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Evaluation of the Revised International Staging System in an independent cohort of unselected patients with multiple myeloma

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ABSTRACT

The Revised International Staging System (R-ISS) was recently introduced in order to improve risk stratification over that provided by the widely used standard International Staging System. In addition to the parameters of the standard system, the R-ISS incorporates the presence of chromosomal abnormalities detected by interphase fluorescence *in situ* hybridization [t(4;14), t(14;16) and del17p] and elevated serum lactate dehydrogenase. The R-ISS was formulated on the basis of a large dataset of selected patients who had participated in clinical trials and has not been validated in an independent cohort of unselected patients. Thus, we evaluated the R-ISS in 475 consecutive, unselected patients, treated in a single center. Our patients were older and more often had severe renal dysfunction than those in the original publication on the R-ISS. As regards distribution by group, 18% had R-ISS-1, 64.5% R-ISS-2 and 18% R-ISS-3. According to R-ISS group, the 5-year survival rate was 77%, 53% and 19% for R-ISS-1, -2 and -3, respectively (P<0.001). The R-ISS could identify three groups with distinct outcomes among patients treated with or without autologous stem cell transplantation, among those treated with either bortezomib-based or immunomodulatory drug-based primary therapy and in patients ≤65, 66-75 or >75 years. However, in patients with severe renal dysfunction the distinction between groups was less clear. In conclusion, our data in consecutive, unselected patients, with differences in the characteristics and treatment approaches compared to the original International Myeloma Working Group cohort, verified that R-ISS is a robust tool for risk stratification of newly diagnosed patients with symptomatic myeloma.

Introduction

Multiple myeloma is a heterogeneous disease and the development of a risk stratification tool has been challenging. Both disease and host characteristics are crucial and should be incorporated in a staging system. The Durie-Salmon staging system (which was based on the levels of M protein, the number of lytic bone lesions, hemoglobin values, serum calcium levels and creatinine) was used for several years.[1] In 2003, the simpler but robust International Staging System (ISS) was introduced; this system is based on β_2-microblobulin and serum albumin levels, and since its introduction it has been the standard for risk stratification of patients with multiple myeloma.[2] Several data have shown that chromosomal abnormalities detected by interphase fluorescence *in situ* hybridization (iFISH) [mainly t(4;14), t(14;16) and del17p] are strong prognostic factors, reflecting the inherent

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genetic characteristics of the disease.[3-6] In addition, elevated serum lactate dehydrogenase (LDH) has been consistently associated with poor prognosis.[7-9]

In order to improve the prognostic performance of the ISS, the International Myeloma Working Group (IMWG) revised the current ISS by adding high-risk cytogenetics [t(4;14), t(14;16) and del17p by iFISH] and elevated serum LDH and thus the Revised-ISS (R-ISS) was proposed as the new system.[10] The formulation of the R-ISS was based on a very large number of patients (3,060 patients) from several independent large prospective trials, who were carefully monitored and reviewed. However, clinical trials exclude patients with severe renal dysfunction or with poor performance status.

Thus, the aim of the current analysis was to validate the new R-ISS in an independent cohort of unselected, consecutive patients with symptomatic myeloma, treated with contemporary regimens and followed rigorously in a single center.

Methods

Consecutive patients with symptomatic myeloma who were treated in our center and who had available ISS stage, cytogenetics [by iFISH for del17p, t(4;14) and t(14;16)], and serum LDH were included in this analysis. Between 2007 and 2014, 475 of the 625 (76%) consecutive patients who started therapy in our center fulfilled the above criteria. Approval for the analysis and publication of the data was obtained from the Scientific/Ethics Committee of "Alexandra" hospital.

R-ISS-1 includes patients with ISS-1 (serum β_2-microblobulin level <3.5 mg/L and serum albumin level ≥3.5 g/dL), no high-risk cytogenetic abnormalities in iFISH [such as del(17p) and/or t(4;14) and/or t(14;16)] and normal LDH levels (below the upper limit of normal). R-ISS-3 includes patients with ISS-3 (serum β_2-microglobulin level >5.5 mg/L) and either high-risk cytogenetic abnormalities in iFISH or elevated LDH levels. R-ISS-2 includes all the other possible combinations.[10] Renal function was evaluated by the estimated glomerular filtration rate (eGFR) which was calculated using the Modification of Diet in Renal Diseases formula.

Interphase fluorescence *in situ* hybridization studies

Plasma cells were separated using anti-CD138–coated magnetic MicroBeads (Miltenyi Biotech, San Diego, CA, USA) following the manufacturer's instructions. At least 100 nuclei were analyzed using a fluorescent light microscope. Patients were considered positive for del17p if ≥20% of the nuclei were positive and for t(4;14) or t(14;16) if ≥10% were positive.[11]

Statistical analysis

Comparisons for categorical variables among different groups were made with the chi-square test, using the Fisher exact test when appropriate. Overall survival was measured from the date of treatment initiation until the date of death or date of last follow up. Progression-free survival was calculated from the date of initiation of therapy until the first date of confirmed progression or death from any cause. Time to event curves were plotted with the method of Kaplan and Meier, and comparisons among groups were made using the log-rank test. For multivariate analysis, factors associated with time to event were introduced into a Cox proportional hazards model. IBM SPSS v20 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

Results

Characteristics of the patients and comparison to International Myeloma Working Group cohort

The analysis included 475 patients with available data on cytogenetics [t(4;14), t(14;16) and del17p by iFISH], serum LDH and ISS. There was no difference in the distribution per ISS stage or elevated LDH between those with or without available cytogenetics, but patients for whom cytogenetic data were available were younger (43% *versus* 31% were ≤65 years, P=0.012) and less often received primary treatment with conventional chemotherapy (2% *versus* 10%), while the frequencies of primary therapy with bortezomib (50% *versus* 44%), lenalidomide (28% *versus* 21.5%) and thalidomide (20% *versus* 24%) were not significantly different.

The median age of the patients was 67 years (range, 27-91 years); 53% of them were >65 years, while 25% were

Table 1. Characteristics of the patients in the analysis.

	N=475
Age median range, years	67 (27-91)
Age ≤65 years, n(%)	222 (47%)
Age 66-75 years, n(%)	133 (28%)
Age >75 years, n(%)	119 (25%)
Males / females	265 (53%)/ 210 (47%)
Median (range) ECOG Performance Status, n.	1 (0-4)
ECOG PS ≥2	44%
ECOG PS ≥2 in patients ≤65 years	33%
ECOG PS ≥2 in patients 65-75 years	53%
ECOG PS ≥2 in patients ≥76 years	54%
ISS-1	115 (24%)
ISS-2	163 (34%)
ISS-3	197 (42%)
High risk cytogenetics [del17p or t(4;14) or t(14;16)]	112 (23.5%)
Increased LDH (>250 IU/L)	70 (15%)
R-ISS-1	86 (18%)
R-ISS-2	306 (64%)
R-ISS-3	83 (18%)
Durie-Salmon stage IA	31 (6.5%)
Durie-Salmon stage IB	252 (53%)
Durie-Salmon stage IIA	93 (19,5)%
Durie-Salmon stage IIB	3 (<1%)
Durie-Salmon stage IIIA	39 (8%)
Durie-Salmon stage IIIB	57 (12%)
Primary therapy	
Chemotherapy	41 (9%)
Thalidomide	92 (19%)
Lenalidomide	110 (23%)
Bortezomib	233 (49%)
ASCT	170 (36%)
Serum creatinine ≥ 2 mg/dL	98 (21%)
Median (range) eGFR in mL/min/1.73 m^2	67 (<5 - >150)
eGFR < 30 mL/min/1.73 m^2	96 (20%)
Hemoglobin < 10 g/dL	234 (49%)
Platelet count <130x10^9/L	56 (12%)
Calcium > 11 mg/dL	85 (18%)

ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; ISS: International Staging System; LDH: lactate dehydrogenase; R-ISS: revised International Staging System; ASCT: autologous stem cell transplanation; eGFR: estimated glomerular filtration rate.

>75 years of age. Compared to the IMWG cohort, our patients were older since in the IMWG cohort only 32% were >65 years. The median eGFR was 67 mL/min/1.73 m^2 and 20% of the patients had an eGFR <30 mL/min/1.73 m^2 (Table 1). In comparison, most of the studies that were included in the dataset for the formulation of the R-ISS had excluded patients with low eGFR and all of them had excluded patients on dialysis. Only 8.6% of our patients did not receive novel agents (thalidomide, lenalidomide or bortezomib) as primary therapy; 42% received immunomodulatory drugs (19% thalidomide-based, 23% lenalidomide-based) and 49% bortezomib-based primary therapy, while 36% underwent autologous stem cell transplantation (ASCT) as part of their frontline therapy (Table 1). *Online Supplementary Table S1* presents the detailed distribution per regimen. In the IMWG cohort, 65% of the patients had received ASCT, 6% had received first-line therapy with conventional chemotherapy, 44% had received proteasome inhibitors and 66% had received immunomodulatory drugs. *Online Supplementary Table S2* summarizes the differences and similarities between the IMWG cohort and our series of patients.

According to standard ISS, 24% of the patients in our cohort were rated as ISS-1, 34% as ISS-2 and 42% as ISS-3 (Table 1). The distribution according to Durie-Salmon staging system is also presented in Table 1. High-risk cytogenetics [t(4;14), del17p or t(14;16)] were present in 23.5% of the patients and elevated LDH was present in 15%. In the IMWG cohort 38% of the patients were rated as ISS-1, 38% as ISS-2 and 24% as ISS-3. Thus, the patients in our cohort more often had ISS-3 and less often ISS-1 disease, probably reflecting the unselected nature of our population, which also included patients with severe renal impairment. In contrast, high-risk cytogenetics and elevated LDH were not different among the two cohorts (24% and 13% in the IMWG cohort, respectively) (*Online Supplementary Table S2*).

Revised International Staging System distribution

According to the R-ISS, 86 (18%) patients were rated as R-ISS-1, 83 (18%) rated as R-ISS-3 and 306 (64%) were rated as R-ISS-2. The distribution within the R-ISS in the original IMWG cohort was 28% for R-ISS-1, 62% for R-ISS-2 and 10% for R-ISS-3. The higher percentage of patients with R-ISS-3 in our cohort was due to the higher proportion of patients with ISS-3 compared to that in the IMWG cohort, since the frequency of high-risk cytogenetics and elevated LDH were similar between the two cohorts. The R-ISS distribution in those ≤65 years was 21%, 60% and 19% for R-ISS-1, -2 and -3, respectively; among patients 66-75 years it was 19%, 63% and 18%, and among those >75 years it was 11%, 74% and 15%, respectively (P=0.128). The differences in the distribution of stages of ISS and R-ISS between the IMWG cohort and our series of patients are presented in *Online Supplementary Table S2*.

Outcomes by Revised International Staging System group

The median follow-up of the entire cohort was 40 months; 57% of the patients have progressed or died and 63% remain alive. The median progression-free survival was 27 months and estimated median overall survival was 63 months. The median progression-free survival for patients rated as R-ISS-1, R-ISS-2 and R-ISS-3 was 34, 28 and 17 months, respectively (P<0.001) (Figure 1A). According to the R-ISS, the probability of overall survival at 3 years was 83%, 69% and 45% and that at 5 years was 77%, 53% and 19% for patients rated as R-ISS-1, R-ISS-2 and R-ISS-3, respectively (Figure 1B; P<0.001 and Table 3).

We then evaluated outcomes according to the R-ISS in

Table 2. Distribution of 475 patients with symptomatic myeloma between R-ISS and ISS stages.

	ISS-1	ISS-2	ISS-3	Total R-ISS
R-ISS-1	86	0	0	86
R-ISS-2	29	163	114	306
R-ISS-3	0	0	83	83
Total ISS	115	163	197	475

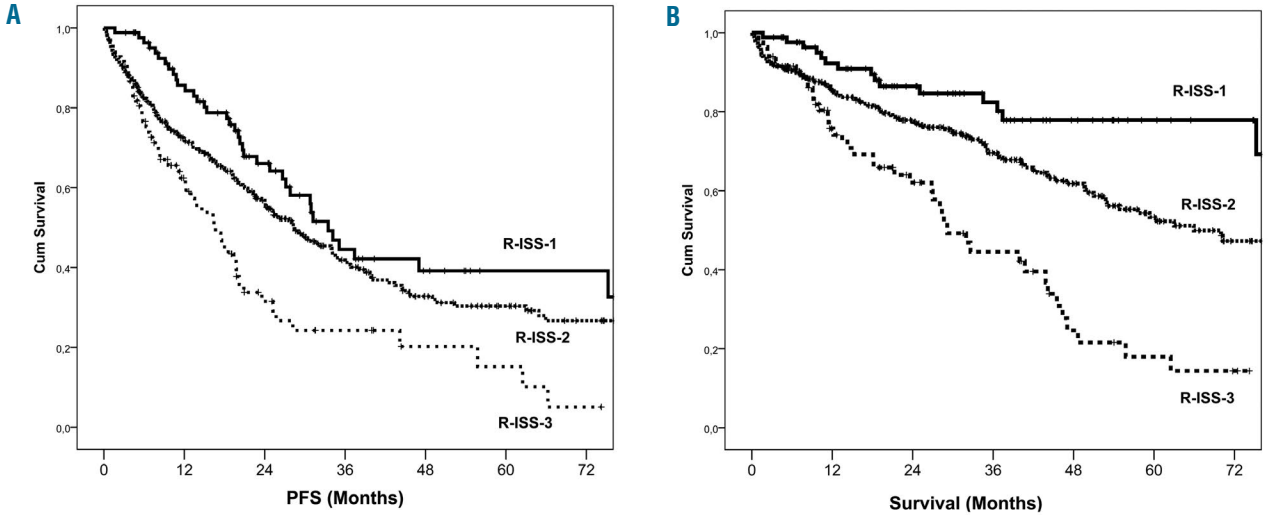

Figure 1. Survival outcomes in 475 patients according to R-ISS group. (A) Progression-free survival (PFS) and (B) overall survival.

patients ≤65, 66-75 and >75 years. The 5-year overall survival rate was 50%, 32% and 21% for patients ≤65 years, 66-75 and >75 years, respectively. In patients ≤65 years, the 5-year overall survival rate was 84%, 71% and 29% for patients in R-ISS-1, R-ISS-2 and R-ISS-3, respectively (P<0.001); for patients 66-75 years, it was 73%, 43% and 18% (P=0.001), while in patients >75 years, the 5-year overall survival rate was 59%, 33% and 0%, respectively (P=0.122). Thus, the R-ISS identified a group of patients >75 years old with a favorable prognosis (Figure 2).

In patients who were not treated with high-dose melphalan and ASCT, the 5-year overall survival rate according to R-ISS stage was 64%, 41% and 13% for RISS-1, RISS-2 and RISS-3 patients, respectively (Figure 3A, P<0.001), while for patients treated with high-dose melphalan and ASCT, the corresponding figures were 93%, 77% and 32%, respectively (Figure 3B; P<0.001). Regarding the type of primary therapy, the 5-year probability of overall survival for patients treated with bortezomib-based upfront therapy was 95%, 69% and 18% for those in the R-ISS-1, RISS-2 and RISS-3 groups, respectively (Figure 3C; P<0.001) and the corresponding figures for

Table 3. Univariate analysis for factors associated with survival using Cox regression.

	N=475 Survival (months)	HR (95% CI)	*P*-value
R-ISS-1	126		<0.001
R-ISS-2	66	II *vs.* I: 1.9 (1.14-3.3)	
R-ISS-3	29	III *vs.* I: 4.2 (2.4-7.5)	
ISS-1	126		<0.001
ISS-2	86	II *vs.* I: 1.75 (1.1-2.8)	
ISS-3	86	III *vs.* I: 3.5 (2.2-5.5)	
Durie-Salmon stage IA	75		0.002
Durie-Salmon stage IB	53	IIA *vs.* IA: 1.28 (0.66-2.5)	
Durie-Salmon stage IIA	86	IIIA *vs.* IA: 1.67 (0.82-3.4)	
Durie-Salmon stage IIB	42	IB *vs.* IA: 3 (0.66-13.8)	
Durie-Salmon stage IIIA	60	IIB *vs.* IA: 2.03 (0.9-4.4)	
Durie-Salmon stage IIIB	30	IIIB *vs.* IA: 2.9 (1.4-5.9)	
Age ≤65 years (A)	109		<0.001
Age 66-75 years (B)	51	B *vs* A:1,9 (1,3-2,7)	
Age >75 years (C)	35	C *vs* A: 3.2 (2.2-4.7)	
Males	66		0.647
Females	62		
High risk cytogenetics [del17p or t(4;14) or t(14;16)] absent	86	1.6 (1.2-2.2)	0.005
High risk cytogenetics [del17p or t(4;14) or t(14;16)] present	44		
Normal LDH (<250 IU/L)	70	1.8 (1.2-2.6)	0.002
Increased LDH (≥250 IU/L)	41		
Primary therapy			
Chemotherapy only	93		
Thalidomide	53		0.047
Lenalidomide	45.5		
Bortezomib	93		
ASCT	109.5	0.35 (0.25-0.5)	<0.001
No ASCT	45.5		
eGFR ≥30 mL/min/1.73 m^2	86	2 (1.45-2.8)	<0.001
eGFR <30 mL/min/1.73 m^2	40		
Hemoglobin ≥10 g/dL	93	1.8 (1.3-2.4)	<0.001
Hemoglobin <10 g/dL	46		
Platelet count ≥130x10^9/L	70	1.8 (1.2-2.7)	0.005
Platelet count <130x10^9/L	43		
Calcium <11 mg/dL	70	1.6 (1.1-2.3)	0.013
Calcium ≥11 mg/dL	44		

Note: *P*-values for interactions between age and ASCT, between age and type of therapy and between ASCT and type of primary therapy were highly significant. HR: hazard ratio, 95%CI: 95% confidence interval for the HR; R-ISS: revised International Staging System; ISS: International Staging System; LDH: lactate dehydrogenase; ASCT: autologous stem cell transplanation; GFR: estimated glomerular filtration rate.

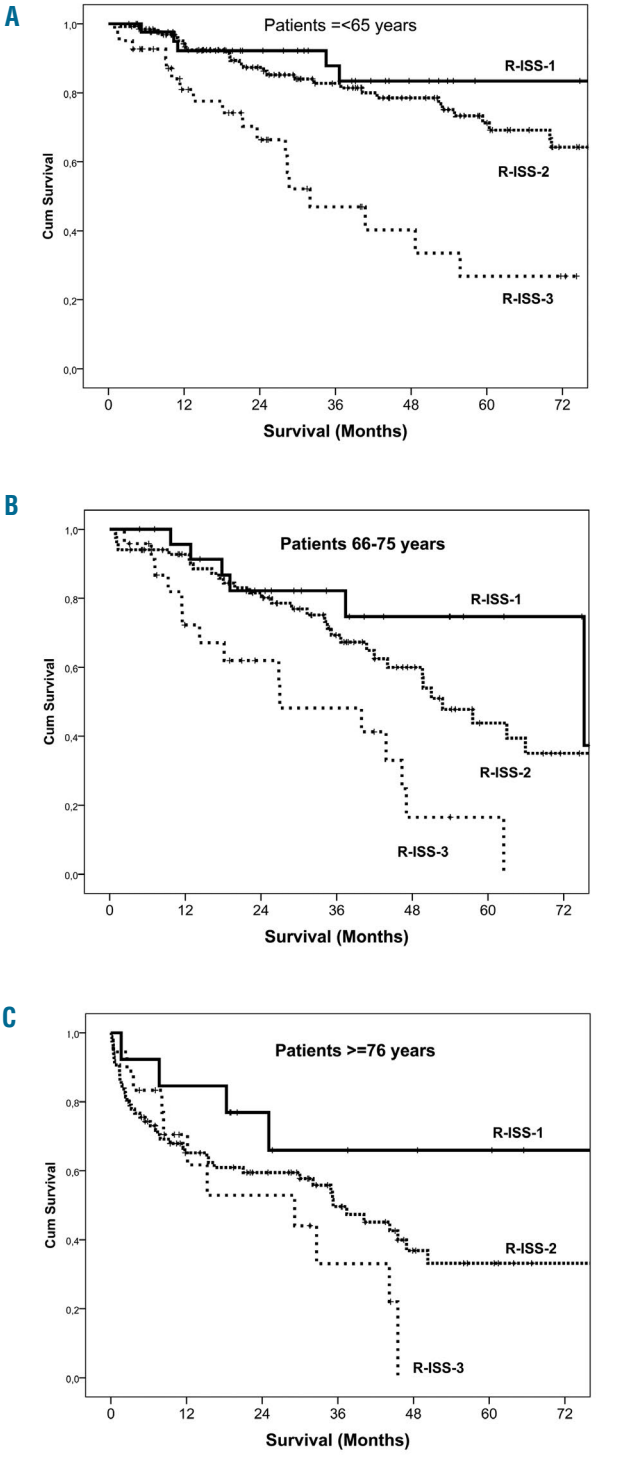

Figure 2. Survival of patients of different age groups according to R-ISS stage. (A) Patients ≤65 years, (B) patients 66-75 years, and (C) patients ≥76 years.

those treated with immunomodulatory drugs were 68%, 41% and 23%, respectively (Figure 3D; *P*=0.002).

We also evaluated the R-ISS in patients with different degrees of renal dysfunction. In patients with eGFR ≥30 mL/min/1.73 m^2, the 5-year overall survival of patients with R-ISS-1, RISS-2 and RISS-3 disease was 76%, 56% and 28% respectively (Figure 4A; *P*<0.001). In patients with eGFR <30 mL/min/1.73 m^2, no patients had R-ISS-1 disease and the median overall survival for R-ISS-2 *versus* R-ISS-3 patients was 42 *versus* 32 months (*P*=0.354), while the probability of 5-year overall survival was 40% *versus* 8%, respectively (Figure 4B); however, the number of patients in each subgroup does not provide enough statistical power to confirm whether the differences in overall survival were statistically significant. *Online Supplementary Figures S2-S5* show the survival curves for each subgroup for the R-ISS *versus* the ISS.

Because there was a strong interaction between therapy and R-ISS distribution, as well as between R-ISS stage and age, we performed a multivariate analysis, which showed that R-ISS stage was an independent prognostic factor associated with survival with a hazard ratio of 1.68 for R-ISS-2 *versus* R-ISS-1 and 3.8 for R-ISS-3 *versus* R-ISS-1 (Table 4).

Discussion

Validation of a prognostic system is an important step for acceptance of the system as a prognostic tool and its incorporation in everyday practice. Our data indicate that the R-ISS, which combines the ISS together with characteristics of the myeloma clone (cytogenetic abnormalities) and elements of the aggressiveness of the plasma cells (reflected by serum LDH), provides significant prognostic information.

Furthermore, the R-ISS retains its prognostic significance even in a population of patients with significant differences from the original IMWG cohort (detailed in *Online Supplementary Table S2*). It is important that the performance of a risk assessment tool is not restricted to a specific patient population so that it can be used more

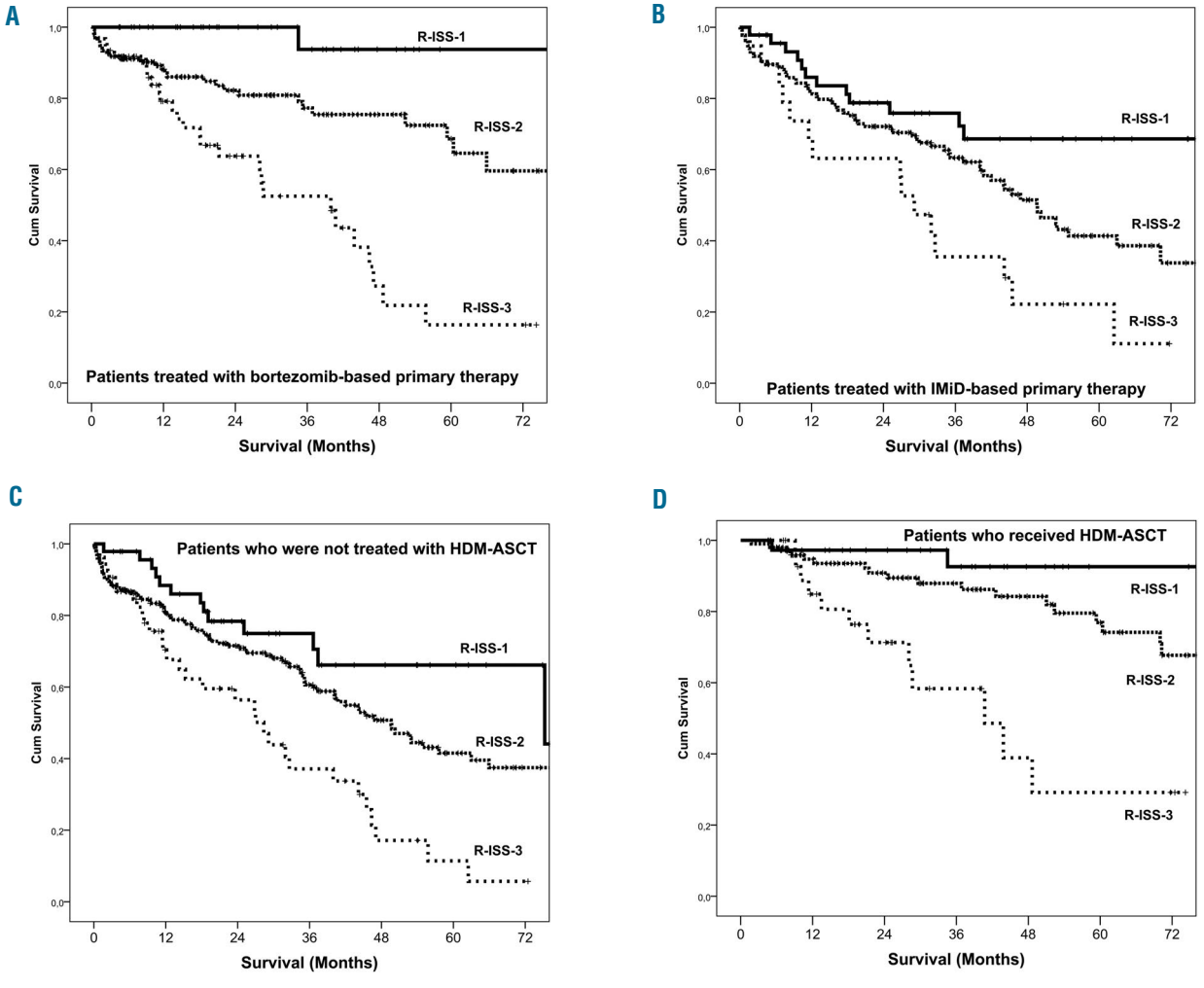

Figure 3. Survival according to the R-ISS for patients who did or did not receive ASCT and depending on first-line treatment regimen. (A) Patients treated with first-line regimens based on bortezomib (B) Patients treated with first-line regimens based on immunomodulatory drugs (IMID). (C) Patients who did not receive high-dose melphalan autologous stem cell transplantation (HDM-ASCT). (D) Patients who received HDM-ASCT.

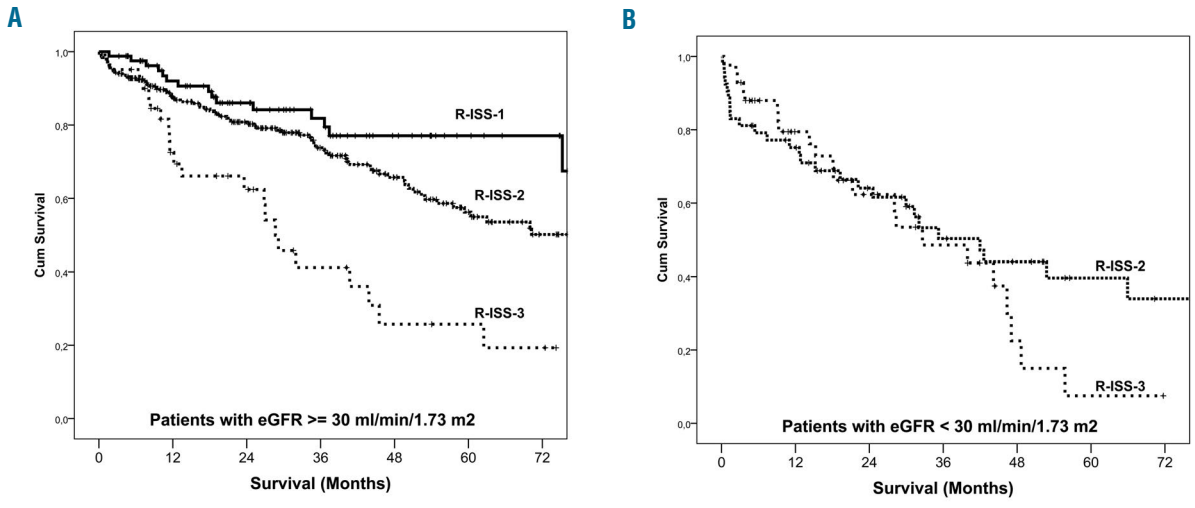

Figure 4. Overall survival according to R-ISS stage in patients categorized by renal fuction. (A) Patients with eGFR ≥30 mL/min/1.73 m^2. (B) Patients with eGFR <30 mL/min/1.73 m^2

extensively. Indeed, our patients were older, less often received ASCT and more often had severe renal dysfunction than the patients in the IMWG cohort.[10] Nonetheless, the R-ISS identified subgroups with very different outcomes among those treated or not with ASCT and among elderly or younger patients. Among patients with severe renal dysfunction (20% of patients in out cohort) only patients with R-ISS-2 or RISS-3 were identified. This is expected because such patients almost invariably have ISS-2 or more often ISS-3 disease due to elevated β_2-microglobulin, related both to disease burden and renal dysfunction. The median overall survival in patients with severe renal impairment (i.e. those with an eGFR <30 mL/min/1.73 m^2) was not significantly different; however, a careful inspection of the curves revealed that there is a clear separation later in the course, resulting in different 5-year survival rates.

In the IMWG cohort, FISH studies were performed in different laboratories with different cutoffs for positivity of del17p or t(4;14).[10] In contrast, in our patients the cutoffs were defined from the outset for del17p, t(4;14) and t(14;16), according to recommendations from the European Myeloma Network (EMN).[11] The rates of high-risk cytogenetics were not, however, very different between our cohort and the IMWG one. The differences in the age composition between the two populations, the fact that the frequency of certain cytogenetic abnormalities may be lower among elderly patients,[12,13] and the use of different cutoffs for positivity may have affected the rates of presence of cytogenetic abnormalities. It is important to note that all our patients had serum LDH measured in the same laboratory, thus, reducing inter-laboratory variability.

As in the original IMWG cohort, most of our patients received therapy with contemporary regimens. Thus, we must postulate that the R-ISS is applicable mostly in patients treated with such regimens, since only very few patients received chemotherapy alone as part of their primary therapy. Importantly, the R-ISS remains robust among patients treated with proteasome inhibitors (bortezomib) or immunomodulatory drugs (thalidomide or lenalidomide) and also among patients treated with or without high-dose melphalan. Whether the R-ISS performs similarly in patients treated with monoclonal antibodies or other novel agents still needs to be evaluated.

Table 4. Multivariate analysis of factors associated with overall survival in univariate analysis, with R-ISS in the model.

	HR	95% CI	*P*-value
R-ISS-1 (reference)	1		
R-ISS-2	1.68	1.03-2.9	0.044
R-ISS-3	3.83	2.1-7.1	<0.001
No HDM-ASCT	1.72	1.1-2.9	0.043
Conventional chemo (reference)	1		
Thalidomide-based	1.13	0.62-2.03	0.690
Lenalidomide-based	1.17	0.63-2.1	0.616
Bortezomib-based	0.93	0.52-1.67	0.805
Age ≤ 65 years (reference)	1		
Age 66-75 years	1.17	0.71-1.94	0.53
Age > 75 years	1.87	1.1-3.2	0.02
Hemoglobin <10 g/dL	1.245	0.890-1.742	0.201
Calcium > 11 mg/dL	1.136	0.757-1.706	0.538
Platelets < 130x10^9/L	1.651	1.074-2.538	0.022
eGFR < 30 mL/min/1.73 m^2	1.322	0.889-1.966	0.168

HR: hazard ratio, 95% CI: 95% confidence interval for HR; R-ISS: revised International Staging System; HDM-ASCT: high-dose melphalan-autologous stem cell transplantation; chemo: chemotherapy; eGFR: estimated glomerular filtration rate.

It is interesting that the median survival of our cohort of myeloma patients is projected to exceed 5 years (median projected overall survival, 63 months). This is important because our patients were an unselected population, were quite elderly, only a minority had received ASCT and 20% presented with severe renal dysfunction. Such data are indicative of the progress that has been achieved over the past decade in the treatment of this disease, mostly due to the introduction of new therapies and to improvements in the use of the currently available treatment options. It is also important that a subset of patients with myeloma (mostly those with R-ISS-1) have a very high probability of a long disease course, with an expected survival well beyond a decade. In contrast, the poor outcome of

patients at high risk, especially of those with R-ISS-3, emphatically demonstrates the need for new therapies and innovative approaches for the treatment of myeloma.

The R-ISS is based on three laboratory variables obtained from a blood sample and the presence or absence of three cytogenetic abnormalities evaluated by iFISH of a bone marrow aspiration sample. This system should be adopted in everyday clinical practice because it provides significant prognostic information. However, there are no prospective data supporting different treatment strategies for patients belonging to different risk groups at diagnosis. Given the poor prognosis of patients with R-ISS-3 disease, it is reasonable to consider a more intensive treatment strategy and exploration of innovative treatments and drugs for such patients, who should be strongly encouraged to participate in clinical trials.

In conclusion, our series of consecutive, unselected patients with symptomatic myeloma, with significant differences in their characteristics and treatment approaches compared to the original IMWG cohort, verified that R-ISS provides significant prognostic information and that it allows the identification of three different groups of patients with clearly different outcomes. Thus, the R-ISS should be used as a standard for the risk stratification of patients with myeloma, for example in the stratification of patients in clinical trials. External validation is crucial and it would be useful to further validate the R-ISS in other cohorts of patients. The potential prognostic role of the R-ISS in patients with relapsed disease may also be evaluated, since this risk stratification tool is so far applicable to newly diagnosed patients and no data exist about its performance beyond first-line therapy.

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