

Hepatic response criteria in light chain amyloidosis: a multicenter validation study

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Abstract

Liver involvement in light chain amyloidosis (AL) is seen in 10–20% of patients and is associated with poor prognosis. The goal of this study was to assess the prognostic impact of the hepatic response criteria. AL patients diagnosed between 2010 and 2015 with liver involvement (serum alkaline phosphatase [AP] >1.5 upper reference limit [URL]) who achieved a hematologic response were included. Hepatic response was defined as >50% reduction (or normalization) of AP from baseline. Hepatic response was assessed at 6, 12, and 24 months after therapy initiation and at best response. Overall survival was assessed from time of therapy initiation. Hepatic response was evaluated in 116 patients. The median baseline serum AP was X2.6 URL. Hematologic very good partial response or better ($\geq$ VGPR) was achieved in 69% of patients. AP decreased with time, with a median reduction of 22%, 34%, and 53% at 6, 12, and 24 months, respectively, and a median AP reduction of 56% at the time of best response. The median time to hepatic response was 13.3 months and was longer for patients undergoing autologous stem cell transplantation. Achievement of hepatic response, particularly as early as 12 months, and at best response, was associated with improved survival, independently of other prognostic factors. Predictors of hepatic response include higher baseline AP level, lower total bilirubin, hematologic $\geq$ VGPR, and cardiac and renal responses, when applicable. Hepatic response measured by the change in AP is a prognostic factor in patients with AL amyloidosis.

Introduction

Liver involvement in AL amyloidosis has been reported in up to 20% of the patients.^{1,2} It is typically encountered as part of multi-organ involvement and is rarely the only organ involved.³ Therefore, large series focusing on hepatic AL amyloidosis are uncommon. Although the prognosis of hepatic AL amyloidosis is poor, it is governed by hepatic and non-hepatic factors.^{4–6} The survival of patients with hepatic AL amyloidosis is poor and did not change over the past

four decades according to two single-center studies that reported the outcomes of patients diagnosed from 1975 to 1997 and 2004 to 2019.^{5,6} However, in more contemporary series, survival was better for those attaining a hematologic response. As survival in AL amyloidosis has improved significantly in the past years, particularly in referral centers,^{7–9} with better hematologic responses achieved with modern therapies,^{10–12} improvement in outcomes in hepatic AL amyloidosis is expected as well.

The International Society of Amyloidosis (ISA) published

hepatic response criteria in 2005.¹³ Hepatic response was defined as a >50% decrease in abnormal alkaline phosphatase (AP) levels or a decrease in liver size by at least 2 cm as determined radiographically. The prognostic value of these criteria was evaluated only in a small series of AL patients with liver involvement who underwent autologous stem-cell transplantation.¹⁴ Therefore, a broader assessment of their prognostic utility and their independence from other factors is required. More recently, Mayo Clinic investigators proposed four-level graded hepatic response criteria in a single-center study,¹⁵ which have not yet been externally validated. This multicenter study aimed to determine the prognostic significance of hepatic response criteria in AL amyloidosis and to establish optimal response definitions.

Methods

The study was approved by the institutional review boards of the participating centers. Patients provided informed consent to the use of their medical records for medical research. Patients with biopsy-proven AL amyloidosis diagnosed between January 2010 and December 2015 were included if they met the following criteria: (i) liver involvement with serum AP >1.5 times the institutional upper reference limit (URL) attributed to liver involvement; (ii) achievement of at least a hematologic partial response (PR) to therapy within 12 months of diagnosis; and (iii) serum AP measurements recorded at least twice annually in the first 3 years and annually thereafter. Hepatic response, assessed at fixed timepoints from treatment initiation (6, 12, and 24 months) and at the best hepatic response, was defined as a >50% reduction in AP, consistent with the ISA criteria.¹³ Receiver operating characteristic analysis also identified a >50% reduction in AP at 12 months as the optimal cut-off point for 5-year survival discrimination (area under the curve, 0.67). Additionally, patients who had normalization of AP were considered to have achieved a hepatic response, regardless of their ability to achieve a >50% reduction in AP. Radiographic assessment

of liver span was not utilized due to its infrequent use in routine practice. Alternatively, the four-graded hepatic response criteria proposed by the Mayo Clinic were also tested;¹⁵ these are based on the reduction in serum AP with cut-off points at 30%, 60%, and absolute AP ≤90 U/L for hepatic PR, hepatic very good partial response (VGPR), and hepatic complete response (CR), respectively (Table 1). Given the limited number of patients to adequately power a four-level analysis of hepatic response, and considering the comparable survival outcomes observed between patients with hepatic VGPR and hepatic CR, we combined these two categories into a collective hepatic CR/VGPR group for all survival analyses. Given the gradual nature of organ response, missing hepatic response data at fixed timepoints were imputed using adjacent timepoint data, affecting 15%, 23%, and 22% of patients at the 6-, 12-, and 24-month intervals, respectively. Serum AP values were standardized as folds of URL to account for inter-institutional variability (*Online Supplementary Table S1*). Cardiac and renal stages were assigned based on established criteria.^{16,17} Graded cardiac and renal responses were used, as previously reported.^{18,19} Pearson χ^2 and Kruskal–Wallis tests were used to compare nominal and continuous variables, respectively. Overall survival (OS) was analyzed using the Kaplan–Meier method and compared via log-rank tests. To mitigate survivorship bias, landmark analyses excluded patients who experienced an event or were lost to follow-up before the assessed timepoint (*Online Supplementary Figure S1*). To evaluate the influence of dynamic hepatic response on OS, we utilized Cox regression models in which hepatic response was treated as a time-dependent covariate. These serial measurements included those at fixed time intervals and at the time of best hepatic response. A multivariable Cox proportional hazards model was used to determine the independent prognostic factors for OS. *P* values <0.05 were considered statistically significant. Statistical analyses were conducted using JMP software (SAS, Cary, NC, USA), SAS (version 9.4.1; SAS Institute), and R (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Hepatic response criteria.

Hepatic response	Criteria
Hepatic response eligibility	Serum AP >1.5 times the institutional upper limit of normal with the increase attributed to liver involvement
2005 ISA binary response criteria	
Hepatic response	>50% decrease in AP from baseline or normalization of AP
No hepatic response	≤50% decrease in AP from baseline
Graded hepatic response criteria	
Hepatic complete response	AP ≤90 U/L
Hepatic very good partial response	>60% decrease in AP from baseline level not meeting hepatic complete response criterion
Hepatic partial response	>30% and ≤60% decrease in AP from baseline
Hepatic no response	≤30% decrease in AP from baseline

AP: alkaline phosphatase; ISA: International Society of Amyloidosis.

Results

Baseline characteristics

One hundred and sixteen patients were included in this study. The median age was 60 years (range, 37–83) (Table 2). The median serum AP level was 2.6-fold the URL (interquartile range [IQR], 1.9–4.4; median absolute value 336 U/L, IQR, [240–567]) with a median total bilirubin (TB) of 0.6 mg/dL (IQR, 0.4–0.9). Fourteen patients (13.2% of those with available data, N=106) had a TB at diagnosis of >1.2 mg/dL. Concomitant kidney involvement was observed in 63.8% of patients, whereas coexisting heart involvement was observed in 56% of patients. Renal and cardiac stages

are provided in Table 2, with an early cardiac stage (stage I/II) documented in 64.6% of the patients. The first-line therapy was bortezomib-based therapy in 66.4% of the patients, followed by ASCT in 19.8% of patients (all high-dose melphalan; 15 patients received full-dose melphalan 200 mg/m², 8 patients received an attenuated dose of 100–140 mg/m²). Patients who received full-dose melphalan exhibited a higher baseline AP than those receiving the attenuated dose (median 3.5-fold vs. 2.0-fold the URL; *P*=0.008). The best hematologic responses were CR, VGPR, and PR in 42.3%, 26.7%, and 31.0% of patients, respectively. The differences in baseline characteristics between patients who did and did not undergo ASCT are presented in *On-*

Table 2. Baseline characteristics and treatment across the whole study cohort and by hepatic response category.

Characteristic or treatment	Whole cohort N=116	Hepatic responders N=75	Hepatic non-responders N=41	<i>P</i>
Age, years, median (range)	60 (37–83)	58 (37–82)	non-responders	0.2
Male sex, N (%)	66 (56.9)	43 (57.3)	N=41	0.89
Lambda restricted, N (%)	69 (59.5)	41 (55.7)	28 (68.3)	0.15
Intact immunoglobulin isotype, N (%)				
IgG	35 (30.2)	24 (32.0)	11 (26.8)	0.40
IgA	6 (5.2)	2 (2.7)	4 (9.8)	
IgM	7 (6)	4 (5.3)	3 (7.3)	
Light chain only	68 (58.6)	45 (60.0)	23 (56.1)	
dFLC, mg/L, median (IQR)	171 (62–509)	155 (63–494)	174 (47–637)	0.89
BMPC %, median (IQR)	10 (6–15)	10 (5–13)	14 (8–20)	0.06
Serum alkaline phosphatase, U/L, median (IQR)	336 (240–567)	390 (252–603)	278 (224–402)	0.01
Serum alkaline phosphatase, x the upper limit of institutional normal, median (IQR)	2.6 (1.9–4.4)	3.0 (2.0–4.7)	2.2 (1.8–3.3)	0.02
Serum total bilirubin, mg/dL, median (IQR)	0.6 (0.4–0.9)	0.5 (0.4–0.7)	0.8 (0.5–1.2)	0.0009
Serum albumin, g/dL, median (IQR)	3.4 (2.6–4.0)	3.1 (2.6–4.1)	3.7 (2.7–4.0)	0.28
Concomitant heart involvement, N (%)	65 (56.0)	44 (58.7)	21 (51.2)	0.44
Concomitant kidney involvement, N (%)	74 (63.8)	51 (68.0)	23 (56.1)	0.20
Cardiac stage, %, I/II/III/IIIB	25.7/38.9/24.8/10.6	28.9/38.4/21.9/11.0	20/40/30/10	0.68
Renal stage, % I/II/III	47.3/37.3/15.4	45.8/34.7/19.4	50.0/42.1/7.9	0.24
Lines of therapy in the first 12 months, N (%)				
1	87 (75)	58 (77.3)	29 (70.7)	0.76
2	25 (21.6)	15 (20.0)	10 (24.4)	
>2	4 (3.4)	2 (2.7)	2 (4.9)	
First-line therapy, N (%)				
Bortezomib-based	77 (66.4)	51 (68.0)	26 (63.4)	0.27
ASCT	23 (19.8)	17 (22.7)	6 (14.6)	
Alkylator-based	9 (7.8)	4 (5.3)	5 (12.2)	
IMiD-based	7 (6.0)	3 (4.0)	4 (9.8)	
Best hematologic response, N (%)				
Complete response	49 (42.3)	35 (46.7)	14 (34.2)	0.03
Very good partial response	31 (26.7)	23 (30.7)	8 (19.5)	
Partial response	36 (31.0)	17 (22.6)	19 (46.3)	

P values <0.05 are statistically significant. dFLC difference between involved and uninvolved light chains; BMPC %: percentage of bone marrow plasma cells; IQR: interquartile range; ASCT: autologous stem-cell transplantation; IMiD: immunomodulatory drug.

line Supplementary Table S2. With a median follow-up of 104 months (95% confidence interval: 99-110 months), 42 deaths were reported (36.2% of the study cohort). The 2-, 5- and 10-year OS rates were 82%, 68%, and 61%, respectively. The median survival was not reached.

Association between liver function abnormalities and disease presentation

Patients with TB >1.2 mg/dL had higher baseline serum AP than those with TB ≤1.2 mg/dL, but this difference was not statistically significant (mean fold of URL: 4.5 vs. 2.5, respectively; *P*=0.12). In addition, patients with serum AP >2.5 folds of URL had lower serum albumin than their counterparts (median 3.0 vs. 3.7 g/dL; *P*=0.02). Serum AP levels did not correlate with any other baseline characteristics listed in Table 2. Specifically, there was no correlation between the AP folds of URL and heart (*P*=0.15) or renal (*P*=0.41) involvement. Patients with TB >0.4 mg/dL had a higher proportion of concomitant cardiac involvement (62.2% vs. 43.8%; *P*=0.07) and a lower proportion of renal involvement (54% vs. 84.4%; *P*=0.001) than those with TB ≤0.4 mg/dL. Overall, patients with TB >0.4 mg/dL were more likely to have cardiac stage IIIA/IIIB than their counterparts, with the difference reaching borderline statistical significance (43.7% vs. 25%; *P*=0.06).

Hepatic response at fixed timepoints

The hepatic response deepened over time, with median serum AP folds of URL of 2.0, 1.8, and 1.3, respectively, at 6, 12, and 24 months from the time of therapy initiation, representing reductions of 22%, 34%, and 53%, respectively, from the baseline value. In addition, two, one, and two patients at the 6-, 12-, and 24-month timepoints, respectively, reached AP values within the reference limit of normal but with less than 50% reduction in AP (range, 40-48% reduction in AP). Overall, of the patients evaluable for response at these timepoints, 17% (19/112), 38%

(39/104), and 55% (52/94), respectively, achieved hepatic response (>50% reduction in serum AP and/or AP reaching the normal reference value) by these landmark timepoints. The proportions of patients achieving alternative graded hepatic responses by these three landmark points are shown in Figure 1A.

Best hepatic response

Most patients (75/116; 65%) achieved a hepatic response at some timepoint; 95% of these patients (*N*=71) had a response based on >50% reduction in AP, while four patients achieved AP normalization without >50% reduction in AP (40-46% reduction in AP). In patients who achieved any hepatic response, the median time to hepatic response was 13.3 months (IQR, 8.6-25). At hepatic response, the median AP level was 1.1-fold of the URL (IQR, 0.9-1.8), representing a 56% reduction in serum AP from the baseline value (IQR, 52-64%). Patients undergoing ASCT as their primary therapy had a longer time to hepatic response than those receiving non-ASCT therapies (median: 23.8 vs. 12.2 months, respectively; *P*=0.09). A larger proportion of patients who underwent ASCT achieved a hepatic response beyond 24 months than the proportion of patients not treated with ASCT (47.1% vs. 12.1%; *P*=0.003). In contrast, the rate of hepatic response between the groups was numerically higher in the ASCT cohort, but not statistically different (73.9% vs. 62.4%; *P*=0.29). An analysis of hepatic response stratified by the depth of hematologic response following ASCT, though limited by small numbers, suggested a trend toward superior hepatic outcomes in those achieving deeper hematologic responses. Of the patients who achieved hematologic CR (*N*=19), 73.7% had a subsequent hepatic response. Furthermore, all three patients who achieved a hematologic VGPR following ASCT also achieved a hepatic response (100%). In contrast, the single patient who achieved a hematologic PR following ASCT did not achieve a hepatic response (0%; *P*=0.1). When examining graded hepatic response categories,

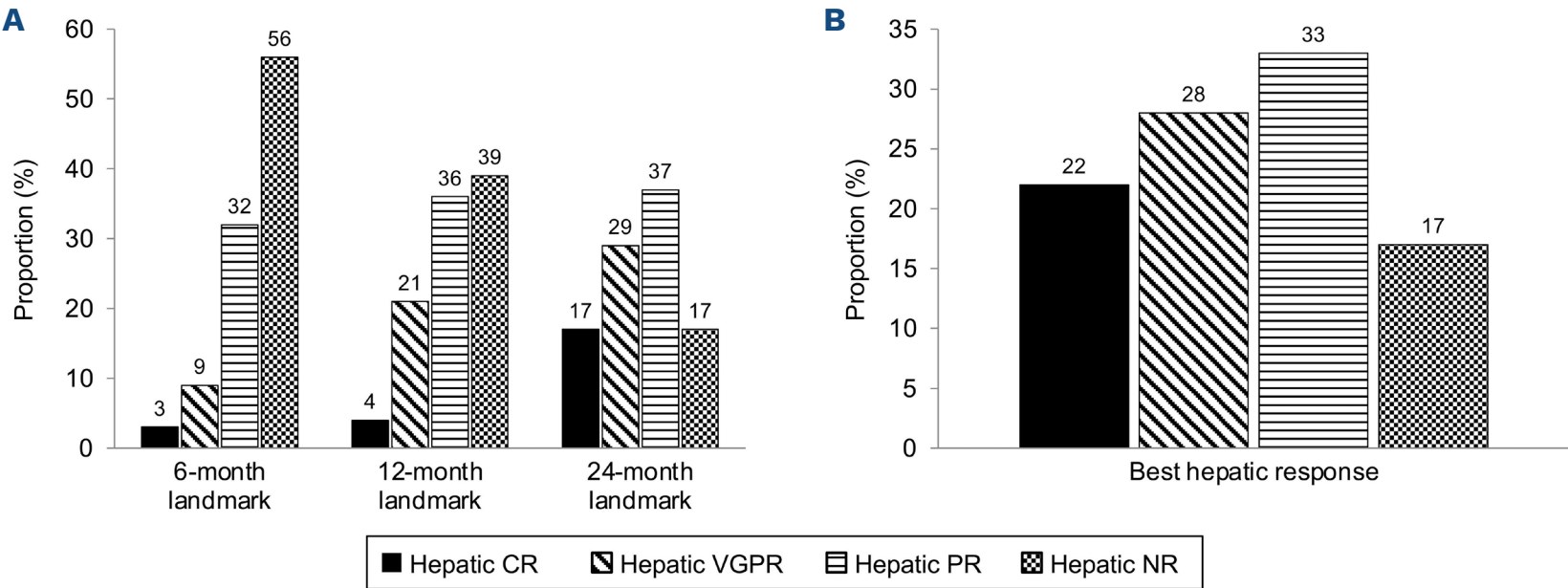


Figure 1. Distribution of graded hepatic response criteria. (A) At landmark timepoints. (B) At best hepatic response. CR: complete response, VGPR: very good partial response; PR: partial response; NR: no response.

patients who had a hematologic CR achieved hepatic CR (31.6%), hepatic VGPR (26.3%), hepatic PR (36.8%), or did not have a hepatic response (5.3%). The patients with a hematologic VGPR after ASCT attained hepatic VGPR (66.7%) and hepatic PR (33.3%), while the one patient with a hematologic PR did not have a hepatic response (100%; $P=0.19$). Of the hepatic responders ($N=75$), bilirubin measurements at the time of response were available for 80% of patients ($N=60$). Their median TB was 0.5 mg/dL (IQR, 0.3-0.5) with six patients (10%) having a TB above 1.2 mg/dL at the time of the hepatic response (range, 1.4-4.0). Four of these patients had elevated bilirubin levels at the time of diagnosis, which eventually normalized. In two patients, TB was within normal limits at diagnosis, and bilirubin was transiently increased at the time of reaching hepatic response. A graphical representation of the proportion of patients who achieved alternative graded hepatic responses is provided in Figure 1B. Using these criteria, 83% of patients achieved a hepatic response, i.e., a hepatic PR (31-60% reduction in AP; 33% of patients), hepatic VGPR (>60% reduction in AP; 28% of patients), or hepatic CR ($AP\leq 90$ U/L; 22% of patients).

Factors associated with hepatic response

Hepatic responders had higher baseline AP and lower TB than hepatic non-responders (Table 2). Patients with serum AP greater than 3 folds of the URL had a higher hepatic response rate than patients with $AP\leq 3$ folds of the URL (78% vs. 54.6%; $P=0.007$). A hepatic response was more likely to occur in patients who achieved a deep hematologic response. Hepatic responses were achieved in 71.4%, 74.2%, and 47.2% of patients who achieved hematologic CR, VGPR, and PR, respectively ($P=0.03$) (Table 2). Among patients with concomitant liver and heart involvement ($N=65$), hepatic responders were more likely to achieve any degree of cardiac response (cardiac PR or better, defined as a >30% reduction in N-terminal pro-B-type natriuretic peptide [NT-proBNP]/brain natriuretic peptide [BNP] from

baseline) than hepatic non-responders (88.6% vs. 33.3%; $P<0.001$). In the cardiac response category, the cardiac CR (NT-proBNP/BNP <350/80 pg/mL), cardiac VGPR (>60% reduction in NT-proBNP/BNP from baseline not meeting the definition for cardiac CR), and cardiac PR (>30% but $\leq 60\%$ reduction in NT-proBNP/BNP from baseline) rates were 31.8%, 34.1%, and 22.7% versus 0%, 14.3%, and 19.0%, respectively. Among patients with coexisting liver and renal involvement ($N=74$), hepatic responders were more likely to achieve a renal response (renal PR or better, defined as >30% reduction in 24-h urine protein) than those who did not achieve a hepatic response (86.3% vs. 60.8%; $P=0.01$). By depth of renal response, renal CR (24-h urine protein <200 mg), renal VGPR (>60% reduction in 24-h urine protein not meeting the definition of renal CR), and renal PR (>30% but $\leq 60\%$ reduction in 24-h urine protein) rates were 43.1%, 29.4%, and 13.7% versus 21.7%, 30.4%, and 8.7%, respectively.

Impact of baseline hepatic variables on survival

Survival was not affected by the baseline serum AP level at any cutoff. Receiver operating characteristic curve analysis for survival at 5 years detected TB at a 0.4 mg/dL cut point as the best threshold for survival discrimination (area under the curve 0.737). Patients with TB greater than 0.4 mg/dL had shorter survival compared to patients with $TB\leq 0.4$ mg/dL (5-year OS 52% vs. 97%; $P<0.001$) (Figure 2A). Survival could not be discriminated against using TB at the 1.2 mg/dL cut point (Figure 2B).

Impact of hepatic response on survival

Kaplan-Meier curves were used to graphically evaluate the influence of hepatic response at 6, 12, and 24 months after treatment initiation and at best hepatic response on survival. While hepatic response at 6 months was not associated with survival ($P=0.62$), patients who achieved a hepatic response at 12 months ($P=0.006$) had a longer survival than those who did not achieve hepatic response

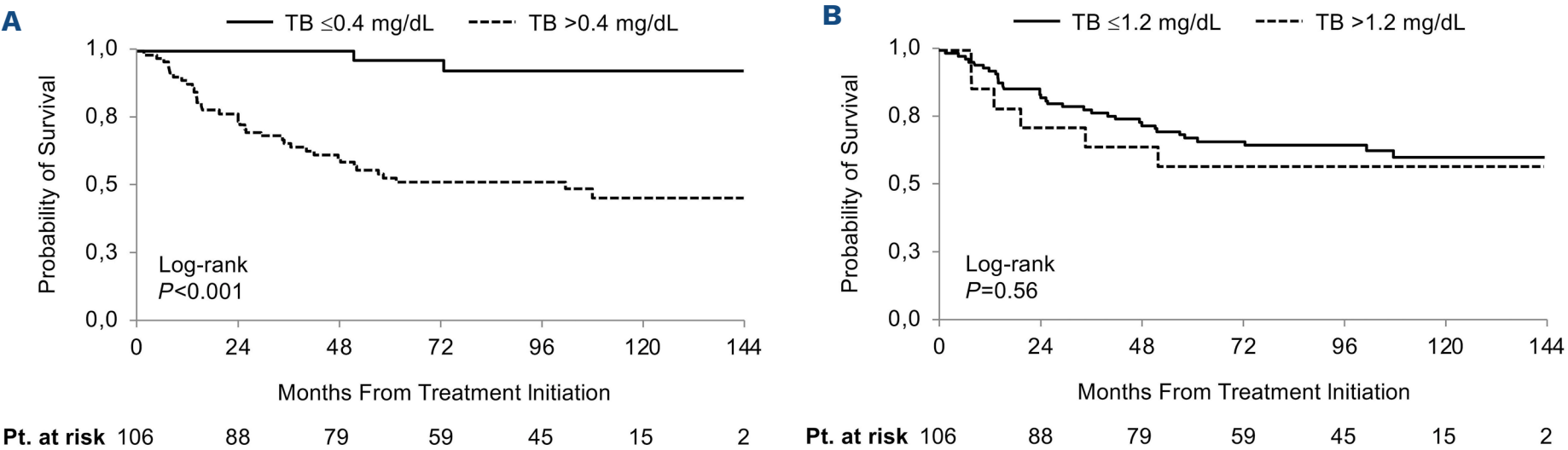


Figure 2. Overall survival by total bilirubin level at baseline. (A) At the 0.4 mg/dL cut-point (best cut-point by receiver operating characteristic curve analysis for 5-year overall survival). (B) At the 1.2 mg/dL cut-point (upper limit of normal). TB: total bilirubin; Pt: patients.

by that timepoint (Figure 3A, B), whereas hepatic response by 24 months tended to correspond with improved survival compared to that of non-responders, although this difference was not statistically significant ($P=0.097$) (Figure 3C). Similarly, the best all-time hepatic response was associated with longer survival compared with that of patients unable to achieve a hepatic response (Figure 3D). Hepatic responders maintained a survival advantage over hepatic non-responders in subgroups based on the status of cardiac stage or renal involvement (Figure 4). Figure 5 depicts survival curves using the alternative graded hepatic responses at landmark timepoints and at the best response. Patients who collectively achieved best hepatic CR/VGPR had a longer survival than those who achieved hepatic PR or did not have a hepatic response. Univariate and multivariate analyses were performed to assess the independent effects of the hepatic response and other factors on survival. The results of these analyses are presented in Table 3. Overall, five variables were found to be significantly associated with OS in the univariate setting: age ≥ 65 years, ASCT use, cardiac stage, best hematologic response, and best hepatic response. In a multivariable model incorporating hepatic response as a time-dependent covariate, four variables remained significantly associated with survival, with hepatic response being the most influ-

ential parameter on survival (hepatic response vs. hepatic non-response: hazard ratio=0.4; $P<0.001$). Results from a similar multivariate model using the three-level graded hepatic response as a time-dependent covariate demonstrated that hepatic VGPR/CR was the most prognostic factor for survival. The results of Cox regression models with hepatic response (using binary or 3-level hepatic response criteria) as a time-dependent covariate in landmark analyses for the different time points are presented in *Online Supplementary Tables S3-S8*.

Discussion

This study, representing one of the largest series of patients with hepatic AL amyloidosis, aimed to determine the prognostic utility of hepatic response criteria for OS. We have shown that hepatic response based on the ISA 2005 binary hepatic response criteria is significantly associated with improved survival independently of other known prognostic factors. Further grading using four-level response classification did not enhance risk-stratification for survival. Although hepatic AL amyloidosis is often present alongside involvement of other organs, the liver can be the organ predominantly involved in some patients, underscoring the

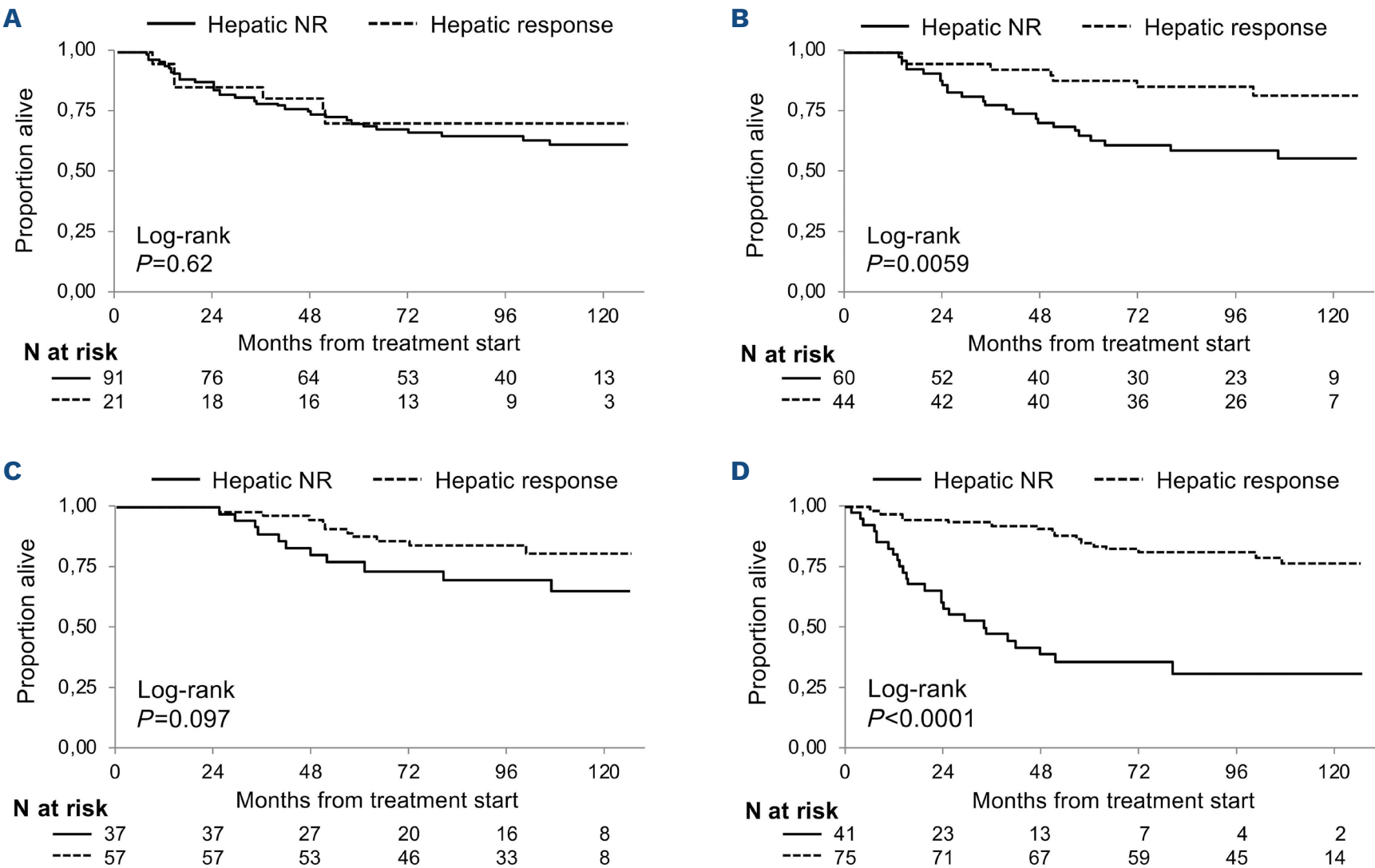


Figure 3. Overall survival stratified by the binary hepatic response status. (A) Six months from the treatment initiation landmark. (B) Twelve months from the treatment initiation landmark. (C) Twenty-four months from the treatment initiation landmark. (D) Best hepatic response. NR: non-response.

need for distinct hepatic response criteria. Notably, hepatic response emerged as the strongest independent prognostic factor for survival in multivariate analyses, emphasizing its importance, even in the context of multi-organ disease. Nonetheless, achieving a deep hematologic response, namely hematologic CR/VGPR, remains essential, as it directly facilitates hepatic response and independently predicts superior survival.

This study highlights the challenges of accurately assessing hepatic response in AL amyloidosis, as the primary measure, serum AP levels, can be affected by factors other than liver amyloid infiltration. Notably, concomitant heart involvement can cause passive liver congestion, further elevating AP levels. Therefore, a reduction in AP may reflect not only hepatic response but also cardiac response. This may explain the exceptionally low hazard ratio for survival for hepatic response in univariate and multivariate analyses, emphasizing the critical role of cardiac response on survival. The hepatic responders in our study were more likely to have renal and cardiac responses, when applicable. While this was expected, hepatic non-responders had far lower concomitant cardiac response rates than concomitant renal response rates (36.3% vs. 64%), whereas the rate of cardiac or renal response among hepatic responders was similar (88.4% and 85.7%). This observation implies the possible

role of cardiac response in lowering AP levels, leading to a hepatic response. While the ideal method to isolate true hepatic recovery is a comprehensive subgroup analysis of patients without cardiac involvement, the limited sample size of only 116 patients restricted us from conducting the ideal, dedicated analysis of patients without cardiac involvement, as this cohort is significantly underpowered. We observed a delayed hepatic response in patients treated with ASCT, with a median time to hepatic response of 23.8 months *versus* 12.2 months in the non-ASCT group. A previous single-center study on organ response among AL patients who underwent ASCT also reported a prolonged time to hepatic response in the transplanted patients, rising from 16% at 12 months to 32% at 24 months,¹⁴ using the same criteria as in this study. A prior study from the same center showed high hepatic response rates at 12 and 24 months (57% and 63%, respectively) but used reduction in hepatomegaly by physical examination as an additional criterion for hepatic response.²⁰ This delay in response possibly reflects treatment-related toxicity, as has been reported for heart and kidney involvement in patients undergoing ASCT;^{21–24} however, this remains speculative. It is noted that the hematologic response was superior in the ASCT cohort than in the non-ASCT cohort, supporting toxicity as a cause of delayed response rather than inadequate hematologic

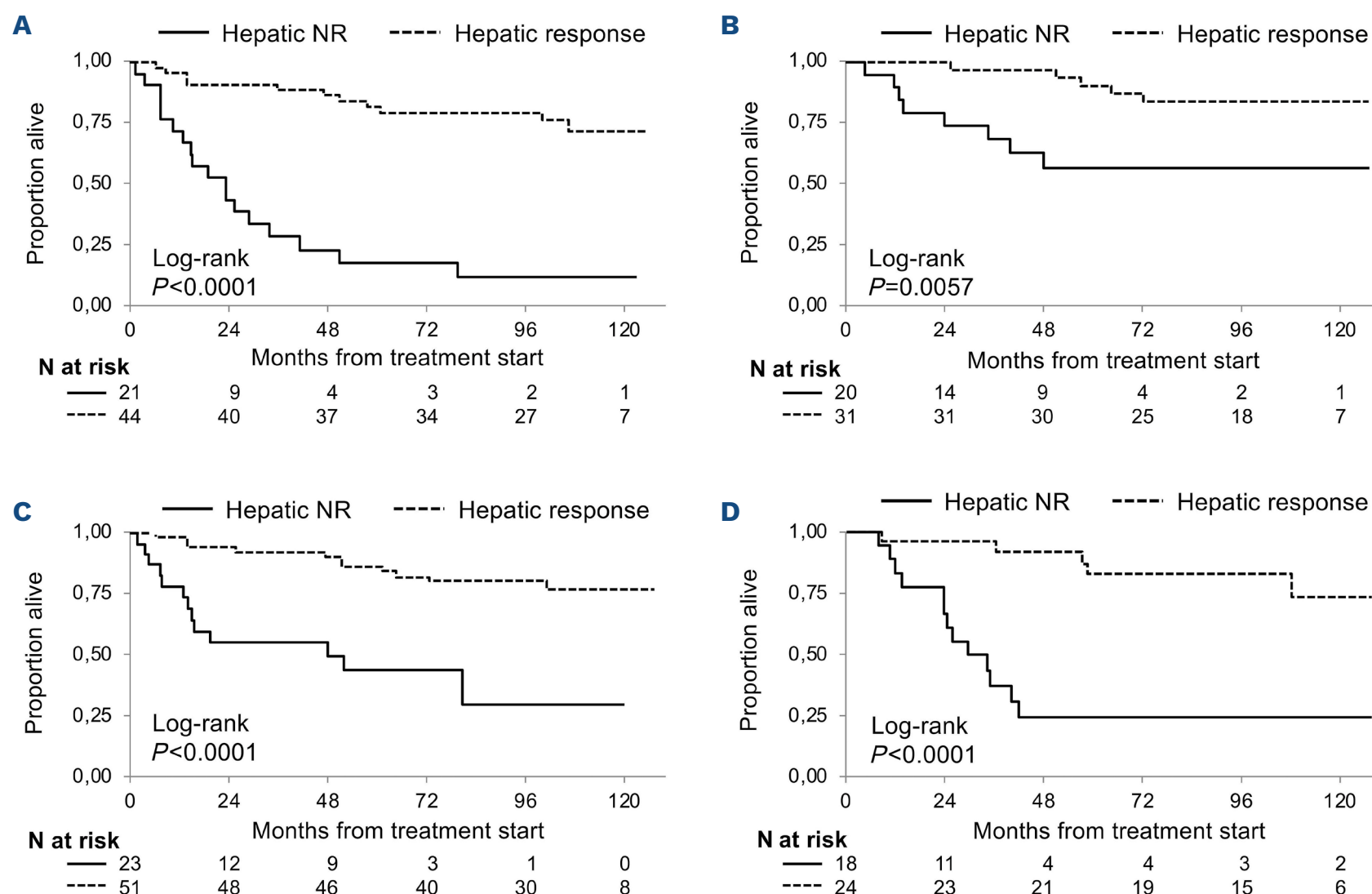


Figure 4. Overall survival stratified by best hepatic response and concurrent heart or renal involvement. (A) Patients with concurrent heart involvement (N=65). (B) Patients without concurrent heart involvement (N=51). (C) Patients with concurrent renal involvement (N=74). (D) Patients without concurrent renal involvement (N=42). NR: non-response.

response to therapy. As patients undergoing ASCT typically have a favorable prognosis, a longer observation period for a hepatic response is feasible before considering interventions to improve it. In contrast, for non-ASCT patients who do not achieve hepatic response within 12-18 months of therapy, initiating or changing anti-plasma cell therapy should be considered, particularly if the underlying clone is not adequately controlled. Ideally, this strategy should be tested in a well-designed clinical trial of patients with persistent organ dysfunction at landmark timepoints and evidence of clonal disease below the threshold of hematologic progression. Therapies against amyloid deposits, if proven effective in clinical trials, may offer an alternative avenue to achieve hepatic response.

The results of our analysis highlight the limitations and complexities of the current hepatic response criteria. Therefore, alternative methods for assessing liver response, particularly imaging-based approaches, are needed. Magnetic resonance elastography, for example, has been assessed in patients with hepatic AL amyloidosis at the time of diagnosis and revealed different patterns of liver involvement, including diffuse, heterogeneous, and focal lesions.²⁵ Our finding that elevated AP levels may predict a higher chance of hepatic response presents a complex issue. While higher AP levels may simply correlate with a greater extent of amyloid

deposition, the relationship between the pattern of liver involvement and the likelihood of response remains uncertain. In such cases, imaging-based modalities, such as magnetic resonance elastography, offer a more sensitive and nuanced method for response assessment, providing critical information on the pattern and burden of liver involvement. Other imaging modalities of interest include FibroScan and administration of amyloid-reactive peptide radiotracer, followed by positron emission/computed tomography.²⁶

The main goal of this study was to assess the prognostic value of the Mayo Clinic’s proposed four-level graded hepatic response criteria.¹⁵ These criteria, which were developed in a single-center study, did not provide additional prognostic discrimination over the established binary ISA 2005 definition. We attribute this outcome primarily to the significantly smaller sample size available for the liver response analysis compared to the samples in our prior studies on graded cardiac and renal responses.^{18,19} Given the infrequent prevalence and inherent heterogeneity of hepatic AL amyloidosis, this small sample size likely lacked the statistical power required to robustly resolve subtle prognostic differences between the four response grades. The limitations of the current liver response biomarker, AP, may also contribute to this observation. AP is a less dynamic

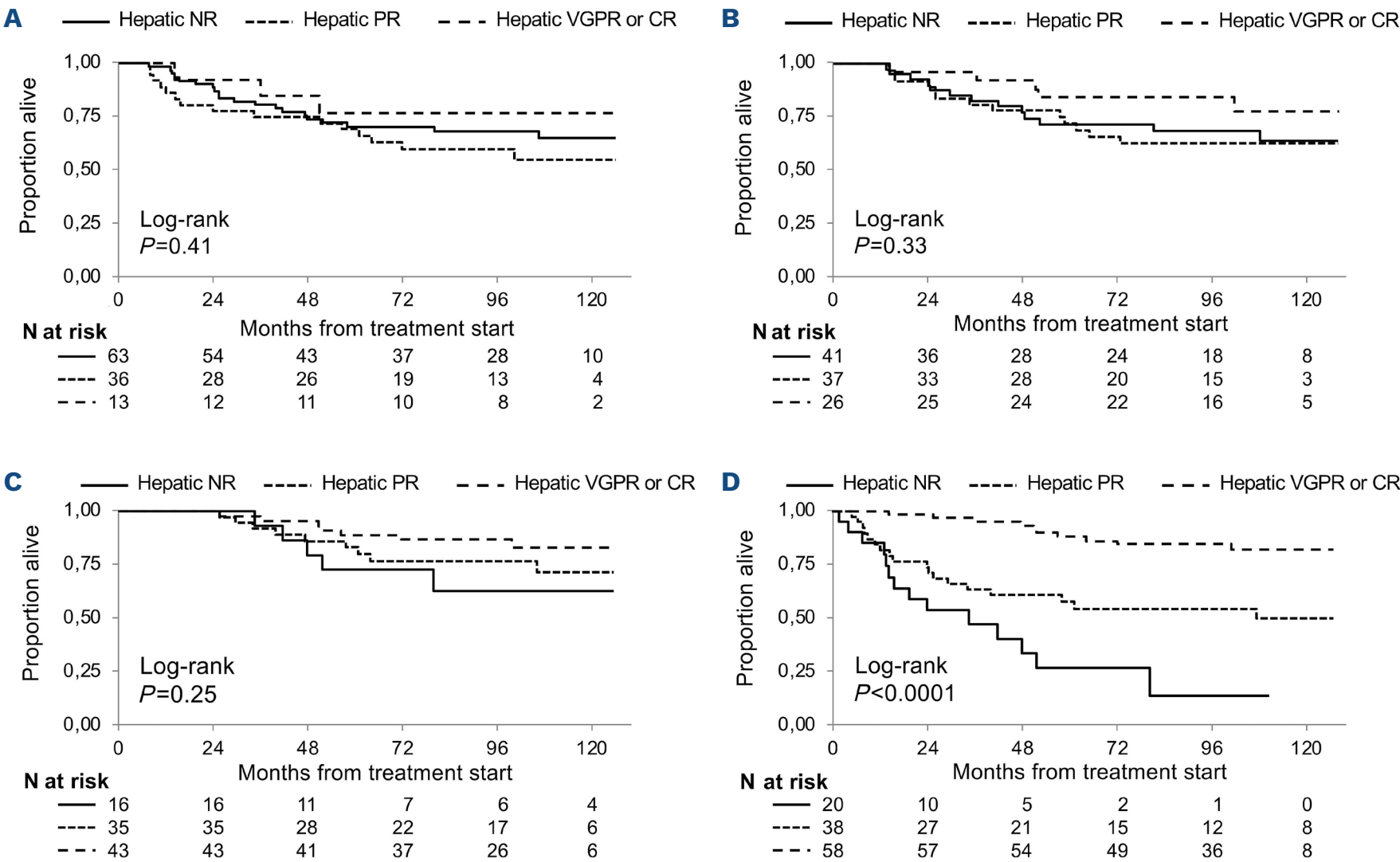


Figure 5. Overall survival stratified by the graded hepatic response. (A) Six months from the treatment initiation landmark. (B) Twelve months from the treatment initiation landmark. (C) Twenty-four months from the treatment initiation landmark. (D) Best hepatic response. NR: non-response; PR: partial response; VGPR: very good partial response; CR: complete response.

Table 3. Univariate and multivariable Cox regression models for overall survival using hepatic response as a time-dependent co-variate.

Variables	Univariate analysis		Multivariate analysis with 2-level hepatic response		Multivariate analysis with 3-level hepatic response	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age ≥65 years (vs. age <65)	2.9 (1.6-5.4)	<0.001	2.1 (1.1-3.9)	0.027	2.1 (1.1-4.0)	0.027
ASCT as primary therapy	0.3 (0.1-0.9)	0.03	0.6 (0.2-2.0)	0.43	0.6 (0.2-2.0)	0.44
dFLC ≥180 mg/L	1.5 (0.8-2.8)	0.17	NA	-	NA	-
Cardiac stage Stage IIIA + IIIB (vs. Stage I + II)	2.1 (1.1-4.0)	0.017	2.0 (1.04-3.9)	0.038	1.9 (1.0-3.7)	0.055
Best hematologic response Hematologic CR/VGPR (vs. hematologic PR)	0.3 (0.2-0.6)	<0.001	0.4 (0.2-0.8)	0.011	0.5 (0.2-0.9)	0.027
Binary hepatic response Response (vs. non-response)	0.4 (0.2-0.9)	0.021	0.4 (0.2-0.8)	0.009	-	-
Graded hepatic response						
Hepatic NR	Reference	-	Reference	-	-	-
Hepatic PR	0.8 (0.4-1.8)	0.66	0.8 (0.3-1.8)	-	-	0.59
Hepatic VGPR/CR	0.35 (0.15-0.9)	0.021	0.3 (0.1-0.9)	-	-	0.025

P values <0.05 are statistically significant. HR: hazard ratio; 95% CI: 95% confidence interval; ASCT: autologous stem-cell transplantation; dFLC: difference between involved and uninvolved light chains; NA: not applicable; CR: complete response; VGPR: very good partial response/complete response; PR: partial response; NR: no response.

organ biomarker compared to NT-proBNP or proteinuria, which exhibit rapid and profound changes in response to treatment. The limited dynamic range of AP may inherently restrict the ability of any graded criteria to distinguish between outcomes, irrespective of sample size. Another explanation for the failure to show a prognostic utility of the four-level hepatic response criteria is the effect of cardiac response on hepatic response, as discussed above. This effect may increase the unpredictability of the impact of hepatic response on survival.

Several studies have indicated that elevated bilirubin levels in patients with hepatic AL amyloidosis, using a cutoff of 2 mg/dL, have prognostic significance.^{5,6} We could not confirm this finding in our study, because only a minority of the patients had TB above the normal value, likely due to our study’s selection criteria. In addition, this study included patients undergoing modern therapies who were more likely to respond to therapy and overcome negative prognostic factors at baseline. However, we did observe that patients with baseline bilirubin >0.4 mg/dL had inferior survival compared with patients with baseline TB of ≤0.4 mg/dL. This finding that a much lower TB cut-off is prognostically significant is novel and likely reflects a difference in patient selection and survivorship bias in our cohort. The traditional >2 mg/dL threshold identifies patients with overt, end-stage liver failure, a group that typically does not survive long. Conversely, the TB >0.4 mg/dL cut-off likely captures subclinical hepatic dysfunction or higher residual amyloid burden that remains prognostically relevant in a healthier, long-surviving population who achieved a hematologic response. This inferior survival may also explain the

lower rate of hepatic response in the former group, due to survivorship bias towards hepatic responders (however, a lower hepatic response seen in this subgroup may lead to the observed inferior survival). The reason for this poorer prognosis in patients with bilirubin levels within the normal range warrants further investigation. Interestingly, this group had a lower rate of renal (but not cardiac) involvement than those with a lower baseline TB. Thus, the inferior survival in patients with TB >0.4 mg/dL may be partly related to a less favorable overall disease presentation. Notably, an inverse correlation between proteinuria and TB has been reported in both diabetic and non-diabetic patients with proteinuria,^{27,28} and a similar effect may occur in AL amyloidosis. The mechanism for this is unclear, but it has been hypothesized that the antioxidant properties of TB may offer renal protection in patients with proteinuria.

Our study has several limitations, including its retrospective nature, which introduces a potential selection bias, as the assessment of hepatic response and its prognostic value was restricted solely to patients who achieved a prior hematologic response. Consequently, the findings are specific to this healthier, selected cohort and may not be generalizable to the entire, unselected treated population, including non-responders who represent a clinically relevant group with the poorest prognosis. Second, this retrospective study is constrained by the absence of consistent imaging data (such as detailed ultrasound or magnetic resonance imaging findings) to directly correlate with biochemical changes in AP. Third, the study’s power is limited for a definitive comparison between two-level and four-level response systems; however, this is the first large multi-

center study to demonstrate the prognostic significance of hepatic response. Finally, we acknowledge the potential for survivorship bias in the assessment of the best hepatic response. To address this, we evaluated the response at fixed timepoints, which supports the prognostic utility of AP in assessing hepatic response. In addition, we performed survival analyses that accommodated hepatic response as a time-dependent covariate in the survival models.

In conclusion, we confirmed the prognostic impact of the ISA 2005 hepatic response criteria as early as 12 months after therapy initiation. These criteria are independent of other known prognostic markers and may, therefore, have clinical implications for patients' management. Recent large-scale study involving 130 patients with hepatic AL amyloidosis further support these findings, highlighting the importance of predictors such as baseline AP in determining hepatic response and OS.²⁹

Disclosures

EM has received an honorarium from Janssen and a consultation fee from Protego (a fee paid to his institution). GP has received honoraria from Janssen, Pfizer, The Binding Site and Sebia Siemens and has served on an advisory board for Janssen. SS has received travel grants from Janssen, MSD, Prothena and Takeda; served on advisory boards for Janssen and Prothena; received honoraria from Janssen, Prothena and Takeda; and received research funding from Sanofi and Janssen. AD has received research funding from Celgene, Millennium Pharmaceuticals, Pfizer and Janssen and has received a travel grant from Pfizer. GM has served on advisory boards for Janssen, Pfizer and Novo Nordisk. PM has received honoraria from Janssen and served on an advisory board for Janssen. UH has received travel grants from Janssen, Prothena and Pfizer; served on advisory boards for Pfizer and Prothena; and received honoraria from Janssen, Pfizer, Alnylam and Akcea. EK has received consultancy fees, honoraria and research funding from Janssen, Amgen and Pfizer; and honoraria from Takeda and Genesis Pharma. MAD has received honoraria from Janssen, Beigene, Takeda, BMS and Amgen. RW has served on advisory boards for Pfizer, Alnylam, Ionis, Regeneron, Janssen and Eidos. VS has received research support from Celgene, Millennium-Takeda, Janssen, Prothena, Sorrento, Karyopharm, Oncocept and Caelum; serves as a consultant for Janssen and Pfizer; and

has served on advisory boards for Proclara, Caelum, Abbvie, Janssen, Regeneron, Protego, Pharmatrace, Telix and Prothena. EP is an employee of Bristol-Myers Squibb since August 2021. SL has received research funds from Karyopharm and Sanofi; has stock ownership in Magenta and Caelum Bioscience; has served on advisory boards for Pfizer, Takeda, Natara, Janssen, Celularity, AbbVie, GSK, Takeda, Karyopharm, Sanofi, Caelum Bioscience and Oncocept; and was a speaker for PeerView, Clinical Care Options (CCO) and RedMed. JB has received honoraria for lectures from Janssen, Celgene/BMS, Amgen, Takeda and Oncocept. MTC has received honoraria for educational lectures from Janssen, Celgene and Amgen; and has served on advisory boards for Janssen, Akcea and Amgen. SKK has received research funding for clinical trials (paid to his institution) from AbbVie, Amgen, BMS, Carsgen, Janssen, AstraZeneca, Novartis, Roche-Genentech, Takeda, Tenebio, Molecular Templates; has provided consulting/advisory board services (with no personal payments) for AbbVie, Amgen, BMS, Janssen, Roche-Genentech, Takeda, AstraZeneca, Bluebird Bio, Epizyme, Secure Biotherapeutics and (with personal payment) for Oncocept, Beigene and Antengene. MAG has served as a consultant for Millennium Pharmaceuticals and has received honoraria from Celgene, Millennium Pharmaceuticals, Onyx Pharmaceuticals, Novartis, GlaxoSmithKline, Prothena, Ionis Pharmaceuticals and Amgen. The remaining authors have no conflicts of interest to disclose.

Contributions

EM and MAG conceived and designed the study. EM, GP, SS, AD, BW, GM, PM, UH, TD, EK, MAD, VS, RS, ML, MG, HL, SL, MSH, MTC, JB, SKK, AW and MAG provided study materials or patients and collected and assembled data. EM, SG, KED and MAG analyzed the data and drafted the initial manuscript. All authors reviewed the manuscript draft, gave approval of the final version and are accountable for all aspects of the work.

Data-sharing statement

The data used in this study are not available for sharing. Due to the multicenter nature of this research and the specific Institutional Review Board restrictions at the various participating sites, individual patient data cannot be shared publicly.

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