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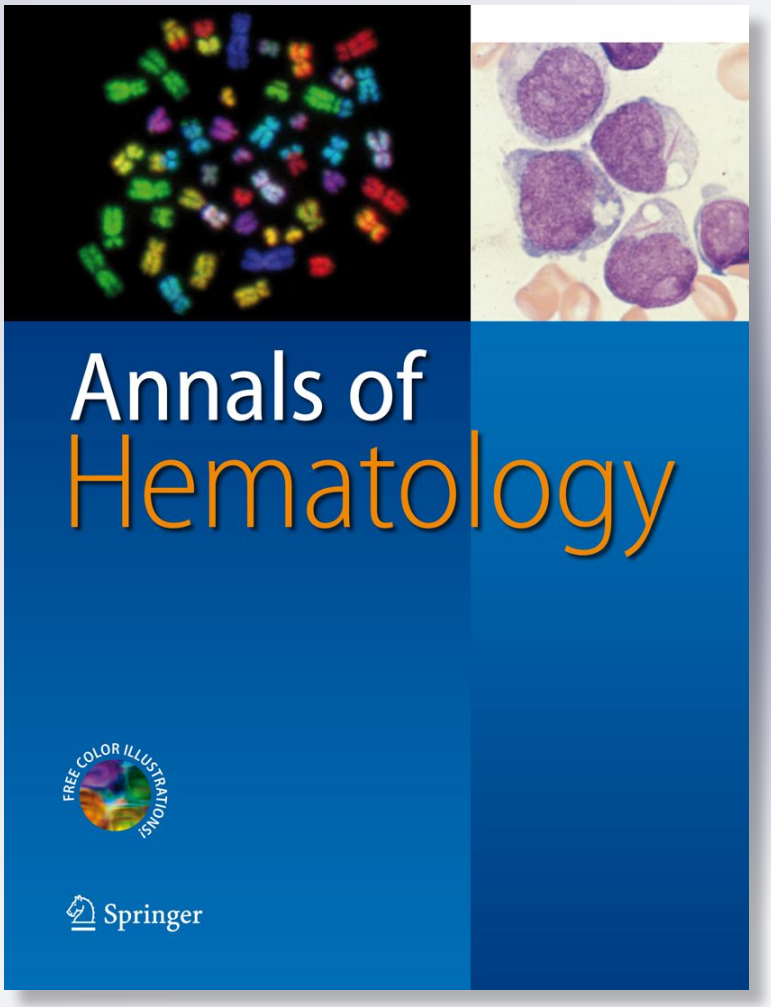

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ORIGINAL ARTICLE

International Staging System predicts prognosis of Chinese patients with multiple myeloma across different calendar periods with application of novel agents

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Abstract The applicability of the International Staging System (ISS) for Chinese patients with multiple myeloma (MM) has not been demonstrated, especially with respect to treatments with novel agents. Newly diagnosed MM patients at Taipei Veterans General Hospital were enrolled between 1996 and 2007. Data regarding clinical features, laboratory tests, and outcome at last follow-up were collected. A total of 389 MM patients (71% male) were enrolled, with median age of 71 years. At diagnosis, 72.7% had Durie–Salmon (DS) stage III disease, 56.2% had ISS stage III disease, and 34% had serum creatinine ≧2.0 mg/dL. Compared with patients diagnosed in the first calendar period 1996–2001, the patients of the second calendar period 2002–2007 were older and more of these patients had received novel agents, especially thalidomide. The median overall survival period was 20.5 months, with a significant increase of patients in the second calendar period (15.3 and 28.2 months, respectively; P=0.002), especially for those with ISS stages I and II. In the Cox proportion model, elevated serum β_2 microglobulin at diagnosis (≧3.5 mg/L), old age (≧65 years), and impaired renal function were found to be independently associated with poor survival. Over the entire period, the ISS was found to be effective in providing an accurate prognosis with respect to different ages and calendar periods. This is the first study to show the applicability of ISS for Chinese patients with MM, especially for those who had received thalidomide.

Keywords Chinese · Multiple myeloma · International Staging System · Serum β_2 microglobulin · Thalidomide

Introduction

The International Staging System (ISS) for multiple myeloma (MM), first proposed in 2005, is based on two

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objective laboratory parameters—serum albumin and serum β_2 microglobulin ($S\beta_2M$) [1]. Its applicability has been demonstrated by additional assessments in terms of geographic regions, age (≧65 years), and treatment type (standard-dose therapy vs. high-dose therapy [HDT] with autologous hematopoietic stem cell transplantation [HSCT]) [1] and subsequent analysis [2, 3]. However, because most of the patients enrolled in the analysis were collected from the clinical trial and through 2002, the applicability of ISS in the patients who received up-to-date treatments (e.g., thalidomide and bortezomib) or who were not enrolled in clinical trials is still under debate. Kastritis et al. first demonstrated the applicability of ISS in unselected Greek patients who started treatment after the introduction of thalidomide [4]. However, the applicability of ISS for patients receiving frontline HDT and autologous HSCT does not agree with the results of different reports [5, 6]. In addition, it is not clear whether ISS is properly applicable for the Chinese population because Chinese individuals were not enrolled in the original analysis [1]. The previous analysis did not demonstrate its applicability in this population [7, 8].

Relative to Western countries, the incidence of MM is relatively low in Asia [9, 10], but it has been markedly increasing in recent decades in Taiwan [11]. Taiwan is an island with a population of approximately 23 million ethnic Chinese. This country has had the national health insurance since 1994 (http://www.nhi.gov.tw/English/webdata/webdata.aspx?menu=11&menu_id=290&webdata_id=2974&WD_ID=290) and provided consistent medical services to all people. Thalidomide has been available since 2002. This agent and additional new anticancer agents have been used to treat patients with MM in Taiwan. In this study, we investigate a cohort of MM patients over a decade in one of the largest general hospitals in Taiwan, with the aim of evaluating survival of MM patients and the applicability of ISS for the Chinese population across different calendar periods when different treatment strategies are employed.

Patients and methods

Patients

Patients diagnosed with MM were enrolled between January 1996 and December 2007 at Taipei Veterans General Hospital. Patients diagnosed with monoclonal gammopathy of undetermined significance (MGUS), POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes), IgM myeloma, and myeloma with amyloidosis were excluded. The diagnoses of these plasma cell dyscrasias were based on commonly accepted criteria [12].

Clinical features, staging, treatment, and response

Data collection was performed by chart review. Clinical features at diagnosis, including age, gender, complete blood counts, blood biochemistry including renal function and $S\beta_2M$, and histology, were recorded. The clinical stages were determined according to the Durie–Salmon (DS) staging system and the ISS [1, 13]. The therapies consisted of induction and salvage treatment modalities. Before the novel therapeutic agents became available in 2002, the major regimens of conventional chemotherapy included melphalan and prednisolone and vincristine, adriamycin, and dexamethasone. After induction or salvage therapy, HDT and HSCT were usually administered to patients under 65 years old. Thalidomide has been administered as salvage therapy since 2002 for most patients with relapsed or refractory myeloma. It was not officially covered by the national health insurance as induction therapy until July 2008. In addition, bortezomib has been used to treat MM patients with relapsed or refractory diseases since June 2007. Lenalidomide was not available in Taiwan at the time of data analysis. Several bisphosphonates, such as clodronate, pamidronate, and zoledronic acid, became sequentially available to be used in the treatment of patients as bone protection agents since the mid-1990s. Overall survival (OS) was measured from the time of diagnosis to the date of death from any cause or until the last follow-up, which was conducted in February 2010.

Statistical analysis

Considering the availability of novel agents, including thalidomide and bortezomib, a 6-year interval and the resulting two calendar periods (i.e., 1996–2001 and 2002–2007) were chosen for subsequent comparison of the parameters studied between MM patients diagnosed in the two periods. Differences in patient and disease characteristics for patients diagnosed at different calendar periods were investigated using Pearson's chi-square test. The cutoff level for exclusion of abnormal laboratory tests was defined according to those in the original ISS study [1]. Survival analysis with the Kaplan–Meier estimate was used with the log-rank test for comparison of OS rates between groups with different ISS stages. The level of statistical significance was set at 0.05 for all tests. Statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL).

Results

Clinical features and treatments of 389 MM patients

As shown in Table 1, a total of 389 patients (288 men, 101 women) with MM were included in this study. The median

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age at diagnosis was 71 years with 70% of patients older than 65 years. The major subtypes of immunophenotypes included IgG (51%), IgA (30%), and light chain disease (LCD, 17%). Clinical stages presented by DS and ISS I/II/III were 7%/20%/73% and 15%/29%/56%, respectively. At diagnosis, the proportions of patients with leukopenia (defined as white cell counts <4,000/μL), anemia (defined as hemoglobin <10 g/dL), and thrombocytopenia (defined as platelet counts <130,000/μL) were 18%, 65%, and 33%, respectively. Hypoalbuminemia (defined as serum albumin <3.5 g/dL), impaired renal function (serum creatinine ≧2.0 mg/dL), and hypercalcemia (defined as corrected serum total calcium >10 mg/dL) were 56%, 34%, and 36% of patients, respectively. Elevated $S\beta_2M$ (defined as $S\beta_2M$ ≧3.5 mg/L) and serum lactate dehydrogenase (LDH greater than the normal value) were noted in 80% and 40% of patients, respectively. In terms of the treatment, the proportions of patients who had received thalidomide, bortezomib, HDT with HSCT, and bisphosphonates were 22%, 8%, 10%, and 74%, respectively (Table 2).

Changes in clinical features and treatments of 389 MM patients between the two calendar periods

As shown in Table 1, in terms of clinical features, the median age at diagnosis (69 vs. 72 years, P=0.016) and the proportion of MM patients with leukopenia at diagnosis (14% vs. 22%, P=0.035) were significantly higher for the patients diagnosed in the second calendar period from 2002 to 2007. The proportion of patients with ages over 70 and 80 years were significantly higher in the second period. Gender distribution, clinical stages, immunophenotypes, and the proportion of patients with anemia, thrombocytopenia, impaired renal function, and hypercalcemia in these two calendar periods were not significantly different.

With respect to treatments, significantly greater proportions of patients diagnosed in the second calendar period received novel agents and HDT plus HSCT (autologous in most) as determined at the last follow-up (Table 2). In particular, treatment of the patients in this group included the administration of thalidomide. Treatment with bisphosphonates was also more common during the second calendar period.

Table 1 Clinical and laboratory features of 389 Chinese patients with MM in terms of different calendar periods

Calendar period/parameters	Overall (%)	1996–2001	2002–2007	P value
No. of patients	389 (100)	178	211	–
Gender—male/female	288 (74)/101 (26)	139 (78)/39 (22)	149 (71)/62 (29)	0.105
Age (years), median (range)	71 (27–91)	69 (27–88)	72 (29–91)	0.016
≧65	271 (70)	120 (67)	151 (72)	0.379
≧70	197 (51)	78 (44)	119 (56)	0.015[a]
≧80	50 (13)	13 (7)	37 (18)	0.004[a]
DS stages I/II/III	28/78/283 (7/20/73)	12/34/132 (7/19/74)	16/44/151 (8/21/72)	0.847
ISS stages I/II/III	51/103/197 of 351 (15/29/56)	22/46/77[a] (15/32/53)	29/57/120 (14/28/58)	0.622
Immunophenotype				0.120
IgG	200 (51)	81 (46)	119 (56)	
IgA	115 (30)	59 (33)	56 (27)	
LCD	67 (17)	33 (19)	34 (16)	
Others	7 (2)	5 (3)	2 (1)	
WBC <4,000/μL	71 of 385 (18)	24 of 174 (14)	47 (22)	0.035[a]
Hemoglobin <10 g/dL	251 of 387 (65)	123 of 176 (70)	128 (61)	0.069[a]
Platelets <130,000/μL	127 of 384 (33)	56 of 173 (32)	71 (34)	0.828[a]
Serum albumin <3.5 g/dL	215 of 385 (56)	95 of 174 (55)	120 (56)	0.681[a]
Serum creatinine ≧2.0 mg/dL	132 of 389 (34)	66 of 178 (37)	66 (31)	0.255
$S\beta_2M$ (mg/L)				
≧3.5	280 of 352 (80)	112 of 146 (77)	168 of 206 (82)	0.285
≧5.5	197 of 352 (56)	77 of 146 (53)	120 of 206 (58)	0.328
Serum LDH greater than the normal value	155 of 385 (40)	73 of 174 (42)	82 (39)	0.602[a]
Serum total calcium (corrected) >10 mg/dL	140 of 385 (36)	67 of 174 (39)	73 (35)	0.457

For the meaning of the abbreviations, refer to the text

[a] Fisher's exact test

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Table 2 Treatment modalities and survival of 389 Chinese patients with MM in terms of different calendar periods

Calendar period/parameters	Overall (%)	1996–2001	2002–2007	*P* value
No. of patients	389 (100)	178	211	–
Thalidomide	86 (22)	12 (7)	74 (35)	<0.001
Bortezomib	32 (8)	2 (1)	30 (14)	<0.001
HDT and HSCT	40 (10)	11 (6)	29 (14)	0.018[a]
Bisphosphonate	289 (74)	119 (67)	170 (81)	0.002
Median OS (months) (95% CI)	20.5 (17.1–24.9)	15.3 (11.9–18.8)	28.2 (21.5–33)	0.002

For the meaning of the abbreviations, refer to the text

[a] Fisher's exact test

Overall survival and prognostic factors

The median OS period of all patients was 20.5 months (95% confidence interval [CI]=16.1–24.9), including 15.3 months in the first calendar period and 28.2 months in the second period (P=0.002; Table 2). As shown in Table 3, several factors noted at diagnosis, including old age (≧65 or ≧70 years), DS stage III, ISS stage III, anemia, thrombocytopenia, hypoalbuminemia, impaired renal function, elevated Sβ_2M at cutoff values of 3.5 and 5.5 mg/L, elevated serum LDH, hypercalcemia, and patients diagnosed in the first calendar period, were associated with a poor prognosis. In the Cox proportion model using these factors at diagnosis (except for DS and ISS themselves and the calendar period), elevated Sβ_2M at diagnosis (≧3.5 mg/L), old age (≧65 years), and impaired renal function were found to be independently associated with a poor survival prognosis, with hazard ratios of 1.949 (95% CI=1.013–1.948, P=0.001), 1.709 (95% CI=1.303–2.914, P<0.001), and 1.610 (95% CI=1.205–2.15, P=0.001), respectively. When using the higher cutoff value of 5.5 mg/L, Sβ_2M remained significant with a hazard ratio of 1.405 (95% CI=1.013–1.948, P=0.041).

Table 3 Prognostic factors of 389 Chinese patients with MM

Calendar period/parameters	*P* value	Hazard ratio	95% CI
Gender—male vs. female	0.091	1.272	0.962–1.68
Age ≧65	<0.001	1.84	1.408–2.406
Age ≧70	<0.001	1.547	1.222–1.958
WBC <4,000/μL	0.982	0.997	0.74–1.342
Hemoglobin <10 g/dL	<0.001	1.747	1.351–2.258
Platelets <130,000/μL	0.040	1.294	1.012–1.654
Serum albumin <3.5 g/dL	0.004	1.412	1.114–1.791
Serum creatinine ≧2.0 mg/dL	<0.001	2.155	1.688–2.752
Sβ_2M ≧3.5 mg/L	<0.001	2.769	1.96–3.913
Sβ_2M ≧5.5 mg/L	<0.001	2.123	1.641–2.746
Serum LDH greater than the normal value	0.011	1.359	1.072–1.724
Serum total calcium (corrected) >10 mg/dL	<0.001	1.513	1.19–1.924
DS stage III	<0.001	2.844	1.589–5.091
ISS stage III	<0.001	3.468	2.279–5.277
Calendar period 1996–2002	0.003	1.439	1.136–1.823

For the meaning of the abbreviations, refer to the text

Applicability of the ISS for Chinese patients

Similar to DS stages (Fig. 1a), the applicability of ISS stages in our patients was further evaluated by examining the median OS of each stage (P<0.001), as shown in Fig. 1b. In addition, the ISS was generally found to be equally robust in both calendar periods (Fig. 2). The OS of ISS stages I and II patients during the second period was significantly better than those in the first period, with the P values 0.009 and 0.024, respectively. However, the different assessment of OS was not significant for ISS stage III between these two calendar periods (P=0.11).

In addition, although older patients have poorer survival than younger patients, it is important to note, as illustrated in Fig. 3, that the ISS applies to both groups with the cutoff values of age at 65 and 70 years (median age of our patients). On the other hand, as far as treatment type is concerned, we were only able to show the applicability of ISS in those who did not receive HDT and HSCT at last follow-up, as shown in Fig. 4.

Discussion

The findings of our study indicate the survival impact provided by novel agents (especially thalidomide) on MM patients in Taiwan and also affirm the applicability of ISS to the Chinese population across different calendar periods. In addition, additional subgroup analysis also demonstrates its applicability in both younger and elderly patients with MM. To our knowledge, this is the largest cohort of an ethnic Chinese population analyzed to test the adequacy of ISS because ethnic Chinese were not enrolled in the original ISS study, which only included Japanese subjects as representative of the Asian population [1]. Similar to the previous study [4], the applicability of ISS was found to be relatively robust for our patients who were diagnosed in the second calendar period and usually had received treatments

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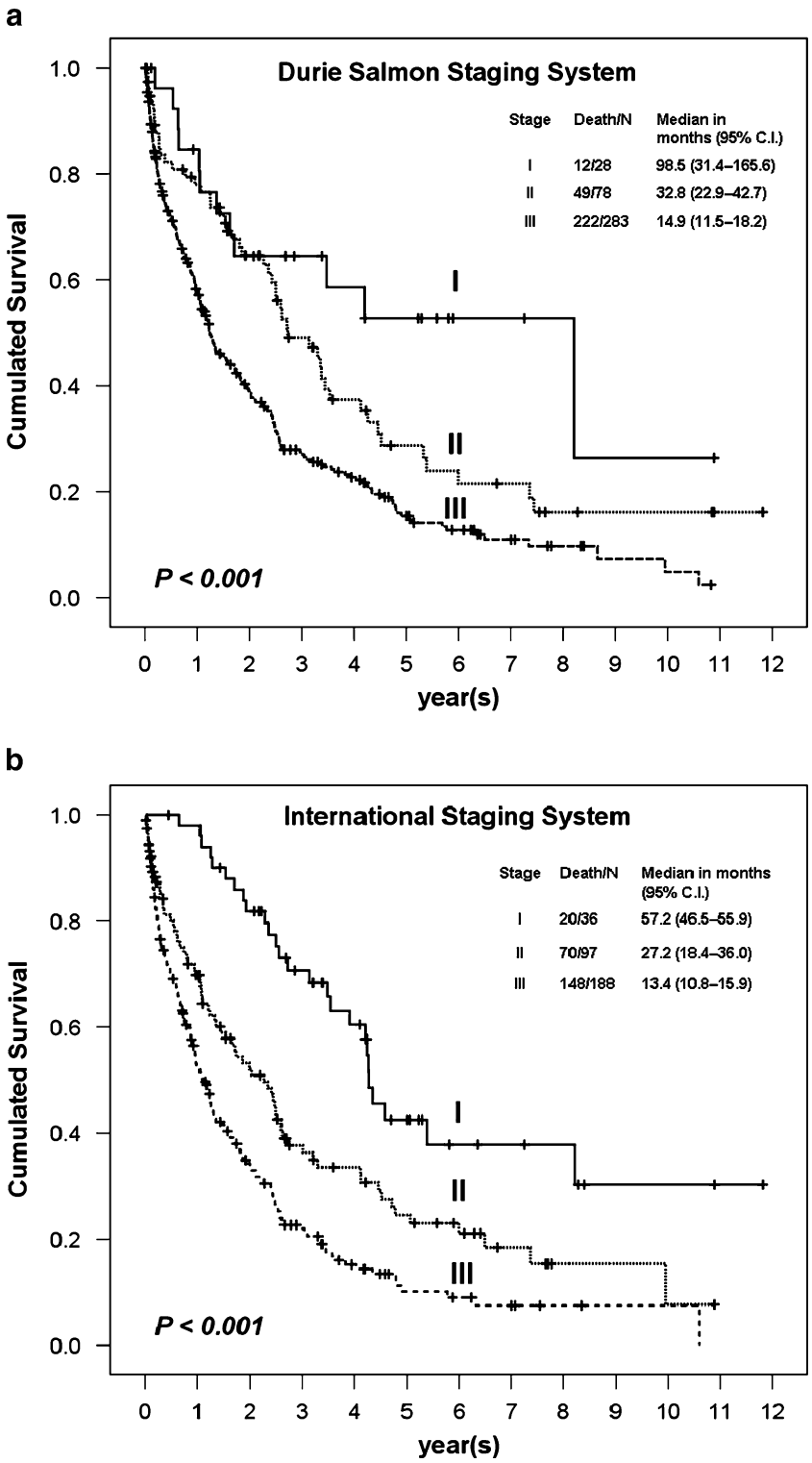

Fig. 1 The curve of the OS of Chinese patients with MM in terms of DS (**a**; n=389) and the ISS (**b**; n=351)

with novel therapeutic agents, especially thalidomide (Table 2 and Fig. 2). In addition, there was a significant improvement of OS in the patients of the second calendar period, indicating the benefit of novel agents, including thalidomide. This is similar to the findings of previous studies [4, 14–16]. However, the OS was improved for those with ISS stages I and II rather than ISS stage III. The most probable cause is the advanced age of our patients (median age 71 years; Table 1). The findings of recent studies showed less of an improvement of OS in elderly MM patients [4, 14, 16] or patients with severe renal impairment [17]. In addition, most of our patients in the

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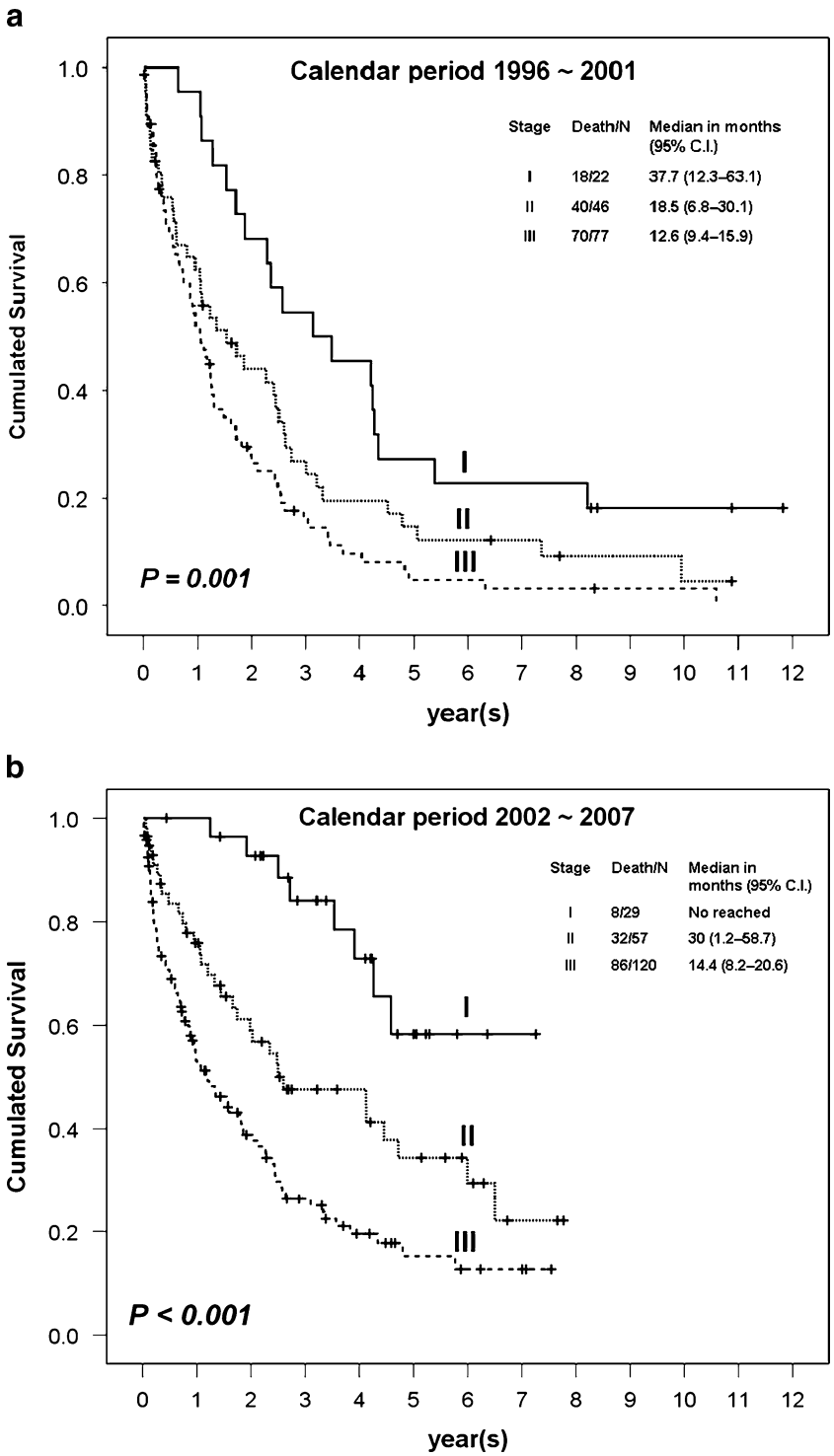

Fig. 2 **a** and **b** The curve of the OS of Chinese patients with MM in terms of different calendar periods and the ISS

second calendar period did not receive frontline treatment with novel agents and this possibly resulted in less benefit.

Compared with those of the original report [1], there were a higher proportion of our patients with ISS stage III (56% vs. 33.6%). Furthermore, compared with the Asian group in the original report [1], the OS of our patients in the first calendar period was relatively shorter (37.7/18.5/12.6 vs. 58/38/24 months for patients with ISS stages I/II/III, respectively), although there was a significant improvement of patients during the second calendar period. First, this discrepancy is partially contributed by the difference in the source of patients either from the community or in clinical

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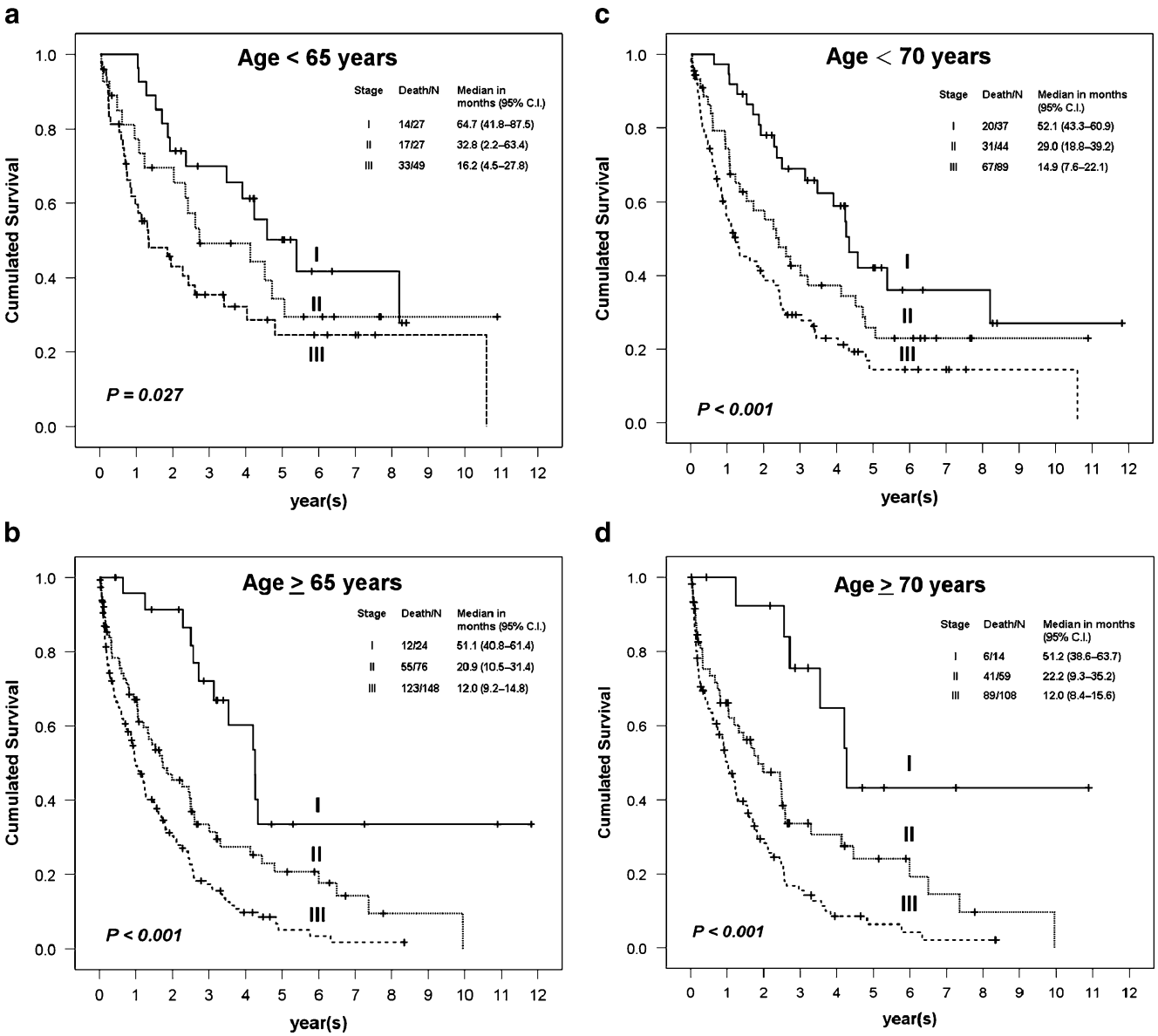

Fig. 3 **a**–**d** The curve of the OS of Chinese patients with MM in terms of different ages and the ISS

trials. As elderly patients with MM were usually under-represented in clinical trials [18], there was the difference of median age at least 10 years, i.e., about 70 years in ours and most of community-based reports in Western countries [18] vs. 60 years in the clinical trials, including the original ISS study [1]. In addition, even with a similar median age (60 years) of patients, there was about 10% difference in the proportion of patients with ISS stage III (i.e., 43% in the reports from China and Korea [8, 19] vs. 33.6% in the ISS study [1]. And, there were a lower proportion of our patients who had received treatments in clinical trials (<10% of our patients vs. 69.1% of the patients in the original ISS study) and HDT and HSCT (10% vs. 26%). It is noteworthy that the median age of our MM patients at diagnosis is significantly higher than those of other Asian countries [7, 19] and, moreover, that the median age was significantly higher in the later period than the median age of patients in recent reports [4, 20]. As elderly patients usually have more comorbidities and resulting similar symptoms, many of these patients with MM were not referred till the diseases became more severe [21]. This may also cause an uneven distribution of each ISS stage—lower ISS stage I vs. higher ISS stage III. Therefore, this would be expected to produce higher proportions of patients with poor prognostic factors including anemia (65% vs. 40%), thrombocytopenia (33% vs. 12%), hypoalbuminemia (56% vs. 40%), elevated $S\beta_2M$ (≧3.5 mg/L, 79% vs. 56%), and elevated serum LDH (40% vs. 26%; Table 1). The progressive aging of the whole population may have contributed along with the increasing incidence of MM in

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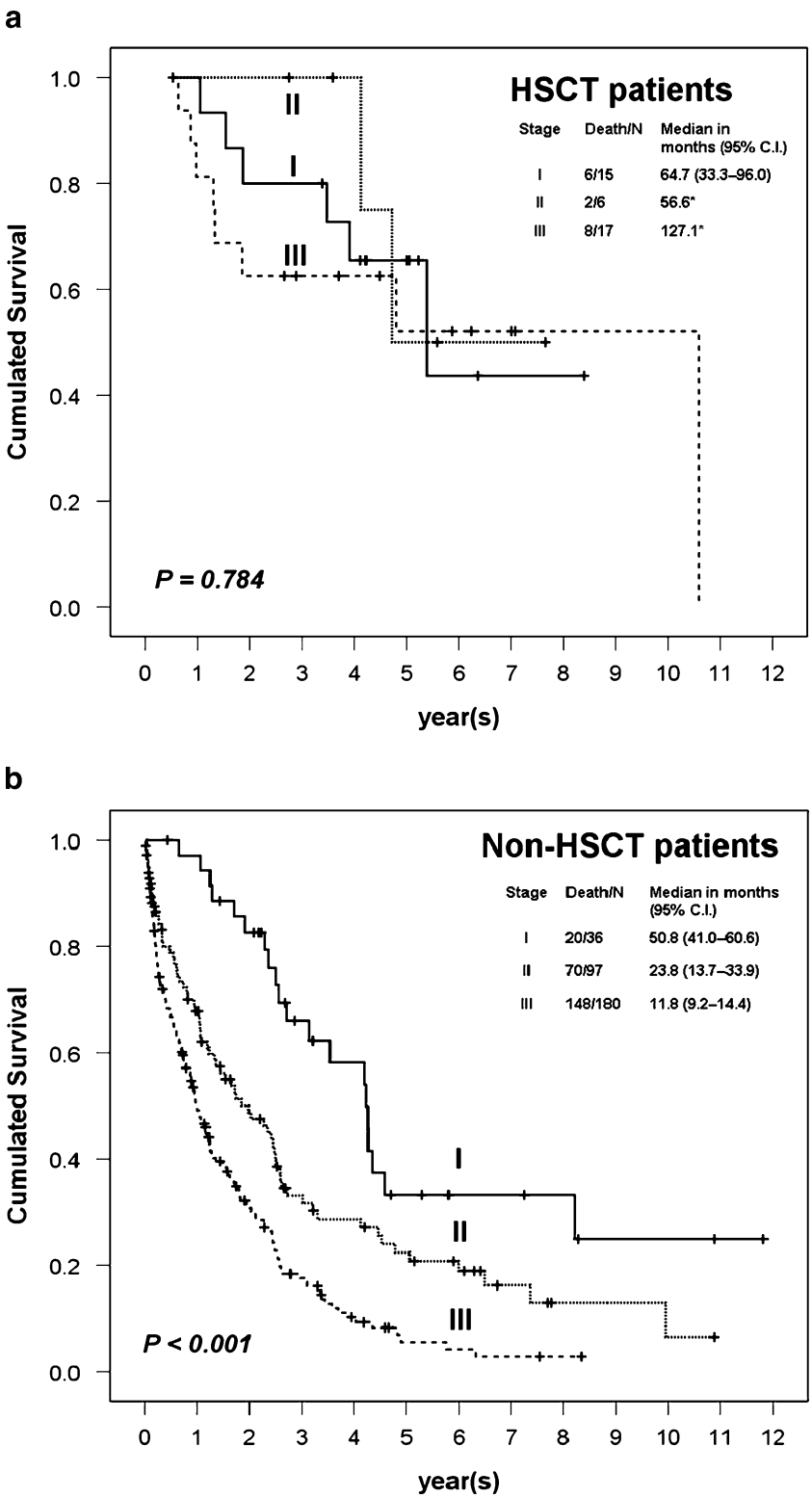

Fig. 4 **a** and **b** The curve of the OS of Chinese patients with MM in terms of the ISS and whether they have received HDT and HSCT

Taiwan [11] as the third common hematologic malignancy behind non-Hodgkin lymphoma and acute myelogenous leukemia. The life expectancy at birth of the whole population of Taiwan was 75.0 years in 1996, 77.2 years in 2002, and 78.4 years in 2007 (data were obtained from National Statistics, Taiwan; http://www.stat.gov.tw/ct.asp?xItem=24811&ctNode=538). A higher proportion of MM patients with leukopenia in the second period of

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our study may also be associated with the increased proportion of elderly patients who typically had poor marrow reserves [22].

The other important factor associated with a lower OS and a higher proportion of ISS stage III in our patients was that more than 30% of our MM patients had impaired renal function (serum creatinine ≧2.0 mg/dL) at diagnosis. Except for the report from Hong Kong [23], this frequency of impaired renal function is higher than that of all of the other reports where the frequency was found to be at about 20% [1, 4, 19, 24, 25]. Additional analysis of our study showed that the proportion of our MM patients with impaired renal function was evenly distributed among all MM patients, rather than predominately in older patients. Although there were a lower proportion of patients with the IgD immunophenotype (because serum IgD was not routinely tested in our hospital), the frequency of patients with LCD (17%), which usually have impaired renal function, was not higher than the previously reported frequency [1, 4, 19]. It is known that the prevalence of end-stage renal diseases in Taiwan is the highest in the world [26]. It is speculated that the previous use of herbal medication to relieve the symptoms of bone pain after the diagnosis of MM may have contributed to this phenomenon [26, 27]. In addition to the underlying mechanisms, it is also important to adjust the policy of clinical management of these patients. Finally, the relatively lower prevalence of MGUS in Asia [10] may also possibly contribute to the lower proportion of our patients with ISS stage I.

The prognostic role of hypoalbuminemia (serum albumin <3.5 g/dL) is lost in the multivariate model of our study, similar to previous findings of several studies with small numbers of MM patients including Weber et al. [1, 28]. In addition, relative to the patients of the original ISS study [1], there were also a lower proportion of our patients with serum albumin≧3.5 g/dL (44% vs. 60% in the original ISS study). This is related to advanced age, higher disease severity, and more frequent renal impairment in our patients. Possibly limited by a smaller number of patients (n=40), the findings of our study did not demonstrate the applicability of ISS in those who had received HDT and HSCT at last follow-up. However, it is worth noting that HDT and HSCT may have improved the survival of our patients with advanced ISS stages, as shown in Fig. 4. To directly evaluate the applicability of ISS to our group of patients, parameters that are reflective of performance status and bone marrow plasma cells at diagnosis were not analyzed in the present study. In addition, cytogenetic changes were not noted because the data were not available for many of the patients in the first calendar period. A recent study from Greece showed that LDH might add further prognostic value to ISS [29], but it was not validated in our data since LDH lost statistical significance in the multivariate analysis.

In conclusion, our study showed that ISS is relatively robust and reliable for predicting the prognosis of Chinese patients with MM, especially in the era of novel agents and multimodality treatment. With a progressive aging of our patients, the OS was found to be significantly improved after novel agents became available, especially for patients in ISS stages I and II. Additional efforts are needed to improve the prognosis of elderly MM patients in ISS stage III.

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References

1. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Blade J, Boccadoro M, Child JA, Avet-Loiseau H, Kyle RA, Lahuerta JJ, Ludwig H, Morgan G, Powles R, Shimizu K, Shustik C, Sonneveld P, Tosi P, Turesson I, Westin J (2005) International staging system for multiple myeloma. J Clin Oncol 23(15):3412–3420
2. Mihou D, Katodritou I, Zervas K (2006) Evaluation of five staging systems in 470 patients with multiple myeloma. Haematologica 91(8):1149–1150
3. Mihou D, Katodritou E, Zervas K (2007) Multiple myeloma staging based on the combination of beta-2-microglobulin and albumin: the role of albumin in the model. Hematology 12 (6):527–531
4. Kastritis E, Zervas K, Symeonidis A, Terpos E, Delimbassi S, Anagnostopoulos N, Michali E, Zomas A, Katodritou E, Gika D, Pouli A, Christoulas D, Roussou M, Kartasis Z, Economopoulos T, Dimopoulos MA (2009) Improved survival of patients with multiple myeloma after the introduction of novel agents and the applicability of the International Staging System (ISS): an analysis of the Greek Myeloma Study Group (GMSG). Leukemia 23 (6):1152–1157
5. Kim H, Sohn HJ, Kim S, Kim K, Lee JH, Bang SM, Kim DH, Sohn SK, Lee JJ, Suh C (2006) New staging systems can predict prognosis of multiple myeloma patients undergoing autologous peripheral blood stem cell transplantation as first-line therapy. Biol Blood Marrow Transplant 12(8):837–844
6. Hari PN, Zhang MJ, Roy V, Perez WS, Bashey A, To LB, Elfenbein G, Freytes CO, Gale RP, Gibson J, Kyle RA, Lazarus HM, McCarthy PL, Milone GA, Pavlovsky S, Reece DE, Schiller G, Vela-Ojeda J, Weisdorf D, Vesole D (2009) Is the International Staging System superior to the Durie–Salmon staging system? A comparison in multiple myeloma patients undergoing autologous transplant. Leukemia 23(8):1528–1534
7. Tao ZF, Fu WJ, Yuan ZG, Wang DX, Chen YB, Hou J (2007) Prognostic factors and staging systems of multiple myeloma. Chin Med J (Engl) 120(19):1655–1658
8. Zhang L, Qi JY, Qi PJ, Wang YF, Zou DH, Yao HJ, An G, Yi SH, Li Q, Qiu LG (2010) Comparison among immunologically different subtypes of 595 untreated multiple myeloma patients in northern China. Clin Lymphoma Myeloma Leuk 10(3):197–204
9. Dores GM, Landgren O, McGlynn KA, Curtis RE, Linet MS, Devesa SS (2009) Plasmacytoma of bone, extramedullary plasmacytoma, and multiple myeloma: incidence and survival in the United States, 1992–2004. Br J Haematol 144(1):86–94

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10. Landgren O, Weiss BM (2009) Patterns of monoclonal gammopathy of undetermined significance and multiple myeloma in various ethnic/racial groups: support for genetic factors in pathogenesis. Leukemia 23(10):1691–1697
11. Huang SY, Yao M, Tang JL, Lee WC, Tsay W, Cheng AL, Wang CH, Chen YC, Shen MC, Tien HF (2007) Epidemiology of multiple myeloma in Taiwan: increasing incidence for the past 25 years and higher prevalence of extramedullary myeloma in patients younger than 55 years. Cancer 110(4):896–905
12. International Myeloma Working Group (2003) Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 121(5):749–757
13. Durie BG, Salmon SE (1975) A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 36(3):842–854
14. Brenner H, Gondos A, Pulte D (2008) Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood 111(5):2521–2526
15. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Zeldenrust SR, Dingli D, Russell SJ, Lust JA, Greipp PR, Kyle RA, Gertz MA (2008) Improved survival in multiple myeloma and the impact of novel therapies. Blood 111(5):2516–2520
16. Brenner H, Gondos A, Pulte D (2009) Expected long-term survival of patients diagnosed with multiple myeloma in 2006–2010. Haematologica 94(2):270–275
17. Haynes RJ, Read S, Collins GP, Darby SC, Winearls CG (2010) Presentation and survival of patients with severe acute kidney injury and multiple myeloma: a 20-year experience from a single centre. Nephrol Dial Transplant 25(2):419–426
18. Mileshkin L, Prince HM (2005) The adverse prognostic impact of advanced age in multiple myeloma. Leuk Lymphoma 46(7):951–966
19. Kim JE, Yoo C, Lee DH, Kim SW, Lee JS, Suh C (2010) Serum albumin level is a significant prognostic factor reflecting disease severity in symptomatic multiple myeloma. Ann Hematol 89 (4):391–397
20. Turesson I, Velez R, Kristinsson SY, Landgren O (2010) Patterns of multiple myeloma during the past 5 decades: stable incidence rates for all age groups in the population but rapidly changing age distribution in the clinic. Mayo Clin Proc 85(3):225–230
21. Friese CR, Abel GA, Magazu LS, Neville BA, Richardson LC, Earle CC (2009) Diagnostic delay and complications for older adults with multiple myeloma. Leuk Lymphoma 50(3):392–400
22. Vestal RE (1997) Aging and pharmacology. Cancer 80(7):1302–1310
23. Chow CC, Mo KL, Chan CK, Lo HK, Wong KS, Chan JC (2003) Renal impairment in patients with multiple myeloma. Hong Kong Med J 9(2):78–82
24. Knudsen LM, Hippe E, Hjorth M, Holmberg E, Westin J (1994) Renal function in newly diagnosed multiple myeloma—a demographic study of 1353 patients. The Nordic Myeloma Study Group Eur J Haematol 53(4):207–212
25. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, Fonseca R, Rajkumar SV, Offord JR, Larson DR, Plevak ME, Therneau TM, Greipp PR (2003) Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 78(1):21–33
26. Hwang SJ, Tsai JC, Chen HC (2010) Epidemiology, impact and preventive care of chronic kidney disease in Taiwan. Nephrology (Carlton) 15(Suppl):23–29
27. Wen CP, Cheng TY, Tsai MK, Chang YC, Chan HT, Tsai SP, Chiang PH, Hsu CC, Sung PK, Hsu YH, Wen SF (2008) All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. Lancet 371 (9631):2173–2182
28. Weber D, Wang M, Delasalle K, Alexanian R (2003) Confirmation of prognostic value of model using B2 microglobulin (B2M) and albumin for multiple myeloma (MM) proposed by the International Myeloma Working Group (IMWG) with similar results using B2M alone. Blood 102(11):abstract 3491
29. Terpos E, Katodritou E, Roussou M, Pouli A, Michalis E, Delimpasi S, Parcharidou A, Kartasis Z, Zomas A, Symeonidis A, Viniou NA, Anagnostopoulos N, Economopoulos T, Zervas K, Dimopoulos MA (2010) High serum lactate dehydrogenase adds prognostic value to the international myeloma staging system even in the era of novel agents. Eur J Haematol 85(2):114–119