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Graded Cardiac Response Criteria for Patients With Systemic Light Chain Amyloidosis

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abstract

PURPOSE Binary cardiac response assessment using cardiac biomarkers is prognostic in light chain amyloidosis. Previous studies suggested four-level cardiac responses using N-terminal prohormone of brain natiuretic peptide improves prognostic prediction. This study was designed to validate graded cardiac response criteria using N-terminal prohormone of brain natiuretic peptide/brain natiuretic peptide.

PATIENTS AND METHODS This retrospective, multicenter study included patients with light chain amyloidosis who achieved at least a hematologic partial response (PR) and were evaluable for cardiac response. Four response criteria were tested on the basis of natriuretic peptide response depth: cardiac complete response (CarCR), cardiac very good partial response (CarVGPR), cardiac PR (CarPR), and cardiac no response (CarNR). Response was classified as best response and at fixed time points (6, 12, and 24 months from therapy initiation). The study primary outcome was overall survival.

RESULTS 651 patients were included. Best CarCR, CarVGPR, CarPR, and CarNR were achieved in 16%, 26.4%, 22.9%, and 34.7% of patients, respectively. Patients in cardiac stage II were more likely to achieve CarCR than patients in cardiac stage IIIA and IIIB (22% *v* 13.5% *v* 3.2%; $P < .001$). A deeper cardiac response was associated with a longer survival (5-year overall survival 93%, 79%, 65%, and 33% for CarCR, CarVGPR, CarPR, and CarNR, respectively; $P < .001$). Fixed time-point analyses and time-varying covariates Cox regression analysis, to minimize survivorship bias, affirmed the independent survival advantage of deeper cardiac responses. Four-level response performed better than two-level response as early as 12 months from therapy initiation.

CONCLUSION Graded cardiac response criteria allow better assessment of cardiac improvement compared with the traditional binary response system. The study re-emphasizes the importance of early diagnosis, which increases the likelihood of deep cardiac responses.

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INTRODUCTION

Systemic light chain (AL) amyloidosis is an uncommon disorder in which monoclonal light chains derived from clonal plasma cells form tissue amyloid deposits, leading to organ dysfunction and death.[1] AL amyloidosis can affect various organs, with the heart being the most common (75%-80% of patients).[2-4] Failure in early diagnosis remains a substantial barrier to improvement in survival. Despite reduction in early death rate over the past 15 years, at least a quarter of patients die within 6 months of their diagnosis.[5]

Response assessment in AL amyloidosis has been focused primarily on the hematologic response, as all available therapies target the underlying plasma cell clone. With the emergence of effective therapies, the achievement of deep hematologic response became a realistic goal. This led to the development of four-level hematologic response criteria,[3,6] which are based on the degree of reduction in circulating light chains and immunofixation studies. These criteria provide a quantitative measure of response and effectively predict survival on the basis of response depth. Recent studies showed that disappearance of measurable clonal plasma cells assessed by using multiparametric flow cytometry study can predict longer progression-free survival and higher organ response rates.[7-11]

Organ response assessment has lagged behind the developments in hematologic response assessment. The initial cardiac response assessment was based on echocardiographic findings and improvement in cardiac functional status.[12] These criteria were subject to interobserver variability and were not assessed for prognostic impact. Subsequently, a reduction in N-terminal brain natriuretic peptide (NT-proBNP) from baseline was linked to a survival advantage in a single-

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Do graded cardiac response criteria in light chain amyloidosis perform better than the current binary cardiac response criteria?

Knowledge Generated

In this multicenter study of 651 patients with light chain amyloidosis and heart involvement, graded cardiac response on the basis of percentage reduction in N-terminal prohormone of brain natiuretic peptide/brain natiuretic peptide from baseline value discriminated four prognostic subgroups, with deeper cardiac response leading to longer survival. The proposed new system has superior performance over the current binary response assessment.

Relevance (*C. Craddock*)

Graded cardiac response emphasizes the importance of deep cardiac response as a predictor of improved survival and offers better prediction of longer-term clinical outcomes for patients. External validation of these data in future prospective studies will be important.*

*Relevance section written by *JCO* Associate Editor Charles Craddock, MD.

center study,[13] leading to a classification of cardiac response into the binary category of response (> 30% reduction in NT-proBNP from baseline) versus no response in an international multicenter study.[3] Recently, BNP-based binary cardiac response was reported to be prognostic.[14] Today, natriuretic peptides are an important tool for cardiac response assessment. The Mayo Clinic proposed that a graded, four-level, cardiac response classification, using NT-proBNP, enhanced survival discrimination,[15] which was subsequently confirmed in a single-center study.[16]

The primary objective of this study was to confirm the value of graded cardiac response criteria over the standard binary response system. A secondary objective was to test the established cardiac progression criteria and assess the relationship between cardiac response and cardiac progression.

PATIENTS AND METHODS

The study was approved by the institutional review board in each participating center. All patients had provided informed consent for the use of their medical records for research purposes. Patients with AL amyloidosis diagnosed between January 2010 and December 2015 were included if (1) they had cardiac involvement and were evaluable for cardiac response, defined as baseline NT-proBNP > 650 pg/mL or BNP > 150 pg/mL; (2) achieved ≥ partial hematologic response to therapy within 12 months of diagnosis; and (3) had natriuretic peptide measurements, at least twice annually in the first 3 years and annually afterward. Patients were excluded if they were previously treated for related hematologic disease, experienced organ progression without initial organ response, or had solid organ transplantation. The European modification of the Mayo 2004 model was used for cardiac staging.[4] A conversion tool for the various cardiac biomarkers was applied, as previously reported.[17] Table 1 lists the tested response and progression criteria. Cardiac responses are reported collectively for NT-proBNP and BNP. Timing and depth of best cardiac response achieved during follow-up were collected. Cardiac response was also assessed at fixed time points (6, 12, and 24 months from treatment initiation). In the fixed time-point analyses and in the time covariate analyses the best response observed by the landmark time was used. When data on cardiac response at fixed time points were missing, we imputed the best response observed before the fixed time point. Imputation of best response was done for 128 (20.8% of patients), 111 (19.5%), and 137 (26.9%) patients at 6, 12, and 24 months, respectively. Further information is provided in the Data Supplement (online only).

Summary statistics were used to characterize patients within and across groups. The Pearson χ^2 test and the Kruskal-Wallis test were used to ascertain differences between nominal and continuous variables, respectively. Overall survival (OS) and time to cardiac progression were assessed using Kaplan-Meier methods. OS was calculated from the start of treatment for best response analyses and from landmark for fixed time-point analyses; patients alive at last follow-up were censored at that time. Time to cardiac progression was calculated from the start of treatment until cardiac progression (Table 1). Patients without cardiac progression were censored at their last evaluation, irrespective of their vital status. Multivariable Cox proportional hazards models were used to evaluate the influence of covariates on outcomes. Two primary approaches were used to minimize potential survivorship bias (ie, patients surviving for longer periods can achieve deeper cardiac responses). The first was through a series of landmark analyses conducted at 6, 12, and 24 months after treatment initiation in those who were alive and in follow-up at that time. The second approach used a time-dependent covariate Cox regression models, with longitudinal cardiac response data (fixed time and best cardiac

TABLE 1. Cardiac Response and Progression Criteria

Category	Definition[a]
Cardiac response criteria	
CarCR	Nadir NT-proBNP ≤ 350 pg/mL (≤ 41.39 pmol/L) or BNP ≤ 80 pg/mL (≤ 9.46 pmol/L)
CarVGPR	> 60% reduction in NT-proBNP/BNP from baseline level not meeting CarCR
CarPR	31%-60% reduction in NT-proBNP from baseline level not meeting CarCR
CarNR	≤ 30% reduction in NT-proBNP from baseline level
Cardiac progression criteria (adopted from Palladini et al[3])	
Any of the following	NT-proBNP/BNP progression: > 30% and > 300 pg/mL (> 35.48 pmol/L) increase or rise in BNP > 30% and > 70 pg/mL (> 8.28 pmol/L) increase from nadir not precipitated by infection, elevated creatinine, or cardiac arrhythmia
	Troponin T/I progression: ≥ 33% increase from nadir
	EF progression: ≥ 10% decrease from best value

Abbreviations: BNP, brain natriuretic peptide; CarCR, cardiac complete response; CarNR, cardiac no response; CarPR, cardiac partial response; CarVGPR, cardiac very good partial response; EF, ejection fraction; NT-proBNP, N-terminal of prohormone brain natriuretic peptide.

[a]Best response by either natriuretic peptide should be considered if both are measured simultaneously.

responses) included in the models. The ability of four-level versus two-level classifications of cardiac response to differentiate OS were evaluated and compared using time-dependent receiver operating characteristic (ROC) and area under the curve (AUC) methods using *timeROC*, *compareC*, and *risksetROC* packages in R. *P* values < .05 were considered significant. Statistical analyses were performed on JMP software (SAS, Cary, NC) and R statistical software (v4.0.3).

RESULTS

A total of 651 patients with AL amyloidosis from 10 institutions were included. Baseline characteristics of the study cohort along with further analyses are summarized in the Data Supplement. The median age at diagnosis was 64 years. Cardiac response was evaluable using NT-proBNP in 494 patients (75.9%), BNP in 109 patients (16.7%), and both NT-proBNP and BNP in 48 patients (7.4%). The median baseline NT-proBNP and BNP was 3,323 pg/mL and 372 pg/mL, respectively. Mayo cardiac stage II, IIIA, and IIIB was present in 47.5%, 38.0%, and 14.5% of patients, respectively. A majority (75.9%) of patients received one line of therapy within 12 months of diagnosis, with bortezomib-based therapy being the most common (70.2%), followed by autologous stem-cell transplantation (15.7%). Hematologic complete response was achieved in 38.2% of patients, while hematologic very good partial response (HemVGPR) and hematologic partial response were achieved in 38.9% and 22.9% of patients, respectively. Forty-three percent of the patients have died (277/651), of which 85% were within 5 years of diagnosis (236/277). The median follow-up was 73.5 months (95% CI, 70.6 to 76.1; range, 4.5-128.0 months).

Best Cardiac Response Assessment

Collectively, best cardiac complete response (CarCR), cardiac very good partial response (CarVGPR), cardiac partial response (CarPR), and cardiac no response (CarNR) were achieved in 16%, 26.4%, 22.9%, and 34.7% of patients, respectively. These figures were 15.4%, 28.7%, 22.7%, and 33.2% in NT-proBNP–assessed patients, and 17.8%, 19.1%, 23.6%, and 39.5% in BNP-assessed patients, respectively. The Data Supplement lists the time to achievement of organ response by response category. The median time to best cardiac response was 12 months (interquartile range, 7-21; medians were 18 months for CarCR, 11.5 months for CarVGPR, and 9 months for CarPR). Patients in cardiac stage II were more likely to achieve CarCR than patients in cardiac stage IIIA and IIIB (22% *v* 13.5% *v* 3.2%; *P* < .001, Data Supplement). Compared with stage IIIB, the odds ratio for achievement of CarCR for stage II and stage IIIA patients was 8.5 (95% CI, 2.6 to 27.7; *P* = .004) and 4.7 (95% CI, 1.4 to 15.7; *P* = .01), respectively.

Fixed Time-Point Response Assessment

Six-month, 12-month, and 24-month NT-proBNP/BNP responses were available for 98.6% (614/623), 98.1% (n = 570/581), and 96.8% (n = 510/527) of patients alive at these landmark time points, respectively (Fig 1). Figure 2A depicts cardiac response categories at fixed time points. The proportion of patients who achieved any cardiac response improved between 6, 12, and 24 months (34.5%, 57.2%, and 71.8%, respectively), with a parallel deeper cardiac response observed over these time points.

The Effect of Depth of Best Cardiac Response on OS

Looking at the influence of best cardiac response achieved on OS, a deeper cardiac response was associated with longer survival (5-year OS 93%, 79%, 65%, and

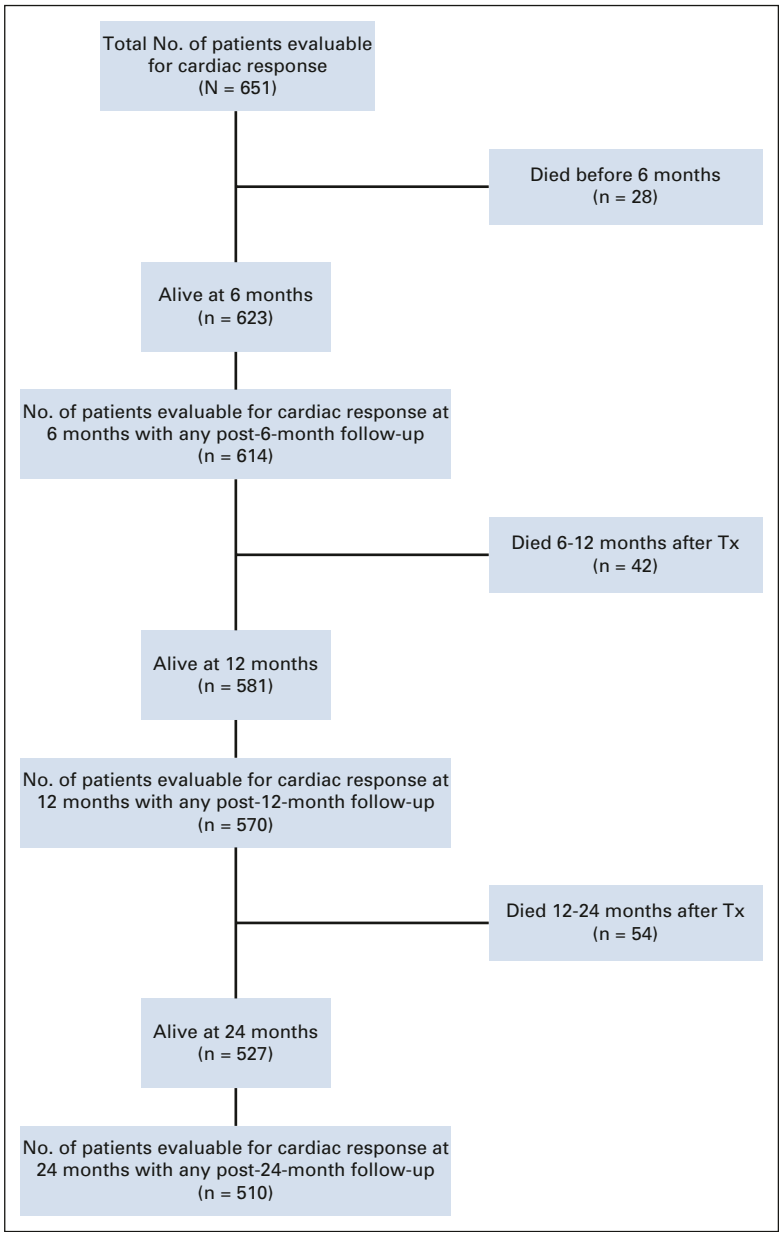

FIG 1. Flow diagram for landmark analysis cohorts. Tx, treatment.

33% for CarCR, CarVGPR, CarPR, and CarNR, respectively; Fig 3A). Separate survival curves for NT-proBNP–assessed and BNP-assessed patients showed a similar pattern for each biomarker (Data Supplement). Excluding patients who had early deaths (ie, within one year of start of treatment) confirmed improved survival in those patients with a deeper cardiac response (5-year OS 93%, 79%, 69%, and 44%, $P < .001$; Fig 3B). A graded cardiac response was prognostic across cardiac stages (Figs 3C and 3D).

Prognostic Influence of Cardiac Response Assessed at Fixed Time Points

Kaplan-Meier curves for landmark analyses of OS by cardiac response groups at 6, 12, and 24 months are provided in Figs 2B-2D. At 6 months, most of the 212 responders achieved a CarPR or CarVGPR, where each of these was significantly associated with a longer survival compared with CarNR (Fig 2B). This survival advantage remained after adjusting for age, cardiac stage, first-line treatment type, AL burden, and best hematologic response in a multivariable model (CarPR [*v* CarNR]: hazard ratio [HR] = 0.59; 95% CI, 0.41 to 0.83; $P = .003$; and CarVGPR [*v* CarNR]: HR, 0.66; 95% CI, 0.41 to 1.04; $P = .072$; Data Supplement). At 12-months, with more patients achieving deeper responses, deeper cardiac response was associated with longer survival (Fig 2C). In adjusted analysis, HRs for survival in relation to those with CarNR favored deeper cardiac response (CarCR: HR, 0.49;

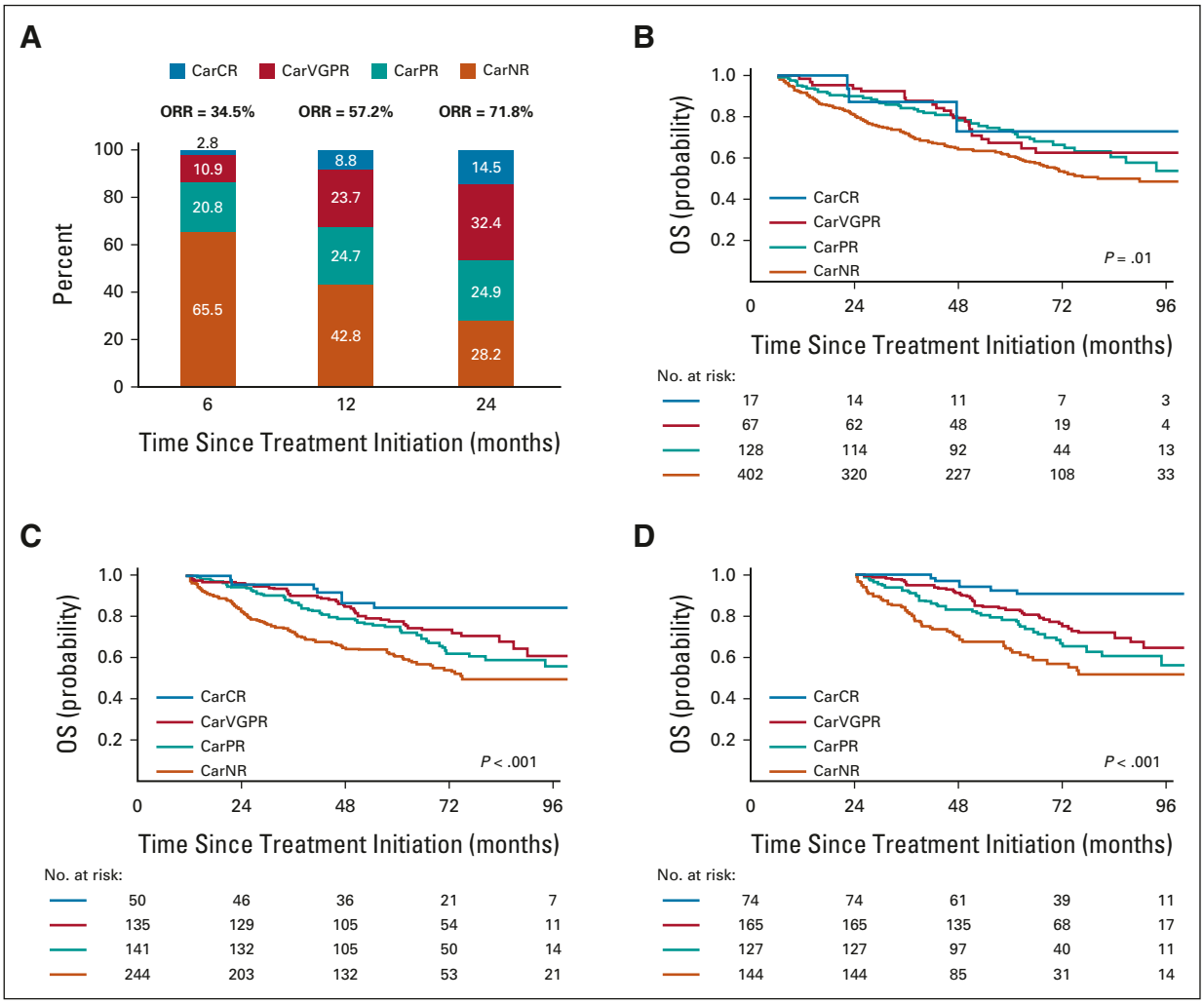

FIG 2. Fixed time-based cardiac response assessment. Please note that the number of patients assessed at fixed time points varies on the basis of data availability and survival of patients (n = 614 at 6 months; n = 570 at 12 months; and n = 510 at 24 months). (A) Cardiac response at 6, 12, and 24 months from treatment initiation. (B) OS stratified by depth of cardiac response at 6 months from therapy initiation (log-rank test *P* values for pairwise comparison between two adjacent cardiac responses: CarPR *v* CarNR *P* = .01; CarVGPR *v* CarPR *P* = .99; CarCR *v* CarVGPR *P* = .6). (C) OS stratified by depth of cardiac response at 12 months from therapy initiation (log-rank test *P* values for pairwise comparison between two adjacent cardiac responses: CarPR *v* CarNR *P* = .007; CarVGPR *v* CarPR *P* = .2; CarCR *v* CarVGPR *P* = .08). (D) OS stratified by depth of cardiac response at 24 months from therapy initiation (log-rank test *P* values for pairwise comparison between two adjacent cardiac responses: CarPR *v* CarNR *P* = .03; CarVGPR *v* CarPR *P* = .09; CarCR *v* CarVGPR *P* = .003). *P* values are based on two-sided log-rank tests. CarCR, cardiac complete response; CarNR, cardiac no response; CarPR, cardiac partial response; CarVGPR, cardiac very good partial response; ORR, overall response rate; OS, overall survival.

95% CI, 0.22 to 1.06; *P* = .071; CarVGPR: HR, 0.51; 95% CI, 0.34 to 0.76; *P* = .0009; CarPR: HR, 0.64; 95% CI, 0.45 to 0.91; *P* = .0135; Data Supplement). At 24 months, nearly half (46.9%) achieved a CarCR or CarVGPR, and again a significant survival advantage was seen with deeper cardiac responses (Fig 2D). CarCR patients had a HR for survival of 0.22 (95% CI, 0.09 to 0.52; *P* = .0006), followed by CarVGPR (HR, 0.48; 95% CI, 0.31 to 0.74; *P* = .0009) and CarPR (HR, 0.65; 95% CI, 0.43 to 0.98; *P* = .039; Data Supplement). A two-level cardiac response (response *v* no response) at 6,12, and 24 months is depicted in the Data Supplement.

Prognostic Influence of Longitudinal Cardiac Response on OS

To overcome potential survivorship bias, a Cox regression model with time-varying covariates was applied. The longitudinal cardiac response measures were incorporated at the fixed time points as well as overall best response. After adjusting for key clinical covariates, the depth of cardiac response in the four-level response classification system was significantly associated with survival discrimination. In relation to CarNR, CarPR was associated with a significant improvement in survival (HR, 0.59; 95% CI, 0.43 to 0.82; *P* = .002). Survival increased with CarVGPR (HR, 0.38;

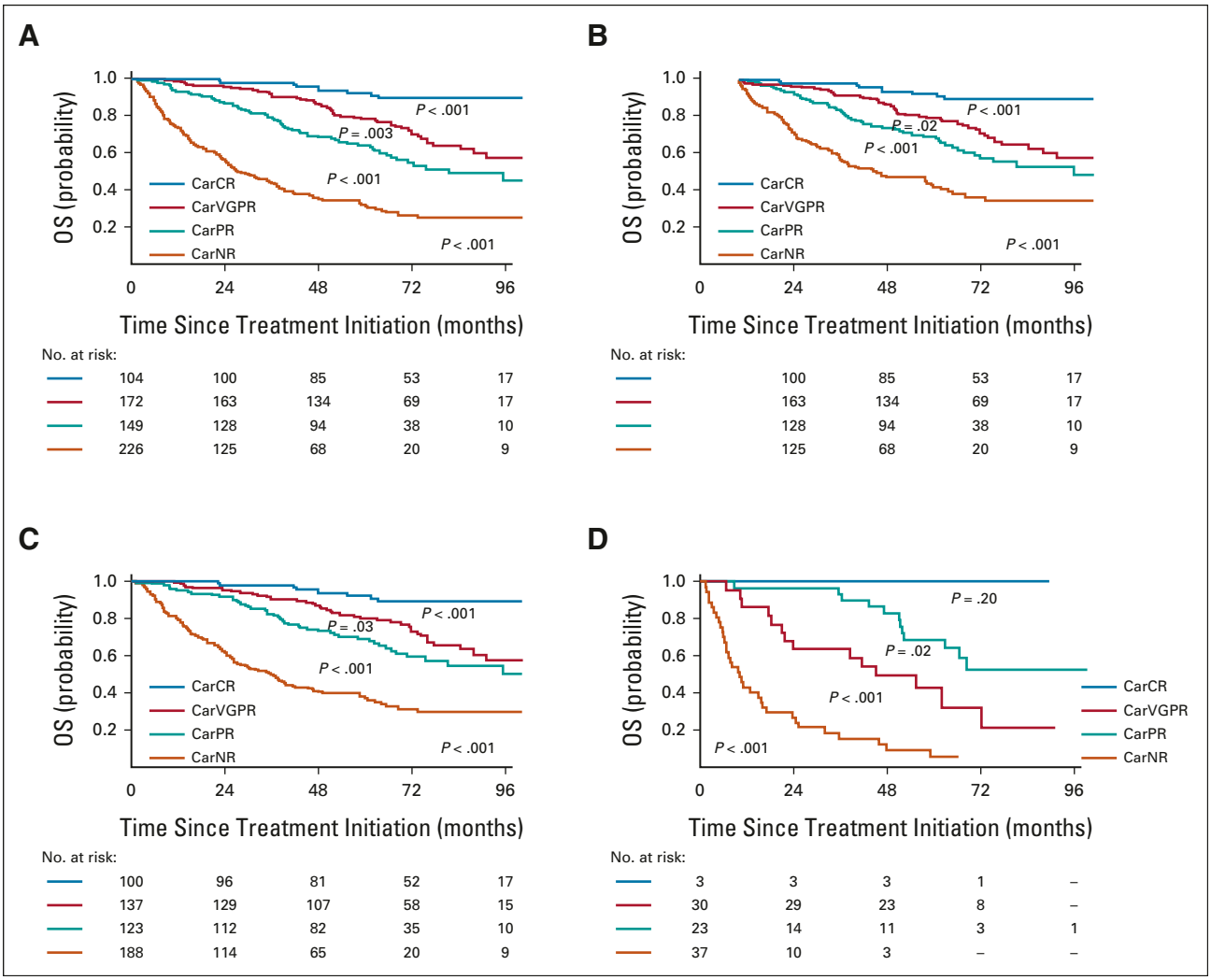

FIG 3. Overall survival stratified by best cardiac response: (A) entire cohort, (B) cohort excluding early deaths (ie, deaths within 1 year of starting treatment), (C) cardiac stage II/IIIA, and (D) cardiac stage IIIB. *P* values are based on two-sided log-rank tests for comparisons across all groups as well as pairwise comparisons between groups. CarCR, cardiac complete response; CarNR, cardiac no response; CarPR, cardiac partial response; CarVGPR, cardiac very good partial response; OS, overall survival.

95% CI, 0.26 to 0.54; $P < .0001$) and CarCR (HR, 0.23; 95% CI, 0.11 to 0.46; $P < .0001$; Table 2).

Prognostic Utility of Four-Level Versus Two-Level Cardiac Response Criteria on OS

Although the two-level cardiac response measure was significantly associated with survival in similar multivariable models in these same subjects (Table 2 and Data Supplement), time-dependent ROC curves and corresponding AUCs showed that the four-level cardiac response criteria had greater prognostic utility for survival. At the 6-month landmark, the four-level response model performed similarly to the two-level response model (Data Supplement). Given the limited numbers of responses achieved by that time point as well as the lack of sufficient deeper responses, the time-dependent AUC measures that capture prognostic effectiveness of each of the models and in relation to each other were similar ($P = .54$; Fig 4A). At the 12-month landmark, the four-level cardiac response model emerged superior to the two-level response model in a multivariable analysis, with a lower HR for death with a deeper cardiac response (Data Supplement). The superiority of four-level cardiac response at 12 months was confirmed in adjusted dynamic ROC curves with corresponding time-dependent AUCs ($P = .015$; Fig 4B). At the 24-month landmark, the graded four-level cardiac response model had significantly widened superiority over the two-level cardiac response model in the multivariable analyses (Data Supplement), and the dynamic ROC analysis solidified the advantage of four-level over two-level response ($P < .0001$; Fig 4C).

Similarly, in time-dependent covariate survival models, the four-level cardiac response multivariable models showed a similar significant association of depth of response with survival (Table 2). Although the two-level

TABLE 2. Univariate and Multivariable Model Results for Overall Survival Using Time-Varying Longitudinal Analysis

	Univariate Analysis		Multivariate Analysis With Four-Level Cardiac Response Classification		Multivariate Analysis With Two-Level Cardiac Response Classification	
Covariate	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***
Best cardiac response to date	0.39 (0.30 to 0.51)	< .0001			0.45 (0.34 to 0.60)	< .0001
Response (*v* NR)			NA			
PR (*v* NR)	0.58 (0.43 to 0.80)	.0008	0.59 (0.43 to 0.82)	.0020	NA	
VGPR (*v* NR)	0.36 (0.26 to 0.50)	< .0001	0.38 (0.26 to 0.54)	< .0001		
CR (*v* NR)	0.12 (0.06 to 0.24)	< .0001	0.23 (0.11 to 0.46)	< .0001		
Age ≥ 65 years (*v* < 65)	1.04 (1.03 to 1.06)	< .0001	1.71 (1.31 to 2.23)	< .0001	1.75 (1.35 to 2.28)	< .0001
Cardiac stage						
IIIa (*v* II)	1.32 (1.01 to 1.73)	.0420	1.23 (0.92 to 1.64)	.1600	1.28 (0.96 to 1.70)	.0920
IIIb (*v* II)	2.65 (1.93 to 3.65)	< .0001	2.74 (1.93 to 3.91)	< .0001	2.82 (1.99 to 4.01)	< .0001
AL burden						
dFLC ≥ 180 mg/L (*v* < 180)	1.32 (1.03 to 1.70)	.0290	1.19 (0.91 to 1.56)	.1900	1.13 (0.87 to 1.47)	.3700
Best hematologic response						
VGPR (*v* PR)	0.50 (0.38 to 0.65)	< .0001	0.61 (0.45 to 0.82)	.0010	0.57 (0.42 to 0.77)	.0002
CR (*v* PR)	0.22 (0.16 to 0.30)	< .0001	0.31 (0.22 to 0.43)	< .0001	0.28 (0.20 to 0.40)	< .0001
Type of first-line treatment						
Bortezomib-based	Reference		Reference		Reference	
ASCT	0.43 (0.28 to 0.65)	< .0001	0.73 (0.47 to 1.13)	.1600	0.72 (0.47 to 1.11)	.1400
Alkylator-based	1.81 (1.30 to 2.52)	.0004	1.61 (1.12 to 2.32)	.0100	1.62 (1.13 to 2.33)	.0080
IMiD-based	1.34 (0.78 to 2.30)	.3000	1.26 (0.67 to 2.36)	.4700	1.38 (0.73 to 2.58)	.3200

NOTE. *P* values are based on Wald test statistics from time-dependent covariate (longitudinal) Cox regression models, and all tests were two-sided.

Abbreviations: AL, light chain amyloidosis; ASCT, autologous stem-cell transplantation; CR, complete response; dFLC, difference between involved and uninvolved light chains; HR, hazard ratio; IMiD, immunomodulatory drug; NA, not available; NR, no response; PR, partial response; VGPR, very good partial response.

cardiac response multivariable model was significant for differentiating survival in these patients, the four-level cardiac response model performed significantly better on the basis of the time-dependent AUC measures ($P < .0001$). In Figure 4D, as one moves beyond 12 months, the depth of response that is reflected through the four-level cardiac response measure significantly improves the ability to differentiate risk of death and OS over the two-level cardiac response measure–based model.

Cross-Validation Analyses

We used cross-validation analyses to assess the robustness of our findings, particularly in comparing the two-level versus four-level response criteria. Details on these analyses are presented in the Data Supplement. Overall, these analyses affirm low prediction error and support the superiority of four-level response criteria over the two-level response.

The Association Between Depth of Hematologic Response and Depth of Cardiac Response

The deeper the hematologic response, the more likely that a deep cardiac response was achieved (Data Supplement). Among hematologic complete response patients, 27% achieved CarCR, 35% CarVGPR, 22% CarPR, and 16% CarNR. These respective figures for HemVGPR were 13%, 27%, 23%, and 37%, and for hematologic partial response were 3%, 11%, 24%, and 62%, respectively.

Cardiac Progression

Cardiac progression was seen in 32% (n = 198) of the 617 patients evaluable for progression. NT-proBNP/BNP progression was noted in 182/617 patients (29%), troponin progression in 53/381 evaluable patients (14%), and echocardiographic progression in 63/587 evaluable patients (11%). The likelihood of cardiac progression was associated with the depth of the hematologic response. The 5-year rate of cardiac progression was significantly lower among hematologic CR patients (20%) compared with HemVGPR patients (39%) and hematologic partial response patients (66%; $P < .001$; Fig 5A). The 5-year rate of cardiac progression was lower for CarCR (7%) compared with CarVGPR (21%), CarPR (34%), and CarNR (64%; $P < .001$; Fig 5B). Cardiac progression was associated with an increased risk of death compared with having no cardiac progression (Data Supplement). Survival curves by type of cardiac progression

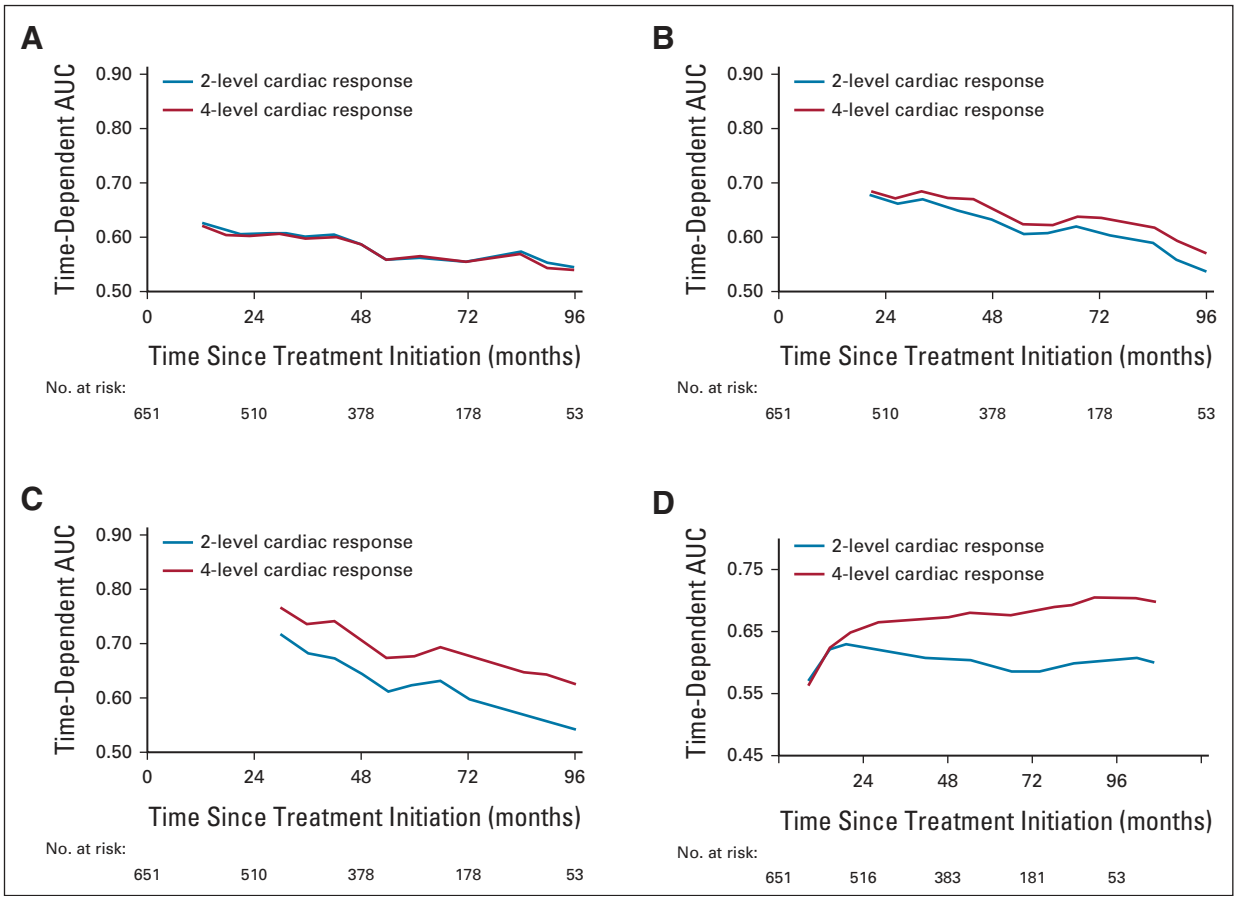

FIG 4. Adjusted dynamic receiver operator characteristic curve and corresponding AUC comparing two-level and four-level cardiac response at: (A) six-month landmark from therapy initiation, (B) twelve-month landmark from therapy initiation, and (C) twenty-four-month landmark from therapy initiation. (D) Best cardiac response. AUC, area under the curve.

are depicted in the Data Supplement. In a multivariate model, depth of hematologic response, depth of cardiac response, and cardiac stage IIIB were independent predictors for time to cardiac progression (Data Supplement).

DISCUSSION

This study provides a comprehensive review of cardiac response in AL amyloidosis, on the basis of a large number of patients with long follow-up periods. We confirmed that grading the depth of cardiac response in AL amyloidosis is prognostic. Importantly, the depth of cardiac response was independent of baseline characteristics and the hematologic response to therapy in predicting survival. These new response criteria will allow more precise classification of the improvement in cardiac dysfunction after successful therapy. The provision of graded cardiac response criteria is a step forward from the current binary cardiac response criteria and is expected to highlight the importance of not only achieving a deep *hematologic* response but also the equally important deep *cardiac* response. With this new tool incorporated into clinical trial design and daily practice, novel ways to pursue deeper cardiac responses can emerge, creating new platforms for survival enhancement in this disease. These criteria are likely to be adopted into drug trials designed to demonstrate benefit of new agents to manage AL amyloidosis.

This study emphasizes the importance of early diagnosis not only to improve patient tolerance of intensive therapy, thereby maximizing the ability of achieving deep hematologic response, but also in terms of increasing the likelihood of deep and durable cardiac response. Organ response is gradual and depends on several factors, including patient's survival, baseline organ impairment, depth of the hematologic response, and hematologic progression. CarCR was more likely in patients presenting with milder cardiac disease, while deep response rates decreased as severity of heart failure advanced. Moreover, as organ response is time-dependent, patients must survive to get to deeper responses, which is more likely in early cardiac stage disease. Cardiac progression was also directly related to baseline cardiac dysfunction and inversely related to the depth of cardiac response, as previously reported.[15,16]

Cardiac response was assessed at designated time points and at best response. Although best cardiac response is not a practical measure for clinical use (as it can only be

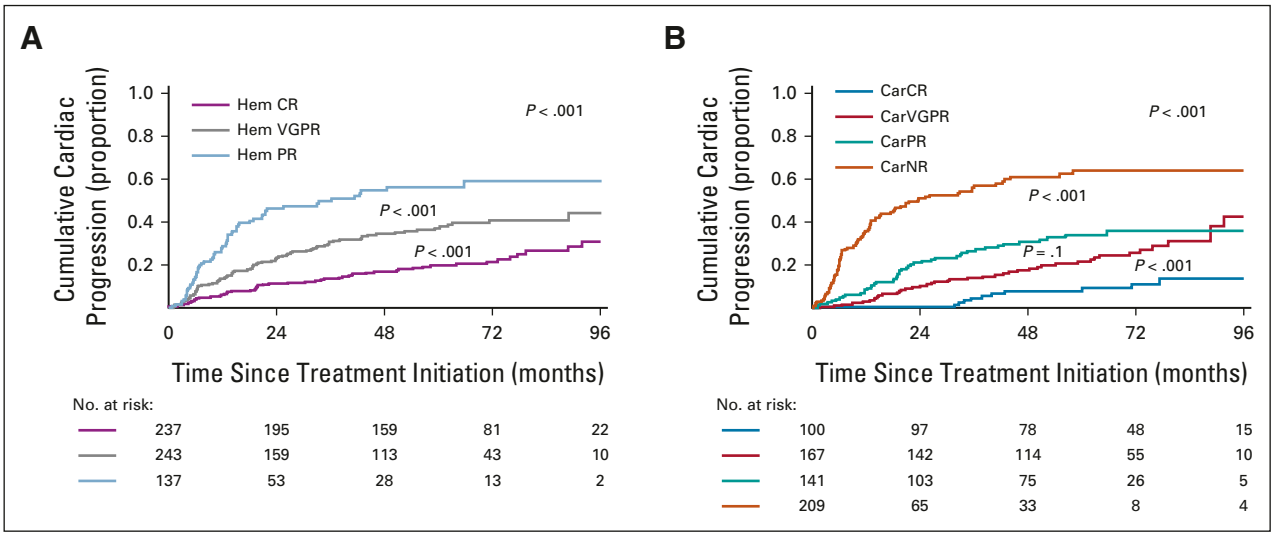

FIG 5. Time to cardiac progression stratified by: (A) best hematologic response and (B) best cardiac response. Time to cardiac progression was calculated from the start of treatment until cardiac progression, as listed in Table 1. Patients without organ progression were censored at their last evaluation, irrespective of their vital status. *P* values are based on two-sided log-rank tests for comparisons across all groups as well as pairwise comparisons between groups. CarCR, cardiac complete response; CarNR, cardiac no response; CarPR, cardiac partial response; CarVGPR, cardiac very good partial response; HemCR, hematologic complete response; HemPR, hematologic partial response; HemVGPR, hematologic very good partial response.

determined retrospectively), it serves as a proof of concept that depth of cardiac response is prognostic. The fixed time response assessment confirms gradual organ improvement, and the superiority of four-level response over two-level response was more significant with time, as response deepened. On the basis of the fixed time-point analyses, we recommend a goal of at least a CarPR by 6 and 12 months from therapy initiation and a goal of at least CarVGPR by 24 months. The implications of these recommendations in the current therapeutic landscape remain unclear. However, the possibility for alternate antiplasma cell therapy may be needed at these designated time points, especially if other causes of organ dysfunction have been excluded and residual clonal disease is evident. Several studies have shown that patients in deep hematologic response with detectable amyloid-producing clonal bone marrow plasma cells assessed by multiparametric flow cytometry have a higher risk for hematologic progression and lower rates of organ response.[7-11] In addition, these response criteria can improve efficacy analysis in clinical trials assessing therapies directed against amyloid or its toxic oligomeric precursors. However, given the gradual nature of cardiac response and as discrimination of survival on the basis of depth of response was only evident as early as 12 months from therapy, we recommend the use of these graded cardiac response only from that time point.

Natriuretic peptides have been used in AL amyloidosis for nearly 20 years as a tool to measure the level of cardiac dysfunction,[18] for cardiac staging,[4,19,20] and for response to therapy.[3,21-25] Their advantage lies in wide availability, low cost, and reproducibility. However, natriuretic peptides have limitations, including their dependency on renal function. Therefore, other methods for cardiac response assessment have been explored. These include echocardiographic strain measurement,[15,26,27] extracellular volume measurement using cardiac magnetic resonance,[28] and functional assessment such as the 6-minute walk test,[29,30] but none demonstrated evidence of superiority over measurements of natriuretic peptides. High-sensitivity troponin T is another cardiac biomarker that can be explored for cardiac response assessment independently and combined with other cardiac response measures. This is particularly relevant as natriuretic peptides can fluctuate both because of cardiac causes as well as extracardiac causes, and troponins have a more stable course.

Several limitations of this study exist. First, its retrospective design creates a selection bias. Second, with missing information on cardiac response at fixed time points, we imputed cardiac responses for approximately 20%-25% of patients on the basis of adjacent measurements. Third, the possibility of survivorship bias cannot be ignored with the use of best cardiac response. However, fixed time-point analyses and time-varying analysis were used to address this limitation. In addition, cardiac progression was noted more commonly with less deep cardiac response. This observation further reduces survivorship bias for deeper cardiac responses, as cardiac progression eliminates further improvement in cardiac response. Finally, with lack of external validation set, data from this study should be interpreted cautiously. Validation sets in this rare disease should preferably include ongoing and future large phase III studies assessing the efficacy of amyloid-

targeted therapies as well as other large studies assessing natriuretic peptide–based cardiac response.

In conclusion, we established and validated previously proposed graded cardiac response criteria in AL amyloidosis in a multicenter collaboration. Application of these criteria into clinical trial end point design and routine clinical practice is encouraged to allow a better assessment of treatment outcome in this disease. This study emphasizes the importance of careful and continuous patient monitoring for satisfactory cardiac response over time. Finally, this study also provides evidence supporting the importance of early diagnosis to achieve deep and durable cardiac responses.

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DISCLAIMER

E.M., S.M.G., and M.A.G. had full access to whole the data of the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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