Impact of time to diagnosis on Mayo stages, treatment outcome, and survival in patients with AL amyloidosis and cardiac involvement

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Abstract

Objective: To study the impact of time to diagnosis on cardiac Mayo stages, treatment outcome, and overall survival.

Methods: We retrospectively analyzed 77 consecutive patients diagnosed between 2015 and 2020 with AL amyloidosis and cardiac involvement. Medical history was recorded in standardized form with the help of a questionnaire.

Results: Time from onset of symptoms of cardiac failure to diagnosis was correlated with the severity of cardiac involvement in modified Mayo 2004 and revised Mayo 2012 staging systems ($r_s = 0.30$, 95% CI: 0.07-0.50, $P = .007$ and $r_s = 0.25$, 95% CI: 0.01-0.45, $P = .03$). Patients with advanced Mayo 2004 stages received reduced-intensity regimens and had a lower probability to achieve adequate hematologic- and cardiac response after first-line treatment than patients with early stages ($r_s = 0.28$, 95% CI: 0.04-0.48, $P = .01$ and $r_s = 0.72$, 95% CI: 0.55-0.82, $P < .0001$) and poorer overall survival ($P = .0004$). Compared with patients diagnosed within the first year, patients diagnosed after 13-18 or ≥19 months from first symptoms had a 3- to 5 times higher risk of dying. Our data indicate that there is a 12-month window within which the diagnosis of AL amyloidosis needs to be established to avoid early deterioration and death.

Novelty Statements:

- What is the new aspect of your work? Our study shows for the first time a significant correlation between delayed diagnosis and advanced cardiac disease, merely allowing treatments with lower dosed regimens, which reduce the probability of achievement of adequate cardiac- and hematologic responses and negatively influences the overall survival.
- What is the central finding of your work? Exceeding one year of time from first symptoms to diagnosis of AL amyloidosis with cardiac involvement dramatically worsens overall survival by 3- to 5-fold.
- What is (or could be) the specific clinical relevance of your work? Shortening the time from first symptoms to diagnosis is likely to have an impact on survival in this devastating disease, underlining the need to increase physicians’ awareness and to develop diagnostic algorithms and specific tests in case of suspicion of amyloidosis.

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1 INTRODUCTION

Systemic light-chain (AL) amyloidosis is a rare acquired protein misfolding disorder with an incidence of about 5-13 per million person-years. It is characterized by extracellular deposition of misfolded amyloidogenic immunoglobulin light-chain fibrils secreted from clonal plasma cells in the bone marrow. Deposition can occur in various organs, except for the central nervous system, leading to organ failure. In most cases, the underlying plasma cell dyscrasia is in a pre-malignant stage, such as monoclonal gamopathy or smoldering multiple myeloma, whereas in 10%-15% multiple myeloma is the underlying disease. Rarely and in about 1% of the cases, other lymphoproliferative diseases are found in patients with AL amyloidosis as pre-existing hematological neoplasms.

Clinical manifestations differ depending on the pattern of affected organs, most prominently patients suffer from symptoms due to cardiac or renal failure. These insidious, unspecific, and misleading symptoms are often misinterpreted leading to delay of the diagnosis. Upon clinical suspicion, a tissue biopsy identifying the green birefringence fibrils on a polarized microscope after staining the sample with Congo red dye and further typing with immunohistochemistry or mass spectrometry is indispensable to formally establish the diagnosis. The treatment is based on anti-plasma cell therapy, including conventional and high-dose chemotherapy regimens, monoclonal antibodies, immunomodulatory drugs, proteasome inhibitors, and corticosteroids. The development of new treatment agents and the selection of patients eligible for autologous stem cell transplantation have led to a marked survival improvement in the last few decades. This is reflected, as published in a study by Quock et al, by the pronounced increase in the prevalence from 15.5 per million person-years in 2007 to 40.5 in 2015, whereas the increase in the incidence rate in this study was mild from 9.7 in 2007 to 14.0 in 2015.

The outcome of AL amyloidosis is strongly associated with the severity of organ involvement, especially heart involvement. The first Mayo cardiac staging system from 2004 including the European staging of advanced cardiac involvement (modified Mayo staging system 2004) and the revised Mayo staging system 2012 are used to determine the degree of cardiac involvement.

In this study, we examined the impact of time to diagnosis (interval from first symptoms of cardiac failure to diagnosis) on the modified Mayo 2004 and revised Mayo 2012 staging systems. Further, we studied the influence of advanced Mayo stages on hematologic response and cardiac response after first-line treatment, as well as overall survival in patients with cardiac involvement.

2 MATERIALS AND METHODS

We retrospectively evaluated 93 consecutive patients who were diagnosed with AL amyloidosis between January 2015 and September 2020 in the outpatient amyloidosis clinic at the University Hospital of Essen, Germany. Of the 93 patients, we identified 77 patients with cardiac involvement.

A questionnaire-based detailed patient history was completed together with the patient at first presentation with special focus on onset of amyloidosis-related symptoms, physician visits, and diagnostic steps. The main symptoms were dyspnea, edema, foamy urine, dysphagia, diarrhea, obstipation, weight loss, orthostatic dysfunction, polyneuropathy, macroglossia, peri-orbital purpura, and reduced performance state. Additionally, medical records regarding visited physicians and hospital admissions were reviewed. In one patient, time to diagnosis was not available due to missing detailed anamnestic data.

The onset of symptoms of heart failure was assessed at the point of time when patients first documented symptoms attributable to cardiac disease and/or abnormal laboratory analyses such as elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac troponin T were recorded. In individual cases, the presence of other comorbidities (coronary heart disease, heart valve diseases etc) that could confuse the clinical symptoms was considered.

The underlying plasma cell dyscrasia was diagnosed as recommended by the International Myeloma Working Group. Patients with symptomatic multiple myeloma were defined by CRAB criteria. Hematologic response after first-line treatment was evaluated as described by Palladini et al and recommended by the International Society of Amyloidosis. The best hematologic response after first-line treatment was assessed. We excluded patients with a difference between the involved and non-involved free light chains (dFLC) lower than 20 mg/L (n = 3), patients with missing follow-up data (n = 3), and two patients who died before initiating treatment. Early deaths within the first two months after starting treatment and before evaluation of hematologic response were considered non-responders (n = 4) according to Milani et al. None of our patients had a low dFLC partial...
remission response (low dFLC-PR) regarding the recently published response criteria for patients with low dFLC levels between 20 and 50 mg/l at diagnosis.\textsuperscript{19}

Organ involvement was assessed as proposed by Gertz et al\textsuperscript{20} and recommended by the 10th International Symposium on Amyloid and Amyloidosis. Measurement of the cardiac biomarkers NTproBNP, cardiac troponin T, cardiac troponin I, and the hematologic marker dFLC was obtained to assess the severity of cardiac disease at diagnosis expressed as modified Mayo 2004 and revised Mayo 2012 staging systems.\textsuperscript{12,14} In the Mayo classification 2004, the severity of cardiac disease was determined using NTproBNP and cardiac troponin I in 2 patients, according to Dispenzieri et al\textsuperscript{13} One patient was excluded from this analysis due to missing cardiac biomarkers. Cardiac response after first-line treatment was evaluated as best cardiac response at least 6 months after initiating treatment or earlier before starting with second-line treatment in cases with disease progression based on measurement of NTproBNP (n = 63). Changes in NTproBNP that were both >30\% and >300 ng/l defined response or progression as proposed by Palladini et al\textsuperscript{15,21} Patients with NTproBNP <650 ng/L at baseline were excluded accordingly (n = 5). Four patients with loss of follow-up data, patients died before initiating treatment (n = 2) and patients receiving treatment during the first 6 months (n = 3) were excluded. Unless otherwise stated, survival was calculated from the date of first diagnosis to death.

Ethical approval for this study was obtained from the ethics committee of the University of Duisburg-Essen, approval number 20-9280 BO.

For statistical analyses, time-to-event end points were analyzed using the Kaplan-Meier estimator, the logrank test for trend, and, when adjusting for covariates, Cox proportional hazards regression. We used Spearman’s rank correlation coefficient ($r_s$) to test the correlation between two categorical or categorical and continuous variables. In significance analyses, two-tailed tests were used. The statistical software applied to calculate the statistical significance was GraphPad PRISM for Mac, version 9.0 and IBM SPSS statistics, version 26.

3 | RESULTS

3.1 | Patient characteristics

The study included 77 consecutive patients presented in our special consultation for amyloidosis with histologically confirmed systemic light-chain amyloidosis with cardiac involvement according to Gertz et al\textsuperscript{20} Median age at diagnosis was 66 years (range 42-85 years), and 53 (69\%) patients were males. The most common underlying disease was monoclonal gammopathy (n = 34, 44\%), smoldering multiple myeloma (n = 26, 34\%), and multiple myeloma (n = 17, 22\%). A lambda light chain was the amyloidogenic monoclonal precursor protein in 60 (78\%) patients (Table 1). Of the 77 patients, 4 had a known pre-existing plasma cell dyscrasia.

### TABLE 1 Patients’ characteristics at first diagnosis

| Patients’ characteristics | Number (Percent) |
|--------------------------|------------------|
| Sex                      |                  |
| Male                     | 53 (69)          |
| Female                   | 24 (31)          |
| Age                      |                  |
| Median (range)           | 66 (42-85)       |
| dFLC                     |                  |
| Median (range)           | 209 (<0.4 - 2694.5) |
| Involved light chain     |                  |
| Lambda                   | 60 (78)          |
| Kappa                    | 17 (22)          |
| PCD                      |                  |
| MG                       | 34 (44)          |
| SMM                      | 26 (34)          |
| MM                       | 17 (22)          |
| Organ involvements       |                  |
| Heart                    | 77 (100)         |
| Kidney                   | 55 (71)          |
| PNS/ANS                  | 32 (42)          |
| GIT                      | 7 (9)            |
| Liver                    | 12 (16)          |
| Lung                     | 5 (6)            |
| Soft tissue              | 30 (39)          |
| NTproBNP (pg/ml)         |                  |
| Median (range)           | 3365.5 (79-87243) |

Abbreviations: ANS, autonomous nervous system; dFLC, difference between involved and non-involved light chain; GIT, gastrointestinal tract; MG, monoclonal gammopathy; MM, multiple myeloma; NTproBNP, N-terminal prohormone of brain natriuretic peptide; PCD, plasma cell dyscrasia; PNS, peripheral nervous system; SMM, smoldering multiple myeloma.

3.2 | Impact of time from first symptoms of heart failure in AL amyloidosis on overall survival

Initially, patients with AL amyloidosis and cardiac involvement predominantly presented to physicians with clinical symptoms compatible with heart failure (n = 21, 27\%), heart and renal failure (n = 46, 60\%), and in 10 patients (13\%), the first symptoms were related to involvement of other organs (gastrointestinal and liver involvement in 6, neurologic symptoms in 3 and soft tissue manifestation in 1 patient). Correct diagnosis was established after occurrence of first symptoms of heart failure within the first 6 months in 45\% (n = 34), within the first year in 74\% (n = 56), and beyond the first year in 26\% (n = 20) of cases. A median of 7 months (range 0-39 months) was required until diagnosis. In the case of known pre-existing plasma cell disease (4/77), a median of 8.5 months was required until diagnosis.

About 27 of 77 patients died in the observation time, and the median overall survival of the overall population was 19 months. To
study the influence of the time elapsing before diagnosis on overall survival, we classified patients into four groups depending on time from first symptoms of cardiac failure to diagnosis (0-6 months \((n = 34)\), 7-12 months \((n = 22)\), 13-18 months \((n = 13)\), and ≥19 months \((n = 7)\)). In patients with NYHA stage I without any relevant heart failure symptoms at diagnosis, the time from first cardiac symptoms to diagnosis was considered to be 0 months \((n = 3)\). The median follow-up time of the study from first diagnosis was 26 months. We observed a statistically significant inverse correlation between survival from the date of diagnosis and the interval between first symptoms and diagnosis \((P = .0001)\) (Figure 1A). While the 5-year survival rate in patients diagnosed within 6 months and 7-12 months after onset of first cardiac symptoms was 79% and 63%, it was reduced to 28% and 19% in patients who were diagnosed after a longer interval (13-18 or ≥19 months), respectively (Figure 1A). In Cox regression analysis including age, sex, dFLC >180 mg/L, plasma cell infiltration in the bone marrow, diagnostic interval, and Mayo stage, only the latter two variables were statistically significantly correlated with overall survival. Patients diagnosed after 0-6 versus 7-12 months did not differ in outcome (data not shown). We therefore constructed a simplified Cox model restricted to diagnostic interval with only three categories (0-12, 13-18, ≥19 months) and Mayo stage with two categories (I-IIa, IIIb). Compared with patients diagnosed within the first year, patients diagnosed after 13-18 or ≥19 months from first symptoms had a 3- to 5 times higher risk of dying (Table 2). To exclude a lead-time bias, we also studied survival from the date of first symptoms. The median follow-up time from first cardiac symptoms was 35 months. Again, patients with short symptoms-to-diagnosis interval fared significantly better than patients with long interval \((P = .03)\) (Figure 1B).

### 3.3 | Impact of delayed diagnosis on cardiac Mayo stages

Clinical experience prompted us to assume that delays in the diagnostic process may lead to more advanced cardiac dysfunction due to disease progression. In our cohort of 77 patients with cardiac

![Figure 1](image-url)
involvement, the severity of cardiac disease was assessed using the modified Mayo 2004 staging system in 76 patients (stage I 4% [n = 3], stage II 25% [n = 19], stage IIIa 38% [n = 29], stage IIIb 33% [n = 25]), and the revised Mayo 2012 staging system in 74 patients (stage I 7% [n = 5], stage II 16% [n = 12], stage III 36% [n = 27], and stage IV 41% [n = 30]). More than 50% of the patients had an advanced cardiac disease at diagnosis ≥ stage III in both Mayo staging systems. There was a significant correlation between the time required to diagnose AL amyloidosis and the severity of cardiac involvement at diagnosis in the modified Mayo 2004 staging system ($r_s = 0.30$, 95% CI: 0.07-0.50, $P = .007$) (Figure 1C) and the revised Mayo 2012 staging system ($r_s = 0.25$, 95% CI: 0.01-0.45, $P = .03$) (Figure 1D).

### 3.4 Impact of advanced Mayo stages 2004 on hematologic and cardiac responses after first-line treatment

Data regarding the administered therapy regimens in our sample were also collected. In most cases, the choice of therapy was based on the recommendations made by Palladini and Merlini. In patients with "intermediate risk," the most common treatment was the CyBorD-regimen (cyclophosphamide, bortezomib, dexamethasone; Mayo stage I, n = 8, 33%; stage II, n = 11, 58%; stage IIIa, n = 17, 59%), whereas patients with "high risk" (Mayo stage IIIb) tended to receive less intense regimens, such as Vd (velcade®, reduced dexamethasone; n = 9, 36%). High-dose melphalan and autologous stem cell transplantation were performed in "low-risk" patients (n = 8, 11%), six of whom (75%) had Mayo stage II (Table 3).

Our data show an association between the severity of cardiac disease expressed as modified Mayo 2004 stages and hematologic response after first-line treatment. While patients in Mayo stages I, II, and IIIa reached an adequate hematologic response (complete remission [CR] or very good partial remission [VGPR]) in 67%, 58%, and 63% of cases, respectively, patients in Mayo stage IIIb reached CR or VGPR in 40% of cases, indicating a significant correlation between advanced Mayo stages (IIIb) and poor hematologic response (Spearman’s rank correlation coefficient, $r_s = 0.28$, 95% CI: 0.04-0.48, $P = .01$) (Figure 2A). In 76% of cases, achieving a complete hematologic response after first-line treatment was followed by a cardiac response, while, in patients reaching VGPR or partial remission (PR), this was only the case in 33% and 8%, respectively. None of the patients without hematologic response experienced a cardiac response, and 70% of hematologic non-responders (NR) died within the first 6 months of initiating therapy. Our data clearly show a significant and strong correlation between hematologic and cardiac response (Spearman’s rank correlation coefficient, $r_s = 0.72$, 95% CI: 0.55-0.82, $P < .0001$) (Figure 2B).

### 3.5 Impact of Mayo stages and hematologic response after first-line treatment on overall survival

Cardiac involvement is a major factor affecting survival in AL amyloidosis. Similar to a study published by Palladini et al, our data revealed a significantly shorter overall survival in patients with advanced as compared to early modified Mayo 2004 stages ($P = .0004$). However, in the revised Mayo 2012 staging system, this difference did not reach statistical significance ($P = .08$) (Figure 3A, 3B). While 6-month overall survival in the modified Mayo 2004 staging system was 100% in stage I, 84% in stage II and 83% in stage IIIa, it was reduced to 52% in stage IIb. In stage IIb, the median overall survival was 9 months. The 6-month overall survival rate according to the revised Mayo 2012 staging system was 80% in stage I, 92% in stage II, 74% in stage III and 66% in stage IV.

We further studied the influence of hematologic response on overall survival. Hematologic response after first-line treatment was a complete remission (CR) in 24 patients (35%), a very good partial remission (VGPR) in 16 patients (23%), a partial remission (PR) in 16 patients (23%), and no response (NR) in 13 patients (19%). Similar to a previous study, our analysis showed a correlation between hematologic response and outcome. With decreasing hematologic response, survival time was increasingly reduced (log rank test for trend $P < .0001$) (Figure 3C). While the survival proportion after 6 months in patients who reached a CR was 96%, a VGPR 81%, and a PR 75%, it dropped to 23% in non-responding patients resulting in a median overall survival of only 4 months.

### 4 DISCUSSION

Clinical experience suggests that delays in diagnosis of AL amyloidosis in patients with cardiac involvement worsen prognosis. In
our study, we performed a detailed workup of the patient’s history by creating a questionnaire focusing on first onset of cardiac symptoms and analyzed the impact of time to diagnosis on survival. To avoid a lead-time bias, we set the starting point of the survival analysis either at the date of amyloidosis diagnosis or at the date of first documented cardiac symptoms. The first approach penalizes patients with long symptoms-to-diagnosis interval, because survival with cardiac disease before the date of diagnosis is not accounted for. By contrast, the second approach favors these patients, because it is restricted to those still alive at the time of diagnosis. Any deaths before the time of diagnosis (which, for lack of a diagnosis, we were unable to consider) would have worsened
the survival curves of patients with long symptoms-to-diagnosis interval. In essence, both types of analysis yielded the same result. Importantly, patients diagnosed within 0-6 and 7-12 months from onset of cardiac symptoms did not differ in outcome, while survival was significantly shortened in patients diagnosed beyond the first year. Our data indicate that there is a 12-month window within which the diagnosis of AL amyloidosis needs to be established to avoid early deterioration and death.

In a cohort of 324 patients presented from 2010 to 2015, Schulman et al. analyzed the impact of time to diagnosis on survival. In that study, 66% had renal and only 50% had cardiac involvement, mostly in early stages (77% stage I or II) according to the Boston University cardiac biomarker scoring system. Survival analysis from diagnosis to death stratified by time from first symptoms to diagnosis showed significant differences between patients diagnosed earlier than 6, between 6 and 12 or >12 months. In contrast, all patients in our sample had cardiac involvement, mostly in advanced stages, which may explain the differences between the two studies. Overall, our data are in line with the results from Schulman et al and underline the urge to achieve an early diagnosis.

Prolonged time to diagnosis significantly worsened survival and led to more advanced disease at the time of diagnosis expressed by advanced Mayo stages. One could speculate that differences in the natural course of the disease from patient to patient could eventually have been mainly responsible for advanced stages, meaning that a more rapid, aggressive progress occurred hampering timely diagnostic workup. Our data argue against this hypothesis, since we clearly show a positive correlation between time to diagnosis and Mayo stages, indicating that the delay in diagnosis itself and not, or to a lesser extent, differences in the natural course of the disease were responsible for advanced clinical deterioration.

In our patient population, the most likely explanation for delayed diagnosis was insufficient physician awareness, since patients visited primary health providers early upon occurrence of symptoms (not shown). This has been demonstrated before by Lousada et al., whose data are in line with our observations. Increasing awareness of primary care physicians, but also specialists, is one of the most promising approaches to improve the prognosis of the disease.

In general, patients were treated according to the recommendations made by Palladini and Merlini (Table 3), following the

**FIGURE 2** (A) Correlation between Mayo stages and hematologic response after first-line treatment, patients with advanced Mayo stage (IIIb) had a significantly poorer hematologic response (PR, NR, death) compared with other Mayo stages. Early deaths represent deaths within the first two months. (B) Correlation between hematologic response and cardiac response after first-line treatment. Early deaths represent deaths within the first 6 months. Abbreviations: CR, complete hematologic remission; NR, no hematologic response; PD, progressive cardiac disease; PR, partial hematologic remission; SD, stable cardiac disease; VGPR, very good partial remission.

**FIGURE 3** Kaplan-Meier survival analysis in patients with AL amyloidosis and cardiac involvement showing overall survival dependent on (A) severity of cardiac involvement in Mayo 2004 staging system, (B) revised Mayo 2012 staging system, and (C) hematologic response after first-line treatment. Abbreviations: CR, complete hematologic remission; NR, no response; PR, partial remission; VGPR, very good partial remission.
experience that the more severe the heart involvement is, the worse anti-plasma cell therapy is tolerated. Patients stratified as "high risk" (modified Mayo 2004 stage IIIb or NYHA ≥ III) predominantly received low-dose combination regimens, patients stratified as "intermediate risk" (Mayo I-IIla) received full-dose therapies, such as the CyBorD or MDex regimen (melphalan, dexamethasone), and transplant-eligible patients were mostly treated with high-dose melphalan and autologous stem cell transplantation. According to our data, this translated into treatment outcome: We observed a significant relation between early modified Mayo stages 2004 and adequate hematologic treatment outcome, defined as achieving CR or VGPR (Figure 2A). Patients with Mayo stage IIIb at first diagnosis reached an adequate hematologic response in only 40% which was significantly worse than the response in Mayo stages I-IIla (Figure 2A). The worse the hematologic response, the less possible the achievement of a cardiac response. Patients with PR reached only in 8% of cases a cardiac response, whereas none of the patients with NR attained a cardiac response (Figure 2B). These data are in line with observations made by Palladini et al in a much larger cohort. Others have shown before that advanced cardiac stages at first diagnosis negatively influence the prognosis.12-14

We clearly show that the longer the time is to establish the diagnosis of AL amyloidosis as a prerequisite for anti-plasma cell therapy, the more advanced is the severity of cardiac involvement with both Mayo staging systems (Figure 1C, 1D). However, in our experience, the modified Mayo staging system from 2004 predicts the probability of survival better than the revised Mayo staging system from 2012 (Figure 3A, 3B). While 2-year survival was 100% in modified Mayo 2004 stage I and 29% in stage IIIb, the difference was much smaller (80% versus 52%) when the revised Mayo staging system from 2012 was applied. Of note, the patients included in this study were diagnosed from 2015 to 2020; therefore, improved treatment regimens, including daratumumab, was possible. In our cohort, 25 of 77 patients (32%) received daratumumab in first or later lines of therapy. One may speculate that therapeutic improvements differentially affect the predictive value of the two staging systems. Further studies in larger cohorts are necessary to confirm this hypothesis.

Patients with pre-existing plasma cell dyscrasia were included (n = 4), and the median time from first symptoms to diagnosis was 8.5 months. As reported by Kourielis et al, the outcome in these patients is not significantly better than patients without a known plasma cell dyscrasia. Hence, the probability that these patients influenced our overall survival results is very limited.

Sidana et al reported that patients with cardiac involvement have a higher degree of plasma cell infiltration in the bone marrow than patients without cardiac involvement. This may explain the high proportion of patients with smoldering myeloma/multiple myeloma in our cohort. The proportion of patients with >10% marrow plasma cells was 57% (n = 42) in our study and 64% in the study reported by Sidana et al.

The main limitation of this study is the relatively small study population with 77 patients and the short median follow-up time of 35 months from the beginning of cardiac symptoms. Further limitations may be the single-center and the retrospective design. Hence, there is a potential inaccuracy in patients statements regarding the onset of symptoms, as these data mainly rely on retrospections. However, patients history was recorded in a standardized manner with a questionnaire focusing on the onset of symptoms. As, and as a potential strength, it was taken by a limited number of amyloidosis experienced physicians, thereby presumably avoiding potential biases in recording. While these limitations are important to consider when interpreting the findings of our analysis, in our eyes they do not override the results: Our data are statistically highly significant, so we do not assume that they were created by chance. Furthermore, the findings actually correspond to clinical observation; In our study, we quantify for the first time the increase in risk depending on the time delays that arise during the diagnosis.

Furthermore, our data clearly show that time delays in diagnosis of AL amyloidosis with cardiac manifestation leads to advanced Mayo stages and cardiac involvement, in turn leading to considerably reduced survival. A delay from first symptoms of cardiac failure to diagnosis of more than 13 and 19 months leads to an 3- to 5-fold risk of death compared with patients diagnosed earlier. Our findings clearly underline the need to increase physicians’ awareness of the disease and to develop diagnostic algorithms and specific tests in case of suspicion of amyloidosis. Shortening the time from first symptoms to diagnosis is likely to have an impact on survival in this devastating disease.

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AUTHOR CONTRIBUTIONS
SO and AC designed the study and gathered the data. SO, EN, KHJ, UD, and A.C analyzed the data. All authors critically reviewed the manuscript. SO, UD, and AC wrote the manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. Ethical restrictions apply to the availability of these data have to be assessed case by case in accordance with the local ethical review committee.

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