Evaluation to Prognostic Staging System of Multiple Myeloma in Novel Agent Era

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Evaluation to prognostic staging system of multiple myeloma in novel agent era

Running title: Prognostic system of multiple myeloma

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Abstract

Purpose This study was to evaluate existing staging system of multiple myeloma (MM) in the real world.

Methods We retrospectively analyzed 886 newly diagnosed MM from two institutions.

Results The overall survival (OS) of eligible patients was 61.0 months. R-ISS held a larger receiver operating characteristic curve (ROC) area (0.603) than that of ISS (0.573) and DS staging system (0.567). In the group of immunomodulatory agents-based regimens, the median OS was 92.0 months in R-ISS I, 63.0 months in R-ISS II and 18.0 months in R-ISS III (p<0.0001). In the group of proteasome inhibitors-based regimens, the median OS was 102.0 months in R-ISS I, 63.0 months in R-ISS II and 22.0 months in R-ISS III (p<0.0001). In different subgroups grouped according to Age, HGB, CREA and Ca, R-ISS also had a good stratification effect. Patients in R-ISS II were further analyzed, which accounted for 69.9% of all R-ISS patients. Using univariable and multivariable Cox analysis, Age>65 years (p=0.001), HGB<100g/L (p<0.001), elevated LDH (p=0.001) and Ca (p=0.010) were independent factors indicating worse prognosis for R-ISS II.

Conclusion R-ISS remains a valuable staging system in the real world of new drug era. But patients classified in R-ISS II still have large heterogeneity.

Introduction

Multiple myeloma (MM) was a kind of malignant disorder with abnormal proliferation of clonal plasma cells, which was often the second most common malignant tumor in hematologic malignancies in many countries(Siegel et al. 2019; Teras et al. 2016). The prognosis of patients with MM was highly variable as a result of the heterogeneity in both myeloma cell biology and multiple host factors. Thus, it was important to use an accurate prognostic model for understanding disease outcome, identifying risk groups, optimizing risk-adapted therapeutic strategies, and informing patients.

Durie-Salmon (DS) staging system was put forward in 1975 on the basis of the commonly available clinical parameters including monoclonal protein levels, hemoglobin level, hypercalcemia, bone lesions and creatinine (CREA) level that predicted myeloma cell tumor burden, and was widely adopted worldwide to evaluate prognosis in myeloma(Durie and Salmon 1975). However, MM staging procedures are still inadequate for detection of the optimal therapeutic procedure for an individual patient. Thereafter, the serum beta2-microglobulin (Sβ2M) was validated as the most powerful prognostic factor(Bataille et al. 1983; Norfolk et al. 1980), and other studies demonstrated that combining additional biochemical factors such as C-reactive protein or serum albumin could improve the predictive value of Sβ2M (Bataille et al. 1992; Bataille et al. 1986). In 2005, the International Staging System (ISS) based on the Sβ2M and serum albumin for MM was introduced(Greipp et al. 2005). However, the ISS did not incorporate the role of intrinsic myeloma cell variability. In order to improve the predictive value of ISS, the International Myeloma Working Group (IMWG) proposed revised ISS (R-ISS) by combining ISS, cytogenetic abnormality (CA) and LDH data(Palumbo et al. 2015). Nevertheless, R-ISS was established based on patients taken from clinical trials of newly diagnosed myeloma, which incorporated patients with good performance status and had multiple exclusion criteria, so there was a number of limitations even though it has been proved equally valid in a real world population with unselected patients(Kastritis et al. 2017; Walker et al. 2018). Currently, different studies may utilize different standards for risk stratification, and so there should be a uniform prognostic stratification standard.

In fact, a single factor was often not enough to determine the prognosis, and many prognostic factors had been shown to have significant value in MM. In this study, we retrospectively analyzed patients with MM from two institutions in China to further evaluate the predictive ability of ISS, R-ISS, DS staging system in the real world, and tried to suggest the inclusion factors needed to create a staging system.

Methods

Patients.

From January 2010 to June 2019, a total of 886 patients newly diagnosed with MM were enrolled in this retrospective study. These cases come from two institutions including Zhongnan hospital of Wuhan University and the second affiliated hospital of Xi'an Jiaotong University, China. All patients were confirmed MM based on IMWG criterion(Rajkumar et al. 2014), as determined by two or more expert hematologist. Patients with smoldering MM, immunoglobulin M related disorders, unclear immunophenotype or primary amyloidosis were excluded. The present study was approved by the institutional review boards of all participating institutions. All procedures in the present study that involved human participants were performed in accordance with the Declaration of Helsinki. The flow chart of analysis in this study was shown in Figure 1.

Clinical data were obtained by reviewing medical records. Baseline data collected included age, sex, ISS, R-ISS, DS staging system, M protein type, serum albumin, serum LDH, Sβ2M, CREA, serum calcium (Ca), hemoglobin (HGB) level, platelet (PLT) level, percentage of clonal bone-marrow plasma-cell, CA detected by Fluorescence in situ Hybridization(iFISH) and treatment strategies. The first-line treatment protocol including chemotherapy, thalidomide-based agents and bortezomib-based agents, and the total number of cycles were recorded in detail. Traditional chemotherapy regimens included MP (melphalan and prednisolone), and VAD (vincristine, adriamycin, dexamethasone) and the like. Serum LDH were classified as normal or high according to the laboratory definition of the normal range of each institution. The cut-off value of baseline variables was categorized by published thresholds(Greipp et al. 2005), or the

upper or lower limit of normal range. The iFISH studies were performed on immunologically recognized plasma cells according to iFISH methods of each institution. Del(17p), translocation t (4;14), and translocation t (14;16) detected by iFISH were considered high risk CA. Besides, imaging examinations included X-ray, computed tomographic (CT) scan imaging, magnetic resonance imaging (MRI) or positron emission tomography-computed tomography (PET-CT) of the whole body to identify bone destruction or extramedullary lesions.

The prognostic evaluation included overall survival (OS) and progression-free survival (PFS). OS was defined as the time from diagnosis to last follow-up or death resulting from any cause. PFS was calculated from the date of diagnosis to the date of disease progression, relapse and death from any cause or the last follow-up. Follow-up of patients not experiencing any of these events was censored at the date of last contact.

Statistical Analysis.

Statistical analyses were performed using IBM SPSS statistics software, version 25.0 and GraphPad Prism7. OS and PFS distributions were estimated using the Kaplan–Meier curve analysis, time-to-event distributions were compared using the log-rank test. OS and PFS were then analyzed through the Cox proportional hazards model, comparing the risk factors by the Wald test. Multivariate analysis was performed with a Cox hazards regression model using forward/ backward stepwise method with the use of threshold values for removal from and addition to the model of P=0.10 and P= 0.05 respectively. Results were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). All reported p values were two-sided at significance-level of 0.05.

Results

Patients' characteristics

From January 2010 to June 2019, 859 newly diagnosed patients with MM from total 886 patients were eligible for further analyses in present study. The median age was 61.0 years (range from 21.0–93.0); 66.9% of patients were≤65 years old, and 33.1% were older than age 65 years; 58.2% of patients were male, and 46.6% of patients were in IgG isotype.

33.8% of the patients received proteasome inhibitor-based regimens, 36.8% received immunomodulatory agent-based regimens. The median number of treatment regimens was 2 (range 1-9) and median number of treatment courses was 4 (range 1-31). The treatment options had no statistic difference to survival (p>0.05). At a median follow-up of 42 months, the median OS was 61.0 months (95% CI 55.6-66.4), the 5-year OS was 53.1% and median PFS was 31.0 months (95% CI 27.6-34.4). The detailed clinical characteristics for all patients are presented in Table 1.

In total, 22.4% of the patients were rated as ISS-I, 38.0% as ISS-II and 39.7% were rated as ISS-III (Table 1). Disposition per D-S staging system was depicted in Table 1. There were 270 patients who performed cytogenetic examination by FISH, and 28.1% of the patients presented high risk CA. Combining with ISS and LDH, a total of 579 patients were able to perform R-ISS staging, and 51 patients (8.8%) were in R-ISS I, 405 patients (69.9%) were in R-ISS II, 123 patients (21.2%) were in R-ISS III. Disposition between R-ISS and ISS or Durie-Salmon staging system of the 579 patients with multiple myeloma was shown in Table 2.

Univariate and Multivariate Analysis

Univariate Analysis

We completed the univariate analysis based on the full analysis dataset by Kaplan–Meier curve analysis (Table 1), and achieved that the baseline factors of Age, HGB, ALB, CREA, Sβ2M, Ca, LDH, ISS, R-ISS, DS staging system, high risk CA were significantly associated with OS, and HGB, ALB, CREA, Sβ2M, Ca, LDH, ISS, R-ISS, DS staging system were significantly associated with PFS. In order to acquire the risk of death about baseline factors, the univariable Cox analysis was done, and the results was shown in Figure 2. The risk of death was similar to the IMWG study for high-risk CA versus standard-risk CA (HR,1.98 vs 2.03 in IMWG), and for high LDH versus normal LDH (HR, 2.46 vs 2.55 in IMWG)(Palumbo et al. 2015).

The ISS, R-ISS and DS staging system were evaluated the ability of stratification for OS and PFS (Figure 3). Compared to ISS and DS staging system, the ROC curve area of R-ISS was superior to that of ISS and DS staging system,

with ROC area of ISS 0.573(95%CI, 0.517-0.629), R-ISS 0.603(95%CI, 0.549-0.657), and D-S staging system 0.567 (95%CI, 0.511-0.622). For the different treatment subgroups, the stratification ability of R-ISS was shown in Figure 4 (A, B). In the group of immunomodulatory agents-based regimens, the median OS was 92.0 months in R-ISS I, 63.0 months in R-ISS II and 18.0 months in R-ISS III (p<0.001). In the group of Proteasome inhibitors-based regimens, the median OS was 102.0 months in R-ISS I, 63.0 months in R-ISS II and 22.0 months in R-ISS III (p<0.001).

Multivariate Analysis

We then included factors that were statistically significant in univariate analysis into multivariate analysis for OS. Since CA has approximately 2/3 of the censored data, it was not included in the multivariate analysis. When R-ISS was included multivariate Cox analysis, Age, PLT, HGB, CREA and Ca were incorporated multivariable model. Sβ2, ALB and LDH were not in the multivariable model because they were included in R-ISS. The results showed that the risk of death was related to five independent prognostic variables: Age>65 years (p=0.001), HGB<100g/L(p=0.010), CREA>177umol/L (p=0.012), Ca>2.5 mmol/L (p=0.007), R-ISS III vs I (p=0.001) and II (p=0.040). These results were listed in Table 3. We further analyzed the stratification effect of R-ISS in different subgroups grouped according to Age (> 65 years, ≤65 years), HGB (≥100g/L, <100g/L), CREA (≤177umol/L, >177umol/L) and Ca (≤2.5mmol/L, >2.5mmol/L). The p value in each group was less than 0.01, and Figure 4 (C, D, E, F, G, H, I, J) showed the stratification ability of R-ISS in each group.

Patients in the stage of R-ISS II

The stage of R-ISS II not only included all patients in ISS II, but also included patients with high-risk CA or high LDH in ISS I and patients without high-risk CA or with normal LDH in ISS III. In present study, 405 (69.9%) patients were in R-ISS II. Then patients in R-ISS II were further analyzed to see if there was still a statistically significant difference in OS between different subgroups. Using univariable Cox analysis, Age > 65 years (p=0.024), HGB <100g/L (p<0.001), elevated LDH (p=0.010) and serum Ca (p=0.011), and renal dysfunction (p=0.011) were association with worse prognosis. Using multivariable Cox analysis, Age, HGB, elevated LDH and serum Ca were independent factors influencing OS (Table

4). This suggested that there was still a great deal of heterogeneity in R-ISS II. The overall survival of each subgroups was shown in Figure 4 (K, L, M, N).

Discussion

MM had obvious heterogeneity in biology and clinic, and prognostic stratification was recommended. It was believed that neither ISS nor DS staging system was strongly predictive of outcomes, and ISS and DS staging system had low concordance in stage assignment(Hari et al. 2009). It was unlikely that any one clinical staging system could fully accommodate the factors that impact outcomes(Hari et al. 2009), which suggested that other prognostic markers were need to be incorporated. Precise prognostic stratification of MM was still in research and exploration(Facon et al. 2019; Jung et al. 2019; Martinez-Lopez et al. 2014; McDonald et al. 2017).

In this study, we evaluated any correlation between baseline clinical findings and the length of OS or PFS in 859 patients. R-ISS significantly classified OS and PFS of patients into different risk groups (p<0.001, Figure 3). R-ISS held larger ROC area (AUC=0.603) than that of ISS and DS staging system in present data. Besides, in the new drug era with different treatment groups, R-ISS can still stratify patients with MM well (Figure 4). R-ISS also had predictive ability on OS in different subgroups based on clinical characteristics (Figure 4). So, to sum up, R-ISS had a strong ability to judge prognosis. However, most patients were classified as R-ISS II, and the survival outcome of patients in this stage was highly heterogeneous in R-ISS II, which was also consistent with previous reports(Jung et al. 2018). This is to be expected, as the stage consisted of patients with various characteristics, i.e. with or without CA, normal or elevated LDH, all ranges of Sβ2M, and accounted for a very high proportion of patients in R-ISS. Therefore, a more sophisticated prognostic system needs to be developed.

Only del (17p), t (4;14), and t (14;16) were considered high-risk CA associated with adverse prognosis in R-ISS, but 1q gain, t (14;20) and del(13q) were also enriched in high-risk patients. Patients might hold one or more poor prognostic cytogenetic markers in non-high-risk group, indicating that a single poor-risk marker was unable to provide strong

prognostic value(Kuiper et al. 2012). However, further heterogeneity may be in the population of the same CA, and the co-occurrence of multiple genetic lesions may have greater significance for predicting outcome than any single abnormality(Hebraud et al. 2015; Kumar et al. 2012; Shah et al. 2018). Even within groups with the same genetic prognostic factors, there may be further heterogeneity(Chng et al. 2014). Therefore, it became obvious that the current definition of a high-risk cytogenetic group was oversimplified and could lead to misclassification of patient prognosis(Perrot et al. 2019). Besides, some studies indicated that patients classified as high risk based on these FISH classifiers had actually favorable survival(Kuiper et al. 2015). With the gene expression profiling (GEP) being extensively investigated as a potential tool for the assessment of risk in MM, studies had proved that the GEP was capable of discriminating patients with different risk stratification irrespective of treatment regime, age and relapse setting(Kuiper et al. 2012). However, GEP was quite complex and costly for routine use, and it will take some time before it can be used routinely.

An ideal prognostic model would include baseline factors such as host factors, tumor characteristics, and treatment response. Although the depth of treatment response and minimal residual disease (MRD) levels had a significant effect on the prognosis of MM(Anderson et al. 2017; Paiva et al. 2015b; Perrot et al. 2018), it was unable to reflect prognosis of patients at the time of the initial diagnosis. On the other hand, the technical requirements for detecting MRD such as next-generation flow and next-generation sequencing were relatively high, expensive and difficult to achieve(Anderson et al. 2017; Martinez-Lopez et al. 2014; Paiva et al. 2015a). Besides, the definition of MRD in different institutions and different methods is not completely consistent. Therefore, it will be difficult to include the treatment strategy and treatment response into prognostic model at initial diagnosis.

In present analysis, when R-ISS were included in multivariate analysis respectively, Age, HGB, CREA and Ca were always statistically significant to OS, indicating their independent predictive role to survival. Besides, Age, HGB, CREA and Ca also were independent factors influencing OS in R-ISS II group. Age, one of the most important host factors, was considered to be a strong prognostic factor for MM(Chretien et al. 2014; Kyle et al. 2003; Pawlyn et al. 2020), which may

result from co-morbidities in elderly patients and the different treatment approaches used in these two populations. In a large cohort from Europe, United States and Japan treated with both conventional and novel agents, there was an incremental shortening of survival in every increasing 10-year age band(Ludwig et al. 2010). Renal impairment, a common complication of MM, was also demonstrated to be associated with poor survival, and was an ISS-independent surrogate predictor of poor prognosis(Hsiao et al. 2012; Laing et al. 2015). Although Sβ2M partially reflected renal function, glomerular filtration rate (GFR) and creatinine level were the most accurate indicators for evaluating renal function. Tumor mass, organ dysfunction, tumor intrinsic variability and host factors were considered to be the most valuable factors in predicting survival duration(Bataille et al. 1986). It will be rational to include Age and organ damage in future prognostic model.

There are some limitations to this research. Firstly, because it was a retrospective study, treatment regimens and cycles varied widely, which lead to the results that the OS between patients in different treatment regimens had no statistical difference. Secondly, due to the low acceptance of transplantation among Chinese patients, the transplantation rate of patients is very low, so most of the patients in this study did not undergo hematopoietic stem cell transplantation. Thirdly, cytogenetic testing has only been performed on some patients, and we were not able to perform R-ISS staging for all patients. In this study, the R-ISS II accounted for approximately 2/3 of the R-ISS, which maybe was an overestimation. Since only patients with defined low-risk cytogenetic changes in ISS I were classified as R-ISS I, and those with unclear cytogenetic types were discarded, and those with unclear cytogenetic types were discarded when the LDH was normal in ISS III, which may partially reduce the ratio of R-ISS III.

In conclusion, in this study, we retrospectively analyzed patients with newly diagnosed MM from two institutions in China, to conclude that R-ISS remains a valuable staging system in the real world of the new drug era. But patients classified in R-ISS II still have large heterogeneity. Age, HGB, elevated LDH and serum Ca were independent factors influencing OS in this group. With the development of new treatment strategies, such as Daratuzumab targeting CD38,

chimeric antigen receptors (CARs) targeting B-cell maturation antigen or CAR-T cells against CD19, which have shown encouraging results in patients with relapsed refractory MM and hold great promise in further improving patient outcomes in MM, a more refined staging system also needs to be developed in the future.

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Authors' contributions

Yufeng Shang analyzed data, draw pictures and wrote manuscript, Yanxia Jin, Hailing Liu, Lu Ding, Xiqin Tong, Honglei Tu, Longkai Zang and Chenyao Lin collected data, Jinsong Hu and Fuling Zhou designed project, provided professional guidance and revised manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration. Written informed consent was received from all patients before inclusion in the study and information was collected from the electronic patient records.

Consent for publication

Not Applicable

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

There is no conflict of interest.

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Figure legends

Figure 1. The flow chart of analysis in this study.

Figure 2. The risk of death about baseline factors using the univariable Cox analysis.

CI, confidence interval. HR, Hazard ratios; L, Low; H, High; BM, bone marrow.

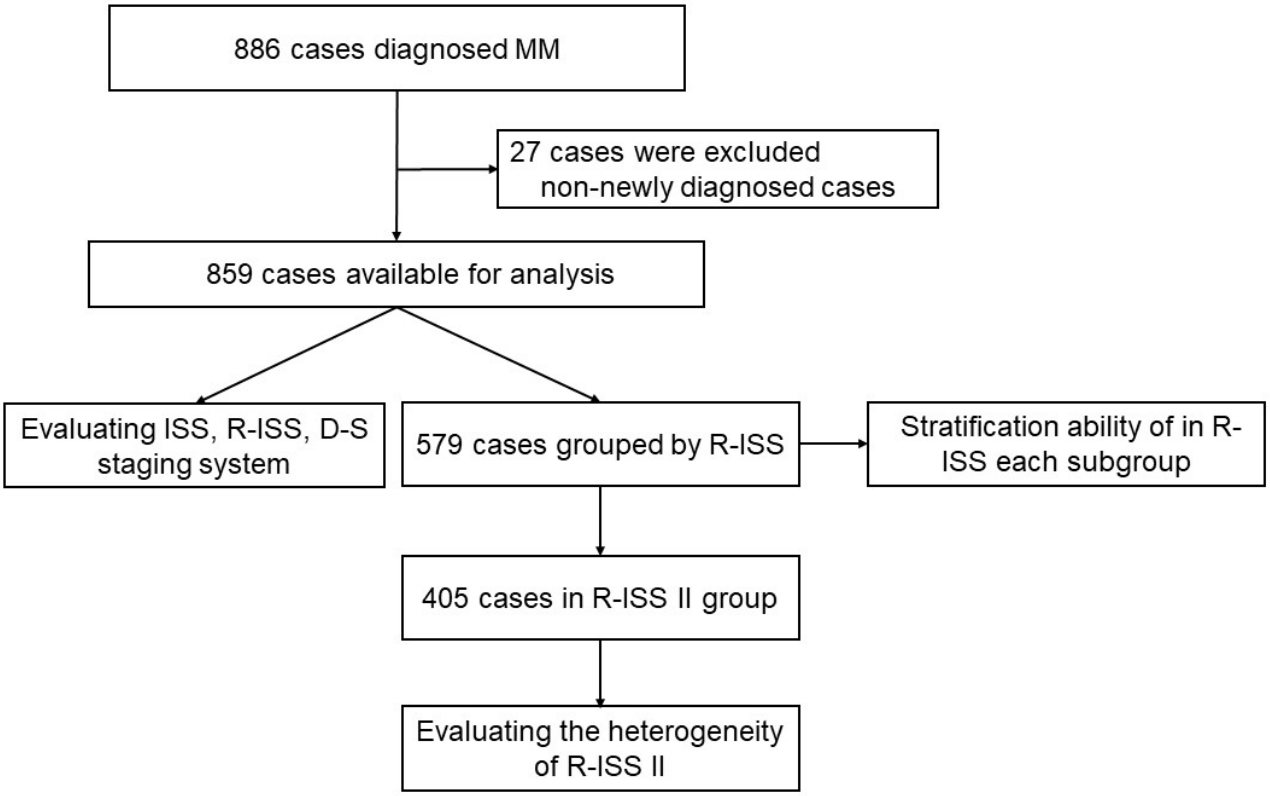
Figure 3. OS and PFS in patients with multiple myeloma stratified by existing staging system. OS in patients with multiple myeloma stratified by ISS (A), R-ISS (B) and DS staging system (C). PFS in patients with multiple myeloma stratified by ISS (D), R-ISS (E) and DS staging system (F).

HR, hazard ratio; NR, not reached. OS, overall survival. PFS, Progression-free survival

Figure 4. OS in patients with multiple myeloma stratified by R-ISS based on different subgroups, and OS in R-ISS II groups by different subgroups using K-M test.

The OS in patients with multiple myeloma stratified by R-ISS in immunomodulatory agents-based regimen groups (A) and proteasome inhibitors-based regimen groups (B). The OS in patients with multiple myeloma stratified by R-ISS in age ≤ 65years (C) and age>65years (D), in HGB≥100g/L (E) and HGB<100g/L (F), in CREA≤177umol/L (G) and CREA>177umol/L (H), in Ca≤2.5mmol/L (I) and Ca>2.5mmol/L (J). OS in patients with multiple myeloma in R-ISS II groups by different subgroups of Age (K), HGB (L), LDH (M) and Ca (N).

CREA, Creatinine; HGB, hemoglobin; OS, Overall Survival; R-ISS, Revised International Staging System



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330 **Figure 1.** The flow chart of analysis in this study.

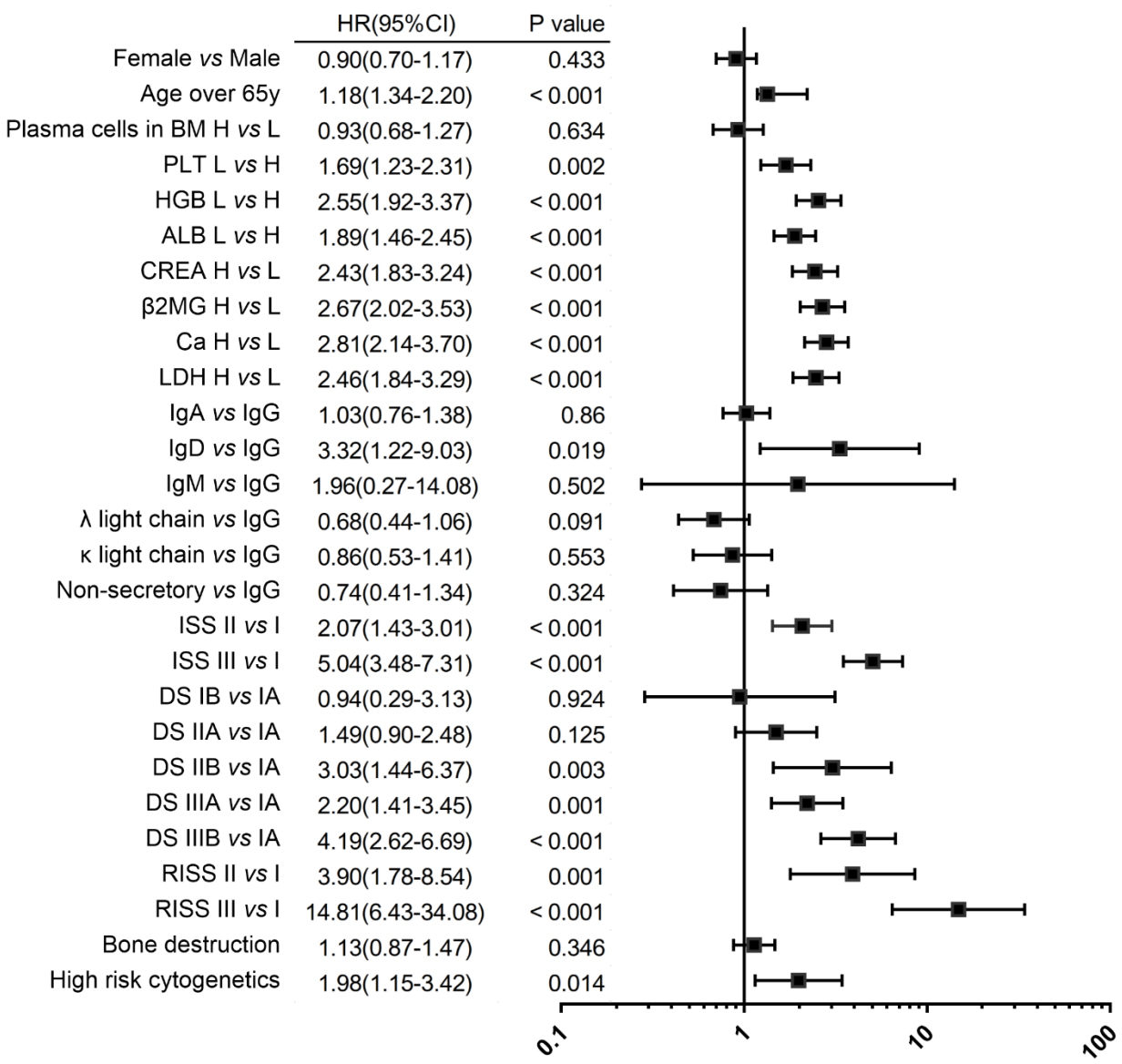


Figure 2. The risk of death about baseline factors using the univariable Cox analysis.

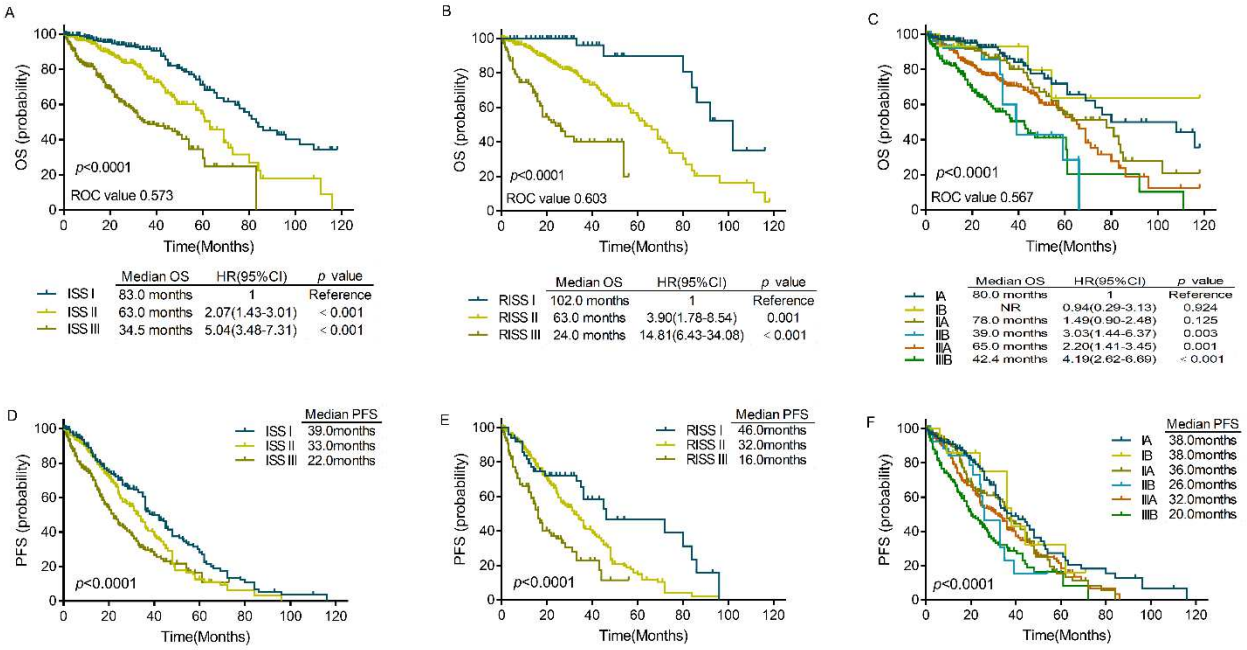
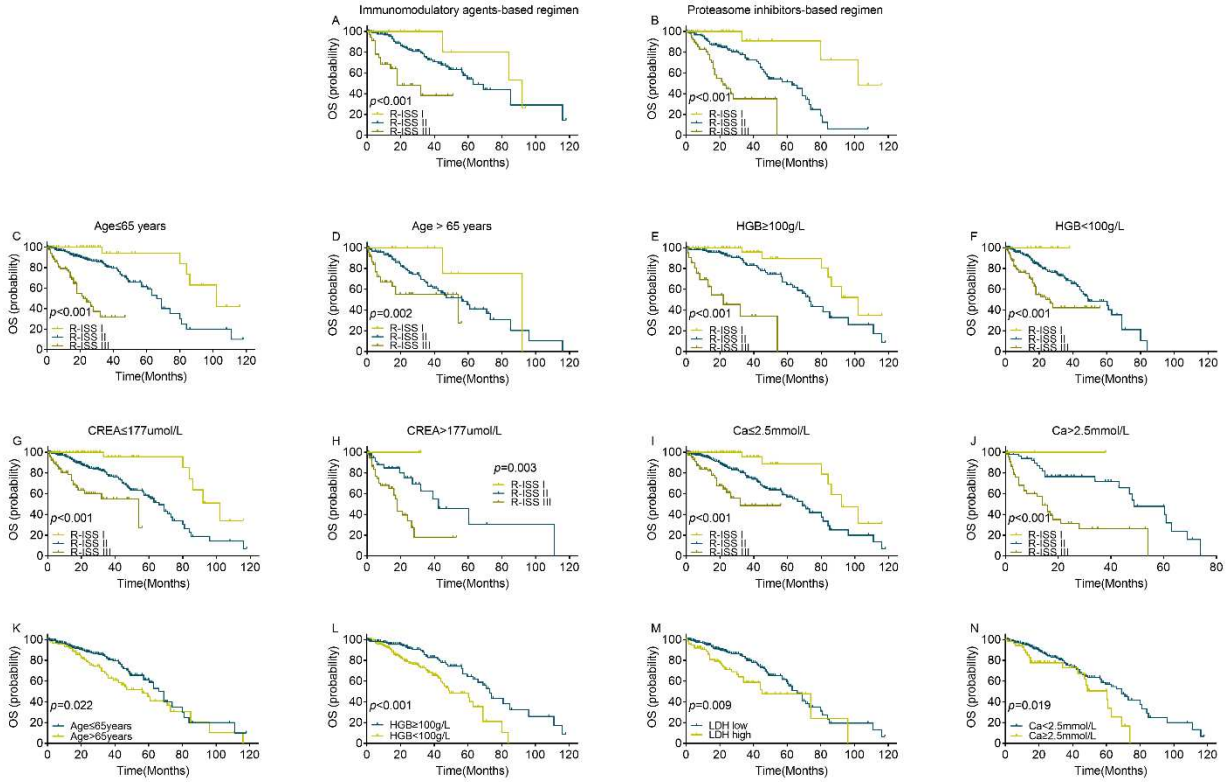


Figure 3. OS and PFS in patients with multiple myeloma stratified by existing staging system. OS in patients with multiple myeloma stratified by ISS (A), R-ISS (B) and DS staging system (C). PFS in patients with multiple myeloma stratified by ISS (D), R-ISS (E) and DS staging system (F).



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342

343 **Figure 4.** OS in patients with multiple myeloma stratified by R-ISS based on different subgroups, and OS in R-ISS II

344 groups by different subgroups using K-M test.

345 The OS in patients with multiple myeloma stratified by R-ISS in immunomodulatory agents-based regimen groups (A) and

346 proteasome inhibitors-based regimen groups (B). The OS in patients with multiple myeloma stratified by R-ISS in age ≤

347 65years (C) and age>65years (D), in HGB≥100g/L (E) and HGB<100g/L (F), in CREA≤177umol/L (G) and

348 CREA>177umol/L (H), in Ca≤2.5mmol/L (I) and Ca>2.5mmol/L (J). OS in patients with multiple myeloma in R-ISS II

349 groups by different subgroups of Age (K), HGB (L), LDH (M) and Ca (N).

350 CREA, Creatinine; HGB, hemoglobin; OS, Overall Survival; R-ISS, Revised International Staging System

Table 1. Patients' characteristics and results of the univariate analyses for overall survival and progression-free survival.

	Median(range) Number (%)	Median PFS (months [95% CI])	3-year PFS (95% CI)	log-rank *p* value	Median OS (months [95% CI])	5-year OS (95% CI)	log-rank *p* value
Sex		31.0(27.6-34.4)		0.74	61.0(55.6-66.4)		0.43
Male	500(58.2%)	32.0(27.5-36.5)	40.8% (35.3-46.3)		60.9(54.5-67.3)	51.2% (43.6-58.8)	
Female	359(41.8%)	31.0(26.0-36.0)	40.8% (34.1-47.5)		63.0(49.9-76.1)	55.8% (47.2-64.4)	
Age(years)	61(21-93)	31.0(27.6-34.4)		0.26	61.0(55.6-66.4)		**<0.001**
≤65	575(66.9%)	33.0(29.5-36.5)	41.9% (36.6-47.2)		69.0(59.2-78.8)	51.2% (43.6-58.8)	
>65	284(33.1%)	30.0(24.3-35.7)	38.5% (31.2-45.8)		51.0(42.3-59.7)	55.8% (47.2-64.4)	
Plasma cells in BM (%)	32.0 (8.0-96.0)	30.0(26.2-33.8)		0.30	78.0(68.7-87.3)		0.63
<33%	343(51.5%)	31.0(26.4-35.6)	39.3% (32.4-46.2)		80.0(58.3-101.7)	56.2% (47.2-65.2)	
≥33%	323(48.5%)	28.0(22.5-33.5)	38.0% (30.9-45.1)		76.0(65.1-86.9)	68.1% (59.5-76.7)	
PLT($x10^9$)	138(5-513)	31.0(27.1-34.9)		0.27	78.0(69.3-86.7)		**0.001**
≥100	562(75.5%)	32.0(28.3-35.7)	41.5% (36.2-46.8)		83.0(72.4-91.6)	67.0% (60.7-73.3)	
<100	182(24.5%)	30.0(24.3-35.7)	35.2% (25.4-45.0)		60.9(42.0-79.8)	51.3% (39.1-63.5)	
HGB(g/L)	90.0(32.8-167.0)	32.0(28.5-35.5)		**<0.001**	61.0(55.2-66.8)		**<0.001**
≥100	319(37.4%)	36.0(33.0-39.0)	46.2% (39.5-52.9)		80.0(71.2-88.8)	67.0% (59.2-74.8)	
<100	534(62.6%)	26.0(21.9-30.1)	37.4% (31.7-43.1)		49.0(40.4-57.6)	40.3% (31.3-49.3)	
ALB(g/L)	33.6(10.6-50.0)	31.0(27.5-34.5)		**0.003**	61.0(55.6-66.4)		**<0.001**
≥35	376(44.5%)	35.0(32.2-37.8)	44.1% (37.8-50.4)		74.0(62.3-85.7)	61.6% (53.6-69.6)	
<35	468(55.5%)	26.0(21.9-30.1)	38.0% (32.1-43.9)		51.0(42.4-59.6)	45.1% (36.9-53.3)	
CREA (umol/L)	85.8(29.0-1687.1)	31.0(27.4-34.6)		**<0.001**	61.0(55.3-66.7)		**<0.001**
≤177	671(80.1%)	34.0(31.8-36.2)	43.5% (38.6-48.4)		69.0(60.1-77.9)	58.2% (51.9-64.5)	
>177	167(19.9%)	20.3(15.9-24.7)	29.0% (19.8-38.2)		34.5(24.8-44.2)	29.7% (16.0-43.4)	
Sβ2M(mg/L)	4.54(0.28-33.90)	31.0(27.6-34.4)		**<0.001**	61.0(55.6-66.4)		**<0.001**
≤3.5	321(37.4%)	36.0(31.5-40.5)	49.5% (43.0-56.0)		78.0(66.0-90.1)	64.6% (56.4-72.8)	
>3.5	538(62.6%)	26.0(22.7-29.3)	34.2% (28.5-39.9)		48.7(38.4-59.0)	45.2% (37.6-52.8)	
Ca(mmol/L)	2.13(1.09-3.90)	31.0(27.3-34.7)		**<0.001**	61.0(55.7-66.3)		**<0.001**
≤2.5	678(80.3%)	34.0(31.1-36.9)	44.1% (39.2-49.0)		73.0(63.3-82.7)	60.0% (53.7-66.3)	
>2.5	166(19.7%)	18.2(13.0-23.4)	28.8% (20.0-37.6)		43.5(32.0-55.0)	26.4% (15.0-37.8)	
LDH	172 (10-961)	31.0(27.1-34.9)		**<0.001**	61.0(55.3-66.7)		**<0.001**
Normal	609(79.4%)	34.0(31.2-36.8)	45.0% (39.9-50.1)		66.0(60.4-71.6)	58.1% (51.4-64.8)	
High	158(20.6%)	18.0(13.8-22.2)	24.9% (15.9-33.9)		32.0(19.7-44.3)	35.3% (22.6-48.0)	

M protein type		31.0(27.6-34.4)		0.65	61.0(55.6-66.4)		0.065
IgG	400(46.6%)	31.0(26.6-35.4)	40.6% (34.5-46.7)		59.0(53.0-65.0)	48.5% (40.1-56.9)	
IgA	216(25.1%)	31.0(24.7-37.3)	39.4% (31.0-47.8)		65.0(55.0-75.0)	55.8% (45.2-66.4)	
IgD	7(0.8%)	21.0(10.2-31.8)	0.0% (0.0-0.0)		31.0(11.9-50.1)	0.0%	
IgM	2(0.2%)	5.0(0.0-0.0)	50.0% (0-100.0)		5.0	0.0%	
λ light chain	115(13.4%)	33.0(25.5-40.5)	42.0% (29.7-54.3)		76.0(55.5-96.5)	70.7% (57.6-83.8)	
κ light chain	66(7.7%)	35.0(23.4-46.6)	49.5% (32.8-66.2)		83.0(33.0-133.0)	59.0% (40.8-77.2)	
Non-secretory	53(6.2%)	33.0(23.7-42.3)	38.0% (20.0-56.0)		84.0(49.9-118.1)	50.1% (23.2-77.0)	
ISS		31.0(27.6-34.4)		**<0.001**	61.0(55.6-66.4)		**<0.001**
I	192(22.4%)	39.0(34.5-43.5)	53.0% (45.0-61.0)		83.0(69.5-96.5)	71.4% (62.2-80.6)	
II	326(38.0%)	33.0(29.1-36.9)	42.7% (35.4-50.0)		63.0(55.5-70.5)	54.7% (44.7-64.7)	
III	341(39.7%)	22.0(18.6-25.4)	29.4% (22.5-36.3)		34.5(22.8-46.2)	34.6% (23.6-45.6)	
DS		32.0(28.3-35.7)		**<0.001**	61.0(55.2-66.8)		**<0.001**
IA	111(12.9%)	38.0(26.3-49.7)	50.5% (39.1-61.9)		80.0(36.5-123.5)	71.9% (59.4-84.4)	
IB	14(1.6%)	38.0(24.5-51.5)	53.6% (22.6-84.6)		-	63.7% (28.6-98.8)	
IIA	153(18.0%)	36.0(31.8-40.2)	47.8% (37.6-58.0)		78.0(52.7-103.3)	54.4% (40.3-68.5)	
IIB	29(3.4%)	26.0(18.9-33.1)	23.2% (1.1-45.3)		39.0(29.3-48.7)	28.6% (0-58.0)	
IIIA	334(39.3%)	32.0(26.5-37.5)	41.5% (34.8-48.2)		65.0(58.3-71.7)	54.8% (45.8-63.8)	
IIIB	209(24.6%)	20.0(15.6-24.4)	30.5% (21.7-39.3)		42.4(30.3-54.5)	41.1% (29.3-52.9)	
R-ISS		31.0(27.0-35.0)		**<0.001**	63.0(54.5-71.5)		**<0.001**
I	51(8.8%)	46.0(10.3-81.7)	58.5% (42.4-74.6)		102.0(82.4-121.6)	89.6% (75.5-100)	
II	405(69.9%)	32.0(28.1-35.9)	42.4% (36.1-48.7)		63. 0(56.4-69.6)	55.5% (46.9-64.1)	
III	123(21.2%)	16.0(13.3-18.7)	22.9% (11.7-34.1)		24.0(16.9-31.1)	0.0%	
Bone destruction		32.0(29.1-34.9)		0.056	61.0(55.2-66.8)		0.34
No	327(39.4%)	35.0(32.1-37.9)	44.4% (37.7-51.1)		63.0(53.7-72.3)	53.3% (44.5-62.1)	
Yes	503(60.6%)	27.0(22.5-31.5)	39.3% (33.6-45.0)		60.9(54.5-67.3)	54.0% (46.2-61.8)	
High risk CA		36.0(28.4-43.6)		0.054	80.0(72.1-87.9)		**0.012**
No	194(71.9%)	36.0(27.4-44.6)	48.9% (39.5-58.3)		84.0(73.1-94.9)	77.4% (68.0-86.8)	
Yes	76(28.1%)	36.0(20.1-51.9)	40.8% (26.3-55.3)		66.0(40.0-92.1)	60.6% (44.3-76.9)	
Treatment		31.0(27.6-34.4)		0.61	61.0(55.6-66.4)		0.45
Immunomodulatory agent-based	316(36.8%)	31.0(26.1-35.9)	39.4% (32.5-46.3)		60.1(54.3-65.9)	51.4% (42.4-60.4)	
Proteasome inhibitor-based	290(33.8%)	33.4(30.3-36.5)	42.0% (34.7-49.3)		59.0(48.5-69.5)	50.0% (41.2-58.8)	
Others	253(29.4%)	26.0(18.4-33.6)	41.9% (33.5-50.3)		86.0(54.6-117.4)	66.5% (55.7-77.3)	

BM, Bone Marrow. CA, Cytogenetic Abnormality. ESR, Erythrocyte Sedimentation Rate. PFS, progression-free survival. OS, overall survival.

Table 2. Disposition between R-ISS and ISS or Durie-Salmon staging system of 579 patients with multiple myeloma.

Variables	R-ISS I (n=51)	R-ISS II (n=405)	R-ISS III (n=123)	Total (n=579)
ISS stages				
ISS I	51 (100.0)	42 (10.4)	0	93 (16.1)
ISS II	0	326 (80.5)	0	326 (56.3)
ISS III	0	37 (9.1)	123 (100.0)	160 (27.6)
DS stages				
DS IA	8 (15.7)	53 (13.1)	4 (3.3)	65 (11.2)
DS IB	1 (2.0)	7 (1.7)	1 (0.8)	9 (1.6)
DS IIA	15 (29.4)	105 (25.9)	5 (4.1)	125 (21.6)
DS IIB	1 (2.0)	11 (2.7)	5 (4.1)	17 (2.9)
DS IIIA	20 (39.2)	159 (39.3)	42 (34.1)	221 (38.2)
DS IIIB	7 (11.8)	70 (17.3)	66 (53.7)	142 (24.5)

Table 3. Multivariate analysis for survival with R-ISS included.

Variables	HR	95% CI for HR		*P* value
		Lower	Upper	
CREA>177umol/L	1.799	1.138	2.844	0.012
Age>65 years	1.832	1.265	2.652	0.001
Ca>2.5 mmol/L	1.908	1.196	3.043	0.007
HGB<100g/L	1.835	1.154	2.917	0.010
R-ISS I	1(Reference)			
R-ISS II vs I	2.483	1.041	5.924	0.040
R-ISS III vs I	5.164	1.916	13.923	0.001
PLT<100x10^9	-	-	-	0.079

Table 4. Univariable and multivariable Cox analysis for survival in patients with R-ISS II.

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
SEX (Female)	0.756(0.509-1.122)	0.164	…	…
Age>65 years	1.562(1.061-2.298)	**0.024**	2.080(1.350-3.206)	**0.001**
Plasma cells in BM ≥33%	0.971(0.601-1.568)	0.903	…	…
High risk CA	1.001(0.499-2.010)	0.997	…	…
Bone destruction	1.254(0.841-1.869)	0.267	…	…
Renal dysfunction	1.798(1.142-2.796)	**0.011**	…	0.098
HGB<100g/L	2.376(1.544-3.656)	**<0.001**	2.893(1.789-4.676)	**<0.001**
PLT<100 x10^9	1.579(0.970-2.571)	0.066	…	…
Ca>2.5 mmol/L	1.905(1.163-3.122)	**0.011**	1.974(1.180-3.303)	**0.010**
ALB <35g/L	1.531(0.981-2.391)	0.061	…	…
Sβ2M >3.5mg/L	1.273(0.861-1.881)	0.227	…	…
Elevated LDH	1.788(1.147-2.788)	**0.010**	2.103(1.329-3.326)	**0.001**
CREA>177umol/L	1.740(0.967-3.131)	0.065	…	…
Treatment	0.971(0.755-1.248)	0.818	…	…

Figures

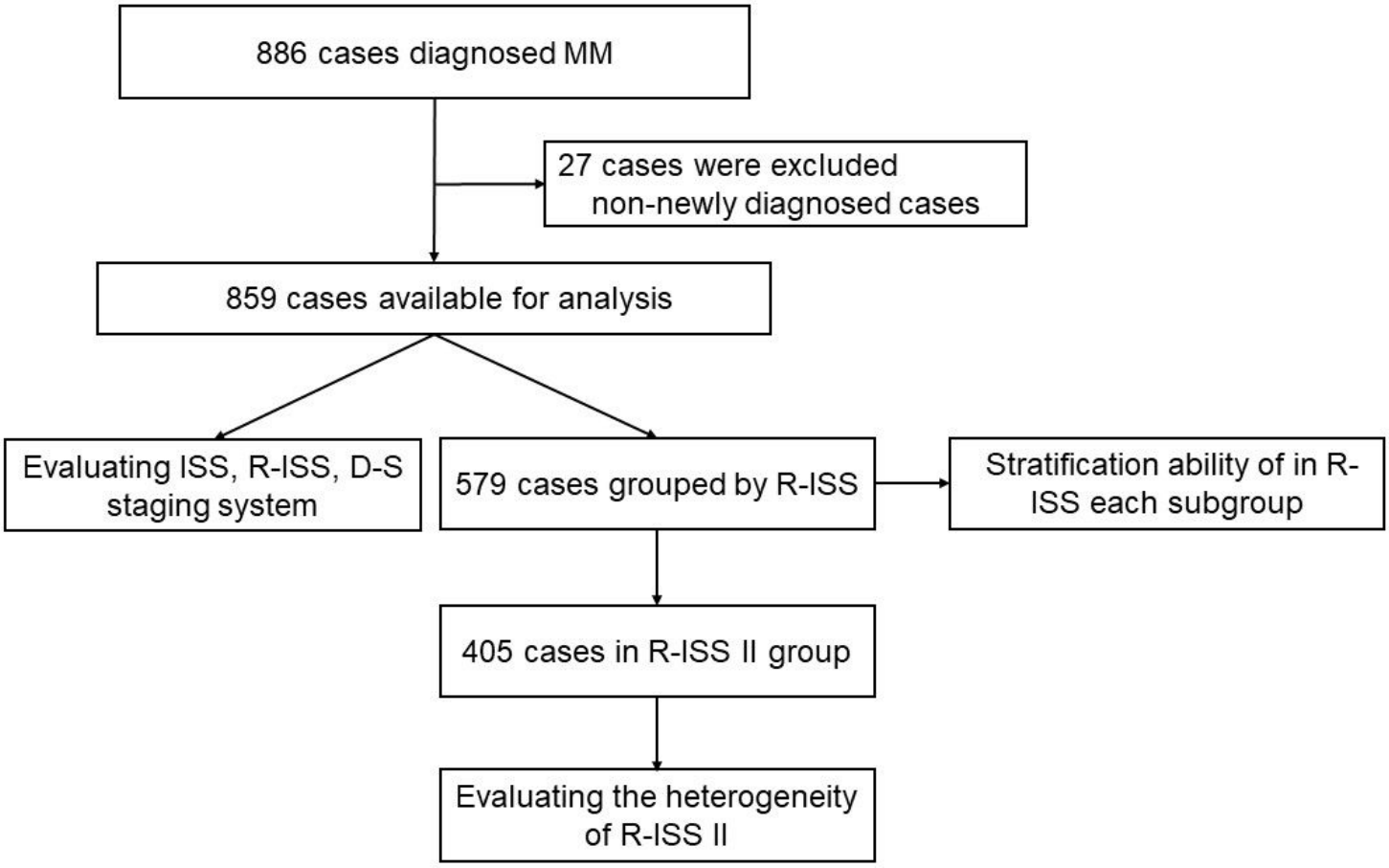

Figure 1

The flow chart of analysis in this study.

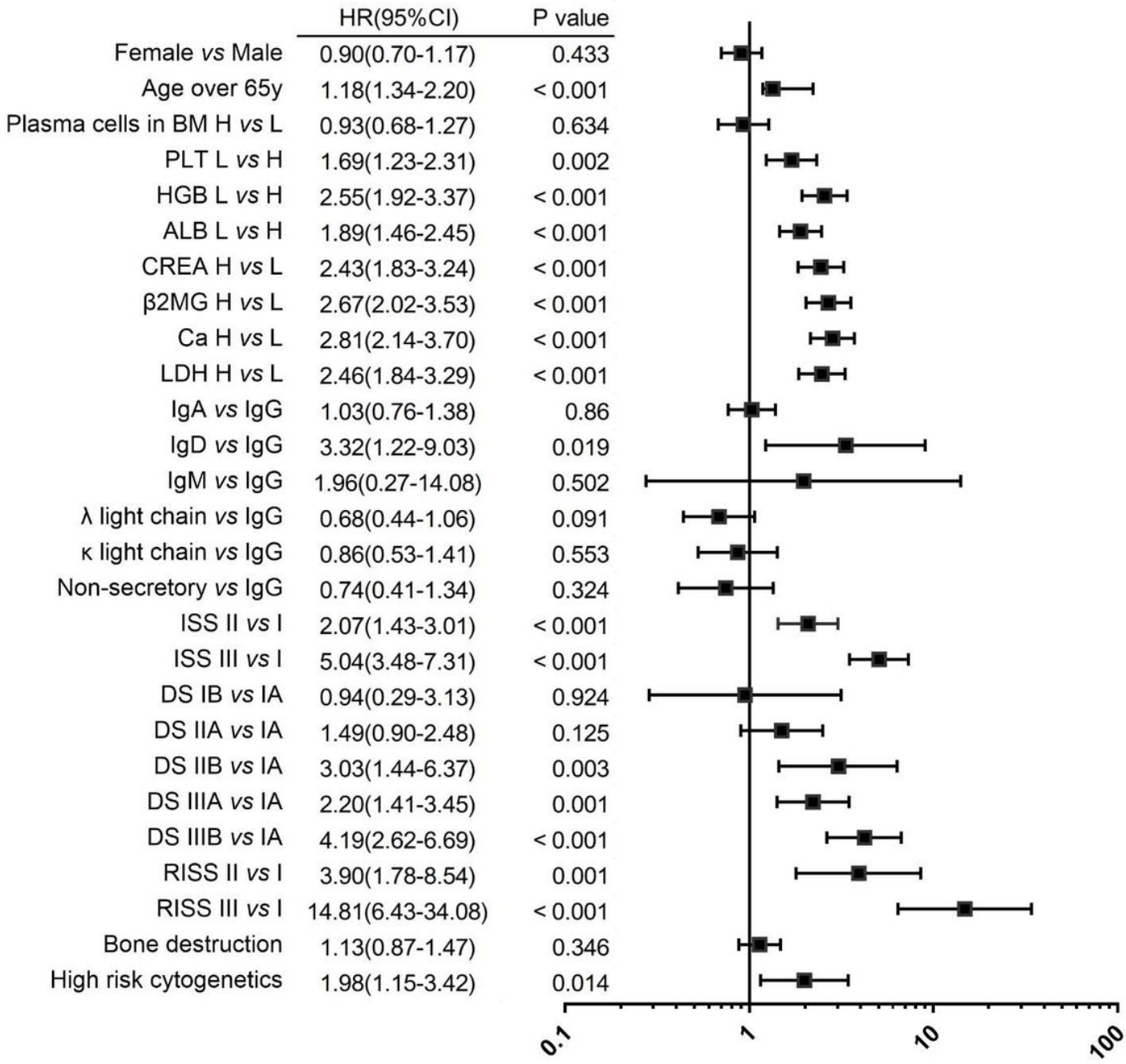

Figure 2

The risk of death about baseline factors using the univariable Cox analysis. CI, confidence interval. HR, Hazard ratios; L, Low; H, High; BM, bone marrow.

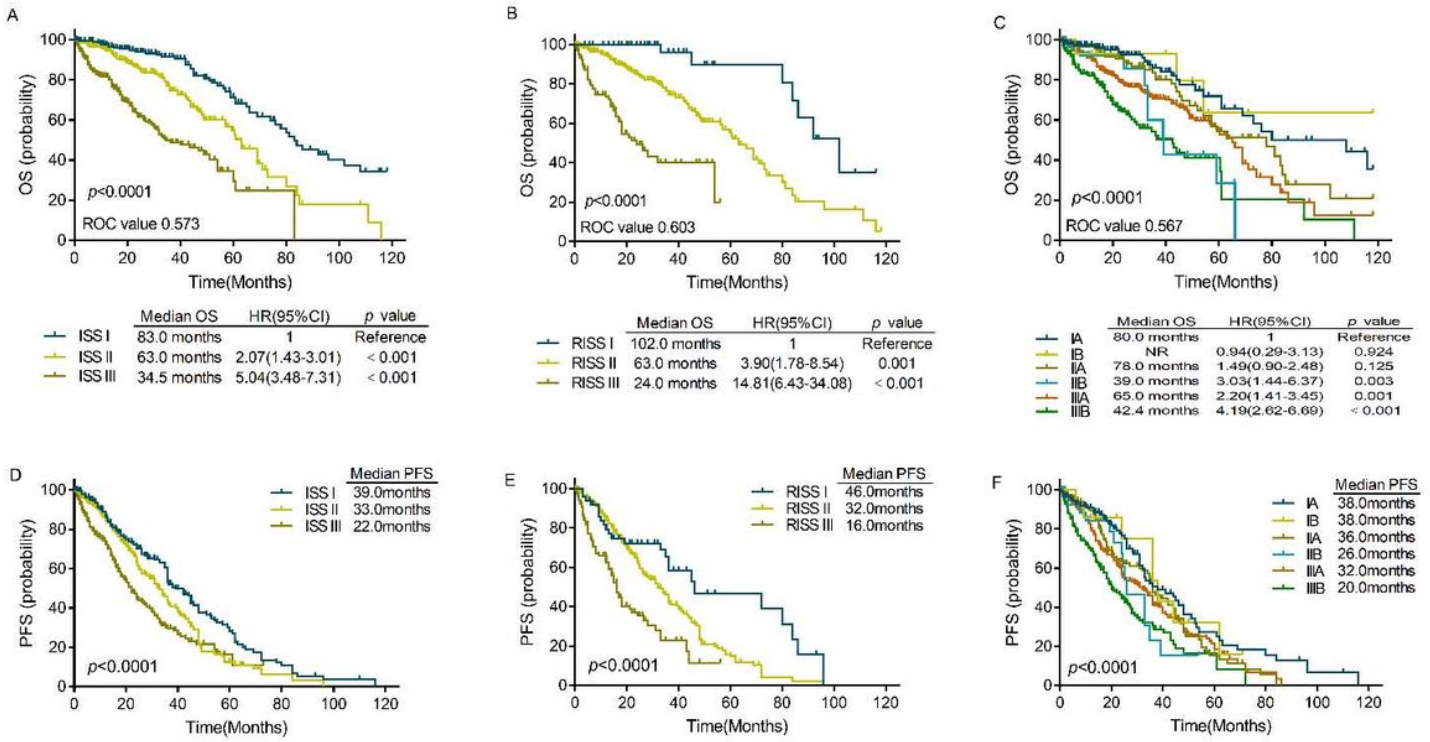

Figure 3

OS and PFS in patients with multiple myeloma stratified by existing staging system. OS in patients with multiple myeloma stratified by ISS (A), R-ISS (B) and DS staging system (C). PFS in patients with multiple myeloma stratified by ISS (D), R-ISS (E) and DS staging system (F). HR, hazard ratio; NR, not reached. OS, overall survival. PFS, Progression-free survival

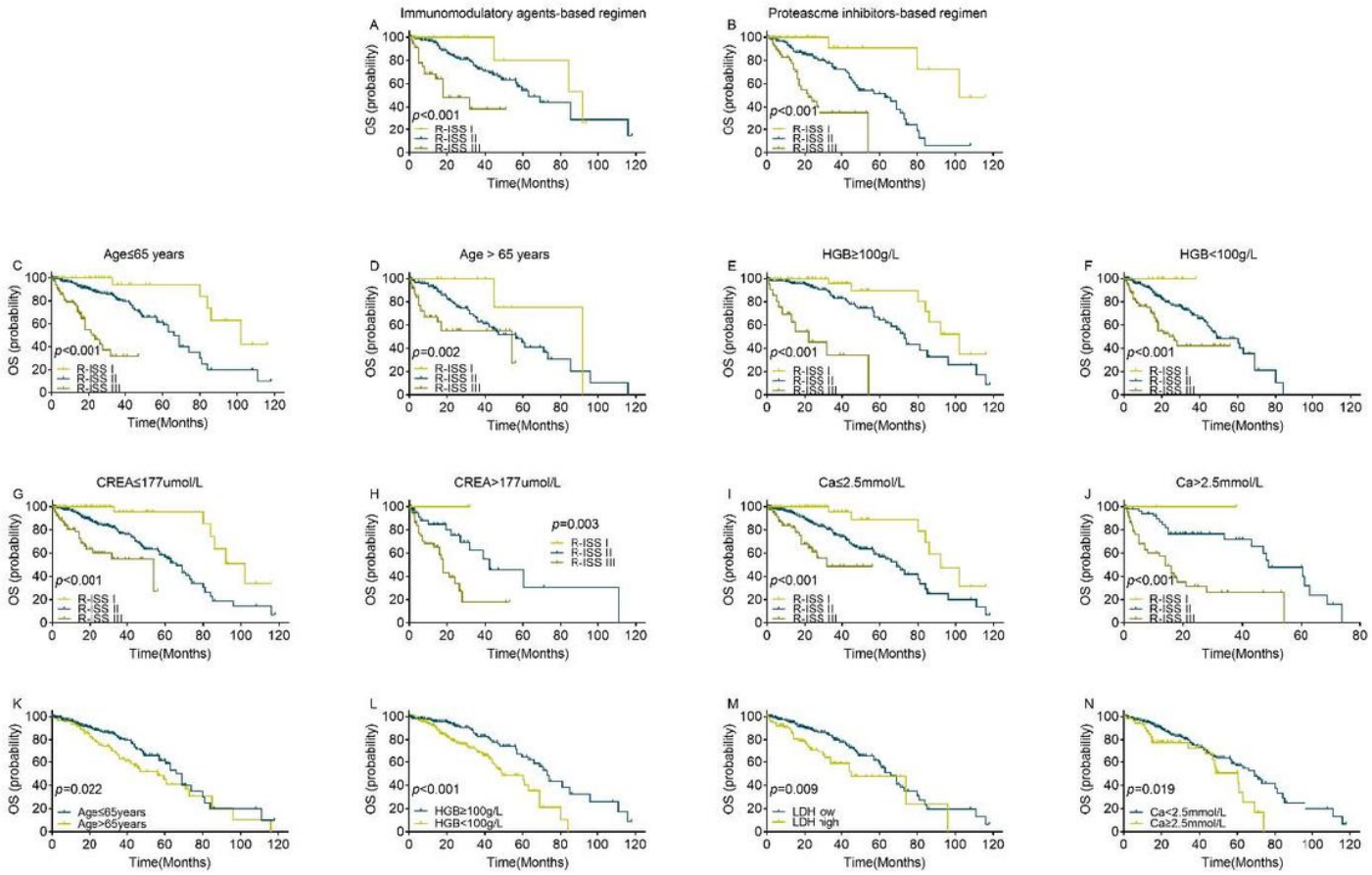

Figure 4

OS in patients with multiple myeloma stratified by R-ISS based on different subgroups, and OS in R-ISS II groups by different subgroups using K-M test. The OS in patients with multiple myeloma stratified by R-ISS in immunomodulatory agents-based regimen groups (A) and proteasome inhibitors-based regimen groups (B). The OS in patients with multiple myeloma stratified by R-ISS in age ≤ 65years (C) and age>65years (D), in HGB≥100g/L (E) and HGB<100g/L (F), in CREA≤177umol/L (G) and CREA>177umol/L (H), in Ca≤2.5mmol/L (I) and Ca>2.5mmol/L (J). OS in patients with multiple myeloma in R-ISS II groups by different subgroups of Age (K), HGB (L), LDH (M) and Ca (N). CREA, Creatinine; HGB, hemoglobin; OS, Overall Survival; R-ISS, Revised International Staging System