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ORIGINAL ARTICLE

Survival differences in multiple myeloma in Latin America and Asia: a comparison involving 3664 patients from regional registries

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Abstract

In previous observational studies, we have separately characterized patients with multiple myeloma (MM) both from Latin America (LA) and from Asia. Here, we analyze these two datasets jointly, in order to assess the overall survival (OS) in these two world regions. Data were available from 3664 patients (1968 from LA and 1696 from Asia); all of whom diagnosed between 1998 and 2007. Approximately, 26% of patients in both world regions underwent transplantation. OS (from diagnosis of MM) was explored with Kaplan–Meier analyses and Cox proportional hazards models. Patients from LA were significantly younger and had hypercalcemia more often than Asian patients, who in turn had higher proportions of anemia and International Staging System (ISS) stage III disease. The median OS was 56 months in LA, and 47 months in Asia (hazard ratio [HR] = 0.83; 95% confidence interval [CI], 0.76 to 0.91; $P < 0.001$). In multivariable analysis, age, ISS stage III, anemia, hypercalcemia, and world region remained significantly associated with OS ($P < 0.001$ for all covariates). These results were largely driven by patients not undergoing transplantation, as no difference in OS emerged between the two world regions in univariable or multivariable analysis for transplanted patients. Despite adverse prognostic features differentially favoring each region, and adjusting for such differences, we found an OS advantage for patients from LA, in comparison with contemporaneous patients from Asia. Whether this is due to different biological features, differences in access to novel agents (especially thalidomide in earlier periods of the study), unmeasured confounders, or the play of chance, remain unknown.

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Introduction

Even though multiple myeloma (MM) is still considered incurable, the past two decades have been characterized by unprecedented improvements in outlook for patients with this disease [1, 2]. Such improvements were made possible by the introduction of autologous transplantation, bone-targeting agents, and several novel classes of systemic anticancer agents, which have allowed for progressive gains in progression-free (PFS) and overall survival (OS) [3]. The advent of immunomodulatory agents, proteasome inhibitors, and the monoclonal antibodies daratumumab and elotuzumab have led to profound transformations in the therapeutic approach to patients with relapsed and newly diagnosed disease. As a result of the use of these agents, the expected median OS in patients with newly diagnosed MM enrolled in clinical trials has increased over the past two decades from around 30 months [4] to approximately 60 months among transplantation-ineligible patients treated with current regimens [5, 6], and even longer among those eligible to transplantation [7, 8].

Unfortunately, access to several of these novel agents in routine clinical practice is not uniform across countries or world regions. In Brazil, for example, access to most novel agents against MM is currently limited or absent under the public health system, which nevertheless attempts to provide full and comprehensive care to all citizens. Thalidomide has been available in Brazil since the first reports of its activity, because at the time, it was one of the agents used to treat leprosy; in Brazil, thalidomide remains one of the most frequently used agents for the management of patients with MM ineligible to transplantation in this country [9]. On the other hand, lenalidomide was approved as late as December 2017, and no proteasome inhibitor or monoclonal antibody is available under the public health system, where at least three quarters of the population receive medical care [10]. A somewhat similar situation is encountered in Asia, a vast continent where disparities in economy, healthcare infrastructure, and access to novel drugs hinder optimal care to every patient with MM [11]. On the other hand, selected countries in these two regions may display a more equitable healthcare system; Argentina, for example, provides universal access to novel agents against MM for patients treated in private or public institutions. Nevertheless, it is conceivable that differences in access to therapy influence patient prognosis [12], and differences in outcome exist across countries [13]. Likewise, it is possible that different biological features characterize patients with MM from different regions. In recent observational studies, we have separately characterized the profile and outcomes of large numbers of patients both from Latin America and from Asia [14–16]. In the current work, we analyze these two datasets jointly, with the main goal of comparing the survival of contemporaneous registry patients from these two world regions.

Methods

Overall study design and ethical aspects

The conception of each individual study has been described previously [14–16]. In brief, there were two independent studies from Latin America, and one from Asia. The first study was conducted in Brazil only and retrospectively assessed 1124 patients with MM diagnosed at 16 institutions between 1998 and 2004 [14]. The second study was an international, multicenter, and retrospective-prospective registry conducted under the auspices of the International Myeloma Foundation Latin America; it included 852 patients with MM diagnosed between 2005 and 2007 in 23 institutions in Argentina, Brazil, Chile, Mexico, and Peru [15]. For this study, patient registration was done in a retrospective fashion, but part of the follow-up was prospective until 2012. The Asian study retrospectively collected data from 3405 patients diagnosed with MM in 23 centers from China, Hong Kong, Japan, Korea, Singapore, Taiwan, and Thailand [16]. In this study, patients had been diagnosed between 1986 and 2011, but only patients with a diagnosis of MM between 1998 and 2007 were included in the present analysis. The protocol for each study was approved by the competent local authorities and institutional review boards, and written informed consent was obtained from all patients. Given the observational nature of these three registries, patient evaluation and treatment were done according to the discretion of the participating investigators and local standards of care.

Collected data

Demographic and clinical data were collected from medical records by locally designated individuals. There were some differences in the data available for analysis among the three original datasets. Uniform data included the date of diagnosis, the stage according to the International Staging System (ISS) [17], the type of monoclonal component, the results of relevant baseline laboratory tests, and the date of the last follow-up or death. Data about eligibility for, and performance of, autologous transplantation varied across datasets. No data were analyzed on response rates, PFS, toxicity, or quality of

life. Data monitoring and analysis were performed under the supervision of study investigators, and the authors vouch for the full contents of the manuscript, which was drafted and reviewed without any involvement of commercial sponsors.

Statistical analysis

The primary outcome measure was OS, defined as the time elapsed between the diagnosis of MM and death from any cause, with censoring of patients who were alive on the last follow-up date. OS was estimated by the Kaplan–Meier method, and differences between groups were compared using the logrank test. The median follow-up was estimated using the reverse Kaplan–Meier method [18]. Two-sided p values < 0.05 were considered as statistically significant. Significant univariate predictors of OS in the Kaplan–Meier analyses were considered for inclusion in Cox regression models, which had as the primary objective of comparing the two world regions with adjustment for known prognostic factors. A backward selection of independent variables was used in the model. Categorical variables were compared between groups using the chi-square test, whereas the Mann–Whitney test was used for numerical variables with non-normal distribution. Statistical analysis was performed using MedCalc®, version 11.0.0.0 (Mariakerke, Belgium).

Results

Demographic and clinical characteristics

A total of 3664 patients were analyzed: 1968 from Latin America and 1696 from Asia. Table 1 shows the country of origin of these patients. In Latin America, there was a large preponderance of patients from Brazil, but the country distribution in Asia was more balanced, except for Thailand. Of note, eight patients from the second Latin American dataset were excluded from analysis due to inconsistent dates. Figure 1S (Supplementary Materials) displays the year of diagnosis of MM, which was relatively similar between both world regions. Table 2 compares the main demographic and clinical features of the patients from the two world regions. Patients from Latin America were significantly younger and had more hypercalcemia/bone lesions than Asian patients, who in turn had more anemia and more advanced ISS stage. The distribution according to sex and immunoglobulin (Ig) isotype also differed, with patients from Latin America slightly more likely to be male and to have IgG MM. Considering patients for whom information on transplantation was available (3360, or 91.7% of the total), this was performed in 26.1% of patients from Latin America and 26.9% of those from Asia.

Table 1 Region and country of origin of 3664 patients with multiple myeloma

Region and country of origin	Number	Percentage
Latin America		
Argentina	56	1.5%
Brazil	1794	49.0%
Chile	43	1.2%
Mexico	22	0.6%
Peru	53	1.4%
Asia		
China	247	6.7%
Hong Kong	105	2.9%
Japan	329	9.0%
Korea	350	9.6%
Singapore	352	9.6%
Taiwan	305	8.3%
Thailand	8	0.2%
Total	3664	100.0%

Comparison of overall survival in the two world regions

At the time of analysis, a total of 758 and 979 patients had died among those from Latin America and Asia, respectively. Figure 1 displays the OS in the two world regions, with a median follow-up of 42 months in Latin America and 66 months in Asia. There was a significant difference in OS between the two world regions, with median OS of 56 months in Latin America and 47 months in Asia (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.76 to 0.91; $P < 0.001$). When data from the two world regions were pooled, significant univariate predictors of OS were age, ISS stage, anemia (hemoglobin < 10 g/dL), and hypercalcemia. The multivariable model fitted to explore the joint influence of these factors on OS, taking world region into account, included age (as a continuous variable), ISS stage III (vs I or II), anemia, and hypercalcemia. As shown in Table 3, world region remained significantly associated with OS ($P < 0.001$).

In order to further explore potential explanations for the difference in OS between the two world regions, OS analyses were conducted in two subgroups of patients according to receipt of transplantation. Figure 2 displays the OS in the two world regions in these two subgroups. For patients undergoing transplantation (Fig. 2a), although the OS was nominally superior in Latin America, this difference was not statistically significant (respective median OS of 92 and 79 months; HR, 0.86; 95% CI, 0.69 to 1.07; $P = 0.158$). Among patients not undergoing transplantation (Fig. 2b), the OS was significantly longer in Latin America than in Asia (respective medians of 47 and 41 months; HR, 0.89; 95% CI, 0.80 to 1.00; $P = 0.042$). In the third, smaller subgroup of patients with no information on

Table 2 Selected features of 3664 patients with multiple myeloma

Characteristic	Latin America Value or number (%) $N = 1968$	Asia Value or number (%) $N = 1696$	P
Age, years			
Median, IQR	60.8 (52.6–69.3)	63.0 (54.0–71.0)	< 0.001
Sex			
Female	954 (48.5%)	742 (43.7%)	0.005
Male	1014 (51.5%)	954 (56.2%)	
Immunoglobulin isotype			
IgG	1021 (59.1%)	898 (54.9%)	0.014
Others	706 (40.9%)	739 (45.1%)	
Hemoglobin			
≥ 10.0 g/dL	856 (44.0%)	646 (39.7%)	0.013
< 10.0 g/dL	1089 (56.0%)	980 (60.3%)	
Bone lesions			
No	251 (13.6%)	514 (37.4)	< 0.001
Yes	1600 (86.4%)	862 (62.6)	
Serum creatinine			
< 2.0 mg/dL	1478 (76.4%)	1230 (78.5%)	
≥ 2.0 mg/dL	456 (23.6%)	336 (21.5%)	0.147
International Staging System stage			
I	361 (24.6%)	301 (20.6%)	
II	626 (42.6%)	564 (38.6%)	< 0.001
III	482 (32.8%)	596 (40.8%)	
Hypercalcemia			
No	1356 (76.1%)	1252 (83.5%)	< 0.001
Yes	427 (23.9%)	247 (16.5%)	
Receipt of transplantation			
No*	1410 (73.9%)	1061 (73.1%)	0.618
Yes	498 (26.1%)	391 (26.9%)	

*Excludes 60 patients with missing information in Latin America and 244 in Asia

IQ interquartile range

transplantation ($N = 304$), there was no significant difference in OS between the world regions (data not shown). The multivariable model with world region, age, ISS stage III, anemia, and hypercalcemia as independent variables was fitted separately for patients with and without transplantation. In the first subgroup, only ISS stage III was retained in the model, with a HR of 1.42 (95% CI, 1.08 to 1.86; $P = 0.012$). As shown in Table 4, the prognostic role of all variables among patients without transplantation was qualitatively similar to the one observed in the overall patient sample, suggesting that the results in this larger subgroup drive the overall results.

Chronological trends in overall survival

In order to assess the potential role of the introduction of novel therapies in the two world regions, OS was analyzed separately in each region according to the biennium of diagnosis. As shown in Fig. 3, there was a chronological trend for progressive increase in OS in Asia (Fig. 3b; $P = 0.009$), but not in Latin America (Fig. 3a; $P = 0.271$). As shown in Table 1S (Supplementary Materials), large differences in OS exist between the two world regions for the first two biennia, but the median OS according to biennium became progressively similar between Latin America and Asia over time. A possible exception is the 2006–2007 biennium, when the median OS in Asia decreased in relation to the previous trend for increase. In order to explore this issue, we compared the baseline features across time among Asian patients, both considering the five biennia and considering the first four versus the last (2006–2007). These analyses provided no explanation for the results seen among Asian patients in 2006–2007 (data no shown).

Discussion

In this large dataset of patients with MM diagnosed between 1998 and 2007, the risk of death was 15% to 18% lower in Latin America than in Asia, even adjusting for known prognostic factors, some of which with different distribution in the two world regions. Whether this finding reflects differing biological features of the disease, differential use of the available therapeutic modalities, other unmeasured confounders, or the play of chance, remains to be determined.

The chief limitation of our study is its observational nature and the retrospective collection of the majority of the data. This study design precludes firmer conclusions about causal links, for example, between region of origin and outcomes. On the other hand, the large sample size and the confirmation of the prognostic role of well-established disease features give support to our main findings. Moreover, as pointed out recently, observational studies may provide complementary information to that obtained in clinical trials by bringing insights on treatment effectiveness in heterogeneous patient populations [19]. Another limitation of this study is the preponderance of patients from a single country in Latin America, namely, Brazil. Although this is by far the largest country in population in that world region, the proportion of patients from Brazil (91.2%) is clearly larger than its population proportion among the countries included. The extent to which this disproportion—essentially due to lower-than-expected inclusion from other countries in the second study from Latin America [15]—affects the results remain uncertain. Finally, the lack of data on actual treatments utilized and on cytogenetic and molecular features of the disease limits our ability to explore these factors as potential determinants of outcomes.

Interestingly, the difference in OS between these two regions seems to be confined to patients who are not eligible to transplantation (with the caveat that receipt—and not

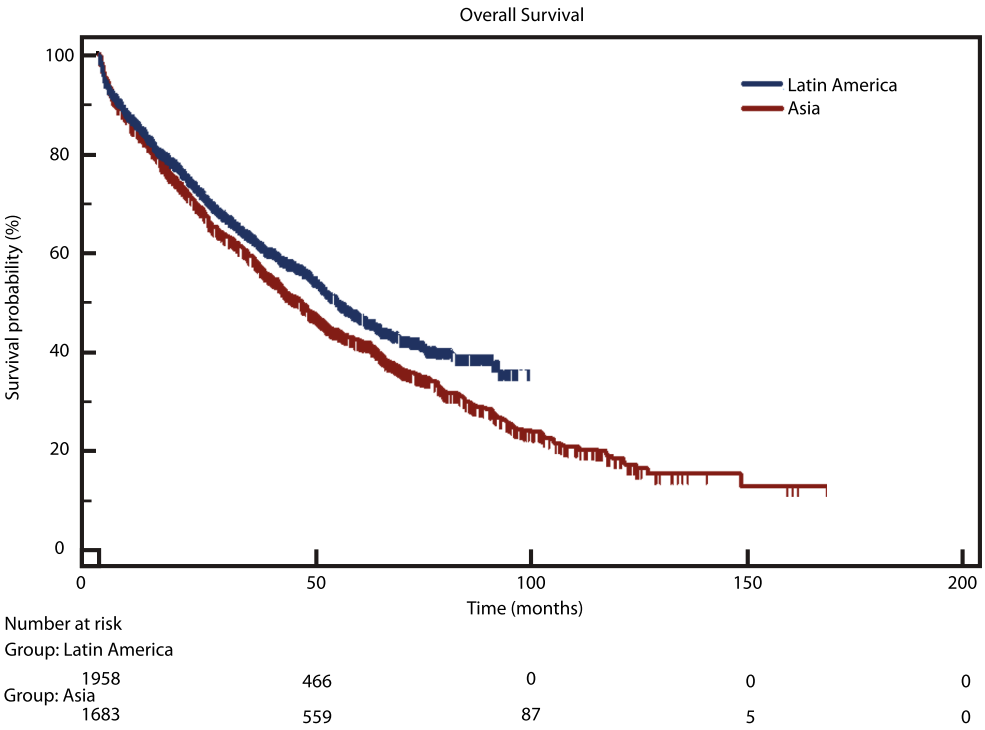

Fig. 1 Overall survival of 3664 patients with multiple myeloma, according to world region

eligibility—to transplantation was used as the classifying variable). This finding suggests that a potential extrinsic factor related to transplant-ineligible patients, and not only intrinsic biological features, underlies the observed OS differences. Moreover, the fact that chronological trends in OS improvement were only apparent in Asia is intriguing, and suggests that these patients have derived benefit from the introduction of novel therapies along the years. Indeed, in the Asian study, novel agents (including bortezomib, thalidomide, and lenalidomide) were administered in the first line to 36% of patients and were shown to have an impact on OS in multivariable analysis [16]. Although stage migration and changes in supportive care cannot be ruled out as potential explanations for these chronological trends in Asia, the inexistence of such trends among patients from Latin America argues against these explanations. Therefore, we propose as unifying explanation for our findings the fact that thalidomide was used in large scale earlier in Latin America, thus improving the outlook mainly for transplantation-ineligible patients, whereas in Asia, other therapies were progressively introduced that eventually bridged the gap in prognosis between the two world regions. Among patients undergoing transplantation, any potential differences in prognosis due to novel agents may have been offset by this treatment.

Table 3 Multivariable Cox proportional hazard models to assess risk factors for death

Variable	Hazard ratio	95% confidence interval	*P*
Age	1.02	1.02 to 1.03	< 0.001
ISS stage III (vs I or II)	1.71	1.52 to 1.92	< 0.001
Anemia	1.25	1.11 to 1.41	< 0.001
Hypercalcemia	1.65	1.44 to 1.88	< 0.001
Latin America (vs Asia)	0.82	0.73 to 0.92	< 0.001

ISS International Staging System, *NA* not applicable

It has been well documented that disparities in outcomes are related to socioeconomic factors among patients with several types of cancer [20–22], including MM [13, 23]. Interestingly, the association between socioeconomic status and mortality has been questioned in the specific setting of transplantation for MM, but this study was relatively small in comparison with others of this type [24]. Given their high prices, access to novel therapies is scarce in several socioeconomic settings. In Brazil, for example, bortezomib has been approved since 2005, but remains unavailable for use in the public health system. Likewise, carfilzomib and daratumumab were approved in Brazil within the past 2 years, and elotuzumab and ixazomib received approval in 2018. Their approval notwithstanding, these novel agents can be used routinely only by the nearly 25% of the Brazilian population with access to private health insurance [10]. In Mexico, improved access to novel agents and transplantation has been underscored as an important step toward bridging the gap in patient outcomes between the public and the private healthcare systems [12]. It should be pointed out that similar barriers in treatment of MM may also apply to other Latin American and Asian countries. Of note, the proportion of

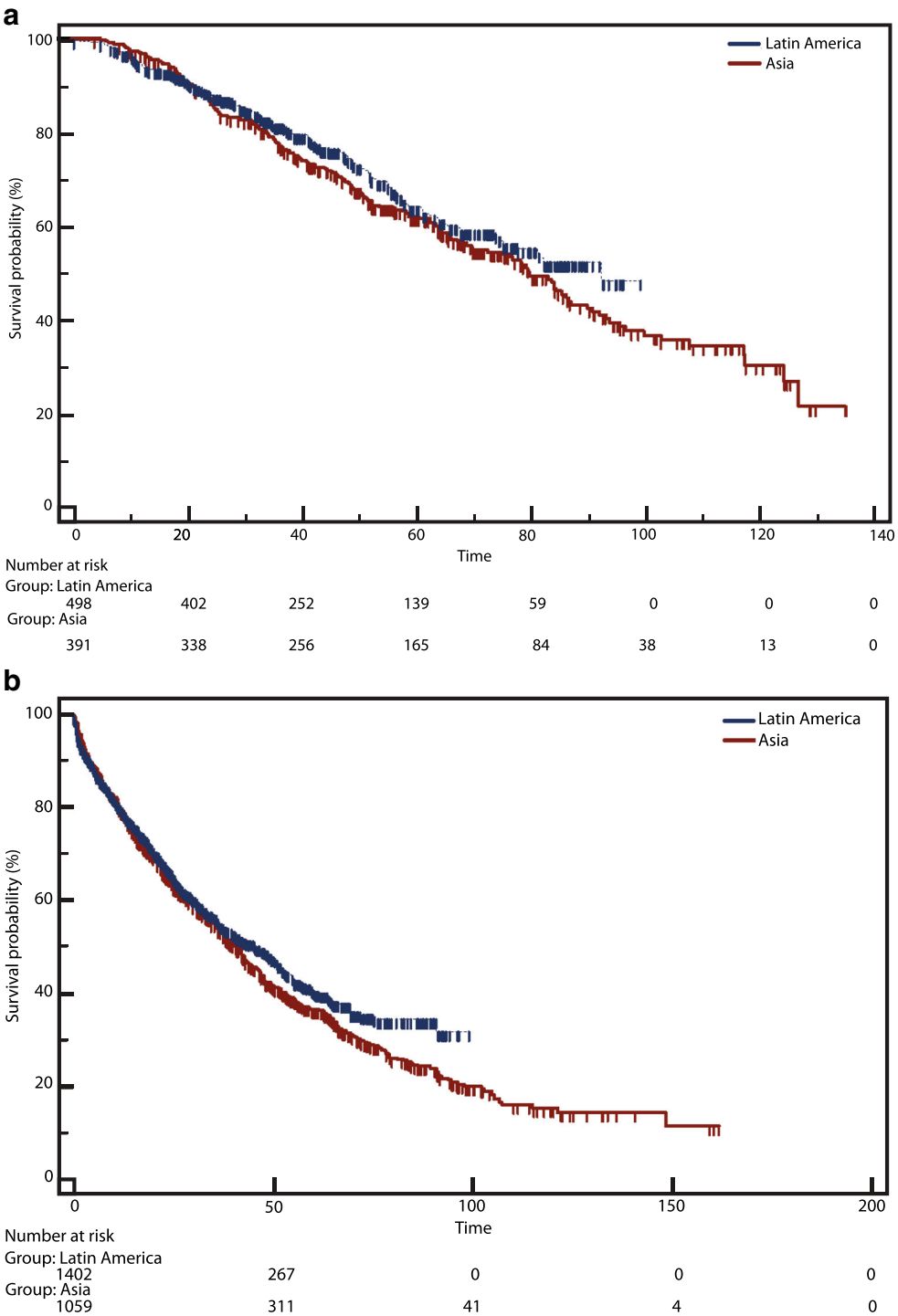

Fig. 2 Overall survival from diagnosis of multiple myeloma, according to world region and receipt of transplantation. **a** Patients undergoing transplantation. **b** Patients not undergoing transplantation

patients receiving transplantation in the current study was low (nearly 26%) in both world regions, in comparison, for example, with the Mayo Clinic experience from 2001 to 2010, from which 37% of patients with MM eventually received transplantation [25].

Geographic differences may affect outcomes in MM [19]. Such an influence may be due to differing genetic background, disease features, or access to therapy, among others factors. We cannot rule out a potential influence of genetic and racial differences within and between these two world regions on the observed outcomes. Our results may be compared with those from the Surveillance, Epidemiology, and End Results (SEER) Program in the USA [26]. Among patients with MM in that catchment area, 5-year OS rates have improved from nearly 35 months in 1998 to 47 months in 2007, the period

Table 4 Multivariable Cox proportional hazard model in patients without transplantation

Variable	Hazard ratio	95% confidence interval	*P*
Age	1.01	1.00 to 1.02	< 0.001
ISS stage III (vs I or II)	1.65	1.44 to 1.90	< 0.001
Anemia	1.29	1.12 to 1.49	< 0.001
Hypercalcemia	1.87	1.60 to 2.18	< 0.001
Latin America (vs Asia)	0.85	0.74 to 0.97	0.015

ISS International Staging System, *NA* not applicable

comprised in our study. Although the OS distribution over time among Asian patients from the current study is consistent with that reported by the SEER registry, the OS distribution from Latin American patients appears superior for reasons that remain unknown. With regard to intrinsic disease features as potential determinants of differences in OS, it is noteworthy that patients from Latin America displayed a more favorable distribution of some prognostic factors (such as age, hemoglobin values, and ISS stage) than Asian patients, who in turn had a lower proportion of hypercalcemia. Whether this differing distribution of prognostic factors reflects true biological

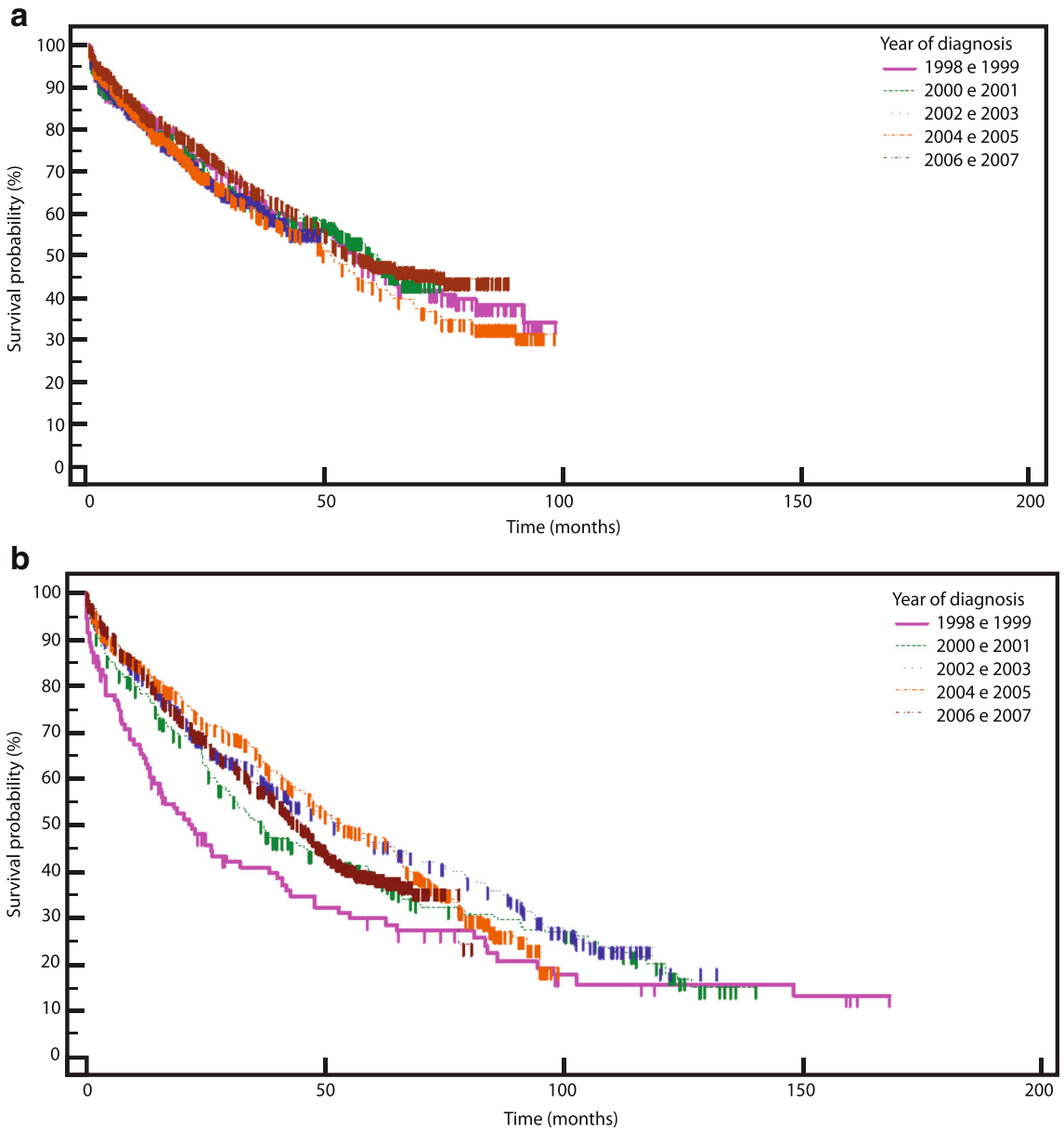

Fig. 3 Overall survival according to biennium of diagnosis of multiple myeloma and world region. **a** Latin America. **b** Asia

differences between these two world regions or differing patterns of diagnosis or referral, it cannot be determined with certainty. Moreover, adjusting for such differences did not substantially change the association between world region and OS. Unfortunately, cytogenetic analysis was not available in the Latin American databases, thus precluding further exploration of potential biological differences with Asia. On the other hand, we have suggested that there are no unique features of MM that are peculiar to Asian patients, notwithstanding some country-specific characteristics [16].

In summary, we have found a lower risk of death among contemporaneous patients with MM from Latin America than in those from Asia. Although the cause of such differences remains to be determined, we propose that the earlier introduction of thalidomide in Latin America improved the outlook for transplantation-ineligible patients, in comparison with those from Asia, in whom the availability of other novel therapies that remain largely unavailable in Latin America appear to have bridged at least in part the gap in prognosis between the two world regions. Follow-up registries in these two world regions may eventually be used to test this proposition.

Compliance with ethical standards

The protocol for each study was approved by the competent local authorities and institutional review boards, and written informed consent was obtained from all patients.

Conflict of interest The authors declare that they have no conflict of interest.

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