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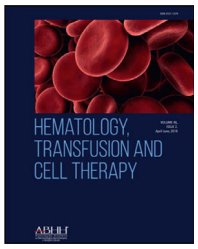

Original article

Impact of the lactate dehydrogenase in association with the International Staging System prognostic score in multiple myeloma patients treated in real life

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ABSTRACT

Introduction: Multiple myeloma is characterized by proliferation of clonal plasma cells. The identification of prognostics factors to identify patient's risk is important. Among the studied factors, it was identified of relevant importance the lactic dehydrogenase.
Objectives: To evaluate the impact of the value of DHL in combination with the score ISS in the medium patients overall survival (OS).
Methods: It is a retrospective cohort with 252 patients with MM recently-diagnosed that attendance in the institution of the study.
Results: To evaluate the association between DHL and ISS, we found 6 new groups to be analyzed: ISS I and normal DHL with medium overall survival not reached, and with DHL loud with medium OS of 69,8 months, ISS II and normal DHL with medium overall survival of 78,8 months and with DHL loud with medium OS of 73,9 months, ISS III and normal DHL with medium overall survival of 46,7 months and with DHL loud with medium OS of 45,5 months.
Conclusion: Through the association of ISS I and normal DHL, ISS III and high DHL and others combinations, we build a new score with superior impact prognostic in our population treated in real life.

Introduction

Multiple Myeloma (MM) presents great diversity of clinical manifestations and patient outcomes, with survival reaching 6 months to 10 years.[1,2] The treatment for MM has quickly evolved due to the advent of new agents, *Car T cells* and the

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better understanding of autologous hematopoietic cell transplantation (HCT), with an important improvement in survival rates, reaching over 5 years.[3-5] Following the development of the diagnostic criteria and new drugs, there was great concern in the evaluation and development of prognostic scores in the attempt to estimate the patient outgoing (Unnecessary plural and possessive removed and shouldn't 'outgoing' be changed to "outcome"???) and survival with greater precision.[6,7]

The first globally developed applicable score was the Durie Salmon in 1975, which sought to correlate clinical characteristics, response to treatment and patient survival with the tumor burden.[8] Other variables continued being studied, such as the plasma cells labeling index in the bone marrow (PCLI), besides factors related to the microenvironment: interleukin-2 (IL-2), IL-6 and tumor necrosis factor alpha (TNF-**α**), among others.[9-11] In 2005, in an attempt to determine more objective pretreatment classifications, a new staging was proposed by the *International Myeloma Working Group (IMWG): the International Staging System (ISS)*. The simplest, cheapest and more reproducible prognostic factor correlated to the survival considered was the Beta-2 microglobulin and albumin combination.[12] In 2015, with the improvement in the cytogenetic studies, the ISS was reviewed, giving rise to the R-ISS (*Revised International Staging System*), thus evincing the importance of chromosomal abnormalities through fluorescence *in situ* hybridization (FISH), with high-risk cytogenetic abnormalities, including the del 17p, t (4,14) and t(14,16) appearing with great impact in the overall survival, in addition to the value of lactate dehydrogenase (LDH).[13]

The LDH is a cytoplasmatic enzyme which catalyzes the reversible conversion of lactate to pyruvate in anaerobic conditions. In neoplastic tissues, its increase occurs due to high glucose rates, instead of oxidative phosphorylation, generating sufficient energy for a fast proliferation of tumor cells related to the tumor initiation, invasive potential, risk of metastasis and tumor relapse.[14]

The importance of LDH in patients with multiple myeloma has been described for several decades[15] and is detected in approximately 10% to 15% of patients at diagnosis. The increase during the course of the disease is related to the increase in the tumor burden, relapse and extramedullary plasmacytoma.[16] In published literary reviews, one can already find such a retrospective analysis between LDH values and the ISS.

However, in an attempt to better locate prognostic factors that reflect the evaluation of survival with real relevance and to validate their use in the public health system, which is lacking in cytogenetic studies by FISH, interest arose regarding the execution of the present study in the real population of our clinical practice within the boundaries of our country. Said analysis has not yet been performed in the conditions presented above.

Methods

This is a retrospective study with 252 patients diagnosed with multiple myeloma monitored in the gammopathy ambulatory at Santa Casa de Misericórdia of São Paulo between January 2007 and December 2016. The population of this study is comprised of patients with the indication for treatment at diagnosis.

For laboratory analysis reference values considered within normality, those used by the institutional lab where the exams were conducted were the following: Beta-2 microglobulin lower than 2.4 mg/L, albumin between 3.5 and 5.2 g/dl and LDH between 240 and 480 U/L. For other defining events, the considered reference values were: creatinine between 0.7 and 1.3 ng/dl, hemoglobin between 12 and 16 g/dl and total calcium between 8.5 and 10.2 mg/dL.

Evaluating the institutional protocols used by the gammopathy group at the ambulatory of the institution, the standards of treatment during the period included in the study changed over the years, initially with VAD (endovenous vincristine 0.4 mg/day for 4 days, endovenous doxorubicin 9 mg/m^2/day for 4 days and oral dexamethasone 40mg/day on D1 to 4, 9 to 12 and 17 to 20), to TD (thalidomide 100 to 200 mg/day, according to the tolerance, and oral dexamethasone 40 mg/week every 28 days ongoing) or CTD (oral cyclophosphamide 50 mg/day, thalidomide 100 to 200 mg/day, according to the tolerance, and oral dexamethasone 40 mg/day every 28 days). For ineligible patients, the standard treatment was the MPT scheme (melphalan 9 mg/m2/4days/month, prednisone 60mg/m2/4days/month and thalidomide 100 mg/day ongoing).

This study has been approved by the Committee on Ethics in Research of the *Irmandade de Misericórdia de Santa Casa* of São Paulo, with the project number 85648/18, according to the Helsinki declaration and Nuremberg code, also complying with the determinations of the *Conselho Nacional de Saúde do Brasil* (Resolution CNS 466/2012). The data were collected from the data bank produced by hematologists belonging to the myeloma group responsible for the outpatient unit. As for the incomplete data, a review of the institution's medical record has been conducted and the patients were clarified and instructed on the study goals and agreed to take part in it upon completing the consent form. An active search for patients with complete record information, but who had missed the follow-up for evaluation of their current status, was conducted. Regarding currently deceased patients, their first-degree relatives or spouses were clarified and instructed on the study and agreed to supply additional data.

Criteria for inclusion and exclusion of patients

Patients who presented criteria for diagnosis of multiple myeloma according to the *International Myeloma Working Group*[16] with indication for treatment at the institution during the described period were included.

Patients who had incomplete information to complete the prognosis score to be studied (albumin and Beta-2 microglobulin), as well as the LDH value, were excluded.

Statistical analysis

The continuous variables were summarized through the variation (minimum and maximum values), mean, pattern

deviation (PD), median and interquartile range (IQR; percentile 25 [Q1]–percentile 75 [Q3]). The categorical variables were described by using absolute and relative frequencies. The Kolmogorov-Smirnov test was used to evaluate the distribution pattern of the numeric variables in the sample.

The survival analysis was performed using the Kaplan-Meier technique, comparing between groups using the log-rank test. The overall survival (OS) was defined as the time elapsed between the date of the diagnosis and the decease.

All analyses were performed using the MedCalc software (Mariakerke, Belgium, v. 11.3.3.0). As a general rule, the two-way significance levels of 5% were used as indicators of statistically significant differences.

Results

Patient clinical and laboratory characteristics

A total of 252 patients had available information regarding the LDH level and the illness stage by the ISS score. The demographic characteristics, including age, sex and year of patient diagnosis, are available in Table 1. Among the laboratory alterations, those evaluated included the hemoglobin value, creatinine, albumin, calcium, LDH and beta-2 microglobulin at diagnosis (Table 1). Anemia (Hemoglobin < 12.0 g/dL), hypercalcemia (Ca ≥ 10.5 mg/dL), bone disease and renal dysfunction (Cr > 2 mg/dl) were present in 72.3%, 15.4%, 83.6% and 22.3% of the cases with available information, respectively. Regarding the MM monoclonal component (Table 1), 62.2%of the cases were of the IgG type. Only three cases (1.2%) of MM were of the non-secretory type. Among the 252 patients, 242 had information on the number of lines of treatment they had received. The number of lines varied from 1 to 10, with the median of 3.0 (2.0–5.0). Among the 248 patients with information on having or not received an autologous HCT, 127 (51.2%) had undergone an autologous HCT.

Staging and distribution of LDH

As Table 2 illustrates, among the 277 patients with available information on the stage of their illness by the Durie Salmon system (DSS), approximately 86% had reached stage III at diagnosis. When assessed according to the ISS score, the distribution was more even with 28.6%, 34.9% and 36.5% of the cases in stages I, II and III, respectively.

The LDH value was classified as normal when it was under the superior limit of reference (*i.e.*, ≤ 480) or high, when over the limit of reference (*i.e.* > 480). The percentages of cases with high LDH (> 480) were of 13.9%, 15.9% and 28.3% among patients with ISS I, II and III, respectively (Table 3).

Overall Survival

The median of the patient follow-up was 62.5 months. In the analysis, the OS was defined as the time elapsed between the date of the diagnosis and the decease or last contact made.

Table 1 – Demographic and laboratory characteristics of patients.

Characteristics	Patients Value or n (%)
Age at diagnosis, years	*n* = 252
Variation	29.6 to 90.5
Mean ± SD	62.9 ± 11.7
Median (IQR)	62.9 (55.1–71.4)
Sex	
Female	112 (44.4)
Male	140 (55.6)
Year of diagnosis	
Until 2010	81 (32.1)
From 2011 to 2016	171(67.9)
SD, standard deviation; IQR, Interquartile Range.	

*Cases with available information on ISS and LDH

Laboratory variable	Patients Value or n (%)
Hemoglobin, g/Dl	*n* = 249
Variation	2.8 a 16.0
Mean ± SD	10.1 ± 2.6
Median (IQR)	10.1 (8.1–12.1)
Hemoglobin, g/Dl	*n* = 249
< 12.0	180 (72.3)
≥ 12.0	69 (27.7)
Creatinine, mg/dL	*n* = 248
Variation	0.30 to 14.9
Mean ± SD	1.52 ± 1.61
Median (IQR)	1.0 (0.8–1.4)
Albumin, g/Dl	*n* = 247
Variation	1.5 to 7.5
Mean ± SD	3.6 ± 0.74
Median (IQR)	3.63 (3.22–4.06)
Calcium, mg/dL	*n* = 247
Variation	1.11 to 15.3
Mean ± SD	9.2 ± 1.82
Median (IQR)	9.2 (8.6–9.9)
Hypercalcemia (calcium ≥ 10.5 mg/dL)	*n* = 247
No	209 (84.6)
Yes	38 (15.4)
LDH,1 U/L	*n* = 252
Variation	34.3 to 2214
Mean ± SD	377.3 ± 207.6
Median (IQR)	330 (266 - 417)
Beta-2-Microglobulin, mcg/Ml	*n* = 235
Variation	0.19 to 39
Mean ± SD	5.6 ± 6.1
Median (IQR)	3.5 (2.1–6.1)

SD, standard deviation; IQR, interquartile range.

Characteristic	Patients Value or n (%)
Monoclonal component	*n* = 249
Non-secretory	3 (1.2)
IgA	57 (22.9)
IgG	155 (62.2)
IgG kappa/IgA lambda	1 (0.4)
IgM	2 (0.8)
Light chain (kappa or lambda)	31 (12.5)

Table 2 – Staging of the patients at diagnosis.

Staging system	Patients Value or n (%)
DSS	*n* = 251
I	8 (3.2)
II	28 (11.2)
III	215 (85.7)
IIIa	159 (63.3)
IIIb	56 (22.3)
ISS	*n* = 252
I	72 (28.6)
II	88 (34.9)
III	92 (36.5)

Our patient OS median was 70.2 months. The OS analysis was conducted according to the ISS staging, resulting in the OS median not being reached for ISS I, while the OS medians were 78.8 and 46.7 months for II and III ISS cases, respectively (Figure 1).

The OS analysis according to the LDH value at diagnosis was also conducted. The OS medians were 76.4 and 68.9 months for patients with an LDH of up to 480 (within normality) and over 480, considered as high, respectively. The comparison between the curves did not demonstrate a statistically significant difference (hazard ratio [HR]: 0.7212; CI95% = 0.4242–1.2258; $p = 0.1739$).

The OS analysis considering the ISS and LDH, showing six new combinations, can be seen in Figure 2. The median overall survival for each subgroup was not reached for ISS I and normal DHL, but was 69.8 months with DHL loud, 78.8 months for ISS II and normal DHL, but was 73.9 months with DHL loud, 46.7 months for ISS III and normal DHL, but was 45.5 months with DHL loud. The comparison between the curves demonstrated a statistically significant difference ($p < 0.0001$).

Once we stratified the patients in a new OS analysis in three new groups: Group 1, with ISS I and normal LDH, Group 2, with ISS III and high LDH and Group 3, with other combinations, new combinations were found. The OS median was not reached for Group I, while the OS medians are between 45.51 and 68.5 for groups 2 and 3, respectively (Figure 3).

Discussion

The LDH value is high in approximately 10 to 15% of patients just diagnosed with MM.[1] In our study we found it high in 19.8% of the cases. That higher percentage may reflect the more advanced stage of illness due to delay in diagnosis in Latin America countries, displaying similarities with data demonstrated in epidemiological studies performed in Latin America and Brazil.[17,18] We emphasize the fact due to this study being a retrospective study not having any analysis to exclude differential diagnoses responsible for increased LDH values, such as hemolytic anemia, hypovitaminosis and association with advanced bone disease, among others.

In our cohort, we have confirmed the validation of the ISS score as an important prognostic tool to be used. Regarding the ISS score, the distribution we found in our cohort was of 28.6%, 34.9% and 36.5% for ISS I, II and III, respectively. The study conducted with the Brazilian population also demonstrated the increase of the ISS II at diagnosis, found as well in

Table 3 – Distribution of patients according to the ISS and LDH value.

	ISS I (*n* = 72)	ISS II (*n* = 88)	ISS III (*n* = 92)
DHL			
Normal (≤ 480; *n* = 202)	62 (86.1)	74 (84.1)	66 (71.7)
High (> 480; *n* = 50)	10 (13.9)	14 (15.9)	26 (28.3)

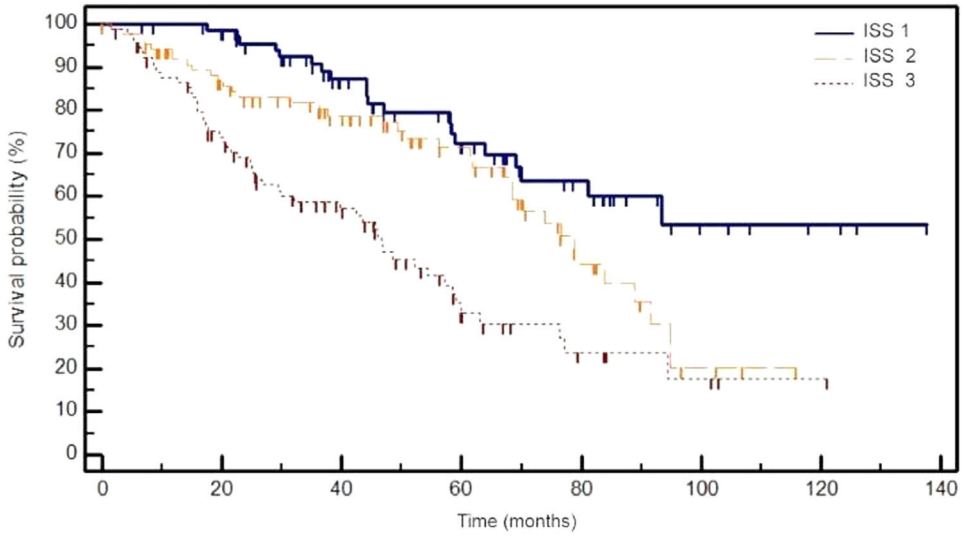

Figure 1 – Overall survival from diagnosis according to ISS stage.

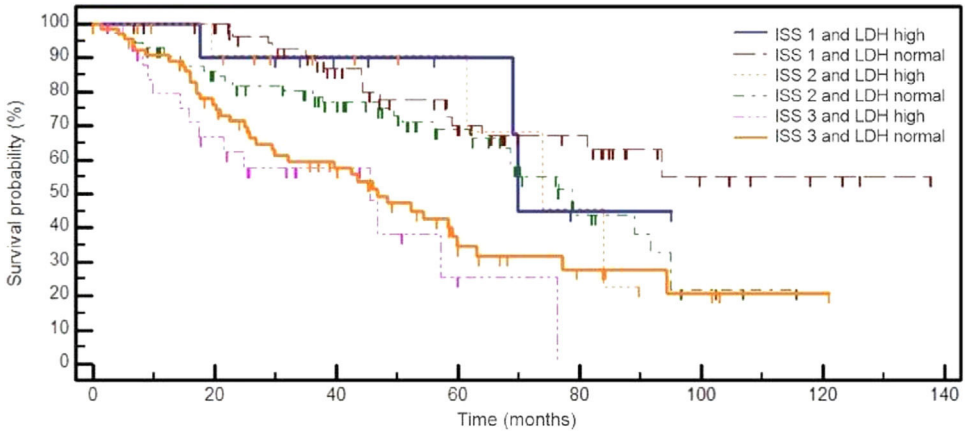

Figure 2 – Overall survival from diagnosis according to the ISS and LDH value.

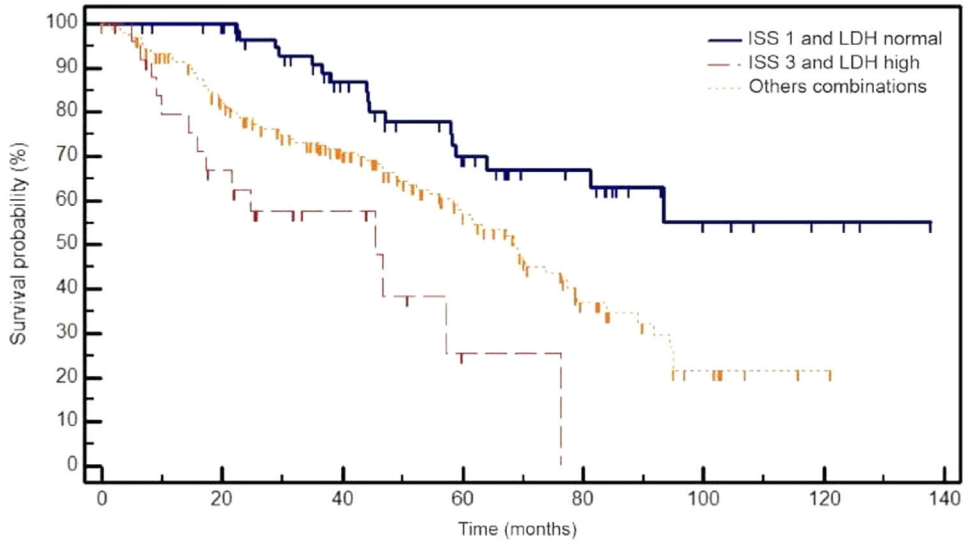

Figure 3 – Overall survival from diagnosis according to the ISS and LDH value in other combinations.

the original study to evaluate the score, which had a similar distribution.[17-19] The medians for the overall survival of all substratifications in our population were over the original study mark, but similar to another study also conducted in Brazil. In the ISS study, patients up to 2005 were included, considering the drugs available at that time. In this study, only 26.1% of the patients were submitted to autologous HCT.[19] In the study previously conducted in Brazil with overall survival rates superior to the original ISS, however inferior to ours, only 25.5% of the patients underwent autologous HCT.[17,18] When assessing our population, 51.2% of the patients had undergone autologous HCT.

Due to the easy access to this procedure at the institution during the described period, most of patients underwent autologous HCT, which helped to increase the OS median in 5 years. We could also consider the information gathered in our analysis as clinical. Patients who entered our services through the emergency area and progressed to death during the first admission are not included in the cohort. In the population of the present study, approximately 42% of the patients were exposed to alkylating agents, 14.6% of these while also making use of melphalan. Regarding the use of an immunomodulator, 59.1% of our patients made use of thalidomide in the first-line induction regimen, showing that to date, even after the inclusion of patients up to 2016, approximately 10 years after the validation of the ISS score, the therapeutic agents we use in our clinical practice are divergent, when compared to the standard of treatment already accessible around the world for many years. A small number of patients had access to a clinical trial during the evaluation period.

Considering the subgroup of patients, classified as only RISS 3 due to being ISS 3 and having high LDH, not considering the cytogenetic risk, we can identify part of that population in our study corresponding to 10.3% of our patients having an overall survival median of 45.5 months. As we evaluated the original RISS study, including only patients that have been enrolled in clinical studies in the age of new agents, published in 2015, RISS3 patients had an overall

Table 4 – Multivariate analysis including LDH, ISS, anemia, hypercalcemia and age.

Variable	P	HR	95% CI of HR
LDH High	0.4468	1.2072	0.7451 to 1.9560
	< 0.0001	2.3674	1.5670 to 3.5767
ISS III			
Anemia (HB < 12 g/dL)	0.6517	1.1248	0.6767 to 1.8695
Hypercalcemia (≥ 10.5 g/dl)	0.3953	1.2680	0.7355 to 2.1861
	0.0360	1.5190	1.0298 to 2.2407
Age > 62.9 years (study median)			

survival median of 43 months, corresponding to 10% of the patients.[13] Such data is very similar to those found in our cohort.

A Greek study conducted by Terpos and collaborators also considered the value of LDH associated with ISS, with 40% of the enrolled patients undergoing autologous HCT and 60%, treatment which included new agents. In that study, patients with ISS 3 and high LDH had a median OS of 17 months,[24] much lower than that of the data we obtained. In the original RISS study, a subanalysis according to the performed treatment was also conducted. When we compared RISS 3 patients who had and had not undergone autologous HCT, we did not find any statistical difference in the survival rates.

However, considering patients with ISS 1 or 2, the autologous HCT had a greater impact with a greater difference and increase in the OS.[13] As previously stated, the autologous HCT in our institutional protocols, not including new agents, may have been the distinguishing factor in approaching the median OS found in the original study to validate RISS.

The survival rates for patients with high LDH and LDH within normality in our cohort were 68 and 76.4 months, respectively. A statistical difference was not demonstrated in that analysis (hazard ratio [HR]: 0.7212; CI95% = 0.4242 −1.2258; $p = 0.1739$). In a study conducted by Gkotzamanidou and collaborators in the period between 1995 and 2008, the LDH value stratified the survival rates with statistical difference, being of 15 months for patients with LDH above the normal level and 44 months for patients with normal LDH.[25] Still in the same aforementioned study, the patients were chronologically separated into groups before and after the year 2000, with a median OS in the high LDH group prior to 2000 of 10 months, and after 2000, of 21 months; therefore, there were inferior values in both groups in comparison to the OS for those with normal LDH. The data reaffirm that, even after the introduction of new therapeutic agents, the value of LDH continues to show its prognosis impact on the disease[25].

In our analysis, when evaluating the associations between ISS and the normal and high values of LDH separately, in the substratification between ISS 3 normal and high values of LDH, with a median OS of 46.7 months and 45.5 months, respectively, we did not find a statistical difference. We evaluated such results, which suggested that in itself the ISS score possesses sufficient applicability and information to stratify patients with highly aggressive diseases and perhaps only the isolated LDH value would not add any information regarding the prognosis impact on patients who have already been classified as having high-risk disease by the ISS.

When analyzing Figure 3, showing patients with new LDH and ISS combinations, we can observe the following results: for patients with ISS I and normal LDH, a median OS not reached and in 5 years of 70%; for patients with ISS III and high LDH, a median OS of 45.5 months and in 5 years of 25.6%, and; for other conducted combinations with a median OS of 68.5 months and in 5 years of 57%, showing a statistical difference. In our group, the LDH in a univariate analysis was not identified as a prognostic factor, nor was it in a multivariate analysis (Table 4). However, with other performed associations of LDH values it was possible to identify new OS rates.

Currently, more objective prognosis evaluations have been obtained with the aid of laboratory methods technology. However, through the use of the association, as illustrated in Figure 3, we built a score, which in our cohort has been demonstrated superior to the ISS score regarding the OS curves distribution and thus, also demonstrated that, even with the most recent MM treatment and diagnosis method advancements, the laboratory exams used for many years still prove to be useful, helping in the caring for, as well as in the performance of, patients on a global scale.

We further emphasize the fact that the population in Latin America is composed of patients treated in public health services, with a shortage of available resources for the evaluation of risks, as well as therapeutic options very distant from the clinical trials. In our cohort, only approximately 9% of the patients have made use of proteasome inhibitors in the first line of the induction treatment, said medication having already been included in first-line protocols for patients with MM as a standard of care for many years. In comparison with many previous studies focused on the prognosis importance of the LDH value, the epidemiological and socioeconomic characteristics of our cohort are distinct, when compared to the standard found in patients in the United States and Europe, reinforcing even more the importance of identifying prognosis factors applicable to our daily reality.

We highlight that one of our limitations was that our study population was not exposed to several new agents currently employed in the clinical practice. As advances in laboratory methods and treatment patterns are so rapid, it is important that a more recent cohort of patients over the last five years be evaluated. It is imperative that the proposed score also be evaluated including this group for validation in different profiles of patients with multiple myeloma and their treatments.

Conclusion

The studied patient prognostic value of LDH did not show any statistical difference. However, through the use of new

combinations (Figure 3), we succeeded in building a new score in which our population proved to be superior to the ISS score regarding the median OS rates distribution. Therefore, we also succeeded in demonstrating that the LDH, when associated with the ISS, has proven its importance in our group. Even with the improvement of clinical methods, the lactate dehydrogenase enzyme reassures its relevance. It is further noteworthy that this laboratory test is of low cost, with applicability and accessibility to most of the worldwide institutions, particularly in our population, as a possible, efficient and applicable tool, which should be highlighted in areas with risk evaluation resource shortages.

Conflicts of interest

The authors have declared there is no conflict of interest.

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