Characterization, outcome and identification of prognostic factors for patients with systemic immunoglobulin light-chain amyloidosis requiring dialysis prior to initial anti-clonal therapy

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Received: February 12, 2025.
Accepted: June 9, 2025.
Early view: June 19, 2025.

https://doi.org/10.3324/haematol.2025.287434

Abstract

AL amyloidosis is a serious disease characterized by the deposition of immunoglobulin light chains in multiple organs. Renal involvement occurs in up to 70% of patients, but only a minority require dialysis before initiating anti-clonal treatment. Understanding the occurrence of end-stage organ damage is crucial to pave the way for reversing deposition. Currently, there is no detailed analysis available for this rare patient subgroup. We conducted a systematic search across three amyloidosis centers and characterized 68 biopsy-proven AL amyloidosis patients who required dialysis prior to initial anti-clonal therapy. In our cohort, the second most affected organ was the heart. Renal parameters exhibited variability. Residual urine output and proteinuria ranged widely, while anuria had developed in only a few patients. Among the treated patients, 84% received bortezomib as first-line therapy. The median overall survival (OS) was 44.8 months, with a median event-free survival (EFS) of 16.8 months. Our univariate statistical analysis revealed that underlying clonal disease, indicated by plasma cell infiltration, but not the difference between involved (amyloidogenic) and uninvolved free light chain, impacted OS. Importantly, higher levels of Troponins were associated with worse OS, confirmed by multivariate analysis, whereas N-terminal pro-natriuretic peptide type B levels and classical echocardiographic parameters, such as septal thickness and longitudinal strain, did not demonstrate significant prognostic value. This study provides crucial insights into this unique cohort of dialysis-dependent AL amyloidosis patients. The underlying clonal disease and markers of cardiac damage are important prognostic criteria. These findings emphasize the need to refine prognostic scoring systems for dialysis-dependent AL amyloidosis patients to better stratify risk and optimize treatment approaches.

Introduction

Systemic amyloidosis is a rare but grave condition that is caused by tissue deposition of protein fibrils.[1] In AL amyloidosis, immunoglobulin light chains derive from a small plasma cell clone and undergo conformational changes, leading to their aggregation and subsequent deposition within various organs.[2] While the heart and kidneys are the most frequently affected organs, AL amyloidosis can affect every organ of the human body except the brain. Renal involvement is observed in up to 70% of AL patients, leading to significant morbidity and a reduced quality of life in these patients.[3,4] Amyloid deposition in the kidneys typically leads to the onset of nephrotic syndrome. If left untreated, further amyloid deposition results in chronic renal failure. The current goal of therapeutic interventions is to target clonal plasma cells to prevent further depositions.[4,5] While possible regression of amyloid deposits has been described in cardiac and hepatic tissues, such reversal has not yet been observed in the kidneys.[6,7] In a

minority of individuals, the decline of renal function due to amyloid necessitates the initiation of dialysis even before the initiation of the first anti-clonal therapy.[8] Certain features such as low serum albumin levels (< 25 g/L) and high alkaline phosphatase levels (> 130 U/L) were associated with mortality in a multivariate analysis at the onset of dialysis that occurred during the course of the disease.[9] There has not yet been a comprehensive examination of the subset of patients who undergo dialysis before starting initial anti-clonal therapy, so there are no established factors for the prognosis of this specific patient subgroup in the existing scientific literature. While it is well-established that patients with advanced heart disease at first diagnosis have a poor survival prognosis,[10-13] those with severe kidney dysfunction requiring dialysis are not as thoroughly characterized. The prognosis of these patients with dialysis dependence prior to initial anti-clonal therapy in AL amyloidosis remains unknown, as they are not included in most prospective trials and rarely reported in retrospective studies.[8] Characterizing this cohort with end-stage renal failure without any treatment interference and understanding how to stratify them into low- *versus* high-risk patients may help the treating physician. Consequently, there is an urgent need to establish prognostic criteria and to gain deeper insights into long-term outcomes of this cohort.

Furthermore, once treatment is initiated in this patient group, evaluating response is challenging because response criteria have not yet been established, complicating hematologic follow-up.

In the light of these considerations, we designed this multicenter study including three amyloidosis centers: Pavia, Heidelberg, Athens. We identified 68 consecutive, previously untreated dialysis-dependent patients with newly diagnosed AL amyloidosis. The primary objective of this study was to assess outcome and establish prognostic criteria.

Methods

Study design and patient selection

We conducted a systematic search in the databases of three amyloidosis centers: the Pavia Amyloidosis Research and Treatment Center, the Heidelberg Amyloidosis Centre, and the Athens Department of Clinical Therapeutics. The objective of this study was to identify patients with AL amyloidosis who were dialysis-dependent prior to the initiation of first-line anti-clonal therapy. We included patients who were diagnosed between the years 2004 and 2022. AL diagnosis required biopsy confirmation on a reliable technique, including immunohistochemistry, immunoelectron microscopy or proteomics analysis.[14-16] All subjects in the study gave written informed consent to participate in the study. The research protocol received approval from the Institutional Ethics Committee, in full accordance with the principles laid out in the Declaration of Helsinki.[17]

Baseline assessments, data collection, and outcome measures

Baseline assessments were standardized across the three amyloidosis centers. Cardiac involvement was defined by echocardiographic parameters (e.g., septal thickness, strain), as well as GFR-corrected biomarkers (N-terminal pro-natriuretic peptide type B [NT-proBNP], high-sensitivity Troponin T [hsTnT], and Troponin I [cTnI]). In some patients, cardiac magnetic resonance imaging (MRI) was performed. For baseline evaluations of cardiac damage, we opted to utilize the threshold values defined in the European modification Stage 3b of the Mayo criteria from 2004 for NT-proBNP and hsTnT. Furthermore, we utilized glomerular filtration rate (GFR)-corrected NT-proBNP values, applying the formula $NTproBNP\_corr = NTproBNP/e^{(1.892-0.025\times eGFR)}$.[18] These NT-proBNP values were employed to develop an adjusted Mayo Staging System. For cTnI, we chose to use a lower threshold consistent with values observed in healthy individuals (≤0.04 μg/L), corresponding to the 99th percentile in humans. BNP levels were only available for one center. The quantification of circulating free light chains (FLC) was performed at baseline, at three, six and/or 12 months after initiation of anti-clonal therapy. Free light-chain concentrations were measured using the Binding Site assay in all three centers. Hematologic response to treatment was evaluated at these time points post therapy initiation, guided by the 2012 International Society of Amyloidosis (ISA) criteria and the 2021 clarification on the definition of complete hematologic response.[19]

The primary endpoint of this study was overall survival (OS) defined as the duration between the initial diagnosis of AL amyloidosis and death. The secondary objective of this research was to assess event-free survival (EFS) which was defined as the period from the timepoint of diagnosis to the occurrence of hematologic disease progression or the need for therapy modification due to an insufficient/absent response or death (which ever occurred first). The decision on the need for new therapy was made by the treating physician and hematologic disease progression was defined by the ISA 2005 criteria.[20]

Statistical analysis

Statistical analyses were carried out with Prism 9.0 software. Median and range were used to describe continuous data. Kaplan-Meier estimates were used to analyze EFS and OS, with the median estimated time of observation calculated based on the median time to censoring (reverse Kaplan-Meier). Kaplan-Meier estimate models were used to analyze the association between baseline characteristics and response at three, six and 12 months and EFS and OS. Log-rank (Mantel-Cox) test was used for statistical testing. A multivariate model was performed with a Cox regression model with months as a time variable and OS/EFS as event variable. P<5% was considered statistically significant.

Results

Patients' characteristics

A total of 68 patients (Heidelberg cohort N=32, Pavia cohort N=24, and Athens cohort N=12) were included. The median time from initiation of dialysis to diagnosis was six days, and the median time from diagnosis to start of therapy was 24 days. These intervals were comparable between the three centers. There were no consistent, study-defined criteria for initiating dialysis across the cohort. In the majority of cases, dialysis was initiated prior to first presentation at the amyloidosis centers, often at external hospitals. In 41 patients, the documented reasons for dialysis initiation included fluid overload with refractory edema (N=16), acute kidney injury (N=9), terminal renal insufficiency (N=5), anuria or oliguria (N=5), acute-on-chronic kidney injury (N=3), uremia symptoms (N=2), and metabolic acidosis (N=1). Baseline evaluations prior to the initiation of anti-clonal therapy included assessment of amyloid organ involvement based on established criteria, echocardiography, measurements of amino-terminal pro-natriuretic peptide type B (NT-proBNP) and troponins to evaluate cardiac health, as well as staging of cardiac damage according to the European Modification of the Mayo 2004 Cardiac Staging System. Additionally, baseline evaluations included the determination of serum creatinine concentration, 24-hour urinary protein excretion measurement, and serum and urine immunofixation electrophoresis for precise identification of amyloid protein and bone marrow puncture. To quantify liver amyloidosis, we employed center- and sex-specific cut-off values for the liver enzymes gamma-glutamyl transferase (gamma-GT) and alkaline phosphatase (AP). A threshold of 1.5 was utilized to distinguish between liver involvement.[21] Plasma cell diseases were categorized based on established CRAB and SLiM criteria, except for the light-chain ratio, which was not utilized to determine the necessity for therapy in this context. Smoldering multiple myeloma (SMM) was defined based on consideration of the IMWG 2014 recommendations, according to which patients with renal impairment requiring dialysis were only classified as SMM if kidney damage was not due to cast nephropathy. In such cases, diagnoses such as AL amyloidosis or MGRS were considered based on renal histology. Renal biopsy data were available for 48 patients. Among these, 13 patients showed additional renal pathologies, including mesangioproliferative glomerulonephritis, interstitial inflammatory infiltrates consistent with thrombotic microangiopathy, acute tubular injury, chronic tubulointerstitial damage, interstitial fibrosis, arteriosclerosis, nodular and global glomerulosclerosis, focal segmental glomerulosclerosis and cast nephropathy. These co-existing lesions were identified in addition to positive immunohistochemistry for AL amyloid in all cases. Relevant comorbidities were present in 40 patients. Arterial hypertension was the most common comorbidity (N=38), followed by type 2 diabetes mellitus (N=8) and coronary heart disease (CHD, N=5). Overall, the patient characteristics were comparable, with some differences between the centers. Monoclonal heavy chain and light-chain type distributions were relatively similar across cohorts, with minor variations. Only one patient had an IgM paraprotein (with an additional IgG). The Athens cohort had the highest percentage of patients with multiple myeloma (MM, 25%). The Heidelberg cohort had the highest prevalence of monoclonal gammopathy of clinical significance (MGCS, 63%). Median dFLC levels varied significantly and the Athens cohort had the highest median value. Most patients were male (65%). The median age was 65 years (range: 41-82 years). Most patients had lambda light chain (71%) and MGCS (53%) as underlying disease. The median dFLC was 207.6 mg/L (range: 0-13,998.5 mg/L). Organ involvement, apart from the kidneys, was most frequently observed in the heart (57%). In patients with cardiac involvement (N=39), septal thickness was significantly increased compared to those without cardiac involvement (15 mm *vs*. 12 mm, $P<0.0001$). The median NYHA stage was also higher (Stage II *vs*. I, $P=0.0259$). Strain values were numerically more impaired (-14.0% *vs*. -16.8%), although this difference did not reach statistical significance ($P=0.347$). Low blood pressure, while frequently observed, could not serve as a reliable marker of cardiac involvement due to multifactorial influences including autonomic dysfunction, hypoalbuminemia, and volume depletion secondary to diuretics and post dialysis. Many patients had involvement of three or more organs (41%). A bortezomib-based therapy was administered in 84% (54 out of 64 patients) of those who received induction therapy across the three centers. Five patients received daratumumab-based therapy as first-line treatment. Due to advanced age and the lack of influence on kidney damage by anti-clonal therapy, initiation of therapy was avoided in 3 patients. Additionally, another patient was diagnosed with a neuroendocrine tumor, which contributed to the decision against chemotherapy. OS of these 4 patients was comparable to the OS rates of the entire cohort, with a median OS of 35.9 months. The OS for the individual patients were 44.8, 12.7, 89, and 27 months, respectively. In a subset of patients (N=11), causes of death were known and included sepsis (N=3), sudden cardiac death (N=2), complications following bowel surgery (N=1), progression of amyloidosis (N=3), COVID-19 infection (N=1), and worsening of congestive heart failure (N=1). Most patients (93% of the cohort) had undergone hemodialysis. A distinct minority, consisting of only 4 patients, was undergoing peritoneal dialysis. Notably, also 3 patients experienced a transition away from dialysis, and we will provide a comprehensive elucidation of this phenomenon in the subsequent sections of this article. Out of the cohort, no patient received a renal transplant. Most patients did not meet transplant criteria due to age >70 years, multi-organ or advanced cardiac involvement, lack of hematologic remission, or personal preference. Patients' characteristics are summarized in Table 1.

Table 1. Baseline variables at diagnosis.

Baseline variables at diagnosis	Heidelberg N=32	Athens N=12	Pavia N=24	All N=68
Male sex, N (%)	25 (78)	7 (58)	12 (50)	44 (65)
Age in years, median (range)	62 (41-78)	63 (53-82)	69 (47-82)	65 (41-82)
Monoclonal heavy chain, N (%)	17 (53)	6 (50)	14 (78)	37 (54)
Light chain, isotype, N (%)	15 (47)	6 (50)	4 (22)	25 (37)
Missing data, N (%)	0 (0)	0 (0)	6 (25)	6 (9)
Light-chain type, N (%)				
Lambda, N (%)	24 (75)	7 (58)	17 (71)	48 (71)
Missing data, N (%)	0 (0)	0 (0)	0 (0)	0 (0)
Underlying clonal disease				
MGCS, N (%)	20 (63)	6 (50)	10 (42)	36 (53)
SMM, N (%)	12 (38)	3 (25)	13 (54)	28 (41)
MM, N (%)	0 (0)	3 (25)	1 (4)	4 (6)
Missing data, N (%)	0 (0)	0 (0)	0 (0)	0 (0)
Receiving induction therapy, N (%)	28 (88)	12 (100)	24 (100)	64 (94)
Bortezomib-based induction therapy, N (%)	26 (94)	9 (75)	19 (79)	54 (84)
Missing data, N (%)	0 (0)	0 (0)	0 (0)	0 (0)
dFLC, mg/L, median (range)	171 (0-8,781)	934 (8-5,970)	116 (0-13,999)	208 (0-13,999)
Missing data, N (%)	0 (0)	0 (0)	0 (0)	0 (0)
% BMC infiltration, median (range)	10 (3-50)	9 (0-90)	11 (1-50)	10 (0-90)
Missing data, N (%)	4 (13)	2 (17)	2 (8)	8 (12)
Organ involvement				
Heart, N (%)	18 (56)	6 (50)	15 (63)	39 (57)
Liver, N (%)	8 (25)	2 (17)	5 (21)	15 (22)
Soft tissue, N (%)	13 (41)	4 (33)	3 (13)	20 (29)
PNS, N (%)	3 (9)	0 (0)	1 (4)	4 (6)
ANS, N (%)	7 (22)	2 (17)	0 (0)	9 (13)
GI, N (%)	10 (31)	1 (8)	0 (0)	11 (16)
Other, N (%)	5 (16)	1 (8)	0 (0)	6 (9)
N of involved organs				
1, N (%)	3 (9)	4 (33)	6 (25)	13 (19)
2, N (%)	11 (34)	3 (25)	13 (54)	27 (40)
≥3, N (%)	18 (57)	5 (42)	5 (21)	28 (41)
Missing data, N (%)	0 (0)	0 (0)	0 (0)	0 (0)
Dialysis type				
Hemodialysis, N (%)	31 (97)	10 (83)	22 (92)	63 (93)
Peritoneal dialysis, N (%)	1 (3)	2 (17)	2 (8)	5 (7)
Missing data, N (%)	0 (0)	0 (0)	0 (0)	0 (0)
Patients stopping dialysis, N (%)	2 (6)	0 (0)	1 (4)	3 (4)
Missing data, N (%)	0 (0)	0 (0)	0 (0)	0 (0)
Diagnosis before 2018, N (%)	21 (66)	9 (75)	10 (4)	40 (59)
Missing data, N (%)	0 (0)	0 (0)	0 (0)	0 (0)
Residual excretion, mL/d, median (range)	950 (0-3,020)	600 (500-700)	NA -	825 (0-3,020)

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Baseline variables at diagnosis	Heidelberg N=32	Athens N=12	Pavia N=24	All N=68
Missing data, N (%)	0 (0)	10 (83)	24 (100)	34 (50)
Anuria, N (%)	6 (19)	7 (58)	4 (17)	17 (25)
Oliguria, N (%)	2 (6)	4 (33)	13 (57)	19 (28)
Missing data, N (%)	1 (3)	0 (0)	0 (0)	1 (1)
u. prot. mg/24 hr, median (range)	5,880 (326-26,760)	5,655 (500-20,000)	5,410 (250-19,000)	5,628 (250-26,760)
Missing data, N (%)	11 (34)	5 (42)	8 (33)	24 (35)
u.alb, mg/24 hr, median (range)	1,671 (8-13,743)	2,623 (1,289-12,000)	4,770 (8-1,800)	2,940 (8-1,800)
Missing data, N (%)	19 (59)	9 (75)	17 (71)	45 (66)
s. alb, g/L, median (range)	29.6 (11-45)	36 (28-49)	31 (11-51)	31 (11-51)
Missing data, N (%)	2 (6)	0 (0)	4 (17)	6 (9)
cTnI, μg/L, median (range)	0.04 (0.01-1)	NA -	0.045 (0-0.44)	0.0445 (0-1)
Missing data, N (%)	13 (41)	12 (100)	1 (4)	26 (38)
hsTnT, pg/mL, median (range)	85.5 (18-268)	177.6 (59-450)	NA -	89.9 (18-450)
Missing data, N (%)	12 (38)	6 (50)	24 (100)	42 (62)
NT-proBNP, ng/L, median (range)	11,000 (63-146,557)	11,356 (680-43,942)	3,822 (3033-17,210)	11,000 (63-1,466,557)
Missing data, N (%)	5 (16)	1 (8)	21 (88)	27 (40)
cNT-proBNP, ng/L, median (range)	2,771 (18-28,139)	1,936 (115-9,960)	978 (740-1,329)	2,328 (18-28,139)
Missing data, N (%)	5 (16)	1 (8)	21 (88)	27 (40)
BNP, pg/mL, median (range)	NA -	NA -	285.5 (22-5,420)	285.5 (22-5,420)
Missing data, N (%)	100 (32)	100 (12)	0 (24)	65 (44)
cBNP, pg/mL, median (range)	NA -	NA -	56.2 (4.2-930.6)	56.2 (4.2-930.6)
Missing data, N (%)	100 (32)	100 (32)	0 (24)	65 (44)
Cardiac stage				
1, N (%)	1 (3)	0 (0)	2 (8)	3 (4)
2, N (%)	6 (19)	2 (17)	14 (58)	22 (32)
3a, N (%)	5 (16)	2 (17)	3 (13)	10 (15)
3b, N (%)	10 (31)	6 (50)	4 (17)	20 (29)
Missing data, N (%)	10 (31)	2 (17)	1 (4)	13 (19)

ANS: autonomic nervous system; BMC: bone marrow clonal; cNT-proBNP: corrected N-terminal pro-natriuretic peptide; cTnI: Troponin I; dFLC: difference between involved (amyloidogenic) and uninvolved free light chain; eGFR: estimated glomerular filtration rate; GI: gastrointestinal; hr: hours; hsTnT: high-sensitivity Troponin T; MGCS: monoclonal gammopathy of clinical significance; MM: multiple myeloma; N: number; NA: not available; NT-proBNP: N-terminal pro-natriuretic peptide type B; PNS: peripheral nervous system; s. alb: serum albumin; s. create: serum creatinine; SMM: smoldering multiple myeloma; u. alb: urinary albumin; u. prot: urinary protein.

Overall survival and event-free survival among the three centers

The median OS for the Heidelberg, Athens, and Pavia cohorts were 62.1 months, 42.7 months, and 31.9 months, respectively (*Online Supplementary Figure S1A*). The median EFS was 21 months for the Heidelberg cohort, 2.6 months for the Athens cohort, and 16.9 months for the Pavia cohort. (*Online Supplementary Figure S1B*). It is worth noting that despite the differences in median survival times, neither the OS nor the EFS demonstrated statistically significant differences between the three cohorts (P=0.260 and P=0.375). Combining the data, the

median OS was 44.8 months and the median EFS was 16.8 months (Figure 1). The median duration of follow-up was 62 months and, again, there was no significant difference among the three centers.

Factors predicting overall survival

Table 2 presents the outcomes of our statistical univariate analysis, examining the association between diverse baseline variables and OS. Patients with MGCS had longer OS compared to those with SMM or MM (Figure 2A). However, there was no significant difference in OS based on the levels of dFLC, the number of organs involved, anuria, serum albumin, AP or gamma-GT levels. Neither NT-proBNP levels or BNP or cardiac staging demonstrated statistical significance. However, there was a tendency towards longer survival rates for patients with lower levels NT-proBNP and cardiac stage 1-3a (*Online Supplementary Figure S2A, B*). There was also no significant association observed between eGFR-corrected NT-proBNP levels, nor between cardiac staging, where the corrected NT-proBNP was utilized, and OS (*Online Supplementary Figure S2C*). Importantly, higher Troponin levels, defined as elevated hsTnT and/or cTnI (Figure 2B), were associated with worse OS rates compared to low Troponin levels. However, the amyloidosis-validated cut-off for cTnI (≥0.1 μg/L) was not correlated with OS (*Online Supplementary Figure S2D*). Clinical and echocardiographic parameters, including septal thickness, longitudinal strain, and NYHA functional class (I *vs.* >I), were evaluated for their prognostic relevance. However, none of these factors demonstrated a statistically significant association with OS (*P*=0.5546, *P*=0.7883, and *P*=0.8660, respectively).

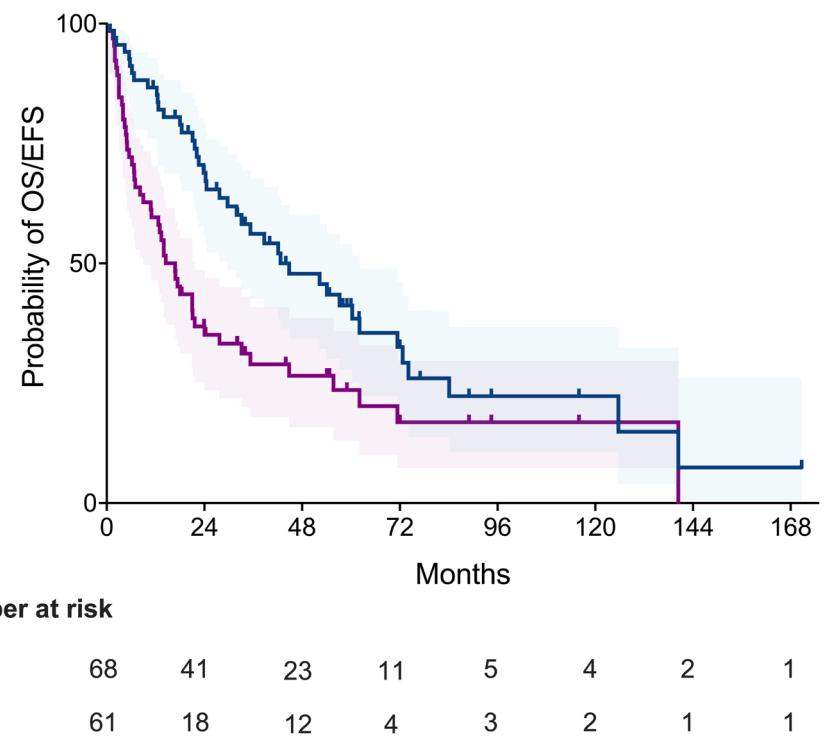

Figure 1. Combined overall and event-free survival of all patients. The median overall survival (OS) was 44.8 months, and the median event-free survival (EFS) was 16.8 months.

Multivariate analysis of overall survival supports the importance of cardiac damage biomarker

Next, we took a closer look at factors affecting patient survival in a multivariate analysis. When considering various factors, including age at diagnosis, light-chain types, the stages of clonal disease, and organ involvement, we found that none of these factors showed a statistically significant influence. However, elevated Troponin levels emerged prominently in our analysis, consistent with our univariate findings (HR 3.5, *P*=0.0050) (Table 3).

Landmark analysis of hematologic treatment response and overall survival

Complete remission (CR) and very good partial remission (VGPR) were reached after three and six months in 16 and 20 patients, respectively. Although OS did not differ

Table 2. Univariate analysis between baseline variables and overall survival.

Baseline variable	Median survival, months	*P*
Patients' characteristics		
Age ≤65 *vs.* >65 years at diagnosis	42.7 *vs.* 44.8	0.958
Male *vs.* female	42.7 *vs.* 52.3	0.67
Diagnosis before 2018 *vs.* in/ after 2018	60.3 *vs.* 33.1	0.173
Hematologic disease activity		
MGCS *vs.* SMM *vs.* MM	60.3 *vs.* 31.9 *vs.* 7.9	0.025
Kappa *vs.* Lambda	72.7 *vs.* 42.1	0.294
dFLC <180 *vs.* ≥180 mg/L	421.1 *vs.* 44.8	0.312
Organ parameter		
1 *vs.* >1 organ involved	94.5 *vs.* 35.3	0.176
Serum albumin <35 *vs.* ≥35 g/L	38.7 *vs.* 60.3	0.792
Anuria *vs.* No anuria	33.1 *vs.* 54.1	0.483
AP <1.5 *vs.* ≥1.5 URL	44.8 *vs.* 27.7	0.235
Gamma-GT <1.5 *vs.* ≥1.5 URL	54.1 *vs.* 35.3	0.106
Heart parameter		
Cardiac Staging System 1-3a *vs.* 3b	54.1 *vs.* 42.7	0.145
Corrected Cardiac Staging 1-3a *vs.* 3b	60.3 *vs.* 42.1	0.461
NT-proBNP <8,500 *vs.* ≥8,500 ng/L	71.4 *vs.* 42.7	0.144
cNT-proBNP <8,500 *vs.* ≥8,500 ng/L	60.3 *vs.* 32.35	0.293
BNP <700 *vs.* ≥700 pg/mL	38.7 *vs.* 22.1	0.135
cBNP <60 *vs.* ≥60 pg/mL	84.1 *vs.* 42.1	0.092
hsTnT <54 *vs.* ≥54 pg/mL	38.7 *vs.* 22.1	0.009
cTnI <0.1 *vs.* ≥0.1 μg/L	38.7 *vs.* 52.3	0.608
cTnI ≤0.04 *vs.* >0.04 μg/L	71.4 *vs.* 27.7	0.007
Elevated Troponin T/ L	71.4 *vs.* 35.3	0.004

AP: alkaline phosphatase; cBNP: corrected B-type natriuretic peptide; cNT-proBNP: corrected N-terminal pro–B-type natriuretic peptide; cTnI: Troponin I; dFLC: difference between involved and uninvolved free-light chain; hsTnT: high-sensitivity Troponin T; URL: upper reference limit.

significantly, patients who achieved CR or VGPR tended to have longer survival compared to those who only attained partial response (PR), stable disease (SD), or progressive disease (PD), with *P* values of 0.1783 at three months, 0.1596 at six months, and 0.2850 at 12 months. Response data were available for 48 patients at three months, 46 patients at six months, and 44 patients at 12 months (Figure 3A-C). Furthermore, patients with a CR did not have longer OS rates when compared to patients with a VGPR/PR/SD/PD at the chosen timepoints (*Online Supplementary Figure S3A-C*).

When analyzing the baseline characteristics of individuals exhibiting favorable response (VGPR/CR) *versus* those with less favorable responses (SD/MR/PD) at the 3-, 6-, and 12-month time points, our analysis yielded results indicating an absence of significant associations between the response state and any baseline characteristic despite involvement of soft tissue being far more common in patients with a worse response at three months. Median percentage reduction of involved light chain was 55.1% (month 3), 55.0% (month 6), and 36.7% (month 12). High reduction (<median *vs.* ≥ median reduction) at month 3 correlated with prolonged OS (72.7 *vs.* 42.1 months, *P*=0.0205), but differences at months 6 and 12 were not significant.

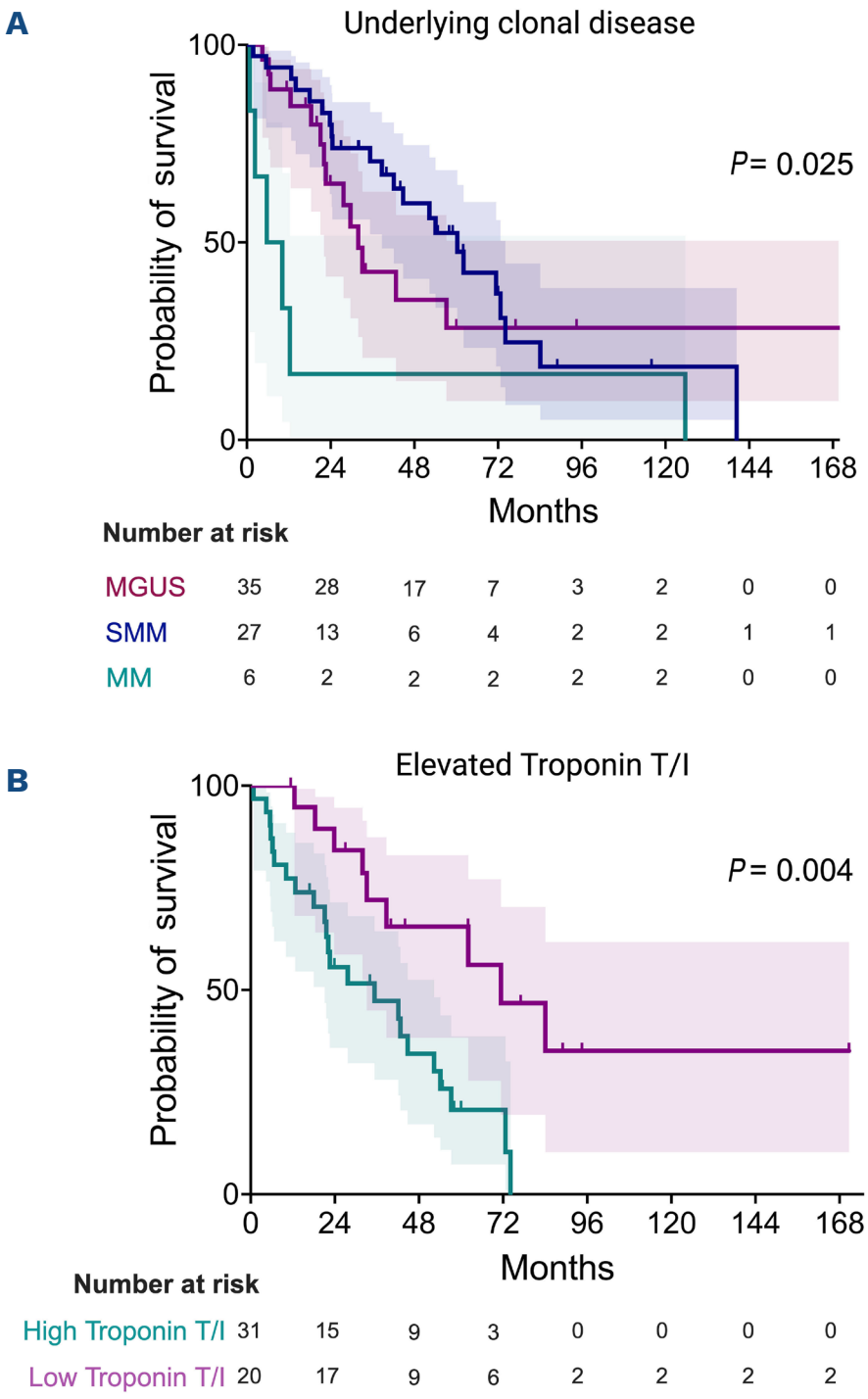

Figure 2. Kaplan-Meier survival analysis of immunoglobulin light-chain amyloidosis patients. (A) Patients with monoclonal gammopathy of clinical significance (MGUS), smoldering multiple myeloma (SMM), and multiple myeloma (MM) had significantly different overall survival (OS), indicating the impact of the underlying plasma cell disorder. (B) Patients with elevated cardiac Troponin T and/or Troponin I levels at diagnosis had significantly shorter OS than those with lower levels.

Factors predicting event-free survival

Table 4 presents the results of our statistical univariate analysis between diverse variables and EFS. EFS was evaluable in 65 patients. Thirty patients had their first event due to inadequate organ or hematologic response or disease progression following their first-line treatment. The first EFS event due to death occurred in 20 patients. The underlying clonal disease was associated with EFS rates. MM patients showed significantly shorter EFS rates (*Online Supplementary Figure S4A*). When examining hematologic disease activity, we found that dFLC levels showed no significant impact on EFS with a trend for worse EFS if higher than 180 mg/L. Another noteworthy finding is related to the number of organs involved: patients with only one organ affected (renal involvement) tend to have significantly longer EFS compared to those with multiple organs involved (*Online Supplementary Figure S4B*). The presence or absence of anuria did not yield a significant effect on EFS. Regarding heart parameters, especially elevated hsTnT levels tended to correlate with shorter EFS. Elevated cTnI, BNP, NT-proBNP, cardiac staging, or eGFR-corrected NT-proBNP and cardiac staging did not show a statistically significant effect, but did tend to lead to shorter EFS rates.

Multivariate analysis of event-free survival

In our multivariate analysis, we systematically assessed several key variables to evaluate their impact on EFS. These variables included age at diagnosis, light-chain type, the underlying clonal disease, involvement of multiple organs,

Table 3. Multivariate analysis between baseline variables and patients' overall survival.

Baseline variable	Hazard Ratio	95% CI	*P*
Age at diagnosis >65 years	0.9103	0.4419-1.872	0.7968
Lambda *vs.* kappa	1.683	0.7164-4.438	0.2579
SMM/MM *vs.* MGCS	1.415	0.6724-2.982	0.3572
>1 organ involved	1.404	0.5794-3.938	0.4801
Elevated Troponin T/I	3.527	1.533-9.092	0.0050

CI: confidence interval; MGCS: monoclonal gammopathy of clinical significance; MM: multiple myeloma; SMM: smoldering multiple myeloma.

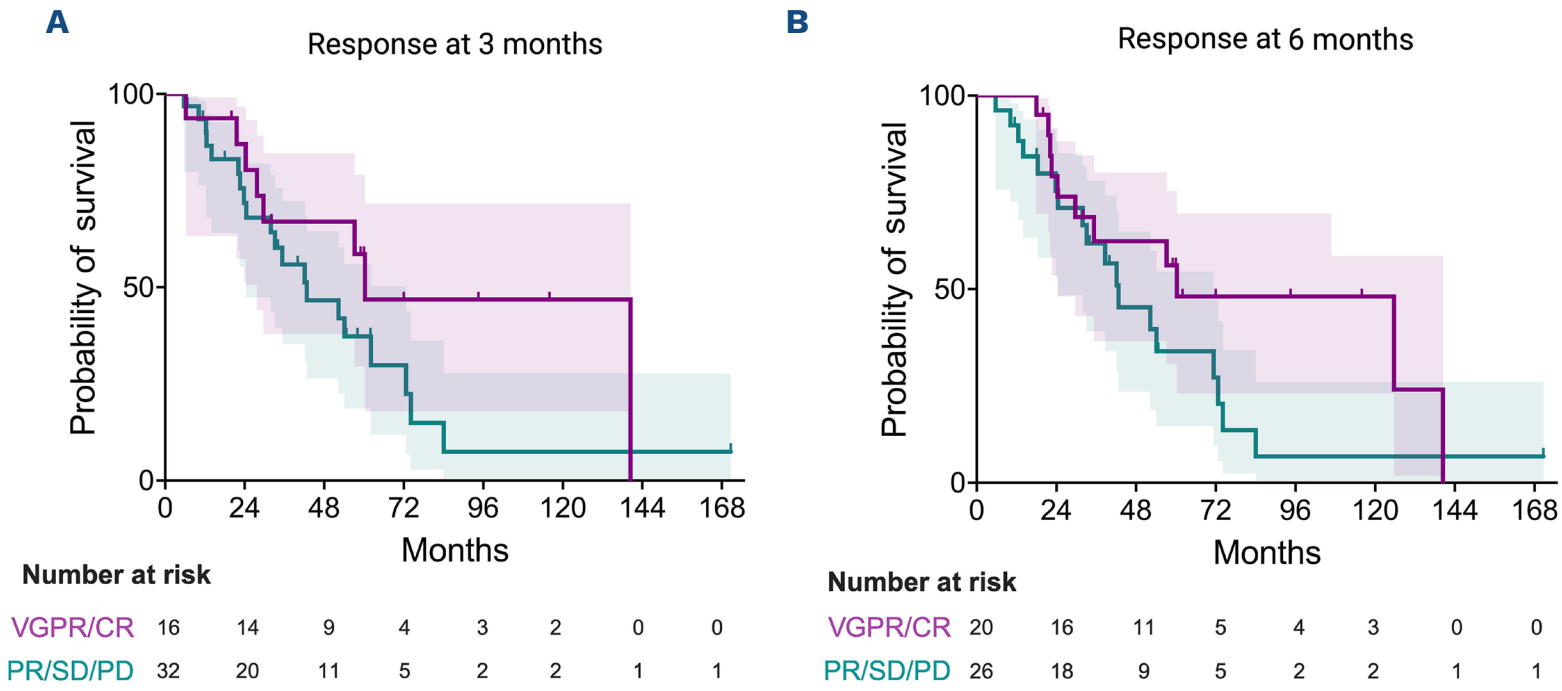

Figure 3. Kaplan-Meier landmark survival analysis of immunoglobulin light-chain amyloidosis patients. (A) At 3 months, (B) 6 months, and (C) 12 months after initiation of anti-clonal therapy, patients achieving complete remission (CR) or very good partial remission (VGPR) tended to have improved overall survival compared to those with partial response (PR), stable disease (SD), or progressive disease (PD). The respective *P* values were 0.1783 (A), 0.1596 (B), and 0.2850 (C).

and elevated Troponin levels. Our analysis did not reveal any statistically significant associations between these variables and EFS individually (Table 5). Nevertheless, a noteworthy trend has emerged, suggesting that patients with involvement of multiple organs may exhibit a tendency towards accelerated disease progression.

Rare cases of renal recovery after dialysis-dependency prior to initial anti-clonal therapy

In our study, we observed 3 patients successfully discontinuing dialysis, highlighting the potential for renal recovery in specific but rare amyloidosis cases.

The first patient, a 60-year-old female with biopsy proven renal involvement, had undergone 20 days of dialysis before therapy initiation. Interestingly, her renal function improved before treatment began, indicating a potential non-therapy-related resolution of acute kidney injury. This suggests that a secondary cause, in addition to amyloid deposition, such as an infection or another trigger, should always be considered in this patient cohort. The second patient, a 70-year-old male underwent treatment with bortezomib and dexamethasone, and within 1.5 months he became dialysis-independent. Notably, he achieved complete remission after three months of therapy, indicating a potential reversal of amyloid deposition if a rapid hematologic response is achieved.

The third patient, also a 70-year-old male with biopsy proven renal involvement, received therapy consisting of six cycles of CyBorDex and became dialysis-free after one year. Impressively, he achieved a very good partial remission within the first month of treatment and maintained this hematologic response throughout the year, indicating once again a potential reversal of amyloid deposition in the case of fast and durable treatment response.

All 3 patients in our study presented with lambda AL amyloidosis and had either SMM or MGCS as the underlying clonal disease. Serum albumin levels were 20.6, 16.9, and 20.7 g/L, respectively. None of the patients experienced anuria, and all had sufficient urine excretion. These observations emphasize the potential for renal recovery in amyloidosis patients, particularly when fast initial hematologic and organ

responses are achieved. They also highlight the importance of individualized treatment approaches and close monitoring of renal function and disease response.

Discussion

Renal involvement in AL amyloidosis remains a significant contributor to morbidity often leading to dialysis dependency and restricted therapeutic options.[3] End-stage renal involvement is still underexplored. In this study, we analyzed a cohort of 68 patients from three different amyloidosis centers in Europe (Heidelberg, Athens, Pavia) who were dependent on dialysis prior to the initiation of anti-clonal therapy. To optimize treatment strategies in renal AL amyloidosis, it is essential to understand the characteristics of patients with renal end-organ damage; this will help us to stratify patients according to their risk status and optimize treatment strategies. The objective of this study was to address this knowledge gap.

Among this cohort of advanced AL amyloidosis patients, the second most common organ affected after the kidneys was the heart. It is notable that a considerable proportion of patients exhibited varying clinical presentation of end-organ damage at the time of diagnosis. This phenomenon highlights the significant heterogeneity in renal presentation within this specific patient subgroup at diagnosis, and the importance of tailored diagnosis and treatment strategies.

The first and obviously striking result of our study was the good OS results, bearing in mind the advanced disease stage of these patients, e.g., 44% in cardiac stage III. In a recent paper, patients with an estimated GFR (eGFR) < 50 had a median OS of 15 months,[22] compared with a median OS of 44.8 months observed in our cohort. This again shows that patients on dialysis at diagnosis represent a specific subgroup and deserve further attention. Notably, the causes of death were documented in only 11 patients, reflecting the challenges of comprehensive outcome tracking in this advanced disease population.

Secondly, our statistical analysis yielded several critical insights into the prognostic factors influencing the survival of dialysis-dependent AL amyloidosis patients. Notably, the underlying clonal disease had an impact on OS and EFS, with patients exhibiting larger clones experiencing a worse outcome. However, other established markers, including the number of involved organs, high dFLC levels, the light-chain type, and patients' characteristics did not exert a significant impact on survival outcomes, so that we could not validate the two published prognostic markers of low serum albumin and elevated alkaline phosphatase levels.[9] Conversely, elevated Troponin levels were associated with worse OS in the univariate model and emerged as a robust predictor of survival in the multivariate analysis, underscoring the importance of these biomarkers as sensitive

Table 4. Univariate analysis between baseline variables and patients' event-free survival.

Baseline variable	Median event-free survival, months	*P*
Patients' characteristics		
Age ≤65 *vs.* >65 years at diagnosis	11 *vs.* 21.6	0.092
Male *vs.* female	16.8 *vs.* 14	0.893
Diagnosis before 2018 *vs.* in/after 2018	14 *vs.* 16.8	0.408
Hematologic disease activity		
MGCS *vs.* SMM *vs.* MM	18 *vs.* 16.8 *vs.* 2	<0.0001
Kappa *vs.* Lambda	10.8 *vs.* 16.9	0.995
dFLC <180 *vs.* ≥180 mg/L	21 *vs.* 14	0.094
Organ parameter		
1 *vs.* >1 organ involved	62.1 *vs.* 14	0.022
Serum albumin <35 *vs.* ≥35 g/L	17.45 *vs.* 13.4	0.485
Anuria *vs.* No anuria	20.45 *vs.* 14.5	0.483
AP <1.5 *vs.* ≥1.5 URL	13.4 *vs.* 13	0.620
Gamma-GT <1.5 *vs.* ≥1.5 URL	16.8 *vs.* 7	0.111
Heart parameter		
Cardiac Staging System 1-3a *vs.* 3b	21 *vs.* 13.2	0.238
Corrected Cardiac Staging 1-3a *vs.* 3b	21 *vs.* 13.4	0.156
NT-proBNP <8,500 *vs.* ≥8,500 ng/L	27.7 *vs.* 13.4	0.264
cNT-proBNP <8,500 *vs.* ≥8,500 ng/L	17.4 *vs.* 13.95	0.227
BNP <700 *vs.* ≥700 pg/mL	10.8 *vs.* 21.1	0.363
cBNP <60 *vs.* ≥60 pg/mL	7.9 *vs.* 17.5	0.210
hsTnT <54 *vs.* ≥54 pg/mL	33.1 *vs.* 11.85	0.063
cTnI <0.1 *vs.* ≥0.1 μg/L	12.7 *vs.* 15.65	0.786
cTnI ≤0.04 *vs.* >0.04 μg/L	21 *vs.* 14.5	0.214
Elevated Troponin T/L	24 *vs.* 14.25	0.152

AP: alkaline phosphatase; BNP: brain natriuretic peptide; cBNP: corrected BNP; cNT-proBNP: corrected NT-proBNP; cTnI: cardiac Troponin I; dFLC: difference between involved (amyloidogenic) and uninvolved free-light chain; EFS: event-free survival; Gamma-GT: gamma-glutamyl transferase; hsTnT: high-sensitivity Troponin T; MGCS: monoclonal gammopathy of clinical significance; MM: multiple myeloma; NT-proBN: N-terminal pro–B-type natriuretic peptide; SMM: smoldering multiple myeloma; URL: upper reference limit.

Table 5. Multivariate analysis between baseline variables and patients' event-free survival.

Variable	Hazard Ratio	95% CI	*P*
Age at diagnosis >65 years	1.752	0.8823-3.60	0.1156
Lambda *vs.* kappa	0.7183	0.3373-1.67	0.4127
SMM/MM *vs.* MGCS	1.209	0.6153-2.38	0.5800
>1 organ involved	2.738	1.014-9.635	0.0724
Elevated troponin T/I	1.583	0.7490-3.59	0.2475

CI: confidence interval; EFS: event-free survival; MGCS: monoclonal gammopathy of clinical significance; MM: multiple myeloma; SMM: smoldering multiple myeloma.

indicators of cardiac damage. We propose the use of cTnI with the newly defined dialysis specific cut-off of 0.04pg/mL and hs-TNT with the amyloidosis specific cut-off of 54 pg/mL. The application of the biological cut-off for hsTnT was not possible due to the absence of any patient exhibiting hsTnT levels within the physiological range. In contrast, NT-proBNP, BNP and eGFR-corrected BNP and NT-proBNP (cNT-proBNP and cBNP) levels did not exhibit a significant impact on OS, emphasizing: a) the intricate interplay between this biomarker and renal function; and b) the difficulties in correcting biomarkers for renal function. Our findings suggest that Troponin may be a more robust prognostic marker than NT-proBNP in dialysis patients due to lower dependence on renal clearance. We observed a notably long OS in patients with Mayo Cardiac Stage 3b, highlighting significant limitations of the classical Mayo Cardiac Staging system for these patients. The significance of BNP levels in dialysis-dependent patients prior to initiating anti-myeloma therapy warrants investigation in future studies.[23] Nevertheless, our analysis aligns with prior studies, demonstrating a robust association of cardiac damage on OS rates.[24] If confirmed in larger, prospective cohorts, these findings may justify a re-evaluation of current prognostic scoring systems for AL amyloidosis and suggest that cardiac involvement, particularly as reflected by Troponin levels, could represent the key determinant of survival in this specific subgroup.

Thirdly, only a slight tendency towards extended survival was observed in patients with favorable hematologic responses (complete remission or very good partial remission). As this finding did not achieve statistical significance, it underscores the need for adapted hematologic response criteria in the context of dialysis dependence. Assessing the percentage reduction of the involved light chain appears to be more informative, with particularly early (three months after therapy initiation) and pronounced reductions being associated with prolonged survival; this highlights the importance of achieving a rapid and deep hematologic response if treatment is needed.

It is noteworthy that our study presented 3 cases of renal recovery in patients who were initially dependent on dialysis. These cases illustrate the potential for renal recuperation, particularly when patients are not anuric and achieve a fast and good therapeutic response. Although this applied to only 2% of the cohort, it emphasizes that dialysis dependency can be reversible in some cases and highlights the need to initiate effective therapy as early as possible. Furthermore, with modern therapies, renal transplantation should be reconsidered in patients achieving at least VGPR.[25]

Of course, our retrospective analyses have some limitations. For example, although we included all available patients from three amyloidosis centers, the number did not reach more than 68 diagnosed in nearly 20 years. We demonstrated that hematologic response status, measured by the classical ISA criteria, did not correlate with OS or EFS rates, underlining the importance of other response assessment methods, as response status measured by FLC is hampered by renal failure; this matches our difficulty in identifying independent prognostic factors for EFS.

In conclusion, our study demonstrates that patients requiring dialysis prior to anti-clonal therapy have far better outcomes than expected, that they can be successfully treated with anti-clonal therapy, and stratified by cardiac damage, which might be best measured by Troponin levels in this subgroup. Furthermore, we noticed that dialysis dependency might be reversible in non-anuric patients if treatment is started quickly and proves to be very effective.

Disclosures

PM has received honoraria from Janssen, Prothena, Sebia, and Pfizer (also research grant), and from Siemens (advisory board). LS has received honoraria from Sanofi (presentation) and Janssen (advisory board). EK has received honoraria from Janssen, GSK, Pfizer, and Genesis Pharma, and research support from Janssen, GSK, and Pfizer. M-SR has received honoraria from BMS, Amgen, Janssen, Sanofi, AbbVie, and Oncopeptides (lectures or presentations); honoraria for advisory board participation from GSK, Pfizer, and Takeda; research support from BMS, Janssen, and Heidelberg Pharma; and travel grants from BMS, Amgen, Janssen, and Oncopeptides. GP has received honoraria for advisory board participation from Alexion, AbbVie, Bayer, Life Molecular Science, Protego, Pfizer, Prothena, and Regeneron. FS has received speaking fees from Pfizer, Alnylam, Janssen, and Bayer, and consulting fees from Pfizer and Bayer. SS has received honoraria as a consultant/adviser, travel grants, honoraria, and research funding from Janssen and Prothena; research funding from Sanofi; honoraria from Pfizer and Takeda; serves as adviser for Telix; and has received travel grants from The Binding Site, Celgene, and Jazz Pharmaceuticals. UH has received honoraria for talks from Janssen, Pfizer, Alnylam, Prothena, and AstraZeneca; financial support for congress participation from Janssen, Prothena, and Pfizer; honoraria for advisory boards from Pfizer, Prothena, Janssen, Alexion, and Alnylam; and financial sponsorship for the Amyloidosis Registry from Janssen. All of the other authors have no conflicts of interest to disclose.

Contributions

EK, GP, UH and SS designed the study. LSS, PM and FT collected clinical data. LSS and TD analyzed clinical data and performed statistical analyses. EK, GP, UH and SS supervised the study. JB, FadS, MZ, CM-T and M-SR critically reviewed the manuscript. LSS, UH and SS wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

Data-sharing statement

The datasets are available from the corresponding author upon reasonable request.

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