A European collaborative study of natural history, outcomes and validation of prognostic/response criteria in IgM related AL amyloidosis

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Abstract:

Purpose

IgM related AL amyloidosis, accounting for 6-10% of all AL cases, is a rare and poorly studied clinical entity. Its natural history and management is not clearly defined. Prognostic and response criteria for AL in general have not been validated in this population.

Patients and Methods

We retrospectively gathered 250 patients diagnosed with IgM-AL amyloidosis from three European amyloidosis centres. Clinical features, haematological response and overall survival were analysed. The validity of current staging and response criteria in non-IgM AL were applied to this series to assess their utility in this patient cohort.

Results

Patients with IgM-AL have a significant IgM paraprotein (median 10g/L), lambda light chain isotype is less frequent and dFLC is evaluable (>50 mg/L) in only 2/3 cases. Bone marrow showed clear Non-Hodgkin's lymphoma as the underlying disorder in 54%. Cardiac involvement is less common (45%) with more frequent lymph node (20%) and neuropathic involvement (28%) compared to non-IgM AL. 57% of patients achieved a haematological response (14% VGPR/CR) with median OS not-reached for patients achieving VGPR/CR, 64 months for PR and 28 months for non-responders ($p<0.001$). On multivariate analysis, cardiac involvement/advanced Mayo disease stage, PN involvement, and low albumin <30g/L were independent factors impacting survival. Combining abnormal NT-proBNP and troponin-T with low albumin and presence of PN gives a better risk model: median OS of patients with none, one or two/more abnormal factors were 73, 55 and 17 months respectively.

Conclusion

IgM-AL is a distinct clinical entity. Low risk disease can be defined by combining cardiac with novel prognostic markers. Deeper haematological responses translate into improved outcomes; yet deep responses remain dismally poor showing the urgent need for novel therapies.

Introduction:

Amyloidosis is a rare systemic disorder of protein misfolding and results from extracellular deposition of beta pleated aggregates of fibrillar proteinaceous materials. The most common type of amyloidosis is light chain amyloidosis (AL), where the amyloidogenic precursor protein is a monoclonal immunoglobulin light chain.[1] In about 45-55% of cases, an intact monoclonal immunoglobulin protein can be identified which is usually IgG or IgA paraprotein associated with an underlying plasma cell disorder. In 5-7% of patients, AL amyloidosis is associated with an underlying IgM paraprotein, described in small series by our groups and from the US.[3,4,5] It has previously been suggested that IgM-AL amyloidosis should be classed as a distinct clinical entity with several distinguishing clinical features from non-IgM AL amyloidosis.[6,7] Given its rarity, IgM-AL remains poorly studied. Since this disorder is different, as all patients have an intact monoclonal protein and appear to have an underlying lymphoproliferative disorder, criteria validated for non-IgM AL have not been formally tested in this disease. The treatment paradigms designed for non-IgM AL have been used in IgM-AL amyloidosis, which may not always be appropriate.

We report the utility of prognostic and response criteria, validated in non-IgM AL amyloidosis in a large series of 250 patients with IgM associated AL amyloidosis seen at three major European amyloidosis centres. We also report the clinical characteristics, and outcomes in this patient cohort. The current report is, to our knowledge, the largest series of IgM related amyloidosis.

Patients and methods:

Two hundred and sixty one newly diagnosed patients with IgM related AL amyloidosis from amyloidosis centres in London (United Kingdom, 149 patients), Pavia (Italy, 81 patients) and Limoges, (France, 31 patients) between January 1990 and December 2012 were, retrospectively, included in this study. IgM related AL amyloidosis was defined as all patients

with confirmed AL amyloidosis with detectable IgM paraprotein demonstrated in the serum or urine by electrophoresis and immunofixation, in the absence of any other monoclonal protein. The presence of amyloid was confirmed by characteristic Congo red staining and AL-type was confirmed by either immunohistochemistry immuno-electron microscopy or immunofluorescence and exclusion of hereditary amyloidosis by appropriate gene sequencing.

All patients were treated according to local protocols and had rigorous protocolized assessments which included evaluation of clonal disease at baseline and after each line of therapy and organ function at baseline. The study was performed with institutional review board approval, and informed consent was obtained from each patient in accordance with the Declaration of Helsinki.

Outcome measures:

Organ involvement was assessed according to the Consensus Opinion from the 10th International Symposium on Amyloid and Amyloidosis.[8] Outcome measures comprised of overall patient survival (OS),hematologic response (HR) to first line treatment and organ response. The primary outcome measure was OS. The validity of currently published staging and response criteria in non-IgM AL were applied to this series to assess the utility of those criteria in this patient cohort including impact of HR to treatment on survival. HR was assessed by serum and urine electrophoresis, immunofixation and free light chain (FLC) assay. HR were defined as per the amyloidosis consensus guidelines.[8] FLC values were considered evaluable for assessing response if the pre-treatment difference between the involved and uninvolved free light chain (dFLC) was >50 mg/L with an abnormal FLC ratio. HR were assessed as per the consensus criteria published by Palladini *et al* [9] and by use of serum paraprotein (PP) response. The response was assessed as the best achieved response after

starting chemotherapy and before any further therapy was given. Those who died early prior to response assessment were categorized as non-responders in the intent to treat analysis (ITT).

Survival was described by means of its median and displayed graphically by Kaplan Meier curves. The association of a series of candidate predictors and survival was assessed by Cox models. The proportional hazard assumption was tested and satisfied in all cases. Linearity of ordinal predictors was verified by means of the likelihood ratio test to compare nested models. Response was treated as a time dependent variable. The effect modification on the relationship of response and survival by Mayo Stage was assessed by including an interaction term in the model. All non-co-linear variables with p-value<0.1 at univariable analysis and with missing data below 20% were included in a multivariable Cox (time-dependent) regression model. For all Cox models, clustered robust standard errors were computed to account for within-country correlation. Model validation was performed by calculating the shrinkage coefficient/noise for calibration and the Harrell's c statistic for discrimination.A 2-sided p-value<0.05 was considered statistically significant. Stata 13.1 (StataCorp, College Station, TX, USA) was used for computation.

Results:

Two hundred and sixty one patients with isolated IgM paraprotein related AL amyloidosis were identified from three European centres. Eleven patients had localised amyloidosis and were excluded from analysis. Ninety five percent (250) of patients had systemic AL amyloidosis and were included in this retrospective study. The baseline demographics including cardiac disease stage are given on Table 1. 45% of those referred before 2004 were >67 years of age, this increased in 2004-2009 period to 51% and then to 64% in 2010-2012.Cardiac, renal, soft tissue and liver involvement were in 45%, 68%, 35% and 17 % of patients at diagnosis. Mayo

stage (available in 216 (86%)) 1, 2 and 3 disease was seen in 40%, 34% and 26% of patients respectively. . Lymph node involvement was detected in 20% of patients at presentation.

A total of 131 (52%) of the patients had a clearly identified lymphoproliferative disorder (predated the AL diagnosis in 39). Thirty four (14%) had a normal bone marrow (BM) with no detectable clonal dyscrasia. Fifteen (6%) had plasma cell predominance in the BM. The BM details were not available for 70 patients (28%). Of the patients with an underlying lymphoproliferative disorder, 97 (39%) had lymphoplasmacytic lymphoma, 34 (14%) had a Non-Hodgkin's lymphoma (NHL) not specifically classified. 2 had chronic lymphocytic lymphoma and 2 had Follicular Lymphoma.

Treatment and response:

Two hundred and twenty eight (91%) patients were treated and eight died prior to starting chemotherapy. Fourteen patients were excluded from treatment analysis as treatment information was not available. Twenty two different combination of regimen were used as first line; grouped into ten categories for ease of analysis and are shown on table 2. The median number of lines of therapies was 1 (range 1-5). Figure 1 shows the changing trend in treatment profile since 1990. The use of Melphalan, Chlorambucil and conventional chemotherapy has reduced over time. Purine Analogues, traditional chemotherapy regimens and Thalidomide were predominantly used during 2005-2009. Since 2010, the use of Rituximab in combination with bortezomib or combination chemotherapy (R-CD or R-CVP/CHOP) was most frequent.

212 of the treated patients had evaluable paraprotein (81 by paraprotein alone) or dFLC (12 by dFLC alone) and 119 by both. HR data was available for 172 patients (78%) (M-protien data in 49 patients). On an ITT analysis, 102 (57%) patents achieved HR (43% partial response (PR), 9% very good partial response (VGPR) and 5% complete response (CR)). Of the 49 patients evaluable for M-protein only response (dFLC not evaluable), 24 achieved PR, 1 CR

and 24 were non-responders. ~~Of the patients with both evaluable M-Protein and dFLC, nine patients had no dFLC response but had achieved PR based on M-protein response. For all other patients, dFLC responses were same as or of a deeper grade than corresponding M-protein response~~. Fifteen patients deemed as non-responders by M-protein alone, had achieved PR (13) and VGPR (2) by dFLC response. Table 2 details treatment regimes, HR with proportion achieving VGPR/CR, median OS and 2 year survival rates and time to next treatment for patients treated with the various first line therapies. The numbers are too small in individual group for meaningful statistical comparisons.

Survival analysis:

The median overall survival was 47.9 months (figure 2a). There was no improvement in survival over time as shown in figure 2b: Patients with no identifiable clonal infiltrate in the BM had best survival (54 months) compared to a lymphoid infiltrate or a plasma cell predominant infiltrate (44 months and 23 months respectively).

Figure 2c-f show survival by disease characteristics. Presence of cardiac involvement conferred significantly worse outcomes (median OS 21 vs. 62.5 months for no cardiac involvement), as did worse Mayo disease stage(median 73, 24 and 10 months for stage 1, 2 and 3 respectively). Other factors associated with poorer outcomes included peripheral neuropathy (PN) or autonomic neuropathy (AN) , low serum albumin (<30g/L) (29 vs 50 months, p=0.008) or higher dFLC (>180 mg/L) (18.9 vs 48 months, p=0.021). In this study only 13% of patients with neuropathy received bortezomib or thalidomide. . Table 3 details univariate and multivariate analysis of factors affecting overall survival (.different multivariate models of NT-proBNP and Mayo stages in supplementary table 2). Combining factors independently predictive of survival (NT-proBNP, troponin T, albumin and presence of PN), a new risk model

is outlined in figure 3a with median survival of patients with none, one or two/more abnormal being 73, 55 and 17 months respectively.

Patients who responded to first line treatment (69 months) had a significantly better survival compared to the non-responders (28 months) ($p<0.012$) (figure 3b). Very good partial response as defined by dFLC remained a predictor of outcome with patients achieving a VGPR/CR with median OS not reached vs. 64 months for those with a PR, ($p=0.183$) and 22 months for non-responders <0.0001 (figure 3c). Patients with only by M-protein response, median OS was not reached for responders.. Responders within mayo stage 2 and 3 had a significantly better outcome compared to the non-responders, whereas, there was no significant difference within mayo stage 1 group, however, the median OS for the responders was 134 months and only 62 months for the non-responders within this latter group (figure 3d-f). Median time to next treatment (TTNT) was 12 months with no significant difference by organ involved (isolated cardiac, renal and liver involvement with 7, 9 and 9 months respectively).

Organ response:

On an ITT analysis of organ response, cardiac, liver and renal responses were 3/57 (5%), 7/26 (27%) and 19/108 (18%). Organ response rates are much lower in the IgM cohort compared to that seen in the IgA/IgG-AL cohort in the era of novel agents. [11]

Discussion

Systemic AL amyloidosis associated with IgM-paraprotein is relatively uncommon variant of AL amyloidosis, accounting for 6% of AL patients.[3] Our groups have previously reported small series of IgM-AL suggesting that this sub-group needs to be clearly recognised as a distinct condition and considered for specific treatment targeting the underlying clone.[5,7,12,13] The cohort reported here is the largest series of patients with IgM related AL amyloidosis from

three major European centres and reports the presenting features, response to treatment and clinical outcomes. This large series allowed identification of novel prognostic factors (peripheral neuropathy and low serum albumin) unique to this patient population. We confirm that deeper haematological responses, although still rare, translate into a significant survival advantage.

Since AL amyloidosis is driven by the amyloidogenic light chains, the overall pattern of organ involvement remains broadly similar to that seen in non-IgM AL amyloidosis.[14,15] The striking difference is less common cardiac involvement compared to non-IgM AL amyloidosis (45% vs ~70% respectively)[15] which may be due to the relatively lower proportion of lambda light chain isotype in IgM and lower light chain clonal burden. There is a higher incidence of soft tissue and lymph node (35%) involvement, (similar to previous reports[4,5]) possibly due to co-existent lymphoma clone at the respective site. The prognostic impact of nerve involvement was unexpected. Only 13% of patients with nerve involvement received bortezomib (or thalidomide) base regimes, raising question about lack of exposure to novel therapies driving poorer prognosis.

Clear and accurate identification of the underlying clonal disorder is key to accurate treatment selection. The underlying clonal disorder is distinctly a non-Hodgkins lymphoma in 54% (of those who had bone marrow biopsy available) of the cases in this series but plasma cell infiltration is still reported in a proportion (6%) as indeed is the lack of identifiable clonal infiltrate (14%). The latter group possibly indicates that the clone was mainly in lymph nodes with no BM involvement, justifying a lymph node biopsy. Given the substantial variability in BM reporting as evident above, accurate haematopathology review and use of molecular markers like MYD88 is critical. The poorer outcome in the group with excess plasma cells, perhaps, lends credence use of agents which actively target plasma cells, such as proteasome inhibitors, to be preferentially used in these cases. ~~Cross sectional imaging in IgM AL~~

~~amyloidosis, particularly to assess lymph node, soft tissue and lung disease, may have an important role. Particularly, in those with lymph node involvement where lymphoid component will respond to treatment but the amyloid may not change – posing a challenge in assessing "true" extent of response.~~ Imaging is important in this condition and its role, including PET-CT, needs clarification.

Contrary to clinical impression and previous publications, 74% of patients in this series had abnormal FLC. Patients with either FLC or paraprotein only response had improved outcomes. Since all patients had a detectable M-protein at a reasonable level, contrary to emerging literature in non-IgM AL amyloidosis, we feel that in IgM-AL both light chains and paraprotein should be used for response assessment.

Based on smaller series from us and other groups, treatment of patients with IgM-AL has evolved; patients with IgM AL do not fare well with the "standard" plasma cell directed treatments, not an unsurprising observation as most cases have an underlying NHL. This series encompasses the changing treatment profiles in this condition. Although a variety of regimes were used, Rituximab now forms a backbone in most regimes and is used with conventional alkylators (R-CD), purine analogues, bendamustine or with bortezomib with possible resultant better outcomes. However, the striking paucity of VGPR/CR (14% vs 44% in bortezomib treated non-IgM patients (56% in mayo stage I cases))[16], highlights the difficulties of deep clonal eradication in low grade NHL. There is a suggestion in this series that patients who reach VGPR have much better outcomes than lesser degrees of responses – 75% alive at 5 years compared to just over 50% of those with PR. This series validates that the goal of VGPR/CR still remains the therapeutic end point in patients with IgM-AL even in Mayo cardiac stage 2 or 3 disease. Achieving improvement in organ function is the final goal of therapy~~. However, t~~The lack of deep clonal responses also translated into poorer organ responses in this patient cohort compared to non-IgM AL.[17,18]

Although the median OS in this series is similar to previous reports[19], OS of early stage disease (Mayo stage 1 and 2) in IgM is poorer than non-IgM patients (75% OS at 5 years for stage I vs. >90% in non-IgM AL[20-22]); half the expected OS in Mayo stage 2 patients compared to non-IgM setting (2 vs ~4 years respectively). Paradoxically, OS of stage 3 appears no different compared to non-IgM-AL possibly due to a lower incidence of very advanced cardiac AL (NT-proBNP >8500 ng/L) in this series and secondly, the lack of a deep clonal response allowing for disease progression. This re-emphasises the need for development of novel agent based, highly and rapidly effective regimes for this patient group.

The factors impacting overall survival are dominated by cardiac involvement as in other non-IgM cases. Other poor prognostic factors were: older age (>67 yrs.) at presentation, AN or PN involvement, serum albumin <30g/L, dFLC >180mg/l, paraprotein >10g/L, liver involvement and >2 organs involvement. On multivariate analysis, independent factors impacting survival were presence of cardiac involvement (or mayo stage), PN and low serum albumin. The latter two are novel prognostic markers in this patient group. Serum albumin levels of <30g/L, has been previously reported to be associated with worse outcomes in IgM-AL and the utility of this marker is confirmed in current study.[5,7] The finding of PN as a significant factor has important therapeutic implication as proteasome inhibitor, bortezomib appears to be effective and PN may potentially limit its use. We propose new prognostic staging system for IgM-AL amyloidosis that include presence of PN and low serum albumin in figure 3a (supplementary table 1). A further study including patients from other major centres to validate this finding is in progress.

We acknowledge that this study has several limitations including its retrospective nature, small number of patients in each treatment group, lack of detailed haematopathology and imaging for lymphoma diagnosis. Prospective studies are t challenging due to rarity of IgM-AL and

difficulty of undertaking studies across national boundaries – wider international collaborative efforts may help to clarify these questions.

In summary, IgM related AL amyloidosis is a rare but distinct clinical entity of AL amyloidosis. A higher proportion of patients have lymph node involvement and lower proportion have cardiac involvement. Accurate characterisation of underlying clonal disorder is critical in the diagnostic work up of patients with IgM-AL. A revised staging system is proposed in this disease which requires further validation. Striving for VGPR/CR continues to be the goal of therapy.Currently, ASCT and bortezomib based regimes appear to be associated with best responses although the prolonged time to next treatment seen with FCR raises the important issue of accurately targeting the lymphoid component of the clone for longer term disease control. Novel targeted therapies need to be further explored in this condition. International tissue and data registry would help to broaden the understanding of this disease.

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Figure Legends

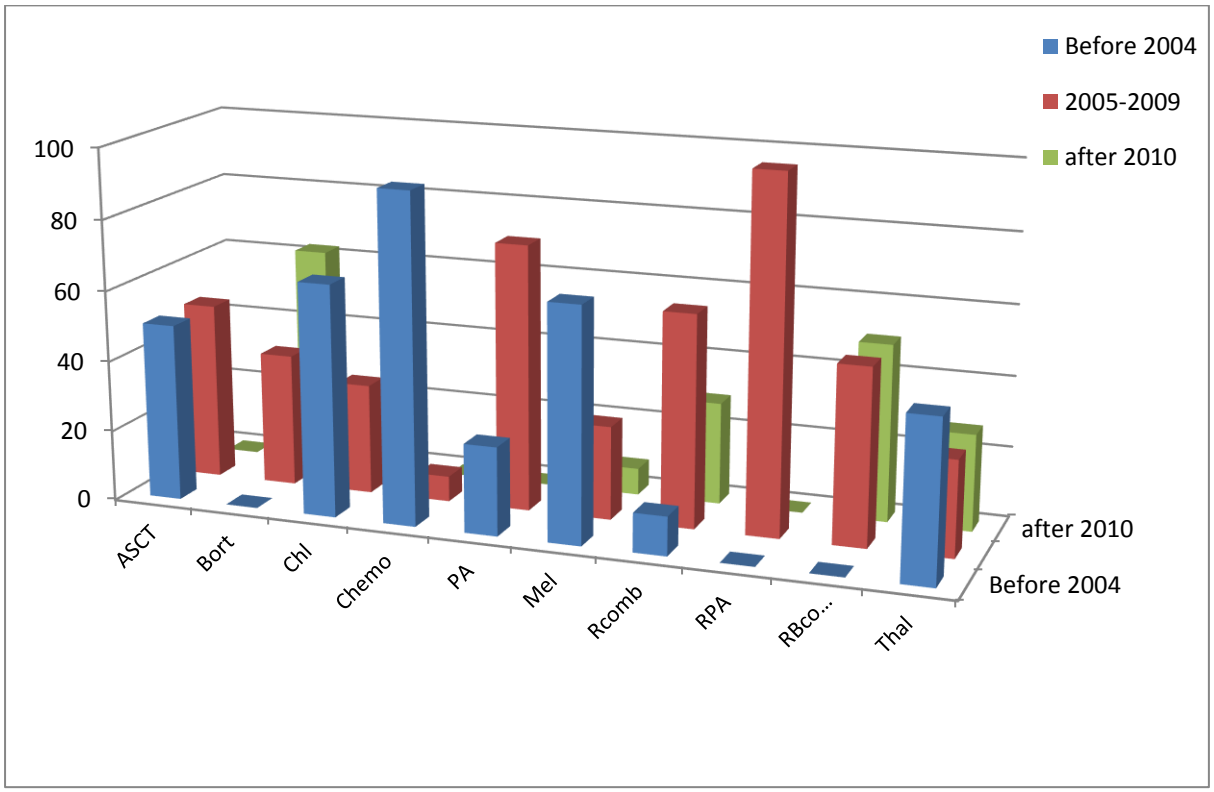
Figure 1: Shows the change in treatment trend over time for the ten different treatment groups; ASCT – Autologous Stem Cell Transplantation, Bortezomib based regimens, Chlorambucil, Conventional chemotherapy - CHOP/COP/VAD, PA – Purine Analogues, Melphalan, Rituximab + Conventional chemotherapy, RPA – Rituximab + Purine Analogues, RBortezomib – Rituximab + Bortezomib and Thalidomide based regimens, for the time period – pre 2004, 2005-2009 and after 2010.

Figure 2: Shows survival curves: **a)** Overall survival of patients with IgM related AL amyloidosis with median survival of 47.9 months; **b)** Survival over time - there was no improvement in the survival over the study period. Median OS - 48 months before 2004, 50 months for 2005-2009 and not reached for 2010 -2012; Figures c-f show survival by organ involvement: **c)** Survival curves by mayo stage - median OS for stage 1, 73 months, stage 2, 24 months and stage 3, 10 months (log rank p <0.001); **d)** Autonomic nervous system (ANS) involvement vs no involvement, median OS 15 months and 51 months respectively (p<0.001); **e)** albumin <30g/l vs >30g/l, median OS 29 months and 50 months respectively (p=0.008); **f)** dFLC >180mg/L vs dFLC <180mg/L, median OS 19 months and 48 months respectively (p=0.021).

Figure 3a-f: a) Shows the proposed new staging system using - BNP >332ng/L, cTnT >0.035 µg/L or cTnI >0.1µg/L, Albumin <30g/L and Involvement of PNS. Stage 1 – no abnormal features, Stage 2 – one abnormal feature and Stage 3 – two or more abnormal features. The median OS for stage 1, 2 and 3 were 73, 55 and 17 months respectively; **b-f)** Survival by response for entire cohort, by mayo stage and type of response; **b)** Median OS for those responded to first line treatment - 69 months and for non-responders – 28 months (p<0.012);

c) Median OS for those achieving a VGPR or better was not reached, PR was 64 months and for non-responders was 22 months; **d)** Median OS for responders within mayo stage 1 was 134 months and for non-responders was 62 months ($p=0.129$); **e)** median OS for responders within mayo stage 2 was 54 months and for non-responders was 8 months, ($p<0.001$) and **f)** Median OS for responders within mayo stage 3 was 29 months and for non-responders was 8 months, ($p=0.005$).

Figure 1:


Before 2004
2005-2009
after 2010
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80
60
40
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ASCT
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after 2010
Before 2004

Figure 2a-f:

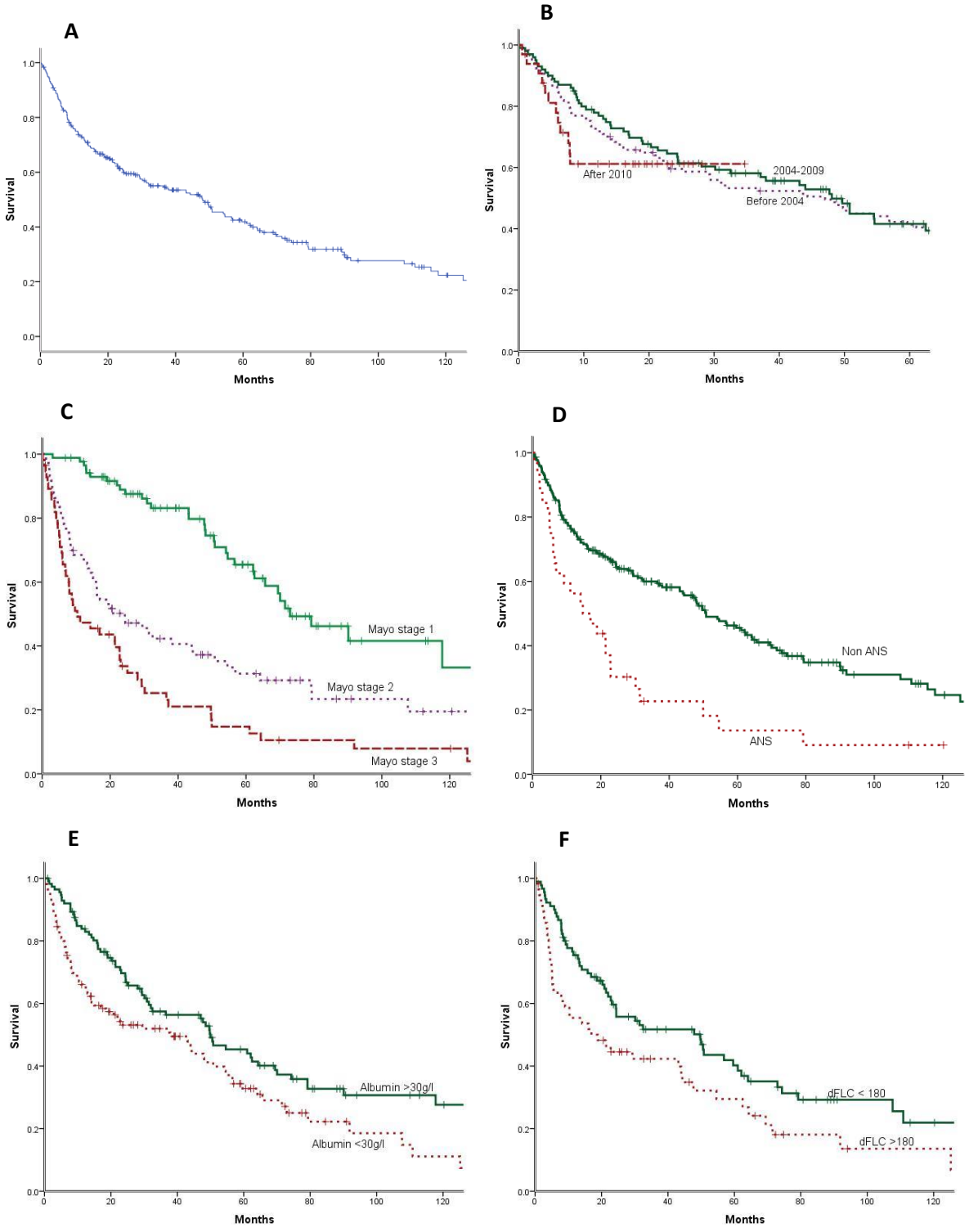
A
Survival
Months
B
After 2010
2004-2009
Before 2004
Survival
Months
C
Mayo stage 1
Mayo stage 2
Mayo stage 3
Survival
Months
D
Non ANS
ANS
Survival
Months
E
Albumin >30g/l
Albumin <30g/l
Survival
Months
F
dFLC < 180
dFLC >180
Survival
Months

Figure 3a-f:

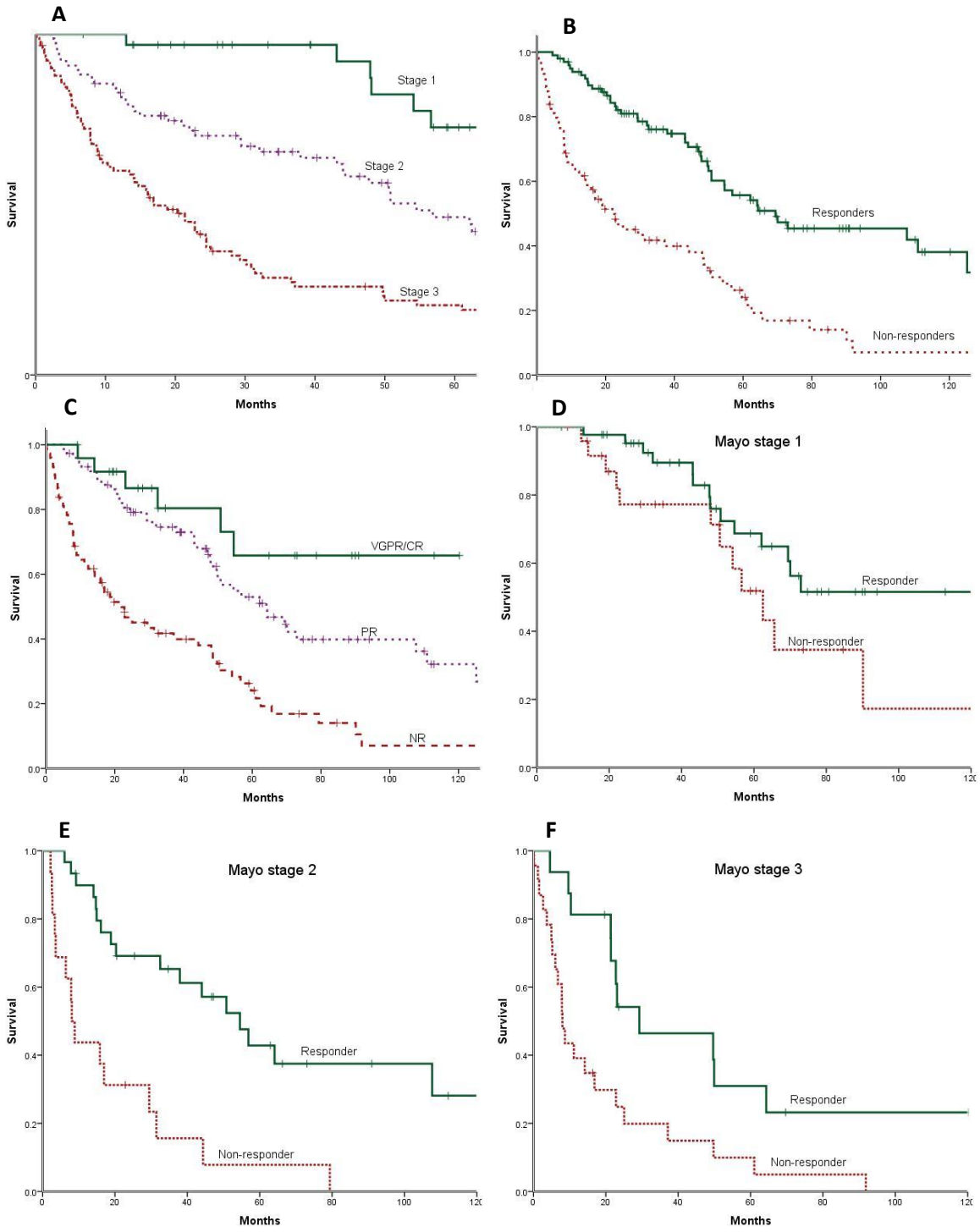
A
Stage 1
Stage 2
Stage 3
Survival
Months
B
Responders
Non-responders
Survival
Months
C
VGPR/CR
PR
NR
Survival
Months
D
Mayo stage 1
Responder
Non-responder
Survival
Months
E
Mayo stage 2
Responder
Non-responder
Survival
Months
F
Mayo stage 3
Responder
Non-responder
Survival
Months

Table 1- Patient demographics at presentation

	Median	No of patients (%)
Age at presentation (0%)	67 (38-89)	250
Sex (Male: Female ratio) (0%)	1.7:1	
Paraprotein concentration (g/L) (14%)	10 (IF-70)	
Monoclonal light chain type (0%)		
• **Kappa**		100 (40)
• **Lambda**		150 (60)
Abnormal FLC ratio (12%)		163 / 221 (74)
Evaluable FLC (12%)		147 / 221 (67)
dFLC (mg/l) at presentation • **Kappa** • **Lambda**	122.3 (30-7762) 100.5 (30-1343) 155 (41-7762)	
Hemoglobin (g/L) (13%)	12.5 (7.8-17.7	
Total white cell count (x 10^9/L) (30%)	7.04 (0.56-23)	
Platelets (x 10^9/L) (30%)	294.5 (18-757)	
Creatinine (µmol/L) (2%)	97.2 (42-ESRD)	
Albumin (g/L) (11%)	35 (12–49)	
Alkaline phosphatase (IU/L) (13%)	129 (42-3488)	
24 hour proteinuria (g/24 hrs) (8%)	1.78 (0-45)	
Creatinine clearance (ml/min) (55%)	64 (ESRD-157)	
Organ involvement (1%)		
No of organs involved	2 (1-6)	
• **1**		81 (32)
• **2**		89 (36)
• **3 or more**		80 (32)
Cardiac (0.8%)		112 (45)
• **NT-proBNP (ng/L) (14%)** **NT-proBNP >8500 ng/L**	609 (17-120737) 19 (9%)	
• **cTnT (ng/ml) / (22%)** • **cTnI (ng/ml)**	0.020(0.003-0.467) 0.020(0.002-0.599)	
• **IVS (mm) (20%)**	12 (7-22)	232 (79)
Mayo stage (14%)		216 (86)
• **Stage 1**		87 (40)
• **Stage 2**		73 (34)
• **Stage 3**		56 (26)
Renal (0%)		169 (68)
Liver (0%)		41 (17)
Soft tissue (0%) • **Lymph node**		80 (35) 50 (20)
PNS (0%)		37 (15)
ANS (0.4%)		32 (13)
GI (1%)		22 (9)

IF – immunofixation; dFLC - difference between involved (amyloidogenic) and uninvolved free light chain; ESRD – end stage renal failure; NT-proBNP - N-terminal pro–natriuretic

peptide type B; cTnT- Cardiac Troponin T; IVS - interventricular septum; PNS – peripheral nervous system; ANS - autonomic nervous system; GI - Gastrointestinal system.

Table 2 – Haematological response, median OS, two year survival and time to next treatment (TTNT) for each treatment group

Treatment type	N (%)	Proportion with cardiac involvement (Mayo stage 3, %)	PR or better % (VGPR or better, %)	Median OS (Months)	2 year survival (%)	TTNT (Months)
ASCT	4 (1.8)	25 (0)	100 (33)	NR	100	NR
Chlorambucil / Cyclophosphamide	62 (27.1)	41 (25)	46 (7)	50.8	73	11
CHOP/COP/VAD	14 (6.1)	21 (33)	62 (0)	49.8	79	21
Melphalan +/-Dex	53 (23)	58 (28)	70 (26)	22.9	49	8
FC/CLAD	12 (5)	42 (25)	40 (0)	31.4	58	10
FCR	11 (4.8)	27 (0)	70 (30)	69.4	73	63
RCD/RCHL/RCVP/RCHOP/RTD	45 (19.7)	44 (23)	63 (15)	91.9	63	20
Bortezomib	8 (3.5)	50 (25)	57 (42)	NR	88	NR
Rituximab+Bortezomib	8 (3.5)	50 (25)	86 (29)	30.2	75	19
Thalidomide	11 (4.8)	36 (27)	63 (9)	37.9	55	5

ASCT – Autologous stem cell transplantation; CHOP - cyclophosphamide, vincristine, doxorubicin and prednisolone; COP - cyclophosphamide, vincristine and prednisolone; VAD – Vincristine, Adriamycin and dexamethasone; FC – Fludarabine and cyclophosphamide; CLAD – Cladribine; FCR – Fludarabine, cyclophosphamide and Rituximab; RCD – Rituximab, cyclophosphamide and dexamethasone; RCHL: Rituximab and Chlorambucil; RCVP - Rituximab, cyclophosphamide, vincristine and prednisolone; RCHOP - Rituximab, cyclophosphamide, vincristine, doxorubicin and prednisolone; NR – Not reached.

Table 3 - Factors affecting overall survival – univariate and multivariate analysis

Factor	Median survival (months)	Univariate HR (95%CI); p-values	Multivariate HR (95%CI); p-values Noise in model: 0.179 Harrell's C coef: 0.75
Age (years) (<67 vs >67)	62 vs 29	1.64 (1.40-1.92); <0.001	1.55 (1.37-1.76); <0.001
Paraprotein >10 vs <10	48 vs 50	1.27 (1.04-1.54); 0.019	1.22 (0.95-1.56); 0.125
dFlc (mg/l) (<180 vs >180)	48 vs 19	1.51 (1.07-2.15); 0.021	
NHL type			
MGUS	54	Ref	
WM/LPL	38	1.43 (0.67-3.06); 1.000	
Other NHL	50	1.35 (0.62-2.94); 1.000	
PC	23	1.54 (0.94-2.54); 0.131	
Cardiac vs Non Cardiac	21 vs 62	2.34 (1.65-3.30); <0.001	2.41 (1.07-5.45); 0.034
Mayo stage			Not included
Mayo stage 1	73	Ref	
Mayo stage 2	24	2.63 (2.14-3.24); <0.001	
Mayo stage 3	10	4.46 (3.11-6.39); <0.001	
Nt-proBNP(ng/l) (>332 vs <332)	19 vs 73	3.15 (2.66-3.72); <0.001	Not included
cTnT >0.035 µg/L or cTnI>0.1µg/L	10 vs 57	2.79 (1.96-3.97); <0.001	
Soft tissue vs no Soft tissue	44 vs 55	0.77 (0.49-1.20); 0.244	1.18 (0.53-2.63); 0.690
PNS vs no PNS	23 vs 50	1.54 (1.21-1.95); <0.001	1.82 (1.56-2.11); <0.001
ANS vs no ANS	15 vs 51	2.27 (1.53-3.37); <0.001	1.72 (0.81-3.64); 0.158
GI vs no GI involvement	24 vs 49	1.19 (0.78-1.84); 0.420	1.43 (0.82-2.47); 0.204
Renal vs non Renal	43 vs 55	1.26 (0.91-1.75); 0.171	1.26 (0.90-1.75); 0.176
Liver vs non Liver	21 vs 51	1.36 (1.22-1.52); <0.001	1.57 (0.98-2.51); 0.059
Albumin (>30g/l vs <30g/l)	50 vs 29	0.64 (0.46-0.89); 0.008	0.56 (0.31-1.02); 0.057
Organ involvement			
1	69	Ref	
2	48	1.34 (0.79-2.29); 0.563	
>3	19	2.42 (1.73-3.37); <0.001	
Haematological response vs no response	69 vs 28	0.58 (0.38-0.88); 0.012	0.56 (0.33-0.94); 0.028
Type of haematological response			
NR	28	Ref	
PR	64	0.64 (0.40-1.04); 0.073	
CR/VGPR	Not reached	0.36 (0.21-0.61); <0.001	

dFLC - difference between involved (amyloidogenic) and uninvolved free light chain; NHL – Non-Hodgkins lymphoma; MGUS – Monoclonal gammonpathy of uncertain significance; WM/LPL – Waldenstrom's macroglobinemia / Lymphaplasmacytic lymphoma; PC – Plasma cell myeloma; NT-proBNP - N-terminal pro–natriuretic peptide type B; PNS – peripheral nervous system; ANS - autonomic nervous system; GI - Gastrointestinal system; NR – Non responders; PR – Partial response; CR/VGPR – Complete response / Very good partial response.

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