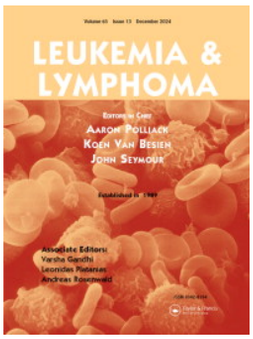

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Validation of the second revision of the international staging system (R2-ISS) for overall survival in multiple myeloma in a real-world cohort: an analysis by the Balkan myeloma study group (BMSG)

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LETTER TO THE EDITOR

Validation of the second revision of the international staging system (R2-ISS) for overall survival in multiple myeloma in a real-world cohort: an analysis by the Balkan myeloma study group (BMSG)

Efstathios Kastritis[a], Eirini Katodritou[b], Sorina Badelita[c], Jelena Bila[d], Güldane Cengiz Seval[e], Zorica Cvetkovic[f], Daniel Coriu[g], Emmanouil Spanoudakis[h], Dimitra Dalampira[b], Aleksandra Sretenovic[d], Aggeliki Sevastoudi[b], Anca Bojan[i], Marko Mitrovic[d], Catalin Danaila[j], Maria Gavriatopoulou[a], Maria Roussou[a], Charalampos Charalampous[a,k], Evangelos Terpos[a], Meral Beksac[f] and Meletios A. Dimopoulos[a]

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Letter to editor

Multiple myeloma (MM) patients exhibit heterogeneous outcomes, necessitating reliable prognostic tools to guide treatment. In 2015, the Revised International Staging System (R-ISS) was developed to enhance the prognostic value of the International Staging System (ISS) by incorporating elevated serum lactate dehydrogenase (LDH) and adverse cytogenetics, including del17p, t(4;14), and t(14;16) [1,2]. Despite its prognostic utility, R-ISS classified approximately 60% of patients into the intermediate-risk category (i.e. R-ISS-II). Additionally, the prognostic significance of +1q21 aberrations was eventually recognized but had not been included in R-ISS [3]. The Revised-2 ISS (R2-ISS) was subsequently proposed, integrating ISS, serum LDH, and the presence of del17p, t(4;14), and +1q21 [4] (Supplemental Figure 1). However, the R2-ISS was developed using data from clinical trial participants only, which prompts the need for external validation in the real-world setting. Other groups have also evaluated R2-ISS in independent cohorts of MM patients treated with various regimens [5–9] or ASCT-treated patients [10–12]. Our study aimed to compare the R-ISS and R2-ISS in a large real-world population of NDMM patients treated within the Balkan Myeloma Study Group (BMSG) within the last 15 years (Supplemental Table 1). We included 1,503 NDMM patients from the BMSG registry diagnosed between 2008–2021, with complete data for R2-ISS calculation (42% of patients treated in the same period). Patients were classified according to both the R-ISS and R2-ISS criteria. R-ISS stage I included ISS stage I with no high-risk cytogenetics and normal LDH levels; stage III included ISS stage III with high-risk cytogenetics and/or elevated LDH; stage II encompassed all remaining patients. R2-ISS classification was based on a score assigned to individual components (Supplemental Figure 1) and discriminated four stages: low risk (I), low-intermediate risk (II), intermediate-high risk (III), and high risk (IV). The Kaplan–Meier method was used for median estimates of overall survival (OS). The Cox proportional hazard model was used to estimate hazard ratios (HR), and the Harrell's Concordance Index (C) was used to measure the performance of different models. A two-sided p-value <0.05 was considered for statistical significance. All statistical analyses and graphs were performed using STATA14.

The median age of the cohort was 66 years, with 53% being over 65 years old and 53% males. ISS stages 1, 2, and 3 were represented by 27%, 30%, and 43% of patients, respectively. Cytogenetic abnormalities were distributed as follows: +1q21 in 25%, del17p in 13%, t(4;14) in 12%, and t(14;16) in 7%. Elevated LDH (>ULN) was found in 20% of patients. Baseline characteristics of the cohort are shown in Supplemental Table 2. According to R-ISS, 20% of patients were stage-1, 60% were stage-2, and 20% were stage-3. R2-ISS distribution was 17% low risk (I), 24% low-intermediate risk (II), 47%

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intermediate-high risk (III), and 12% high risk (IV). Regarding upfront treatment, 44% received bortezomib-based induction, 26% received IMiD-based therapy, 22% received a combination of bortezomib and IMiD, and 4% received anti-CD38-containing therapy. Autologous stem cell transplantation was performed in 30% of patients. The median follow-up was 50 months. Median estimated OS for the four R2-ISS stages was 116, 104, 56, and 34 months, respectively, with a 5-year OS rate of 76%, 70%, 48%, and 38% ($p < 0.001$) (Figure 1). While OS did not differ significantly between stages I and II (HR: 1.148, $p = 0.349$), it was significantly different between stages II and III ($p < 0.001$) and stages III and IV ($p < 0.001$). For transplanted patients, the median estimated OS for the four stages was 156, 178, 116, and 78 months, respectively (no difference between stage I and II, $p = 0.74$), was significant for stage II vs III ($p = 0.007$) and was marginal for stage III vs IV ($p = 0.063$). For non-transplanted, the median estimated OS was 80, 74, 47, and 19 months, respectively, without difference for R2-ISS-I v R2-ISS-II ($p = 0.142$), but significant for R2-ISS-I or -II vs R2-ISS-III ($p = 0.003$) and R2-ISS-III vs R2-ISS-IV ($p = 0.002$) (Supplemental Figure 2). The C-index for OS at 5 years was 0.693 (95% CI 0.652-0.734) for R2-ISS, compared to 0.628 (95% CI 0.584-0.672) for R-ISS, similar to the C-index values observed in the original cohorts (training and validation sets) [2,4]. Regarding risk reclassification among R-ISS and R2-ISS, among R-ISS-3 patients, 50% were classified as R2-ISS-IV and 50% as R2-ISS-III; thus, R2-ISS identified higher-risk patients more accurately, with the median OS for R2-ISS-III patients being 44 months vs. 34 months for R2-ISS-IV. Among R-ISS-2 patients, 6% were R2-ISS-IV, 62% were R2-ISS-III, and 32% were R2-ISS-II, effectively differentiating risk groups: median estimated OS was 104, 54 and 37 months respectively ($p < 0.001$). Among R-ISS-I patients, 78% were R2-ISS-I and 22% were R2-ISS-II (Figure 2). Our study examined the largest [5–12] real-world external validation cohort of the R2-ISS staging system in MM. Despite validation in other cohorts, the implementation of a new staging system in clinical practice requires extensive and thorough validation in different MM populations to prove clinical validity and applicability. In our real-world cohort, the R2-ISS identified significant differences in OS across stages II and III and stages III and IV. In addition, R2-ISS discriminated high-risk MM patients better compared to the R-ISS, especially within the intermediate-risk R-ISS group (60% of MM patients). However, the outcomes between stages I and II in both transplanted and non-transplanted patients were similar, suggesting that further refinement may be needed for low-risk patients. A similar observation has also been made by other groups [9,11,12] in the real world-setting. The discrimination is also less optimal in ASCT-treated patients, both in our cohort and in others [11]. This raises the question of whether a simplified risk stratification—collapsing stages I and II into a low-risk group (0 to 1 points), creating an intermediate group (1.5 to 2.5 points), and a high-risk group (3 points or greater)—might be more effective and less complex for clinician use.A plausible explanation may be the use of effective therapies that essentially abrogate the effect of some marginal "high-risk" features or the need for prolonged follow-up in order to see differences among patients with generally good prognoses. It is notable that the estimated median OS among 'low risk' patients (R2-ISS-I & R2-ISS-I-II) exceeds 112 months in our ASCT-treated patients. Similar outcomes of stage I and II diseases were not shown in the original training and validation cohorts [4], further highlighting the need for extensive validation of the prognostic systems in different real-world cohorts. The differences observed in the outcomes between patients in our cohort and those of the original study can mainly be attributed to the inclusion of an unselected, more diverse, real-world patient population in the BMSG registry, many of whom would not have been eligible to participate in clinical trials. In

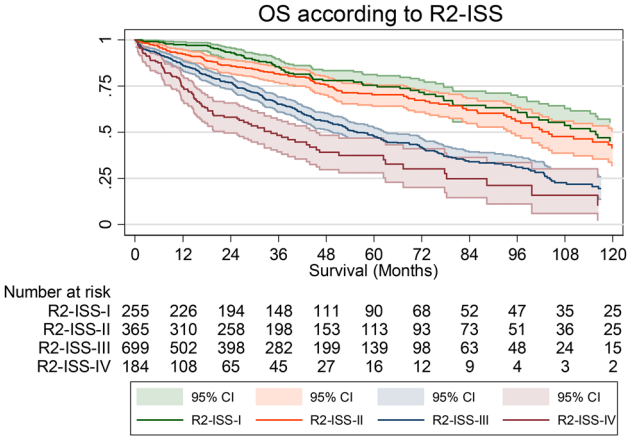

Figure 1. Time-to-event analysis (KM curve) of the survival estimate for R2-ISS in our cohort.
Median OS for the four R2-ISS stages was 116, 104, 56, and 34 months, respectively, with a 5-year OS rate of 76%, 70%, 48%, and 38% ($p < 0.001$)

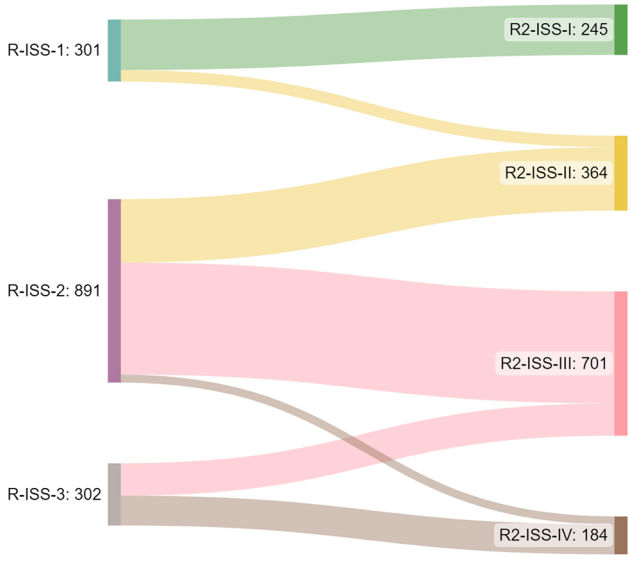

Figure 2. Redistribution of patients from R-ISS (left) to R2-ISS in our cohort.

addition, only 30% of our patients were transplanted upfront, compared to 65% of patients in the original cohort. In the original cohort, patients were treated between 2005 and 2016, while we included patients treated between 2008–2021; this difference may also have an impact on the results of our validation. Thus, compared to R-ISS, it seems that R2-ISS can more effectively and precisely identify patients at very high risk and with poor prognosis who may benefit from more advanced and novel treatments and which should be prioritized for participation in clinical trials. This is especially important for R-ISS-2 patients, who constitute most NDMM patients and frequently exhibit heterogeneous outcomes. Not of less importance, R2-ISS reclassifies patients into lower-risk groups, which is important for clinical trial data interpretation and design of new trials. Given the increasing treatment options and more effective first-line therapies (as with quadruplets), identifying those who may have similar benefits from less aggressive strategies is of relevance. Limitations of the study include the paucity of patients treated with quadruplet therapy or triplets containing anti-CD38, which has become the new standard of care in myeloma [13,14]; nonetheless, such patients were not included in the original R2-ISS development and validation cohort [4] or external validation cohorts [5–12] either. In addition, while clinically important for risk stratification, R2-ISS does not incorporate patient characteristics known to be prognostic in myeloma [15–17]. In conclusion, the R2-ISS offers a more precise tool for identifying high-risk MM patients than R-ISS, which is crucial for tailoring aggressive treatment strategies and prioritizing patients for clinical trials of novel therapies. Our validation in a real-world population underscores the need for continuous evaluation and refinement of prognostic models to ensure they meet the needs of diverse patient populations. The observed discrepancies between clinical trial cohorts and real-world data highlight the importance of validating new staging systems across various settings to enhance their applicability and reliability and the complex nature of multiple myeloma, which cannot be captured effectively in simplified models.

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Authorship contributions

EK designed the study, collected and analyzed the data, and wrote the manuscript:EK, SB, JB, GCS, ZC, DC ES, DD, AS, AggS, AB, MM, CD, MG, MR, CC, ET, MB, MAD collected data, critically revised the manuscript; all authors were involved in patient management andapproved the final version.

Disclosure statement

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Data sharing statement

For original data, please contact ekastritis@med.uoa.gr

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