JACC: ASIA VOL. 5, NO. 1, 2025

ORIGINAL RESEARCH

Cardiac Response Dynamics in Newly Diagnosed Light-Chain Amyloidosis Patients With Early and High-Quality Hematologic Response

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ABSTRACT

BACKGROUND The goal of hematological response has been well established in the treatment of systemic light chain amyloidosis. However, the pattern of cardiac response remains unknown.

OBJECTIVES This study was designed to investigate the cardiac response dynamics in patients with an early and high-quality hematological response.

METHODS This retrospective study included newly diagnosed patients who achieved a hematological response of very good partial response or better within 3 months after treatment beginning. Four cardiac response criteria were tested at fixed time points (3, 6, 12, and 24 months after therapy initiation): cardiac complete response, cardiac very good partial response, cardiac partial response (carPR), and cardiac no response.

RESULTS A total of 201 patients were included, with the median follow-up 37.0 months (Q1-Q3: 18.0-56.5 months). The cardiac response reached a plateau at 24 months, while cardiac complete response, cardiac very good partial response, and carPR were achieved in 21.4% (28 of 131), 38.9% (51 of 131), and 20.6% (27 of 131) of the patients, respectively. At every fixed time point within 12 months after treatment initiation, patients who achieved a carPR or better consistently had better survival than did those who did not. At 3 months, an NT-proBNP concentration ≥3,716 pg/mL was the only factor associated with a decreased likelihood of achieving a carPR within 12 months (OR: 0.269; 95% CI: 0.137-0.512; $P < 0.001$).

CONCLUSIONS This study emphasizes the importance of monitoring cardiac response dynamics for disease surveillance. In patients who achieve early and high-quality hematological response, it is important to achieve carPR within 12 months. (JACC Asia. 2025;5:74–84) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 24, 2024; revised manuscript received October 8, 2024, accepted October 10, 2024.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2024.10.005

Systemic light chain (AL) amyloidosis is a rare disease characterized by the accumulation of misfolded immunoglobulin light chains in tissues, leading to organ damage. The heart is the most commonly involved organ in AL amyloidosis, and its involvement is a major contributor to morbidity and mortality.[1-4] Patients in Mayo 2004 stage IIIb, which indicates severe cardiac involvement, have particularly poor survival rates.[5] Currently, the evaluation of AL amyloidosis response mainly focuses on hematological response, because it is directly related to plasma cell clones and shows a rapid response. At least a very good partial response (VGPR) in hematological response is widely accepted as a treatment goal.[6] Recent studies have also focused on the depth of cardiac response.[7] The development of a composite hematologic/organ response model by the Mayo Clinic in 2021 represents an important step in combining hematological response with organ response (heart, kidney, liver) for early assessment of treatment benefit at 6 months, with greater predictive ability in overall survival (OS) compared with hematological response or organ response assessed in isolation, and has been validated by the cohort at our center.[8,9] However, the assessment of cardiac response speed has been relatively neglected, and there is a lack of studies that comprehensively analyze cardiac response depth and speed.

The introduction of powerful antiplasma cell drugs, such as daratumumab, has significantly improved the prognosis of patients with AL amyloidosis; approximately 80% of patients now achieve a hematological VGPR or better response, and the remission rate has accelerated.[1] Therefore, it is important to analyze the dynamic changes, influencing factors of cardiac response, and its correlations with the prognosis in patients who achieve early and high-quality hematological response. This approach will help establish early organ response goals and integrate both hematological and cardiac responses as treatment endpoints. These findings will also aid in the development and adjustment of drug regimens to improve patient outcomes.

In this retrospective study, the primary objective was to investigate the cardiac response dynamics in patients who achieved early and high-quality hematological response. The second objective was to identify a new therapeutic goal and a new predictor of cardiac response to better guide treatment.

METHODS

PATIENTS. This study was conducted with the approval of the Institutional Review Board of Peking Union Medical College Hospital and in accordance with the ethical guidelines of the Declaration of Helsinki. Patients newly diagnosed with AL amyloidosis between January 1, 2008, and November 18, 2022, were included if they met the following criteria: 1) had cardiac involvement (baseline N-terminal pro-B-type natriuretic peptide [NT-proBNP] >650 pg/mL or brain natriuretic peptide [BNP] >150 pg/mL) and an evaluable cardiac response (at least 2 NT-proBNP or BNP records during treatment); 2) received antiplasma cell therapies; and 3) achieved a hematological VGPR or better response within 3 months after treatment initiation. Patients were excluded for the following: 1) they were treated for related hematologic diseases or died within 3 months after treatment initiation; or 2) they had a baseline difference between involved and uninvolved free light chain (dFLC) <20 mg/L caused by a lack of validated response criteria. The European Mayo 2004 and 2012 models were used for cardiac staging.[10,11]

ABBREVIATIONS AND ACRONYMS

carCR = cardiac complete response

carNR = cardiac no response

carPR = cardiac partial response

carVGPR = cardiac very good partial response

CR_H = hematological complete response

PR_H = hematological partial response

$VGPR_H$ = hematological very good partial response

RESPONSE CRITERIA. Hematological response was defined as follows: for a baseline dFLC >50 mg/L, partial response (PR_H) was defined as a more than 50% reduction in dFLC; very good partial response ($VGPR_H$) was defined as a dFLC<40 mg/L; and complete response (CR_H) was defined as negative serum and urine immunofixation electrophoresis with a normal free light chain (FLC) ratio and levels. For baseline dFLC ≥20 and ≤50 mg/L, PR_H was defined as dFLC <10 mg/L, with no $VGPR_H$, and CR_H was defined as the same as previously mentioned. Progressive disease was defined as a 50% increase in serum monoclonal protein to >5 g/L; a 50% increase in urine monoclonal protein to >200 mg/d with a visible peak for $VGPR_H$/PR_H; detectable monoclonal protein or an abnormal FLC ratio with double involved free light chain (iFLC) for CR_H; or a 50% increase in iFLC to >100 mg/L.[12] Hematological response was further divided into 2 categories: stringent response of free light chain (SR_{FLC}) was defined as dFLC <10 mg/L or iFLC ≤20 mg/L while unstringent response of free light chain (UR_{FLC}) was defined as dFLC ≥10 mg/L and iFLC >20 mg/L.[1,13]

Cardiac response was assessed using NT-proBNP or BNP and was defined as follows: cardiac no response (carNR) was defined as a <30% reduction in baseline NT-proBNP; cardiac partial response (carPR) was defined as a 31% to 60% reduction in NT-proBNP; cardiac very good partial response (carVGPR) was defined as a >60% reduction in NT-proBNP/BNP;

cardiac complete response (carCR) was defined as a nadir NT-proBNP ≤350 pg/mL or BNP ≤80 pg/mL; and cardiac progressive disease was defined as a >30% increase from nadir and >300 pg/mL in NT-proBNP or a >30% increase from nadir and >70 pg/mL in BNP, not related to infection, elevated creatinine (Cr), or cardiac arrhythmia.[7] Based on the distribution of estimated glomerular filtration rate (eGFR), 30 mL/min/1.73 m^2 was chosen as the cutoff value. For patients with eGFR <30 mL/min/1.73 m^2, BNP was used for cardiac response assessment. For patients with baseline eGFR ≥30 mL/min/1.73 m^2, if renal function deteriorated after treatment (eGFR <30 mL/min/1.73 m^2), NT-proBNP was replaced with BNP to continue monitoring changes in cardiac response.

During the follow-up period, the depths of hematological and cardiac response were recorded at fixed time points (3, 6, 12, 18, and 24 months after treatment initiation). The last follow-up date was November 18, 2023.

In cases where patients achieved different depths of cardiac response at different time points, individuals who met multiple criteria at the same time were classified into the greater depth group to ensure data independence between groups. For example, individuals who achieved carPR at 6 months and carVGPR at 24 months were classified into the "13- to 24-month carVGPR" group.

STATISTICAL ANALYSIS. Continuous variables are presented as medians and ranges, and categorical variables are presented as absolute values and percentages. OS was calculated from 3 months after treatment initiation until death from any cause or the date of the last follow-up. Survival curves were generated using the Kaplan-Meier method and compared using the 2-sided log-rank test, as well as Cox regression analysis. Before Cox regression analysis, a proportional hazard test was performed to find whether the effect of covariates on outcomes over time was stationary. A competing risk model was employed to evaluate the impact of time to cardiac response on OS, with lost visits or deaths occurring before the fixed time point treated as competing events for achieving a carPR. Sensitivity analysis was performed to calculate sensitivity, specificity, positive predictive value, and negative predictive value. Multicollinearity was evaluated in multivariable regression using the variance inflation factor (VIF), with a cutoff above 5 serving as evidence of multicollinearity in the univariate model, and multivariate logistic regression models were used for predicting cardiac response at 12 months. The Pearson's chi-square test or Fisher exact test was used as a nonparametric test, and Bonferroni adjustment was used when comparing multiple groups. The statistical analyses were performed using SPSS version 26.0 (IBM Corp) and the R package 4.0.2 (R Foundation for Statistical Computing). $P < 0.05$ was considered indicative of statistical significance.

TABLE 1 Baseline Demographic and Clinical Characteristics of 201 Patients

Age, y	59 (34-85)
Male	117 (58.2)
Amyloid light-chain type λ	166 (82.6)
NYHA functional class (n = 190)	
I	23 (11.4)
II	93 (46.3)
III	67 (33.3)
IV	7 (3.5)
Mayo 2004 (n = 200)[a]	
II	92 (46.0)
IIIa	78 (39.0)
IIIb	30 (15.0)
Mayo 2012 (n = 200)[a]	
I	16 (8.0)
II	40 (19.9)
III	78 (38.8)
IV	66 (32.8)
Laboratory values	
cTnI, μg/L	0.1 (0.01-7.35)
NT-proBNP, pg/mL	3,865 (653-35,000)
eGFR, mL/min/1.73 m^2	81.52 (14.96-161.20)
ALP, U/L	94 (38-1,456)
24-h UP, g	0.88 (0.00-27.92)
dFLC, mg/L	220.3 (22.2-57,486.3)
BMPC, %	4 (0-29)
Organ involvement	
Renal	107 (53.2)
Hepatic	40 (19.9)
Gastrointestinal	4 (2.0)
Neurological	12 (6.0)
Treatment categories	
PI-based regiments	144 (71.6)
Daratumumab-based regiments	52 (25.9)
ASCT	1 (0.5)
Melphalan-based regimens	4 (2.0)

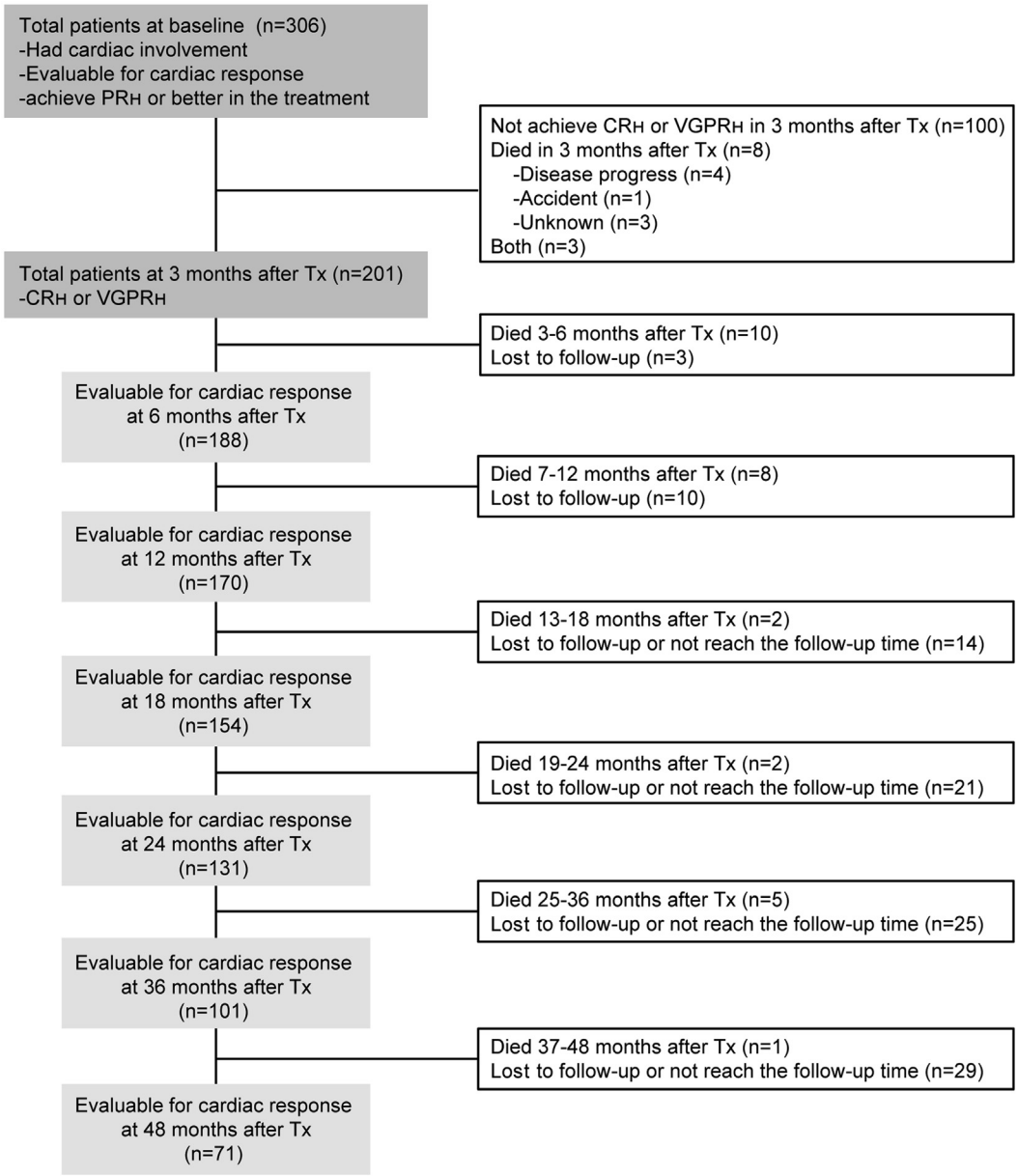
Values are median (range) or n (%). [a]One patient could not be evaluated for Mayo 2004 or 2012 models because of the lack of cardiac troponin (cTn) I and cTnT testing.

ALP = alkaline phosphatase; ASCT = autologous stem cell transplantation; BMPC = bone marrow plasma cell; dFLC = difference between involved and uninvolved free light chain; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PI = proteasome inhibitor; UP = urine protein.

RESULTS

A total of 201 newly diagnosed AL amyloidosis patients were enrolled in this study. Table 1 provides an overview of the patients' demographic and clinical characteristics. The median age at diagnosis was 59 years, and men accounted for 58.2% (117 of 201) of the cohort. Mayo stage IIIb disease was present in a

FIGURE 1 **Flow Diagram for Landmark Analysis Cohorts**

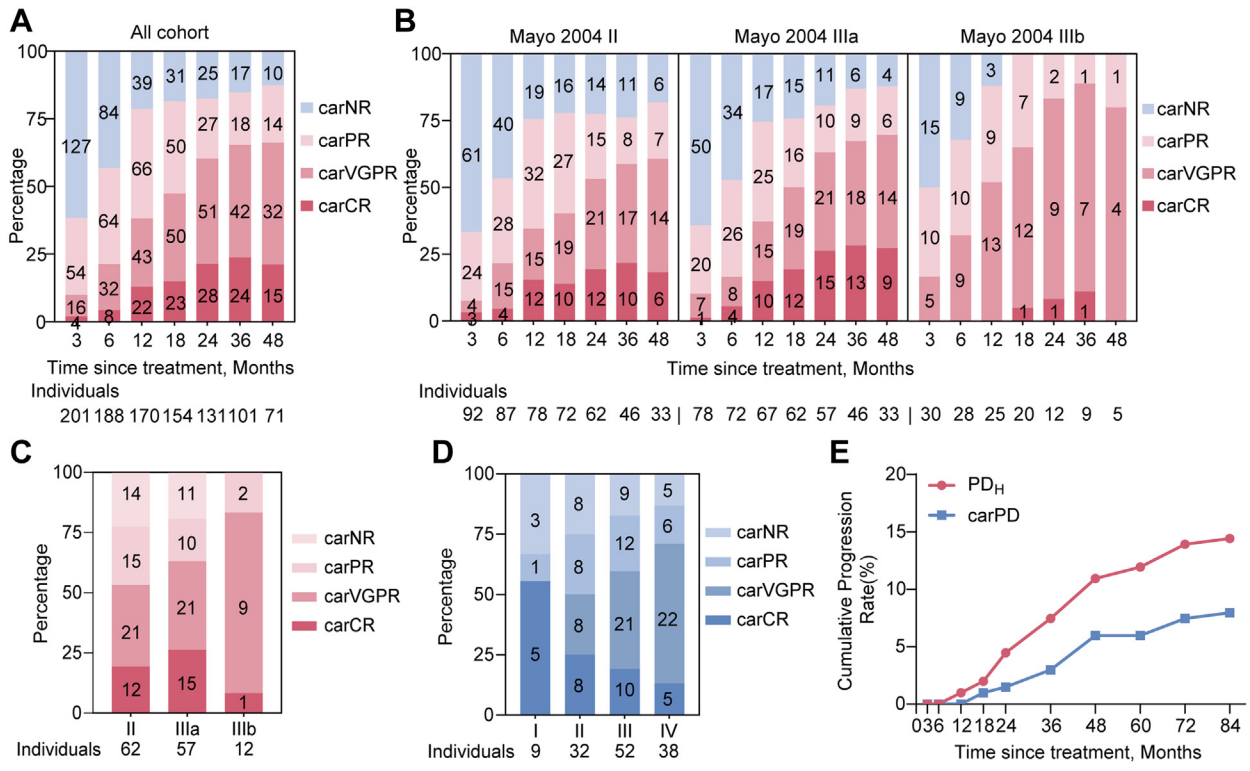


A total of 201 patients were involved in the study after 105 patients were excluded because of not achieving complete response (CR_H) or very good partial response ($VGPR_H$) or dead in 3 months after treatment initiation. At every fixed time point, patients were excluded because of death or loss to follow-up. PR_H = hematological partial response; Tx = treatment.

total of 30 (15.0%) patients. Aside from the heart, the kidney was the most commonly involved organ, affecting 53.2% (107 of 201) of the patients. A majority of patients (71.6%, 144 of 201) received proteasome inhibitor-based therapy as their primary treatment, whereas 25.9% (52 of 201) were treated with daratumumab-based regimens.

CARDIAC RESPONSE DYNAMICS. The number of patients assessed at fixed time points varied based on the data availability and patient survival (**Figure 1**, Supplemental Table 1). At 3 months, the carCR, carVGPR, carPR, and overall cardiac response were 2.0% (4 of 201), 8.0% (16 of 201), 26.8% (54 of 201), and 36.8% (74 of 201), respectively. These

FIGURE 2 Cardiac Response Pattern

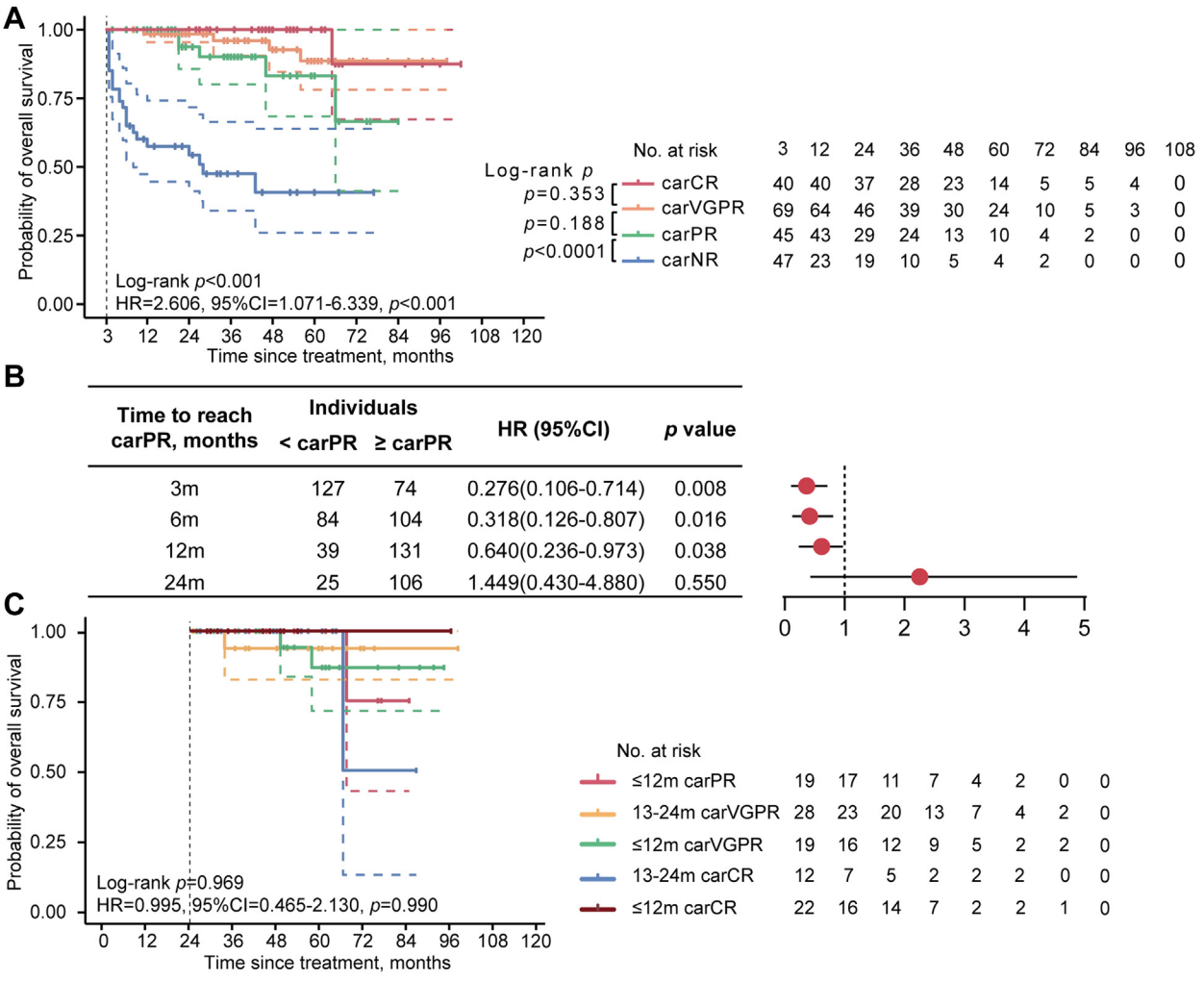


(A-B) Distribution of cardiac response at each fixed time points in all patients (A) and different Mayo 2004 stages (B). (C) Distribution of cardiac response in Mayo 2004 models at 24 months. (D) Distribution of cardiac response in Mayo 2012 models at 24 months. (E) Cumulative hematological and cardiac progression rate at fixed time points. carCR = cardiac complete response; carNR = cardiac no response; carPD = cardiac progressive disease; carPR = cardiac partial response; carVGPR = cardiac very good partial response; PD_H = hematological progressive disease.

percentages increased to 21.4% (28 of 131), 38.9% (51 of 131), 20.6% (27 of 131), and 80.9% (106 of 131), respectively, at 24 months. The proportion of cardiac response did not change greatly after 24 months. In other words, most patients reached a plateau at 24 months, and the Mayo 2004 model had no effect on the generation of the plateau (Figures 2A and 2B). At 24 months, the overall cardiac response rate increased as the stage progressed in both the Mayo 2004 and 2012 models (Mayo 2004, stage II 77.4% (48 of 62), stage IIIa 80.7% (46 of 57), stage IIIb 100.0% (12 of 12); chi-square = 5.554; $P = 0.062$; Mayo 2012, stage I 66.7% (6 of 9), stage II 75.0% (24 of 32), stage III 82.7% (43 of 52), stage IV 86.8% (33 of 38); chi-square = 2.753; $P = 0.431$) (Figure 2C). According to the Mayo 2012 model, as the stage progressed, the proportion of carVGPR gradually increased (stage I 0.0% (0 of 9), stage II 25.0% (8 of 32), stage III 40.4% (21 of 52), stage IV 57.9% (22 of 38); chi-square = 17.262; $P = 0.001$), while the percentage of carCR and carNR showed a downward trend (carCR, stage I 55.6% (5 of 9), stage II 25.0% (8 of 32), stage III 19.2% (10 of 52), stage IV 13.2% (5 of 38); chi-square = 7.083; $P = 0.069$; carNR, stage I 33.3% (3 of 9), stage II 25.0% (8 of 32), stage III 17.3% (9 of 52), stage IV 13.2% (5 of 38); chi-square = 2.753; $P = 0.431$) (Figure 2D). There was a relatively rapid increase in the number of patients who experienced cardiac progression between 24 and 48 months after treatment began (Figure 2E).

THE EFFECT OF CARDIAC RESPONSE DYNAMICS ON OS. During the median follow-up of 37.0 months (Q1-Q3: 18.0-56.5 months), 33 patients died, and the median OS was not reached. The 1/3/5-year OS rates were 90.9%/84.7%/79.4%, respectively. Looking at the influence of the best cardiac response achieved on OS, only patients with carNR had a markedly shorter survival (median 28 months; 95% CI not available), with no difference in survival between patients with

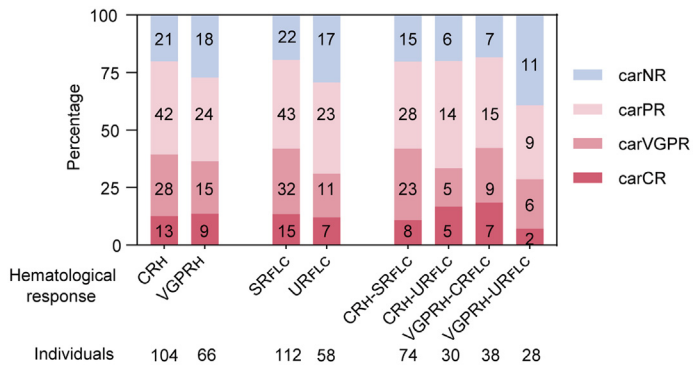
FIGURE 3 **The Effect of Cardiac Dynamics on OS**



(A) OS stratified by depth of best cardiac response at 3 months from treatment initiation. (B) Forest plots of HR for overall survival (OS) based on weather carPR or better is achieved at the fixed time point, calculated by competing risk model. The red circle represents HR and the horizontal line represents 95% CI. (C) OS stratified by time to reaching different cardiac responses. The dashed lines in the Kaplan-Meier curve plots represent the 95% CI. Abbreviations as in Figure 2.

carCR, carVGPR, and carPR (carCR vs carVGPR, log-rank $P = 0.353$; HR: 2.715; 95% CI: 0.303-24.340; $P = 0.372$; carVGPR vs carPR, log-rank $P = 0.188$; HR: 2.377; 95% CI: 0.6331-8.922; $P = 0.200$; carPR vs carNR, log-rank $P < 0.001$; HR: 6.622; 95% CI: 2.505-17.510; $P = 0.001$) (Figure 3A). Moreover, there was no difference in survival between patients in different Mayo 2004 or 2012 stages (Mayo 2004 model, log-rank $P = 0.289$; HR: 1.469; 95% CI: 0.908-2.376; $P = 0.117$; Mayo 2012 model, log-rank $P = 0.259$; HR: 1.532; 95% CI: 0.999-2.351; $P = 0.051$) (Supplemental Figure 1). At every fixed time point within 12 months after treatment initiation, patients who achieved a carPR or better consistently had better survival than those who did not achieve a carPR (Figure 3B). For patients who achieved a carPR as best cardiac response, individuals who achieved a carPR within 12 months had a better prognosis than did those who achieved a carPR within 13 to 24 months (log-rank $P = 0.006$; HR: 889.131; 95% CI: 1.306 to 1.150×10^{12}; $P = 0.007$) (Supplemental Figure 2). Additionally, no significant difference in OS was found between patients who reached a carPR within 12 months and those who achieved a carVGPR or carCR within 12 or 24 months (log-rank $P = 0.969$; HR: 0.995; 95% CI: 0.465-2.130; $P = 0.990$) (Figure 3C).

FIGURE 4 Influencing Factors of Cardiac Response



Distribution of cardiac response at 12 months in different hematological response of 3 months after treatment initiation. SR_{FLC} = stringent response of free light chain; UR_{FLC} = unstringent response of free light chain; other abbreviations as in Figures 1 and 2.

A NEW CARDIAC RESPONSE PREDICTOR FOR THE carPR WITHIN 12 MONTHS. At 3 months after treatment initiation, CR_H and $VGPR_H$ were achieved in 61.7% (124 of 201) and 38.3% (77 of 201), respectively, and the overall cardiac response rates at 12 months in the 2 groups were 79.8% (83 of 104) and 72.7% (48 of 66), respectively. There was no difference in prognosis between the CR_H and $VGPR_H$ groups (log-rank $P = 0.519$; HR: 1.251; 95% CI: 0.630-2.485; $P = 0.522$) (Supplemental Figure 3A). When considering the FLC response, patients in the UR_{FLC} group had a lower cardiac response rate than those in SR_{FLC} the group (70.7% [41 of 58] vs 80.4% [90 of 112]; chi-square = 2.020; $P = 0.155$), and a worse prognosis (log-rank $P = 0.013$; HR: 2.321; 95% CI: 1.169-4.608; $P = 0.016$) (**Figure 4A**, Supplemental Figure 3B). Specifically, patients in the $VGPR_H$-UR_{FLC} cohort had a worse prognosis (log-rank $P = 0.009$; HR: 2.532; 95% CI: 1.228-5.224; $P = 0.012$) (Supplemental Figure 3C) and a lower likelihood of achieving a cardiac response within 12 months (60.7% [17 of 28] vs CR_H-SR_{FLC} 79.7% [59 of 74], CR_H-UR_{FLC} 80.0% [24 of 30], $VGPR_H$-SR_{FLC} 81.6% (31 of 38); chi-square = 3.867, 2.600, 3.538, respectively; $P = 0.049$, $P = 0.107$, $P = 0.060$, respectively) (**Figure 4A**).

The baseline demographic and clinical characteristics between patients with 12-month carPR and non-carPR were not significantly different (Supplemental Table 2). At 3 months, routine collected review items included dFLC, NT-proBNP, alkaline phosphatase, 24-hour urine protein, Cr, and eGFR. Of these variables, only NT-proBNP and the hematological response were significantly different between the 2 groups (Supplemental Table 3). Combining the results of univariate logistic regression and clinical experience, hematological response, NT-proBNP, eGFR, and Cr at 3 months were included in the logistic regression without multicollinearity (NT-proBNP, VIF = 1.092, Tol = 0.916; Cr, VIF = 1.892, Tol = 0.529; eGFR, VIF = 1.951, Tol = 0.513) and corrected for sex and age as confounders. The cutoff values are determined by the median. According to the multivariate logistic regression analysis, an NT-proBNP concentration ≥3,716 pg/mL was the only factor associated with a decreased likelihood of achieving a carPR within 12 months (OR: 0.269; 95% CI: 0.137-0.512; $P < 0.001$) (**Table 2**). The sensitivity analysis revealed great predictive power of median as cutoff value (sensitivity 72.3%, 95% CI: 59.6%-82.3%; specificity 60.9%, 95% CI: 51.9%-69.3%; positive predictive value 48.5%, 95% CI: 38.3%-58.8%; negative predictive value 81.3%, 95% CI: 71.7%-88.2%). The carPR rates of patients with NT-proBNP levels <3,716 pg/mL and ≥3,716 pg/mL were 81.3% (78 of 96) and 51.5% (50 of 97), respectively, at 12 months (chi-square = 10.059; $P < 0.001$); and 88.5% (85 of 96) and 58.8% (57 of 97), respectively, at 24 months (chi-square = 22.007; $P < 0.001$).

DISCUSSION

Currently, the primary treatment goal for AL amyloidosis is hematological response, particularly in the early stages of treatment. However, with the introduction of potent antiplasma cell drugs and therapies targeting deposited light chains in organs into clinical trials, there is a growing need for organ response to become the treatment goal following a hematological response.[1,14-16] Given that a hematological response is required within 3 months or even 1 month, it is crucial to establish new response targets in follow-up treatment, particularly for the heart.[17] In our study, we focused on patients who achieved an early and high-quality hematological response and explored new targets for determining cardiac response during treatment through the study of cardiac response dynamics (**Central Illustration**).

Unlike previous studies that focused primarily on the median time to onset of cardiac remission after the start of treatment, we first observed that the cardiac response reached a plateau at 24 months.[1,6] This plateau stage indicated that the improvement in cardiac function mainly occurred within the first 24 months in this group of patients, providing valuable guidance for educating and managing patients. For example, it can help patients to have a rational expectation of how much their cardiac function will

TABLE 2 Univariate and Multivariate Logistic Regression Models for 12-Month Cardiac Partial Response

	Univariate Analysis		Multivariate Analysis[a]	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
NT-proBNP ≥3,716 pg/mL (vs <3,716 pg/mL)	0.266 (0.136-0.504)	<0.001	0.269 (0.137-0.512)	<0.001
Cr ≥80.5 μmol/L (vs <80.5 μmol/L)	0.602 (0.328-1.093)	0.097	0.717 (0.279-1.806)	0.481
eGFR ≥78.85 mL/min/1.73 m^2 (vs <78.85 mL/min/1.73 m^2)	1.258 (0.695-2.288)	0.450	0.773 (0.306-1.920)	0.581
$VGPR_H$-UR_{FLC} (vs CR_H+$VGPR_H$-SR_{FLC})	0.467 (0.216-1.008)	0.051	1.921 (0.842-4.382)	0.118

[a]Corrected for sex and age.

Cr = creatinine; CR_H = hematological complete response; SR_{FLC} = stringent response of free light chain; UR_{FLC} = unstringent response of free light chain; $VGPR_H$ = hematological very good partial response; other abbreviations as in Table 1.

improve and better cooperate with treatment; from an academic perspective, a 24-month cardiac response can be used as an efficacy endpoint in clinical trials. Within 24 months, the depth of cardiac response should be achieved; after 24 months, vigilance should be maintained for the occurrence of cardiac progression.

Among patients who achieved early and high-quality hematological response, we observed no significant difference between those who achieved carPR within 12 months and those who achieved carCR or carVGPR within 12 or 24 months. This suggested that targeting the depth of carPR within 12 months was important. Although 131 patients were still alive at 24 months, after the patients were grouped according to time, the sample sizes of the 2 carPR groups were defective and led to the great HR, which is exactly the real survival situation, because many patients had gradually deepened cardiac response during treatment, and only a few patients still maintained carPR within 24 months. These findings differed from those of the newly proposed 4-level cardiac response model, which concluded that the prognosis of patients improved with the deepening of cardiac response and recommended reaching at least carPR within 12 months and carVGPR within 24 months.[7] This difference might be partly caused by the sample size, but it is more likely because of the variation in patient populations. The 4-level cardiac response model focused on patients with at least PR_H within 12 months of diagnosis. However, our study specifically emphasized individuals with early and high-quality hematological response who already had a survival advantage over patients with poor hematological response, and the high quality of hematological response attenuated the effect of different cardiac response grades. We believe that it is meaningful to consider the cardiac response goal after achieving the hematological response goal.

In clinical practice, the 12-month carPR proposed by our study represents an important treatment target. For patients who do not achieve a 12-month carPR, treatment may need to be maintained or switched if there is room for deeper hematological response. Additionally, the 12-month carPR could also serve as an endpoint for future clinical studies. Although our study focused primarily on cardiac response dynamics, we also found that traditional hematological response (CR_H and $VGPR_H$) had no significant effect on prognosis in patients with high-quality hematologic responses, whereas UR_{FLC} was associated with worse outcomes. Perhaps for such patients, more attention should be paid to the FLC response. Additionally, patients with VGPR-UR_{FLC} exhibited a significantly worse depth of cardiac response than did patients with other types of high-quality hematological response. In the present study, patients diagnosed between 2008 and 2022 were included. Although there had been great advances in the treatment of AL over the past 20 years, changes in treatment had not resulted in a significant increase in the proportion of patients who achieved carPR within 12 months. For patients who did not meet our treatment goals, timely adjustment of antiplasma cell therapy regimens or performing autologous hematopoietic stem cell transplantation for consolidation might be necessary to pursue deeper hematological response, thereby creating the possibility of achieving carPR within 24 months (before reaching the plateau).

For patients who achieve early and high-quality hematological response, baseline characteristics may be less valuable as a guide for subsequent treatment. Instead, NT-proBNP at 3 months could serve as a predictor of subsequent cardiac response. Patients with NT-proBNP ≥3,716 pg/mL at 3 months might be closely monitored for the possibility of not achieving carPR during treatment, and their cardiac function requires closer supervision. As for why $VGPR_H$-UR_{FLC}

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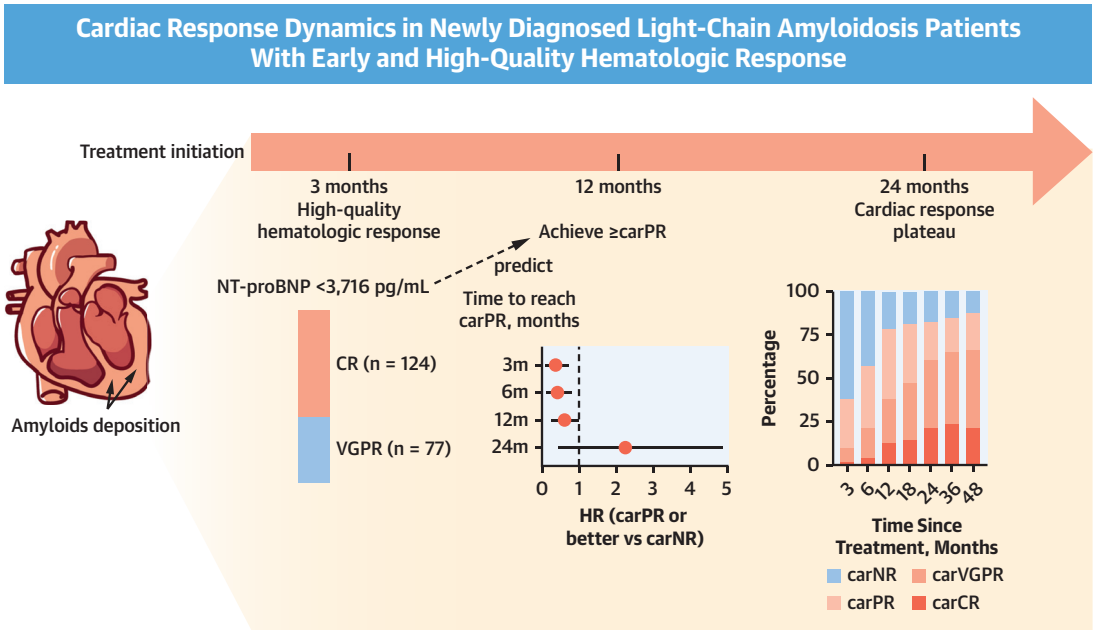
CENTRAL ILLUSTRATION Cardiac Response Dynamics



Xu C-y, et al. JACC Asia. 2025;5(1):74–84.

For newly diagnosed light-chain amyloidosis patients who achieved a high-quality hematologic response within 3 months, it is important to achieve at least cardiac partial response at 12 months for better prognosis, and NT-proBNP at 3 months could help predict the cardiac response at 12 months. At 24 months, the cardiac response reached a plateau. carCR = cardiac complete response; carNR = cardiac no response; carPR = cardiac partial response; carVGPR = cardiac very good partial response; CR = complete response; VGPR = very good partial response.

did not lead to a lower likelihood of reaching a 12-month carPR in the multivariate analysis, we considered it might be caused by the survivor bias.

Although natriuretic peptide has been an important part of the assessment of cardiac function in AL amyloidosis, it undeniably has some limitations and is particularly susceptible to renal function. Currently, attempts have been made to incorporate other methods into the assessment of cardiac function, such as echocardiography and cardiac magnetic resonance imaging, that can provide more comprehensive data on cardiac response kinetics; high-sensitivity troponin T, which has a more stable course of change, might be used for cardiac response assessment alone or in conjunction with other cardiac response indicators.

Based on the currently observed cardiac response kinetics, in terms of the underlying mechanisms, a large part of the generation of early cardiac response may originate from the decline of FLC in blood, which relieves the myocardial toxicity of FLC. Cardiac response gradually enters a plateau phase because a portion of the amyloid deposits are difficult to remove. This suggests that removal of amyloid will be an important therapeutic development in the future. Emerging therapies currently in clinical trials (CAEL-101, Birtamimab) directly targeting light chains may lead to faster and deeper organ response.[15,18]

STUDY LIMITATIONS. First, its retrospective design carries potential selection bias. Second, only patients who achieved early and high-quality hematological response were included, and the cardiac response dynamics of patients who experienced early death or PR_H were not studied. Third, as the current definition of clinical progression is not well defined, the impact of cardiac response dynamics was assessed only in terms of overall survival rather than progression-free survival. Besides, although cardiac response has been assessed with BNP in patients with impaired renal function, it is undeniable that BNP is also inevitably affected by renal insufficiency, and that the assessment of efficacy in patients whose renal function

deteriorates during the course of treatment is compromised to some extent. Last, the number of patients with cardiac progression in this cohort limited our ability to assess whether a hematological rapid response could prevent early cardiac progression.

CONCLUSIONS

This study is the first to provide a comprehensive review of cardiac response dynamics in a large cohort of AL amyloidosis patients who achieved high-quality hematological response within 3 months after treatment initiation. We introduced the concept of a 24-month plateau and proposed a new treatment target for the duration and depth of cardiac response. Additionally, we found the predictive value of NT-proBNP at 3 months. We advocate the incorporation of new treatment targets into clinical endpoint design and routine clinical practice to better evaluate treatment outcomes for this disease. Finally, this study emphasizes the importance of cardiac response dynamics for disease monitoring and underscores the need for timely modification of antiplasma cell therapy regimens to achieve satisfactory hematological and cardiac responses at different stages of treatment. Future studies may focus on establishing integrated organ response kinetics (heart, kidney, and liver). In addition, the benefit of adjusting antiplasma cell therapies in patients who do not achieve 12-month carPR is worth exploring. In addition, echocardiography, cardiac magnetic resonance imaging, and troponin might help to analyze the cardiac response kinetics more comprehensively.

ACKNOWLEDGMENTS The authors thank Dr Gao Yajuan for patient follow-up and Dr Han Hongxiao for helpful discussions.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by the National Natural Science Foundation of China (Grant No. 82200230 to Dr Shen); the CAMS Innovation Fund for Medical Sciences (Grant No. 2022-I2M-C&T-B-013 to Dr Li); and the National High Level Hospital Clinical Research Funding (Grant No. 2022-PUMCH-C-051 to Dr Li). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS cardiac response dynamics, immunoglobulin light chain amyloidosis, NT-proBNP, retrospective study

APPENDIX For supplemental tables and figures, please see the online version of this paper.