openheart

Diagnostic pathways, cardiac manifestations and outcomes in light chain amyloidosis: analysis of a US claims database

Genevieve Lyons,[1] Jeffrey Thompson,[1] Isabelle Lousada,[2] Julia Catini,[3] Richa Manwani,[4] Mathew S Maurer[5]

To cite: Lyons G, Thompson J, Lousada I, *et al*. Diagnostic pathways, cardiac manifestations and outcomes in light chain amyloidosis: analysis of a US claims database. *Open Heart* 2025;**12**:e003124. doi:10.1136/openhrt-2024-003124

Received 11 December 2024
Accepted 12 March 2025

[1]Global Health Economics and Outcomes Research, Alexion Pharmaceuticals Inc, Boston, Massachusetts, USA
[2]Amyloidosis Research Consortium Inc, Newton, Massachusetts, USA
[3]Global Medical Affairs, Alexion Pharmaceuticals Inc, Boston, Massachusetts, USA
[4]Clinical Development, Alexion Pharmaceuticals Inc, London, UK
[5]Cardiac Amyloidosis Program, Centre for Advanced Cardiac Care, New York-Presbyterian/Columbia University Irving Medical Center, New York, New York, USA

Correspondence to
Dr Mathew S Maurer; msm10@cumc.columbia.edu

ABSTRACT

Background Patients with light chain (AL) amyloidosis, a rare life-threatening disease, often go through a lengthy diagnostic journey. We qualitatively and quantitatively characterised the diagnostic pathway and the impact of delayed diagnosis on health outcomes among patients with AL amyloidosis.

Methods We conducted a retrospective cohort analysis of adults (age ≥18 years) with ≥2 AL amyloidosis diagnoses (index date: first diagnosis date) using the IQVIA PharMetrics Plus US claims data from 1 January 2016 to 31 December 2022. We stratified patients based on time from first cardiovascular (CV) manifestation onset to diagnosis. Patients were categorised as having a delayed diagnosis if the first CV manifestation occurred >1 year prior to diagnosis, and patients were categorised as without a delayed diagnosis if the first CV manifestation occurred <1 year prior to diagnosis.

Results Our study included 470 patients (mean age 61.8 years, 60% males). In the 24 months before diagnosis, CV manifestations occurred in 86% of patients and renal manifestations in 74%. Patients most frequently visited on average four different cardiologists. Patients were most frequently diagnosed by haematologists/oncologists (49.8%). Patients with a delayed diagnosis (179/470, 38.1%) were twice as likely as those without a delayed diagnosis to have CV-related emergency room visits (adjusted OR: 1.98; 95% CI: 1.21 to 3.24; p<0.010). Patients with a delayed diagnosis were one and a half times more likely than those without a delayed diagnosis to have CV-related inpatient hospitalisations (adjusted OR: 1.65; 95% CI: 1.1 to 2.46; p=0.020).

Conclusions This claims database study suggests that patients with delayed diagnosis experienced more CV-related emergency room visits and inpatient hospitalisations, underscoring the need for timely diagnosis of AL amyloidosis and the role of cardiologists in the diagnostic pathway.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with light chain (AL) amyloidosis go through a lengthy and arduous diagnostic journey.

WHAT THIS STUDY ADDS

⇒ In this study, cardiologists appeared to be the most visited specialty prior to diagnosis of AL amyloidosis. Delayed diagnosis of AL amyloidosis resulted in a significant number of cardiovascular (CV)-related emergency room visits and hospitalisations. Our observation and analysis underscore that cardiologists can play a critical role in the early diagnosis of patients with AL amyloidosis due to the CV manifestations that patients present with before receiving a diagnosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Improved suspicion, recognition and understanding of AL amyloidosis among all healthcare providers, especially those in cardiology, may aid patients in receiving a timely diagnosis and thus improve outcomes.

INTRODUCTION

Light chain (AL) amyloidosis, a rare disorder, is characterised by a plasma cell dyscrasia that produces amyloidogenic immunoglobulin ALs.[1 2] These ALs misfold and aggregate to form insoluble amyloid fibrils that are deposited in different tissues.[1 2] These deposited amyloid fibrils can cause progressive and debilitating multiorgan dysfunction, leading to significant morbidity and mortality.[1–3] The heart and kidneys are most frequently affected, which can lead to restrictive cardiomyopathy and proteinuria, respectively.[4] Cardiac function is impaired due to the deposited amyloid fibrils and direct cardiac myocyte toxicity caused by circulating ALs.[5] Patients with cardiac AL amyloidosis are at a considerable risk of early mortality, with a 5-year survival rate of 35%.[3 6 7]

Patients with AL amyloidosis often present with non-specific clinical manifestations, including those suggestive of cardiomyopathy, nephropathy, neuropathy and hepatomegaly.[4 8] The lack of disease-specific

manifestations results in misdiagnosis and diagnostic delays of up to 3 years.[4 9 10] Diagnostic delays often result in progressive organ damage, poor prognosis and higher early mortality.[1] Early diagnosis is imperative to ensure patients benefit from early initiation of treatment, thereby improving survival and quality of life.[11]

AL amyloidosis is currently managed with therapies that control plasma cell proliferation with the aim of decreasing amyloidogenic immunoglobulin AL production, and in turn, preventing further amyloid deposition.[12] In January 2021, the US Food and Drug Administration approved daratumumab, a monoclonal antibody, which binds to the CD-38 protein that is expressed by plasma cells and is indicated for use in combination with cyclophosphamide, bortezomib and dexamethasone for treating AL amyloidosis.[7] Current anti-plasma cell dyscrasia therapies may allow existing amyloid deposits to gradually regress, although the mechanism and time required are uncertain and shown to occur only in a proportion of patients.[12 13]

Although current anti-plasma cell dyscrasia therapies aim to halt the production of AL fibrils resulting in amyloid deposition, the associated organ damage, which considerably increases the risk of mortality, may still remain and/or worsen if a rapid and deep haematologic response is not obtained at an early stage of disease.[13] Therefore, early, accurate diagnosis is critical in limiting amyloid deposition by enabling prompt therapeutic intervention for halting the production of amyloidogenic ALs, which may ultimately improve patient outcomes.[14] However, data on a patient's diagnostic journey are scarce. Most available data are based on patient interviews and surveys that are qualitative and have limitations such as selection bias.[4 10] Therefore, we aimed to evaluate the impact of diagnostic pathways on outcomes in patients with AL amyloidosis using real-world data from a US claims database.

METHODS

Study design and data source

In this retrospective cohort study, we included data extracted from the IQVIA PharMetrics Plus US claims database from 1 January 2016 to 31 December 2022, for adults (age ≥18 years) with at least 2 diagnoses of AL amyloidosis (International Classification of Diseases, 10th Revision (ICD-10): E85.81). IQVIA PharMetrics Plus is a health plan claims database consisting of adjudicated claims for more than 210 million enrolees in the USA since 2006.[15] This database contains information on procedures, inpatient (IP) and outpatient diagnoses, retail and mail order prescription medications, provider specialty, and place of service (POS). All data are Health Insurance Portability and Accountability Act compliant to protect patient privacy. The index date was the date of the first diagnosis of AL amyloidosis. We analysed data collected during the baseline period of 24 months (730 days) prior to diagnosis and the follow-up period of 6 months (180 days) after diagnosis.

Patients

Our study included patients with at least 2 diagnoses of AL amyloidosis during the identification period of 1 January 2018 to 30 June 2022; age≥18 years at diagnosis; treatment naive prior to diagnosis; and with at least 24 months continuous coverage before diagnosis, at least 6 months follow-up, and treated within 6 months of diagnosis (figure 1). We excluded patients with missing and/or masked age or sex data or diagnosed with transthyretin amyloidosis.

Outcomes

We identified AL amyloidosis manifestations, including cardiovascular (CV), renal, gastrointestinal/hepatic, neurologic and other/multiorgan manifestations, using diagnostic codes in the US claims database (table 1). During the 24 months prior to diagnosis (baseline period), we determined the proportion of patients experiencing each manifestation and each specialist visited by the patients. Outcomes based on emergency room (ER) visits and IP hospitalisations during the follow-up period were analysed. ER visits were identified using POS code 23 in conjunction with procedure codes 10030-69979 (ie, not exclusively laboratory or radiology-related visits), revenue codes 0450, 0452, 0456, 0459, 0981 and/or procedure codes 99281-99288. IP hospitalisations were identified using POS 21 and a facility ('F') record type.

Increased cardiac burden is associated with poor prognosis.[3] Therefore, we evaluated the outcomes based on delayed diagnosis (defined as first CV manifestations (table 1) occurring between 1 and 2 years, the earliest time point of our data analysis, prior to diagnosis) and without a delay in diagnosis (defined as first CV manifestations occurring less than 1 year prior to diagnosis). Specifically, we applied the same analysis to atrial fibrillation (AFib), a clinical complication of cardiac AL amyloidosis that is associated with cardiac amyloid load and comorbidities.[16]

Statistical analysis

Kaplan-Meier analysis was conducted to estimate the probability of manifestations occurring at different time points relative to diagnosis (index date). Correlation analysis was conducted to analyse the co-occurrence of organ manifestations. Outcomes over the follow-up period were analysed using multivariable logistic regression. Logistic regression was used to analyse the crude and adjusted OR for all-cause and CV-related IP hospitalisations and ER visits in patients with and without delayed diagnosis. Adjustment variables included age, sex and multiple myeloma (MM) diagnosis at diagnosis (index date). Statistical analysis was performed using Python V.3, an object-oriented programming language.

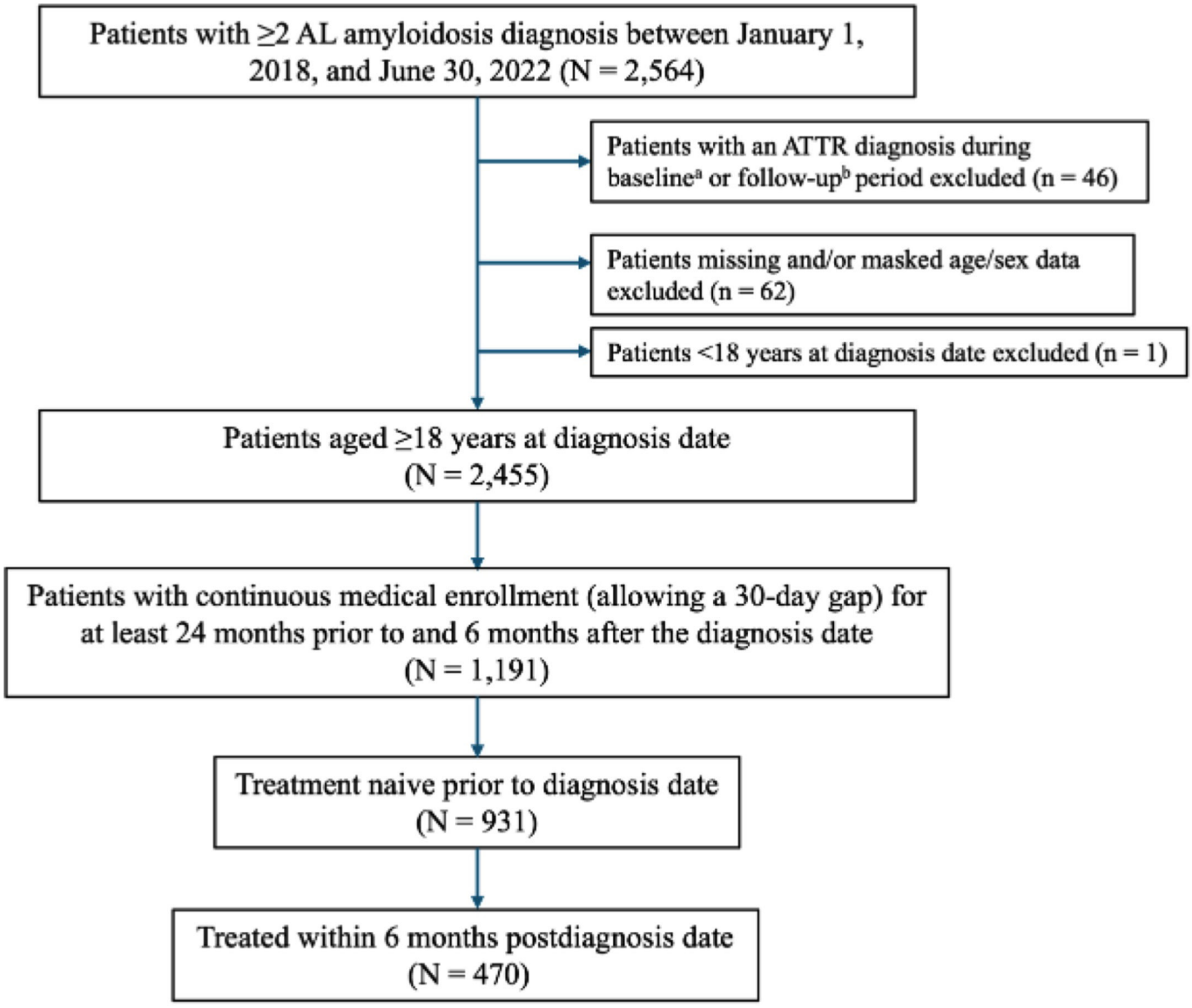

Figure 1 Identification of the study population. [a]Baseline period is 24 months prior to the diagnosis date. [b]Follow-up period is 6 months after the diagnosis date. AL, light chain; ATTR, transthyretin amyloidosis.

RESULTS

Study population

Overall, we identified 2564 patients with at least 2 diagnoses of AL amyloidosis in the IQVIA PharMetrics Plus database. A total of 2455 patients were adults (age ≥18 years) at diagnosis. Of these, 470 patients met the study inclusion criteria (figure 1). The mean age of the cohort was 61.8 years, and more than one-half of the patients (60%) were male (table 1). AL amyloidosis was the primary diagnosis in 67% of the patients. MM was also listed as a diagnosis in 22% of patients. The patient population primarily consisted of those with commercial insurance (table 2).

Top specialists involved in the diagnostic journey

During the 24 months prior to diagnosis, patients may have visited multiple physicians of the same specialty or different specialties. Overall, 72% of patients visited cardiologists compared with 45% who visited haematologists/oncologists, and 43% who visited nephrologists (figure 2A). During the 24 months prior to diagnosis, patients most frequently visited on average four different cardiologists, followed by two nephrologists and one haematologist/oncologist (figure 2A). Patients had on average 6.4 visits with cardiologists compared with an average of 4 visits with nephrologists and 3.7 visits with haematologists/oncologists during the 24 months prior to diagnosis (figure 2A). The most common medical specialty diagnosing AL amyloidosis was haematology/oncology (49.8%); 7% of diagnoses were made by cardiology (figure 2B).

Timing of the first manifestation

CV manifestations (table 1) occurred in 38% of patients more than 1 year prior to diagnosis and in 86% of patients at any point within the 24-month period prior to diagnosis

Table 1 Manifestations of AL amyloidosis in the US claims database

Manifestation	
Cardiovascular	Heart failure, dyspnoea, syncope and collapse, cardiomegaly, atrial fibrillation and flutter, other cardiac arrhythmias, cardiomyopathy, pleural effusion, fatigue, hypotension, unclassified oedema, myocarditis, atrioventricular and left bundle-branch block, other conduction disorders, paroxysmal tachycardia, myocardial degeneration, presence of heart assist device
Renal	Nephrotic syndrome, proteinuria, renal disease, ascites, oedema
Gastrointestinal/hepatic	Nausea/vomit, diarrhoea, constipation, abdominal pain, hepatomegaly and splenomegaly, bloating, early satiety, weight loss
Neurologic	Peripheral neuropathy, autonomic neuropathy, numbness/pain, erectile dysfunction, dizziness
Other/multiorgan	Dysphagia, carpal tunnel syndrome, purpura, macroglossia, submandibular swelling, jaw claudication, nail dystrophy, lack of appetite, change in taste (and smell)

AL, light chain.

(table 3). Renal manifestations (table 1) occurred in 18% of patients more than 1 year prior to diagnosis and in 74% of patients at any point within the 24-month period prior to diagnosis. The cumulative probability of experiencing a manifestation at various time points prior to diagnosis is shown in figure 2C.

Table 2 Patient demographics

	AL amyloidosis cohort (N=470)
Age at diagnosis date	
Mean (SD)	61.8 (9.6)
Age at diagnosis date, n (%)	
26–44	16 (3.4)
45–64	293 (62.3)
65+*	161 (34.3)
Sex, n (%)	
Male	282 (60.0)
Female	188 (40.0)
Payer channel at diagnosis, n (%)	
Commercial (self-insured)	246 (52.3)
Commercial (fully insured)	145 (30.9)
Medicare cost/supplemental	60 (12.8)
Medicare advantage	19 (4.0)

*The low percentage of older patients could be attributed to the underrepresentation of Medicare in the dataset.
AL, light chain.

The most common initial CV manifestations were nonspecific and included dyspnoea, fatigue and other heart manifestations, observed in approximately 20% of patients (in >50% of those with CV manifestations) more than 1 year prior to diagnosis (figure 2D). About 5.7% of patients experienced AFib more than 1 year prior to diagnosis. Patients often presented with both CV and renal manifestations. Overall, 76% of patients who first presented with CV manifestations also presented with renal manifestations, and 88% of patients who first presented with renal manifestations also presented with CV manifestations.

Diagnostic delay

There were 179/470 (38.1%) patients with a delayed diagnosis (first CV manifestation >1 year prior to diagnosis) and 291/470 (61.9%) patients without a delayed diagnosis (first CV manifestation <1 year prior to diagnosis). Patients with delayed diagnosis were diagnosed with AL amyloidosis on average 597 days from the onset of their first CV manifestation (figure 3). These patients first visited a haematologist on average 494 days after the onset of their first CV manifestation. They received an AL diagnosis on average 103 days after the haematologist visit.

Patients without delayed diagnosis were diagnosed with AL amyloidosis on average 91 days from their first CV manifestation (figure 3). These patients first visited a haematologist on average 62 days after their first CV manifestation. They received an AL amyloidosis diagnosis on average 29 days after the haematologist visit.

Outcomes over the follow-up period (6 months postdiagnosis)

One-half (234/470; 50%) of the patients had ≥1 all-cause ER visit. More than one-third (85/234, 36%) of these patients had a CV-related ER visit (CV manifestation was the primary diagnosis code on the claim related to the ER visit). Similarly, almost one-half (221/470; 47%) of the patients had ≥1 all-cause IP hospitalisation. More than three-fourths (174/221; 79%) of these patients had a CV-related IP hospitalisation (CV manifestation was the primary diagnosis code on the claim related to the hospitalisation).

Outcomes in patients with delayed diagnosis

24% of patients with a delayed diagnosis had a CV-related ER visit compared with 14% without a delayed diagnosis (table 4). During the 6 months postdiagnosis, the risk of CV-related ER visits in patients with a delayed diagnosis was twice that in patients without a delayed diagnosis (adjusted OR: 1.98; 95% CI: 1.21 to 3.24; p<0.010; figure 4). 42% of patients with a delayed diagnosis had a CV-related IP hospitalisation compared with 34% of patients without a delayed diagnosis (table 4). The risk of CV-related IP hospitalisations in patients with a delayed diagnosis was more than one and a half times that in patients without a delayed diagnosis (adjusted OR: 1.65; 95% CI: 1.10 to 2.46; p=0.020; figure 4).

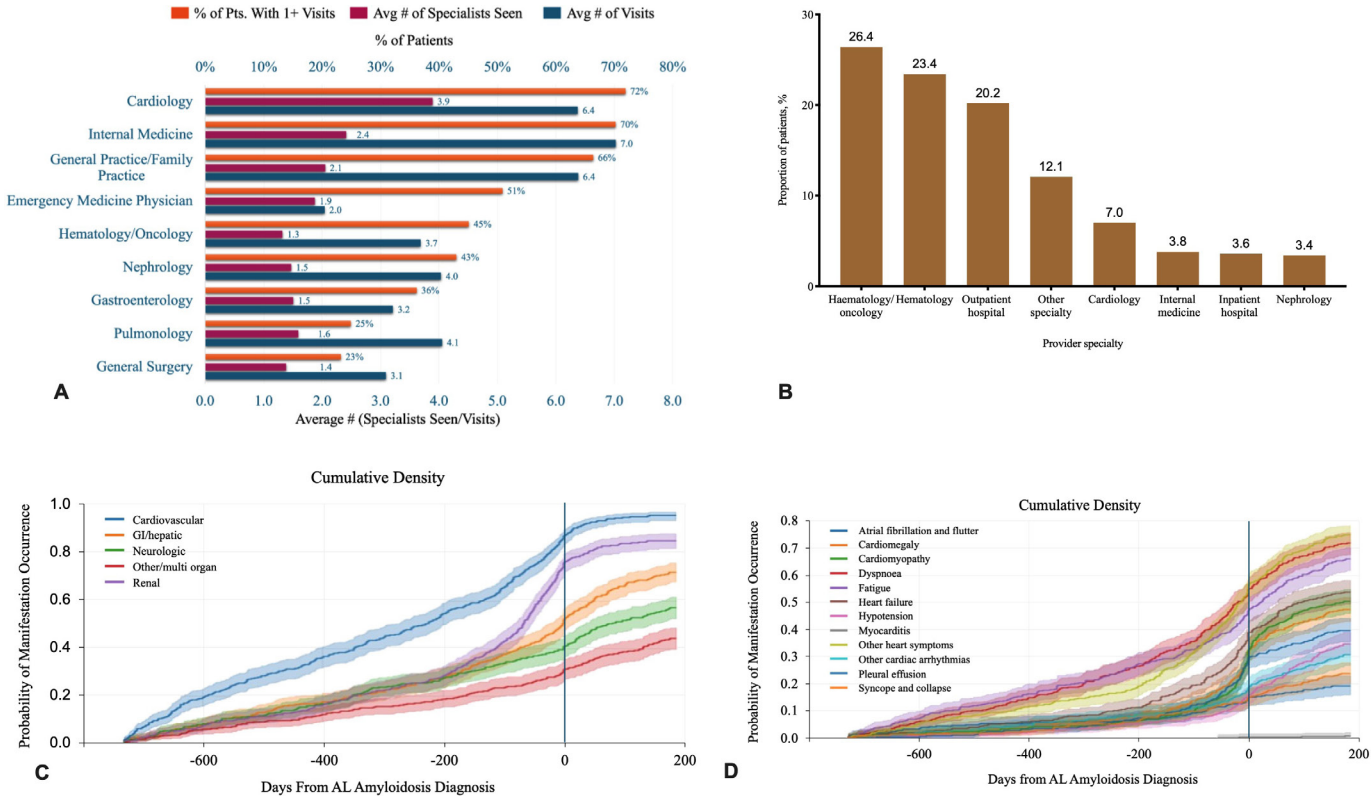

Figure 2 (A) Diagnostic journey: specialist patterns prior to diagnosis. (B) Provider specialty at diagnosis. (C) Timing of first manifestation. (D) Timing of first cardiovascular manifestation. In outpatient and inpatient hospital settings, the details of the specialty that made the final diagnosis are not available. AL, light chain; Avg, average; GI, gastrointestinal; Pt, patient.

37% of patients with AFib and a delayed diagnosis had a CV-related ER visit compared with 17% of patients with AFib without a delayed diagnosis (table 4). The risk of CV-related ER visits in patients with AFib and a delayed diagnosis was three times that in patients with AFib without a delayed diagnosis (adjusted OR: 3.22; 95% CI: 1.39 to 7.50; p<0.010; figure 4). 48% of patients with AFib and a delayed diagnosis had a CV-related IP hospitalisation compared with 36% of patients with AFib without a delayed diagnosis (table 4). Although not statistically significant, the risk of CV-related IP hospitalisations in patients with AFib and a delayed diagnosis was twice that in patients with AFib and without a delayed diagnosis (adjusted OR: 1.78; 95% CI: 0.80 to 3.94; p=0.15).

Similarly, patients with a delayed diagnosis had higher all-cause ER visits and IP hospitalisations than those without a delayed diagnosis (figure 4).

DISCUSSION

This claims database study evaluated the diagnostic journey and impacts of delayed diagnosis on health outcomes in patients with AL amyloidosis in the USA. Our findings suggest that patients with AL amyloidosis most commonly experienced non-specific CV manifestations at least 1 year prior to their diagnosis. This is consistent with earlier reports of patients with AL amyloidosis who

Table 3 Onset of the first manifestation during prediagnosis date and postdiagnosis date

	Prediagnosis date					Postdiagnosis date		
Patients presenting with	24–12 months	12–6 months	6–1 months	≤1 month	At any point within 24 months prediagnosis date	≤1 month	1–6 months	At any point within 6 months postdiagnosis date
Cardiovascular, n (%)	179 (38)	87 (19)	103 (22)	35 (7)	404 (86)	25 (5)	22 (5)	47 (10)
Renal, n (%)	86 (18)	56 (12)	154 (33)	51 (11)	348 (74)	23 (5)	30 (6)	53 (11)
Gastrointestinal/hepatic, n (%)	88 (19)	49 (10)	74 (16)	21 (4)	237 (50)	30 (6)	72 (15)	102 (21)
Neurologic, n (%)	85 (18)	48 (10)	43 (9)	9 (2)	185 (39)	26 (6)	57 (12)	83 (18)
Other/multiorgan, n (%)	63 (13)	26 (6)	37 (8)	13 (3)	140 (30)	14 (3)	53 (11)	67 (14)

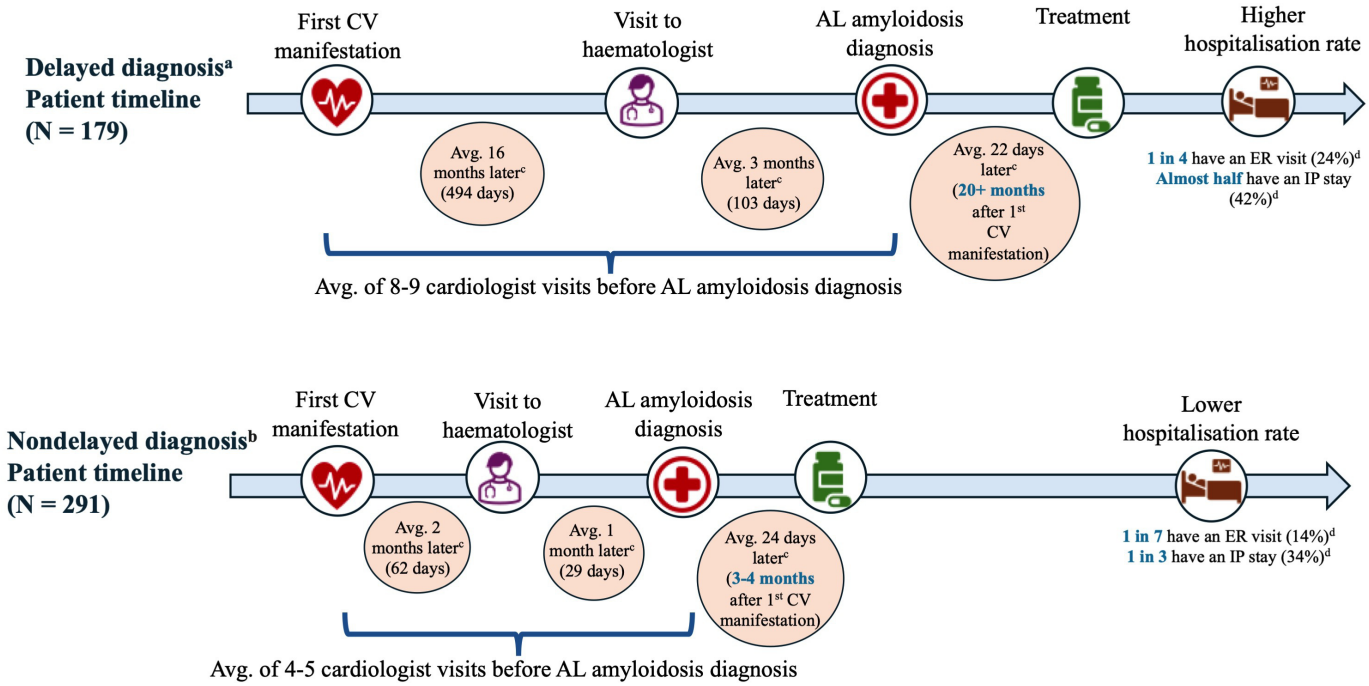

Figure 3 Diagnostic timeline pathway. [a]Delayed diagnosis is defined as patients whose first CV manifestation appears more than 1 year prior to the diagnosis date. [b]Non-delayed diagnosis is defined as patients whose first CV manifestation appears less than 1 year prior to the diagnosis date. [c]All time intervals are calculated as the median of the date difference. [d]Restricted to CV-related ER visits and IP stays during the 6-month follow-up period. AL, light chain; Avg., average(mean); CV, cardiovascular; ER, emergency room; IP, inpatient.

had non-specific symptoms that overlapped with other CV diseases.[4]

The diagnosis of AL amyloidosis may have been delayed due to non-specific manifestations, despite frequent visits to specialists, including cardiologists, nephrologists and haematologists/oncologists. As CV manifestations were the most common, cardiologists were the most frequently visited medical specialty in this study. Almost 75% of patients with AL amyloidosis frequently visited cardiologists before receiving a confirmed diagnosis. In a previous survey-based study, more than 25% of patients visited six different physicians, including cardiologists, nephrologists, haematologists and oncologists, prior to being diagnosed with AL amyloidosis.[4] In a recently published retrospective real-world study, patients with AL amyloidosis had a delayed diagnosis despite frequent visits with multiple physicians.[17] Interestingly, one study showed that patients with cardiac involvement had a 43% higher likelihood of a delayed diagnosis than those with renal involvement.[4] These findings suggest that non-specific CV manifestations may hinder prompt diagnosis.

In this study, patients suspected to have AL amyloidosis based on initial CV manifestations were mainly diagnosed by haematologists/oncologists after referrals, with few patients diagnosed by cardiologists. Our real-world data are consistent with previous reports derived

Table 4 Patients experiencing at least 1 ER visit and at least one hospitalisation during the follow-up period

	CV manifestations		Concomitant AFib	
	Delayed diagnosis* N=179 (%)	No delayed diagnosis† N=291 (%)	Delayed diagnosis N=27 (%)	No delayed diagnosis N=443 (%)
≥1 ER visit, n (%)				
All-cause	104 (58)	130 (45)	21 (78)	213 (48)
CV-related	43 (24)	42 (14)	10 (37)	75 (17)
≥1 hospital day, n (%)				
All-cause	92 (51)	129 (44)	14 (52)	207 (47)
CV-related	76 (42)	98 (34)	13 (48)	161 (36)

*Delayed diagnosis is defined as the occurrence of CV manifestations more than 1 year prior to the diagnosis date.
†No delayed diagnosis is defined as the occurrence of CV manifestations less than 1 year prior to the diagnosis date.
AFib, atrial fibrillation; CV, cardiovascular; ER, emergency room.

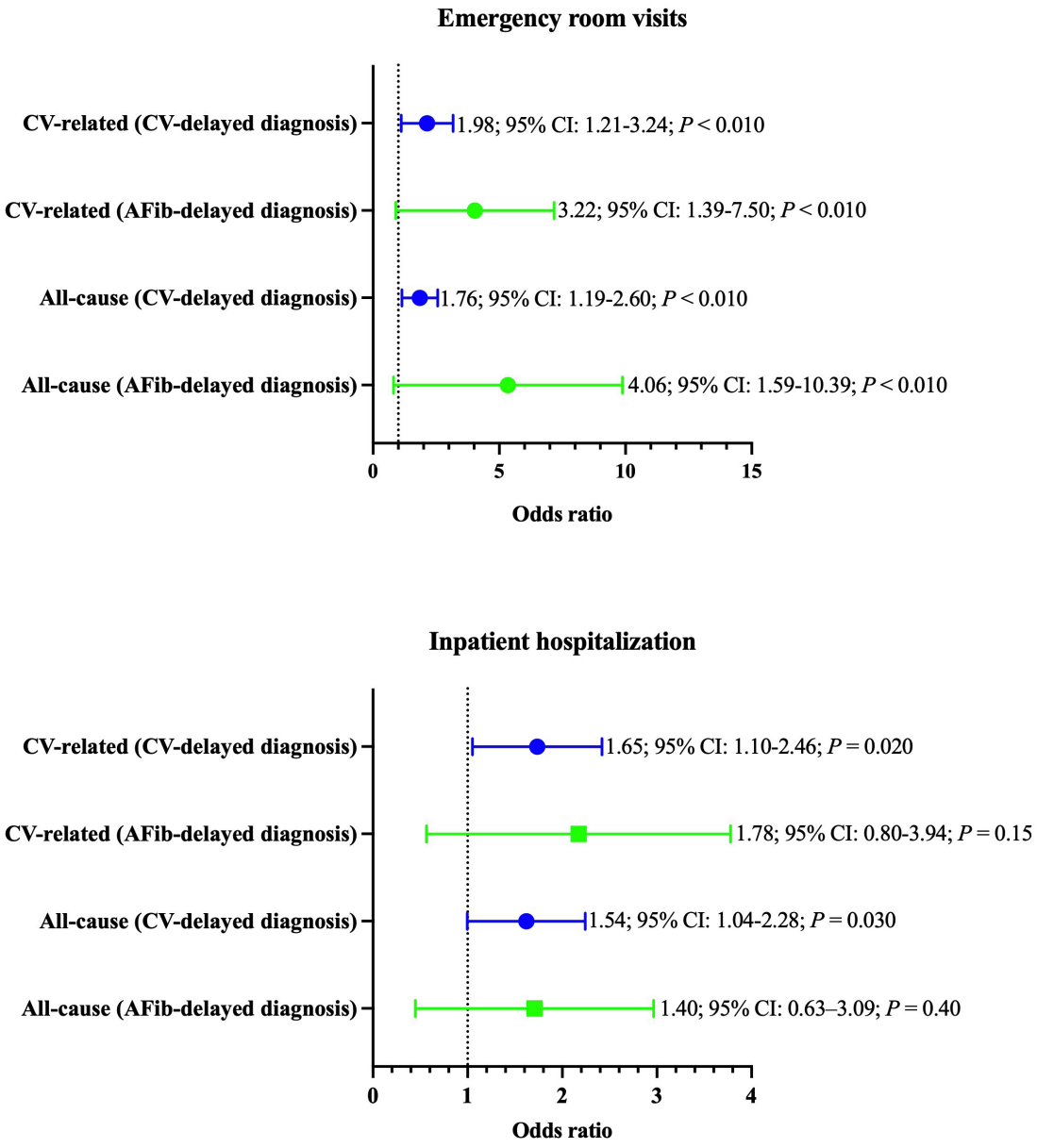

Figure 4 Outcomes over follow-up (6 months postdiagnosis). Delayed diagnosis is defined as the occurrence of CV manifestations more than 1 year prior to the diagnosis date. No delayed diagnosis is defined as the occurrence of CV manifestations less than 1 year prior to the diagnosis date. AFib, atrial fibrillation; CV, cardiovascular.

from patient/caregivers' surveys.[10] Since AL amyloidosis is primarily diagnosed by haematologists, this highlight missed opportunities by cardiologists who could have a crucial role in the early diagnosis of AL amyloidosis in patients who present CV manifestations, allowing for prompt referrals to haematologists for appropriate treatment.

The diagnostic journey for patients with AL amyloidosis may be long and arduous.[17] Almost 40% of patients in this study had symptom onset over a year prior to diagnosis, and the time to their first haematology visit was longer among those with a delayed diagnosis than those without a delayed diagnosis. Time from the first haematology visit to diagnosis was also more than three times longer than in those without delayed diagnosis, suggesting that diagnostic challenges in these patients continue even at this stage. It is possible that these patients with delayed diagnosis may require multiple investigations and biopsies before a definitive diagnosis is established (although this study did not collect data on investigations). Once the diagnosis was established, the time to treatment appeared similar in patients with and without a delayed diagnosis.

To the best of our knowledge, this is the first real-world study that explored the effects of delayed diagnosis on important outcomes such as ER visits and IP hospitalisation. Patients with a delayed diagnosis experienced twice as many CV-related ER visits and one and a half more IP hospitalisations (in the 6 months after diagnosis) compared with those without a delayed diagnosis (age, sex and MM diagnosis-adjusted OR: 1.98; 95% CI: 1.21 to 3.24; p<0.010; adjusted OR: 1.65; 95% CI: 1.1 to 2.46; p=0. 020, respectively). Notably, patients with AFib and

delayed diagnosis were three times more likely to have a CV-related ER visit and four times more likely to have an all-cause ER visit than those with AFib and without delayed diagnosis. Our findings suggest that delayed diagnosis may lead to poor outcomes such as increased risk of hospitalisation and emergency care. This is consistent with previous reports that patients with longer time between symptom onset and diagnosis have poorer survival outcomes.[18] Diagnostic delays in patients with AL amyloidosis can also have a devastating impact on their quality of life.[4] Furthermore, disease severity can increase emergency care and hospitalisation, which may lead to increased healthcare costs and place a substantial financial burden on patients.[19 20]

Our findings highlight the importance of timely diagnosis of AL amyloidosis. This may be achieved by raising physician awareness of cardiac amyloidosis and emphasising the urgency of accurate typing and diagnosis of AL amyloidosis. Improved systems and tools are also required to facilitate early diagnosis, for example, artificial intelligence-based assessment of electrocardiograms that may raise suspicion of AL amyloidosis, AL amyloidosis-sensitive and specific imaging tracers that may abrogate the need for invasive biopsies with lengthy waiting times.

The IQVIA PharMetrics Plus claims database primarily includes commercially insured patients. Therefore, the results may not be generalisable to those who are uninsured or Medicare or Medicaid populations. These populations may be relevant because AL amyloidosis is more common in the elderly population. The current study included patients with AL amyloidosis who were identified using ICD-10 diagnostic codes in the claims database. Therefore, there is a likelihood that patients with AL amyloidosis who were not identified using ICD-10 diagnostic codes were not captured in the study. This selection bias is an inherent limitation of observational studies using a claims database. The database only includes data from the USA; therefore, conclusions cannot be drawn about the global diagnostic pathway in AL amyloidosis. The paucity of clinical details in the claims database makes it challenging to correlate claims with manifestations. There could be a possibility that patients were already diagnosed with AL amyloidosis beyond the timeframe specified in this study. Therefore, it is possible that some patients were not newly diagnosed at the time of diagnosis. Crucially, our study captures only patients who were treated within 6 months of diagnosis and would not include patients who died before treatment was initiated or those whose treatment was initiated 6 months after diagnosis; the diagnostic pathway for such patients may well differ.

CONCLUSIONS

Prior to diagnosis, patients with AL amyloidosis (>70%) are more likely to have CV manifestations than any other organ system, and CV manifestations precede those related to other organ systems. This real-world study substantiates the finding that even though cardiologists are the most visited specialty prior to diagnosis, patients are still not being diagnosed with AL amyloidosis by cardiologists; the diagnosis is being made primarily by haematologists/oncologists. The findings that the bulk of hospitalisations that occur within the first 6 months of diagnosis appear to be CV related. The long duration (delayed diagnosis) of CV manifestations increases the risk of ER visits and hospitalisation. Diagnostic delays are known to adversely impact healthcare outcomes. Therefore, improved suspicion, recognition and understanding of the emergency that AL amyloidosis poses among all healthcare providers, especially those in cardiology, may aid patients in receiving a timely diagnosis.

Acknowledgements Medical writing assistance was provided by Sonali K. Kalra, PhD, of rareLife solutions and funded by Alexion, AstraZeneca Rare Disease.

Contributors GL designed and conducted the analysis. All authors contributed to the interpretation of the results and critical review and revision of the manuscript. All authors approved its final form. GL is the guarantor and responsible for overall content of the manuscript.

Funding The study was funded by Alexion, AstraZeneca Rare Disease.

Competing interests GL, JT, JC and RM are employees of Alexion, AstraZeneca Rare Disease and hold stock in the company. IL does not have a conflict of interest to disclose. MSM reports grant support from NIH R01HL139671 and R01AG081582-01; grants and personal fees from Alnylam, Eidos, Ionis, Attralus, Pfizer and Prothena; and personal fees from AstraZeneca, Intellia and Novo-Nordisk.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Alexion, AstraZeneca Rare Disease will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods like data deidentification, pseudonymisation or anonymisation (as required by applicable law), and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at https://www.alexionclinicaltrialtransparency.com/data-requests/.

REFERENCES

1 Wechalekar AD, Fontana M, Quarta CC, *et al*. AL Amyloidosis for Cardiologists: Awareness, Diagnosis, and Future Prospects: *JACC: CardioOncology* State-of-the-Art Review. *JACC CardioOncol* 2022;4:427–41.
2 Al Hamed R, Bazarbachi AH, Bazarbachi A, *et al*. Comprehensive Review of AL amyloidosis: some practical recommendations. *Blood Cancer J* 2021;11:97.
3 Dittrich T, Kimmich C, Hegenbart U, *et al*. Prognosis and Staging of AL Amyloidosis. *Acta Haematol* 2020;143:388–400.
4 McCausland KL, White MK, Guthrie SD, *et al*. Light Chain (AL) Amyloidosis: The Journey to Diagnosis. *Patient* 2018;11:207–16.
5 Martinez-Rivas G, Bender S, Sirac C. Understanding AL amyloidosis with a little help from *in vivo* models. *Front Immunol* 2022;13:1008449.
6 Sabinot A, Ghetti G, Pradelli L, *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* 2023;59:101040.
7 Palladini G, Milani P, Malavasi F, *et al*. Daratumumab in the Treatment of Light-Chain (AL) Amyloidosis. *Cells* 2021;10:545.
8 Zanwar S, Gertz MA, Muchtar E. Immunoglobulin Light Chain Amyloidosis: Diagnosis and Risk Assessment. *J Natl Compr Canc Netw* 2023;21:83–90.
9 Fotiou D, Dimopoulos MA, Kastritis E. Systemic AL Amyloidosis: Current Approaches to Diagnosis and Management. *Hemasphere* 2020;4:e454.
10 Lousada I, Comenzo RL, Landau H, *et al*. Light Chain Amyloidosis: Patient Experience Survey from the Amyloidosis Research Consortium. *Adv Ther* 2015;32:920–8.
11 Palladini G, Milani P, Merlini G. Management of AL amyloidosis in 2020. *Blood* 2020;136:2620–7.
12 Wechalekar AD, Cibeira MT, Gibbs SD, *et al*. Guidelines for non-transplant chemotherapy for treatment of systemic AL amyloidosis: EHA-ISA working group. *Amyloid* 2023;30:3–17.
13 Hassan H, Anwer F, Javaid A, *et al*. Progress in research: Daratumumab improves treatment outcomes of patients with AL amyloidosis. *Crit Rev Oncol Hematol* 2021;165:103435.
14 Milani P, Cibeira MT. Monitoring Patients with Light Chain (AL) Amyloidosis during and after Therapy: Response Assessment and Identification of Relapse. *Hemato* 2022;3:98–108.
15 IQVIA. 2022. Available: https://www.iqvia.com/locations/united-states/library/fact-sheets/iqvia-pharmetrics-plus [Accessed 08 Mar 2024].
16 Papathanasiou M, Jakstaite A-M, Oubari S, *et al*. Clinical features and predictors of atrial fibrillation in patients with light-chain or transthyretin cardiac amyloidosis. *ESC Heart Fail* 2022;9:1740–8.
17 Dou X, Liu Y, Liao A, *et al*. Patient Journey Toward a Diagnosis of Light Chain Amyloidosis in a National Sample: Cross-Sectional Web-Based Study. *JMIR Form Res* 2023;7:e44420.
18 Schulman A, Connors LH, Weinberg J, *et al*. Patient outcomes in light chain (AL) amyloidosis: The clock is ticking from symptoms to diagnosis. *Eur J Haematol* 2020;105:495–501.
19 McCausland KL, Rizio AA, White MK, *et al*. Associations between Health-Related Quality of Life and Self-Reported Emergency Room Department Visits and Inpatient Hospitalizations: Insights from a Secondary Data Analysis of Patients with Light-Chain (AL) Amyloidosis. *Pharmacoecon Open* 2019;3:367–75.
20 Quock TP, Yan T, Chang E, *et al*. Healthcare resource utilization and costs in amyloid light-chain amyloidosis: a real-world study using US claims data. *J Comp Eff Res* 2018;7:549–59.