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Limited utility of Mayo 2012 cardiac staging system for risk stratification of patients with advanced cardiac AL amyloidosis - analysis of a uniformly treated cohort of 1,275 patients

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Systemic light chain (AL) amyloidosis is a rare incurable disorder caused by extracellular deposition of misfolded light chain protein fibrils causing organ dysfunction. Cardiac involvement is present in approximately two thirds of cases at diagnosis. Survival depends largely on the severity of cardiac involvement as well as haematologic response to treatment (1, 2). Two validated cardiac staging systems, Mayo 2012 (stage I-IV) (3) and European modification of the standard Mayo staging system 2004 (stage I-IIIb) (4, 5), stratify patients according to different thresholds of biomarkers of disease involvement. The Mayo 2012 model divides patients based on three biomarkers: high-sensitivity troponin T□<40□ng/L, NT-proBNP□<1800□pg/mL, and serum difference between involved and uninvolved free light chain (dFLC) <180□mg/L. The European modification of Mayo 2004 stratifies patients based on two biomarkers: high-sensitivity troponin T□<50ng/L and NT-proBNP□<332□ng/L with stage III sub-classified into two sub-stages using NT-proBNP at 8500□ng/L cut off. Patients included in these original models were not treated with a uniform induction chemoimmunotherapy protocol and treated with regimens such as oral melphalan dexamethasone, which are now rarely used. There is a need to re-assess the predictive performance and robustness of these staging systems with current treatment approaches. We report here the comparison of cardiac staging in a large cohort of 1275 patients with AL amyloidosis uniformly treated with bortezomib-containing regimens in the first-line setting from the ALchemy study.

Patients enrolled in a prospective observational study at the United Kingdom National Amyloidosis Centre treated with bortezomib-based regimens from 2010–2019 were analysed. Diagnosis of AL amyloidosis was confirmed by histology and typed with immunohistochemistry or mass spectrometry, or if not available, for patients with biopsy confirmed amyloidosis and cardiac involvement alone, if they also had a negative DPD-Tc99m bone scan. Written consent was obtained from all patients in accordance with the Declaration of Helsinki.

Haematologic responses were assessed by investigators as per consensus criteria (6). Overall survival (OS) was defined as time from diagnosis to death from any cause or last follow-up. OS estimates

were generated using the Kaplan-Meier method and groups were compared using Cox regression and the log-rank test. Outcomes were stratified according to Mayo 2012 and the European modified classification. Discrimination of models was evaluated using Harrell's C concordance statistic, estimating the proportion of all pairs sampled whose predicted outcomes follow the order of the observed outcomes. Sensitivity and specificity analysis were performed at 6 months, 1 year, 2 years and 5 years. Statistical analyses were conducted using STATA v18 (STATAcorp, Texas).

1275 patients (755 male, 520 female) were included. Median age at presentation was 67 years (range 29-89), with a median of two involved organs (range 1-5); 812 (64%) had cardiac involvement, 892 (70%) renal and 154 (12%) liver involvement. All patients were treated with first-line bortezomib-based therapy: bortezomib-cyclophosphamide-dexamethasone in 1190 [93%]; bortezomib-dexamethasone in 48 [4%]; bortezomib-thalidomide-dexamethasone in 21 [2%] and 16 other bortezomib combinations. None were treated with a daratumumab-based combination or autologous stem cell transplant (ASCT) upfront; 95 (7%) had ASCT at a subsequent line of therapy. Patients were classified by Mayo 2012 staging as: stage I, II, III, IV in 199 (16%), 329 (26%), 413 (32%) and 334 (26%) cases, respectively and by European modified staging as: stages I, II, IIIa and IIIb in 219 (17%), 436 (34%), 424 (33%) and 196 (15%), respectively.

The median follow-up was 76 months (95% confidence interval [CI] 72-79), median OS was 82 months (95% CI 65-110) and 3-year OS was 60% (95% CI 57-63). Whilst both Mayo 2012 and European modification models were predictive of OS, the European modification discernibly discriminated those with the poorest outcomes (figure 1a-b). Median OS by European staging for stage I, II, IIIa, IIIb was: not reached (NR), NR, 36 and 7 months respectively, compared with Mayo 2012 stage I, II, III, IV: NR, 137, 37, and 26 months respectively. European stage II, IIIa, IIIb had a hazard ratio (HR) for death of: 2.24 (95% CI 1.61-3.12), 4.13 (95% CI 2.99-5.69) and 8.22 (95% CI 5.86-11.52), respectively. Mayo stage II, III, IV had a HR of: 2.26 (95% CI 1.57-3.26), 4.18 (95% CI 2.97-5.90) and 5.33 (95% CI 3.77-7.53), respectively (table 1).

Both staging systems were able to re-divide stages of the other system, identifying patients with better or worse outcomes. The proportions and median OS are reported according to each stage of the European modified staging systems and sub-grouped further by the Mayo 2012 staging system (table 2). 59 (18%), 153 (46%) and 122 (37%) of Mayo 2012 stage IV were European stage II, IIIa and IIIb, respectively. Strikingly, median OS in those with Mayo IV ranged from 5-74 months when stratified by European staging. Median OS of those with Mayo IV with NT-proBNP $\geq$8500 ng/L compared with those <8500 ng/L was 58 months (95% CI 34-86) vs 5 months (94% CI 3-8) (log-rank p<0.001) (figure 1c). There was no interaction of dFLC with European stage (p=0.31). The values of Harrell's C were 0.64 (95% CI 0.62-0.66) and 0.68 (95% CI 0.66-0.70) for Mayo and European models, indicating the models correctly ordered survival times for pairs of patients 64% and 68% of the time, respectively. Sensitivity and specificity at 6 months, 1 year and 5 years timepoints were 46.3%/78.3%, 41.6%/79.1% and 35.5%/81.8% for Mayo IV and 38.9%/89.8%, 37.0%/92.0% and 25.5%/93.3% for European IIIb (supplementary table 1).

Current treatments in AL amyloidosis are aimed at eliminating the underlying plasma cell clone with anti-plasma cell therapies to reduce the production of light chains. The seminal ANDOMEDA trial lead to global approval of daratumumab-cyclophosphamide-bortezomib-dexamethasone (dara-VCD) in the management of newly diagnosed patients with AL amyloidosis showing superior responses to those treated with standard cyclophosphamide-bortezomib-dexamethasone (7). Dara-VCD is now considered the standard of care for patients with European modified stage I-IIIa. However, patients with advanced cardiac involvement (stage IIIb) were excluded and therefore are treated with alternative approaches or dose attenuation.

The European modification was derived from 346 patients with Mayo stage III disease from four European centres (UK, Italy, Germany, Greece) from 2001-2010. The most frequent regimen was oral melphalan-dexamethasone (44%) followed by thalidomide combination (28%) with only 23 (7%) patients receiving a bortezomib combination. The chemotherapy regimens used in the total of 810

patients that the Mayo 2012 model was based varied, including 583 without upfront ASCT or clinical trials, and then separately with 303 patients with high dose chemotherapy and ASCT upfront and 103 patients enrolled in clinical trials of lenalidomide-dexamethasone, cyclophosphamide-lenalidomide-dexamethasone and pomolidomide-dexamethasone (3). EMN23, the largest retrospective observational study of patients with systemic AL amyloidosis, showed changes in treatment regimens delivered over the last decade in Europe (8). Bortezomib-based regimens are now the standard front-line treatment with only rare patients treated with alkylators alone or immunomodulatory agent-based regimens. Improved outcomes were observed in all stages, except for patients with cardiac European stage IIIb disease with a median OS around 5 months. This remains an area of unmet need.

With two different staging systems in use for risk stratification of AL amyloidosis, there is potential for stage to be confounder. It is often assumed that European stage IIIb and Mayo 2012 stage IV denote the same or similar groups of patients from a prognostic perspective with the former being widely used in Europe and latter in the USA. This has become increasing crucial as there is increasing clinical trial focus on this poor risk group of patients. International consensus guidelines recommend the enrolment of all eligible patients into clinical trials (9) and therefore it is essential that clinical trial endpoints are robust and meaningful. Post-hoc analysis of the phase III VITAL study suggested improved outcomes in the Mayo stage IV subgroup with the anti-fibril antibody, birtamimab (10). Further results in phase III trials of anti-fibril antibodies are awaited (CAEL101-301: NCT04504825 in European modification stage IIIb patients; AFFIRM-AL: NCT04973137 in Mayo stage IV patients).

Our data demonstrates that advanced stage cardiac involvement remains a prognostic predictor of adverse outcomes. In our cohort of bortezomib-treated patients, the European modification was more discriminatory for poorer outcome, as reported elsewhere with heterogenous treatment regimens (11, 12). In our cohort, the European modification had a higher concordance probability and stage IIIb had a greater specificity at all time points (6 months, 1 year, 2 years, 5 years) compared with Mayo IV. This implies most patients classified as high risk by stage IIIb will have an event by that

point and lead to a higher positive predictive value for death. Those with European IIIb have the poorest outcomes despite modern treatment of recent decades (8) and still represent the true unmet treatment need. Even Mayo 2012 stage IV patients are further discriminated by NT-proBNP < or > 8500 ng/L threshold. This is particularly critical in clinical trials to correctly identify the high-risk patients. The importance in clinical practice is to avoid inappropriate or unnecessary alternative treatment approaches in those that are not truly high risk. Although specificity is poor and sensitivity low, the higher sensitivity of Mayo IV implies its ability to identify more patients who have an event – this may still reflect the impact of the high dFLC and the clonal biology which is not captured in the European modification. The needs to be further explored and may be critical to trial designs where maintenance or longer term treatment approaches are studied.

It has been suggested that the Mayo 2012 staging system predicts late survival more accurately and the European modification predicts early mortality; the current data confirm these observations. The Mayo system gives equal weighting to plasma cell burden (dFLC) and each cardiac biomarker. The relative importance of cardiac organ function may reduce over time in those that survive beyond the critical 6-12 months. A 3-year landmark analysis showed an increase in relative likelihood of correct survival prediction for Mayo 2012 vs European modification of 7% (n=457), but only 3.5% at 1 year landmark (n=688) and overall the European staging system had an increase of 3% for the entire cohort when compared with Mayo (n=1005) (13). Our current analysis raises serious concerns regarding interchangeability of the staging systems and impact of therapies on the reliability of the models. The Mayo 2012 staging, utilising additional dFLC, did not discriminate the most advanced disease as well suggesting that treatment markedly impacts the predictive capability of cardiac staging systems. Amyloidogenic light chains in amyloidosis have been shown to induce cell stressors which are highly sensitive to proteasome inhibition, more so than those produced by myeloma plasma cells (14). In the era of bortezomib-treated patients with more effective therapy (8), the dFLC appears less prognostic. This may be a significant factor in the performance of staging systems.

Given the results of ANDROMEDA, daratumumab-based treatments may have an even greater impact in ameliorating the adverse prognostic significance of high presenting dFLC.

Limitations of this study include the lack of complete datasets for all patients at baseline. Our data represents a UK population uniformly treated and should be replicated in other populations.

These data should be taken into consideration when using cardiac staging systems in the clinic as well as for clinical trial design. Additionally, functional data from echocardiography and cardiac magnetic resonance imaging are important for assessing patients outcomes in AL amyloidosis. There is a need to update AL staging incorporating these new observations.

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Table 1. Overall survival by staging system

	n	Median OS (95% CI)	HR (95% CI)	p value*
Mayo 2012				
Stage I	199	NR	Reference	<0.001
Stage II	329	137 (137-NR)	2.26 (1.57-3.26)	
Stage III	413	37 (31-58)	4.18 (2.97-5.90)	
Stage IV	334	26 (16-34)	5.33 (3.77-7.53)	
European modification				
Stage I	219	NR (137-NR)	Reference	<0.001
Stage II	436	NR (111-NR)	2.24 (1.61-3.12)	
Stage IIIa	424	36 (31-52)	4.13 (2.99-5.69)	
Stage IIIb	196	7 (6-10)	8.22 (5.87-11.53)	

*Log-rank test for trend

p<0.001 for all levels European Stage I v II, II v IIIa, IIIa v IIIb; Mayo I v II, II v III. III v IV (p=0.0019)

Table 2. Comparison of Mayo 2012 and European modification staging systems

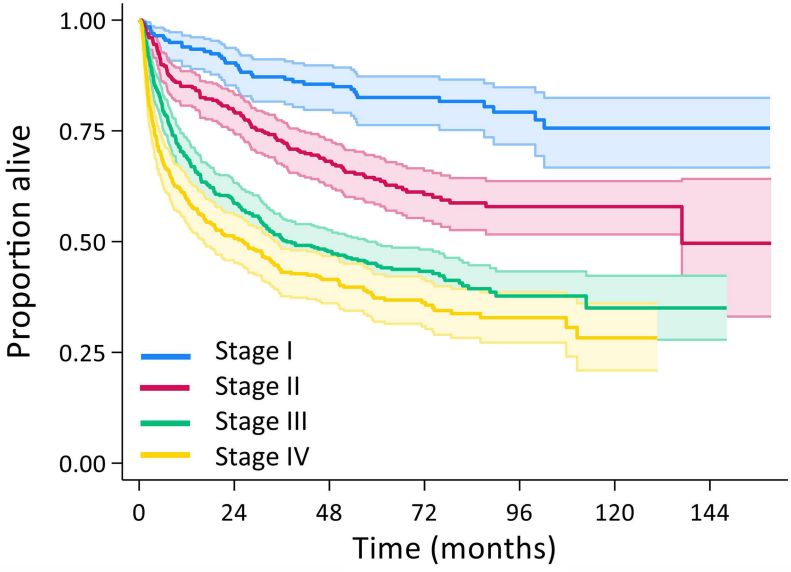
	Mayo I			Mayo II			Mayo III			Mayo IV		
European	n	Median OS	95% CI	n	Median OS	95% CI	n	Median OS	95% CI	n	Median OS	95% CI
Entire group	-	NR	-	-	137	137-NR	-	37	31-58	-	26	16-34
I	125	NR	-	80	137	NR	14	83	25-NR	-	-	-
II	74	NR	102-NR	159	NR	NR	144	77	49-NR	59	74	45-NR
IIIa	-	-	-	90	46	31-62	181	30	19-60	153	43	29-62
IIIb	-	-	-	-	-	-	74	11	8-24	122	5	3-8

NR, not reached

Figure 1

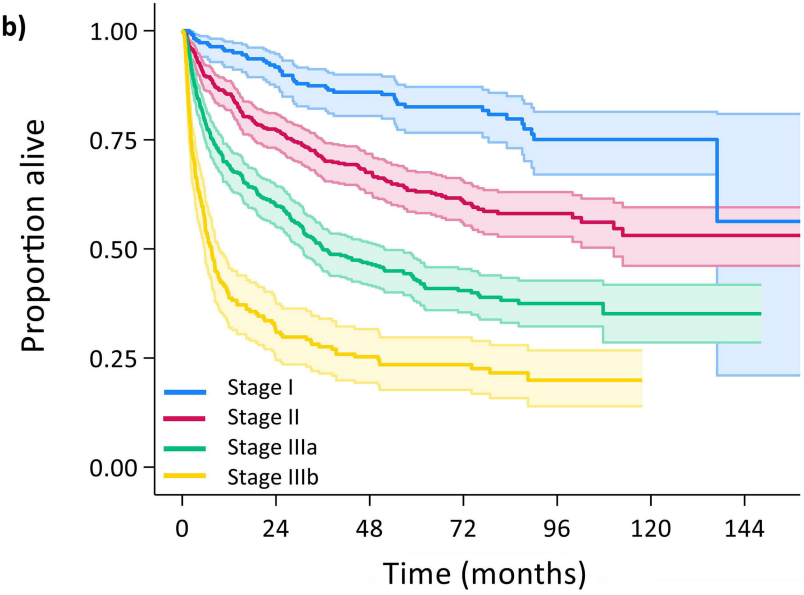
Overall survival by staging system a) Overall survival by Mayo 2012 staging b) Overall survival by European modified staging c) Mayo IV stratified by NTproBNP 8500ng/L threshold

a)



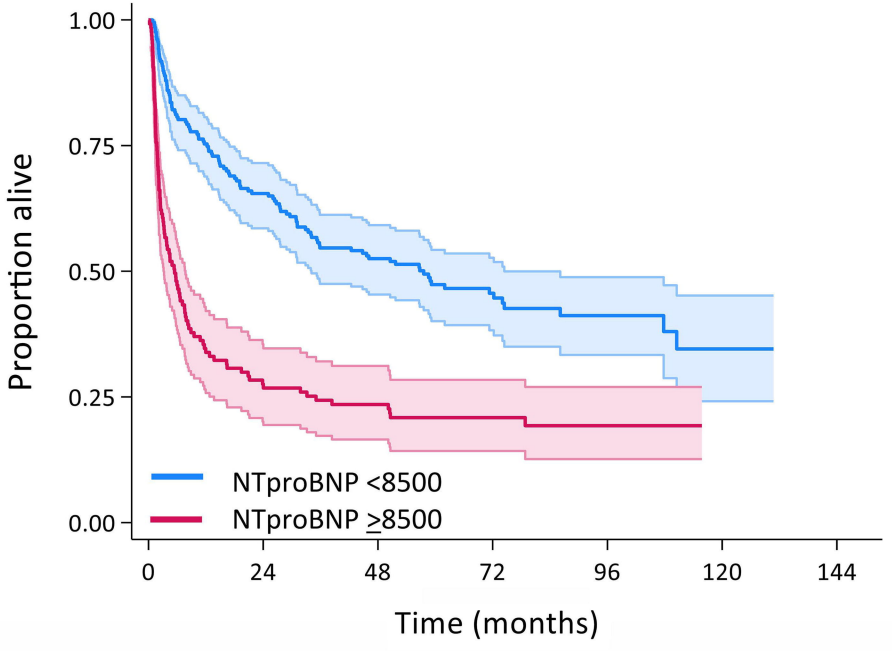
Number at risk							
Stage I	199	173	152	100	54	18	2
Stage II	329	249	195	104	49	13	1
Stage III	413	228	172	95	35	6	1
Stage IV	334	165	126	63	22	5	0

b)



Number at risk							
Stage I	219	195	169	105	49	15	2
Stage II	436	319	259	147	70	19	1
Stage IIIa	424	242	173	84	33	8	1
Stage IIIb	196	59	44	26	8	0	0

c)



Number at risk							
NTproBNP <8500	207	130	98	48	19	5	0
NTproBNP ≥8500	127	35	28	15	3	0	0

Supplementary table 1. Sensitivity and specificity for Mayo Stage IV and European modification stage IIIb

Timepoint	Mayo IV	European IIIb
6 months		
Sensitivity	46.3%	38.9%
Specificity	78.3%	89.8%
1 year		
Sensitivity	41.6%	37.0%
Specificity	79.1%	92.0%
2 years		
Sensitivity	38.8%	31.9%
Specificity	80.0%	92.8%
5 years		
Sensitivity	35.5%	25.4%
Specificity	81.8%	93.3%