a relevant ICD-9/ICD-10 code (Table 1). The mean (SD) of CCI in all prevalent patients and incident patients was 4.3 (3.2) and 3.3 (2.9), respectively. Common individual comorbidities in the CCI were renal disease (39.3% in prevalent patients; 26.4% in incident patients), congestive heart failure (33.2; 23.1%) and moderate or severe liver disease (28.6; 25.3%). Other common conditions observed

Table 2. Utilization of inpatient hospitalizations, outpatient services and treatment for all prevalent patients, by each calendar year.

| | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | All |
|---|---|---|---|---|---|---|---|---|---|---|
| N | 349 | 573 | 713 | 792 | 972 | 1059 | 1031 | 1031 | 806 | 7326 |
| Number of inpatient hospitalizations, mean (SD): | 1.15 (1.45) | 1.15 (1.49) | 1.12 (1.59) | 0.96 (1.42) | 1.01 (1.54) | 0.95 (1.44) | 0.91 (1.30) | 1.00 (1.51) | 0.95 (1.76) | 1.00 (1.50) |
| – 0, n (%) | 150 (43.0) | 248 (43.3) | 326 (45.7) | 400 (50.5) | 493 (50.7) | 534 (50.4) | 533 (51.7) | 538 (52.2) | 434 (53.8) | 3656 (49.9) |
| – 1, n (%) | 89 (25.5) | 162 (28.3) | 198 (27.8) | 210 (26.5) | 249 (25.6) | 288 (27.2) | 269 (26.1) | 237 (23.0) | 195 (24.2) | 1897 (25.9) |
| – 2, n (%) | 66 (18.9) | 81 (14.1) | 97 (13.6) | 97 (12.2) | 111 (11.4) | 133 (12.6) | 127 (12.3) | 131 (12.7) | 103 (12.8) | 946 (12.9) |
| – 3+, n (%) | 44 (12.6) | 82 (14.3) | 92 (12.9) | 85 (10.7) | 119 (12.2) | 104 (9.8) | 102 (9.9) | 125 (12.1) | 74 (9.2) | 827 (11.3) |
| No. of ED visits, n (%) | 0.76 (1.98) | 0.72 (2.19) | 0.80 (2.11) | 0.72 (2.55) | 0.72 (2.17) | 0.75 (2.81) | 0.64 (1.63) | 0.72 (1.41) | 0.71 (1.65) | 0.72 (2.10) |
| No. of non-ED outpatient services, n (%) | 43.0 (30.0) | 44.2 (37.9) | 44.4 (37.7) | 42.9 (35.2) | 45.6 (39.0) | 46.0 (35.4) | 44.4 (32.8) | 47.0 (36.8) | 46.9 (37.9) | 45.2 (36.2) |
| Hematopoietic stem cell transplantation, n (%) | 14 (4.0) | 19 (3.3) | 34 (4.8) | 28 (3.5) | 29 (3.0) | 39 (3.7) | 34 (3.3) | 48 (4.7) | 29 (3.6) | 274 (3.7) |
| AL chemo-based treatment, n (%): | 242 (69.3) | 399 (69.6) | 485 (68.0) | 494 (62.4) | 666 (68.5) | 702 (66.3) | 698 (67.7) | 735 (71.3) | 623 (77.3) | 5044 (68.9) |
| – Bortezomib, n (%) | 16 (4.6) | 64 (11.2) | 105 (14.7) | 133 (16.8) | 191 (19.7) | 226 (21.3) | 224 (21.7) | 258 (25.0) | 204 (25.3) | 1421 (19.4) |
| – Melphalan, n (%) | 66 (18.9) | 95 (16.6) | 109 (15.3) | 73 (9.2) | 67 (6.9) | 51 (4.8) | 28 (2.7) | 23 (2.2) | 16 (2.0) | 528 (7.2) |

AL: Amyloid light-chain; ED: Emergency department; SD: Standard deviation.

included multiple myeloma (38.9% in prevalent patients; 15.5% in incident patients), monoclonal gammopathy of undetermined significance (19.6; 15.8%) and hypothyroidism (17.7; 16.2%) (Table 1).

## Healthcare utilization & costs among prevalent AL amyloidosis patients

The majority (68.9% [n = 5044]) of all patients used AL chemotherapy-based treatment at least once during the 9-year period (Table 2). The use of any AL chemotherapy-based treatment remained stable during the study period. However, for specific treatments, there was an increased use of bortezomib during the study period from 4.6% in 2007 to 25.3% in 2015; in contrast, the use of melphalan decreased from 18.9% in 2007 to 2.0% in 2015.

Hospitalization was common: 50.1% (n = 3670) of the overall study sample was admitted at least once and 11.3% (n = 827) were hospitalized three or more times (Table 2). Among admitted patients, mean (SD) length of stay was 14.7 (19.5) days (not shown in table). Rates of any hospitalization decreased from 57.0% in 2007 to 46.2% in 2015. Almost three-quarters of patients (72.0% [n = 5274]) had an ED visit at least once during the 9-year period (Table 2) and 6.8% (n = 496) had more than three ED visits (not shown in table). ED visits remained stable during the study period. Patients had a mean (SD) of 45.2 (36.2) non-ED outpatient visits per year. Non-ED outpatient visit rates increased from 30.0% in 2007 to 37.9% in 2015 during the study period.

Mean (SD) total annual all-cause healthcare costs were $101,855 (148,965) for all patients (Table 3). The majority of the total costs were for medical services (mean [SD] $88,801 [144,491]), with $50,126 (86,232) accrued in the outpatient, $37,909 (100,892) inpatient and $766 (3650) ED settings. Total costs increased over time from $92,866 in 2007 to $114,030 in 2015. Total medical (non-outpatient pharmacy) costs increased from $80,099 in 2007 to $97,513 in 2015. ED visit costs increased from $685 in 2017 to $1,043 in 2015. Other outpatient

**Table 3. All-cause healthcare costs† for all prevalent patients, by each calendar year.**

| | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | All |
|---|---|---|---|---|---|---|---|---|---|---|
| N | 349 | 573 | 713 | 792 | 972 | 1059 | 1031 | 1031 | 806 | 7326 |
| Total costs, mean (SD) [median] | $92,866 (154,220) [49,225] | $93,456 (122,899) [47,799] | $101,634 (156,242) [48,685] | $96,415 (154,277) [43,885] | $94,368 (130,712) [48,056] | $98,575 (133,174) [53,928] | $101,197 (148,735) [52,585] | $115,463 (170,943) [58,530] | $114,030 (160,415) [61,018] | $101,855 (148,965) [51,939] |
| Total outpatient pharmacy costs | $12,768 (19,450) [4999] | $11,880 (21,453) [3896] | $11,691 (24,099) [3951] | $12,107 (24,731) [3660] | $11,850 (23,520) [3567] | $11,406 (25,083) [2868] | $13,521 (27,936) [3002] | $15,126 (30,902) [3316] | $16,517 (33,084) [3637] | $13,054 (26,606) [3501] |
| Total medical (non-outpatient pharmacy) costs | $80,099 (150,481) [36,436] | $81,576 (120,685) [33,980] | $89,944 (152,649) [37,006] | $84,307 (149,637) [34,424] | $82,518 (126,074) [37,501] | $87,168 (129,259) [41,599] | $87,677 (143,173) [36,557] | $100,337 (166,573) [45,097] | $97,513 (154,831) [42,644] | $88,801 (144,491) [38,936] |
| Total inpatient hospitalization costs | $43,178 (128,426) [7495] | $37,583 (78,311) [8212] | $44,160 (117,407) [7643] | $37,878 (114,900) [0] | $33,640 (81,024) [0] | $33,069 (75,764) [0] | $34,423 (87,654) [0] | $43,446 (121,706) [0] | $39,243 (107,569) [0] | $37,909 (100,892) [802] |
| Total ED visit costs | $685 (2861) [0] | $631 (2416) [0] | $575 (2135) [0] | $638 (3448) [0] | $832 (4710) [0] | $824 (3573) [0] | $630 (2593) [0] | $893 (3216) [0] | $1,043 (5681) [0] | $766 (3650) [0] |
| Other outpatient medical costs | $36,235 (56,731) [19,096] | $43,363 (71,066) [19,261] | $45,209 (76,125) [18,989] | $45,791 (75,115) [20,135] | $48,045 (79,066) [21,684] | $53,276 (90,363) [23,614] | $52,623 (98,353) [20,617] | $55,998 (98,687) [25,633] | $57,227 (92,872) [26,081] | $50,126 (86,232) [22,100] |

†Costs were adjusted to 2015 dollars. ED: Emergency department; SD: Standard deviation.

**Table 4. Utilization of inpatient hospitalizations, outpatient services and treatment for incident patients.**

| | All incident patients | Incident patients with 2+ years follow-up | |
|---|---|---|---|
| | Post year 1 | Post year 1 | Post year 2 |
| N | 2018 | 887 | 887 |
| Number of inpatient hospitalizations, mean (SD): | 1.32 (1.67) | 1.05 (1.27) | 0.57 (1.14) |
| – 0, n (%) | 715 (35.4) | 344 (38.8) | 604 (68.1) |
| – 1, n (%) | 667 (33.1) | 325 (36.6) | 157 (17.7) |
| – 2, n (%) | 301 (14.9) | 126 (14.2) | 79 (8.9) |
| – 3+, n (%) | 335 (16.6) | 92 (10.4) | 47 (5.3) |
| Total days of stay (among patients with hospitalizations), no. patients, mean (SD) | 1303 16.9 (22.1) | 543 12.5 (15.6) | 283 10.4 (14.2) |
| No. of ED visits, mean (SD): | 0.78 (2.10) | 0.73 (2.23) | 0.63 (1.66) |
| – 0, n (%) | 1254 (62.1) | 577 (65.1) | 607 (68.4) |
| – 1, n (%) | 441 (21.9) | 189 (21.3) | 164 (18.5) |
| – 2, n (%) | 173 (8.6) | 57 (6.4) | 58 (6.5) |
| – 3+, n (%) | 150 (7.4) | 64 (7.2) | 58 (6.5) |
| No. of non-ED outpatient services, n (%) | 48.0 (37.1) | 49.2 (35.6) | 39.7 (36.1) |
| Hematopoietic stem cell transplantation, n (%) | 142 (7.0) | 62 (7.0) | 14 (1.6) |
| AL chemo-based treatment, n (%): | 1635 (81.0) | 599 (67.5) | 486 (54.8) |
| – Bortezomib | 522 (25.9) | 163 (18.4) | 74 (8.3) |
| – Melphalan | 185 (9.2) | 71 (8.0) | 20 (2.3) |

ED: Emergency department; SD: Standard deviation.

medical costs increased from $36,235 in 2007 to $57,227 in 2015. Outpatient pharmacy costs increased slightly from $12,768 in 2007 to $16,517 in 2015.

### Healthcare utilization & costs among incident AL amyloidosis patients

In subgroup analyses with incident AL amyloidosis patients, healthcare utilization differed between all incident patients and those with ≥24 months of follow-up (Table 4). With regard to inpatient hospitalizations, among all incident AL amyloidosis patients, 64.6% (n = 1303) were hospitalized at least once during post year 1, and 16.6% (335) were hospitalized three or more times. In comparison, 61.2% (n = 543) of the incident patients with

Table 5. All-cause healthcare costs† for incident patients.

| | All incident patients | Incident patients with 2+ years follow-up | |
|---|---|---|---|
| | Post year 1 | Post year 1 | Post year 2 |
| N | 2018 | 887 | 887 |
| Total costs, mean (SD) [median] | $122,180 (159,074) [69,494] | $104,672 (134,993) [52,273] | $68,502 (121,711) [25,423] |
| Total outpatient pharmacy costs | $11,661 (23,543) [3218] | $11,987 (23,438) [3396] | $12,630 (27,485) [3103] |
| Total medical (non-outpatient pharmacy) costs | $110,519 (154,625) [56,991] | $92,685 (128,630) [42,281] | $55,871 (114,643) [16,586] |
| Total inpatient hospitalization costs | $54,053 (116,851) [14,493] | $38,603 (78,687) [10,149] | $18,381 (62,965) [0] |
| Total ED visits costs | $787 (4082) [0] | $700 (3218) [0] | $655 (2396) [0] |
| Other outpatient medical costs | $55,679 (77,855) [28,166] | $53,382 (82,416) [22,897] | $36,835 (80,408) [12,490] |

†Costs were adjusted to 2015 dollars. ED: Emergency department; SD: Standard deviation.

≥24 months of follow-up were hospitalized at least once during post year 1 and 10.3% (n = 92) were hospitalized three or more times. These rates (among newly diagnosed patients with ≥24 months of follow-up) declined over time, as 31.9% (n = 283) were hospitalized at least once during post year 2 and 5.3% (n = 47) were hospitalized three or more times.

With regard to ED visits, 37.9% (n = 764) of all incident patients had at least one ED visit in post year 1 and 7.4% (n = 150) had at least three ED visits. Among incident patients with ≥24 months of follow-up, 34.9% (n = 310) had at least one ED visit in post year 1 and 31.6% (n = 280) had at least one ED visit in post year 2. Non-ED outpatient service visits declined slightly among patients with ≥24 months of follow-up from a mean (SD) of 49.2 (35.6) visits in post year 1 to 39.7 (36.1) in post year 2.

Mean (SD) total annual all-cause healthcare costs among all incident patients were $122,180 (159,074) in post year 1 (Table 5). Medical (non-outpatient pharmacy) costs were $110,519 (154,625), with $55,679 (77,855) accrued in the outpatient, $54,053 (116,851) inpatient and $787 (4082) ED settings. Among incident patients with ≥24 months of follow-up, total mean (SD) costs decreased over time from $104,672 (134,993) in post year 1 to $68,502 (121,711) in post year 2 (Table 5). Total medical (non-outpatient pharmacy) costs declined from $92,685 (128,630) in post year 1 to $55,871 (114,643) in post year 2.

## Discussion

Using two commercial and Medicare supplemental healthcare claims databases, we found that AL amyloidosis chemotherapy-based treatment prescribing practices changed, with increased use of bortezomib and decreased use of melphalan from 2007 to 2015; total mean annual healthcare costs increased during the 9-year study period; and among a subgroup of incident patients with at least 2 years of follow-up, total healthcare utilization and costs decreased over time. The present study provides information about healthcare utilization and costs associated with AL amyloidosis in a real-world setting.

Our analysis indicates individuals with AL amyloidosis have a substantial burden of comorbidities. CCI increased slightly over the 9-year study period, which may reflect an increase in morbidities in the general population or improved coding practices [18]. Many of the observed conditions, including congestive heart failure, renal disease and liver disease, likely represent manifestations of the disease process.

### Healthcare utilization & costs among prevalent AL amyloidosis patients

In our analysis with all prevalent patients, the use of any chemotherapy treatment remained stable during the study period, but specific treatments, such as bortezomib and melphalan increased and decreased, respectively, from 2007 to 2015. This change in treatment practice over the 9-year study period is likely due to the fact that: studies published in this time period showed that bortezomib, with its rapid action and ability to inhibit proteasome enzyme complexes within cells, leads to high response rates and good tolerance; [19,20] and bortezomib had been increasingly used as a first-line therapy in AL amyloidosis during the study period. Hospitalization was common: half of AL amyloidosis patients were admitted at least once during the year and more than 11% were hospitalized at least three-times.

The average total annual healthcare costs among all prevalent AL amyloidosis patients from 2007 to 2015 data were $101,855. These costs, which included outpatient pharmacy and medical costs (i.e., inpatient hospitalizations,

ED visits and outpatient medical costs), increased over time from $92,866 in 2007 to $114,030 in 2015. Because our analysis is the first known study to examine healthcare costs over time associated with AL amyloidosis, we are unable to compare this trend to other analyses with this specific patient population.

### Healthcare utilization & costs among incident AL amyloidosis patients

Among incident AL amyloidosis patients, in the first year after diagnosis, healthcare utilization and costs were lower in a subgroup of patients who had at least 2 years of follow-up, compared with patients with shorter post-index follow-up enrollment. This may be because patients who lived longer (i.e., at least 2 years post-diagnosis) had less severe disease and/or were healthier overall. For example, these patients with at least 2 years of follow-up had a slightly lower burden of comorbidities, as measured by the CCI, compared with patients with less than 2 years of follow-up.

Additionally, in a subgroup of patients with at least 2 years of follow-up, healthcare utilization and costs declined over time. Specifically, rates of hospitalization declined from 61.2% 1 year after diagnosis to 31.9% 2 years after diagnosis. Also, rates of AL chemotherapy-based treatment declined slightly from 67.5% 1 year after diagnosis to 54.8% in the second year after diagnosis. Total costs declined from $104,672 in the first year after diagnosis to $68,502 in the second year after diagnosis. Similar trends have been shown in breast, lung, colorectal and prostate cancer [21,22]. Although we did not examine diagnostic tests or surgeries specifically, it may be that more of these tests and/or surgeries are performed in the first year after diagnosis, with more of them likely to be from inpatient facilities, than later in the disease course, leading to higher costs immediately after diagnosis.

This study does not shed light on long-term healthcare utilization and costs among the incident patients. If we had been able to follow all of these newly diagnosed AL amyloidosis patients until death, we likely would have found an increase in costs over their lifetime, peaking in the final months of life. This hypothesis is supported by a previous study that found the greatest costs to be accrued at the time of initial diagnosis and in the final months of life among heart failure patients [23]. In other words, when these newly diagnosed AL amyloidosis patients are examined as part of the prevalent population, their healthcare costs increase over time, as shown in our analysis.

### Study limitations

This study has limitations. First, there is no diagnosis code in ICD-9-CM or ICD-10-CM specific to AL amyloidosis and no generally accepted or clinically validated method for identifying this condition using health insurance claims data, the codes for this study were selected with clinical expert input to eliminate as many non-AL amyloid patients as possible (e.g., by excluding 277.31, familial Mediterranean fever and E85.3, secondary systemic amyloidosis). We further required patients to have received treatment consistent with expert recommendations for AL amyloidosis. This requirement would be expected to decrease the sensitivity but increase the specificity of our identification algorithm. Nonetheless, a small proportion of patients with transthyretin-related hereditary amyloidosis would likely still have been included in our sample. We are planning to validate the algorithm we used in a future study using data collected from medical records. Second, our dataset included commercially insured patients only who were either healthy enough to be employed or closely related to an employed person, so findings may not precisely reflect the US population due to this healthy-worker bias. Third, the administrative claims used in this study were collected for reimbursement purposes and the completeness and accuracy of medical coding is subject to data coding restrictions and data entry error. Fourth, presence of comorbidities was determined based upon having at least one claim with a relevant ICD-9/ICD-10 code, not a clinical diagnosis, so misclassification, diagnostic uncertainty or coding errors were possible. Fifth, we observed a high overlap of multiple myeloma and AL amyloidosis in prevalent patients. Our data are not clinically detailed enough to determine which diagnosis was most appropriate for these patients. Sixth, the healthcare cost estimates may be underestimated as claims for patients who die outside of the hospital were not available, and services not covered by insurance or rendered 'out-of-network' were not included. Seventh, the subgroup of patients with at least 2-year enrollment were less sick, as measured by CCI and had lower comorbid disease burden, compared with those with shorter enrollment. For example, in patients with less than 1 year of enrollment, 31.4% of them had congestive heart failure, compared with 17.4% found in patients with at least 2 years of enrollment. This reduces the generalizability of the cost findings in this healthier subgroup. Lastly, cost estimates include direct healthcare costs only, and do not take into account important indirect costs associated with caregiver burden, loss of productivity or reduced quality of life.

## Conclusion

Our analysis indicates: evidence of changes in practice patterns with regard to prescribing specific AL chemotherapy-based treatments, with increased use of bortezomib and decreased use of melphalan; total annual healthcare costs increased over time among prevalent AL amyloidosis patients; and among a subgroup of incident patients with at least 2 years of follow-up, total healthcare utilization and costs decreased from the first year following diagnosis to the second year. This study is the first to provide a comprehensive report of the real-world AL amyloidosis disease burden in the US population with AL amyloidosis.


### Summary points

- Amyloid light-chain (AL) amyloidosis is a rare, progressive and typically fatal disease caused by extracellular deposition of misfolded immunoglobulin light chains.
- This manuscript examines healthcare utilization and costs associated with AL amyloidosis in the US using real-world, nationally representative health insurance claims data.
- This information on AL amyloidosis is vital to understanding the current burden on the healthcare system of this life-threatening disease, and it provides a baseline against which to monitor trends.

**Methods**

- We employed a mixed method approach with cross-sectional and longitudinal analyses of two separate patient populations: prevalent and incident AL amyloidosis patients, respectively.
- Patients with AL amyloidosis were identified in 2007–2015 claims databases if they had: ≥1 inpatient or 2 outpatient claims consistent with AL amyloidosis; and received ≥1 AL specific treatments following diagnosis.
- We reported descriptive statistics on healthcare costs and utilization by calendar year and overall. Costs were adjusted to 2015 US$.

**Results & conclusion**

- Hospitalization was common: 50.1% (n = 3670) were admitted at least once during the year and 11.3% (827) three or more times.
- Use of bortezomib during the study period increased from 4.6% in 2007 to 25.3% in 2015, while use of melphalan decreased from 18.9% in 2007 to 2.0% in 2015.
- Costs among prevalent patients increased over time ($92,866 in 2007 to $114,030 in 2015).
- Among a subgroup of incident patients with at least 2 years of follow-up, total healthcare utilization and costs decreased from the first year following diagnosis to the second year.
- Our study indicates: evidence of changes in practice patterns with regard to prescribing specific AL chemotherapy-based treatments; total annual healthcare costs increased over time among all prevalent AL amyloidosis patients; 3) among a subgroup of incident patients with at least 2 years of follow-up, total healthcare utilization and costs decreased from the first year following diagnosis to the second year.


### Author contributions

All authors were equally involved in the design of the study. E Chang conducted the statistical analyses and all authors contributed equally in the interpretation of results and writing of the manuscript.


### Financial & competing interests disclosure

TP Quock is an employee of Prothena Biosciences Inc., which funded the research described in this manuscript. S Guthrie was employed by Prothena Biosciences Inc. at the time the study was conducted and completed. MS Broder, E Chang and T Yan are employees of the Partnership for Health Analytic Research, LLC, which received funding from Prothena Biosciences Inc. 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.

J Munday, an employee of PHAR, LLC, provided writing assistance. S Gokhale, an employee of PHAR, LLC, provided technical assistance and proofreading of the manuscript.

### 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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