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a Danish population-based cohort study

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TITLE:
Smoldering multiple myeloma risk factors for progression: a Danish population-based cohort study.

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ABSTRACT:
Several risk scores for disease progression in Smoldering Multiple Myeloma (SMM) patients have been proposed, however, all have been developed using single center registries. To examine risk factors for time to progression (TTP) to Multiple Myeloma (MM) for SMM we analyzed a nationwide population-based cohort of 321 newly diagnosed SMM patients registered within the Danish Multiple Myeloma Registry between 2005 and 2014. Significant univariable risk factors for TTP were selected for multivariable Cox regression analyses. We found that both an M-protein ≥ 30g/l and immunoparesis significantly influenced TTP (HR 2.7, 95%CI(1.5;4.7), p=0.001, and HR 3.3, 95%CI(1.4;7.8), p=0.002 respectively). High free light chain (FLC) ratio did not significantly influence TTP in our cohort. Therefore, our data do not support the recent IMWG proposal of identifying patients with FLC ratio above 100 as having ultra-high risk of transformation to MM. Using only immunoparesis and M-protein ≥ 30g/l, we created a scoring system to identify low, intermediate and high risk SMM. This...
first population-based study of SMM patients confirms that an M-protein $\geq 30g/l$ and immunoparesis remain important risk factors for progression to MM.

Introduction
Smoldering (asymptomatic) multiple myeloma (SMM) is defined as having a monoclonal protein (M-protein) of $3g/dl$ ($30g/l$) or urinary monoclonal protein $\geq 500mg/24h$ and/or 10-60% bone marrow clonal plasma cells and no end-organ damage (1). Although a recent clinical trial showed that high risk SMM patients may benefit from early treatment before multiple myeloma (MM) criteria are met, guidelines recommend a “watchful waiting” approach using M-protein, routine biochemistry and blood count as well as skeletal survey, preferably MRI, for follow-up every 4-6 or 6-12 months, depending on disease stability (1–3).

Current risk models for progression from SMM to MM include presence of immunoparesis (reduction in one or more of the uninvolved immunoglobulin), aberrant plasma cell percentage (PC)% $> 95\%$ (defined by flow cytometry) and bone marrow PC% (BMPC%) $\geq 10\%$ together with abnormal free light chain ratio (FLCr) and M-protein $\geq 30g/l$ (4–6). Recently, chromosomal aberrations and focal bone marrow lesions on MRI have also been used to define progression risk in SMM(7,8). Furthermore, a new 4-gene (GEP4) high risk SMM signature (SWOG S0120) has been developed by the Arkansas Group (9). However, currently there is no consensus on how to classify low, intermediate or high risk SMM and one study has shown discrepancies between major risk models when applied to the same cohort (10).
The aim of this population-based study was to assess risk factors for progression to multiple myeloma in SMM patients using the Danish Multiple Myeloma Registry (DMMR), which includes information on all diagnosed SMM patients in Denmark since 2005.

Methods

Study population

The DMMR is population-based, covering all new multiple myeloma cases in Denmark since 1 January 2005 (11,12). Symptomatic MM patients in the DMMR are defined according to the IMWG 2003 criteria (13). All hematological centers are obliged to register all patients with multiple myeloma (and other malignant plasma cell disorders) at the time of diagnosis, and subsequently report data concerning the initial treatment and response to treatment. Patients are identified by the 10-digit Civil Personal Registration number (CPR-number) used for all public records within the Danish National Health Service. These data are linked with the National Patient Registry in Denmark to ensure that all myeloma diagnoses are correct and capture any potential myeloma patients who are not reported to the registry at time of diagnosis. As of 1 January 2014, 2879 cases of newly diagnosed MM (including SMM) have been registered. The DMMR contains information about time of diagnosis, patient age, gender, M-protein type and concentration, uninvolved immunoglobulin concentrations (as measured with standard nephelometry), International Staging System (ISS) score, bone lesions, bone marrow clonal plasma cell involvement and routine biochemistry. Our study involved all newly diagnosed SMM patients registered in the DMMR between 1 January 2005 and 31 December 2013. All SMM patients met the criteria according to the International Myeloma Working Group (IMWG) 2010 consensus report, and no patients received any anti-myeloma treatment (2). We chose a cut-off value of 3 months from the
date of diagnosis of SMM with no progression/events and excluded 9 patients due to early
death and 2 patients due to early progression. This led to a study population of 321 SMM
patients (Table 1). We defined immunoparesis as at least one uninvolved immunoglobulin
below reference levels IgG < 6.1 g/l, IgA < 0.70 g/l and/or IgM < 0.39 g/l at diagnosis.

Statistics
The sample size of our cohort was found to be acceptable for investigating factors
associated with progression. With a power of 0.8 and a two-sided level of significance of
0.05, a Hazard ratio of 1.9 is needed to find a significant association. Baseline characteristics
were described using median, interquartile range (IQR) and range for continuous variables
and by frequencies and percentages. Proportional hazard assumption and linearity of
continuous variables were investigated. Univariable Cox regression analysis was used to
estimate risk factors for time to progression (TTP) with hazard ratios (HR) and 95% CI.
Significant univariable risk factors were selected for multivariable Cox regression analyses.
First, all significant risk factors were entered in a model and afterwards a backward
selection method was used to eliminate insignificant risk factors. The Kaplan-Meier method
was then used for estimation of progression rate.

All statistical analyses were performed using SPSS ver. 22.0 (IBM corporation, Armonk, NY,
USA) and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria). This
study was approved by the Danish Data Protection Agency (jr.no. 2014-331-0790 and 30-
1269) and the Danish Health and Medicines Authority (jr.no. 3-3013-676/1).
Results

Three-hundred-twenty-one of 2879 MM patients met the criteria for SMM, corresponding to 11% of the total Danish MM population. This is slightly lower than observed in a recent Swedish analysis that reported a SMM prevalence of 14.4% of all myeloma patients in line with previous studies(14,15). The median age at diagnosis was 70 years and the male-female ratio was 46% (males) to 54% (females) (Table 1). Free light chain (FLC) analyses were introduced in the standard myeloma diagnostic work-up in Denmark from 2007. Therefore, results on FLCr measured within 2 months of diagnosis could be obtained in 209 (65%) patients diagnosed after 2007, of whom 51% (n = 106) had an abnormal ratio < 1/8 or > 8 as defined by Dispenzieri et al (5). Sixty-nine percent of the cohort (216 of 313 with registered serum immunoglobulins) had immunoparesis. Three SMM cases (1%) had BMPC% ≥ 60%, and 23 (11%) had a documented FLCr ≥ 100 (with involved FLC > 100mg/l), thus fulfilling the recent IMWG updated criteria for symptomatic MM (no data on focal lesions on MRI are registered in the DMMR)(1).

Prognostic factors for disease progression to MM:

Univariable risk factors for TTP were tested for all 321 SMM cases. Sixty-one patients progressed to MM within a median follow up time of 729 days (median TTP not reached). The total number of patients that progressed at 2 years was 50, which was equivalent to 82% of all patients who progressed within the follow-up period (IQR 383-1376 days). Results for TTP are shown in Table 1. Of notice high clonal BMPC % was a significant risk factor for progression (p = 0.02) using PC% as continuous variable but BMPC % was not significant when defined as ≥ 10% versus <10% (HR 0.8 (0.2;3.3) p=0.75). High M-protein level at diagnosis was a risk factor for TTP, in particular, when immunoglobulin levels were above...
30g/l (HR 3.0 p =0.0003). The presence of immunoparesis significantly shortened TTP (HR 3.7 p < 0.0002). In the 209 patients with FLC measured at diagnosis, a high FLC ratio (the ratio between the highest of either kappa or lambda subtype and the lowest) did not significantly increase the risk of progression (HR 1.5 (0.9;2.3, p=0.10). Similarly, an abnormal FLCr (>8 or <0.125) did not significantly increase the risk of progression (n=106, HR 1.8 (0.8;3.8), p=0.12). Twenty-three patients with a FLCr ≥ 100 (with involved FLC > 100mg/l) showed an increased 2-year progression risk of 30.4% (95CI 5.4;48.8) compared to patients with FLCr of 0.01-100 (figure 2). However, this difference was only near-significant with a HR = 2.4 (1.0;5.9), p=0.06.

**Risk score for SMM progression to MM.**

Multivariable Cox regression on significant univariable risk factors for TTP (BMPC%, M-protein level ≥ 30 g/l, immunoparesis, B2M, and albumin levels) demonstrated M-protein levels ≥ 30g/l and presence of immunoparesis as independent risk factors for progression (HR 2.7 p=0.001 and HR 3.3 p=0.02, respectively) (Table 2). We constructed a risk model based on the risk factors M-protein ≥ 30g/l and presence of immunoparesis. Each risk factor was assigned 1 point and we categorized patients into low-risk (0 points, n = 90), intermediate risk (1 point, n= 165) and high risk (2 points, n = 42) (Figure 1, Table 2). Risk of progression at 2 years was 5%, 18% and 38% for a score of 0, 1 or 2 risk factors, respectively, and increased to 9%, 24% and 55%, respectively, at 5 years from diagnosis (Figure 1, P<0.001, table III). We tested the same risk stratification on the population using the new IMWG criteria for SMM. Exclusion of these “ultra-high risk” SMM patients (n=26) with BM PC >60% or FLCr ≥ 100 did not affect the risk stratification, in fact, the risk of
progression at 2 years was then 4%, 17% and 44% with the score 0, 1 or 2, respectively (p<0.0001). Furthermore, the impact of FLCr was tested in a multivariable analysis on the subgroup of patients with FLC registered (n=209). Multivariable cox regression using near significant (p<0.2) univariable values immunoparesis, M-protein level ≥ 30 g/l, abnormal FLCr, BMPC% and albumin levels did not change the impact of FLCr on TTP (HR 1.1 p=0.86). In this subgroup we did not find FLCr to be an independent risk factor for TTP.

Discussion

We report the first population-based, large retrospective cohort study on independent risk factors for progression in smoldering multiple myeloma. In line with previous single center studies, we found that M-protein ≥ 30g/l and presence of immunoparesis are markers for time to progression to MM in SMM.

There is increasing knowledge on risk factors for progression in myeloma precursor diseases. The question is how we best define the high risk group given the wide range of new risk factors. A recent meta-analysis on different treatment strategies in SMM demonstrated that only high risk SMM patients in the PETHEMA clinical trial did benefit from early treatment, which underlines the need for a clear definition of this subgroup of patients (16). In the PETHEMA clinical trial, high risk SMM was defined by PC% ≥ 10, high M-protein (≥ 20g/l for IgA, ≥ 30g/l for IgG or ≥ 1g/24h for urinary Bence-Jones protein) or one of these two plus ≥ 95% aberrant plasma cells and immunoparesis defined as (a reduction of at least 25%) in 1 or 2 uninvolved immunoglobulins below reference values (3). Sixty-nine percent of our cohort presented with immunoparesis at diagnosis, which is in line with previous findings of 52-83% (4,17). We analyzed the impact of different levels of suppression of the uninvolved immunoglobulins on risk of progression and found no
difference between patients with 25% reduction as compared to those with 50% or 75% reduction (hazard ratios 3.5, 2.5 and 2.6, respectively). Suppression of two versus one uninvolved immunoglobulins indicated a higher risk of progression in our study; however, the differences in HR were limited (Table 2). Our findings support and simplify immunoparesis as a risk factor of progression in SMM: suppression of one uninvolved immunoglobulin below normal level is sufficient to identify increased risk of progression to multiple myeloma.

Dispenzieri et al. showed that PC % > 10 had a higher impact on progression than both M-protein > 3g/dl and abnormal FLCr (5). In contrast, we found that a PC% ≥ 10 did not contribute as an independent risk factor in our cohort. However, this result is questionable, as only 5 of our patients had PC % < 10 at diagnosis, leaving the statistical power too low to detect any differences. We showed that high PC % was a significant risk factor for progression as a continuous value; however, it failed in the multivariate analysis and could therefore not be included in our risk score (Table 1). In line with the IMWG diagnostic criteria, the bone marrow PC % was, in our cohort, estimated using the highest value of either the bone marrow biopsy stained with hematoxylin and eosin, the bone marrow aspirate or from the bone marrow imprint at the time of diagnosis. The Mayo Clinic study used an average of the aspirate and biopsy estimates of PC % which could therefore possibly result in a lower median PC count than in our cohort (5,17).

The updated IMWG criteria includes FLCr ≥ 100 (with involved FLC > 100mg/l) and BMPC% > 10 as a criterion for MM. This recommendation was based on 2 studies that showed 76% and nearly 100% 2-year progression risk in SMM patients with FLCr ≥ 100, respectively (6,18). The goal for IMWG to change the definitions was to identify SMM patients that have

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a ≥ 80% risk of progression to myeloma within 2 years. Upfront treatment of these patients should be considered to avoid early onset of irreversible organ damage, e.g. bone destruction. In our population-based study, we found that 23 patients fulfilling these criteria had only a 30% 2-year progression risk for symptomatic MM (figure 2). A risk below 80% of progression to MM, namely a 64% risk, was also observed in the recent study by Waxman et al.(19). Patients with high FLCr are probably at increased risk of development of renal affection and should be carefully observed. However, our data and the Waxman study do not support FLCr above 100 as a stand-alone ultra-high risk criterion.

Surprisingly, we only found a trend towards an association between abnormal FLCr > 8 or below 1/8 and risk of progression in the Danish SMM population (HR 1.9 (95%CI 0.9;4.1), p=0.10). We may have introduced a bias because only 65% (n=209) of patients had FLCs measured at diagnosis, all of which were diagnosed after 2007 leaving the median follow up for TTP shorter (653 vs. 729 days) and the number of progression events substantially lower (n=28 vs. n=60) than the entire cohort. Still, our multivariable analysis of this subgroup of patients could not detect an increased risk of progression and we can only speculate what impact the FLCr would have made if the entire cohort had FLC measurements registered.

Our definition of high-risk SMM patients did not meet the near 80% progression risk at 2 years, which by IMWG has been proposed as a definition of imminent symptomatic disease. Our cohort represents the general myeloma population and likely includes more SMM patients with an indolent disease than other single center studies. In fact, only 11 patients of the 209 with available FLC data fulfilled the 2008 Mayo Clinic high-risk criteria, and only four of these patients had progressed within 2 years. Waxman et al. recently proposed a SMM risk classification model (The Penn model) using BM PC ≥ 40%, FLCr ≥ 50 and albumin ≤ 3.5
g/dl to define SMM patients with a 81% risk of progression within 2 years after diagnosis (19). Only three patients in our cohort fulfilled these high risk criteria (none progressed to MM within the follow-up), and we are therefore not able to validate the Penn model risk classification. Low albumin level did correlate to increased risk of progression (albumin cont. HR 0.5, p=0.01)) in univariable analysis; however, albumin was not an independent risk factor in the multivariable analysis (Tables I and II).

The Penn model is based on single center observations. Here, we introduce the first population-based prognostic scoring system using two easily assessable markers; immunoparesis and M-protein level. Our risk score is simple, easily performed, and does not require advanced diagnostics. Examinations of aberrant PC markers by flow cytometry, cytogenetics and gene expression profiling are not available at all centers. Importantly, our risk score also proved robust in patients still identified as SMM patients after introduction of the updated IMWG SMM criteria (1), although we do not have data on how many patients that would have been classified as symptomatic MM due to the MRI criteria of more than one bone marrow focal lesion. We recommend that patients with our definition of high risk SMM should be observed more carefully and considered candidates for randomized clinical trials.

ACKNOWLEDGMENTS:
The authors would like to thank the University of Copenhagen Graduate School of Health and Medical Sciences for funding of a PhD Scholarship to RS.
AUTHORSHIP:

RS: data collection, analysis, wrote the first draft of the article. TWK: statistical support. MS, AJV, NA, PG: data collection, analysis. HG, UCF, NFA, CH, KTA, BØ, RSP, PP: data collection. All authors reviewed the draft and provided detailed comments and inputs and contributed to as well as approved the final manuscript. All authors have no conflict of interest to declare.

References:


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Table I:

Smoldering Multiple Myeloma Cohort (n=321) | Univariable Time to Progression (TTP)

Median Follow up: 729 days

Number of events: 61

<table>
<thead>
<tr>
<th>Age, median (Interquartile range, (IQR))</th>
<th>HR</th>
<th>95% CIs</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;65, &gt;65)</td>
<td>0.7</td>
<td>0.4;1.2</td>
<td>p=0.17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender (F/M) (number (%))</th>
<th>HR</th>
<th>95% CIs</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F/M)</td>
<td>0.9</td>
<td>0.5;1.5</td>
<td>p=0.69</td>
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</table>

<table>
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<tr>
<th>BM PC% (n=320), median, (IQR)</th>
<th>%PC (continuous values)</th>
<th>HR</th>
<th>95% CIs</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (11;20)</td>
<td>1.02</td>
<td></td>
<td>1.01;1.04</td>
<td>p=0.02</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>P-M-protein (number (%))</th>
<th>M-protein-subtype (IgA versus IgG)</th>
<th>HR</th>
<th>95% CIs</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA 110 (34%)</td>
<td>0.8</td>
<td></td>
<td>0.5;1.4</td>
<td>p=0.42</td>
</tr>
<tr>
<td>IgG 182 (57%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCD 10 (3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM 3 (1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than one 5 (2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown 11 (3%)</td>
<td></td>
<td></td>
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</table>

<table>
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<tr>
<th>M-protein (g/l) (IQR) (n = 303)</th>
<th>M-protein &lt;30 g/l, ≥30g/l</th>
<th>HR</th>
<th>95% CIs</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>16 (9.4;25)</td>
<td>3.0</td>
<td></td>
<td>1.7;5.2</td>
<td>p=0.0003</td>
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</table>

<table>
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<tr>
<th>Urine-M-protein, (number (%))</th>
<th>M-protein-subtype (IgA versus IgG)</th>
<th>HR</th>
<th>95% CIs</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>No data 93 (29%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present 143 (45%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present 85 (26%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

| Subtype | Kappa 49 (58%) | Lambda 34 (40%) | Unspecified 2 (2%) |

<table>
<thead>
<tr>
<th>Immunoparesis (Yes/no), (number (%))</th>
<th>M-protein-subtype (IgA versus IgG)</th>
<th>HR</th>
<th>95% CIs</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>214 (69%) / 98 (31%)</td>
<td>3.7</td>
<td></td>
<td>1.7;8.1</td>
<td>p=0.0002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number. of suppressed uninvolved immunoglobulins (number (%))</th>
<th>Immunoparesis (0 ref,1 versus 2)</th>
<th>HR</th>
<th>95% CIs</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 98 (31.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 95 (30.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;=2 119 (38.1%)</td>
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<thead>
<tr>
<th>Reduction level of uninvolved immunoglobulin (number (%))</th>
<th>Immunoparesis (0 ref,1 versus 2)</th>
<th>HR</th>
<th>95% CIs</th>
<th>P</th>
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</thead>
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<tr>
<td>25% 164 (52%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% 110 (35%)</td>
<td></td>
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Table 2:

Multivariable analysis

<table>
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<tr>
<th>Time to progression from SMM to MM (n = 297)</th>
<th>HR</th>
<th>95% CIs</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoparesis present</td>
<td>3.3</td>
<td>(1.4;7.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>M-protein ≥ 30g/l</td>
<td>2.7</td>
<td>(1.5;4.7)</td>
<td>0.001</td>
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</tbody>
</table>

HR=Hazard Ratios. CI= Confidence Interval
Table 3:

<table>
<thead>
<tr>
<th>Risk score</th>
<th>%</th>
<th>95% CIs</th>
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</thead>
<tbody>
<tr>
<td>0 (low)</td>
<td>4.8%</td>
<td>(0.1; 9.3)</td>
</tr>
<tr>
<td>1 (int.)</td>
<td>18.1%</td>
<td>(11.4; 24.3)</td>
</tr>
<tr>
<td>2 (high)</td>
<td>38.4%</td>
<td>(20.9; 52.0)</td>
</tr>
</tbody>
</table>

CI= Confidence Interval
Figure 1

Proportion progressed to MM

Time from diagnosis (months)

Numbers at risk

- 0

- 1

- 2

P < 0.0001
Figure 2

Proportion progressed to MM

Time from diagnosis (months)

- Fl Cr < 100
- FlCr ≥ 100

P = 0.06
Figure legends:

Table 1: Baseline characteristics and univariable risk factors for progression for the Danish smoldering multiple myeloma population 2005-2014.

Table 2: Multivariable analysis of risk factors for progression in the Danish SMM population.

Table 3: 2 year progression risk for the SMM risk score model.

Figure 1: Risk score model for time to progression (TTP) using immunoparesis and M-protein ≥ 30g/l.

Low risk was defined as a score of 0, (no immunoparesis and M-protein <30g/l), intermediate risk with a score of 1 (immunoparesis or M-protein ≥30g/l) and high risk with a score of 2 (immunoparesis and M-protein ≥ 30g/l). The model predicted a 38% progression risk at 2 years (24 months) and 50% at 3 years (36 months) from diagnosis for the high risk group.

Figure 2: Risk of progression for patients with FLCr ≥ 100 vs. compared to patients with FLCr < 100.

Twenty-three patients (11%) had a FLCr ≥ 100 (or FLCr ≤ 0.01) and iFLC >100mg/l, and 186 patients had FLCr 0.01-100. The 2-year (24 months) progression risk was 30.4% (95CI 5.4%;48.8%) with a HR = 2.4 (1.0;5.9), p=0.06 for the patients with FLCr ≥ 100.

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