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ORIGINAL ARTICLE

Chronic kidney disease stage 5 as the prognostic complement of International Staging System for multiple myeloma

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Abstract

Background: Reversal of renal impairment (RI) in patients with multiple myeloma (MM) has been evaluated using the estimated glomerular filtration rate ($eGFR_{MDRD}$) formula developed by the Modification of Diet in Renal Disease study group. However, the prognostic impact of $eGFR_{MDRD}$ at diagnosis of MM is not well studied, particularly its use in conjunction with the International Staging System (ISS). *Methods:* Newly diagnosed patients with MM were enrolled between 1996 and 2007. Data on clinical features, laboratory tests, and overall survival were compared in terms of corresponding $eGFR_{MDRD}$. *Results:* A total of 387 patients with MM (median age, 71 yr) were enrolled. At diagnosis, 56% had ISS stage III disease; the median values of serum creatinine (SCr) and $eGFR_{MDRD}$ were 1.4 mg/dL and 38.2 mL/min/1.73 m^2, respectively. Thirty-four percent of patients had SCr of ≥2.0 mg/dL, and 81.2% had chronic kidney disease stages 3–5 (CKD 3–5). Higher CKD stages were significantly more common in men, older patients (≥65 yr), and those with Durie–Salmon and ISS stage III, light-chain diseases, anemia, thrombocytopenia, hypercalcemia, elevated serum β_2 microglobulin, or lactate dehydrogenase. In the Cox regression model, CKD 4–5 or CKD 5 alone was independently associated with poor survival. A diagnosis of CKD 5 was shown to be useful in identifying the subgroup of ISS-III patients at high risk – those with a median overall survival of 7.2 months. *Conclusions:* Our study demonstrates the prognostic impact of $eGFR_{MDRD}$ in patients with MM and CKD 5 as the ISS-independent surrogate predictor of poorest prognosis.

Key words chronic kidney disease; glomerular filtration rate; International Staging System; multiple myeloma; serum β_2 microglobulin

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The International Staging System (ISS), relying primarily on the 2 parameters of serum β_2 microglobulin ($S\beta_2M$) and serum albumin, is currently used to determine the prognosis of patients with multiple myeloma (MM) (1). As MM patients with renal impairment (RI) also usually have elevated $S\beta_2M$ and hypoalbuminemia, the prognostic impact of RI is thought to be properly represented in the ISS (1, 2). However, MM patients with severe RI are associated with early mortality (3–5) and are categorized as medical emergencies (6, 7). In the largest series of 107 MM patients with severe acute kidney injury [defined as a serum creatinine (SCr) level of ≥500 μM (5.66 mg/dL)] (8), the median overall survival (OS) of only 7–8 months did not improve across two decades. In addition, the OS was lower than that among patients with ISS-III (29 months in the original study) (1). Therefore, the ISS may have limitations in properly identifying the prognosis of MM patients with severe RI. Therefore, ISS may

require additional modification or complementary, RI-related parameters.

Recently, the International Working Group on Myeloma suggested evaluation of acute kidney injury in patients with MM using a set of criteria called RIFLE (risk, injury, failure, loss, and end-stage kidney disease) or AKIN (Acute Kidney Injury Network) (9). They also suggested evaluating RI in patients with MM who had a stabilized SCr level by using the estimated glomerular filtration rate (eGFR) formula (abbreviated as $eGFR_{MDRD}$ hereafter) developed by the Modification of Diet in Renal Disease (MDRD) Study Group (9). Under these recommendations, RI degree would then be staged according to the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (KDOQI) classification of chronic kidney disease (CKD) (10). The RIFLE/AKIN criteria cannot be easily applied for MM diagnosis (2). However, $eGFR_{MDRD}$ is relatively simple for clinical use and has been used to evaluate the reversal of RI following anti-myeloma treatment with novel agents (9). Because of the increased application of $eGFR_{MDRD}$, it would be clinically useful to know whether the $eGFR_{MDRD}$-rated RI recorded at MM diagnosis still has prognostic relevance.

In the recent analysis of patients with MM in Taiwan (11), they were relatively older, with a median age of 71 yr, and had the highest frequency of RI (34%, defined as an SCr of ≥2.0 mg/dL) at diagnosis (11) compared with other reports [which usually list a frequency of about 20% (1, 12–15)]. Taking advantage of the higher incidence of RI, the current study evaluated the prognostic value of $eGFR_{MDRD}$ and CKD stage at MM diagnosis and found that higher CKD stages still have prognostic relevance, independent of ISS.

Patients and methods

Patients

Patients newly diagnosed with MM between January 1996 and December 2007 at Taipei Veterans General Hospital were enrolled, as previously described (11). Two patients who had the unusual value of SCr at 0.1 mg/dL were excluded, because they were diagnosed before 2000 and the validation of the data was limited. Plasma cell dyscrasias were diagnosed based on commonly accepted criteria (16). Clinical features at diagnosis – age, gender, complete blood counts, blood biochemistry (including renal function), and histology and clinical stages according to the Durie–Salmon (DS) staging system (17) and ISS (1) – were recorded.

Before novel therapeutic agents became available in 2002, the major regimens of conventional chemotherapy for these conditions comprised melphalan and prednisolone (MP) and vincristine, adriamycin, and dexamethasone (VAD). High-dose therapy (HDT) and hematopoietic stem cell transplantation (HSCT) were usually administered to patients aged < 65 yr. Patients with relapsed or refractory myeloma received salvage therapy in the form of thalidomide (since 2002) or bortezomib (since 2007). Several bisphosphonates, such as clodronate, pamidronate, and zoledronic acid, became sequentially available for treatment as bone-protection agents beginning in the 1990s. Dialysis was usually administered only in response to uncontrolled conditions related to renal failure, including metabolic acidosis, hyperkalemia, and fluid overload.

In this study, eGFR was calculated using the modified MDRD formula: eGFR in milliliters per minute per 1.73 m^2 = $186 \times (SCr)^{-1.154} \times (age)^{-0.203}$ (×0.742, if women), in which SCr was the first value measured at diagnosis of myeloma. The degree of RI was described according to the definition of CKD stages as follows: stage 3 (abbreviated as CKD 3 hereafter), eGFR of 30–59 mL/min/1.73 m^2; CKD 4, eGFR of 15–29 mL/min/1.73 m^2; and CKD 5, eGFR of < 15 mL/min/1.73 m^2 or undergoing dialysis (10). Because of the limited availability of information on kidney damage, patients with an eGFR of ≥90 mL/min/1.73 m^2 (originally CKD 1) or eGFR of 60–89 mL/min/1.73 m^2 (originally CKD 2) were grouped together as CKD 1–2. We measured OS 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

Differences in patient and disease characteristics for those diagnosed at different CKD stages were investigated using Pearson's Chi-square test. We used the same cutoff level for excluding abnormal laboratory tests as in the original ISS study (1). We performed survival analysis using the Kaplan–Meier estimate, applying the log-rank test to compare OS rates among groups characterized by 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, USA).

Results

Clinical and laboratory features of patients with MM in relation to $eGFR_{MDRD}$ and CKD stages

For the 387 patients enrolled, the median age was 71 yr, with 69% of patients older than 65 yr (Table 1). The clinical stages included DS stage III (DS-III) in 72.6% of patients and ISS-III in 56% of patients. Sixty-seven (17.3%) patients had light-chain myeloma. At diagnosis,

Table 1 Clinical features and treatments of 387 Chinese patients with multiple myeloma in terms of chronic kidney disease (CKD) stages

Parameters/CKD (eGFR, mL/min/1.73 m^2)	Total (%)	CKD 1–2 (≧60) (%)[1]	CKD 3 (30–59) (%)[1]	CKD 4 (15–29) (%)[1]	CKG 5 (<15) (%)[1]	*P*-value
No. of patients (%)	387 (100)	73 (18.8)	165 (42.6)	68 (17.7)	81 (20.9)	–
eGFR[2] (mL/min/1.73 m^2), median (range)	38.2 (1.5–168.7)	73.7 (60.1–168.7)	42.7 (30.1–59.9)	22.9 (15.2–29.7)	8.6 (1.5–14.9)	<0.001[3]
SCr, median (mg/dL) (range)	1.4 (0.4–26.7)	0.84 (0.4–1.1)	1.3 (1.0–1.9)	2.2 (1.8–3.3)	5.1 (3.2–26.7)	<0.001[3]
≥2.0	132 (34.1)	0 (0)	2 (1.2)	53 (77.9)	77 (95.1)	<0.001
Calendar period 1996–2001	176 (45.5)	28 (38.4)	74 (44.8)	36 (52.9)	38 (46.9)	0.374
Gender, male	286 (73.9)	28 (38.4)	135 (81.8)	56 (82.4)	67 (82.7)	<0.001
Age, median (yr) (range)	71 (27–91)	62 (27–81)	72 (44–91)	71.5 (47–90)	71 (41–88)	<0.001[3]
Age ≥ 65	269 (69.5)	33 (45.2)	125 (75.8)	51 (75)	60 (74.1)	<0.001
Age ≥ 70	195 (50.4)	24 (32.9)	94 (57)	35 (51.5)	42 (51.9)	0.008
Stages – Durie–Salmon III	281 (72.6)	47 (64.4)	104 (63)	58 (85.3)	72 (88.9)	<0.001
Stages – ISS – III	197 of 352 (56)	14 of 66 (21.2)	64 of 156 (41)	53 of 60 (88.3)	66 of 70 (94.3)	<0.001
Light-chain myeloma	67 (17.3)	14 (19.2)	15 (9.1)	14 (20.6)	24 (29.6)	0.001
Serum albumin < 3.5 g/dL	215 of 385 (55.8)	36 (49.3)	92 of 164 (56.1)	41 of 67 (61.2)	46 (56.8)	0.557
Sβ_2M ≥ 3.5 mg/L	280 of 352 (79.5)	32 of 66 (48.5)	122 of 156 (78.2)	58 of 60 (96.7)	68 of 70 (97.1)	<0.001
Sβ_2M ≥ 5.5 mg/L	197 of 352 (56)	14 of 66 (21.2)	64 of 156 (41)	53 of 60 (88.3)	66 of 70 (94.3)	<0.001
Serum total calcium (corrected) > 11.5 mg/dL	69 of 385 (18)	4 (5.8)	11 of 164 (6.7)	22 of 67 (32.8)	32 (39.5)	<0.001
Serum LDH > normal value	155 of 385 (40.3)	26 (35.6)	52 of 164 (31.7)	31 (45.6)	46 of 80 (57.5)	0.001
WBC < 4000/μL	71 of 385 (18.4)	16 (21.9)	33 (20)	10 of 66 (15.2)	12 (14.8)	0.565
Hemoglobin < 10 g/dL	251 (64.9)	34 (46.6)	93 (56.4)	54 (79.4)	70 (86.4)	<0.001
Platelets < 130 000/μL	127 of 384 (33.1)	14 (19.2)	51 of 164 (31.1)	24 of 67 (35.8)	38 of 80 (47.5)	0.002
Thalidomide[4]	86 (22.2)	22 (30.1)	42 (25.5)	13 (19.1)	9 (11.1)	0.020
Bortezomib[4]	32 (8.3)	8 (25.0)	15 (9.1)	4 (5.9)	5 (6.2)	0.610
HDT and HSCT[4]	40 (10.3)	15 (20.5)	15 (9.1)	6 (8.8)	4 (4.9)	0.011
Bisphosphonate[4]	288 (74.4)	50 (68.5)	131 (79.4)	50 (73.5)	57 (70.4)	0.239

Abbreviations: refer to the text.

[1]% of each CKD subgroup.

[2]Based on the modified MDRD formula.

[3]Kruskal–Wallis test.

[4]Indicated treatments which were once given at last follow-up.

the median values of SCr and $eGFR_{MDRD}$ were 1.4 mg/dL (range, 0.4–26.7) and 38.2 mL/min/1.73 m^2 (range, 1.5–168.7), respectively. Thirty-four percent of patients had RI with SCr of ≥2.0 mg/dL, and 81.2% of patients had CKD stages 3–5, including 42.6% (n = 165) with CKD 3, 17.7% (n = 68) with CKD 4, and 20.9% (n = 81) with CKD 5, with median values for SCr (mg/dL) of 1.3 (1.0–1.9), 2.2 (1.8–3.3), and 5.1 (3.2–26.7), respectively.

As shown, higher CKD stages were significantly more common in men, older patients (older than either 65 or 70 yr), and those with DS-III, ISS-III, light-chain myeloma, elevated Sβ_2M (at either ≥3.5 mg/L or ≥5.5 mg/L), hypercalcemia [serum total calcium (corrected), >11.5 mg/dL], elevated serum lactate dehydrogenase (LDH), anemia, and thrombocytopenia. On the other hand, there was no significant association of higher CKD stages with hypoalbuminemia, leukopenia, or earlier calendar period (1996–2001) at diagnosis. In terms of treatment, more patients with RI at lower CKD stages received thalidomide and HDT/HSCT at the last follow-up (Table 1).

Prognostic value of CKD stages at diagnosis of MM

The prognostic impact of different CKD stages was examined. The results showed a correlation with OS, with the median OS [95% confidence interval (CI)] for CKD 1–2 vs. 3 vs. 4 vs. 5 being 35.6 (23.8–47.3) vs. 29.4 (23.1–35.7) vs. 14.7 (8.9–20.6) vs. 7.2 (4.4–10.0) months, respectively (P < 0.001; Fig. 1). In addition, the univariate analysis, which included all patients, showed that several scales of RI were associated with a lower OS – including SCr of ≥2 mg/dL [hazard ratio (HR) = 2.159; 95% CI = 1.692–2.756, P < 0.001], CKD 3–5 (HR = 1.876; 95% CI = 1.354–2.600, P < 0.001), CKD 4–5 (HR = 2.217; 95% CI = 1.744–2.818, P < 0.001), and CKD 5 (HR = 2.645; 95% CI = 2.007–3.484, P < 0.001) – as were other factors such as earlier calendar period (1996–2001) at diagnosis (HR = 1.436; 95% CI = 1.133–1.819, P = 0.003), older age (≧65 yr; HR = 1.853; 95% CI = 1.418–2.423, P < 0.001), DS–III (HR = 1.898; 95% CI = 1.430–2.521, P < 0.001), ISS–III (HR = 2.104; 95% CI = 1.628–2.719, P < 0.001), hypoalbuminemia

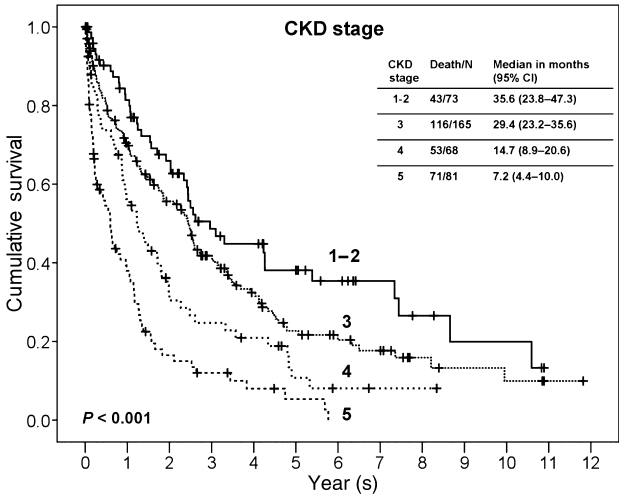

Figure 1 The curve of the overall survival of 387 Chinese patients with multiple myeloma in terms of RI classified according to the CKD stages.

(HR = 1.418; 95% CI = 1.118–1.798, $P = 0.004$), elevated Sβ_2M at 3.5 mg/L (HR = 2.78; 95% CI = 1.968–3.928, $P < 0.001$), hypercalcemia (HR = 2.092; 95% CI = 1.567–2.793, $P < 0.001$), elevated LDH (HR = 1.366; 95% CI = 1.078–1.731, $P = 0.01$), anemia (HR = 1.723; 95% CI = 1.334–2.224, $P < 0.001$), and thrombocytopenia (HR = 1.294; 95% CI = 1.012–1.654, $P = 0.04$).

To find additional factors (aside from DS) independently influencing the OS, we used the Cox regression model on factors with $P < 0.1$ in the univariate analysis. To compare the relative contribution of ISS and RI, these models used different cutoff values or severity of Sβ_2M (either ≥3.5 or ≥5.5 mg/L), ISS, and RI (SCr ≥ 2 mg/dL, CKD 3–5, CKD 4–5, or CKD 5; Table 2). In these models, four factors were consistently and independently associated with a lower OS: old age (≥65 yr), earlier calendar period at diagnosis, hypercalcemia and elevated Sβ_2M (either ≥3.5 mg/L or ≥5.5 mg/L) or ISS. The prognostic impact of RI varies and depends on the categorical scales used. As shown in Table 2, the categorical factor CKD 3–5 was not significant in these models, but CKD 4–5 and CKD 5 were independently associated with a lower OS, especially the latter.

CKD 5 as a complement to ISS

As CKD 4–5 or CKD 5 were independently associated with a lower OS, the CKD stages of patients with ISS-III ($n = 197$) were examined and found to be evenly distributed from CKD 3 to CKD 5, including 32.5% ($n = 64$), 26.9% ($n = 53$), and 33.5% ($n = 66$) in CKD 3, 4, and 5, respectively. To further evaluate the prognostic impact of Sβ_2M and RI in our patients, we scored them according to the criteria of ISS and CKD stages, respectively (Table 3), and compared the median OS of patients with the sum of scores at different values for both factors. As shown in Table 3 and Fig. 2A, patients were stratified into four risk groups according to OS. In comparison, the median OS of patients in the low, intermediate-1 (INT-1), and intermediate-2 (INT-2) risk groups (50.8, 29.4, and 15.0 months, respectively; Fig. 2A) was comparable to that of patients with ISS I–III (51.2, 27.2, and 12.9 months, respectively). Patients in the high-risk group (with Sβ_2M of ≥5.5 mg/L and CKD 5 at diagnosis) had the poorest prognosis, with a median OS of 7.2 months (95% CI = 4.9–9.5).

Therefore, using the original ISS criteria and the high-risk group described previously, we modified the ISS into four stages (modified ISS), in which stage IV indicates patients with Sβ_2M of ≥5.5 mg/L and CKD 5, and stage III included only those in the original ISS-III who had an RI less than CKD 5. Comparing to those with the original ISS-III [median SCr: 2.2 mg/dL (range, 0.6–26.7); and median $eGFR_{MDRD}$: 23.8 mL/min/1.73 m^2 (range, 1.5–102.5)], the median values of SCr and $eGFR_{MDRD}$ were 1.6 mg/dL (range, 0.6–3.3) and

Table 2 The hazards of RI rated as different scales in the Cox regression models containing different cutoff values of Sβ_2M or ISS

Cox regression models[1]	Hazard ratios of RI (95% CI; *P*-values)			
	SCr ≥ 2.0 mg/dL (vs. SCr < 2.0 mg/dL)	CKD 3–5 (vs. CKD 1–2)	CKD 4–5 (vs. CKD 1–3)	CKD 5 (vs. CKD 1–4)
Sβ_2M ≥ 3.5 mg/L	1.515 (1.122–2.044; $P = 0.007$)	1.099 (0.744–1.625; $P = 0.634$)	1.519 (1.126–2.048; $P = 0.006$)	2.133 (1.535–2.964; $P < 0.001$)
Sβ_2M ≥ 5.5 mg/L	1.397 (1.012–1.928; $P = 0.042$)	1.242 (0.845–1.824; $P = 0.270$)	1.404 (1.007–1.956; $P = 0.045$)	1.944 (1.386–2.726; $P < 0.001$)
ISS (categorical)	1.413 (1.025–1.948; $P = 0.035$)	1.130 (0.766–1.666; $P = 0.538$)	1.411 (1.016–1.959; $P = 0.040$)	1.983 (1.414–2.782; $P < 0.001$)

CKD, chronic kidney disease; ISS, International Staging System; RI, renal impairment.
[1]Factors also in the models, refer to the text.

Table 3 The scoring system of multiple myeloma based on Sβ_2M and chronic kidney disease (CKD) stages at diagnosis and resulting risk groups in 352 patients

Prognostic factors	Score 1	2	3	4	5
Sβ_2M (mg/L)	<3.5	≥3.5 and <5.5	≥5.5	–	–
CKD stage	–	1 and 2	3	4	5

Risk group	Sums of scores	No. of patients (%)	Median OS (95% CI) (months)	Median SCr (range) (mg/dL)	Median eGFR (range) (mL/min/1.73 m^2)
Low	3, 4	86 (22)	50.8 (40.1–61.5)	0.9 (0.4–1.7)	64.6 (31.1–168.7)
INT-1	5	74 (19)	29.4 (22.4–36.4)	1.2 (0.6–2.2)	46.6 (22.7–102.5)
INT-2	6, 7	126 (32)	15.0 (8.9–21.2)	1.8 (1.0–5.8)	30.2 (7.6–59.3)
High	8	66 (17)	7.2 (4.9–9.5)	5.1 (3.3–26.7)	9.0 (1.5–14.3)

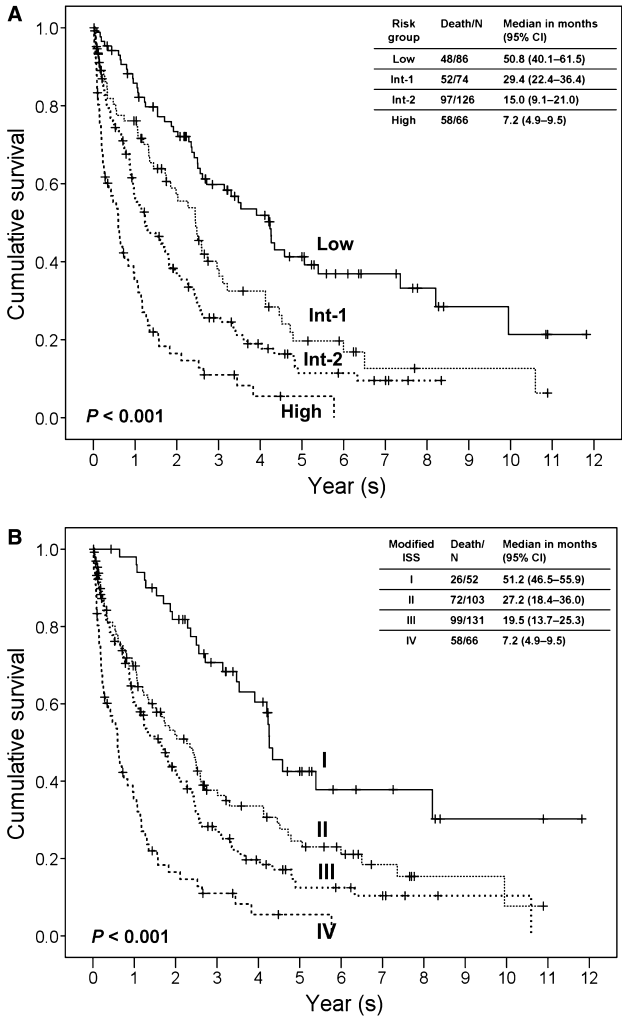

Figure 2 The curve of the overall survival of 352 Chinese patients with multiple myeloma according to risk groups, based on (A) Sβ_2M and CKD stages at diagnosis and (B) according to the modified ISS.

34.6 mL/min/1.73 m^2 (range, 15.2–102.5) for patients with modified ISS-III, and 5.1 mg/dL (range, 3.3–26.7) and 9.0 mL/min/1.73 m^2 (range, 1.5–14.3) for those with modified ISS-IV. As shown in Fig. 2B, there was a significant difference in OS among patients in these four stages of modified ISS. As there was an improvement in OS in our patients across these two calendar periods (1996–2001 and 2002–2007) (11), we also compared the OS of patients with modified ISS-IV in these two periods. It showed no significant improvement, with a median OS of 7.1 months (95% CI, 4.1–10.1) and 7.2 months (95% CI, 3.1–11.2) in the first and second calendar periods, respectively ($P = 0.264$).

Discussion

Our findings provide evidence supporting the value of $eGFR_{MDRD}$-based CKD stages at diagnosis of MM in relation to clinical and laboratory features and prognosis; furthermore, these findings identify CKD 5 as a potential complement to ISS-III for identifying the poorest prognosis (1). As shown in Table 1, $eGFR_{MDRD}$-based CKD stages provided more discriminative information than SCr regarding clinical and laboratory features and prognosis (Table 1), reinforcing the findings of recent studies (2, 18). For patients with MM, physicians have relied solely on an elevated SCr level to diagnose RI, to decide when to initiate treatment, and even as the component of DS used to determine the prognosis (17, 19). However, SCr may vary with other factors such as age, sex, and muscle mass (9). As shown in our study, there was significant variation of SCr in patients with MM, especially for ISS-III [median SCr: 2.2 mg/dL (range, 0.6–26.7)]. Several studies have shown the correlation of GFR-at-diagnosis to the prognosis of patients with MM using different methods, including chromium-51-labeled ethylenediaminetetraacetic acid (^{51}Cr EDTA) (20), cystatin C (21, 22), and 24-h urinary creatinine clearance (23). The MDRD formula for evaluating creatinine clearance is relatively simple but has only been validated in patients with CKD. As $eGFR_{MDRD}$ has been used to evaluate the reversal of RI following

treatment with novel agents (9), our findings, and those by Dimopoulos *et al.* (2), provide additional evidence for the prognostic relevance of $eGFR_{MDRD}$ at MM diagnosis. These findings indicate that $eGFR_{MDRD}$ has the potential benefit of helping to identify patients at risk – not that it would replace the potential usefulness of the recommended RIFLE or AKIN criteria (9). It is not unusual for patients with MM to experience rapid deterioration of renal function within days. On the other hand, although the $eGFR_{MDRD}$ formula includes age as a factor, older age ($\geqq$65 yr) remained an independent prognostic factor whenever $eGFR_{MDRD}$-based CKD stage was included in the Cox regression model (Table 2).

In addition, the criteria for identifying patients with the poorest prognosis [i.e., CKD 5 in patients with ISS-III (i.e., $S\beta_2M \geq 5.5$ mg/L)] are relatively simple and easily applicable in the management of this subgroup of patients with MM. These results are significant for several reasons. First, the proportion of our patients with RI at diagnosis did not decline across the study period (Table 1). The awareness provided by early MM diagnosis may be countered by progressive aging in the general population and by increasing age of diagnosis. Second, $eGFR_{MDRD}$-based CKD 5 might provide clinicians a simple and fast alert to identify and treat patients at risk for early mortality as soon as possible. This is especially relevant whenever novel agents and new renal replacement or rescue modalities are immediately available (9, 24–28) and whenever an ideal model to identify prognostic factors associated with early mortality or extremely poor prognosis is not immediately available (1, 5, 29, 30). Incidentally, the median OS and SCr at diagnosis (median SCr: 5.1 mg/dL) of our MM patients with modified ISS-IV (Table 3 and Fig. 2B) were comparable with those of 107 MM patients with severe acute kidney injury [SCr $\geq$ 500 μM (5.66 mg/dL)] (8). In addition, the survival of patients in both studies failed to improve across the study periods (12 and 20 yr (8), respectively).

Our findings may show additional prognostic value of RI, which should be tested in larger studies, for example the original ISS database (1) by using the data to calculate the CKD stage. A recent analysis of 1516 Greek patients by Dimopoulos *et al.* (2) suggested that ISS remains unaffected by the degree of RI, even in patients with ISS-III. Although the number of patients was relatively small in our and several previous reports (18, 23), these studies suggest that RI remained prognostic even in ISS. In fact, in the study by Dimopoulos *et al.*, CKD 3–5 has marginal significance ($P = 0.054$) in older patients (age, >60 yr), but the prognostic impact of CKD 4–5 or CKD 5 alone was not shown (2). In comparison with the patients studied by Dimopoulos *et al.* (2), our patients were relatively older (median age, 71 vs. 66 yr) and had a higher rate of RI (defined as SCr $\geq$ 2.0 mg/dL; 34.1% vs. 20.5%) and ISS-III (56% vs. 33%) at diagnosis. In addition, more of the patients studied by Dimopoulos *et al.* (12) might have received front-line treatments with novel agents. The median level of $eGFR_{MDRD}$ in our patients was relatively lower (38.2 vs. 65 mL/min/1.73 m^2), and the median OS in ISS-III was lower (13.4 vs. 25 months). Patients with CKD 4 and 5 showed a difference in OS (15 and 7.2 months, respectively) in our study but not in that by Dimopoulos *et al.* (25 and 21 months). It is reasonable to speculate that severe RI still affects ISS, especially in the elderly.

Considering CKD is prevalent in the elderly of Taiwan (31) with the highest prevalence of end-stage renal diseases (ESRD) in the world (32), it is reasonably speculated that the prognosis of our MM patients with RI at diagnosis may be partially contributed by pre-existing CKD, thus weakening the importance of our findings. As described (2), this confounding effect is not easily overcome except for the availability of the information including renal function before diagnosis of myeloma, the course of renal function over a time period, or even with renal biopsies. Dimopoulos *et al.* used the feature measurable Bence-Jones proteinuria to identify those patients with MM whose RI at diagnosis was probably associated with myeloma. Of them, CKD 3–5 had marginal significance in patients >65 yr (2). The alternate way is to examine the reversal rate of RI in our patients. Using the definitions including (1) the fall of an initially elevated SCr concentration to the reference range, i.e., 1.5 mg/dL (19, 24), or (2) a decrease in SCr of at least 50% when the fall of SCr remained above 1.5 mg/dL in patients that did not undergo dialysis (33), there was a 47.5% of reversal rate in our 101 MM patients with SCr $\geqq$ 2.0 mg/dL between 1999 and 2007, which was not inferior to those previously reported (manuscript in preparation) (4, 19). On the other hand, as elderly patients usually have comorbidities, including CKD, diabetes and hypertension, the higher prevalence of RI at diagnosis for MM in ours and elderly patients with MM from other reports may represent a real and unavoidable condition in a progressively aging population. Therefore, the prognostic impact of RI at diagnosis for MM cannot be overlooked, even when using ISS. The application of this novel, risk-grouping system based on CKD and $S\beta_2M$ requires additional studies for validation, especially among the elderly.

Although more than 80% of our patients had an RI of CKD 3–5, most did not receive the currently recommended front-line treatments with novel agents and renal replacement therapy (9, 26, 34). Significantly, based on the classification of CKD stages, we can properly identify patients with MM who require aggressive and timely treatments with novel agents and modalities of renal rescue to treat their RI.

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