

Letter

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The R2-ISS in a Multicenter Cohort of Chinese Patients With Newly Diagnosed Multiple Myeloma

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Multiple myeloma (MM) is a complex disease with highly heterogeneous tumor biology, especially involving cytogenetic abnormalities.¹ Consequently, MM patients display markedly diverse clinical characteristics, therapeutic responses, and outcomes.^{2,3} In this context, the international staging system (ISS) was developed to predict the prognosis of MM patients in 2005,⁴ which was later updated and named revised ISS (R-ISS) in 2015.⁵ Although the R-ISS has widely been used as a powerful tool to guide daily practice till present, some considerable limitations (eg, a large proportion of R-ISS II patients with varied outcomes, not reflecting the significance of 1q gain/amplification and concurrent high-risk cytogenetic abnormalities [HRCAs]) have been emerging.^{6–9} In this context, several new prognostic scoring systems have been reported,^{10,11} the most recent of which is the second revision of ISS (R2-ISS) updated by the European Myeloma Network (EMN).¹²

In the R2-ISS,¹² 5 risk variates with the highest impact on both progression-free survival (PFS) and overall survival (OS) were weighted according to their OS impact, including ISS III 1.5, ISS II 1.0, del(17p) 1.0, lactate dehydrogenase high 1.0, t(4;14) 1.0, and 1q+ (either 1q gain or amplification) 0.5. However, t(14;16) was not included because patients with this HRCA had only a trend toward a shorter PFS than those without it, but

not statistically significant, although its role was significant in predicting OS. According to the R2-ISS, patients could be categorized into 4 groups with different risk scores that is, 0 (I), 0.5 to 1.0 (II), 1.5 to 2.5 (III), and 3.0 to 5.0 (IV). In 2 independent cohorts, the R2-ISS was able to sharply stratify newly diagnosed MM (NDMM) patients into these 4 groups with significantly different OS and PFS, including R2-ISS I (19.2% or 11.1% of all patients), II (30.8% or 26.5%), III (41.2% or 51.6%), and IV (8.8% or 10.7%). Moreover, the R2-ISS was able to predict the OS of both transplant-eligible and transplant-ineligible patients, and patients who received different upfront treatments (eg, proteasome inhibitors [PIs], immunomodulatory drugs [IMiDs], or both). Of note, this scoring system could further discriminate OS and PFS of R-ISS II patients, underlining its value in re-stratifying this large heterogeneous group of NDMM patients. With these advantages, this new simple algorithm would be expected to be applied soon in clinical practice to improve the performance of the currently using risk stratification systems such as R-ISS (especially further stratification of R-ISS II patients). However, since the R2-ISS was developed and validated in the European population of NDMM patients enrolled in multiple clinical trials, its prognostic property remains to be verified in other populations and in a real-world setting. In this context, the R2-ISS has recently been validated using real-world data in Australian and New Zealand population.¹³ Considering the significance of 1q+ in the R2-ISS, the Chinese population of NDMM patients may be particularly susceptible to this scoring system due to their high frequency (~50% of NDMM patients) of 1q+ and its prognostic value as reported earlier by our group.¹⁴

To this end, we carried out a retrospective analysis of the real-world data collected from daily practice to further validate the R2-ISS in a cohort of 1005 MM patients newly diagnosed between November 27, 2009 and November 20, 2019, at 6 centers nationwide in China (Table 1). This study was approved by the Institutional Review Boards of the First Hospital of Jilin University (Approval No. 2016-087). All patients had given written informed consent to the use of clinical data according to the Declaration of Helsinki. The inclusion criteria of this study were patients who had complete baseline information for R2-ISS scoring, particularly involving cytogenetics in CD138⁺ cells by fluorescence in-situ hybridization (FISH) that must include the probes for del(17p) (cutoff, 20%), t(4;14) (cutoff, 7.3%), and 1q+ (cutoff, 5.5%) including gain (3 copies) and amplification (≥4 copies) as described previously,¹⁴ and who must receive novel agents (PIs, IMiDs, or both) for upfront treatment. It is noteworthy that the cutoffs for some HRCAs such as t(4;14) and 1q+ was lower than those usually recommended, which might, at least in part, contribute

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Table 1
Characteristics of Patients With Newly Diagnosed Multiple Myeloma in Our Cohort (n = 1005)

	N (%)
Age, y	61 (27–89)
Median (range)	
<65	639 (63.6)
≥65	366 (36.4)
Sex	
Male	590 (58.7)
Female	415 (41.3)
M protein	
IgG	452 (45.0)
IgA	249 (24.8)
IgD	61 (6.1)
Light chain	215 (21.4)
Non/oligosecretory	27 (2.7)
Biclonal	1 (0.0)
ISS	
I	169 (16.8)
II	306 (30.4)
III	530 (52.7)
R-ISS	
I	118 (11.7)
II	624 (62.1)
III	263 (26.2)
LDH, U/L	
Normal	740 (73.6)
Elevated	265 (26.4)
BMPcS, % (n = 562)	
<30	204 (36.3)
≥30	358 (63.7)
β2-MG, mg/L (n = 567)	
<5.5	243 (42.9)
≥5.5	324 (57.1)
Organ involvement	
Hypercalcemia (n = 1003)	143 (14.3)
Renal failure (n = 1004)	261 (26.0)
Anemia (n = 948)	635 (67.0)
Bone disease (n = 963)	887 (92.1)
Extramedullary lesion (n = 960)	
Yes	193 (20.1)
ALB, g/L (n = 899)	
<35	523 (58.2)
≥35	376 (41.8)
PLT, 10 ⁹ /L (n = 1002)	
<100	149 (14.9)
≥100	853 (85.1)
Cytogenetics	
High risk	615 (61.2)
+1q	521 (51.8)
del(17p)	113 (11.2)
del(13q) (n = 978)	412 (42.1)
del(1p) (n = 413)	35 (8.5)
IGH translocations	364 (36.2)
t(11;14)	130 (12.9)
t(4;14)	138 (13.7)
t(14;16)	22 (2.2)
Treatments	
PI	511 (50.8)
IMiD	177 (17.6)
PI + IMiD	317 (31.5)
ASCT	122 (12.1)
Responses (n = 917)	
sCR	114 (12.4)
CR	207 (22.6)

(Continued)

Table 1 (Continued)

	N (%)
VGPR	244 (26.6)
PR	235 (25.6)
MR	58 (6.3)
SD	59 (6.4)

ALB = albumin; ASCT = autologous stem cell transplantation; BMPcS = bone marrow plasma cells; β2-MG = β2-microglobulin; CR = complete response; IMiDs = immunomodulatory drugs; LDH = lactate dehydrogenase; M protein = monoclonal protein; PI = proteasome inhibitor; PLT = platelet; PR = partial response; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response.

to a relatively higher percentage of high-risk patients (eg, 1q+) in this cohort, thus representing one limitation of this study. All patients were treated in the real-world setting, of whom 511 (50.8%), 177 (17.6%), and 317 (31.5%) received PI-, IMiD-, and PI plus IMiD-based induction, and 122 (12.1%) received autologous stem cell transplantation (ASCT). According to the International Myeloma Working Group consensus criteria,¹⁵ 114 (12.4%), 207 (22.6%), 244 (26.6%), 235 (25.6%), 58 (6.3%), and 59 (6.4%) of 917 evaluable patients had a stringent complete response, complete response, very good partial response, partial response, minimal response, and stable disease, respectively. PFS was defined as the time from diagnosis until disease progression, relapse, or death due to any cause. Patients who did not progress or relapse were censored on the last date when they were seen alive and event free. OS was defined as the time from diagnosis until death due to any cause or last follow-up.

With a median follow-up of 35.5 months (95% confidence interval [CI], 32.8–38.2), median PFS and OS were 25.2 (95% CI, 23.1–27.3) and 53.0 (95% CI, 48.1–57.9) months, respectively. A total of 1005 patients with NDMM were categorized into R-ISS I (118, 11.7%), II (624, 62.1%), and III (263, 26.2%), with the largest proportion of patients in the R-ISS II group.¹² As expected, the R-ISS could clearly stratify NDMM patients on both PFS (Suppl. Figure S1A) and OS (Suppl. Figure S1B), with $P < 0.001$ for each comparison between R-ISS I, II, and III. According to the R2-ISS,¹² all patients (n = 1005) were then scored and divided into 4 groups: R2-ISS I (75, 7.5%), II (160, 15.9%), III (582, 57.9%), and IV (188, 18.7%). Compared with those reported by the EMN,¹² there were relatively fewer patients with low (R2-ISS I) and low-intermediate risk (R2-ISS II) but more patients with intermediate-high (R2-ISS III) and high risk (R2-ISS IV) in this cohort. Moreover, every group of patients in this cohort had also relatively shorter PFS and OS, consistent with the fact that majority of patients had more advanced disease, primarily due to late diagnosis, but much fewer patients received ASCT (a main limitation of this study) mostly due to unaffordability, in our cohort than those reported by the EMN (Suppl. Table S1). Of note, the differences in PFS (Figure 1A) and OS (Figure 1B) were significant for almost all comparisons between the 2 groups ($P < 0.001$), except R-ISS I versus II (PFS, $P = 0.056$; OS, $P = 0.075$), probably due to a relatively small number of low-risk patients (eg, ISS or R-ISS I) in our cohort. Moreover, the R2-ISS largely remained its risk-stratifying property in the subgroups of patients with different treatments, particularly in distinguishing the patients with R2-ISS III or IV from those with R2-ISS I or II. In addition, the R2-ISS might work well in patients who did not receive ASCT, for either age >65 years (Figure 1C and Suppl. Figure S2A) or age ≤65 years (Suppl. Figure S2B, C), compared with those who received ASCT (Suppl. Figure S3A, B). Similarly, the R2-ISS also separated patients with different risk levels in the ones who received either PI- or IMiD-based induction (Figure 1D and Suppl. Figure S4A) better than those who received PI plus IMiD-based induction (Suppl. Figure

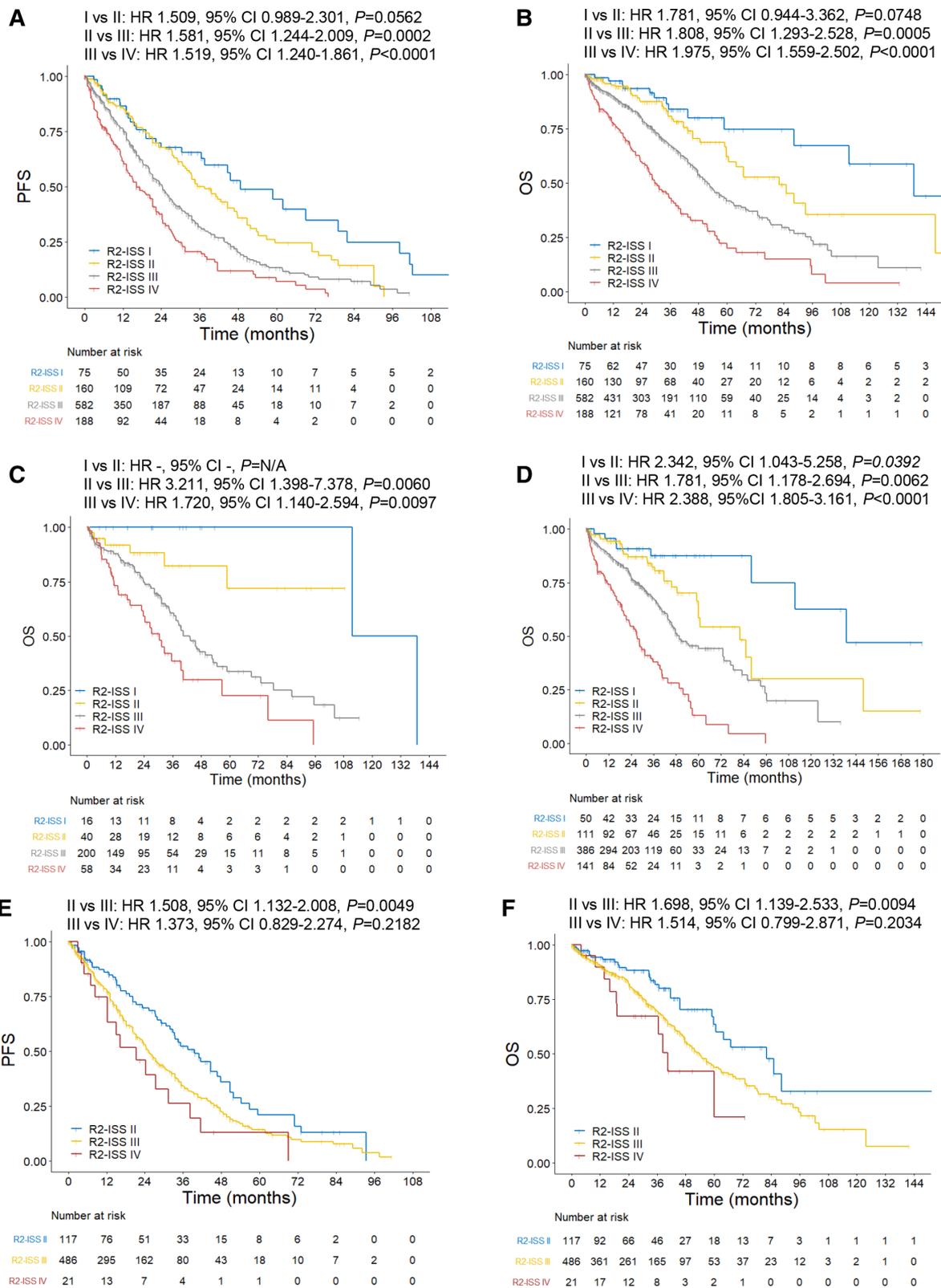


Figure 1. Survival of newly diagnosed multiple myeloma (NDMM) patients according to the R2-ISS. (A, B) PFS (A; median: 48.7, 37.5, 24.3, and 16.3 mo for R2-ISS I-IV, respectively) and OS (B; median: 139.0, 82.2, 51.8, 29.5 mo for R2-ISS I-IV, respectively) of all patients (n = 1005). (C) OS of patients with age >65 y (n = 314; median: 125.3, not reached [NR], 43.3, and 30.5 mo for R2-ISS I-IV, respectively). (D) OS of patients who received either proteasome inhibitor (PI)- or immunomodulatory drug (IMiD)-based induction (n = 688; median: 139.0, 82.8, 49.7, and 27.1 mo for R2-ISS I-IV, respectively). (E, F) PFS (E; median: 39.6, 25.3, and 21.3 mo for R2-ISS II-IV, respectively) and OS (F; median: 82.2, 53.8, and 40.5 mo for R2-ISS II-IV, respectively) of R2-ISS II patients (n = 624). OS = overall survival; PFS = progression-free survival; R2-ISS = second revision of international staging system.

S4B, C). However, due to the small number of patients in some subgroups, these results should be interpreted with caution. Nonetheless, these observations support that the R2-ISS could well discriminate NDMM patients with different risk levels and predict their outcomes (both PFS and OS) at diagnosis, although treatments might influence its performance.

One of the main aims for developing the R2-ISS is to better stratify R-ISS II patients,^{12,13} which account for about 60% of patients with considerably heterogeneous outcomes in this cohort. We thus validated whether the R2-ISS would be able to re-stratify the R-ISS II patients and predict their outcomes more precisely. In R-ISS II patients (n = 624), there were 117 (18.8%), 486 (77.9%), and 21 (3.4%) patients with R2-ISS II, III, and IV (Suppl. Figure S4D). The differences in PFS (Figure 1E) and OS (Figure 1F) were statistically different between R2-ISS II versus III or IV ($P < 0.01$ for each comparison), consistent with those reported by the EMN.¹² However, no significant difference was observed between R2-ISS III and IV ($P > 0.05$ for both PFS and OS), similar to the results from the training set, but not the validation set, in the study reported by the EMN.¹² Moreover, a comparison of patient outcomes between R-ISS and R2-ISS suggests that the capability to further re-stratify R-ISS II patients might represent an advantage for the R2-ISS (Suppl. Table S2). Therefore, these observations support the notion that the R2-ISS could re-stratify patients with R-ISS II, particularly in the case of distinguishing R2-ISS III and IV from R2-ISS II.

In summary, this study provides the evidence for the value of the R2-ISS recently updated by the EMN in the risk stratification of NDMM patients, particularly those categorized as R-ISS II by the R-ISS staging system, in an entirely independent cohort of patients with considerable differences in baseline characteristics (eg, more advanced disease and HRCAs) and treatments (ie, in the real-world setting, rather than clinical trials in the EMN study¹²). Thus, this new simple prognostic tool warrants further attention in future investigations and practice.

AUTHOR CONTRIBUTIONS

PY, FZ, YD(1), GG, HX, XL, SY, WX, YM, XQ, ML, YD(2), and FJ performed the research. FJ, PY, and YD(2) analyzed and interpreted the data. FJ and YD(2) conceived and planned the study design, and wrote the article. All authors approved the article.

DATA AVAILABILITY

Original data are available upon reasonable request to corresponding authors.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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