Use of the Second Revision of the International Staging System for prognostic stratification of multiple myeloma patients in real-world clinical practice and the importance of sub-groups, including age

The Second Revision of the Revised International Staging System (R2-ISS) for multiple myeloma (MM)[1] is a recent update of the R-ISS[2] for the purpose of further risk stratification of R-ISS stage II, by adding gain of 1q ($1q^+$) using interphase fluorescence *in situ* hybridization (iFISH) as proposed by the European Myeloma Network (EMN). To assess the utility of the R2-ISS in real-world clinical practice, we retrospectively reviewed 218 patients who were diagnosed at Kameda Medical Center from January 2014 to August 2022. All analyses performed in our study were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the institutional review board of Kameda Medical Center. Patients signed informed consent for their data and photographs to be published.

Of the 218 patients in the study, 18 patients were excluded because iFISH data for classification by R2-ISS were not available (11 patients) or they were untreated (7 patients); the remaining 200 consecutive MM patients had received treatments for MM and had complete data for calculating the R2-ISS. iFISH analysis was performed at a commercially available laboratory (SRL Inc., Tokyo, Japan) on whole bone marrow cells before June 2015 and on purified plasma cells after that date. Table 1 compares our cohort and the EMN training cohort. Median age of our patients was 74 years, which is 14 years older than that of the EMN cohort but is more consistent with the current age of real-world myeloma patients globally, and especially in Japan.[3-5] Furthermore, 32% and 43% of patients had elevated lactate hydrogenase (LDH) and ISS stage III, respectively, compared to 25% and 16% in the EMN cohort. The frequencies of del17p, t(4;14), and $1q^+$ were 8%, 10% and 29% in our cohort and 12%, 12% and 37% in the EMN cohort with a marginally higher frequency seen in the latter. According to R2-ISS, our cohort had fewer stage I and II and more stage III and IV disease. Importantly, the proportion of patients with a $1q^+$ did not differ significantly between the two groups. In terms of treatment, more patients received proteasome inhibitors and CD38 antibody-based treatment, and fewer patients underwent autologous stem cell transplantation (autoSCT). With a median follow-up of 31.5 months (range, 0-108 months), the median progression-free survival (PFS) was 46 months (95% Confidence Interval, 36-67 months) and the median overall survival (OS) was not reached (NR) in our entire cohort (*Online Supplemen-*

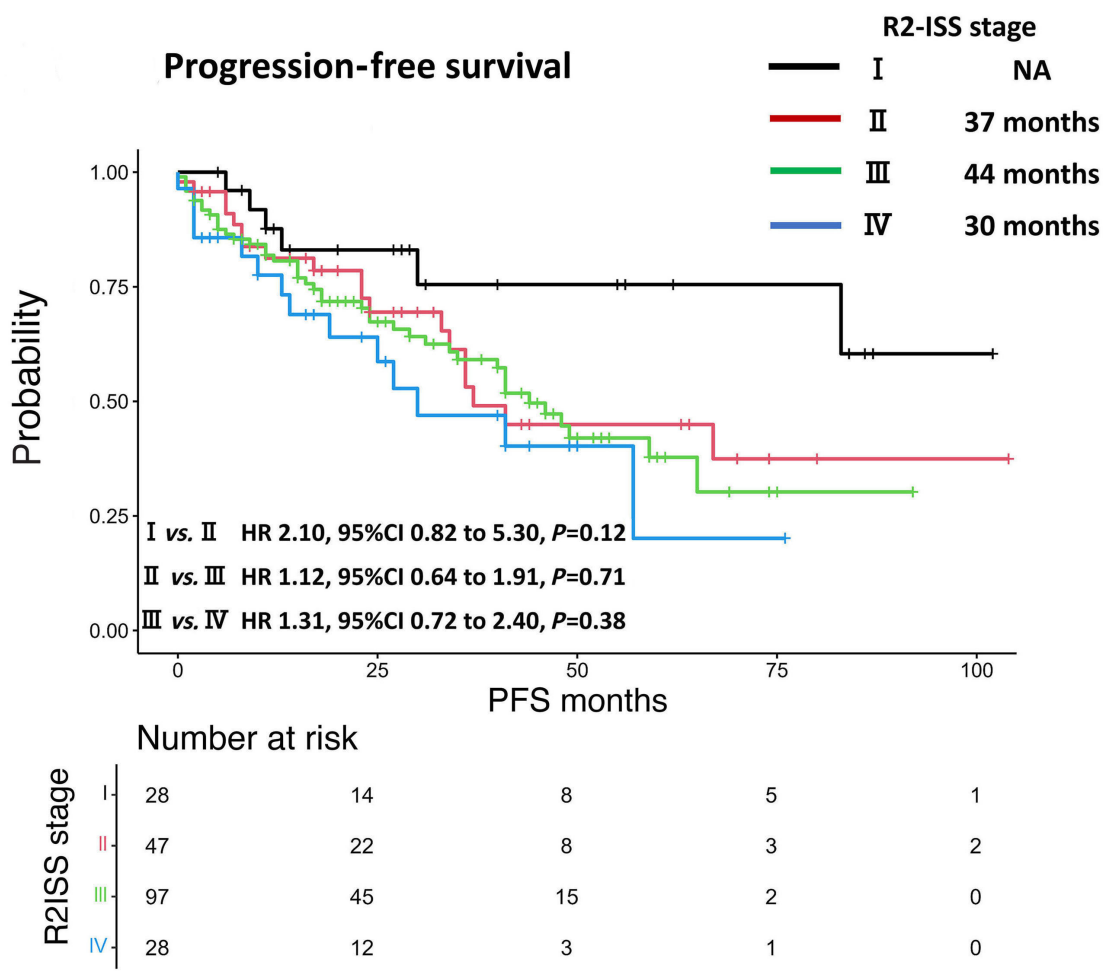
Table 1. Comparison of patient characteristics between our cohort and the training cohort of the European Myeloma Network.

	Our cohort (N=200)	EMN (N=2,226)
Study period	2014-2022	2005-2016
Age in years		
Median (IQR)	74 (30-91)	60 (54-65)
≤65, N (%)	49 (25)	1,720 (77)
>65, N (%)	151 (75)	506 (23)
Sex, N (%)		
Male	104 (52)	1,271 (57)
ISS, N (%)		
I	47 (24)	839 (37)
II	67 (34)	845 (38)
III	86 (43)	551 (25)
R-ISS, N (%)		
I	32 (16)	597 (27)
II	125 (63)	1,372 (62)
III	43 (22)	257 (12)
R2-ISS, N (%)		
I	28 (14)	423 (19)
II	47 (24)	690 (31)
III	97 (49)	913 (41)
IV	28 (14)	200 (9)
Elevated LDH, N (%)	63 (32)	363 (16)
del(17p), N (%)	15 (7.5)	258 (12)
t(4;14), N (%)	19 (9.5)	277 (12)
$1q^+$, N (%)	59 (29)	820 (37)
$gain^+$	49 (24)	-
amp^+	10 (5)	-
Treatment, N (%)		
IMiD	7 (3.5)	506 (23)
IMiD-PI	79 (40)	1,485 (67)
PI	82 (41)	235 (11)
CD38-MoAb containing	32 (16)	0
AutoSCT	75 (38)	TE: 1,855 (83)

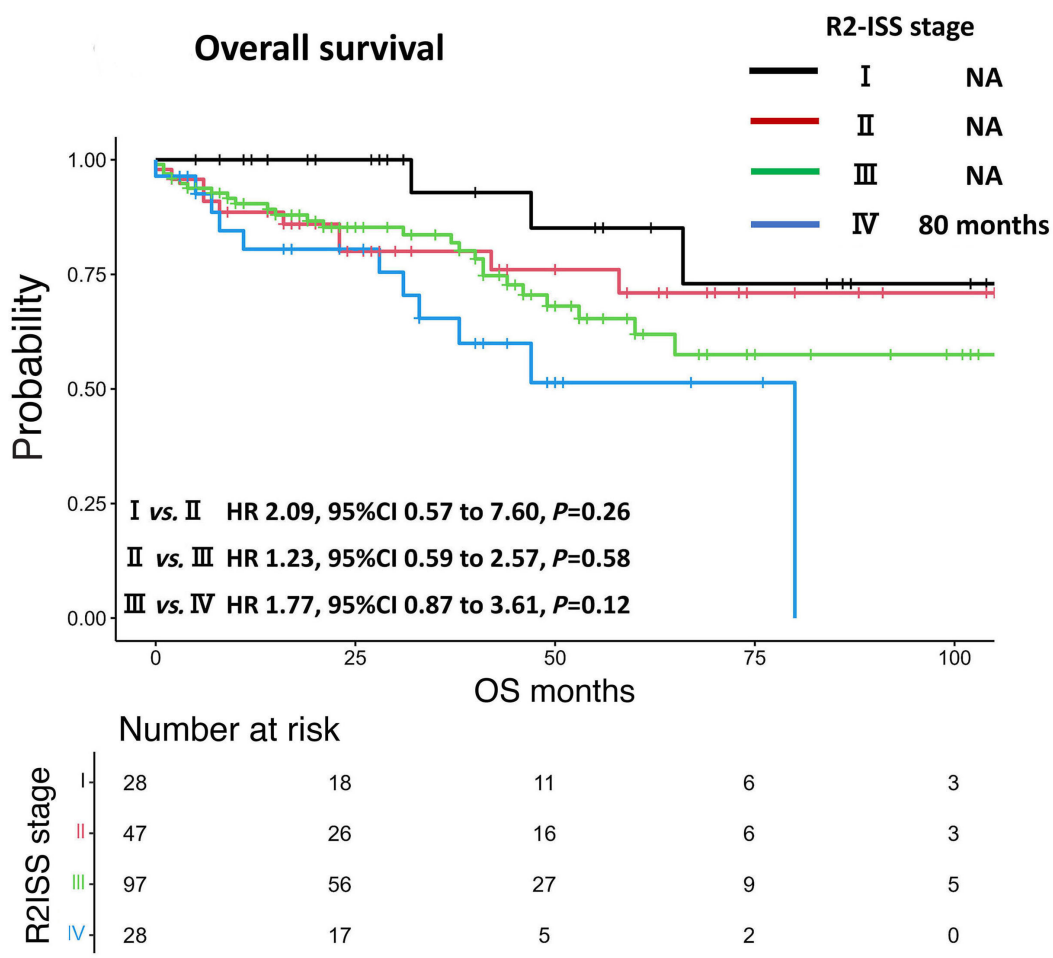
autoSCT: autologous stem cell transplant; EMN: European Myeloma Network; IMiD; immunomodulatory drugs; IQR: interquartile range; ISS: International Staging System; LDH: lactate dehydrogenase; MoAb: monoclonal antibody; N: number; PI: proteosome inhibitor; R-ISS: Revised-International Staging System; R2-ISS: Second Revision of Revised International Staging System; TE: transplant eligible.

tary Figure S1). The Kaplan-Meier curves of PFS and OS according to stage in R2-ISS are shown in Figure 1A and B, respectively. In R2-ISS, the median PFS was NR, 37, 44, and 30 months for stages I, II, III and IV, and median OS was NR for stage I-III and 80 months for stage IV. Patients with stage I in R2-ISS appeared to have better PFS than all other groups, although this did not prove to be statistically significant upon analysis. Similarly, patients with stage IV in R2-ISS tended to have worse OS than those with stage III; however, the differences were also not statistically significant. We obtained similar results through subgroup analysis, specifically within

A



B



Continued on following page.

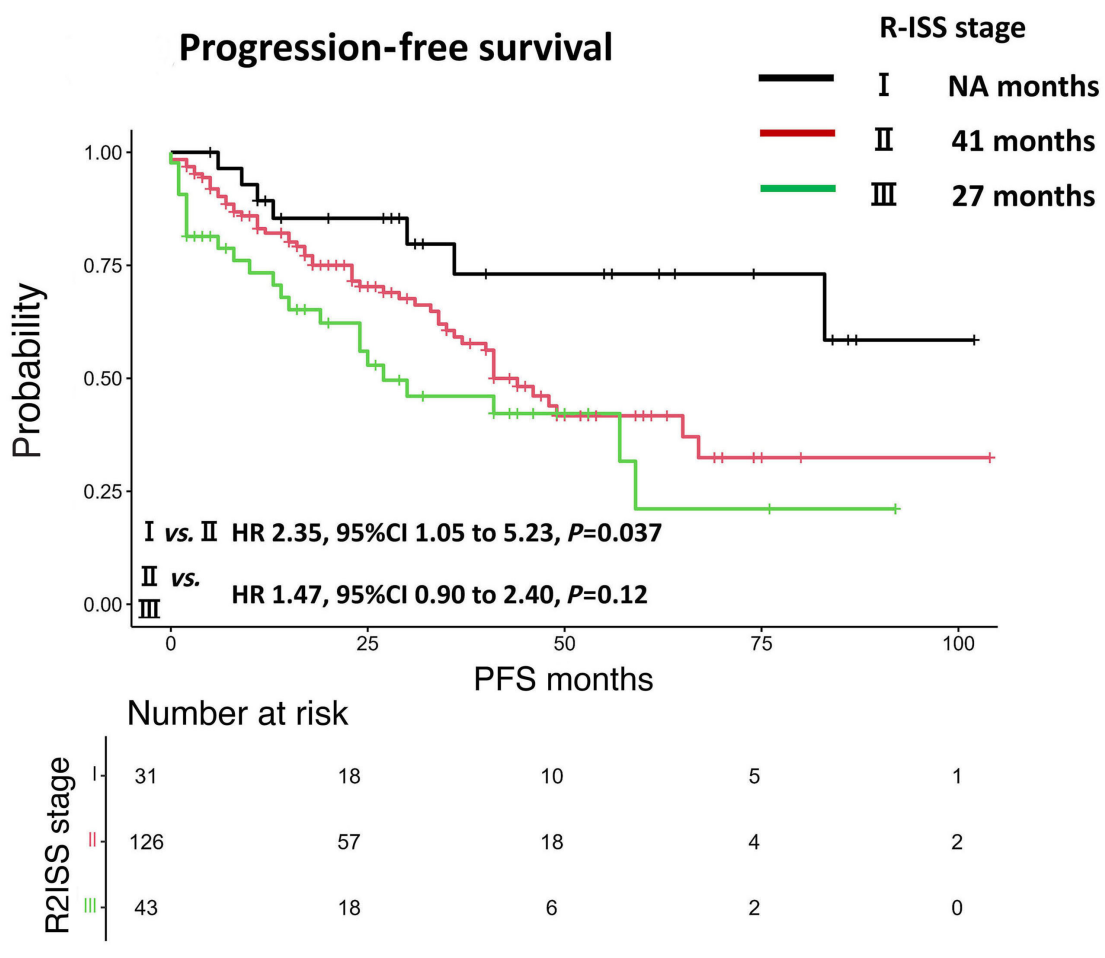


Figure 1. Survival outcomes in our cohort. Kaplan-Meier survival curves according to the Second Revision of the Revised International Staging System (R2-ISS) (A) progression-free survival (PFS) and (B) overall survival (OS), and to the Revised-International Staging System (R-ISS) (C) PFS and (D) OS.

the transplant eligible and transplant ineligible groups (*Online Supplementary Figure S2*). Regardless of age or transplant eligibility, by R2-ISS, our cohort did not divide into four clear groups. In our cohort, patients with R-ISS

stage II could be divided between 33% R2-ISS stage II and 64% with stage III, but unlike the EMN cohort, there were no significant differences in PFS or OS between these two groups. Conversely, the Kaplan-Meier survival curves based on the R-ISS showed that median PFS was 41 and 27 months in stage II and III patients, and were not clearly distinguishable; however, those patients with stage I had a significantly better OS rate. In terms of OS, the survival curves of the three groups were clearly separated with median survival NR in stages I-II and 54 months in stage III, respectively. Importantly, stages II and III also had significantly different survival estimates. (Figure 1C, D)

We next examined the distribution of patients classified with the ISS, R-ISS, LDH, and cytogenetic abnormalities when reclassified with the R2-ISS (*Online Supplementary Table S1*). Among the 67 patients classified ISS stage II, 35 (52%), 29 (43%), and 3 (4.5%) were reclassified to R2-ISS II, III, IV, respectively; of the 86 patients with ISS stage III, 61 (71%) and 25 (29%) were reclassified to R2-ISS III and IV, respectively. Of the 125 patients with R-ISS stage II, 43 (34%), 78 (62%), and 4 (3.2%) were reclassified as R2-ISS stage II, III, and IV.

These differences between our cohort and the EMN cohort may be explained in part by the differences in the age of the patients and the treatments they consequently received. Myeloma is a disease of the elderly and the median age of 60 years in the EMN cohort differs from that of patients in general clinical practice globally.[3-5] In addition to being significantly older, our cohort had more stage III patients in the ISS stage and more stage III and IV patients in the R2-ISS than in the EMN cohort. Despite these differences, patients in our cohort appeared to have a better OS, although with the shorter observation period this requires further confirmation and follow up. However, this may be due to the EMN cohort being enriched for patients from clinical trials conducted from 2005-2016, when there were few effective agents such as CD38 antibodies, carfilzomib, ixazomib and pomalidomide. In fact, our study aligns more with other recent studies. For example, a sub-analysis of the MAIA trial using daratumumab, lenalidomide, and dexamethasone revealed a PFS of 28 months in R-ISS stage III patients over 70 years of age,[6] which is almost comparable to our report. In addition, a subgroup analysis of the ALCYONE trial[7] documented a PFS of 32.9 months for patients with R-ISS stage III in the daratumumab, bortezomib, melphalan, and prednisone arm in frail patients who were not eligible for transplantation. These findings emphasize the importance of considering cohorts of patients exposed to the current and more effective new drugs in order to accurately reflect myeloma treatment outcomes. R2-ISS incorporates information on $1q^{+}$ to further refine risk stratification, and we believe it should be regarded as one of several factors to be taken into account. Other critical considerations include patient age, co-morbidities, and overall health status, as well as the availability of newer agents and treatment modalities. Risk classifications that do not use cohorts of patients exposed to the various effective new drugs currently in use may not, therefore, best reflect current treatment outcomes. Limitations of this study include its single institution context and the relatively short follow-up period, but it does include a substantial number of patients, as our center serves a very large region in Japan. While there are few reports about Asian genetic polymorphism, the relation between polymorphism and outcome is unclear. Moreover, Asian clinical and cytogenetic profiles (except age) showed trends similar to the Western studies.[8] Another factor is that treatment interruptions are common in socially vulnerable, frail and older patients.[9] However, the fact that many of our patients are receiving new treatments developed within the last decade provides a major strength to this analysis and reinforces the real-world nature of our cohort.

Given the evolution of myeloma treatment over the last decade, the prognosis of MM has changed dramatically, and nearly half of the newly diagnosed MM patients under 70 years of age are expected to survive more than 10 years. The proposed R2-ISS classification may be useful for identifying homogeneous risk groups in clinical trials. It can certainly be challenging to handle real-world data accurately because the heterogeneity of treatments and relatively short observation periods might obscure the true impact of each risk factor. However, evaluating only data of prospective studies might be inadequate to better reflect current practice, available therapy, and outcome.[10] Therefore, we suggest that any future modifications to the R2-ISS should be derived and evaluated using real-world data as well as from prospective studies. Moreover, this is especially relevant as we better understand the effect of age and other factors on the heterogeneity of treatment effects in the era of novel therapy, as illustrated by the OCEAN study where age impacted on outcome across both arms of this pivotal phase III study.[11]

In summary, subgroup considerations such as age may be one of several significant aspects that each clinician should bear in mind in interpreting clinical trial data and applying these findings to real-world practice. In the modern era, in which the population is aging, there are increasing numbers of older and potentially frailer patients who would not meet rigorous eligibility criteria for clinical trials and thus the impact of novel agents on their long-term outcomes may be more difficult to translate, whilst this group nonetheless constitutes an ethical and societal priority. The insights gained from these additional assessments should in turn individualize patient care when referring to data derived from clinical trials and our most up-to-date and clinically relevant staging systems, so further improving outcome.[12]

Authors

Yuka Uesugi, Daisuke Ikeda, Ami Fukumoto, Rikako Tabata, Daisuke Miura, Kentaro Narita, Masami Takeuchi and Kosei Matsue

Division of Hematology/Oncology, Kameda Medical Center, Kamogawa, Chiba, Japan

Correspondence:
Y. UESUGI - y-uesugi@med.showa-u.ac.jp

https://doi.org/10.3324/haematol.2023.284173

Received: September 1, 2023.
Accepted: November 22, 2023.
Early view: November 30, 2023.

Disclosures

No conflicts of interest to disclose.

Contributions

YU and KM conceived and designed the study, collected data, performed the statistical analysis, wrote the manuscript, and provided patient care. DI, AF, RT, DM, KN and MT collected the data and provided patient care. All authors reviewed and approved the manuscript.

Data-sharing statement

The datasets generated during and/or analyzed during the current study are available from Yuka Uesugi or Kosei Matsue on reasonable request.

References

1. D'Agostino M, Cairns DA, Lahuerta JJ, et al. Second Revision of the International Staging System (R2-ISS) for Overall Survival in Multiple Myeloma: a European Myeloma Network (EMN) report within the HARMONY project. J Clin Oncol. 2022;40(29):3406-3418.
2. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: a Report from International Myeloma Working Group. J Clin Oncol. 2015;33(26):2863-2869.
3. Phekoo KJ, Schey SA, Richards MA, et al. A population study to define the incidence and survival of multiple myeloma in a National Health Service Region in UK. Br J Haematol. 2004;127(3):299-304.
4. Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Björkholm M. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. J Clin Oncol. 2007;25(15):1993-1999.
5. Rosko A, Giralt S, Mateos M-V, Dispenzieri A. Myeloma in elderly patients: when less is more and more is more. Am Soc Clin Oncol Educ Book. 2017;37:575-585.
6. Facon T, Cook G, Usmani SZ, et al. Daratumumab plus lenalidomide and dexamethasone in transplant-ineligible newly diagnosed multiple myeloma: frailty subgroup analysis of MAIA. Leukemia. 2022;36(4):1066-1077.
7. Mateos M-V, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone versus bortezomib, melphalan, and prednisone in transplant-ineligible newly diagnosed multiple myeloma: frailty subgroup analysis of ALCYONE. Clin Lymphoma Myeloma Leuk. 2021;21(11):785-798.
8. Kim K, Lee JH, Kim JS, et al. Clinical profiles of multiple myeloma in Asia-an Asian Myeloma Network study. Am J Hematol. 2014;89(7):751-756.
9. Terao T, Tsushima T, Miura D, Narita K, Takeuchi M, Matsue K. Social frailty predicts worse outcomes in patients with multiple myeloma: a novelty in an old approach. EJHaem. 2020;1(1):103-112.
10. Richardson PG, San Miguel JF, Moreau P, et al. Interpreting clinical trial data in multiple myeloma: translating findings to the real-world setting. Blood Cancer J. 2018;8(11):109.
11. Schjesvold FH, Dimopoulos M-A, Delimpasi S, et al. Melflufen or pomalidomide plus dexamethasone for patients with multiple myeloma refractory to lenalidomide (OCEAN): a randomised, head-to-head, open-label, phase 3 study. Lancet Haematol. 2022;9(2):e98-110.
12. Terpos E, Mikhael J, Hajek R, et al. Management of patients with multiple myeloma beyond the clinical-trial setting: understanding the balance between efficacy, safety and tolerability, and quality of life. Blood Cancer J. 2021;11(2):40.