scientific reports

Check for updates

OPEN

Incidence and prevalence of light chain amyloidosis in the United States in 2019–2021 using Optum EHR data

Pedro A. Laires[1,2]✉, Shona Fang[3], Jennifer Evans[3], Jeffrey Thompson[3], Abhishek Gaur[4], Brendon Staruk[4], Ankita Gupta[4] & Richa Manwani[5,6]

Immunoglobulin light chain amyloidosis (AL amyloidosis) is among the most common forms of systemic amyloidosis. Using electronic health records (EHR) data from the United States, we aimed to estimate the incidence and prevalence of AL amyloidosis over time, to evaluate the distribution of different disease stages, and to assess patients' demographic characteristics. We conducted a retrospective cohort study using Optum EHR data from 2016 to 2022. AL amyloidosis was defined by ≥ 2 ICD-10-CM codes or positive mentions in the EHR that were ≥ 30 days apart. Incident and prevalent patients were included. Staging was assessed using cardiac biomarkers (whenever available) according to the European modification of the 2004 Mayo staging system. A total of 1976 AL amyloidosis patients were identified. In 2021, the estimated AL amyloidosis incidence was 16.7 per million person-years in adults, and the prevalence was 69.0 per million adult population. Among patients with staging available near the time of diagnosis (41.7% of incident patients), the following distribution was observed: 16.1% Stage I, 44.5% Stage II, 20.6% Stage IIIa, and 18.8% Stage IIIb. At the most recently available staging assessment, combined Stage IIIa and IIIb was more common among males (38.6% vs. 27.1%) and was more common with increasing age (25.7% for 40–49 years vs. 38.5% for 80+ years). We observed the highest prevalence of AL amyloidosis published to date. This may be due to true increased prevalence, consistent with reports of improved survival in AL amyloidosis.

Keywords Amyloidosis, Epidemiology, Multiple myeloma

Immunoglobulin light chain amyloidosis (AL amyloidosis) is a rare disease caused by aggregation of misfolded immunoglobulin light chains that deposit in various tissues, most notably in the heart and kidney[1], and is among the most common forms of systemic amyloidosis[2]. Amyloid deposits can cause life-threatening organ dysfunction and early mortality[1]. Along with improved therapies, an increased understanding of the epidemiology of AL amyloidosis is needed to potentially improve disease outcomes, for example by contributing to earlier diagnosis and risk stratification.

Previous studies of AL amyloidosis in the United States (US) have reported incidence rates ranging from 8 to 16 per million persons per year with similar to somewhat lower rates reported in European countries[3–5]. The most recent reported age- and sex-adjusted estimate of prevalence in the US was 50.1 per million persons in 2015[6], with similar results reported from Sweden in 2019[7]. Both studies from the US and Sweden reported an increase in the prevalence of AL amyloidosis over time[6,7], likely reflecting increased disease recognition and survival[8]. Estimates of the incidence and prevalence of AL amyloidosis in the US using data more recent than 2015 have not been published.

AL amyloidosis can have different degrees of disease severity and expected survival, driven primarily by the extent of cardiac dysfunction[1]. Accordingly, several AL amyloidosis disease staging systems have been proposed to categorize patients on the basis of prognosis[2]. One of the most commonly reported is the European modification of the 2004 Mayo[9,10]. This system (stages: I, II, IIIa, and IIIb) is based upon results from N-terminal pro-hormone brain natriuretic peptide (NT-proBNP) and serum cardiac troponin (TnT) enzyme measurements.

[1]AstraZeneca Rare Disease, Alexion Pharma Spain S.L., Av. Diagonal, 615 6° Planta, 08028 Barcelona, Spain. [2]NOVA National School of Public Health, Public Health Research Center, Universidade NOVA de Lisboa, Lisbon, Portugal. [3]AstraZeneca Rare Disease, Alexion, Boston, USA. [4]Optum, Eden Prairie, USA. [5]AstraZeneca Rare Disease, Alexion, Uxbridge, UK. [6]University College London Hospital, London, UK. ✉email: pedro.laires@alexion.com

At the time of diagnosis, approximately 43–47% of patients had Stage IIIa or IIIb disease according to reports from single tertiary referral centers in the US[11] and Germany[12]. Patients with advanced staging have been shown to have significantly shorter median overall survival[11,12]. The numbers and characteristics of patients in various stages in the general population of the US (i.e., multicenter studies) have not been reported.

Compilations of electronic health records (EHR) can provide information about disease conditions and laboratory results for large general populations. Using EHR data, we aimed to estimate the incidence and prevalence of AL amyloidosis over time by age and sex, to evaluate the distribution of different AL amyloidosis stages at the time of diagnosis and at the most recent clinical assessment, and to assess the demographic characteristics of patients overall and by stage.

Methods

We conducted a retrospective cohort study using Optum EHR data from 01 January 2016 through 31 March 2022. Optum's longitudinal EHR repository is derived from healthcare provider organizations in the US, including more than 700 hospitals, 7000 clinics, and 106 million patients.

All data used for this analysis were de-identified and accessed in full compliance with the Health Insurance Portability and Accountability Act (HIPAA). Due to the retrospective nature of the study and the de-identified status of the database used, the need for ethics approval and informed consent was deemed unnecessary according to national regulations known as United States law 45 CFR 46.101(b)(4). This study followed the guidelines set forth by the International Society of Pharmacoeconomics Outcomes Research (ISPOR) for the responsible retrospective analysis of administrative claims data.

Clinical, claims and other medical administrative data was obtained from both inpatient and ambulatory EHR, practice management systems and other internal systems. Information was processed, normalized, and standardized across the continuum of care from both acute hospitalisations and outpatient visits. Optum data elements include demographics, medications prescribed and administered, immunizations, allergies, lab results (including microbiology), vital signs and other observable measurements, clinical and inpatient stay administrative data and coded diagnoses and procedures. Optum death data are retrieved from multiple sources, including the Centers for Medicare and Medicaid Services, the US Social Security Administration Death Master File, discharge status from the EHRs, and third-party obituary data. In addition, Optum uses natural language processing (NLP) computing technology to transform critical facts from physician notes into usable datasets. The NLP data provides detailed information regarding signs and symptoms, family history, disease related scores, genetic testing, medication changes, and physician rationale behind prescribing decisions that might never be recorded in the EHR.

AL amyloidosis qualifying events were defined by the ICD-10-CM code E85.81 in structured data portions of the EHR or positive mentions of the presence of AL amyloidosis, primary amyloidosis, systemic amyloidosis, or primary systemic amyloidosis in the clinical features or Symptoms, Disease, and Signs (SDS) tables, which comprise more than 10,000 mapped words or sets of words that are automatically extracted from physician notes. The index identification period was 01 January 2017 to 31 March 2022, and the first AL amyloidosis qualifying event during the index identification period was considered the index date. Patients were included if they had ≥ 2 AL qualifying events ≥ 30 days apart during the index identification period. Patients were also included if they had ≥ 1 AL amyloidosis qualifying event between 01 January 2016 and 01 January 2017 (i.e., the year prior to the index identification period) and 1 AL amyloidosis qualifying event in 2017 that was ≥ 30 days apart from the earliest event in 2016. Patients were required to be ≥ 18 years old on the index date for inclusion. All patients were required to have ≥ 12 months of data available prior to their index date (baseline period). An overview of the study periods is shown in Supplemental Fig. 1.

Patients were considered to have incident AL amyloidosis if they had no AL amyloidosis qualifying events during the baseline period. If patients had AL amyloidosis qualifying events during the baseline period, then they were considered to have prevalent AL amyloidosis. Due to the chronic nature of AL amyloidosis, incident and prevalent patients were considered to have prevalent AL amyloidosis for the remainder of the study period unless they died or became unobservable in the data (i.e., no further EHR activity), irrespective of any subsequent AL amyloidosis qualifying events.

Patients' demographic features, including age, sex, race/ethnicity, and residence by US Census Division were determined as of the index date. Other medical conditions were identified during the 12-month baseline period and 12-month follow-up period after the index date based upon ICD-10-CM codes. The Charlson Comorbidity Index (CCI) score was calculated during the 12-month baseline period for all patients based upon ICD-10-CM codes[13].

AL amyloidosis staging was assessed using cardiac biomarkers (whenever available) according to the European modification of the 2004 Mayo staging system[9] and incorporated the Boston University staging system[14]. The cardiac biomarkers assessed and the thresholds for elevation were as follows: cardiac TnT ≥ 0.035 mcg/L; high sensitivity cardiac TnT ≥ 50 ng/L; cardiac troponin I (TnI) ≥ 0.1 mcg/L; brain natriuretic peptide (BNP) ≥ 81 ng/L; NT-proBNP ≥ 332 ng/L. The AL amyloidosis stages were defined as follows: Stage I—no elevation of cardiac troponin or BNP/NT-proBNP; Stage II—elevation of either cardiac troponin or BNP/NT-proBNP but not both; Stage IIIa—elevation of both cardiac troponin and BNP/NT-proBNP but BNP < 700 ng/L and NT-proBNP < 8500 ng/L; Stage IIIb—elevation of both cardiac troponin and BNP/NT-proBNP with BNP ≥ 700 ng/L or NT-proBNP ≥ 8500 ng/L. All laboratory tests were required to be performed within 2 weeks of each other. For incident AL amyloidosis patients, staging must have occurred within 2 months prior to the index date and 12 months after the index date; if more than one assessment was performed during this time period, then the staging results from the date closest to the index date were chosen. If more than one laboratory test value was found on the same day, then the highest value was chosen. For prevalent (i.e., all) AL amyloidosis patients, the most recent staging assessment available was reported.

For the determination of projected incidence and prevalence, the denominator of the total number of patients for each calendar year consisted of the total number of EHR patients age ≥ 18 years with ≥ 12 months of pre-index clinical data. Optum membership counts were adjusted to US Census Bureau data counts (https://data.census.gov) to derive the projected age- and sex-adjusted counts. Projection of prevalent/incident AL amyloidosis cases in the US was based on the age- and sex-specific prevalent/incident proportions from the database multiplied by the corresponding US census population counts by year, age, and sex taken. AL amyloidosis prevalence was determined as a 12-month period prevalence for each calendar year, rather than a point prevalence. Incidence was determined annually for each calendar year. Changes in the incidence and prevalence were assessed using the compound annual growth rate.

Results

As shown in the cohort attrition diagram in Fig. 1 a total of 1976 patients met the study eligibility criteria. The characteristics of the included patients are shown in Table 1. The median age at study index date was 67 years. There was a slight male predominance (54.4%), and most patients were Caucasian (76.6%).

Among all 1976 AL amyloidosis patients included in the study, 817 (41.3%) had any available staging assessment. At the most recent available staging, 276 patients had Stage IIIa or Stage IIIb (33.8% of patients with any staging assessment available). Stage IIIa or IIIb was more common among males (181/469 = 38.6%) compared to females (94/347 = 27.1%). Stage IIIb was more common among African Americans (42/158 = 26.6%) compared to all other race/ethnicity groups (113/659 = 17.1%). The percentage of patients with Stage IIIa or IIIb disease increased with increasing age: 23.3% for 40–49 years, 29.1% for 50–59 years, 30.6% for 60–69 years, 40.2% for age 70–79 years, and 36.4% for 80+ years.

Among 804 incident AL amyloidosis patients, 335 (41.7%) had staging available near the time of diagnosis (Table 2). The following distribution of stages was observed: 16.1% Stage I, 44.5% Stage II, 20.6% Stage IIIa, and 18.8% Stage IIIb. Stage IIIa or IIIb disease was more common among males (89/191 = 46.6%) compared to females (43/144 = 29.9%). Stage IIIa or IIIb disease was uncommon in patients diagnosed prior to age 50 years.

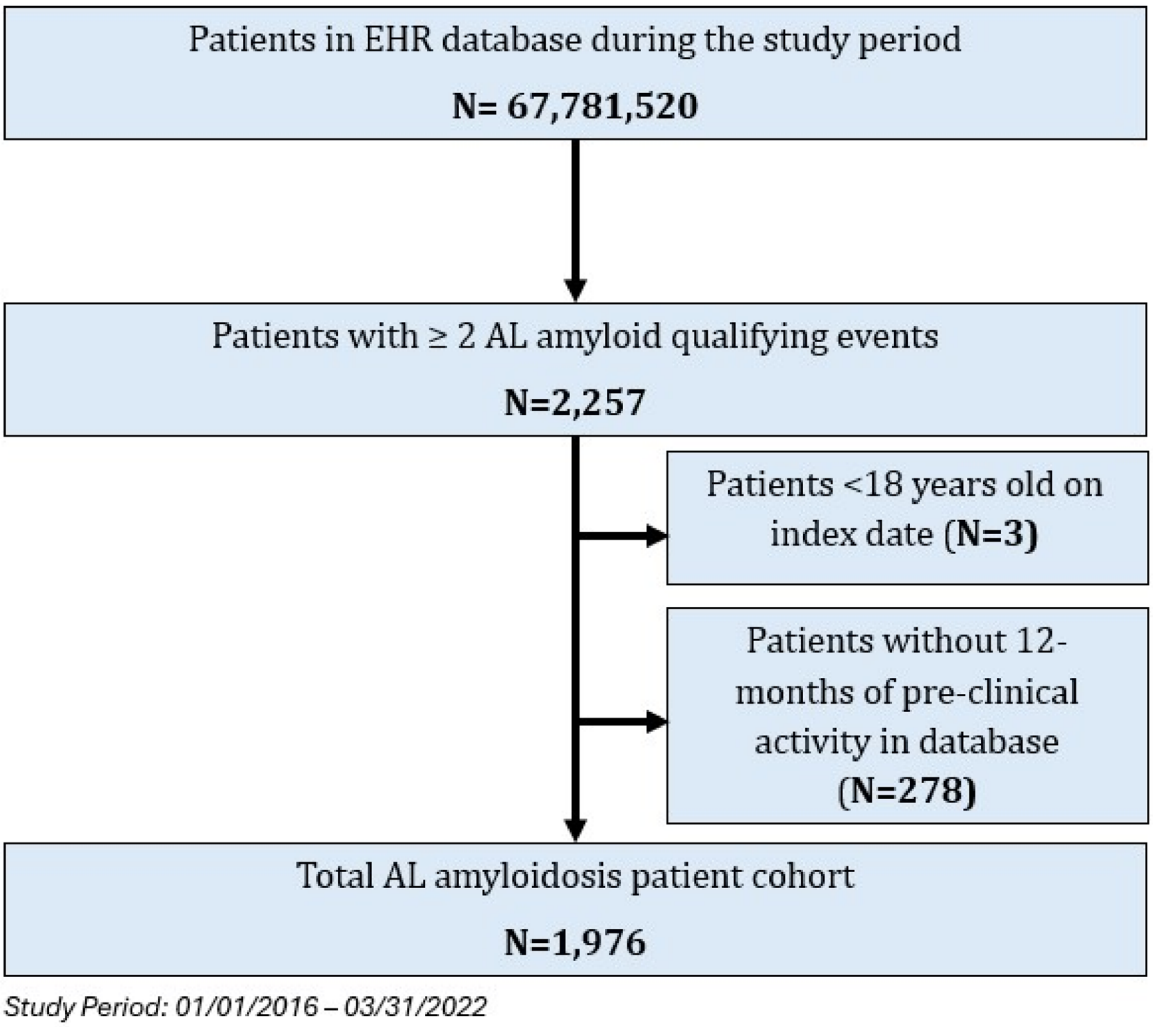

Fig. 1. Cohort attrition diagram.

Characteristic	Overall N = 1976	Stage at most recent assessment				
		Stage I N = 188	Stage II N = 353	Stage IIIa N = 121	Stage IIIb N = 155	Staging not available N = 1159
Mean age at index date (SD), years	66.2 (11.6)	61.9 (10.0)	68.4 (10.5)	68.5 (10.9)	67.6 (11.8)	66.0 (12.0)
Median age at index date (IQR), years	67 (59, 75)	62 (55, 70)	69 (61, 76)	70 (61, 77)	69 (60, 76)	67 (58, 75)
Male	54.4%	54.8%	52.4%	66.9%	64.5%	52.2%
Age category at index date, years						
18–29	0.5%	0.0%	0.0%	0.0%	0.0%	0.9%
30–39	1.1%	1.1%	0.6%	0.8%	1.3%	1.3%
40–49	5.5%	9.0%	4.5%	2.5%	4.5%	5.7%
50–59	17.3%	26.1%	14.5%	13.2%	16.1%	17.3%
60–69	29.5%	35.6%	33.7%	29.8%	29.7%	27.1%
70–79	32.1%	25.0%	29.2%	39.7%	34.2%	33.1%
80+	14.1%	3.2%	17.6%	14.1%	14.2%	14.8%
US census division						
Mountain	2.9%	1.1%	2.0%	0.0%	1.9%	4.0%
West North Central	12.3%	14.9%	12.2%	21.5%	16.8%	10.3%
East North Central	42.2%	55.3%	47.3%	39.7%	45.2%	38.3%
New England	13.1%	7.5%	9.4%	13.2%	7.7%	15.9%
Mid-Atlantic	13.4%	6.4%	13.3%	10.7%	15.5%	14.5%
South Atlantic/West South Central	8.5%	6.4%	9.9%	8.3%	4.5%	8.9%
East South Central	1.5%	0.5%	1.7%	0.8%	1.9%	1.6%
Pacific	3.1%	4.3%	0.9%	4.1%	1.9%	3.6%
Other/unknown	3.2%	3.7%	3.4%	1.7%	4.5%	3.0%
Race/ethnicity						
African American	15.3%	14.9%	17.9%	20.7%	27.1%	12.4%
Asian	1.5%	1.6%	1.1%	0.0%	1.9%	1.7%
Caucasian	76.6%	78.2%	75.9%	74.4%	64.5%	78.4%
Hispanic	3.5%	3.2%	2.6%	2.5%	5.2%	3.8%
Other/unknown	3.0%	2.1%	2.6%	2.5%	1.3%	3.6%

Table 1. Characteristics of AL amyloidosis patients. *IQR* interquartile range, *SD* standard deviation.

Characteristic	Incident AL amyloidosis patients N = 804	Stage near time of diagnosis*				
		Stage I N = 54	Stage II N = 149	Stage IIIa N = 69	Stage IIIb N = 63	Staging not available N = 469
Mean age at index date (SD), years	67.7 (11.3)	60.9 (11.1)	69.8 (10.5)	69.3 (9.7)	68.7 (9.3)	67.6 (11.7)
Median age at index date (IQR), years	69 (61, 76)	63 (53, 71)	70 (63, 78)	70 (61, 77)	68 (62, 76)	69 (61, 76)
Male	54.2%	53.7%	49.0%	76.8%	57.1%	52.2%
Age category at index date, years						
18–29	0.5%	0.0%	0.0%	0.0%	0.0%	0.9%
30–39	1.1%	3.7%	0.7%	0.0%	0.0%	1.3%
40–49	5.1%	11.1%	3.4%	1.5%	3.2%	5.8%
50–59	15.3%	22.2%	12.8%	20.3%	11.1%	15.1%
60–69	30.0%	31.5%	32.9%	23.2%	42.9%	28.1%
70–79	33.8%	29.6%	31.5%	40.6%	31.8%	34.3%
80+	14.2%	1.9%	18.8%	14.5%	11.1%	14.5%

Table 2. AL amyloidosis staging near the time of diagnosis. *IQR* interquartile range, *SD* standard deviation. *Staging must have occurred within 2 months prior to the index date and 12 months after the index date; if more than one assessment was performed during this time period, then the staging results from the date closest to the index date were chosen.

Patient population	Incidence per 1 million person-years in adults			Prevalence per 1 million adults		
	2019	2020	2021	2019	2020	2021
All Adults ≥ 18 years old	14.4	13.4	16.7	37.5	48.0	69.0
Female ≥ 18 years old	11.7	10.4	16.2	31.7	40.7	62.6
Male ≥ 18 years old	17.2	16.5	17.1	43.6	55.5	75.6
Age 18–29 years	0.2	0.0	1.5	0.5	0.8	1.5
Age 30–39 years	1.3	0.5	3.5	3.9	4.6	13.2
Age 40–49 years	4.1	6.3	7.4	15.9	18.0	24.7
Age 50–59 years	10.8	15.5	19.5	40.1	52.8	68.7
Age 60–69 years	30.7	24.4	27.9	76.2	91.6	122.5
Age 70–79 years	52.4	49.6	48.8	120.7	157.1	224.6
Age 80+ years	43.7	26.4	48.4	96.0	133.5	217.4

Table 3. Annual age- and sex-adjusted incidence and prevalence of AL amyloid.

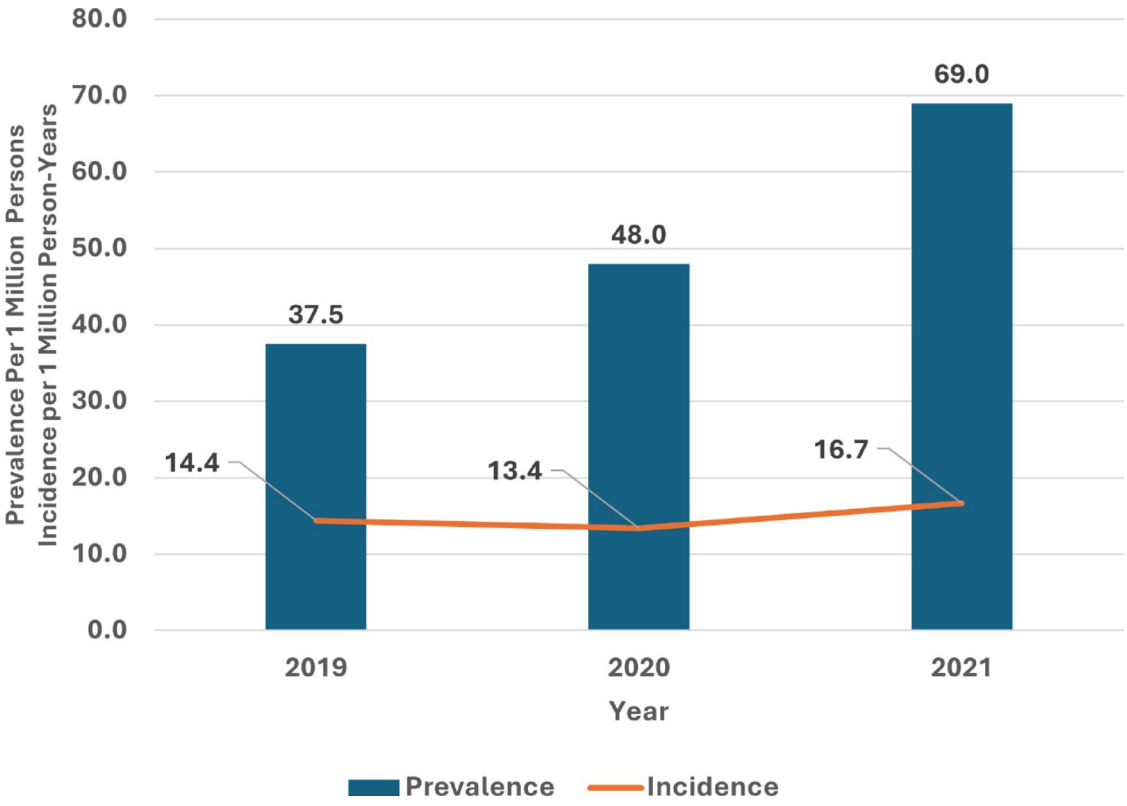

Fig. 2. Trends in incidence and prevalence of AL amyloidosis from 2019 to 2021.

In the older age strata, the percentages of patients with Stage IIIa or IIIb disease were similar to each other: 40.4% for 50–59 years, 39.4% for 60–69 years; 43.2% for 70–79 years, and 37.0% for 80+ years.

The annual age- and sex-adjusted incidence and prevalence for the years 2019–2021 are shown in Table 3. The incidence of AL amyloidosis was higher for males than females. However, a higher annual growth was observed in females during the analysed period of time (17.5% vs. – 0.2% in males). Across all study years, the age stratum 70–79 years had the highest incidence and 18–29 years had the lowest. The prevalence was also highest in the 70–79 years age stratum, reaching 224.6 cases per million persons in 2021.

As shown in Fig. 2, both the incidence and prevalence increased from 2019 to 2021. The incidence ranged from 14.4 cases per million person-years in adults in 2019 (95% confidence interval (CI) 13.9, 14.9) to 16.7 cases per million person-years in adults in 2021 (95% CI 16.2, 17.2), an annual growth rate of 7.5%. The prevalence changed from 37.5 cases per million adults in 2019 (95% CI 36.7, 38.2) to 69.0 cases per million adults in 2021 (95% CI 68.0, 70.0), an annual growth rate of 35.7%. The highest prevalence estimate was observed in males aged over 80 in 2021 (259.3 cases per million), followed by males aged 70–79 in that same year (251.7 cases per million).

Table 4 lists the most common other medical conditions among patients with AL amyloidosis. In the 12-months prior to incident diagnosis of AL amyloidosis, the most common medical conditions were essential hypertension, hyperlipidemia, chronic kidney disease, and breathing abnormalities. Among patients with prevalent AL amyloidosis, the most common medical conditions observed in the 12 months following their index dates were essential hypertension, hyperlipidemia, chronic kidney disease, multiple myeloma, and heart failure. In the 12 months following the index date, heart failure was observed in 38% and 41%, and cardiomyopathy was observed in 31% and 34% of the prevalent and incident AL amyloidosis patients, respectively. The median CCI score during the 12-month baseline period was 4 for both incident and prevalent patients.

Discussion

Using a nationally representative large EHR database from the US, we identified 1976 patients with AL amyloidosis. In 2021, the estimated incidence of AL amyloidosis was 16.7 cases per million person-years in adults, and the prevalence was 69.0 cases per million adults. These estimates were age- and sex-adjusted to match the US population and are consistent with previously reported results. One published study of the incidence and prevalence of AL amyloidosis in the US analyzed administrative claims data[6]. The reported sex- and age-adjusted incidence of AL amyloidosis ranged from 10.8 to 15.2 cases per million person-years between 2008 and 2015, and the prevalence was estimated to be 50.1 cases per million, increased from 20.1 cases per million in 2007[6]. This study by Quock TP and colleagues was however particularly limited by the lack of AL-specific diagnosis ICD codes at the time of their analysis, leading to potential misclassification bias[6]. This study also required patients to have received AL-specific treatment for inclusion, with potential to omit patients that did not receive treatment (e.g. too unwell or opted for palliation). An earlier study of patients in the United Kingdom with Stage IIIb AL reported that 17% of patients had died before initiation of treatment[15].

A population-based study of computerized records from 1990 to 2015 in Olmsted County, US, reported a similar age- and sex-adjusted incidence estimate of 16 cases per million person-years during the years 2010–2015[4].

Condition	12-Month Look-back period		12-Month follow-up period	
	Incident patients	Prevalent patients	Incident patients	Prevalent patients
Potentially AL amyloidosis-related conditions				
Chronic kidney disease	31%	35%	43%	44%
Multiple myeloma	19%	24%	40%	38%
Heart failure	25%	26%	41%	38%
Other anemias	25%	29%	33%	35%
Breathing abnormalities	31%	31%	37%	34%
Lymphoid neoplasms of uncertain behavior	29%	29%	39%	33%
Other disorders of fluid, electrolyte and acid–base balance	20%	21%	36%	32%
Cardiomyopathy	17%	19%	34%	31%
Malaise and fatigue	18%	20%	29%	27%
Soft tissue disorders NEC	25%	23%	26%	24%
Atrial fibrillation and flutter	17%	17%	26%	24%
Chronic ischemic heart disease	19%	19%	27%	24%
Sleep disorders	19%	19%	23%	23%
Acute kidney failure	17%	17%	27%	23%
Edema NEC	20%	21%	25%	22%
Proteinuria	16%	18%	16%	16%
Other conditions				
Essential hypertension	52%	53%	58%	56%
Hyperlipidemia	46%	47%	52%	51%
Gastro-esophageal reflux	24%	23%	28%	25%
Type 2 diabetes mellitus	19%	21%	23%	23%
Other joint disorder NEC	19%	20%	19%	20%
Dorsalgia	20%	19%	20%	20%
Heart disease complications	17%	18%	21%	20%
Charlson comorbidity index				
CCI score, mean (SD)	4.1 (3.2)	4.0 (3.0)	NA	NA
CCI score, median (IQR)	4 (2, 6)	4 (2, 6)	NA	NA

Table 4. Most frequently occurring medical conditions and Charlson comorbidity index. *CCI* Charlson comorbidity index, *IQR* interquartile range, *NA* not applicable, *NEC* not elsewhere classified; *SD* standard deviation.

Study	Region	Maximum incidence per million person-years	Maximum prevalence per million population
Quock et al.[6]	US	15.2	50.1
Kyle et al.[4]	US	16	NR
Kumar et al.[16]	38 developed countries	10.4	51.3
Mellqvist et al.[7]	Sweden	15.1	47.0
Mohty et al.[17]	France	12.5	58
Hou et al.[18]	Taiwan	6.6	NR
Zampieri et al.[19]	Italy	13.7	NR
Wisniowski et al.[20]	Australia	12.1	NR
Pinney et al.[21]	England	5*	NR

Table 5. Selected previously published estimates of the incidence and prevalence of AL amyloidosis. *NR* not reported, *US* United States. *Minimum estimate.

Regarding AL amyloidosis incidence and prevalence estimates outside the US, investigators applied the results from Quock[6] to the populations of 31 countries in Europe plus Brazil, Canada, Japan, Russia, South Korea, Taiwan, and the US. They reported a crude incidence of 10.4 per million person-years for a total of 14,982 cases in 2018[16]. The 20-year period prevalence was reported as 51.3 per million population for a total of 73,567[16] Using linked national registers, investigators reported the incidence of AL amyloidosis in Sweden to increase from 10.5 cases per million per year in 2011 to 15.1 cases per million per year in 2019, with the age-standardized incidence rate based on the European population ranging from 5.4 to 6.8 per million person-years[7]. The 5-year prevalence increased from 32.0 cases per million in 2011 to 47.0 per million in 2019[7]. Investigators in the Limousin region of France reported a crude yearly incidence of AL amyloidosis of 12.5 (95% confidence interval (CI) 5.6, 19.4) per million inhabitants with a calculated prevalence of 58 (95% CI 43, 73) per million inhabitants[17]. Using a population-based claims database, investigators reported the age-adjusted annual incidence of AL amyloidosis in Taiwan to range from 5.3 to 6.6 per million per year over the years 2016 through 2018[18]. Of note, this study was limited by the lack of a specific diagnosis code for AL amyloidosis during the study period, which likely resulted in under-ascertainment of cases[18]. Using a database from a single institution in Florence, Italy, investigators reported the incidence of AL amyloidosis to range from 5.3 to 13.7 per million person-years over the study period from 2005 through 2020[19]. Using histopathology reports from Queensland, Australia, investigators reported the incidence of AL amyloidosis to be 12.1 (95% CI 10.5, 13.9) per million person-years in adults aged ≥ 20 years from 2009 to 2013[20]. Investigators in England used data from death certificates and from referrals to the National Amyloidosis Centre (NAC) to estimate the minimum incidence of AL amyloidosis to be 5 per million population per year in 2008[21]. While investigators attempted to account for patients not referred to the NAC, under-ascertainment of AL amyloidosis patients seems likely[21]. In summary, studies conducted outside the US without significant methodological limitations have reported incidence rates typically in the range of 10–15 per million person-years and prevalence rates ranging from 47 to 58 per million. A summary of previously published studies is shown in Table 5.

We observed an annual growth rate of 35.7% in the prevalence of AL amyloidosis from 2019 (37.5 cases per million adults in 2019) to 2021 (69.0 cases per million adults in 2021). Previous reports also noted an increase in the prevalence of AL amyloidosis over time, including an annual growth rate of 11.9% in the US from 2007 to 2015[6] and 4.9% in Sweden from 2011 to 2019[7]. Possible explanations for an increase in the prevalence of AL amyloidosis include increased incidence (likely due to increased recognition and proper diagnosis) and improved survival due to diagnosis earlier in the disease course and increased effective therapeutic options (such as proteasome inhibitors, immunomodulatory therapies, anti-CD38 antibodies, Bcl-2 inhibitors and selected use of autologous stem cell transplantation)[3,8,22–25]. This is consistent with reports of improving survival in AL amyloidosis over the past decade[8,23]. Improved survival in multiple myeloma has also been reported[26]. It should be noted that the annual growth rate in prevalence observed in our study was exceptionally high and may be partially attributable to the introduction and slow real-world uptake of the AL amyloidosis-specific ICD-10-CM code (E85.81) during the study period. Nevertheless, this limitation would not be expected to falsely increase the observed prevalence, but rather only the increase in prevalence from one year to the next. Also, the 3-year duration of the assessment of prevalence was relatively short to derive definitive conclusions about time trends.

At the time of AL amyloidosis diagnosis, 39.4% of patients in our study had Stage IIIa or IIIb. This is slightly lower than the 44% reported from a large retrospective study of patients from 10 European countries[27], as well as the 43% and 47% reported from single centers in the US[11] and Germany[12], respectively. Of note, these previously published studies reported data from tertiary referral centers, which may be subject to referral bias resulting in overrepresentation of advanced-stage disease. In our study conducted using a broader and likely more representative data source, there were 18.8% of patients with Stage IIIb compared to 17.6% in the large European retrospective study[27] and 18% in the US[11] and 24% in Germany[12]. However, only 41.7% of incident AL amyloidosis patients had staging performed near the time of diagnosis in our study, compared with 88% in the previously reported US study[11]. Patients with more advanced cardiac involvement may have died before staging biomarkers were performed, potentially leading to the underrepresentation of Stage III patients. While Mayo re-staging has been found to be prognostic[11], Mayo staging is generally confined to the time of diagnosis and there is a paucity of data on staging in those patients who are not newly diagnosed (i.e., prevalent patients). Of

note, older patients within this cohort were more likely to have advanced Mayo staging, consistent with previous findings[28].

We observed notable demographic features of the AL amyloidosis patients in this study. Although the majority of patients in our study were Caucasian, 15.3% were African American and 3.5% were Hispanic. This is in contrast to the 8% non-Hispanic Black and 4% Hispanic race and ethnicity distribution observed among 2416 AL amyloidosis patients evaluated at a single academic medical center in the US[29]. The greater proportion of African-American patients observed in our study may be more representative of the US overall, being less subject to referral bias to a single center. The incidence of AL amyloidosis for females increased during the study period while the incidence for males did not. A similar observation was reported in an analysis of US claims data using an earlier study period[6]. Rather than a true increase in the incidence among females, a recent increase in recognition and diagnosis of AL amyloidosis in females is possible, similar to the experience in transthyretin amyloidosis (ATTR)[30]. The mean age in the incident AL amyloidosis patients was 67.7 years, which is older than the mean of 64 years reported in analysis of US claims data[6]. As neither study was truly population-based, it is difficult to draw definitive conclusions about the differences in age at incidence.

We assessed the other medical conditions of patients with AL amyloidosis. The most common medical conditions were either high-prevalence conditions among the general population of older patients (e.g. hypertension was found in approximately one-half of our study population, which is similar to what has been reported by the Centers for Disease Control and Prevention in the adult US population[31]) or conditions likely to be related to AL amyloidosis (chronic kidney disease, multiple myeloma, heart failure, cardiomyopathy). Among incident and prevalent patients within the 12-month look-back period, the commonest likely AL amyloidosis-related codes (reported in one-quarter to one-third of patients) were chronic kidney disease, breathing abnormalities, lymphoid neoplasm of uncertain significance (likely monoclonal gammopathy of uncertain significance), and heart failure. Within the 12-month follow-up period, the commonest likely AL amyloidosis-related medical conditions (in approximately 40% of patients) among incident and prevalent patients were: chronic kidney disease, multiple myeloma, and heart failure. Of note, approximately 40% of patients received ICD-10-CM codes for heart failure in the 12-month follow-up period, compared to approximately 26% in the 12-month look-back period. The proportion with multiple myeloma (approximately 40% in the 12-month follow-up period) was similar to that reported in previous studies[17,32]. While it has been reported that approximately 8% of patients have symptomatic multiple myeloma at the time of diagnosis of AL amyloidosis, an additional 38% have > 10% bone marrow plasmacytosis, thus meeting multiple myeloma diagnostic guidelines if a myeloma-defining event is present[33]. The multimorbidity found in AL patients, with symptoms that generally mimic those of other better-known conditions, aggravates delayed diagnosis of these patients. This reinforces the need for better awareness of this disease. Its delayed identification leads to progression to more advanced stages and further organ damage, which is directly linked with reduced survival odds.

This study has several limitations. First, the ICD-10-CM code used to identify patients (E85.81) was first introduced in October 2017, approximately 21 months into the study period. Prior to October 2017, there was no specific ICD code available for AL amyloidosis. The effects of the timing of this change on patient identification in the study are uncertain. However, this limitation is less likely to affect the most recent results, which is why incidence and prevalence estimates in this study were only reported for 2019–2021. Additionally, the inclusion of patients with positive mentions in the EHR SDS tables likely increased the sensitivity to identify patients with AL amyloidosis while also decreasing the specificity by erroneously including patients with other forms of systemic amyloidosis (e.g., ATTR amyloidosis). However, excluding patients who were identified exclusively using the term "systemic amyloidosis" resulted in only an approximately 6% decrease in the prevalence (*data not shown*). Also, patients with ICD-10-CM codes or positive mentions for both AL amyloidosis and ATTR amyloidosis were not excluded. However, excluding patients with both AL amyloidosis and ATTR amyloidosis ICD-10 codes in the absence of AL amyloidosis-specific treatment, resulted in only an approximately 5% decrease in the prevalence (*data not shown*). The number of patients with AL amyloidosis who did not receive any specific diagnosis codes or positive mentions in the EHR (i.e., false negatives) is expected to be small in 2021, more than 3 years after the introduction of the specific code. Second, it is possible that some patients were miscoded, either in error or deliberately to ensure reimbursement for off-label medications. Third, the Optum data set is not population-based and may not precisely reflect the US population with respect to geography, healthcare access, and overall likelihood of seeking medical care; however, we used data from more than 100 million patients and weighted our incidence and prevalence results according to the US census data. The study period included the COVID-19 pandemic era; the effects on case ascertainment and healthcare access during this period are uncertain. Fourth, our approach to require a 1-year continuous enrolment prior to the index date may lead to the underestimation of the AL prevalence because it is likely to proportionally impact further the numerator than the denominator; however, this challenge is common to EHR-based epidemiological analyses. Finally, as mentioned, less than one-half of the patients had sufficient data available to assess staging at any time during the study period; the reason for this is uncertain. Staging performed after the diagnosis of AL amyloidosis may possibly have been influenced by treatments received and selective attrition of patients.

Conclusions

In conclusion, we used a large representative EHR database from the US to provide recent estimates of the incidence and prevalence of AL amyloidosis. To our knowledge, this is the first study to capture the contemporary epidemiology of AL amyloidosis in a large general US population, to use a specific ICD-10 code for AL amyloidosis, and that did not require treatment for patient inclusion. It is also the first to examine staging with the European modification of the 2004 Mayo system in a broad US population and to report race/ethnicity characteristics. The prevalence of AL amyloidosis may be increasing with time, with this study reporting the highest prevalence published to date, perhaps in part due to the recent availability of a specific ICD-10 code, but

also possibly due to increased disease identification and extended patient survival. The proportion of patients with advanced disease (Stage IIIa or IIIb) at diagnosis is similar to previously reported cohorts from specialty care centers. Increased recognition and improved treatments will hopefully continue to decrease the morbidity and mortality of AL amyloidosis.

Data availability

The data that support the findings of this study are available from Optum but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Alexion and Optum. Requests should be made the corresponding author, Pedro Laires.

Received: 7 February 2025; Accepted: 27 June 2025
Published online: 11 July 2025

References

1. Merlini, G. et al. Systemic immunoglobulin light chain amyloidosis. *Nat. Rev. Dis. Primers* **4**(1), 38 (2018).
2. Gertz, M. A. & Dispenzieri, A. Systemic amyloidosis recognition, prognosis, and therapy: A systematic review. *JAMA* **324**(1), 79–89 (2020).
3. Sabinot, A. et al. State-of-the-art review on AL amyloidosis in Western Countries: Epidemiology, health economics, risk assessment and therapeutic management of a rare disease. *Blood Rev.* **59**, 101040 (2023).
4. Kyle, R. A. et al. Incidence of AL amyloidosis in Olmsted County, Minnesota, 1990 through 2015. *Mayo Clin. Proc.* **94**(3), 465–471 (2019).
5. Schulman, A. et al. Patient outcomes in light chain (AL) amyloidosis: The clock is ticking from symptoms to diagnosis. *Eur. J. Haematol.* **105**(4), 495–501 (2020).
6. Quock, T. P., Yan, T., Chang, E., Guthrie, S. & Broder, M. S. Epidemiology of AL amyloidosis: A real-world study using US claims data. *Blood Adv.* **2**(10), 1046–1053 (2018).
7. Mellqvist, U. H. et al. Epidemiology and clinical outcomes of light-chain amyloidosis in Sweden: A nationwide population-based study. *Eur. J. Haematol.* **111**(5), 697–705 (2023).
8. Ravichandran, S., Lachmann, H. J. & Wechalekar, A. D. Epidemiologic and survival trends in amyloidosis, 1987–2019. *N. Engl. J. Med.* **382**(16), 1567–1568 (2020).
9. Palladini, G. et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. *Blood* **126**(5), 612–615 (2015).
10. Dispenzieri, A. et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: A staging system for primary systemic amyloidosis. *J. Clin. Oncol.* **22**(18), 3751–3757 (2004).
11. Abdallah, N. et al. Prognostic restaging after treatment initiation in patients with AL amyloidosis. *Blood Adv.* **5**(4), 1029–1036 (2021).
12. Dittrich, T. et al. Performance analysis of AL amyloidosis cardiac biomarker staging systems with special focus on renal failure and atrial arrhythmia. *Haematologica* **104**(7), 1451–1459 (2019).
13. Manitoba Center for Health Policy. *Concept: Charlson Comorbidity Index* [Available from: http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?printer=Y&conceptID=1098.
14. Lilleness, B., Ruberg, F. L., Mussinelli, R., Doros, G. & Sanchorawala, V. Development and validation of a survival staging system incorporating BNP in patients with light chain amyloidosis. *Blood* **133**(3), 215–223 (2019).
15. Manwani, R. et al. Rapid hematologic responses improve outcomes in patients with very advanced (stage IIIb) cardiac immunoglobulin light chain amyloidosis. *Haematologica* **103**(4), e165–e168 (2018).
16. Kumar, N. et al. Global epidemiology of amyloid light-chain amyloidosis. *Orphanet J. Rare Dis.* **17**(1), 278 (2022).
17. Mohty, D. et al. Incidence and prevalence of light chain amyloidosis: A population-based study. *Eur. Heart J.* **39**(supp_1), P1813 (2018).
18. Hou, H. A. et al. A population-based cohort study of the epidemiology of light-chain amyloidosis in Taiwan. *Sci. Rep.* **12**(1), 15736 (2022).
19. Zampieri, M. et al. Incidence of light chain amyloidosis in Florence metropolitan area, Italy: A population-based study. *Amyloid* **28**(3), 211–212 (2021).
20. Wisniowski, B. et al. The epidemiology of amyloidosis in Queensland, Australia. *Br. J. Haematol.* **186**(6), 829–836 (2019).
21. Pinney, J. H. et al. Systemic amyloidosis in England: An epidemiological study. *Br. J. Haematol.* **161**(4), 525–532 (2013).
22. Palladini, G. & Milani, P. Advances in the treatment of light chain amyloidosis. *Curr. Opin. Oncol.* **34**(6), 748–756 (2022).
23. Staron, A. et al. Marked progress in AL amyloidosis survival: A 40-year longitudinal natural history study. *Blood Cancer J.* **11**(8), 139 (2021).
24. Muchtar, E. et al. Improved outcomes for newly diagnosed AL amyloidosis between 2000 and 2014: Cracking the glass ceiling of early death. *Blood* **129**(15), 2111–2119 (2017).
25. Sanchorawala, V. Systemic light chain amyloidosis. *N. Engl. J. Med.* **390**(24), 2295–2307 (2024).
26. Rajkumar, S. V. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. *Am. J. Hematol.* **97**(8), 1086–1107 (2022).
27. Palladini, G. et al. The management of light chain (AL) amyloidosis in Europe: Clinical characteristics, treatment patterns, and efficacy outcomes between 2004 and 2018. *Blood Cancer J.* **13**(1), 19 (2023).
28. Sachchithanantham, S. et al. Clinical profile and treatment outcome of older (>75 years) patients with systemic AL amyloidosis. *Haematologica* **100**(11), 1469–1476 (2015).
29. Staron, A., Connors, L. H., Zheng, L., Doros, G. & Sanchorawala, V. Race/ethnicity in systemic AL amyloidosis: Perspectives on disease and outcome disparities. *Blood Cancer J.* **10**(11), 118 (2020).
30. Prasad, M. et al. Evolving epidemiology of transthyretin amyloid cardiomyopathy due to increased recognition in women. *Int. J. Cardiol.* **374**, 116–119 (2023).
31. Centers for Disease Control and Prevention (CDC). *Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among US Adults Aged 18 Years and Older Applying the Criteria from the American Association of Cardiology and American Heart Association's 2017 Hypertension Guidelines—NHANES 2017–2020*. Cited 2023 May 12. Available from: https://millionhearts.hhs.gov/data-reports/hypertension-prevalence.html.
32. Quock, T. P., Yan, T., Chang, E., Guthrie, S. & Broder, M. S. Real-world burden of comorbidities in US patients with AL amyloidosis [abstract]. *Blood* **130**(Supplement 1), 5595 (2017).
33. Kourelis, T. V. et al. Coexistent multiple myeloma or increased bone marrow plasma cells define equally high-risk populations in patients with immunoglobulin light chain amyloidosis. *J. Clin. Oncol.* **31**(34), 4319–4324 (2013).

Acknowledgements
Timothy Beukelman, a medical writer supported by funding from Alexion to Epi Excellence, LLC, provided drafts and editorial assistance to the authors during preparation of this manuscript.

Author contributions
All authors participated in the design of the study, the analysis or interpretation of data, and critical review of the draft manuscript. All authors approved the final version of the manuscript.

Funding
This study was entirely funded by Alexion.

Declarations

Competing interests
PAL, SF, JE, JT and RM are employees of Alexion, AstraZeneca Rare Disease, and may own stock/have stock options in the company. AG, BS and AG are Optum® employees.

Ethics approval and consent to participate
This study was considered not human subjects research. The data was certified as de-identified by an independent statistical expert following HIPAA statistical de-identification rules and managed according to Optum customer data use agreements.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-09498-7.

Correspondence and requests for materials should be addressed to P.A.L.