Annals of Hematology (2019) 98:951–962
https://doi.org/10.1007/s00277-018-3568-2

ORIGINAL ARTICLE

Simplified novel prognostic score for real-life older adults with multiple myeloma—registry-based analysis

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Received: 9 April 2018 / Accepted: 26 November 2018 / Published online: 11 December 2018

Abstract

The main goal was to find a simple prognostic to evaluate overall survival of patients older than 65 years of age with myeloma. Retrospective registry-based analysis from the Registry of Monoclonal Gammopathies was conducted. Patients over 65 years with symptomatic myeloma were included. The four major parameters with impact on survival were identified: male gender, age > 75, creatinine > 152 μmol/L, and ECOG performance status 2–4. The patients were scored as good (0 points), intermediate good (1 point), intermediate poor (2 points), poor (3–4 points). Patients (1410 MM) were included. Median OS (months) was 65.7 (95% CI 49.8–81.7) for good, 51.0 (44.1–57.8) for intermediate good, 32.2 (26.2–38.2) for intermediate poor, and 18.9 (15.1–22.7) for poor. The differences in OS were statistically significant ($p < 0.0001$). Good score was used as reference for hazard ratios, which for each other score were 1.43 (1.09–1.84) for intermediate good, 2.58 (2.00–3.33) for intermediate poor, and 3.88 (2.94–5.10) for poor. Time to progression showed medians (months) 20.5 (17.4–62.4) for good, 19.3 (17.0–21.7) for intermediate good, 19.6 (16.2–23.0) for intermediate poor, and 13.0 (10.8–15.2) for poor. The suggested scoring system provides readily available information about the prognosis of MM patients above 65 years.

Keywords Multiple myeloma · Older adults · Prognostic factors

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00277-018-3568-2) contains supplementary material, which is available to authorized users.

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Introduction

Multiple myeloma (MM) is the second most frequent hematologic malignancy which typically affects individuals in elderly age. The median age at diagnosis is reported to be 65–70 years and roughly one third of patients are older than 75 years [1]. An increase in the absolute numbers of older adults with myeloma can be expected since the projected mean age in the general population is rising [2]. The overall prognosis of patients with myeloma depends greatly on many variables. The more advanced age myeloma population is known to have a worse prognosis than younger patients [3]. This is directly related to the general health of the patient and secondarily to our ability to deliver optimal treatment to poor patients.

Many stratification models have been developed to evaluate the prognosis of the individual patient. The most frequently used prognostic stratification model—ISS—uses beta-2-microglobulin and albumin to estimate the prognosis of the patients [4]. Recently, genetic abnormalities have been added as additional information to this model (R-ISS) to better predict the disease outcomes [5]. However, none of the models reflects the patient's general health and condition. The importance of comorbidities, overall performance, ability to handle the treatment, and of course age itself are variables that clearly affect the outcome of the older adults with myeloma. Simple screening strategies that might identify patients at risk of poor outcomes might help us to estimate better the prognosis of each individual. This could lead to better treatment planning, sparing of unnecessary adverse events related to the treatment, and perhaps decrease the overall costs of the therapy.

Many strategies have now been validated and are available for assessing the performance status of the older adults, and models for risk stratification have been proposed for myeloma patients [6]. Geriatric assessment tools are now used, especially activity of daily living (ADL), instrumental activity of daily living (IADL) [7] and Cumulative Illness Rating Scale (CIRS) [8]. Some of these scoring systems have been successfully implemented in the treatment of hematologic patients, such as in the case of chronic lymphocytic leukemia, where CIRS is widely used [9]. These models cannot always be used in the specific settings of hematologic malignancies since they were designed and validated for the general geriatric population.

The Czech Myeloma Group Registry of Monoclonal Gammopathies (RMG) is a long-term flagship project that aims to monitor the diagnosis and treatment of monoclonal gammopathies in the Czech Republic. The registry was established in 2007 and comprises four active modules: MM, monoclonal gammopathies of undetermined significance (MGUS), and light-chain amyloidosis and Waldenström's macroglobulinemia. Data from the registry provide important information regarding the demographics, diagnosis, treatment, and survival of patients with monoclonal gammopathies including MM. In the current analysis, data from the RMG was used to find a simple novel prognostic model that could be widely applicable to estimate the overall survival of patients older than 65 years of age with myeloma. The main goal of the study was to find simple surrogate markers that might replace the necessity of complete geriatric assessment and that could be available at the time of diagnosis without the need of complex examinations.

Patients and methods

This was a retrospective analysis based on data from the Czech Registry of Monoclonal Gammopathies (RMG: https://rmg.healthregistry.org/). All patients signed informed consent forms for data collection upon entering the RMG. The consent form has been approved by the ethical committees of the respective hospitals. Parameters of interest included in the registry in all multiple myeloma patients contain all demographic data, disease characteristics in full detail, and treatment intervals including OS, time to progression (TTP), progression-free survival (PFS), and time to next treatment (TNT). The treatment response and time-to-event endpoints were assessed according to the current recommendations [10].

Diagnosis of myeloma was established based on IMWG criteria (International Myeloma Working Group [11]. All patients over the age of 65 with symptomatic myeloma were included in the analysis. Basic demographic data and disease characteristics were obtained. Patient characteristics were analyzed with respect to overall survival. A selected set of the most significant parameters that significantly influence outcome in terms of overall survival were identified according to Cox regression analysis, and a survival model was constructed.

For this particular analysis, the cohort comprised patients with newly diagnosed multiple myeloma diagnosed in 2007–2016 who initiated any frontline therapy and the dataset was selected to include demographic parameters, disease characteristics, ISS categorization, performance status, bone marrow aspiration cytology, and various clinical laboratory tests (e.g., hemoglobin, platelet count, albumin, creatinine, β_2-microglobin, LDH, and CRP). Since the laboratory analyses were done in multiple laboratories, each laboratory provided lower and upper limit cut offs for each individual parameter measured. All registry patients who had symptomatic MM and had a full set of key parameters for treatment evaluation and for calculation were suitable for inclusion.

Statistical methods

Data were described by absolute and relative frequencies for categorical variables and by median (5th–95th percentile) for quantitative variables. Using the Kaplan-Meier

method, time to progression and overall survival were plotted. The Kaplan-Meier estimates were completed by the Greenwood confidence interval. The log-rank test was used to estimate the statistical significance of the difference between the curves. The Cox proportional hazards model was applied to explore the univariate and multivariate significance of risk factors. Time-dependent ROC analysis was used to define a cut-off level for creatinine, age, and ECOG (see Supplementary Table 2 for details). *P* values less than 0.05 were considered statistically significant (all tests two-sided). Analysis was performed in the SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, version 23.0. Armonk, NY: IBM Corp.) and software R version 3.2.3 (www.r-project.org).

Results

Overall, 2081 patients above the age of 65 were found to have an identifiable valid registry entry in the Czech Myeloma Group RMG. Univariate analysis of selected disease and patient-related parameters was applied on the whole cohort of these patients. In the patients with a complete dataset of parameters, those parameters that indicated the most significant impact on survival were processed in the multivariate analysis and model construction. Data from 1410 (68%) MM patients were available for final analysis. Patients (671) were not included due to incomplete data (not validated or missing data). An overview of patient demographics, disease characteristics, ISS categorization, and other parameters of interest (performance status, bone marrow aspiration cytology, and various clinical laboratory tests such as hemoglobin, platelet count, albumin, creatinine, β_2-microglobin, LDH, and CRP) is detailed in Table 1. The median follow-up of the whole cohort of patients was 22.0 months (range 0–141.8 months). The frontline treatment administered is summarized in Table 2.

An analysis of OS (from diagnosis and from initiation of treatment) revealed the most significant impact was from four variables. These parameters identified by Cox proportional hazards model comprise gender (male vs. female), age (above 75 vs. 66–75), creatinine level (at cutoff 152 μmol/L), and ECOG performance status (0–1 vs. 2–4). Hazard ratios (HRs) of each variable are shown in Table 3 (see Supplementary Table 2 for univariate analysis).

The risk score was constructed taking all the above-mentioned factors together. Each factor was assigned one point, and the overall score was calculated for each individual patient. Each patient is scored one point per each risk parameter (male, age above 75, creatinine above 152 μmol/L, and ECOG PS 2–4). The sum of the points gives the total score. The four risk categories are then identified: good (0 points), intermediate good (1 point), intermediate poor (2 points), poor (3–4 points, 3 and 4 points show the same OS; therefore, the score was merged into one category, see Supplementary Fig. 1). Table 4 refers to the numbers of patients in each score category and their clinical features (see Supplementary Table 3 for cytogenetic data).

An analysis of the data showed median OS (all in months) was 65.7 (95% CI: 49.8–81.7) for good, 51.0 (95% CI 44.1–57.8) for intermediate good, 32.2 (95% CI 26.2–38.2) for intermediate poor, and 18.9 (95% CI 15.1–22.7) for poor. The differences in OS were highly statistically significant ($p < 0.0001$). Good was used as a reference for HR, and for each other score, HR was 1.418 (95% CI 1.093–1.841) for intermediate good, 2.581 (95% CI: 1.998–3.333) for intermediate poor, and 3.876 (95% CI 2.944–5.102) for poor. The results for OS are detailed in Table 5. Corresponding Kaplan-Meier survival curves are shown in Fig. 1. Analysis of TTP showed median TTP (months) of 20.5 (95% CI 17.4–23.6) for good, 19.3 (95% CI 17.0–21.7) for intermediate good, 19.6 (95% CI 16.2–23.0) for intermediate poor, and 13.0 (95% CI 10.8–15.2) for poor. There was a statistically significant difference in TTP in the poor group compared to the others. Analysis of PFS showed median PFS (months) of 20.2 (95% CI 17.2–23.2) for good, 18.1 (95% CI 16.2–20.0) for intermediate good, 14.4 (95% CI 11.9–16.9) for intermediate poor, and 9.9 (95% CI 7.3–12.4) for poor. The results are detailed in Tables 6 and 7 and corresponding survival curves can be seen in Figs 2 and 3.

Discussion

Treatment of the older adults with any cancer remains a clinical challenge. Comorbidities, age, and frailty of the elderly population makes treatment more difficult and sometimes impossible. The decision for intensive treatment versus reduced treatment or palliative care is often difficult. Our study has identified several simple variables that may help in the decision-making process in routine practice.

Male gender and performance status as a risk factor for earlier death

Men die at an earlier age than women [12]. This phenomenon exists in the general population worldwide and can be observed also in our cohort of myeloma patients. There is probably no single explanation for female survival advantage [13], but this fact should be taken into account. According to the Czech Statistical Office (https://www.czso.cz/csu/czso/home), the life expectancy at birth of females is 82 years and of males 76 years. Male gender therefore represents an independent survival disadvantage also valid for MM population.

Performance status is one of the issues in daily routine that might aid our decision-making process. It has been clearly

Table 1 Basic characteristics of patients older than 65 years at the frontline

Characteristics at the first line ($N = 1410$ patients)		
Patient characteristics	Variable	N (%)[a]
Age (years)	Continuous	72.0 (66.0–83.0)
Gender	Women	691 (49.0%)
	Men	719 (51.0%)
ISS ($N = 1348$)	Stage 1	316 (23.4%)
	Stage 2	460 (34.1%)
	Stage 3	572 (42.4%)
Performance status	0	169 (12.0%)
	1	755 (53.5%)
	2	332 (23.5%)
	3	132 (9.4%)
	4	22 (1.6%)
Disease characteristics at the frontline initiation		
Hemoglobin level (g/L) ($N = 1409$)	Continuous	104.0 (77.0–139.0)
Thrombocyte count (10E9/L) ($N = 1409$)	Continuous	204.0 (87.2–361.0)
Calcium total level (mmol/L) ($N = 1406$)	Continuous	2.3 (2.0–2.9)
Albumin level (g/L) ($N = 1389$)	Continuous	36.8 (24.0–46.6)
Creatinine level (μmol/L)	Continuous	100.0 (58.0–510.0)
Beta2microglobulin (mg/L) ($N = 1322$)	Continuous	4.7 (2.1–22.6)
LDH level (μkat/L) ($N = 1322$)	Continuous	3.2 (1.9–6.0)
CRP level (mg/L) ($N = 1370$)	Continuous	4.0 (0.5–56.0)
Serum M-protein level (g/L) ($N = 1328$)	Continuous	26.1 (0.0–66.1)
Bone marrow aspiration cytology (%) ($N = 1292$)	Continuous	21.1 (0.4–72.0)
Light chain type ($N = 1390$)	Kappa	845 (60.8%)
	Lambda	527 (37.9%)
	Biclonal	18 (1.3%)
M-protein type ($N = 1407$)	lgG	839 (59.6%)
	lgA	283 (20.1%)
	LC only	218 (15.5%)
	Other	67 (4.8%)
Osteolytic lesions X-ray ($N = 1406$)	Negative	232 (16.5%)
	1–2 osteolytic lesions	727 (51.6%)
	More than 2 lesions or accelerated osteoporosis	447 (31.7%)
Extramedullary mass ($N = 1394$)	No	1284 (92.1%)
	Yes	110 (7.9%)

[a] Count (relative frequencies) for categorical variables and median (5th–95th percentiles) for continuous variable

shown in our cohort, that ECOG 3–4 represents a major adverse independent prognostic factor (HR 1.869). These data are consistent with a recent report by Terebelo et al. who showed in an analysis from USA that poor performance score especially combined with older age represents a major risk factor for early death [14].

Age is an important outcome variable

Age above 75 years represents an independent prognostic factor for survival in our cohort of patients. Although the younger elderly (65–70) can be frequently treated by the same protocols as generally more youthful patients, their survival is still shorter. Moreover, older adults present more frequently with adverse prognostic features [15]. The relative survival of the very elderly above the age of 75 has not changed during the past 20 years whereas survival in the younger elderly (65–70) has been improved significantly after the introduction of novel agents [16]. It is difficult to state what the current survival of the more elderly above 75 would be. One of the main reasons for this is the fact that these patients are underrepresented in clinical trials because of frequent comorbidities as exclusion criteria. In another study by Costa et al., it has been shown that real-life patients are in fact much older than those

Table 2 Treatment type for patients older than 65 years at the frontline

Descriptive statistics in risk groups[a]	Good ($N = 255$)	Intermediate good ($N = 514$)	Intermediate poor ($N = 420$)	Poor ($N = 221$)	p value[b]
Treatment modality ($N = 1410$)					
Bortezomib-based	126 (49.4%)	303 (58.9%)	288 (68.6%)	163 (73.8%)	< 0.001
Thalidomide-based	96 (37.6%)	141 (27.4%)	87 (20.7%)	46 (20.8%)	
Lenalidomide-based	17 (6.7%)	29 (5.6%)	14 (3.3%)	4 (1.8%)	
Bortezomib + thalidomide-based	8 (3.1%)	20 (3.9%)	15 (3.6%)	3 (1.4%)	
Other novel drugs-based	6 (2.4%)	12 (2.3%)	3 (0.7%)	0 (0.0%)	
Without new drugs	2 (0.8%)	9 (1.8%)	13 (3.1%)	5 (2.3%)	
Transplantation ($N = 1410$)					
No	228 (89.4%)	480 (93.4%)	404 (96.2%)	216 (97.7%)	< 0.001
Yes	27 (10.6%)	34 (6.6%)	16 (3.8%)	5 (2.3%)	
Final response to therapy ($N = 1081$)					
sCR, CR	18 (8.9%)	51 (12.5%)	29 (9.5%)	11 (6.7%)	0.017
VGPR	58 (28.6%)	125 (30.6%)	99 (32.4%)	39 (23.8%)	
PR	70 (34.5%)	126 (30.9%)	81 (26.5%)	41 (25.0%)	
MR	18 (8.9%)	29 (7.1%)	28 (9.2%)	13 (7.9%)	
SD	12 (5.9%)	24 (5.9%)	21 (6.9%)	21 (12.8%)	
PG	27 (13.3%)	53 (13.0%)	48 (15.7%)	39 (23.8%)	
ORR (PR +)	146 (71.9%)	302 (74.0%)	209 (68.3%)	91 (55.5%)	< 0.001

[a] Described using N (%) for categorical and median (5th–95th) percentile for continuous variables

[b] p value of ML chi-square test of independency for categorical and Kruskal-Wallis test for continuous variables

participating in clinical trials [17]. In a study by Panitsas et al., only 2 out of 89 patients above 85 were treated in clinical trials [18]. On the other hand, the outcomes in the cohort by Panitsas were favorable. Although age itself cannot be viewed as a contraindication for any treatment, accumulation of comorbidities over time tends to limit the selection of treatment for this specific age group. However, this fact does not generally mean that the treatment is not successful. Our data confirm that the success of treatment in prognostically poor patients is limited when age is combined with other adverse factors.

Renal impairment influences the outcome

Renal impairment in myeloma represents a challenging issue in the treatment of patients. The important fact is that patients with moderate and severe renal impairment are frequently excluded from participation in clinical trials, not to mention patients on dialysis who are usually totally ineligible. Palumbo et al. reported an analysis of patients with renal impairment in the FIRST trial where a significant number of patients improved their renal function [19]. However still, no patient on dialysis was included. An interesting analysis has been reported by Hus et al. The authors dealt with the prognostic impact of multiple variables in a bortezomib-treated real-life older adult population. It was found that decreased renal function was related to shorter survival of these patients even when treated with bortezomib [20].

Treatment selection in older adult population

Only an insignificant number of patients (29/1410, 2%) were not treated with novel drugs frontline. The majority received bortezomib-based combination treatment (usually doublet) as

Table 3 Multivariate Cox proportional hazards model for selected predictors

Characteristics of patients older than 65 years at the frontline with risk factors available ($N = 1410$)	Multivariate model	
	HR (95% CI)	p value
Gender: men vs. women	1.316 (1.124–1.541)	0.001
Age (years) > 75 vs. 66–75	1.437 (1.221–1.692)	< 0.001
Creatinine level (μmol/L) > 152 vs. ≤ 152	1.613 (1.365–1.905)	< 0.001
Performance status: 2–4 vs. 0–1	1.869 (1.594–2.191)	< 0.001

Table 4 Basic characteristics per risk group—clinical features

Descriptive statistics in risk groups[a]	Good ($N = 255$)	Intermediate good ($N = 514$)	Intermediate poor ($N = 420$)	Poor ($N = 221$)	p value[b]
Sex ($N = 1410$)					
Women	255 (100.0%)	239 (46.5%)	164 (39.0%)	33 (14.9%)	< 0.001[c]
Men	0 (0.0%)	275 (53.5%)	256 (61.0%)	188 (85.1%)	
Age (years) ($N = 1410$)	70.0 (66.0–75.0)	71.0 (66.0–81.0)	75.0 (66.0–83.0)	77.0 (67.0–86.0)	< 0.001[c]
Serum M-protein level (g/L) ($N = 1328$)	28.9 (0.0–65.3)	26.6 (0.0–66.9)	23.9 (0.0–63.9)	25.7 (0.0–72.0)	0.117
Bone marrow aspiration cytology (%) ($N = 1292$)	19.0 (0.0–67.4)	22.0 (0.6–70.0)	21.2 (0.8–70.0)	22.7 (0.6–77.6)	0.092
Performance status ($N = 1410$)					
0	54 (21.2%)	80 (15.6%)	31 (7.4%)	4 (1.8%)	< 0.001[c]
1	201 (78.8%)	350 (68.1%)	174 (41.4%)	30 (13.6%)	
2	0 (0.0%)	61 (11.9%)	147 (35.0%)	124 (56.1%)	
3	0 (0.0%)	22 (4.3%)	59 (14.0%)	51 (23.1%)	
4	0 (0.0%)	1 (0.2%)	9 (2.1%)	12 (5.4%)	
ISS ($N = 1348$)					
Stage 1	96 (39.5%)	162 (32.4%)	50 (12.6%)	8 (3.8%)	< 0.001
Stage 2	98 (40.3%)	186 (37.2%)	129 (32.6%)	47 (22.5%)	
Stage 3	49 (20.2%)	152 (30.4%)	217 (54.8%)	154 (73.7%)	
Hemoglobin level (g/L) ($N = 1409$)	108.0 (83.0–136.0)	108.0 (79.0–143.0)	102.0 (78.0–137.0)	93.3 (71.0–133.0)	< 0.001
Thrombocyte count (10E9/L) ($N = 1409$)	217.0 (89.0–357.0)	212.0 (88.6–361.0)	199.0 (90.1–375.0)	172.0 (71.0–286.0)	< 0.001
Calcium total level (mmol/L) ($N = 1406$)	2.3 (2.1–2.7)	2.3 (2.0–2.8)	2.3 (1.9–3.1)	2.3 (2.0–3.2)	0.235
Albumin level (g/L) ($N = 1389$)	38.9 (27.2–47.1)	37.5 (25.4–47.2)	35.2 (24.7–45.7)	33.6 (22.0–45.0)	< 0.001
Creatinine level (μmol/L) ($N = 1410$)	77.0 (54.0–129.0)	92.0 (57.0–258.0)	129.5 (60.5–573.5)	240.0 (86.0–765.0)	< 0.001[c]
Beta2microglobulin (mg/L) ($N = 1322$)	3.5 (1.9–9.1)	4.0 (2.0–15.4)	6.1 (2.4–28.0)	10.1 (3.0–38.0)	< 0.001
LDH level (μkat/L) ($N = 1322$)	3.2 (1.9–5.2)	3.2 (1.8–5.9)	3.3 (1.9–6.0)	3.2 (1.8–7.6)	0.325
Osteolytic lesions X-ray ($N = 1406$)					
Negative	31 (12.2%)	75 (14.6%)	75 (17.9%)	51 (23.3%)	0.004
1–2 osteolytic lesions	131 (51.4%)	258 (50.3%)	229 (54.7%)	109 (49.8%)	
More than 2 lesions or accelerated osteoporosis	93 (36.5%)	180 (35.1%)	115 (27.4%)	59 (26.9%)	
Extramedullary mass ($N = 1394$)					
No	235 (92.9%)	464 (91.2%)	383 (92.3%)	202 (93.1%)	0.767
Yes	18 (7.1%)	45 (8.8%)	32 (7.7%)	15 (6.9%)	

[a] Described using N (%) for categorical and median (5th–95th) percentile for continuous variables

[b] p value of ML chi-square test of independency for categorical and Kruskal-Wallis test for continuous variables

[c] This parameter defines the risk groups

the frontline option. Thus, almost no patient was disqualified for treatment with novel agents. Interestingly, 37.6% of good risk patients received thalidomide frontline. It has been a standard regimen during the past (MPT) and also highly used induction treatment (CTD) before ASCT. Since 10.6% of these patients underwent ASCT, it might explain the reason for higher Thalidomide use in this cohort upfront. Even more so, the greatest proportion of patients from the poorest risk population received bortezomib frontline treatment. The time to progression did not differ across the groups with the exception of patients scored as poor, where it was significantly shorter. The poor-risk group shows significantly more patients in ISS stage 3 myeloma. Since this group suffers from the most significant renal impairment, it is logical that these patients will have higher proportion of stage 3 myeloma. It also explains why bortezomib was the most commonly used drug in this specific cohort. The reasons for poor TTP (and also much less response) might be our inability to deliver enough treatment intensity because of adverse events during the frontline therapy. Cytogenetic changes are unlikely to play a role since all the groups are well balanced in terms of cytogenetic changes. This problem might be viewed as not selecting inferior drug but selecting inferior dose. This group of patients could benefit from less toxic and highly effective treatment (like lenalidomide).

Table 5 Overall survival from frontline treatment in risk groups

	Risk category ($N = 1410$)			
	Good	Intermediate good	Intermediate poor	Poor
N baseline	255	514	420	221
N event	80	194	226	144
Median (95% CI)	65.7 (49.8–81.7)	51.0 (44.1–57.8)	32.2 (26.2–38.2)	18.9 (15.1–22.7)
% survival (95% CI)				
1 year	93.8 (89.9–96.2)	87.0 (83.6–89.8)	73.7 (69.0–77.8)	61.2 (54.1–67.4)
2 years	87.7 (82.5–91.4)	77.3 (73.1–81.0)	62.0 (56.8–66.8)	41.7 (34.5–48.7)
3 years	76.9 (70.1–82.3)	66.7 (61.5–71.3)	47.3 (41.6–52.7)	27.3 (20.6–34.4)
4 years	65.5 (57.4–72.4)	54.1 (48.2–59.7)	34.5 (28.5–40.5)	23.5 (16.9–30.6)
5 years	53.6 (44.4–62.0)	42.4 (35.9–48.7)	25.4 (19.3–31.9)	20.3 (13.6–28.0)
v6 years	46.2 (36.2–55.6)	35.8 (29.1–42.5)	19.7 (13.6–26.7)	14.7 (8.1–23.1)
7 years	39.2 (28.1–50.0)	32.5 (25.6–39.6)	12.7 (6.6–21.0)	12.2 (5.9–21.1)
8 years	34.3 (21.5–47.4)	29.0 (21.4–37.0)	8.5 (2.5–19.1)	12.2 (5.9–21.1)
univariate model				
HR (95% CI)	Reference	1.418 (1.093–1.841)	2.581 (1.998–3.333)	3.876 (2.944–5.102)
p value		0.009	< 0.001	< 0.001
HR (95% CI)	0.705 (0.543–0.915)	Reference	1.819 (1.500–2.206)	2.733 (2.200–3.395)
p value	0.009		< 0.001	< 0.001
HR (95% CI)	0.388 (0.300–0.501)	0.550 (0.453–0.667)	Reference	1.502 (1.218–1.852)
p value	< 0.001	< 0.001		< 0.001
HR (95% CI)	0.258 (0.196–0.340)	0.366 (0.295–0.455)	0.666 (0.540–0.821)	Reference
p value	< 0.001	< 0.001	< 0.001	

When looking at time to progression (Table 6), there was no difference among the first three groups and differed only for the poorest risk population. Obviously, almost no patients in the current report had been scheduled for continuous treatment, since as of January 2018, it has not been and still is not a standard approach in the Czech Republic. Recent trials have shown a benefit of continuous treatment with lenalidomide (FIRST trial) [21]. In this trial, the frontline treatment in all arms lasted for 18 months. There was no significantly different outcome during these first 18 months of treatment. In our cohort, the poorest risk patients show a median time to progression of only 13.0 months and median overall survival 18.9 months. The trend towards continuous treatment is now being proposed for everybody based on results from the recent FIRST trial where continuous treatment with lenalidomide achieved the best results [22]. The benefit for OS in the older adult population may be less clear when analyzing data from our study. Based on our data, the majority of patients with adverse prognostic features will progress before the end of 18 months of treatment, and half will die by the end of the treatment. From this point of view, it might seem reasonable to select fixed duration treatment for poor patients.

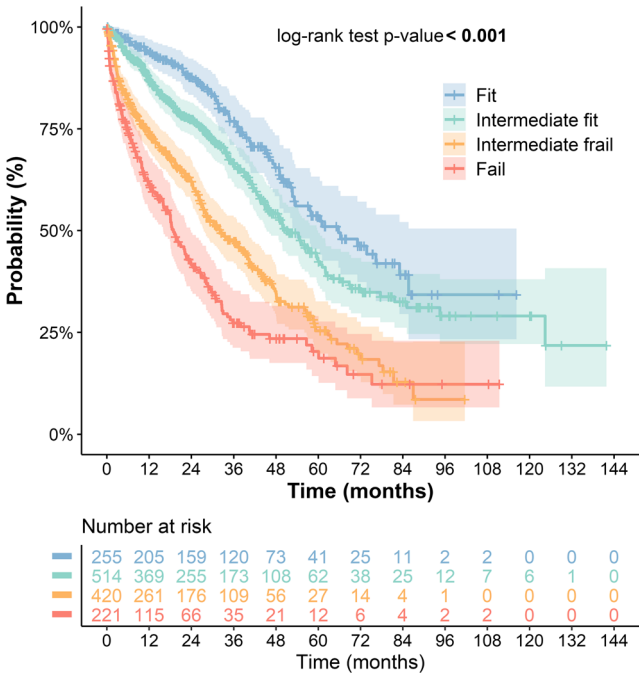

Fig. 1 Overall survival from the frontline treatment in risk groups ($N = 1410$)

Autologous stem cell transplantation (ASCT) has been used in a minority of patients and its use gradually decreased according to increasing patient frailty in our cohort. Clinical trials using autologous transplantation have been traditionally designed for patients under the age of 65 years. Data supporting the use of autologous transplantation above the age of 65 are infrequent and mainly based on retrospective

Table 6 Time to progression from frontline treatment in risk groups

Time to progression	Risk category ($N = 1410$)			
	Good	Intermediate good	Intermediate poor	Poor
N baseline	255	514	420	221
N event	161	292	235	135
Median (95% CI)	20.5 (17.4–23.6)	19.3 (17.0–21.7)	19.6 (16.2–23.0)	13.0 (10.8–15.2)
% survival (95% CI)				
12 months	71.5 (65.1–76.9)	70.2 (65.7–74.3)	65.7 (60.5–70.4)	53.5 (45.9–60.5)
24 months	40.7 (33.8–47.5)	42.3 (37.3–47.2)	38.4 (32.8–44.0)	26.8 (19.9–34.1)
36 months	24.1 (18.0–30.6)	31.1 (26.1–36.2)	25.8 (20.3–31.6)	17.6 (11.4–25.0)
48 months	19.4 (13.7–25.9)	24.5 (19.6–29.8)	18.3 (13.0–24.3)	13.4 (7.2–21.6)
60 months	14.6 (9.0–21.3)	19.3 (14.3–24.9)	13.8 (8.3–20.6)	13.4 (7.2–21.6)
72 months	14.6 (9.0–21.3)	12.4 (7.5–18.7)	13.8 (8.3–20.6)	13.4 (7.2–21.6)
84 months	10.9 (4.7–20.0)	10.7 (5.7–17.3)	13.8 (8.3–20.6)	–
96 months	–	10.7 (5.7–17.3)	–	–
Univariate model				
HR (95% CI)	Reference	0.947 (0.781–1.149)	1.128 (0.923–1.379)	1.608 (1.278–2.022)
p value		0.582	0.239	< 0.001
HR (95% CI)	1.056 (0.871–1.280)	Reference	1.191 (1.002–1.415)	1.697 (1.383–2.083)
p value	0.582		0.047	< 0.001
HR (95% CI)	0.886 (0.725–1.083)	0.840 (0.707–0.998)	Reference	1.425 (1.153–1.762)
p value	0.239	0.047		0.001
HR (95% CI)	0.622 (0.494–0.782)	0.589 (0.480–0.723)	0.702 (0.568–0.867)	Reference
p value	< 0.001	< 0.001	0.001	

analyses [23]. There has been no randomized trial in patients above 65 using ASCT with full-dose conditioning (melphalan 200 mg/m2). There have been only two randomized clinical trials evaluating reduced-intensity conditioning (melphalan 100 mg/m2) [24, 25]. The results were conflicting. There was a clear benefit of transplantation in the Italian trial but no novel drug was included. The French study did not support the use of ASCT compared to MPT. The importance of ASCT with reduced conditioning in the era of modern drugs is unclear. Retrospective data suggest that this approach has promising efficacy in the population above the age of 65 years. A study by Merz et al. [26] reported outcomes for older patients undergoing ASCT. This analysis included 26 patients aged 70–75 years all having received melphalan 200 mg/m^2. No increased mortality was observed. The PFS is significantly longer in the older adult myeloma population as reported by an Arkansas group [27]. Age itself does not seem to influence survival in eligible patients [28]. It seems reasonable to offer ASCT to good patients above 65 even at full-dose melphalan, and this method is probably underused. We also analyzed the frontline treatment administered to the patients (Table 2). Briefly, bortezomib was the most widely used agent (either in doublet with corticosteroid or triplet with corticosteroid and alkylating agent) even in the poor group (73.8% of patients). ASCT was used in 82 patients (5.8% of all patients). Obviously, it was more frequently used in the good group (27 patients, 10.6%) but was used in patients across all groups.

Combined scoring system for estimation of overall survival of myeloma patients

Real-life needs real tools: useful and simple. Nowadays, there is no routine assessment done for older adults with myeloma in routine practice. We tried to find a tool that could guide physicians to select appropriate treatment strategy for individual patient. On one hand, there is a group of good-risk patients who could be selected for more intensive treatment strategies like ASCT or triplet or even quadruplet regimens. On the other hand is the poor-risk group of patients who are unlikely to do well and need strictly individualized approach and "no harm" strategy is of definite preference. Our score is simple and able to estimate prognosis of individual patients based on a panel of routinely and readily available variables. The advantage of our model over the others might be seen especially in its

Table 7 Progression-free survival from frontline treatment in risk groups

Progression-free survival	Risk category ($N = 1410$)			
	Good	Intermediate good	Intermediate poor	Poor
N baseline	255	514	420	221
N event	168	328	304	172
Median (95% CI)	20.2 (17.2–23.2)	18.1 (16.2–20.0)	14.4 (11.9–16.9)	9.9 (7.3–12.4)
% survival (95% CI)				
12 months	69.3 (62.9–74.8)	66.3 (61.7–70.4)	57.6 (52.5–62.3)	44.4 (37.4–51.1)
24 months	39.4 (32.7–46.1)	39.1 (34.3–43.9)	30.9 (26.0–35.9)	20.1 (14.6–26.2)
36 months	23.3 (17.4–29.7)	28.4 (23.8–33.2)	18.7 (14.5–23.5)	11.4 (7.0–17.0)
48 months	18.8 (13.3–25.1)	21.5 (16.9–26.4)	11.1 (7.4–15.7)	8.7 (4.5–14.6)
60 months	14.1 (8.8–20.7)	15.8 (11.4–20.8)	6.3 (3.0–11.1)	8.7 (4.5–14.6)
72 months	14.1 (8.8–20.7)	9.1 (5.3–14.3)	6.3 (3.0–11.1)	8.7 (4.5–14.6)
84 months	10.6 (4.6–19.4)	7.1 (3.5–12.2)	4.2 (1.2–10.0)	–
96 months	–	7.1 (3.5–12.2)	–	–
Univariate model				
HR (95% CI)	Reference	1.019 (0.846–1.228)	1.398 (1.157–1.688)	1.942 (1.569–2.404)
p value		0.842	0.001	< 0.001
HR (95% CI)	0.981 (0.815–1.182)	Reference	1.372 (1.173–1.604)	1.905 (1.583–2.294)
p value	0.842		< 0.001	< 0.001
HR (95% CI)	0.715 (0.592–0.864)	0.729 (0.623–0.853)	Reference	1.389 (1.152–1.675)
p value	0.001	< 0.001		0.001
HR (95% CI)	0.515 (0.416–0.637)	0.525 (0.436–0.632)	0.720 (0.597–0.868)	Reference
p value	< 0.001	< 0.001	0.001	

simplicity. Several scoring systems have been proposed for evaluation of the older adults with myeloma. None of the previously published systems has been implemented into routine practice as a large-scale widely accepted model. General models used in hematology such as HCT-CI (hematopoietic cell transplantation-specific comorbidity index) [29] or Kaplan-Feinstein (KF) Index [30] have not been specifically designed for myeloma patients, and their use is probably limited. General prognostic myeloma models such as the most widely used R-ISS do not reflect the nature of the individual patient [5]. Palumbo et al. in his study combined age, ADL, IADL, Charlson Comorbidity Index (CCI), and several disease variables (cytogenetics, ISS stage) to construct a frailty score to predict outcome for individual patients [6]. Patients included in the analysis were participants of clinical trials and therefore a selected population with median age 74 years (comparable to our cohort). Three-year OS was 84% in fit patients compared with 76% in intermediate fit patients and 57% in frail patients. It is necessary to mention that this system includes more than 30 variables and is not easy to evaluate in each individual. Time-consuming questionnaires that may each take up to 15 min to fill in are often an obstacle for use

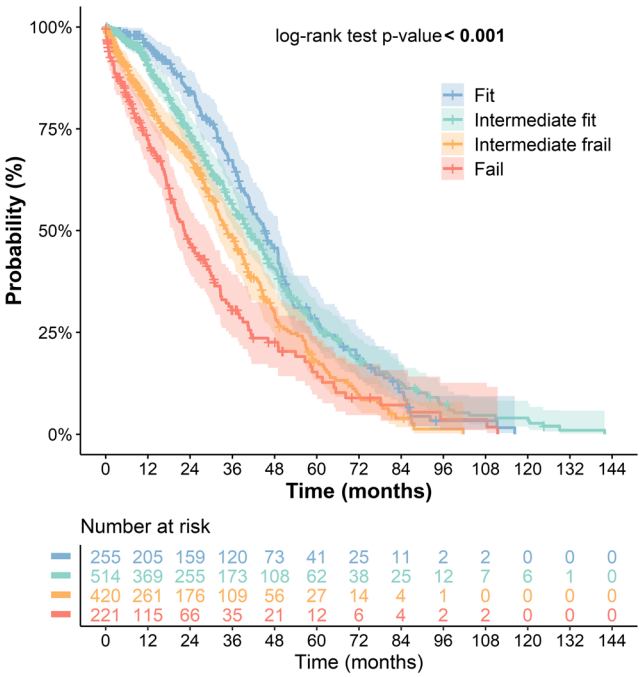

Fig. 2 Time to progression from the frontline treatment in risk groups ($N = 1410$)

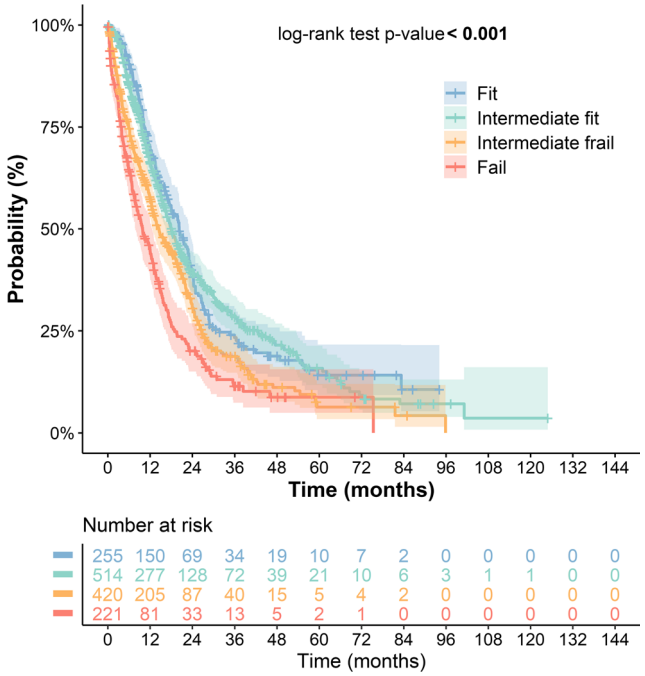

Fig. 3 Progression-free survival from the frontline treatment in risk groups ($N = 1410$)

in daily routine and are probably the main reason why this very good scoring has not reached general popularity. Our four categories show very similar results at 36 months for the first 3 groups, with an additional very poor-risk group showing even worse outcome (76.9%, 66.7%, 47.3%, and 27.3% in our cohort). Engelhardt et al. conducted a study evaluating six tools (the Katz ADL, IADL, CCI, HCT-CI, KF Index, and R-MCI) and compared their applicability with previous observations by Palumbo on a smaller cohort of patients who were somewhat younger and also included patients on clinical trials (63 years median) and received different treatments (such as carfilzomib) [31]. These data showed 3-year OS of 91%, 77%, and 47% surviving based on a frailty score for fit, intermediate-fit, and frail patients, respectively. Again, the main disadvantage is the complexity of the scoring system. Engelhardt et al. based on previous observations constructed a new revised myeloma comorbidity index (R-MCI) [32]. This work very much simplified the score to 9 points with 5 variables only (renal function, lung function, performance status, age, and frailty), making it a good decision-making tool which is far better for implementation in daily routine. Cytogenetics can be added to this model as an additional variable. The median OS in the fit group was 10.1 years, 4.4 in intermediate groups, and 1.2 years in the frail group. When compared to our cohort, the good group of an unselected population showed median OS 5.5 years, intermediate 1 group 4.25 years, intermediate 2 group 2.7 years, and poor group 1.6 years. Our scoring compared to the score reported by Engelhardt shows poorer results in the fitgroup of patients which might reflect treatment differences (such as low use of ASCT in our cohort compared to 47.9% of patients being transplanted in the German cohort) and of course the lower age of the German cohort (63 years versus our 72 years). Our system went further and assigned 1 point per item with only four items calculated. The information gained could be considered similar to the above-mentioned more complex scoring systems. The comparison of parameters included in the mentioned scoring systems is summarized in Table 8. Tailoring the treatment especially for very frail patients is an urgent clinical need. Estimation of prognosis is therefore one of the useful options for achieving such goal.

Strengths and limitations of the study

The obvious limitation of the study is its retrospective nature and the limitations associated with that. The heterogeneity of treatment received by the patients reflects the time the patients were treated during the quite-long observation period, with reference to the standards of treatment currently in force. The data were not independently validated on another large-scale cohort of patients (another such cohort of similar size and population is hard to find). The registry of monoclonal gammopathies (RMG) was established in 2007 and has become one of the flagship projects of the Czech Myeloma Group [33, 34]. The registry collects prospective data from patients with multiple myeloma and other monoclonal gammopathies. One of the major advantages of the registry is that it is regularly monitored, and data are validated by an external body. More than 1400 patients represent a large amount of data which is the main

Table 8 Parameters included in the scoring systems

	Clinical	Laboratory	Cytogenetics	Parameters considered	Comment	Reference
IMWG score	YES	NO	NO	34	Very complex	Palumbo et al. [6]
R-MCI	YES	NO	YES	5	Can be used without cytogenetics, younger	Engelhardt et al. [32]
KFI	YES	NO	NO	12	Not designed for myeloma	Kaplan & Feinstein [30]
HCT-CI	YES	YES	NO	17	Not designed for myeloma	Sorror et al. [29]
R-ISS	NO	YES	YES	4	No clinical parameter	Palumbo et al. [5]
Current study	YES	YES	NO	4	Available for all, older adults with myeloma	

strength of the study. The study reflects the real-life data of a mixed population of patients who received treatment based on daily practice decision-making. The results can be interpreted as a valid view on what is possible in routine practice outside the scope of clinical trials.

Conclusion

Real life needs really simple tools. Our suggested simple tool can help the treating physician to estimate the survival of the individual patient during the first visit at the department. It has the potential to become a tool to tailor the treatment (like offering ASCT or not or on the other hand limit the treatment toxicity). The suggested scoring system provides information about the prognosis of the patient regardless of other disease-related parameters and is generally comparable to other frequently more complicated scoring systems. It is available for all myeloma patients and can be easily implemented into routine practice.

Acknowledgements Supported by program PROGRES Q40/08 and by MH CZ-DRO (UHHK, 00179906). The authors are grateful to Ian McColl MD, PhD for assistance with the manuscript.

Authors contributions JR designed the study, analyzed the outcomes, and wrote the manuscript.
RH wrote, reviewed, and approved the manuscript.
LB did all statistical analysis and wrote and reviewed the manuscript.
LP reviewed and approved the manuscript.
IŠ reviewed and approved the manuscript.
JM reviewed and approved the manuscript.
EG reviewed and approved the manuscript.
AJ reviewed and approved the manuscript.
TJ reviewed and approved the manuscript.
MS reviewed and approved the manuscript.
AH reviewed and approved the manuscript.
VM wrote, reviewed, and approved the manuscript.

Compliance with ethical standards

The consent form has been approved by the ethical committees of the respective hospitals.

Conflict of interest The authors declare that they have no conflict of interest.

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