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DR. LOUISE REDDER (Orcid ID : 0000-0003-3965-2025)

DR. ANNETTE JUUL VANGSTED (Orcid ID : 0000-0002-2131-731X)

DR. LENE KONGSGAARD NIELSEN (Orcid ID : 0000-0003-2083-3870)

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Corresponding author mail id: louise.redder3@rsyd.dk

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Validation of the UK Myeloma Research Alliance Risk Profile, a new Clinical Prediction Model for Outcome in Patients with Newly Diagnosed Multiple Myeloma not Eligible for Autologous Stem-Cell Transplantation; A Population-Based Study from the Danish National Multiple Myeloma Registry

Louise Redder, MD[1], Tobias Wirenfeldt Klausen, M.S.[2], Annette Juul Vangsted, MD, PhD[3], Henrik Gregersen, MD, PhD[4], Niels Frost Andersen, MD, PhD[5], Robert Schou Pedersen, MD, PhD[6], Agoston Gyula Szabo MD[7], Mikael Frederiksen, MD[8], Ulf Christian Frølund, MD[9], Carsten Helleberg, MD[2], Lene Kongsgaard Nielsen, MD, PhD[1,10], Per Trøllund Pedersen, MD[11], Morten Salomo, MD, PhD[3],

Peter Gimsing, MD, DMSc[3], Henrik Frederiksen, MD, Professor[1,12,13] and Niels Abildgaard, MD, Professor[1,12,13]

[1]Department of Haematology, Odense University Hospital, Odense, Denmark; [2]Department of Haematology, Herlev Hospital, Herlev, Denmark; [3]Department Haematology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [4]Department of Haematology, Aalborg University Hospital, Aalborg, Denmark; [5]Department of Haematology, Aarhus University Hospital, Aarhus, Denmark; [6]Department of Haematology, Holstebro Hospital, Denmark; [7]Department of Haematology, Vejle Hospital, Vejle, Denmark; [8]Department of Haematology, Hospital of Southern Jutland, Aabenraa, Denmark; [9]Department of Haematology, Zealand University Hospital, Roskilde, Denmark; [10]Department of Internal Medicine and Cardiology, Regional Hospital Viborg, Denmark; [11]Department of Haematology, South-Western Hospital, Esbjerg, Denmark; [12]Academy of Geriatric Cancer Research (AgeCare), Odense University Hospital, Odense, Denmark; [13]Department of Clinical Research, University of Southern Denmark, Odense, Denmark.

Introduction

The heterogeneity of patients with multiple myeloma (MM) is significant based on both the biology of the malignant plasma cells and age and comorbidity of the patients, causing a wide range in survival from few months to more than 10 years(Rajkumar, 2018). This has caused a need for prognostic models. The International Staging System (ISS) was introduced in 2005(Greipp *et al*, 2005) and later improved by inclusion of high-risk cytogenetic aberrations and lactate dehydrogenase (LDH) in the revised ISS (R-ISS)(Palumbo *et al*, 2015a). A number of other scoring systems have been introduced that include patient related factors, e.g. the IMWG frailty score (Palumbo *et al*, 2015b) the revised myeloma comorbidity index (R-MCI)(Engelhardt *et al*, 2017), Haematopoietic Cell Transplant Comorbidity Index (HCT-CI)(Saad *et al*, 2014), Myeloma prognostic index(MPI) (Kim *et al*, 2017) and Charlson Comorbidity Index (CCI)(Bila *et al*, 2015). All of these have been tested in patients with MM, but not implemented in the daily clinic. Some of the scores are rather time consuming to use, others have not achieved international credit and recognition, which might be some of the reasons why consensus is still lacking in the field.

Latest, the UK Myeloma Research Alliance introduced a new clinical prediction model for outcome in patients with newly diagnosed MM, ineligible for autologous haematopoietic stem-cell transplantation (ASCT)(Cook *et al*, 2019). The score or Myeloma Risk Profile (MRP) includes WHO performance status (PS), ISS stage, age and C-reactive protein (CRP) as prognostic variables. The score is calculated by the formula: Score = (PS – 2) * 0.199 + (age – 74.4) * 0.0165 + (ISS – 2) * 0.212 + (log(CRP + 1) – 2.08) * 0.0315, where PS and ISS are defined as numbers between 0-4 and 1-3, respectively, and CRP is in mg/L. By this calculation, patients with MM are stratified into one of the following three risk groups: low risk: score < -0.256, medium risk: -0.256 ≤ score ≤ -0.0283 and high risk: score > -0.0283.

The MRP score was generated based on two prospective clinical trial cohorts; the NRCI-XI study(Jackson *et al*, 2019) as training set or internal validation, and the MRC-IX study(Morgan *et al*, 2011) as test set or external validation. Both trials investigated conventional oral alkylating agents, cyclophosphamide or melphalan, in combination with thalidomide, lenalidomide, and/or bortezomib; thus including drugs typically used in treatment of elderly patients with MM. Establishment of the model included 1,852 patients in the training set and 520 patients in the test set. All patients were recruited as part of clinical trials and therefore met defined inclusion and exclusion criteria.

Since only 36.6 % of newly diagnosed patients with MM above 65 years in the general population meet the inclusion criteria in clinical trials(Klausen *et al*, 2019), we found it relevant to validate the MRP score in a population-based setting.

Methods

We performed a study of the entire cohort of newly diagnosed transplant ineligible patients with MM above 65 years in the Danish National Multiple Myeloma Registry (DMMR). The DMMR includes all Danish patients with MM diagnosed since the first of January 2005 and provides validated information about baseline characteristics and first and second lines of therapy(Gimsing *et al*, 2016). Transplant ineligibility was in the study period defined consistently according to the National MM guideline and registered in the DMMR at diagnosis. Transplant eligibility in a patient above 65 years would as minimum request absence of significant heart, lung and liver dysfunction and a good performance status.

At the 31th of December 2014, 2,926 patients with treatment demanding MM were registered, of whom 1,803 patients were above 65 years and found to be ineligible for ASCT, and constituted the patient population for this study.

Of the study population, 426 patients had one or more missing values for calculation of the MRP score, most often this was caused by missing ISS. Thus, 1,377 patients were evaluable with a median follow-up of 64.7 months (Table 1). Patients were treated according to standard of care in Denmark during the 10 year registration period, which included an upfront conventional alkylating agent, most frequently melphalan in 37.7%, thalidomide-based in 25.6%, bortezomib-based in 26.1%, and lenalidomide based in 2.7% of cases, while 7.9% received only palliative, mostly steroid-based therapy.

Results

When calculating the MRP score we found 28.5% to be low-risk, 25.1% medium-risk and 46.4% high-risk. Compared to the UK dataset we found a higher proportion of high-risk patients. As shown in Figure 1, the Kaplan-Meier curves separate into three risk groups, with a highly significant hazard ratio of 2.91 (95% CI:

2.49-3.40) in the high-risk group and 1.53 (95% CI: 1.27-1.83) in the medium risk group for prediction of risk of death compared to the low-risk group. For the low-risk group we observed a median overall survival of 55.0 months in contrast to a median survival of only 13.9 months in the high-risk group and 35.9 month in the medium-risk group (Table S1). The Kaplan-Meier curves for progression free survival (PFS) also showed a significant spread with a hazard ratio of 2.06 (95% CI: 1.79-2.37) for prediction of risk of progression in the high-risk group and 1.39 (95% CI: 1.17-1.63) in the medium risk group (Figure 1).

Treatment patterns have changed during the study period. To test the performance of the risk model over time, we compared patients diagnosed from 2005-2009 with those diagnosed from 2010-2015. We observed no significant difference in the performance of the model during the two periods (supplementary Table S2). In test for interaction between year of diagnosis and MRP the p value was 0.5.

We looked further into the association between the MRP and other clinical and para-clinical data of established prognostic or clinical importance, e.g. LDH, haemoglobin, creatinine, bone disease and response to first-line of therapy(Rajkumar, 2018). As expected the high-risk group had significantly higher creatinine, lower haemoglobin, marginally more advanced bone disease and higher LDH levels compared to the low-risk and medium-risk groups (Table 1). However, in absolute figures the differences between these variables in the three risk groups were not particularly evident. The outcome and responses to first line of therapy were significantly different in the three groups. The proportions of early death and primary refractory disease were highest in the high-risk group. Also, the median duration of first line therapy was shorter in the high-risk group. Patients with high-risk scores had a significantly shorter median time on anti-myeloma treatment, 132 days, than observed in the medium and low-risk groups; 191 and 216 days, respectively ($P < 0.0001$). Achieved Very Good Partial Response (VGPR) or better was seen more frequently in the low-risk group (Table 1).

In 426 patients (23.6%) one or more parameters for calculation of the MRP risk profile were lacking in our material. The characteristics of patients with incomplete data are compared to the included patients in Table S2. Patient age in the two subgroups was the same, but patients in the incomplete data group who were diagnosed closer to start of the DMMR, received fewer novel drugs, had higher CRP values, and shorter survival. The most common reason for missing data was lack of beta-2-microglobuline measurement.

Discussion

The results align with the expectations to a prognostic risk profile and confirm that the MRP score divides newly diagnosed elderly patients with MM who are ineligible for ASCT into truly different risk groups.

We would like to highlight the crucial importance of validating prognostic models in the general population as we did in this study, particularly if the models are sought to be implemented in the daily clinic and not only for risk group stratification in clinical trials. The MRP score does not include information on comorbidity or patient frailty, besides PS as a potential surrogate, nor does it include functional testing, such as geriatric assessments (Engelhardt *et al*, 2017)(Palumbo *et al* 2015). While inclusion of these factors could improve the prognostic and predictive information of the score, it would make the scoring process more burdensome and less feasible in the daily clinic. Improvement of the prognostic information could though be expected by inclusion of high risk FISH aberrations as seen in the revised-ISS(Palumbo *et al*, 2015b).

An important aspect of a prognostic score is its ability to predict the feasibility of planned treatment. In our population more early deaths, shorter PFS and lower treatment responses were observed in the MRP high-risk group, and moreover, we observed that time on treatment was associated with the MRP score. Thus, a MRP high-risk score identifies patients who are particular challenged by early drop-out of treatment. However, the reason for treatment discontinuation cannot be identified by our data, e.g. whether it is caused by toxicity, lack of response, patient or physician decision. Prospective trials testing different treatments and supportive care strategies in MRP high-risk patients should be performed.

Partly caused by the population-based nature of our dataset, complete data were not available in all newly diagnosed patients. However, the population with missing data was comparable to the study population in most parameters (Table S2) except that they were diagnosed earlier, had significantly higher CRP and shorter survival. In most cases the missing data were due to lack of beta-2-microglobuline. Combined with the observation of higher CRP values the most likely explanation for missing beta-2-microglobuline and poorer prognosis in these patients is probably that they presented with infection and were admitted to hospital in the late hours where focus on myeloma diagnostic work-up was low. Moreover, because the patients were diagnosed in the earlier years of the registry, they seem to have received less effective treatment and therefore had shorter survival. In the early years of the registry there may also have been less focus on beta-2-microglobuline measurement and thereby ISS staging. However when testing the performance of the MRP score over time we found no difference when comparing patients diagnosed from 2005-2009 with patients from 2010-2015.

Conclusion

Our real world population-based data confirm that the MRP score is a robust and valuable risk assessment tool for newly diagnosed patients with MM older than 65 years and ineligible for ASCT. An important advantage of the MRP score is that it is calculated from easily accessible parameters that are part of the

routine diagnostic work-up of myeloma patients. Prospective trials testing different treatments and supportive care strategies based on the Myeloma Risk Profile are warranted.

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Author contributions LR, TWK, LKN, HF and NA conceived and designed the work, interpreted the results, drafted the manuscript and approved the final version. AJV, HG, NFA, RSP, AGS, MF, UCF, CH, PTP, MS and PG interpreted the results, revised the manuscript and approved the final version.

Compliance with ethical standards

The project has been approved by the Danish health authorities.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

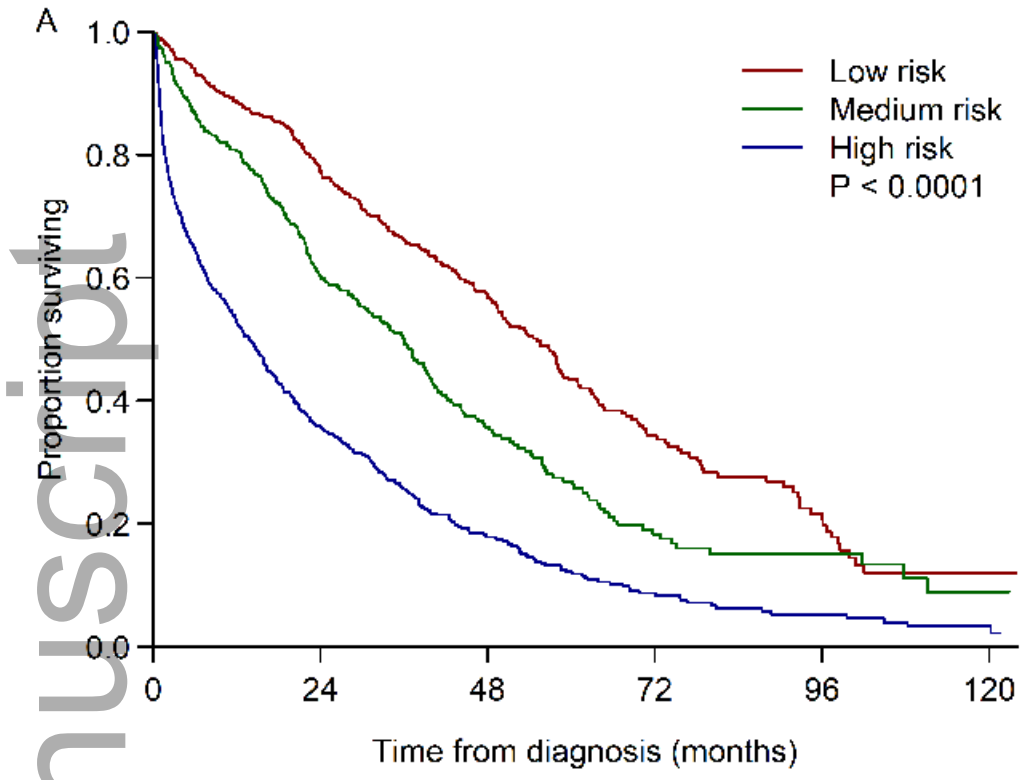
Table 1. Patient demographics and clinical characteristics of 1,377 patients with newly diagnosed multiple myeloma according to Myeloma Risk Profile (MRP) risk groups

	Low-risk	Intermediate-risk	High-risk	P
Numbers of patients (%)	393 (28.5%)	345 (25.1%)	639 (46.4%)	
Variables included in MRP index				
Age, years (IQR)	72 (69-77)	75 (71-80)	78 (74-84)	
WHO Performance status				
0	196 (49.9%)	78 (22.6%)	8 (1.3%)	
1	183 (46.6%)	220 (63.8%)	182 (28.5%)	
2	14 (3.6%)	42 (12.2%)	233 (36.5%)	
3	0 (0%)	5 (1.4%)	140 (21.9%)	
4	0 (0%)	0 (0%)	76 (11.9%)	
C-reactive protein, mg/L (IQR)	4 (2-10)	5 (2-14)	12 (5-34)	
International Staging System				
I	259 (65.9%)	27 (7.8%)	21 (3.1%)	
II	121 (30.8%)	193 (55.9%)	182 (28.5%)	
III	13 (3.3%)	125 (36.2%)	437 (68.4%)	
Beta2-microglobuline, mg/L (IQR)	2.8 (2.2-3.6)	4.7 (3.8-6.7)	6.9 (4.9-11.8)	
Albumin, g/L (IQR)	39 (36-42)	34 (31-39)	32 (27-37)	
Other variables				
Gender				
Female	188 (47.8%)	154 (44.6%)	297 (46.5%)	0.74**

Male	205 (52.2%)	191 (55.3%)	342 (53.5%)	
Lactate dehydrogenase, U/L (IQR)	171 (146-205)	172 (145-220)	189 (148-243)	0.0001
Hemoglobin, mmol/L (IQR)	7.1 (6.5-8.0)	6.4 (5.7-7.0)	6.1 (5.6-6.7)	<0.0001
Creatinine, µmol/L (IQR)	80 (66-95)	98 (77-133)	117 (82-228)	<0.0001
Bone disease				0.027
None	65 (16.4%)	55 (16.1%)	95 (15.1%)	
Osteoporosis only	47 (12.0%)	48 (14.0%)	90 (14.3%)	
Few osteolytic lesions	113 (28.9%)	87 (25.4%)	124 (19.7%)	
Multiple osteolytic lesions	167 (42.7%)	152 (44.4%)	319 (50.8%)	
Treatment				
First line Treatment				
Alkylator based*	127 (35.2%)	111 (34.8%)	247 (40.7%)	<0.0001
Thalidomide based	106 (29.4%)	94 (29.5%)	129 (21.3%)	
Lenalidomide based	19 (5.3%)	8 (2.5%)	8 (1.3%)	
Bortezomib based	90 (24.9%)	91 (28.5%)	155 (25.5%)	
Other or no treatment	19 (5.3%)	15 (4.7%)	68 (11.2%)	
Missing information	32	36	32	
Treatment duration in days (IQR)	216 (120-300)	191 (94-284)	132 (49-235)	<0.0001
Missing	4	2	18	
Response				<0.0001
sCR	3 (0.9%)	5 (1.6%)	5 (0.9%)	
CR	24 (6.9%)	23 (7.6%)	25 (4.6%)	
VGPR	83 (23.7%)	51 (16.8%)	62 (11.4%)	

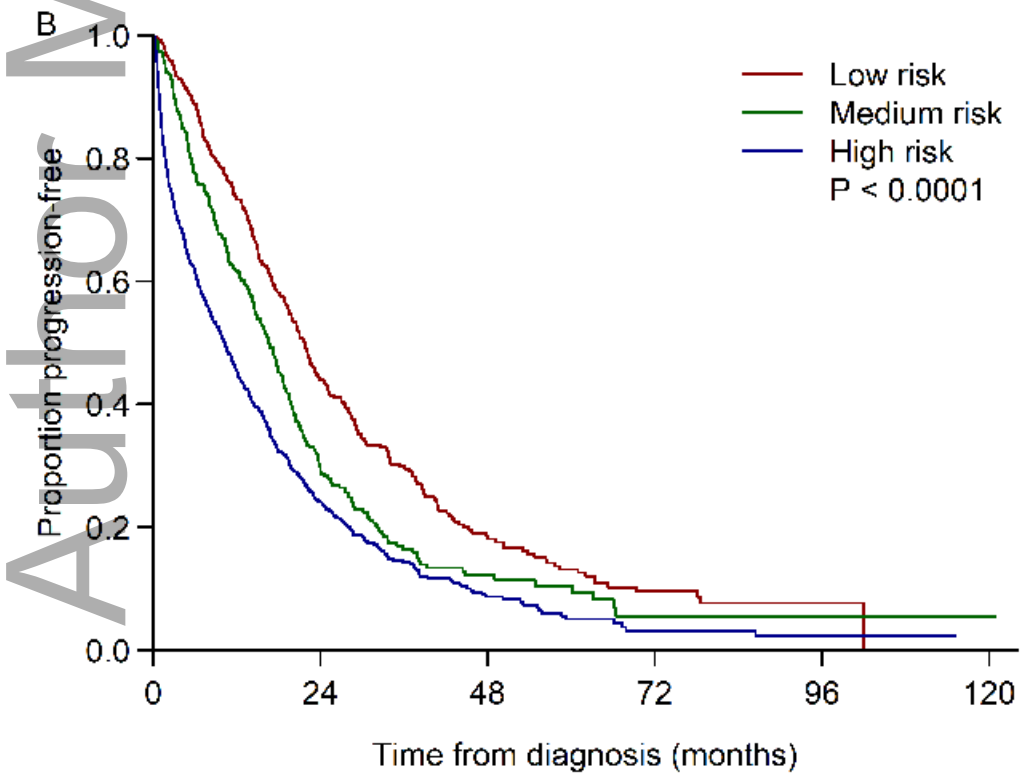
PR	133 (38.0%)	118 (38.8%)	169 (31.2%)	
SD	73 (20.9%)	55 (18.1%)	99 (18.3%)	
PD	13 (3.7%)	27 (18.1%)	60 (11.1%)	
Deceased	21 (6.0%)	25 (8.2%)	122 (22.5%)	<0.0001**
Missing	43	41	97	0.11**
≥CR	27 (7.7%)	28 (9.2%)	30 (5.5%)	0.16**
≥VGPR	110 (31.4%)	79 (26.0%)	92 (17.0%)	<0.0001**
≥PR	243 (69.4%)	197 (64.8%)	261 (48.2%)	<0.0001**
Follow-up (month)	64.7			

IQR: Interquartile range. sCR: Stringent Complete Remission. CR: Complete Remission. VGPR: Very Good Partial Response. PR: Partial Response. SD: Stable Disease. PD: Progressive Disease. *)Alkylator-based treatment only. Distribution given in N (%) for categorical variables and median (IQR) for continuous unless otherwise stated. P-values calculated using Chi-square test for categorical variables and Kruskal-Wallis test for continuous and ordinal variables unless otherwise stated. **) Chi-square test for trend over the risk groups.



Patients at risk (Patient events)

LR	393	(87)	277	(64)	149	(52)	62	(19)	23	(8)	3
MR	345	(135)	192	(65)	78	(30)	25	(4)	11	(3)	2
HR	639	(408)	209	(92)	79	(32)	23	(8)	9	(3)	3



Patients at risk (Patient events)

LR	361	(194)	134	(67)	37	(16)	14	(2)	2	(0)	0
MR	319	(214)	81	(39)	17	(6)	4	(0)	2	(0)	1
HR	607	(416)	105	(57)	26	(11)	5	(1)	3	(0)	0

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