Comparative survival analysis using the International Stratification Score (ISS) in newly-diagnosed multiple myeloma in the Uruguayan population

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Abstract

Background and aims. Multiple myeloma is a frequent hematologic malignancy, in which the International Stratification Score (ISS) is widely used to estimate the overall survival. However, there are no studies in Latin America evaluating its performance. This study aims to describe the ISS performance in the overall survival estimation for newly diagnosed multiple myeloma patients in Uruguay.

Methods. This is a retrospective registry-based survival analysis through the Grupo Uruguayo de Mieloma Múltiple (GUMMA) database, including newly diagnosed multiple myeloma patients from January 2001 until May 2019.

Results. 249 patients were included, 51.81% males and an average age of 63.49 years. According to ISS and Durie-Salmon score (DSS), 47.79% and 82.3% were ISS III and DSS III, respectively. Also, 32.3% were DSS B. Auto hematopoietic stem cell transplantation was performed in 31.73% of patients, and bortezomib was used in 44.18% as frontline therapy. The overall survival was 80% for ISS1, 64.9% ISS2, and 48.6% ISS3 (Log-Rank; p <0.01). The average overall survival was 116.5 months for ISS 1, 77.6 months for ISS 2, and 57.8 months for ISS 3. The hazard ratio between ISS II and ISS I was 2.42 (95% CI 1.10-5.33; p<0.05), and 3.94 (95% CI 1.88-8.26; p<0.05) between ISS III and ISS II.

Conclusion. The ISS staging system allows an adequate stratification of patients according to overall survival in the real-practice setting. However, considering the relevance of the new cytogenetic advances, it is necessary to increase the availability and quality of iFISH in Latin America.

Keywords: multiple myeloma, survival analysis, Uruguay

Background and aims

Multiple myeloma (MM) is a lymphoproliferative disorder characterized by the proliferation of plasma cells and is considered the second most frequent hematologic malignancy [1].

In the western world, the age-standardized incidence rate is around 5 cases per 100,000 population, with a median age at diagnosis of 66 to 70 years [2]. Regarding Uruguay, the reported incidence is 2.1 to 3.5 cases per 100,000 inhabitants [3].

The outcomes of MM patients are variable depending on myeloma cell biology, host factors, and choice of therapy. Therefore, identifying risk factors related to survival is essential for establishing the adequate treatment. In 1975, Durie and Salmon developed the first staging system, bringing together simple clinical parameters and showing its correlation with myeloma cell mass. Novel prognostic parameters have emerged with time. In 2005, an international staging system (ISS) was created to predict survival, establishing three groups according to the levels of serum albumin (< or ≥ 3.5 g/dl) and ß2-microglobulin (< or ≥ 5 mg/L) [4]. Later on, a revised version of the ISS (R-ISS) was published, adding chromosomal abnormalities detected by interphase fluorescent in situ hybridization (iFISH) and serum lactate dehydrogenase

(LDH) [4, 5]. This score uses the tumor burden and disease biology, creating a unified prognostic index; however, lack of standardization, limited availability, and cost of iFISH are factors against its widespread use in real practice. A recent report from the Latin American Myeloma Group (GELAMM) focusing on access to diagnostic analysis in 13 countries showed that iFISH was available in only 32% of the public and 67% of private institutions [6]. Also, in most institutions, no plasma cell sorting is done [6].

The ISS score provides useful information to assess the prognosis of newly-diagnosed MM (NDMM) patients in a variety of settings, including age, type of therapy, geographical regions, even in the relapse setting [7]. Its broad applicability makes this score one of the most practical outside clinical trials or reference centers.

This study aims to describe the ISS score performance to estimate the overall survival in NDMM patients in Uruguay.

Methods

This was a retrospective registry-based, survival analysis based on the Grupo Uruguayo de Mieloma Múltiple (GUMMA) database, including active NDMM patients from January 2001 until May 2019.

Demographic data, disease characteristics, and time from diagnosis to the initiation of treatment, treatment choice, and response to therapy, including overall survival (OS) were analyzed.

MM was diagnosed using standard criteria [8], and survival was measured from the onset of non-radiative frontline therapy to the time of death or last contact.

In this analysis, patients were included if they had active NDMM, a complete dataset of parameters allowing ISS staging, and relevant parameters for treatment outcomes evaluation. Smoldering MM was excluded.

Statistical analysis

Statistical analysis was done using SPSS v.25 and Excel 2013 for Microsoft Windows. Survival was plotted through the Kaplan-Meier (log-rank) method; p values were considered statistically significant when <0.05 and presented along with confidence intervals (CI). Additionally, the univariate and multivariate analyses were done using Cox regression. Variables included were autologous hematopoietic stem cell transplantation (auto-HSCT), use of Bortezomib, percentage of plasma cells in bone marrow, monoclonal spike, hemoglobin, calcium, Durie-Salmon system (DSS) stage B, and age.

Kruskal-Wallis test was used to compare quantitative variables between groups and chi-square was used to compare proportions between groups.

Ethics committee´s consent was obtained at each participating center of the Uruguayan Myeloma Registry.

Results

Of the 314 NDMM cases included in the database, 249 met the inclusion criteria. Among them, the average age was 63.44 years, and the majority of patients were male.

Distribution of patients according to ISS and DSS groups revealed 47.79% ISS III, 82.3% DSS III, and 32.3% DSS B.

Auto-HSCT was performed in 31.73% of patients, and bortezomib was used in 44.18% as frontline therapy. Table I shows the detailed characteristics of the patients.

Table I. Baseline patient characteristics.

	x̄	DS
Age (years)	63.44	11.85
	N	**%**
Total	249	100.00
Female	120	48.19
Male	129	51.81
Scoring systems		
ISS III	119	47.79
ISS II	82	32.93
ISS I	48	19.28
DS III	205	82.33
DS II	34	13.65
DS I	10	4.02
DS A	169	67.87
DS B	80	32.13
Clinical characteristics		
Age >65 years	117	46.99
Hemoglobin <8.5 g/dl	84	33.73
Ca >12 mg/dl	23	9.27
Hemodyalisis requirment*	30	12.05
IgG Kappa	89	35.74
IgG Lambda	44	17.67
IgA Kappa or Lambda	56	22.49
IgM Kappa or Lambda	1	0.40
LCM Kappa or Lambda	51	20.48
Non-secretor myeloma	4	1.61
PC ≥60%**	53	21.29
Treatment		
HSCT	79	31.73
BBR	110	44.18
Non-BBR	139	55.82

x̄, average; SD, standard deviation; ISS, international staging System; DS, Durie-Salmon; LCM, Light chain myeloma; HSCT, Hematopoietic stem cell transplantation; BBR, bortezomib based regimes; *, At diagnosis; **, bone marrow infiltration.

R-ISS was available in only 57 patients (22.89%). Of these, 6 (10.53%), 36 (63.16%), and 15 (26.32%) corresponded to R-ISS I, R-ISS II, and R-ISS III, respectively. Additionally, 11 patients initially classified as ISS III were re-classified as R-ISS II.

Comparison among ISS groups

ISS III group had higher monoclonal component, plasma cells percentage in bone marrow, beta 2 microglobulin, creatinine, and calcium, while hemoglobin and albumin were lower compared with other risk groups. The differences between groups using the Kruskal-Wallis test were statistically significant (p<0.05) (Table II).

Survival analysis

At a median follow-up of 34.7 months, 98 patients died (39.36%).

Table II. Baseline Patient Characteristics, by ISS group.

	ISS I		ISS II		ISS III		
	N	%	N	%	N	%	
Total	48	100	82	100	119	100	
Female	22	45.83	38	46.34	60	50.42	
Male	26	54.17	44	53.66	59	49.58	
DS III	37	77.08	63	76.83	105	88.24	
DS II	9	18.75	13	15.85	12	10.08	
DS I	2	4.17	6	7.32	2	1.68	
DS A	44	91.67	70	85.37	55	46.22	*
DS B	4	8.33	12	14.63	64	53.78	
HSCT	26	54.17	28	34.15	25	21.01	
BBR	16	33.33	26	31.71	64	53.78	*
Non-BBR	32	66.67	56	68.29	55	46.22	
	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	
Age (years)	58.23	11.91	65.43	10.55	64.17	12.16	
Albumin	3.99	0.31	4.35	5.34	3.35	0.66	**
B2m	2.48	0.83	4.01	0.92	12.01	10.56	**
PC%	28.13	24.12	34.12	22.47	42.18	23.19	**
MC	2.11	1.71	2.44	2.17	3.25	2.41	**
Hb	11.11	2.09	9.92	1.79	8.46	1.99	**
Crea	1.07	0.84	1.27	0.97	3.41	3.38	**
Ca	8.82	1.52	9.41	1.27	10.19	2.50	**

$\bar{x}$, average; SD, standard deviation; ISS, international staging System; DS, Durie-Salmon; LCM, Light chain myeloma; HSCT, Hematopoietic stem cell transplantation; BBR, bortezomib based regimes, * Statistically significant (p<0.05) comparison between proportion through chi-square test, ** Statistically significant (p<0.05) comparison between groups through Kruskal-Wallis test.

The OS was 80% for ISS1, 64.9% ISS2, and 48.6% ISS3 (Log-Rank; p <0.01). The average OS per group was 116.5 months for ISS 1, 77.6 months for ISS 2, and 57.8 months for ISS 3 (Fig. 1). The hazard ratio between ISS II and ISS I was 2.42 (95% CI 1.10-5.33; p<0.05), and 3.94 (95% CI 1.88-8.26; p<0.05) between ISS III and ISS II (Fig 1). In the multivariate analysis, auto-HSCT was the only significant variable associated with OS (Fig. 2).
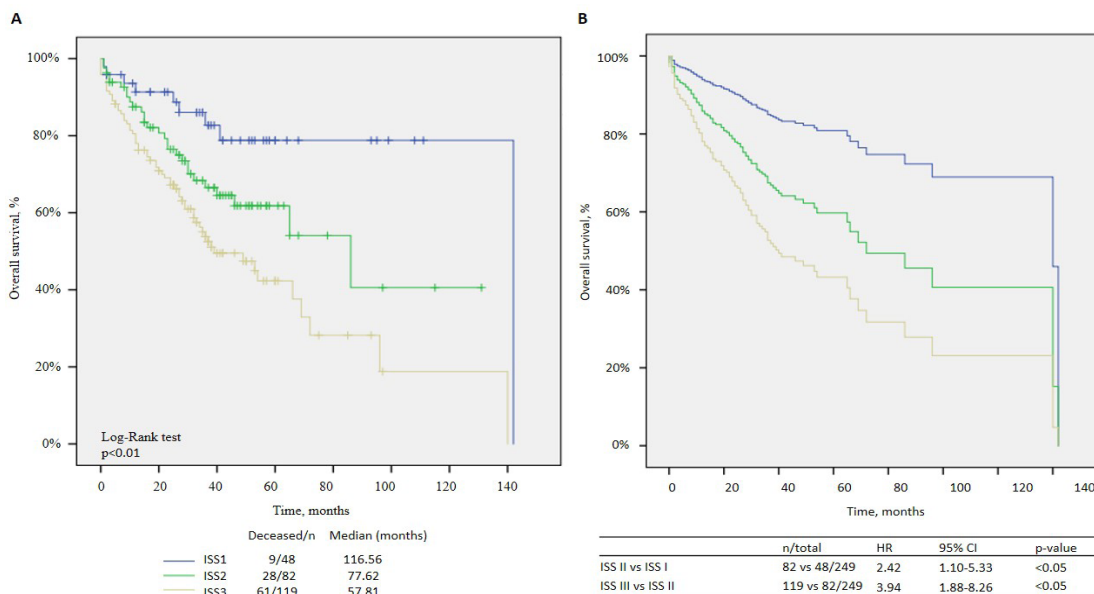

Figure 1. A) Overall survival comparison using Kaplan-Meier and log-rank test according to ISS groups; **B)** Cox regression model and hazard ratios estimation according to ISS groups; CI, confidence intervals; HR, Hazard ratios.
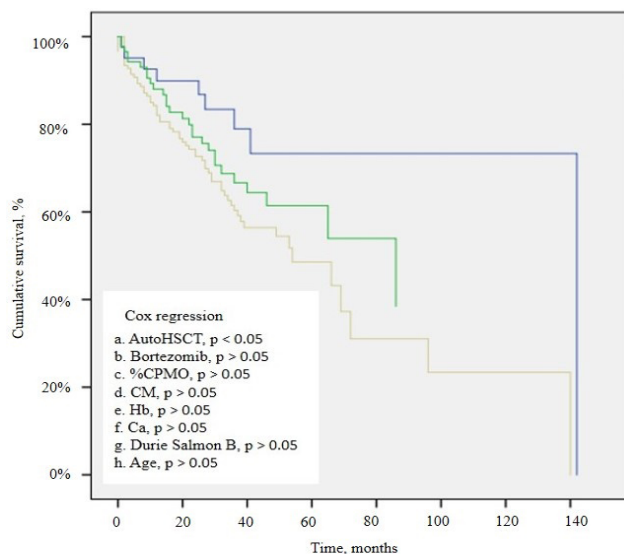
Figure 2. Multivariate Cox regression model and significance of the influence of variables in the overall survival according to ISS groups.

Comparison between DSS groups

When the DSS was used to classify NDMM patients, no difference was found in OS between groups DSS I, DSS II, and DSS III using Kaplan Meier analysis (log-rank >0.05). However, we found significant differences in OS when comparing DSS A and B, 86.5 months in DSS A, and 57.0 months in DSS B (log-rank<0.05).

Survival analysis in patients older than 65 years

Patients older than 65 years had a median OS of 57.7 months compared to a median OS of 92.72 months for <65 (log-rank<0.05).

Discussion

Although MM continues to be an incurable disease, novel therapeutic strategies have improved the clinical course and survival [9]. However, biological and clinical characteristics at diagnosis affect the prognosis and determine therapeutic strategies to overcome adverse conditions [10].

Most of our patients were male, around 60 years of age, and diagnosed at an advanced symptomatic stage, a situation similar to those reported in other Latin American countries. In this context, a study that includes Argentina, Brazil, Chile, Mexico, and Peru reported an average age of 60.9 years, 53.1% males, DSS III in 68.9%, and ISS III in 34.2% of patients [11]. Also, in other continents, MM has been diagnosed in advanced stages, such as China, where a study reported DSS III and ISS III in 85.2% and 54.9%, respectively [12]. However, our results contrast with those reported in the US, where 15% of MM patients are below 65 years of age, whereas approximately half of our population belong to this age group. [13].

Nowadays, new diagnostic criteria, including myeloma defining events in asymptomatic patients, allow an earlier diagnosis. Therefore, we expect that in future reports fewer patients would be newly diagnosed at advanced stages of the disease.

ISS staging criteria were available in the majority of patients included in the database, showing that this is a widely used score. While Greipp et al. reported median survival of 62, 44, and 29 months for ISS I, ISS II, and ISS III, we have found a median survival of 116.5, 77.6, and 57.8 months for ISS I, ISS II, and ISS III, respectively [4]. This discrepancy can be explained by differences in frontline therapies. In Greipp´s study, frontline therapy was not detailed, with 76% receiving "standard-dose treatment". This analysis was done between 1981 and 2002, when standard frontline therapy was probably different from current protocols. In our analysis, approximately 44% of patients received Bortezomib as frontline therapy, while no patient received Lenalidomide-based therapy. Since 2011, Bortezomib was provided frontline to NDMM with high-risk cytogenetics abnormalities or renal failure. Nevertheless, as new evidence emerged, Bortezomib has become the standard first-line therapy, whereas Lenalidomide was not available until 2019.

A Czech study recently conducted to validate the R-ISS and IMWG scores found that the majority of NDMM patients were DSS III (70.3%) and 26.7% DSS B [14]. Similarly, a Turkish study found that in patients older than 65 years, 21% were ISS I, 37% ISS II and 42% ISS III. Based on DSS, 21% IA, 33.5% IIA, 3.8% IIB, 39% IIIA, 2.87% IIIB [15].

In 2005, a study conducted in a Brazilian cohort of 339 patients, the majority were cataloged as stage II (n=264), and the survival for the groups ISS II and III were 61 and 19 months, while the median survival of ISS I group was not presented [16].

Creatinine and age remain important prognostic factors in MM. This is in line with the results published by Greipp et al [4], who showed that both were powerful predictors of survival, although they were not finally included in the ISS score.

Our results suggest that ISS was better at classifying groups according to OS compared to DSS. Similar findings have been reported by Conte et al., who showed a certain superiority of ISS and an impact of DSS B in OS was shown [17].

Study limitations

Our study has limitations, particularly regarding the number of patients, the lack of Lenalidomide as frontline therapy, and the reduced number of patients classified using R-ISS. However, this reflects real-life practice.

Another limitation is that this was a retrospective registry-based study. Thus, it is recommended to conduct prospective studies to validate our results.

Conclusion

The ISS staging system is practical, widely available, and allows an adequate stratification of patients according to OS. Creatinine and age remain essential prognostic factors. Also, frontline consolidation with HSCT has an additional impact on survival.

Although the prognostic impact of cytogenetic abnormalities is well documented, lack of plasma cell sorting and cost do not make it useful in Latin America as yet.

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