

## Revised Prognostic Staging System for Light Chain Amyloidosis Incorporating Cardiac Biomarkers and Serum Free Light Chain Measurements

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### A B S T R A C T

#### Purpose

Cardiac involvement predicts poor prognosis in light chain (AL) amyloidosis, and the current prognostic classification is based on cardiac biomarkers troponin-T (cTnT) and N-terminal pro-B-type natriuretic peptide (NT-ProBNP). However, long-term outcome is dependent on the underlying plasma cell clone, and incorporation of clonal characteristics may allow for better risk stratification.

#### Patients and Methods

We developed a prognostic model based on 810 patients with newly diagnosed AL amyloidosis, which was further examined in two other datasets: 303 patients undergoing stem-cell transplantation, and 103 patients enrolled onto different clinical trials.

#### Results

We examined the prognostic value of plasma cell-related characteristics (ie, difference between involved and uninvolved light chain [FLC-diff], marrow plasma cell percentage, circulating plasma cells, plasma cell labeling index, and  $\beta_2$  microglobulin). In a multivariate model that included these characteristics as well as cTnT and NT-ProBNP, only FLC-diff, cTnT, and NT-ProBNP were independently prognostic for overall survival (OS). Patients were assigned a score of 1 for each of FLC-diff  $\geq$  18 mg/dL, cTnT  $\geq$  0.025 ng/mL, and NT-ProBNP  $\geq$  1,800 pg/mL, creating stages I to IV with scores of 0 to 3 points, respectively. The proportions of patients with stages I, II, III and IV disease were 189 (25%), 206 (27%), 186 (25%) and 177 (23%), and their median OS from diagnosis was 94.1, 40.3, 14, and 5.8 months, respectively ( $P < .001$ ). This classification system was validated in the other datasets.

#### Conclusion

Incorporation of serum FLC-diff into the current staging system improves risk stratification for patients with AL amyloidosis and will help develop risk-adapted therapies for AL amyloidosis.

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### INTRODUCTION

Primary systemic or light chain (AL) amyloidosis is characterized by the presence of monoclonal plasma cells and deposition of immunoglobulin light chain-derived amyloid deposits in various organs.<sup>1,2</sup> The outcome of patients with AL amyloidosis is highly dependent on the spectrum and severity of organ involvement, especially cardiac involvement.<sup>3</sup> However, significant variability exists in outcome among patients with similar clinical presentation, partly related to subjectivity in assessing degree of organ involvement. Although autologous peripheral blood stem-cell transplantation (SCT) can improve the outcome of selected

patients, a majority of patients with amyloidosis are ineligible for this approach because of significant organ involvement.<sup>4-7</sup> Alternative treatments such as melphalan and dexamethasone with or without novel drugs like lenalidomide and bortezomib seem promising.<sup>8-11</sup> Hence, it is important to develop risk classification systems that will allow more accurate assessment of prognosis and potentially help select the optimal therapy. Moreover, appropriate classification will help compare outcomes with currently available therapy regimens that have only been explored in phase II trials, which makes evaluation of their value difficult because of population differences.

Current staging systems or prognostic classification models use serum levels of cardiac troponins

Characteristic	No. of Patients*	Median	Range†
Male sex	810		
No.		508	
%		63	
Performance status (0, 1)	745		
No.		559	
%		75	
Circulating plasma cells	293		
No.		40	
%		14	
Age, years	810	63	48-75
FLC-diff, mg/dL	758	18	2.5-103
Bone marrow plasma cells, %	707	10	4-30
PCLI, %	541	0	0-0.6
$\beta_2$ -microglobulin, $\mu$ g/mL	720	3	1.9-7.5
cTnT, ng/mL	810	0.025	0-0.16
NT-proBNP, pg/mL	810	1,800	80-13,000
Ejection fraction, %	751	62	40-72
Septal thickness, mm	746	14	10-18
Serum uric acid, mg/dL	700	6.5	4.2-9.9
Serum creatinine, mg/dL	785	1.1	0.8-2.2
Serum albumin, g/dL	800	2.8	1.6-3.5
Total bilirubin, mg/dL	765	0.6	0.1-12.5
Serum carotene, $\mu$ g/dL	625	129	59-267

Abbreviations: cTnT, cardiac troponin T; FLC-diff, free light chain difference; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCLI, plasma cell labeling index.  
 \*Patients with data available.  
 †10th to 90th percentiles.

(ie, troponin T [cTnT] or I) as well as brain natriuretic peptide (BNP) and its N-terminal propeptide (NT-ProBNP).<sup>12-15</sup> Given the significant impact of cardiac involvement on outcome, it is not surprising that markers of cardiac injury and dysfunction have emerged as powerful prognostic factors in AL amyloidosis.<sup>14,15</sup> Cardiac muscle injury results in release of the troponins, which provides a sensitive and specific marker of cardiac injury. NT-ProBNP is released from myocardial cells in response to increased wall stress, and levels increase with both asymptomatic and symptomatic left ventricular dysfunction, making it a useful tool in the diagnosis of cardiac failure and a

strong prognostic factor in congestive heart failure.<sup>16</sup> However, the underlying abnormality in AL amyloidosis is the clonal plasma cell, which is the source of the amyloidogenic light chain deposited in the tissues.<sup>17,18</sup> Although measurements of organ involvement may predict for the short-term outcome in these patients, long-term outcomes are more likely to be determined by factors related to the underlying clonal disorder. Here we show that a staging system incorporating both cardiac biomarkers and level of amyloidogenic light chain synthesis can help explain the heterogeneity in outcome seen among patients with AL amyloidosis and form the basis for development of risk-adapted treatment strategies for this disorder.

## PATIENTS AND METHODS

### Study Population

We identified 810 patients with AL amyloidosis seen at our institution within 90 days of diagnosis who had results available for serum cTnT and NT-ProBNP and were thus classifiable by the current staging system. Clinical and laboratory data were extracted from a prospectively maintained database, and detailed follow-up was available for all patients. In a proportion of patients, serum immunoglobulin free light chain (FLC) assay and assays for cTnT and NT-Pro-BNP were performed on archived specimens as part of previous studies.<sup>12,17</sup> We then examined two additional sets of patient data to further evaluate the new prognostic model; one was a group of 303 patients who underwent SCT (using the laboratory values from the pretransplantation period); the other was a group of 103 patients enrolled onto three different clinical trials (again using laboratory measurements from the time of trial enrollment).<sup>10,19,20</sup> The Mayo Foundation Institutional Review Board approved the study, and all patients consented to have their medical records reviewed according to institutional review board practices and Health Insurance Portability and Accountability Act guidelines.

### Laboratory Methods

Serum FLC was determined using the Freelite assay (Binding Site, Birmingham, United Kingdom) per manufacturer guidelines, as previously described.<sup>21</sup> Normal range for kappa FLC is 0.33 to 1.94 mg/dL; lambda, 0.57 to 2.63 mg/dL; and FLC ratio (ie, kappa to lambda ratio), 0.26 to 1.65. The clonal FLC burden was measured as the FLC difference (FLC-diff), which is not affected by extremely low (suppressed) kappa or lambda measurements that tend to skew the ratio and is therefore more reproducible. cTnT was measured with a sensitive fourth-generation assay (Roche Diagnostics, Indianapolis, IN; normal, < 0.01 ng/mL). NT-ProBNP levels were measured with an automated double-incubation sandwich assay (Roche Diagnostics; normal, < 171 pg/mL).  $\beta_2$ -microglobulin was measured using standard assays (normal range,

**Table 2.** Results of Univariate and Multivariate Analyses of Various Prognostic Factors

Prognostic Factor	Comparison	No. of Patients*	Univariate		Multivariate 1†		Multivariate 2‡	
			Risk Ratio	P	Risk Ratio	P	Risk Ratio	P
FLC-diff, mg/dL	> 18 v $\leq$ 18	758	1.6	< .001	1.4	.01	1.4	.002
Plasma cells, %	> 10 v $\leq$ 10	707	1.5	< .001	1.2	.2	NI	NA
PCLI, %	> 0 v 0	541	1.3	.009	1.3	.09	NI	NA
$\beta_2$ -microglobulin, mg/dL	> 3 v $\leq$ 3	720	1.9	< .001	1.5	< .01	NI	NA
Circulating plasma cells	Yes v no	293	1.5	.08	NI	NA	1.2	.1
cTnT, ng/mL	> 0.03 v $\leq$ 0.03	810	3.0	< .001	NI	NA	2.4	< .001
NT-proBNP, pg/mL	> 1,800 v $\leq$ 1,800	810	2.3	< .001	NI	NA	1.4	.004

Abbreviations: cTnT, cardiac troponin T; FLC, free light chain; FLC-diff, free light chain difference; NA, not applicable; NI, not included in model; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCLI, plasma cell labeling index.

\*Patients with data available for the variable.

†Model examining plasma cell clone-related characteristics.

‡Model examining FLC and cardiac biomarkers.

0.7 to 1.8  $\mu\text{g}/\text{mL}$ ). Presence of circulating plasma cells was determined using flow cytometry using antibodies to surface CD138 and CD38.<sup>22</sup> Plasma cell labeling index (PCLI) is a measure of plasma cell proliferation and was determined via a slide-based assay that uses bromodeoxy uridine uptake by the dividing plasma cells, as described before.<sup>23</sup>

### Statistical Analysis

The continuous variables were dichotomized using their median value for the current analysis. Cox proportional hazards analysis was used to identify factors that were prognostic for overall survival (OS). OS was defined as the time from diagnosis to death, with patients alive at the time of last follow-up censored at that date. For the transplantation cohort, OS was defined as the time from SCT until death, with those alive censored at the date of last follow-up. For the clinical trial cohort, OS was defined as the time from study enrollment until death, with those alive censored at the date of last follow-up. Survival curves were constructed according to the Kaplan-Meier method, and the survival curves were compared using log-rank test. Fisher's exact test was used to test differences in nominal variables. Differences in continuous variables between groups were compared using Wilcoxon signed rank test. All analyses were performed using JMP 9.0 (SAS, Cary, NC).

## RESULTS

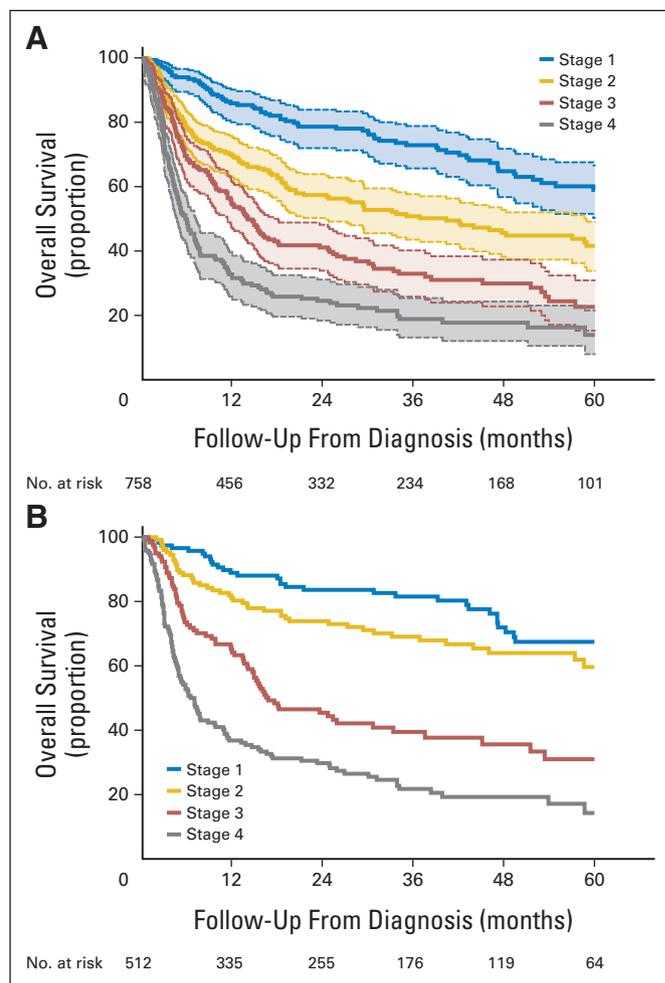
Baseline characteristics of the 810 patients included in the current study are listed in Table 1. The median age was 63 years (range, 26 to 89 years); 508 (63%) were men. The median estimated follow-up for the entire cohort was 52 months (95% CI, 48 to 56). At the time of last follow-up, 318 patients (39%) were alive, with a median follow-up of 42 months.

### Identification of Prognostic Variables

We considered the following plasma cell clone-related characteristics: FLC-diff, maximum bone marrow plasma cell percentage on aspirate or biopsy,  $\beta_2$ -microglobulin, PCLI, and presence or absence of circulating plasma cells. Of these, serum FLC and circulating plasma cells have previously been described to have prognostic value in AL amyloidosis.<sup>17,24</sup> Median values were used to dichotomize continuous variables: FLC-diff, 18 mg/dL;  $\beta_2$ -microglobulin, 3.0 mg/dL; PCLI, 0%; and bone marrow plasma cell percentage, 10%. Although all the variables except for presence of circulating plasma cells were significant predictors of OS in univariate analysis, in a multivariate analysis model, only FLC-diff and  $\beta_2$ -microglobulin were independently prognostic. We also examined the prognostic value of previously described cardiac prognostic markers cTnT and NT-ProBNP, using the median values of 0.025 ng/mL and 1,800 pg/mL, respectively, for cutoffs; both were independently prognostic for OS. In a multivariate model that included these two factors along with FLC-diff and  $\beta_2$ -microglobulin, only cTnT, NT-ProBNP, and FLC-diff were independently predictive of OS. The hazard ratios associated with these variables in univariate and multivariate analyses are listed in Table 2.

### Development of a Prognostic Model

We assigned a score of 1 for each of the three prognostic variables (cTnT  $\geq$  0.025 ng/mL, NT-ProBNP  $\geq$  1,800 pg/mL, and FLC-diff  $\geq$  18 mg/dL); this was used to divide patients into four stages (I, II, III, and IV) with scores of 0, 1, 2, and 3, respectively. Fifty-two patients did not have FLC results available and were excluded from the final model development, leaving 758 patients. The numbers of patients with stages I, II, III, and IV disease were 189 (25%), 206 (27%), 186 (25%), and 177 (23%), respectively. The median OS from diagnosis for those



**Fig 1.** (A) Kaplan-Meier curves for overall survival (OS) from diagnosis among 758 patients based on the new staging system; shaded areas indicate the 95% CI estimates. (B) Kaplan-Meier curves for OS from diagnosis among 512 patients based on the staging system, substituting B-type natriuretic peptide for N-terminal pro-B-type natriuretic peptide. (A, B) Patients surviving beyond 5 years were censored at the 5-year mark. Numbers of patients at risk at each time point are shown below the x-axis. Survival curves were compared using log-rank test.

with stages I, II, III, and IV disease was 94.1 months (95% CI, 64 to 154), 40.3 months (95% CI, 24 to 59), 14.0 months (95% CI, 11 to 18), and 5.8 months (95% CI, 5 to 7), respectively ( $P < .001$ ). The 5-year survival estimates for those with stages I, II, III, and IV disease were 59%, 42%, 20%, and 14% respectively (Fig 1A).

Given that BNP levels are used at some institutions in place of NT-ProBNP and have been shown to have prognostic value similar to that of NT-ProBNP, we also evaluated the model using BNP in place of NT-ProBNP. The median value of 400 ng/mL was used as the cutoff. In a similar fashion, we assigned a score of 1 for each of the three prognostic variables (cTnT, BNP, and FLC-diff), and the sum of the scores was used to divide the patients into four stages (I, II, III, and IV) with scores of 0, 1, 2, and 3, respectively. There were 512 patients with all three variables available for analysis, with 121 (24%), 128 (25%), 119 (23%), and 144 (28%) of the patients in stages I, II, III, and IV, respectively. The median OS from diagnosis for those with stages I, II, III, and IV disease was as follows: not reached, 68.8 months (95% CI, 59 to not reached), 16.7 months (95% CI, 14 to 31), and 6.7 months

**Table 3.** Comparison of Baseline Features Between Different Stages

Characteristic	Stage I (n = 189)		Stage II (n = 206)		Stage III (n = 186)		Stage IV (n = 177)		P
	Median	Range*	Median	Range*	Median	Range*	Median	Range*	
Male sex									NS
No.		119		131		114		113	
%		63		64		61		64	
Performance status (0, 1), %		89		81		72		58	< .001
Age, years	61	47-73	62	47-74	66	50-78	63	49-76	< .001
FLC-diff, mg/dL	5.2	1-14	22	4-128	17	5-97	55	22-192	< .001
cTnT, ng/mL	0.01	< 0.01-0.02	0.01	< 0.01-0.06	0.05	0.01-0.2	0.1	0.05-0.3	< .001
NT-proBNP, pg/mL	230	40-1,180	760	60-4,280	3,990	1,070-17,450	8,900	2,890-23,220	< .001
Ejection fraction, %	65	56-75	63	46-73	60	36-71	53	32-67	< .001
Septal thickness, mm	11	9-16	13	10-16	15	11-19	16	12-20	< .001
Serum uric acid, mg/dL	5.7	4-8.5	6.1	4-8	7.1	4.4-10	8.2	5-12	< .001
Serum creatinine, mg/dL	1	0.8-1.7	1	0.8-1.8	1	0.8-2.9	1.1	0.9-3.0	< .001
Serum total bilirubin, mg/dL	0.5	0.2-1	0.5	0.3-1.3	0.6	0.3-1.4	0.8	0.3-1.8	< .001
Serum carotene, $\mu$ g/dL	164	78-347	121	60-235	131	59-271	97	49-183	< .001
Serum albumin, g/dL	2.6	1.4-3.7	2.9	1.7-3.6	2.8	1.7-3.4	3	2-3.5	.001

Abbreviations: cTnT, cardiac troponin T; FLC-diff, free light chain difference; NS, not significant; NT-proBNP, N-terminal pro-B-type natriuretic peptide.  
\*10th to 90th percentiles.

(95% CI, 5 to 10), respectively ( $P < .001$ ). The 5-year survival estimates for those with stages I, II, III, and IV disease were 68%, 60%, 27%, and 14%, respectively (Fig 1B). Given the impact of renal function on NT-ProBNP, we also examined the prognostic value of the variable according to serum creatinine. Among those patients with creatinine  $\leq 1.5$  mg/dL, median OS for patients with NT-ProBNP  $\geq 1,800$  pg/mL was 10.5 months, compared with median not reached for those with NT-ProBNP  $< 1,800$  pg/mL. Among patients with creatinine  $> 1.5$  mg/dL, median OS for those with NT-ProBNP  $\geq 1,800$  pg/mL was 11.3 months, compared with 44 months for those with lower NT-ProBNP.

Next, we compared the distribution of baseline characteristics across the four stages. As summarized in Table 3, there was increasing organ involvement, increasing tumor burden, and decreasing performance status across the five groups.

### Validation of the Prognostic Model

We first examined the staging system in the subgroup of patients who did not receive a transplant or were enrolled onto any of the clinical trials (n = 583). The numbers of patients with stages I, II, III, and IV disease were 125 (22%), 144 (25%), 160 (27%), and 154 (26%), respectively. The median OS for those with stages I, II, III, and IV disease was 55, 19, 12, and 5 months, respectively ( $P < .001$ ; Fig 2A). We then evaluated the staging system in two other clinical settings, both later in the course of disease and reflecting two different treatment strategies. First, we examined the outcome among 303 patients undergoing high-dose chemotherapy and autologous SCT for AL amyloidosis who had all three variables available from the time of SCT. The numbers of patients with stages I, II, III, and IV disease were 129 (43%), 87 (29%), 49 (16%), and 38 (13%), respectively. The proportions of patients in the lower stages were higher in the transplantation population compared with the distribution at diagnosis, as would be expected given the careful selection of patients for this procedure. The median OS was not reached for those with stage I disease, and it was 96.5, 58.2, and 22.2 months for those with stages II, III, and IV disease, respectively ( $P < .001$ ). The 4-year OS estimates were 87%, 72%, 56%,

and 46% for those with stages I, II, III, and IV disease, respectively (Fig 2B).

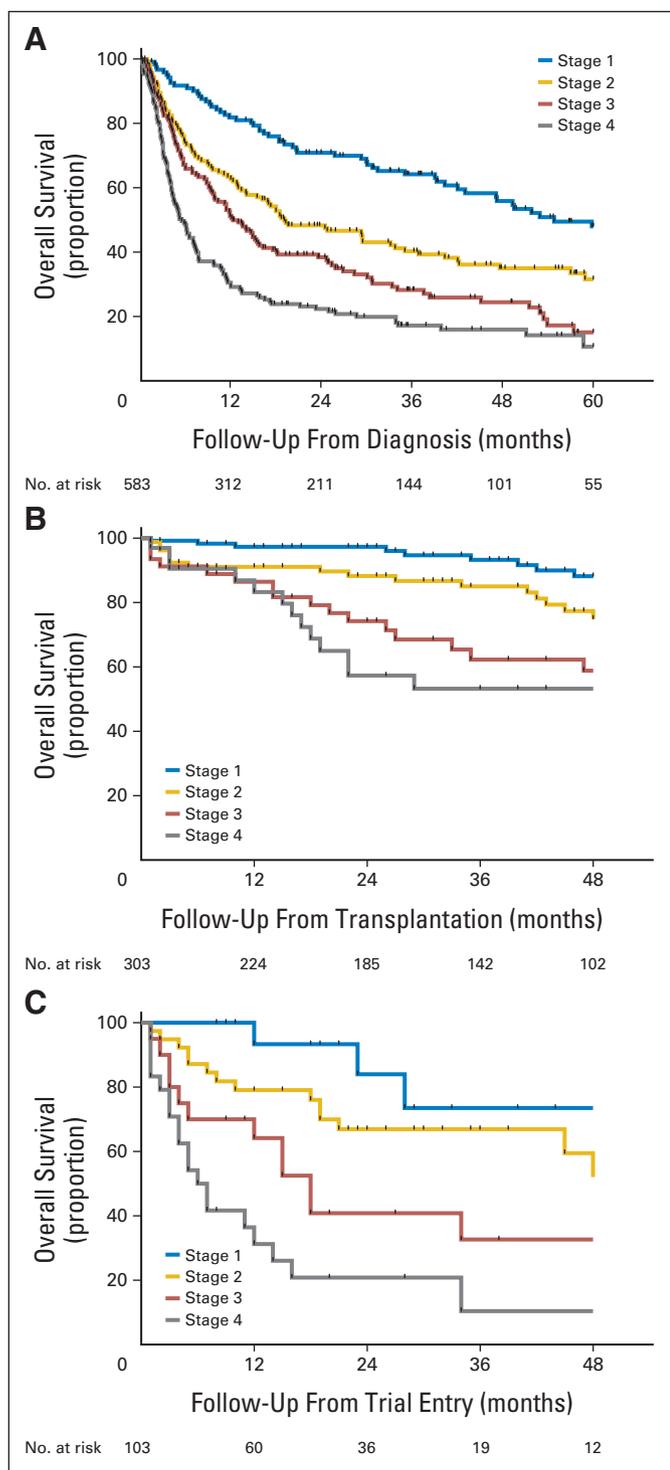
The staging system was then applied to a group of 103 patients who were enrolled onto three different clinical trials, evaluating lenalidomide with or without dexamethasone; cyclophosphamide, lenalidomide, and dexamethasone; and pomalidomide and dexamethasone. Laboratory values from the time of the study entry were used to stage these patients. There were 18%, 38%, 20%, and 24% of patients with stages I, II, III, and IV disease, respectively. The median OS from the time of study entry was not reached for patients with stage I and was 62.8, 16.8, and 5.8 months for patients with stages II, III, and IV disease, respectively ( $P < .001$ ). The 4-year survival estimates were 73%, 52%, 31%, and 10% for patients with stages I, II, III, and IV disease, respectively (Fig 2C).

### Comparison With Older Staging System

We then examined how the new system grouped patients in each of three stages of the previous staging system using cTnT and NT-ProBNP. The proportions of patients grouped by the previous staging system, subgrouped further by the new system, and their respective 5-year survival outcomes are listed in Table 4. As demonstrated in this analysis, the new system was able to identify patients with different outcomes from among the previous stage groups.

## DISCUSSION

AL amyloidosis is characterized by a relatively low burden of clonal plasma cells and involvement of multiple organs by immunoglobulin light chain–derived amyloid fibrils.<sup>2,25</sup> The outcome of patients with AL amyloidosis is heterogeneous, with nearly 40% of patients succumbing to advanced organ involvement in the first year after diagnosis.<sup>26</sup> Although the median OS from diagnosis among all patients is approximately 1 year, OS is significantly better among those who are alive at 1 year from diagnosis. It is clear that different factors determine outcomes early in the course of the disease compared with later. The



**Fig 2.** (A) Kaplan-Meier curves for overall survival (OS) from diagnosis among the subgroup of 583 patients based on the new staging system. Patients surviving beyond 5 years were censored at the 5-year mark. (B) Kaplan-Meier curves for OS from stem-cell transplantation among 303 patients based on the new staging system. Patients surviving beyond 4 years were censored at the 4-year mark. (C) Kaplan-Meier curves for OS from time of trial entry among 103 patients enrolled onto different trials based on the new staging system. Patients surviving beyond 4 years were censored at the 4-year mark. (A, B, C) Numbers of patients at risk at each time point are shown below the x-axis. Survival curves were compared using log-rank test.

spectrum and severity of organ involvement, especially cardiac involvement, usually dictate early outcome, with cardiac biomarkers such as cTnT, NT-ProBNP, and serum uric acid strongly predicting for 1-year mortality.<sup>12,26</sup> However, the long-term outcome of patients with AL amyloidosis is likely to depend more on the progression of organ involvement, which in turn will depend on the progression of synthesis of amyloidogenic FLC.<sup>18,27,28</sup> We have previously shown that serum FLC is a powerful prognostic feature in patients with AL amyloidosis.<sup>17</sup> In addition, we have also shown that other plasma cell clone-related factors such as the proliferation rate of plasma cells and presence of plasma cells in the peripheral circulation have prognostic value in this disease.<sup>24,29</sup>  $\beta_2$ -microglobulin is an important prognostic factor in myeloma, part of the International Staging System, and often considered a surrogate marker of tumor burden.<sup>30</sup> In the current study, we explored additional plasma cell-related characteristics to determine if these would allow us to explain some of the heterogeneity seen in patient outcome.

As expected, we found several plasma cell clone-related factors to be highly prognostic for outcome in this disease, underscoring the impact of the plasma cell clone on eventual outcome. In addition to the previously described factors, we showed that the plasma cell burden in the marrow and  $\beta_2$ -microglobulin had significant prognostic value, but in the multivariate analysis, which included only factors related to clonal burden, only FLC-diff and  $\beta_2$ -microglobulin were prognostic. Moreover, when considered together with the cardiac biomarkers,  $\beta_2$ -microglobulin lost significance, and only FLC-diff remained significant in terms of plasma cell clone-related characteristics. This is consistent with our previous observations regarding the strong prognostic value of FLC-diff in this disease and its correlation with degree of involvement of various organs.

In the current model, which was developed based on a large cohort of patients with long follow-up, the addition of FLC-diff to the cardiac biomarkers clearly allows better classification of patients in terms of outcome. The new system allows identification of patients with a better outcome from among those grouped in stages I and II in the previous system as well as patients with an outcome worse than previously predicted from among those grouped in stage III. This clearly shows the value of the new model to provide better discrimination of patients, which will allow development, and testing of treatment strategies targeted towards specific patient groups based on risk. The cutoff values for the cardiac biomarkers are different in the current model compared to the previous system. We elected to use the median values in order to divide the patients into equal groups for the current model. Although the cTnT cutoff of 0.025 ng/mL is similar to the 0.035 ng/mL from the previous system, the NT-ProBNP cutoff of 1,800 pg/mL is quite different from the prior value of 332 pg/mL. The cutoff of 332 pg/mL was previously chosen as it was the lower limit of detection for the assay, and it results in the exclusion of the majority of patients with cardiac involvement from stage I. The use of 1800 pg/mL as the cutoff allows better discrimination within the group of patients with cardiac involvement, thus identifying a group of patients with better outcome. As would be expected, there is worsening of the degree of organ involvement, other than cardiac involvement, with advancing disease stage confirming the strong relationship between severity of organ involvement and survival.

We have further validated the model system in two sets of patients receiving different types of therapy and with more advanced disease stage. The ability to predict outcome among patients undergoing

**Table 4.** Comparison of the New and Previous Staging Systems Using cTnT and NT-ProBNP

New Stage	Previous Stage I			Previous Stage II			Previous Stage III		
	No. of Patients	Median OS	95% CI	No. of Patients	Median OS	95% CI	No. of Patients	Median OS	95% CI
Entire group	—	86	60 to 106	—	43	31 to 69	—	7.3	6 to 11
I	112	93.6	60 to 154	77	97.7	43 to NR	—	0	
II	47	61.6	44 to 124	130	29.4	18 to 77	29	11.5	4 to 40
III	—	0		64	26.8	11 to 45	122	13.2	9 to 15
IV	—	0		—	0		176	6	5 to 7

Abbreviations: cTnT, cardiac troponin T; NR, not reached; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OS, overall survival.

SCT is particularly important, because this patient group typically represents those with limited organ involvement and relatively preserved performance status. Although the OS of this group of patients was better compared with the other two sets studied, the model was able to classify patients into groups with different outcomes. This will allow exploration of alternate treatment strategies among the higher-risk patients. Finally, the system still retains its ability to predict outcome among a patient group, albeit smaller, with more advanced disease undergoing non-SCT-based treatments often later in the course of their disease. These results highlight the wide applicability of this system.

In conclusion, we have improved on the previous prognostic staging system using biomarkers by incorporating serum FLC measurements into the system. This revised Mayo staging system for AL amyloidosis allows us to better discriminate between groups with different outcomes, enabling better prognostic classification. The model seems to be generalizable to a wide spectrum of patients, which should encourage routine incorporation into clinical trials, thus allowing better comparison of results from different trials.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject

matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

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