The Prognostic Importance of the 6-minute walk test in AL amyloidosis

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Key Points

Question:

What is the value of baseline and post-chemotherapy 6-minute walk test (6MWT) in predicting prognosis in systemic AL amyloidosis?

Findings:

In this prospective observational study, 6MWT was measured at baseline and following chemotherapy finding that baseline 6MWT significantly decreased with worsening cardiac stage and was independent of cardiac Mayo stage in predicting survival. At follow up, only patients in a complete haematological response improved their 6MWT and an improvement in 6MWT of ≥33m was independent of haematological response in predicting survival.

Meanings:

The 6MWT is prognostic in AL amyloidosis both at baseline and following cytotoxic chemotherapy

Abstract (348 words/max 350)

Importance

In AL amyloidosis, organ response assessment is based on surrogates (e.g. cardiac biomarkers). An objective functional test, capturing overall clinical improvement, is required and the six-minute walk test (6MWT) has potential to be used for this purpose.

Objective

To validate the prognostic value of the 6MWT in AL amyloidosis at baseline and post-chemotherapy.

Design, Settings and Participants

All patients from a prospective single-centre observational study of newly diagnosed AL amyloidosis conducted at the UK National Amyloidosis Centre (2012-2017), were included.

Main Outcomes and Measures

Overall survival (OS) based on baseline and improvement in 6MWT was assessed and compared to cardiac Mayo staging and haematologic response post-chemotherapy.

Results

Of 799 evaluable patients, 564 (70.6%) had cardiac involvement. Median baseline 6MWT was 362m (0-700m). 6MWT distance progressively decreased with worsening cardiac disease stage (458m, 404m, 331m and 168m for cardiac Mayo stages I, II, IIIa and IIIb respectively ($p<0.0001$)) Median OS was 70.0(56.8-83.2) months. In patients with a baseline 6MWT of ≥300m, median OS was not reached vs. 25.0(18.1-31.9) months if <300m and a median OS of 5.0(2.8-7.2) months ($p<0.0001$) in those unable to attempt the test. On multivariable testing, 6MWT ≥300m independently predicted better outcomes (HR 2.97 [2.38-3.72], $p<0.0001$).

Following chemotherapy, only patients in a complete haematological response (CR) improved between baseline and 12 months ($p=0.001$). Improvement in 6MWT by ≥33m at 12 months prolonged survival in patients with cardiac involvement by amyloidosis ($p=0.005$) and specifically in Mayo IIIb patients (OS NR vs. 70.0 [51.4-88.6] months, $p<0.0001$). A 33m improvement was independent of haematological response in predicting survival (CR [reference], Very good partial response [VGPR]: HR 2.02 [1.08-3.80], $p=0.03$; Partial response [PR]: HR 3.51 [1.83-6.73], $p<0.0001$; Nil response [NR]: HR 5.61 [2.88-10.92], $p<0.0001$; 6MWT improvement ≥33m: HR 1.61 [1.01-2.59], $p=0.047$).

Conclusions and Relevance

The 6MWT is prognostic in AL amyloidosis and a baseline distance of ≥300m independently predicts better survival. Inability to attempt 6MWT at baseline is an extremely poor prognostic indicator. At 12 months, improvement in 6MWT of ≥33m predicts better survival. These data suggest that 6MWT has utility in AL amyloidosis for baseline prognosis and assessing response.

Keywords: 6-minute walk test, amyloidosis, survival, myeloma

Introduction

Systemic AL amyloidosis is characterised by the deposition of misfolded light chain immunoglobulins, produced by a clonal cell population, in organs leading to progressive and often devastating dysfunction (1). Cardiac involvement, the major determinant of prognosis, is documented in approximately three-quarters of cases (2) and often presents with features of a restrictive cardiomyopathy (3). Fatigue and impairment of functional capacity is an important but difficult to capture feature of systemic amyloidosis. The specific impact of functional capacity on survival is well recognised in cardiac failure (4) from other causes as well as in specific diseases such as pulmonary hypertension (5).

Assessment for treatment, responses to treatment and stratification of outcomes in AL amyloidosis is based on blood tests and imaging. However, a simple global standardised reproducible measure of individual function would provide additional objective measures to assess fitness for chemotherapy, impact of chemotherapy, improvement after treatment or worsening with disease progression. The 6-minute walk test (6MWT) is an easy-to-administer standardised measure of functional capacity. The 6MWT has also been accepted by regulatory agencies as a valid clinical trial end-point in trials of systolic heart failure and pulmonary hypertension (6).

The 6MWT involves walking across a flat surface for exactly six minutes at a self-selected pace to better reflect the level of exertion required for activities of daily living (7). A 6MWT distance of <300m predicts poor outcomes in patients with cardiac failure (8-11). Clinical trials of interventions in heart failure suggest that an increase of 30-50m may be considered clinically meaningful (12). A large study of nearly 400 patients with pulmonary hypertension concluded that the minimal important difference (MID) of the 6MWT in this subgroup was approximately 33m (5).

Data on utility of 6MWT in AL amyloidosis remain scarce. The Boston amyloidosis group reported a small series of patients with and without cardiac involvement showing a reduction in the 6MWT in those with cardiac involvement correlating with worsening New

York Heart Association (NHYA) dyspnoea grade (13, 14). In AL amyloidosis, measurement of treatment response remains challenging and is based on surrogates such as cardiac biomarkers. A formal functional test to capture overall clinical improvement is required and the 6MWT has the potential to be used for this purpose.

This study, the largest ever to evaluate the 6MWT in AL amyloidosis, aims to validate the prognostic importance of this test at baseline in a treatment-naïve population and build upon this by evaluating the utility of the 6MWT at regular time points thereafter.

Method

All patients from a prospective observational study of newly diagnosed treatment-naïve AL amyloidosis (ALCHEMY), seen at the UK National Amyloidosis Centre (NAC) (October 2012 – August 2017) were included. The diagnosis of AL amyloidosis was confirmed by Congo red staining of a tissue biopsy whilst subtype was confirmed by immunohistochemistry using specific antibodies or mass spectrometry. All patients had a detailed baseline assessment inclusive of both clonal markers and biochemical markers of organ function and echocardiography. This assessment was repeated at 6, 12, 18, 24, 36 and 48 month follow up.

The 6-minute walk test was conducted in accordance with the American Thoracic Society guidelines (7). The result was used to calculate a percentage of the predicted value for age, sex, height and weight (15). Patients were excluded if they met criteria for any absolute or relative contraindication, namely resting heart rate >120 beats per minute, systolic blood pressure >180mmHg and/or diastolic blood pressure >100mmHg. A distance of <300m was chosen to represent a poor performance cut-off as previously reported as a useful prognostic marker of subsequent cardiac death (8-11). There is limited published literature to define a clinically meaningful improvement in 6MWT. In the setting of cardiac rehabilitation post-myocardial infarction(16), chronic heart failure(17) and pulmonary hypertension(5), the minimum clinically important difference in 6MWT has been reported to

be 25-33m. Consequently, we took the highest of these values and deemed 33m to represent a reasonable minimum value indicative of a meaningful improvement.

Haematological and organ responses were defined as per international consensus criteria (18, 19). Specifically, a haematological CR is defined by the absence of a detectable monoclonal protein with normalisation of the free light chain ratio. A VGPR represents a difference between light chains (dFLC) of <40mg/L whilst a partial response (PR) represents a dFLC decrease of >50% from baseline. A cardiac response was defined by reduction in N-terminal pro hormone brain natriuretic peptide (NT-proBNP) (>30% and >300ng/L) assuming a baseline of ≥650ng/L or ≥2 class decrease in the NYHA class. Overall survival (OS) was defined as time from diagnosis to death from any cause.

Statistical analysis was performed using SPSS version 25 (IBM Corporation, Armonk, NY, USA). Approval for analysis and publication was obtained from the National Health Service institutional review board; written consent was obtained from all patients in accordance with the Declaration of Helsinki. The Kaplan-Meier method was used to analyse survival outcomes. Multivariable modelling by Cox regression analysis was performed on factors found to significantly impact survival on univariate analysis. Pearson's correlation coefficient was used to calculate correlation. Non-parametric t-tests were used to compare continuous variables. All p values were 2-sided with a significance level of <0.05. All walk test results are reported as median meters walked/median percentage predicted (e.g. 334m/67%).

Results

Eight hundred and seven patients were identified of which 7 patients were excluded on the basis of an initial contraindication (2 heart rate >120bpm, 5 blood pressure >180mmHg/>100mmHg). One patient was excluded due to immobility secondary to an unrelated neurological condition. Baseline characteristics are included within **Table 1**. Of 799 patients, 564 (70.6%) patients had cardiac involvement. A total of 716 (89.6%)

attempted the test whilst 83 (10.4%) were unable to do so despite the lack of a contraindication.

The median 6MWT for the entire cohort was 362m (0-700m). Patients with cardiac involvement had significantly shorter baseline distances (cardiac vs. non-cardiac: 337.0m/64% vs. 421.0m/84% [p<0.0001]). The baseline 6MWT worsened with increasing Mayo disease stage (Stage I – 458.0m/91.0%, Stage II – 404.0m/80.0%, Stage IIIa – 331.0m/65.0%, Stage IIIb – 168.0m/34.0% [p<0.0001]) (**Figure 1**). A shorter baseline 6MWT correlated significantly with other prognostic measures of functional status such as Eastern Cooperative Oncology Group (ECOG) performance status (-0.629, p=0.01) and NYHA stage (-0.397, p=0.01).

Patients were followed up for a median of 32.0(range: 1.0-90.0) months. Median OS from diagnosis was 70.0(95%CI: 56.8-83.2) months (**Figure 2A**) reducing to 32.0(95%CI: 23.1-40.9) months in patients with cardiac involvement. The median OS of patients achieving ≥300m at baseline was not reached (vs. 25.0(95%CI: 18.1-31.9) months if <300m and 5.0(95%CI: 2.8-7.2) months if unable to attempt 6MWT (p<0.0001) (**Figure 2B**). A baseline 6MWT of ≥300m remained prognostic when patients with and without cardiac involvement were analysed separately (Cardiac involvement: ≥300m: 75.0 months, <300m: 21.0(95%CI: 12.5-29.5) months, unable to attempt 6MWT: 4.0(95%CI: 2.2-5.8) months; p<0.0001. No cardiac involvement: ≥300m: Not reached, <300m: Not reached, unable to attempt 6MWT: 15.0(95%CI: 4.4-25.6) months; p<0.0001). In patients with the most advanced cardiac involvement (Mayo IIIb), the 6MWT remained prognostic (≥300m: 61[95%CI: 4.2-117.8] months vs. <300m: 4.0[95%CI: 1.3-6.9] months vs. unable to walk: 1.0[95%CI: 0.3-1.7] months, p<0.0001) (**Figure 2C**).

On multivariable analysis, a baseline 6MWT of ≥300m was an independent predictor of better outcomes in a model incorporating Mayo staging (**Table 2A**).

Change in 6MWT was assessed according to haematological response to treatment (**Table 3**). At 6 months, 162 (20.3%) patients had died and 539 (67.4%) patients were

evaluable. Of these, 358 patients had 6MWT data at all of baseline, 6 and 12 months for a comparable analysis. In evaluable patients, haematological responses were: CR – 91 (25.4%), VGPR – 142 (39.7%), PR – 78 (21.8%) and NR – 47 (13.1%). There was no significant difference in baseline 6MWT between patients in differing response categories (p=0.19). Since all patients with AL amyloidosis undergoing chemotherapy suffer from significant treatment emergent adverse events, median 6MWT decreased significantly at 6 months, most markedly in those in a lesser haematological response; possibly a deeper response allowing for a degree of early recovery or lack of disease progression. The absolute decrease in 6MWT between baseline and 6 months was: CR – 17.0m (p=0.004), VGPR – 23.5m (p=0.003), PR – 48.0m (p=0.001) and NR – 77.0m (p=0.001). Patients achieving a deeper haematological response (CR/VGPR) walked greater distances at 6 and 12 month follow up that those in PR/NR (6 months: 387.0m [75.0%] vs. 352.0m [71.0%], p=0.009; 12 months: 409m [79.0%] vs. 359.5m [74.0%], p=0.005). Furthermore, patients in a CR at 12 months walked significantly further than those in a VGPR (437.0m/85.0% vs. 395.5m/76.5%, p=0.009). In patients achieving a CR, there was a significant improvement in 6MWT between 6 and 12 months (414m/79.0% to 437m/85.0%, p=0.001) whilst in patients achieving lesser responses, 6MWT did not change significantly between 6 and 12 months. At 12m, patients meeting criteria for a cardiac organ response walked further (403.0m/79.0% predicted vs. 322m/63.5% predicted, p<0.0001). Cardiac responders (n=125) demonstrated a median absolute improvement of 5% (p=0.002) of predicted 6MWT at 12 months whilst non-responders (n=96) worsened by 11.5% (p<0.0001).

We also assessed serial changes in 6MWT. A total of 198 patients with data available at all time points (0, 6, 12, 18 and 24 months) were included to ensure comparability (i.e. any patient who died before 2 years is excluded). Median 6MWTs at 0, 6, 12, 18 and 24 months were 418.5m/80.5%, 391.0m/73.5%, 415.0m/78.0%, 427.5m/81.5% and 417.0m/82.0% respectively. The baseline 6MWT distance was shorter in patients with cardiac AL amyloidosis (396.0m/74.0% vs. 437.0m/88.0%, p=0.0008). There was a significant reduction in the 6MWT distance at 6 months (418.5m/80.5% to 391.0m/73.5%,

p=0.0002) followed by a subsequent improvement at 12 months (391.0m/73.5% to 415.0/78.0%, p=0.02). The 6MWT did not significantly improve after 12 months at the 18 and 24 month time-points (p=0.23 and p=0.11 respectively). Significant differences in 6MWT distance between Mayo stage I, II and II persisted at 12 months (Stage I: 435.0m/85.0%; Stage II: 395.0m/79.0%, Stage III: 345.0m/67.0%, p<0.0001). Patients with a poor baseline 6MWT (<300m) achieved a greater median improvement in 6MWT at 12m of 24.5m (188.5m/41.5% vs. 213.0m/44.0%, p<0.0001) compared to a median worsening of 11m in those with 6MWT of ≥300m at baseline (440.0m/86.0% vs. 429.0m/82.0%, p=0.34).

Thirty-one patients with Mayo IIIb disease returned for assessment at 12m. The stage IIIb patients who had repeat 6MWT at 12 m, had a median baseline 6MWT of 300.0m/56.0% (n=31) in comparison to just 92.0m/18.5% in those who did not return at 12 months (n=70, 64/70 [91.4%] had died prior to 12 months; 6 lost to follow up) (p<0.0001).

An improvement of ≥ 33m was considered to be the minimum clinically meaningful increase in 6MWT as described above (5). Overall, 28.2% of patients improved their 6MWT distance by at least 33m by 12 months. Of patients achieving a complete haematological and cardiac response, 36.6% and 47.2% improved by ≥ 33m compared to 26.7% and 17.7% patients in a lesser haematological response and cardiac non-responders respectively (p=0.03 and p<0.0001 respectively). Patients with cardiac involvement who improved by ≥33m at 12 months lived longer (not reached vs. 74 months, p=0.005) (**Figure 2D**) whilst there was no survival difference based on a ≥33m improvement in those without cardiac involvement (not reached in either category, p=0.404). In patients who achieved a baseline 6MWT of <300m but improved by ≥33m at 12 months, the median OS was not reached (vs. 35.0 [25.7-44.3] months in those who improved by <33m, p=0.006). On multivariable analysis, an improvement in 6MWT of ≥33m was independent of haematological response in predicting better survival in patients with cardiac AL amyloidosis (**Table 2B**). In a landmark analysis of patients with Mayo stage III disease alive at 12 months those patients who

improved by ≥33m at 12 months lived longer (OS NR vs. 70.0 [51.4-88.6] months, p<0.0001).

Discussion

This study confirms the prognostic value of the 6MWT in a large cohort of uniformly treated patients with systemic AL amyloidosis. Baseline 6MWT independently predicts survival and a baseline 6MWT <300m identifies patients with a shorter prognosis whilst those unable to attempt the 6MWT have especially poor outcomes. At 1 year, only patients achieving a haematological CR improve their 6MWT. An absolute improvement of ≥33m at 12 months is independent marker of better overall survival.

Standardised functional testing is crucial in assessment of cardiovascular diseases. A seminal multicentre study demonstrated the prognostic value of the 6MWT in subjects with left-ventricular dysfunction (20). It has since been applied to a range of conditions including pulmonary hypertension (5), respiratory disease (21) and renal failure (22). A recent study of Tafamidis in transthyretin-type (ATTR) cardiac amyloidosis (23) reported a lower rate of decline in 6MWT distance in patients treated with Tafamidis compared to placebo.

In systemic AL amyloidosis, Pulido and colleagues(14) reported the prognostic value of the 6MWT but no group have applied specific baseline distance cut-offs, which could be applicable as inclusion / exclusion criteria in a trial setting. A walk test of <300m defines patients in a poor prognostic category in cardiovascular disease (8-11). The current study confirms the prognostic value of this cut-off in patients with AL amyloidosis irrespective of cardiac involvement suggesting that 6MWT can be considered a functional marker in all patient with amyloidosis.

Biomarker-based staging remains the cornerstone of prognostic classification in AL amyloidosis. Patients with an NT-proBNP >8500 ng/L (stage IIIb in the European modification of the Mayo staging) have an especially poor prognosis of just 3-6 months (24). However, we demonstrate even this group is heterogeneous as those patients with a baseline 6MWT ≥300m (25.7% of the stage IIIb patients) have a median OS of 61.0 months (vs. 4.0 months if 6MWT <300m). Patients unable to attempt the 6MWT at baseline have a

poor OS of just 5 months irrespective of Mayo stage. These findings suggest the utility of 6MWT in risk stratification of patients with AL amyloidosis and could represent a useful addition to the inclusion/exclusion criteria in clinical trials. Due to small patient numbers within this subgroup, these findings require validation in larger clinical studies.

In systemic AL amyloidosis, therapy aims to suppress the underlying plasma (or B) cell clone, reducing the amyloidogenic free light chains to prevent further amyloidotic deposits within organs (1). It is well documented that depth of response correlates with improved patient survival. Current treatment algorithms advocate further treatment in patients failing to achieve a CR or VGPR to first-line therapy (25). Assessing functional improvement in amyloid patients is less well defined, made more challenging due to multi-organ involvement. In chronic heart failure, improvement in 6MWT distance is a proven measure associated with better outcomes. (26) Our group previously reported that 6MWT was generally stable or had improved in patients in a CR or VGPR at 12 months (13). This larger cohort confirms that at six months (the usual time point where patients have finished induction chemotherapy), there was an overall decrease in the 6MWT distance (median baseline 6MWT was 362.0m reducing to 337.0m in patients with cardiac AL amyloidosis), that was least marked in patients who achieve a deep response to treatment. This likely represents the adverse impact of chemotherapy (inclusive of fatigue and neuropathy) on this already fragile patient population. The improvement in 6MWT at 12 months that was clearly linked to the depth of the patient's haematological response. There was an excellent correlation between biomarker-based cardiac response and improvement in the 6MWT distance with a 5% improvement compared an 11% worsening on those who did not have a biomarker based cardiac response. The corroborates previous data from Decker *et al* previously demonstrated that patients achieving a cardiac response improve their median 6MWT in a small study of 22 patients (27). Our data confirms that deep haematological and organ responses are associated with improvements in median 6MWT distance in systemic AL amyloidosis.

A defined “clinically meaningful” improvement has been posited in other cardiovascular diseases and a range of improvement from 25-33m has been used (5, 16, 17, 21). We used the largest of these values (33m) as a minimum value representative of clinically meaningful improvement. Patients who achieved a haematological CR or cardiac response were more likely to achieve a ≥33m improvement. Furthermore, a ≥33m improvement at 12 months was associated with a survival benefit. One of most powerful factors influencing survival in AL amyloidosis remains the depth of haematological response. We show here that a ≥33m improvement in the 6MWT distance provided incremental and independent prognostic information over and above haematological response in predicting OS. If validated in other studies, an improvement in 6MWT could be incorporated into clinical trials as a secondary endpoint and marker of improved functional capacity.

Our study is limited by the single centre design and the fact that there is missing data at each time point due to patient’s being lost to follow up. However, all analyses only incorporate patients who had evaluable results at all-time points included within a particular analysis to ensure comparability. There is also the potential from a learning effect from repeated 6-minute walk tests, which was not accounted for within this study. However, previous studies have suggested that the learning effect does not persist at 6 months (28). Furthermore, many patients with AL amyloidosis would be unable to undergo the 6MWT on two occasions at the same consultation.

Conclusion

Baseline 6MWT is predictive of survival and independent of Mayo staging for defining prognosis in systemic AL amyloidosis. Patients achieving a deep haematological or cardiac response perform better at follow up testing. Patients who walk ≥33m further on repeat testing at 12 months live longer and this measure predicts survival independently of haematological response. Our data suggests that the 6MWT is a good prognostic indicator in AL amyloidosis and has the potential to be used as an additional prognostic criterion in the initial baseline assessment of patients and could be a useful criterion to determine clinical

trial eligibility. Improvement in 6MWT is predictive of outcomes and may be incorporated into clinical trial design as a functional endpoint in patients with systemic AL amyloidosis.

Author Contributions

OCC and ADW conceived the study, analysed data and wrote the manuscript. OCC, AS and RM collected the data. SR, DF, SL, SS, SM, CJW, HJL, PNH, JDG, AMN and MF contributed to the manuscript and provided critical input. All authors reviewed the final version of the manuscript.

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Disclosure Statement

No conflicts of interest to declare

Table 1. Baseline Patient Characteristics

n=799	Median (range) or n (%)
Age (years)	69 (32-92)
Males / Females	334 (41.8) / 465 (58.2)
NYHA Class	
1	207 (25.9)
2	394 (49.3)
3	82 (10.3)
4	4 (0.5)
Unrecorded	112 (14.0)
ECOG	
0	192 (24.)
1	314 (39.3)
2	221 (27.7)
3	36 (4.5)
Unrecorded	36 (4.5)
Kappa / Lambda	168 (21.0) / 633 (79.0)
Median dFLC, mg/L	168 (0-15898)
Cardiac Involvement	564 (70.6)
NT-proBNP, ng/L	2174 (25-93776)
High-sensitivity cardiac troponin T, ng/L	52 (3-689)
LV wall thickness (mm)	13 (6-22)
Mayo Stage	
I	125 (15.6)
II	261 (32.7)
IIIa	286 (35.8)
IIIb	101 (12.6)
Unrecorded	26 (3.3)
Renal Involvement	552 (69.1)
Serum creatinine, μmol/L	98 (26-979)
GFR, ml/min	64 (<15->90)
Proteinuria, g/24h	3.3 (0-36)
Albumin, g/L	34 (13-53)
Liver involvement	113 (14.1)
No. organs involved	2 (1-5)

Abbreviations: NYHA: New York Heart Association Classification of Heart Failure; ECOG: Eastern Cooperative Oncology Group Performance Status; dFLC: difference between involved and uninvolved free light chains; NT-proBNP: N-terminal pro hormone brain natriuretic peptide; LV: Left ventricle; eGFR: estimated glomerular filtration rate.

Table 2: Multivariable models incorporating:

A) Mayo staging and 6-minute walk test ≥ 300m at baseline

	Hazard ratio	95% confidence interval	P value
Mayo I (reference)			0.000
Mayo II	2.21	1.35-3.64	0.002
Mayo IIIa	3.92	2.42-6.34	<0.0001
Mayo IIIb	6.08	3.63-10.12	<0.0001
6MWT > 300m	2.97	2.38-3.72	<0.0001

B) Haematological response and change in 6-minute walk test (reduction of ≥33m) at 12 months in patients with cardiac AL amyloidosis

	Hazard ratio	95% confidence interval	P value
CR (reference)			0.000
VGPR	2.02	1.08-3.80	0.029
PR	3.51	1.83-6.73	<0.0001
NR	5.61	2.88-10.92	<0.0001
∆6MWT ≥ 33m	1.61	1.01-2.59	0.047

Abbreviations: CR: complete response; VGPR: very good partial response; PR: partial response; NR: no response; 6MWT: 6-minute walk test.

Table 3: 6MWT distance and percentage predicted according to haematological response at baseline, 6 and 12 months

	Baseline		6 months		12 months		P value
	m	%	m	%	m	%	
CR	431	83	414	79	437	85	0.001
VGPR	403.5	76	380	73	395.5	76.5	0.02
PR	413	79	365	71	362.5	74	0.0007
NR	437	83	360	71	355	70	0.0002

Abbreviations: m: metres; CR: complete response; VGPR: very good partial response; PR: partial response; NR: no response; 6MWT: 6-minute walk test.

Figure 1: Baseline 6-minute walk test distance by Mayo stage

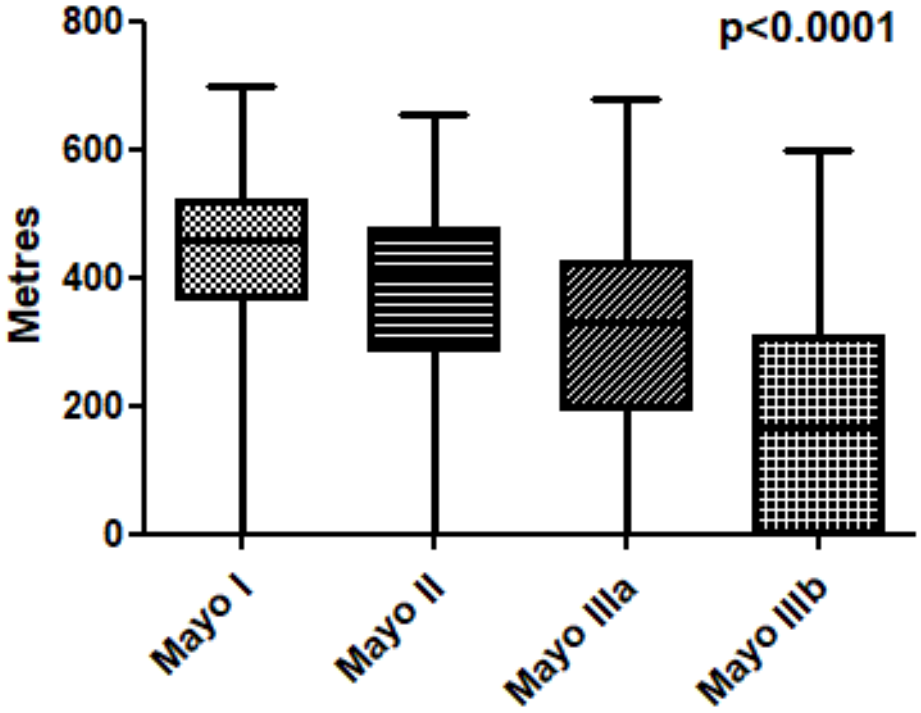


Figure 2

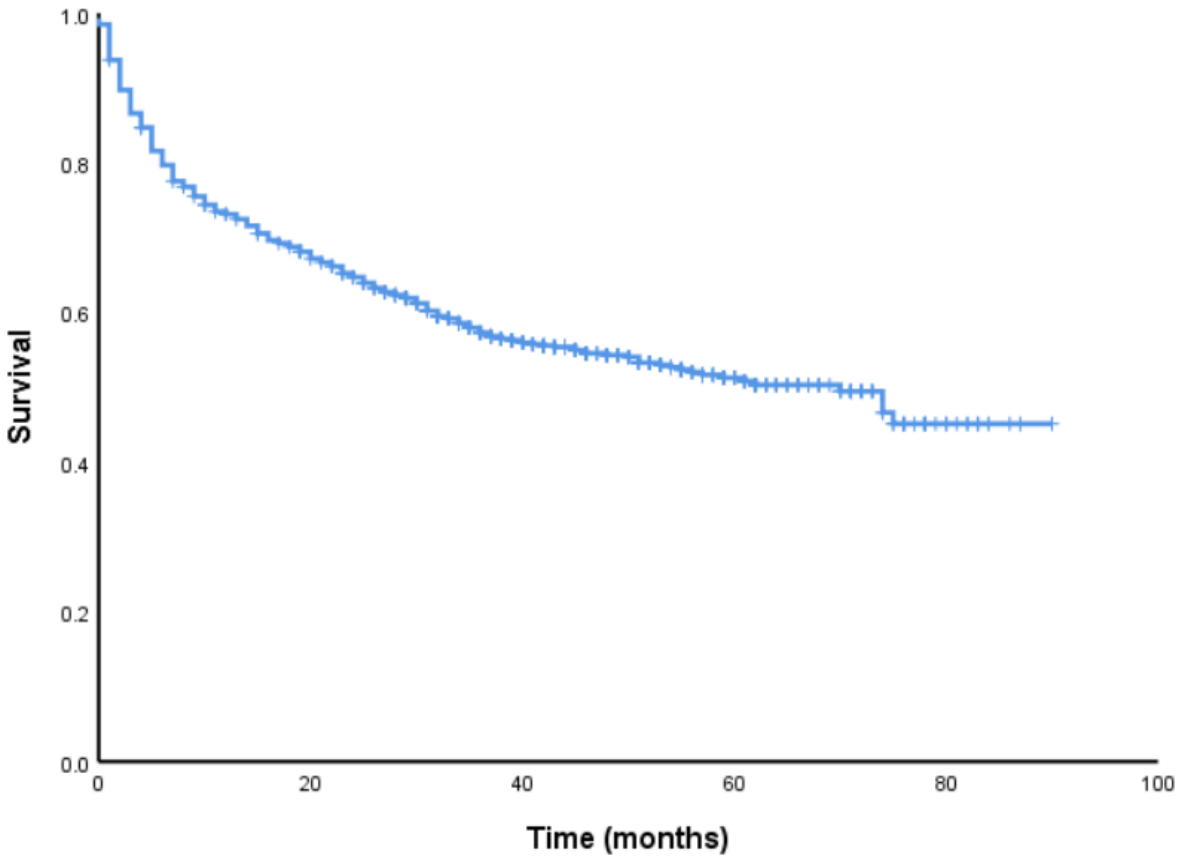
A) Overall survival

B) Overall survival by 6-minute walk test distance

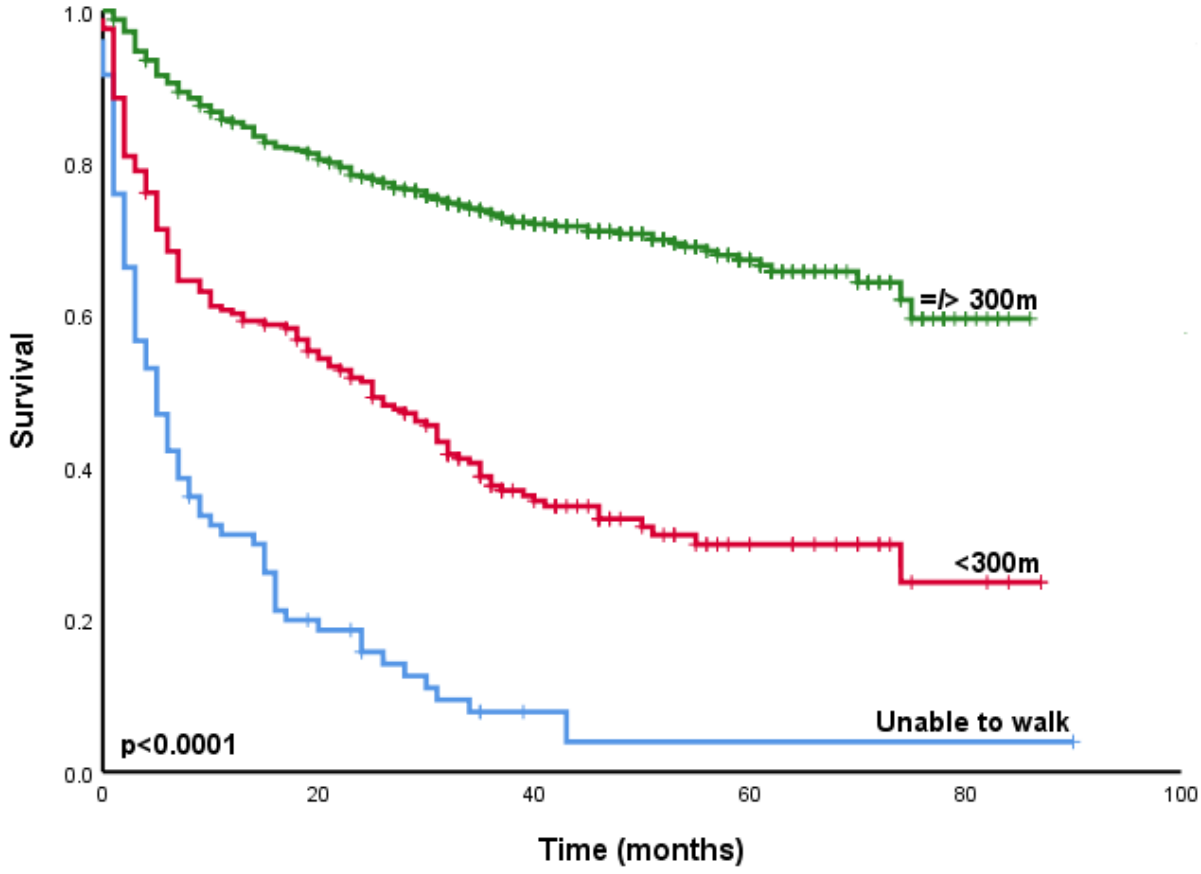
C) Overall survival by 6-minute walk test distance in patients with Mayo IIIb disease

D) Overall survival by improvement in 6MWT of ≥33m at 12 months in patients with cardiac AL amyloidosis

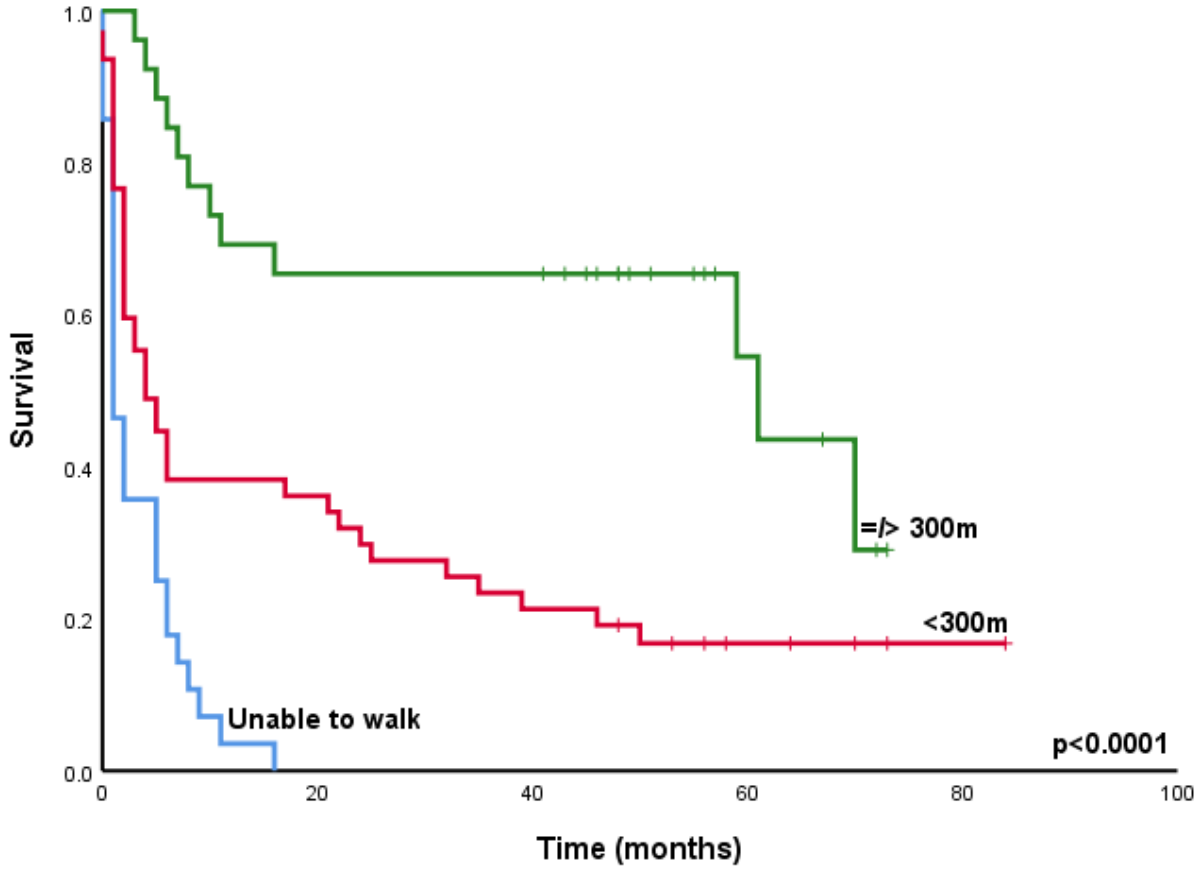
A)



B)


1.0
0.8
0.6
0.4
0.2
0.0
Survival
=/> 300m
<300m
Unable to walk
p<0.0001
0
20
40
60
80
100
Time (months)

C)


1.0
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Survival
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20
40
60
80
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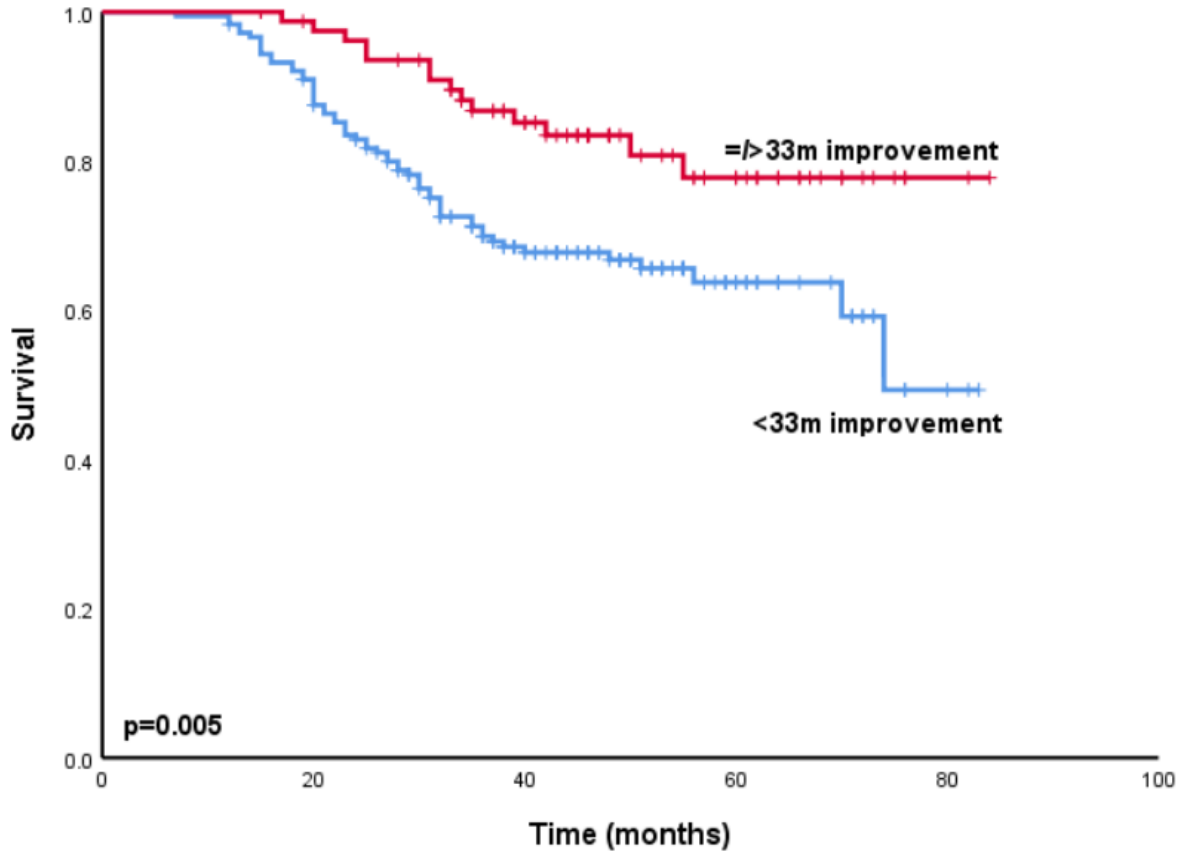
Time (months)

D)


1.0
0.8
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Survival
=/>33m improvement
<33m improvement
p=0.005
0
20
40
60
80
100
Time (months)

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