Research Article

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Mortality and healthcare costs in medicare beneficiaries with AL amyloidosis

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Aims: Examine mortality and healthcare costs in Medicare beneficiaries with newly diagnosed immunoglobulin light chain (AL) amyloidosis. **Patients & methods:** Cases were identified in 2012–2015 Medicare 5% data with ≥1 inpatient/≥2 outpatient claims consistent with AL amyloidosis and ≥1 AL-specific treatment. Cases were matched 3:1 with disease-free controls. Descriptive statistics were reported. **Results:** A total of 249 (33.3%) cases were matched to 747 (66.7%) controls. A total of 19.7% of cases died within 1 year of follow-up versus 5.5% of controls; 30.6 versus 11.8% died within 2 years ($p < 0.001$). Mean (SD) costs in 1-year of follow-up were significantly higher among cases versus controls ($71,040 [65,766] vs $13,722 [27,493]; $p < 0.001$). **Conclusion:** Mortality was nearly four-times higher, and costs nearly five-times higher in beneficiaries with AL amyloidosis versus controls.

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Keywords: AL amyloidosis • healthcare costs • insurance claims • Medicare • mortality • secondary data analysis

Amyloidoses refer to a group of rare protein folding disorders characterized by extracellular tissue deposition of misfolded and aggregated autologous proteins as β-pleated sheet fibrils [1]. Immunoglobulin light chain (AL) amyloidosis accounts for approximately 70% of all systemic amyloidoses and is therefore the most common form of these diseases [2]. The monoclonal light chains can irreversibly damage all organs, except the central nervous system, when they are deposited in the form of amyloid fibrils in tissues [3]. Current estimates suggest that at least 12,000 adults are affected by AL amyloidosis in the US, and this number may rise as an increasing prevalence rate was observed in our previous study with claims data [4]. In addition, the disease predominantly affects older adults, many of which are Medicare beneficiaries. Therefore, with rapid population aging coupled with increasing prevalence of AL amyloidosis, the number of Medicare beneficiaries with the disease will likely rise in the future [4,5].

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, data used and progression of the disease [6–9]. However, survival following AL amyloidosis diagnosis has not been examined using real-world, nationally representative data in the USA. In our previous study with claims data, approximately 40% of patients had Medicare, and we were unable to examine mortality because these data were unavailable. In comparison, the current study examines both survival and costs in Medicare patients.

In a search of PubMed, we found no studies that examined the economic burden of AL amyloidosis using nationally representative, real-world data. However, in a previous study, we estimated the cost of AL amyloidosis patients was $122,180 in the year following diagnosis [10].

As the disease mainly affects individuals with advanced age, [11] most US patients with the condition are Medicare beneficiaries. In the current study, we sought to examine time to death, death rates and healthcare costs in the 1 year following diagnosis among Medicare beneficiaries with newly diagnosed AL amyloidosis. Specifically, we compared these outcomes between patients with AL amyloidosis (cases) and population-based, AL amyloidosis disease-free controls to provide greater context for the burden of illness that patients with AL amyloidosis face.

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Patients & methods

Data sources

We used 2011–2016 data from the 5% Medicare Limited Data Set (LDS) for this retrospective, matched case–control study. The LDS contains a 5% random sample of Medicare beneficiaries, which is representative of the overall population covered by Medicare, the largest insurer of people aged 65 years and older in the USA. Data included information about year of birth, sex, race or ethnic origin, date of death (if deceased), reasons for Medicare entitlement and Medicare Advantage Plan (health maintenance organization) enrollment.

Medicare Part A and Part B files contain Medicare reimbursed claims from the following settings for fee-for-service enrollees: inpatient, outpatient, emergency room, physician office, skilled nursing facility, hospice, home health agency and durable medical equipment. Specifically, we used both beneficiary-level and claim-level data from the following individual files: Master Beneficiary Summary File, Inpatient File, Home Health Agency File, Outpatient File, Carrier (Physician/Supplier Part B Claims) File, Durable Medical Equipment File, Hospice File, Skilled Nursing Facility File.

We linked beneficiary information across Medicare files using encrypted identification numbers that are included on all patient- and claim-level files.

The Medicare claims data were created in accordance with the principles of the Health Insurance Portability and Accountability Act (HIPAA). The analysis of the LDS is exempt from a Privacy Board review.

Study population

The study population was comprised of the following two cohorts of Medicare beneficiaries: newly diagnosed AL amyloidosis beneficiaries, and matched, disease-free beneficiaries.

Cases: beneficiaries with incident AL amyloidosis

As there is no diagnosis code specific to AL amyloidosis, the following algorithm was used to identify Medicare beneficiaries with AL amyloidosis during the study identification (ID) period (01/01/2012 to 12/31/2015). Beneficiaries with AL amyloidosis were identified if they had at least one inpatient claim or 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 position on claims in the inpatient, outpatient or carrier files between 01/01/2011 and 12/31/2016 with the first observed diagnosis date (index date) occurred during the ID period, and received an intravenous treatment recommended in expert guidelines [12–16] for AL amyloidosis (bendamustine, bortezomib, carfilzomib, cyclophosphamide, dexamethasone, prednisone, lenalidomide, melphalan, pomalidomide, thalidomide or hematopoietic stem cell transplant) within 90 days prior to or any time on or after the index date in the study period. As Medicare Part D data are not available in the study database, treatments were limited to hematopoietic stem cell transplant, injectable drugs and oral prescription drugs covered under Medicare Part A and Part B. The first observed AL amyloidosis diagnosis date was the index date. To ensure that all beneficiaries were newly diagnosed AL amyloidosis patients, they were excluded if they had any diagnosis of AL amyloidosis during the 1 year prior to the index date (baseline period).

The above beneficiaries were required to be age $\geq$66 years on the index date to ensure $\geq$1 year of pre-index eligibility; have continuous enrollment in fee-for-service Medicare and be eligible for Medicare Parts A and B for 1 year prior to the index date; and be enrolled in fee-for-service Medicare for at least 1 year after the index date, with the exception of beneficiaries who died during the year. All beneficiaries were followed until the end of enrollment, death or study end, whichever occurred first.

Population-based, disease-free controls: beneficiaries without AL amyloidosis

Among patients who never had a single claim consistent with AL amyloidosis in the study period, controls were matched with cases in a 3:1 ratio based on age, gender, race and geographic location. Controls were assigned to have the same index date as the corresponding case. The same insurance type and continuous enrollment inclusion criteria were applied to the controls as the cases (see Figure 1 for the study timeline). A similar matching approach has been used in a previous study [17].

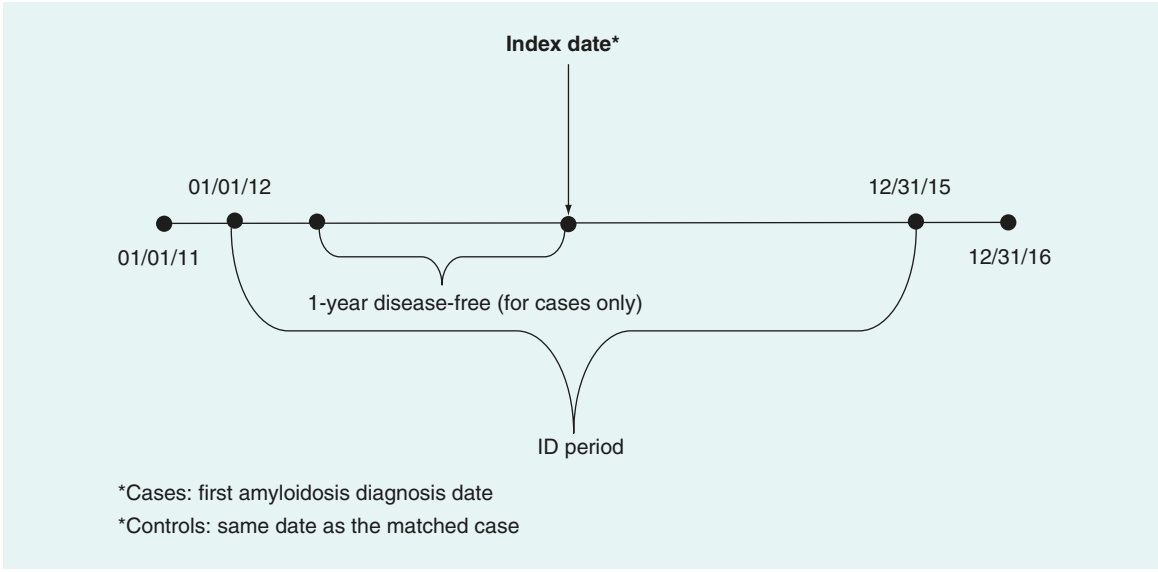

Figure 1. Study timeline for the matched case–control cohort.
*Cases: first amyloidosis diagnosis date.
*Controls: same date as the matched case.
ID: Identification.

Study measures & statistical analysis

Patient demographic & clinical characteristics

For cases and controls, we reported the patient demographic and clinical characteristics during baseline (1-year period prior to the index date). 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 (MGUS; 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), hypotension (ICD-9-CM: 458.xx; ICD-10-CM: I95.xx), hyperlipidemia (ICD-9-CM: 272.0x-272.4x; ICD-10-CM: E78.0x-E78.5x), carpal tunnel syndrome (ICD-9-CM: 354.0x; ICD-10-CM: G56.00, G56.01, G56.02, G56.03) and end-stage renal disease (ICD-9-CM: 585.6, 996.81, V42.0, V45.1, V56.0, V56.1, V56.2, V56.3, V56.31, V56.32, V56.8, E879.1; ICD-10-CM: N18.9, T86.10-T86.13, T86.19; HCPCS: 90935, 90937, 90940, 90945, 90947, 90951-90970, 90989, 90993, 90997, 90999). Presence of these clinical characteristics was determined based upon having at least one claim with a relevant ICD-9/ICD-10/HCPCS code.

Mortality & healthcare costs

For cases and controls, we reported death rates overall in the 1-year follow-up period and time-to-death over the entire follow-up. We reported total costs and the following cost components for cases and controls in the 1-year follow-up period: inpatient hospitalization; skilled nursing facilities; hospice; ED; and non-ED outpatient service, which included costs from non-ED outpatient hospitals, home health agencies, noninstitutional providers and durable medical equipment. Services not covered by Medicare insurance were not included.

Statistical analysis

Descriptive statistics including means, standard deviations and relative frequencies and percentages for continuous and categorical data, respectively, were reported, stratified by case versus control status. T-tests and Chi-square tests for continuous and categorical variables, respectively, were performed. Additionally, to calculate time to mortality, Kaplan–Meier survival analysis was performed. Cost estimates were converted to 2016 (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 (SAS Institute Inc., NC, USA).

Table 1. Attrition table: newly diagnosed immunoglobulin light chain amyloidosis patients.

Step/definition	n
A. No. of patients with at least one inpatient claim or two outpatient claims for AL amyloidosis diagnosis[†] in any position in inpatient hospital, outpatient hospital or carrier files between 01/01/2012 and 12/31/16 with the first diagnosis date (index date) occurred during ID period (1/1/2012–12/31/2015) among CMS LDS databases	2566
B. Of A, no. of patients who had no AL amyloidosis diagnoses in baseline period (1 year prior to the index date)	2220
C. Of B, no. of patients who received an AL amyloidosis treatment[‡] (covered by Part A or Part B plan) within 90 days prior to or any time on or after index date within study period	460
D. Of C, no. of patients who were continuously enrolled in baseline with qualified plan (Part A and Part B with fee-for-service plan)	289
E. Of D, no. of patients who were continuously enrolled for at least 1 year since index date (except died within 1 year) with qualified plan	279 (55 died within 1 year; 21 [8%] with ESRD[§])
F. Of E, no. of patients who were 66 or older	249[¶]

[†]International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes: 277.30 or 277.39 or International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes: E85.4x, E85.8x (excluding E85.82) or E85.9x.
[‡]HSCT, injectable drugs, or oral prescription drugs covered under Medicare parts A or B.
[§]With Medicare status as aged with ESRD, disabled with ESRD, or ESRD only at index.
[¶] Final sample of newly diagnosed AL amyloidosis patients in this study.
AL: Immunoglobulin light-chain; CMS: Centres for Medicare and Medicaid Services; ESRD: End-stage renal disease; HSCT: Hematopoietic stem cell transplant; LDS: Limited data set.

Results

Patient demographic characteristics & comorbidities

In the 2011–2016 data from the 5% Medicare LDS, 249 (33.3%) newly diagnosed AL amyloidosis Medicare beneficiaries were identified and matched to 747 (66.7%) disease-free controls. As shown in Table 1, 2566 patients had at least one inpatient or two outpatient claims for AL amyloidosis between 01/01/2012 and 12/31/2016, with the first diagnosis date occurring during the ID period (01/01/2012–12/31/2015). Of those 2566 patients, 2220 patients had no AL amyloidosis diagnosis in the baseline (1-year disease free) period; 460 patients received an AL amyloidosis treatment within 90 days of the index date; 279 patients were continuously enrolled during baseline in a qualified health plan and were continuously enrolled for at least 1 year following the index date (except those who died within 1 year). This left 249 patients with AL amyloidosis who were 66 or older in the study.

The mean (SD) age of newly diagnosed AL amyloidosis beneficiaries and disease-free controls was 76 (6.2) years; 41.8% of both newly diagnosed AL amyloidosis beneficiaries and disease-free controls were female; all US regions were represented; and the majority (90.4%) of both newly diagnosed AL amyloidosis beneficiaries and disease-free controls were white. Significantly more newly diagnosed AL amyloidosis beneficiaries were over 65 years old with end-stage renal disease compared with disease-free controls (6.0 vs 0.8%; $p < 0.001$). Enrollment length (from index date to the end of enrollment in the qualified health plan or study end [12/31/2016]) was significantly shorter in newly diagnosed AL amyloidosis beneficiaries than disease-free controls (mean [SD] 801 [488.0] days vs 933 [430.1] days; $p < 0.001$). Significantly more newly diagnosed AL amyloidosis beneficiaries died during follow-up than disease free controls (36.9 vs 15.3%; $p < 0.001$); and significantly more newly diagnosed AL amyloidosis beneficiaries died less than 1 year (≤364 days) after the index date than disease free controls (19.7 vs 5.4%; $p < 0.001$; Table 2).

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. The mean (SD) of CCI in AL amyloidosis patients was 5.0 (3.6) compared with 2.1 (2.5) in disease-free controls. Common individual comorbidities in the CCI in AL amyloidosis patients were congestive heart failure (36.1% in AL amyloidosis patients compared with 11.2% in controls), cerebrovascular disease (27.7%; 16.1%), chronic pulmonary disease (37.8%; 22.5%), moderate or severe liver disease (29.7%; 10.2%), renal disease (35.7%; 13.8%), diabetes without chronic complications (42.6%; 29.2%) and malignancy/lymphoma/leukemia (35.7%; 15.1%). Furthermore, hypothyroidism (cases: 32.1%; controls: 22.2%) and hyperlipidemia (77.5%; 65.6%) were common among newly diagnosed AL amyloidosis beneficiaries (Table 3).

Mortality

Based on the Kaplan–Meier survival analysis, 3 months after the index date, 7.6% of newly diagnosed AL amyloidosis beneficiaries had died compared with 1.2% of disease-free controls. 6 months after the index date, 13.7% of newly

Table 2. Final matched† cohort: patient demographics.

Variables	Newly diagnosed AL amyloidosis patients	Matched disease-free controls	All	p-value
n (%)	249 (33.3%)	747 (66.7%)	996 (100%)	
Age, year†, mean (SD)	76 (6.2)	76 (6.2)	76 (6.2)	n/a
66–74	124 (49.8)	372 (49.8)	496 (49.8)	n/a
75–84	100 (40.2)	300 (40.2)	400 (40.2)	
85+	25 (10.0)	75 (10.0)	100 (10.0)	
Female†, no. (%)	104 (41.8)	312 (41.8)	416 (41.8)	n/a
Region†, no. (%)	50	150	200	n/a
Midwest	(20.1)	(20.1)	(20.1)	
Northeast	47 (18.9)	141 (18.9)	188 (18.9)	
South	111 (44.6)	333 (44.6)	444 (44.6)	
West	41 (16.5)	123 (16.5)	164 (16.5)	
Race†, no. (%)	225	675	900	n/a
White	(90.4)	(90.4)	(90.4)	
Black	19 (7.6)	57 (7.6)	76 (7.6)	
Other/unknown		15 (2.0)	20 (2.0)	
CMS status, no. (%)	234	741	975	< 0.001
Aged without ESRD	(94.0)	(99.2)	(97.9)	
Aged with ESRD	15 (6.0)			
Days of follow-up (from index date to end of enrollment of qualified plan or study end [12/31/2016]), mean (SD) [Median]	801 (488.0) [762]	933 (430.1) [890]	900 (448.7) [867]	< 0.001
Died during follow-up, no. (%)	92 (36.9)	114 (15.3)	206 (20.7)	< 0.001
Died less than 1 year after index date, no. (%)	49 (19.7)	40 (5.4)	89 (8.9)	< 0.001

†Disease-free controls were matched with cases in a 3:1 ratio based on age, gender, race and geographic location.
Note: Some cells suppressed to comply with CMS cell size suppression policy.
AL: Immunoglobulin light chain; CMS: Centers for Medicare and Medicaid Services; ESRD: End-stage renal disease; SD: Standard deviation.

diagnosed AL amyloidosis beneficiaries had died compared with 2.7% of disease-free controls. One year (≤365 days) after the index date, 19.7% of newly diagnosed AL amyloidosis beneficiaries had died compared with 5.5% of disease-free controls. 18 months after the index date, 26.6 and 8.2% of newly diagnosed AL amyloidosis beneficiaries and disease-free controls had died, respectively. 2 years after the index date, 30.6 and 11.8% of newly diagnosed AL amyloidosis beneficiaries and disease-free controls had died, respectively (all $p < 0.001$; Figure 2; Table 4).

Healthcare Costs

Mean (SD) total annual all-cause Part A and Part B healthcare costs in the 1-year follow-up period were statistically significantly higher ($p < 0.001$) in newly diagnosed AL amyloidosis beneficiaries than in disease-free controls ($71,040 [65,766] vs $13,722 [27,493]). The majority of total costs among newly diagnosed AL amyloidosis beneficiaries accrued from inpatient hospital costs ($28,126 [40,409]) and non-ED outpatient service costs (mean [SD] $37,137 [37,363]; Table 5).

Discussion

Using data that are nationally representative of Medicare beneficiaries, we found that almost 20% of newly diagnosed AL amyloidosis beneficiaries died within 1 year of diagnosis, while 5.5% of age, gender, race and geographic region-matched disease-free controls died in the 1-year follow-up period. Healthcare costs for Medicare Part A and Part B were a mean of $71,040 for newly diagnosed AL amyloidosis beneficiaries compared with $13,722 for disease-free controls in the 1-year follow-up period. The present study provides information about incremental mortality and healthcare costs associated with AL amyloidosis in the year following diagnosis in a real-world setting. Our study indicates that individuals with newly diagnosed AL amyloidosis have a substantial burden of comorbidities. Several of the observed conditions, including congestive heart failure, renal disease and liver disease, likely represent manifestations of the AL amyloidosis disease process.

Table 3. Final matched cohort: patient baseline comorbidities.

Variables	Newly diagnosed AL amyloidosis patients	Matched disease-free controls	All	p-value
n	249	747	996	
Charlson comorbidity index, mean (SD) (Median)	5.0 (3.6) [4]	2.1 (2.5) [1]	2.9 (3.1) [2]	< 0.001
Myocardial infarction, no. (%)	37 (14.9)	40 (5.4)	77 (7.7)	< 0.001
Congestive heart failure, no. (%)	90 (36.1)	84 (11.2)	174 (17.5)	< 0.001
Peripheral vascular disease, no. (%)	35 (14.1)	83 (11.1)	118 (11.8)	0.213
Cerebrovascular disease, no. (%)	69 (27.7)	120 (16.1)	189 (19.0)	< 0.001
Dementia, no. (%)		19 (2.5)	25 (2.5)	0.907
Chronic pulmonary disease, no. (%)	94 (37.8)	168 (22.5)	262 (26.3)	< 0.001
Rheumatologic disease, no. (%)	24 (9.6)	28 (3.7)	52 (5.2)	< 0.001
Peptic ulcer disease, no. (%)		14 (1.9)	24 (2.4)	0.056
Mild liver disease, no. (%)			14 (1.4)	0.351
Moderate or severe liver disease, no. (%)	74 (29.7)	76 (10.2)	150 (15.1)	< 0.001
Renal disease, no. (%)	89 (35.7)	103 (13.8)	192 (19.3)	< 0.001
Diabetes without chronic complications, no. (%)	106 (42.6)	218 (29.2)	324 (32.5)	< 0.001
Diabetes with chronic complications, no. (%)	44 (17.7)	59 (7.9)	103 (10.3)	< 0.001
Malignancy/lymphoma /leukemia, no. (%)	89 (35.7)	113 (15.1)	202 (20.3)	< 0.001
Metastatic solid tumor, no. (%)	15 (6.0)		21 (2.1)	< 0.001
Multiple myeloma, no. (%)	37 (14.9)	0 (0.0)	37 (3.7)	< 0.001
Monoclonal gammopathy of undetermined significance, no. (%)	34 (13.7)		37 (3.7)	< 0.001
Hypothyroidism, no. (%)	80 (32.1)	166 (22.2)	246 (24.7)	0.002
Waldenström's macroglobulinemia, no. (%)				< 0.001
Carpal tunnel syndrome, no. (%)	23 (9.2)	15 (2.0)	38 (3.8)	< 0.001
Malignancy/lymphoma/leukemia, excluding multiple myeloma, no. (%)	67 (26.9)	113 (15.1)	180 (18.1)	< 0.001
Hypotension, no. (%)	45 (18.1)	34 (4.6)	79 (7.9)	< 0.001
Hyperlipidemia, no. (%)	193 (77.5)	490 (65.6)	683 (68.6)	< 0.001
End stage renal disease[†], no. (%)	14 (5.6)		24 (2.4)	< 0.001

[†]ICD-9-CM diagnosis code: 585.6, 996.81, V42.0, V45.1, V56.0, V56.1, V56.2, V56.3, V56.31, V56.32, V56.8, E879.1; ICD-10-CM diagnosis code: N18.9, T86.10-T86.13, T86.19; HCPCS: 90935, 90937, 90940, 90945, 90947, 90951-90970, 90989, 90993, 90997, 90999
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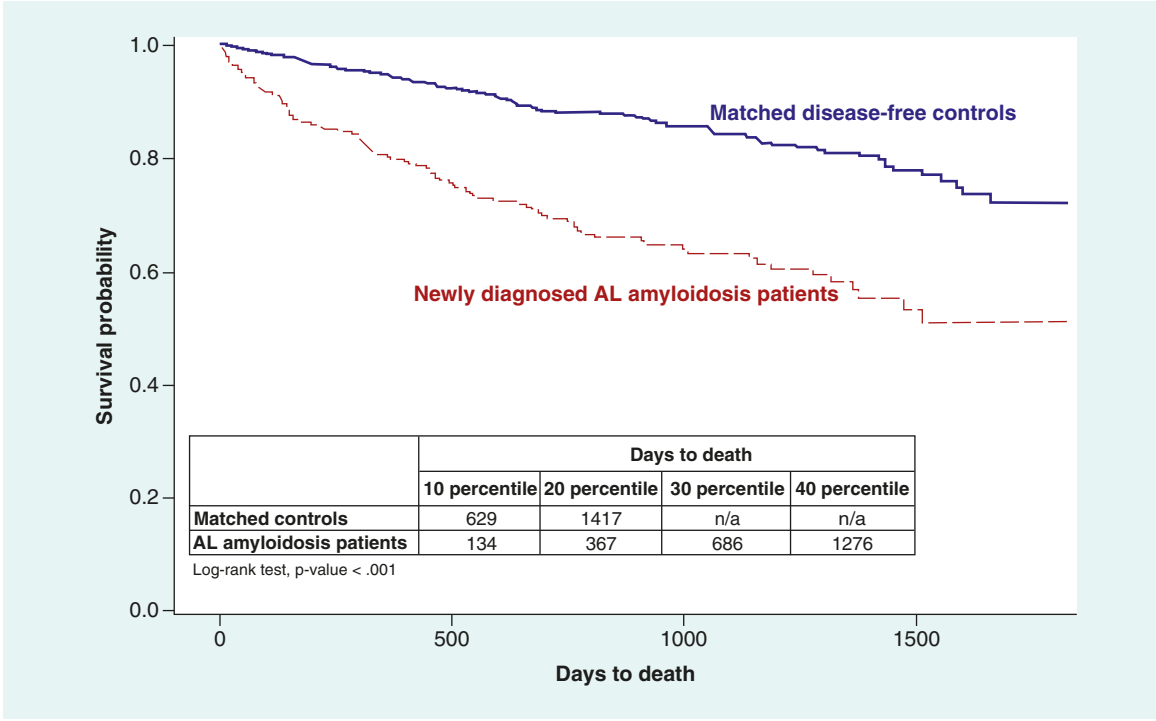
Table 4. Mortality of matched controls compared with immunoglobulin light chain amyloidosis patients.

Group		At 3 months	At 6 months	At 12 months	At 18 months	At 24 months
Matched controls	CDI (95% CI)	1.2% (0.6%–2.3%)	2.7% (1.7%–4.1%)	5.5% (4.1%–7.4%)	8.2% (6.4%–10.4%)	11.8% (9.6%–14.5%)
	# of enrollees at risk	738	727	707	583	460
AL amyloidosis patients	CDI (95% CI)	7.6% (4.9%–11.7%)	13.7% (10.0%–18.6%)	19.7% (15.3%–25.2%)	26.6% (21.5%–32.6%)	30.6% (25.1%–37.0%)
	# of enrollees at risk	230	215	200	157	100

AL: Immunoglobulin light chain; CDI: Cumulative death incidence.

Mortality

Death within 1 year after the index date was almost four-times higher in newly diagnosed AL amyloidosis beneficiaries than disease-free beneficiaries. To date, no studies have provided nationally representative data on survival in Medicare beneficiaries with newly diagnosed AL amyloidosis. However, several European and clinical studies have examined survival in these patients. For example, in a Swedish population-based study that used the nationwide Swedish Patient Registry, Weiss *et al.* (2016) found that 30% of patients diagnosed with AL amyloidosis between 2010 and 2013 died within 1 year of diagnosis; and 39% of patients died within two years [6]. A study by Muchtar *et al.* on patients with AL amyloidosis diagnosed and seen at Mayo Clinic between 2010 and 2014 found



	Days to death			
	10 percentile	20 percentile	30 percentile	40 percentile
Matched controls	629	1417	n/a	n/a
AL amyloidosis patients	134	367	686	1276

Log-rank test, p-value < .001

Figure 2. Time to death.
[a]Cumulative Death Incidence.
AL: Immunoglobulin light chain.

Table 5. Final matched cohort: healthcare Part A and Part B coverage costs in the 1-year [†] follow-up period.

Costs	Newly diagnosed AL amyloidosis patients	Matched disease-free controls	All	p-value
n	249	747	996	–
Post 1 year total costs (Part A and Part B coverage), mean (SD)	$71,040 (65,766)	$13,722 (27,493)	$28,051 (47,554)	< 0.001
Inpatient hospital costs	$28,126 (40,409)	$4768 (15,872)	$10,608 (26,425)	< 0.001
Skilled nurse facility costs	$4423 (13,130)	$1142 (5,943)	$1962 (8,454)	< 0.001
Hospice costs	$910 (3,945)	$263 (2,044)	$424 (2,662)	0.014
ED costs	$443 (897)	$193 (659)	$256 (733)	< 0.001
Non-ED outpatient service costs	$37,137 (37,363)	$7355 (11,284)	$14,801 (24,696)	< 0.001

[†]All patients, except those who died within 1 year, had at least 1 year of follow-up.
AL: Immunoglobulin light chain; ED: Emergency department; SD: Standard deviation.

a 2-year death rate of 40% [18]. These death rates are higher than those in our analysis likely due to differences in patient populations and data used, as patients seen at the Mayo Clinic are probably sicker than average Medicare patients with AL amyloidosis.

The mortality rate found in our study may be lower than those found in other studies because patients whose disease is so far progressed that they do not receive treatment are excluded from our study.

Healthcare costs

The incremental cost of AL amyloidosis is very high. In the 1-year follow-up period, healthcare costs were more than five times higher in AL amyloidosis beneficiaries than in disease-free beneficiaries. To date, no studies have provided

nationally representative data on healthcare costs in Medicare beneficiaries with newly diagnosed AL amyloidosis. However, in a study by Hari *et al.* that used administrative claims data on adult patients with relapsed/refractory AL amyloidosis, total average healthcare costs in the 1 year following AL amyloidosis relapse or refractory state were $139,143. The authors state that these costs were similar to those for newly diagnosed AL amyloidosis patients, but the exact cost is not provided [19]. Patients in the Hari *et al.* study differed from those included in our study because patients with relapsed/refractory AL amyloidosis lived long enough to receive a second line of treatment. In comparison, Quock *et al.* performed a study on newly diagnosed AL amyloidosis patients ≥18 years old using Truven MarketScan® Commercial and Medicare Supplement Databases (Truven Health Analytics, MI, USA) and found a mean total cost of $122,180 in the 1-year post-diagnosis period [10]. The average cost found in this previous study may be higher than what we found in the current study because we were unable to include costs associated with prescription drugs covered by Medicare Part D in the current study due to lack of access to these data. For example, in the Quock *et al.* study, mean total outpatient pharmacy costs for all prevalent AL amyloidosis patients between 2007 and 2015 were $13,054; if these pharmacy costs were not included in this previous study, mean total costs would have been similar to those found in the current study [10].

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, 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, 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. Third, 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. Fourth, 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. Fifth, 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. Sixth, we did not match based upon clinical factors, such as cardiovascular disease, as the goal of our study is to describe the incremental burden of illness AL amyloidosis patients face compared with population-based, disease-free controls. We would expect that patients with amyloidosis would have many more comorbid illnesses than matched controls. If we matched by comorbidity, we would be unable to estimate the burden of the disease, as the comparison group would (because of matching) have an abnormally high burden of disease for their age. Lastly, due to lack of access to Part D data, patients treated with prescription drugs covered under Part D were not included in our study. However, we plan to replicate the study using the Medicare 100% data file, which includes Part D data, in the near future.

Conclusion

In summary, this analysis shows that among newly diagnosed AL amyloidosis Medicare beneficiaries, about 20% die within 1 year of diagnosis; and a mean of $71,040 is spent for Part A and Part B coverage in the 1 year following diagnosis.

This study is the first to provide a comprehensive report of the real-world mortality and healthcare costs associated with AL amyloidosis in a US Medicare population with newly diagnosed AL amyloidosis.

Future perspective

With a rapid aging population and increasing prevalence of AL amyloidosis, the number of Medicare beneficiaries with the disease is expected to increase over the coming years. Despite its high mortality and high burden of disease, AL amyloidosis is under-diagnosed. Awareness is essential for timely detection and treatment of AL amyloidosis. The hope of new therapies on the horizon may also offer opportunities to enhance the survival and reduce the burden of the disease.

Summary points

Background

- Current estimates suggest that at least 12,000 adults are affected by immunoglobulin light chain (AL) amyloidosis in the USA, and this number may rise, as an increasing prevalence rate was observed in our previous study with claims data.
- The disease predominantly affects older adults, many of which are Medicare beneficiaries. With rapid population aging and increasing prevalence of AL amyloidosis, the number of Medicare beneficiaries with the disease will likely rise in the future.
- We sought to examine time to death, death rates and healthcare costs in the 1 year following diagnosis among Medicare beneficiaries with newly diagnosed AL amyloidosis.

Methods

- We used 2011–2016 data from the 5% Medicare Limited Data Set for this retrospective, matched case–control study.
- The study population was comprised of the following two cohorts of Medicare beneficiaries: newly diagnosed AL amyloidosis beneficiaries, and matched, disease-free beneficiaries.
- For cases and controls, we reported the patient demographic and clinical measures during baseline (1-year period prior to the index date), mortality during the entire follow-up period and healthcare cost measures during the 1-year follow-up period.

Results

- A total of 249 (33.3%) cases were matched to 747 (66.7%) controls. 19.7% of cases died within 1 year of follow-up versus 5.5% of controls; 30.6 vs 11.8% died within 2 years ($p < 0.001$). Mean (SD) costs in 1-year of follow-up were significantly higher among cases versus controls ($71,040 [65,766] vs $13,722 [27,493]; $p < 0.001$).

Conclusion

- In summary, this analysis shows that among newly diagnosed AL amyloidosis Medicare beneficiaries about 20% die within 1 year of diagnosis; and a mean of $71,040 is spent for Part A and Part B coverage in the 1 year following diagnosis.
- This study is the first to provide a comprehensive report of the real-world mortality and healthcare costs associated with AL amyloidosis in a US Medicare population with newly diagnosed AL amyloidosis.

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Authors' 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.

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