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RESEARCH ARTICLE

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Severe renal impairment as an adverse prognostic factor for survival in newly diagnosed multiple myeloma patients

Xuduan Chen[1] | Xiaofeng Luo[2] | Yanping Zu[3] | Hajji Ally Issa[2] | Linlin Li[1] | Hong Ye[1] | Ting Yang[2] | Jianda Hu[2] | Lixin Wei[1]

[1]Department of Nephrology, Fujian Medical University Union Hospital, Fuzhou, China

[2]Fujian Institute of Hematology, Fujian Provincial Key Laboratory on Hematology, Fujian Medical University Union Hospital, Fuzhou, China

[3]Department of Nephrology, Fujian Provincial Hospital Jinshan Branch, Fuzhou, China

Correspondence
Lixin Wei, Department of Nephrology, Fujian Medical University Union Hospital, Fuzhou, Fujian, China.
Email: lixinwei66@126.com

Jianda Hu, Fujian Institute of Hematology, Fujian Provincial Key Laboratory on Hematology, Fujian Medical University Union Hospital, Fuzhou, Fujian, China.
Email: drjiandahu@163.com

Ting Yang, Fujian Institute of Hematology, Fujian Provincial Key Laboratory on Hematology, Fujian Medical University Union Hospital, Fuzhou, Fujian, China.
Email: yang.hopeting@gmail.com

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Abstract

Background: Renal impairment (RI) is associated with poor survival in newly diagnosed multiple myeloma (MM) patients. Renal function recovery has been one of the main therapeutic goals in those patients.

Methods: The records from 393 newly diagnosed MM patients in our hospital between January 2012 and December 2016 were retrospectively analyzed. RI was defined as an eGFR < 40 mL/min according to the novel IMWG criteria. RI patients were categorized based on their renal function at diagnosis: severe RI: eGFR < 30 mL/min, and mild RI: 30 mL/min ≤ eGFR <40 mL/min. We explored whether RI, and particularly severe RI, was an adverse prognostic factor for survival, and investigated the impact of renal function recovery on survival.

Results: Severe RI, hemoglobin <100 g/L, LDH ≥ 245 U/L, hyperuricemia, 1q21 amplification, and lack of novel agent treatment were associated with decreased overall survival (OS). Severe RI patients with renal response had a median OS of 27 months compared with 18 months for those patients without renal response ($P = .030$), but their median OS was still significantly lower than that for patients without severe RI, which was 51 months. In severe RI patients, the overall renal response rate in bortezomib-based regimens was significantly higher than that in nonbortezomib-based regimens.

Conclusion: Our results suggest that severe RI is an adverse prognostic factor for survival in newly diagnosed MM patients, restoration of renal function may improve survival, and bortezomib-based regimens may be the preferred treatment in patients with severe RI.

KEYWORDS

bortezomib, multiple myeloma, overall survival, renal impairment, renal response

1 | INTRODUCTION

Multiple myeloma (MM) is a malignancy that is characterized by abnormal proliferation of plasma cells and production of a monoclonal immunoglobulin (also known as M protein).[1] There were approximately 160 thousand new MM cases and 106 thousand MM-related deaths worldwide in 2018.[2] Renal impairment (RI) is a common and serious complication in newly diagnosed MM patients, affecting up to 40% of those patients, with 2%-4% of those requiring dialysis treatment.[3,4] RI in MM patients is due to various causes such as cast nephropathy, light chain deposition disease, amyloidosis, hypercalcemia, and other factors, with historically a very poor outcome.[5,6]

Despite the fact that the wide use of novel therapies, such as proteasome inhibitors and immunomodulators, have yielded to significant improvements in outcome of MM patients,[1] RI, and particularly severe RI, is still a challenging problem in newly diagnosed MM patients, associated with high risk of early death and poor prognosis.[3,7-10] More recently, the International Myeloma Working Group (IMWG) criteria recommended that RI in MM patients was defined as a creatinine clearance (CrCl) <40 mL/min, and estimated glomerular filtration rate (eGFR) as assessed by the Modification of Diet in Renal Disease (MDRD) formula could be used for evaluation of CrCl. Therefore, eGFR <40 mL/min can be utilized to fulfill the RI criteria of MM.[5,11] Additionally, severe RI defined as an eGFR <30 mL/min has been used to analyze the outcomes of MM patients in several studies,[7,8,12] but the RI definition from the novel IMWG criteria was not used simultaneously in those studies. In the present study, we applied the above RI and severe RI definitions together to explore whether RI, and particularly severe RI, was an adverse prognostic factor for survival and whether restoration of renal function can improve outcomes in newly diagnosed MM patients.

2 | PATIENTS AND METHODS

2.1 | Patient characteristics

The charts from 393 newly diagnosed MM patients between January 1, 2012 and December 31, 2016 in our hospital were retrospectively reviewed. A diagnosis of MM was made if the patient fulfilled the IMWG criteria.[11] Patients with smoldering myeloma, solitary plasmacytoma, and primary plasma cell leukemia were excluded from the study. Multiple baseline clinical and laboratory variables were recorded, such as age, sex, hemoglobin, serum creatinine (sCr), β_2 microglobulin, albumin, uric acid and lactate dehydrogenase (LDH), serum calcium corrected by albumin, serum monoclonal protein spike, bone marrow plasma cell percentage, molecular cytogenetics status by fluorescent in situ hybridization (FISH) (The probes were as follows: GLP RB1, GLP 1q21, GLP P53, GLP D13S319, GLP IGH), and MM stage based on the International Staging System (ISS) classification.[13] According to the IMWG criteria, anemia was defined as levels of hemoglobin <100 g/L, and hypercalcemia was defined as levels of serum calcium >2.75 mmol/L.[5] Serum β_2 microglobulin was classified into three stages, that is, <3.5 mg/L, 3.5-5.5 mg/L, and >5.5 mg/L, based on the ISS classification. Hyperuricemia was defined as levels of serum uric acid ≥430 μmol/L. Levels ≥ 245 U/L for LDH were considered elevated. Early mortality was defined as death within 2 months of diagnosis. Overall survival (OS) was calculated from the day of diagnosis until death or the final follow-up date, whichever occurred first.

The research project was approved by the University Ethics Committee and has been performed in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki and its later amendments.

2.2 | Diagnostic criteria of RI

Renal impairment in newly diagnosed MM patients was defined as an eGFR <40 mL/min according to the novel IMWG criteria.[5] For further analyses in the present study, RI patients were categorized based on their renal function at diagnosis: severe RI group: eGFR < 30 mL/min, and mild RI group: 30 mL/min ≤ eGFR <40 mL/min. The eGFR was calculated by the MDRD equation using the simplified four-variable MDRD formula: $eGFR = 175 \times (sCr)^{-1.154} \times (\text{age in years})^{-0.203} \times 0.742$ (if female) × 1.212 (if patient is black).[4]

2.3 | Treatment regimens

The treatment regimens were recorded as supportive treatment alone, conventional chemotherapy (containing various combinations of vincristine, doxorubicin, dexamethasone, cyclophosphamide, etoposide, cisplatin, and melphalan), novel agent (proteasome inhibitors including bortezomib and carfilzomib, and/or immunomodulators including thalidomide and lenalidomide)-based regimens, and novel agent-based regimens followed by autologous stem cell transplantation (ASCT).

2.4 | Renal response criteria

Renal response was evaluated according to the IMWG criteria for the definition of renal response to therapy.[5] Complete response (CR_{renal}) was defined as a sustained increase in baseline eGFR to ≥60 mL/min (lasting for ≥ 2 months). Partial response (PR_{renal}) was defined as a sustained increase of eGFR from a baseline eGFR of <15 mL/min to 30-59 mL/min, and minor response (MR_{renal}) was defined as a sustained increase in eGFR from <15 mL/min to 15-29 mL/min or depending on baseline eGFR, from 15-29 mL/min to 30-59 mL/min. No response (NR_{renal}) was defined as failure to meet any of the above mentioned renal response criteria. Early death was defined as death

TABLE 1 Comparison of clinical characteristics in MM patients with RI and non-RI

Clinical characteristics	All patients (n = 393)	RI (n = 121)	non-RI (n = 272)	*P*-value
Age (years), median (range)	60 (24-85)	61 (37-85)	60 (24-85)	.170
Sex (male), (N (%))	221 (56.2)	65 (53.7)	156 (57.4)	.503
Hemoglobin (g/L), median (IQR)	83.0 (66.0-105.5)	71.0 (62.0-87.0)	92.0 (71.0-111.0)	<.001
Albumin (g/L), median (IQR)	30.0 (25.0-36.7)	28.2 (23.2-36.3)	30.8 (25.6-37.3)	.026
Uric acid (μmol/L), median (IQR)	428.5 (377.0-551.0)	569.0 (465.5-688.5)	380.0 (312.0-478.0)	<.001
LDH (U/L), median (IQR)	164.0 (128.0-212.0)	179.5 (135.3-238.5)	159.0 (125.0-201.0)	.003
Serum corrected calcium (mmol/L), median (IQR)	2.5 (2.4-2.7)	2.6 (2.4-3.1)	2.4 (2.3-2.6)	<.001
Serum creatinine(μmol/L), median (IQR)	87.0 (65.0-176.0)	293.0 (184.5-568.0)	72.0 (60.0-89.0)	<.001
eGFR mL/min, median (IQR)	70.7 (31.4-93.3)	16.3 (7.7-28.5)	86.0 (68.3-99.5)	<.001
M Proteins types				
IgG (N [%])	211 (53.7)	52 (43.0)	159 (58.5)	.004
IgA (N [%])	100 (25.5)	33 (27.3)	67 (24.6)	.579
IgM (N [%])	3 (0.8)	0 (0)	3 (1.1)	
Light chain only (N [%])	75 (19.1)	36 (29.8)	39 (14.3)	<.001
Biclonal (N [%])	1 (0.3)	0 (0)	1 (0.4)	
Unknown (N [%])	3 (0.8)	0 (0)	3 (1.1)	
Serum β_2 microglobulin (mg/L), median (IQR)	4.0 (2.5-8.6)	10.0 (5.0-10.0)	3.1 (2.0-5.0)	<.001
Plasma cells (%), median (IQR)	30.0 (16.0-52.1)	35.0 (20.3-62.8)	27.0 (13.0-49.8)	.003
ISS stage (N [%]) (378 pts) <.001				
I	59 (15.6)	0 (0)	59 (22.1)	
II	210 (55.6)	52 (46.8)	158 (59.2)	
III	109 (28.8)	59 (53.2)	50 (18.7)	
FISH detection (249 pts)				
RB1 deletion (N [%])	83 (33.3)	32 (47.1)	51 (28.2)	.005
1q21 amplification (N [%])	90 (36.1)	26 (38.2)	64 (35.4)	.674
P53 deletion (N [%])	38 (15.3)	17 (25.0)	21 (11.6)	.009
13q14.3 deletion (N [%])	67 (26.9)	25 (36.8)	42 (23.2)	.032
IgH rearrangement (N [%])	83 (33.3)	25 (36.8)	58 (32.0)	.481
Requiring dialysis (N [%])	20 (5.1)	20 (16.5)	0 (0)	<.001
Treatment regimens (N [%]) .320				
Supportive treatment alone	16 (4.1)	7 (5.8)	9 (3.3)	
Conventional chemotherapy	65 (16.5)	20 (16.5)	45 (16.5)	
Novel agent-based regimens	276 (70.2)	87 (71.9)	189 (69.5)	
Novel agent-based regimens followed by ASCT	36 (9.2)	7 (5.8)	29 (10.7)	
Early mortality	40 (10.2)	28 (23.1)	12 (4.4)	<.001

Abbreviations: ASCT, autologous stem cell transplantation; eGFR, estimated glomerular filtration rate; FISH, fluorescent in situ hybridization; IQR, interquartile range; ISS, international staging system; LDH, lactate dehydrogenase; pts, patients; RI, renal impairment.

within 2 months of diagnosis, so renal response was not evaluated in these patients.

2.5 | Statistical methods

SPSS (version 21.0, SPSS Inc.) software was used to perform the statistical analysis. Descriptive statistics of continuous variables were presented as median and interquartile range (IQR). All categorical parameters were summarized as proportions. The Mann-Whitney *U* test was used for continuous variables. The statistical significance of differences in the measured variables between subgroups was tested with the Chi-square test or the Fisher's exact test, where appropriate, for categorical analysis. Cox proportional hazard analysis was used to identify factors that were prognostic for OS. Survival curves were constructed according to

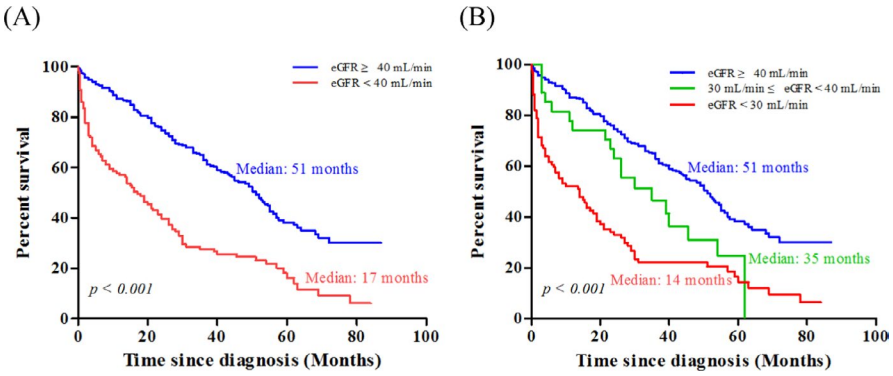

FIGURE 1 A, Kaplan-Meier plot comparing overall survival between patients with non-RI (eGFR ≥ 40 mL/min) and RI (eGFR < 40 mL/min). B, Kaplan-Meier plot comparing overall survival between patients with non-RI (eGFR ≥ 40 mL/min), mild RI (30 mL/min ≤ eGFR <40 mL/min), and severe RI (eGFR < 30 mL/min)

the Kaplan-Meier method, and the curves were compared using log-rank test.

3 | RESULTS

3.1 | Patient characteristics

Data from 393 newly diagnosed MM patients were included in the present study. The median age at diagnosis was 60 years (range 24-85). The male to female ratio was 1.3:1. Comparison of clinical characteristics in patients with or without RI is described in Table 1. Of these, 121 patients were RI and 272 patients were non-RI. RI accounted for 30.8% of all patients. Compared to non-RI group, RI group had significantly lower hemoglobin and serum albumin, higher serum calcium corrected by albumin, uric acid, β_2 microglobulin, LDH, and bone marrow plasma cell percentage (all $P < .05$). The percentages of RB1 deletion, P53 deletion, and 13q14.3 deletion and early death were significantly higher in RI group than those in non-RI group by the Chi-square test (all $P < .05$).

3.2 | Impact of renal function and treatment regimens on survival

The last follow-up was conducted in March 31, 2019. During a median follow-up period of 32 months, the median OS from diagnosis was assessed as 39 months (95% CI 31-47). The median OS for RI patients was 17 months (95% CI 12-22) compared with 51 months (95% CI 45-57) for non-RI patients ($P < .001$) (Figure 1A). Upon RI categorizations as described in the methods, the median OS for patients with non-RI, mild, and severe RI was 51, 35, and 14 months, respectively ($P < .001$; Figure 1B).

Different treatment regimens were used in this study. Among 393 patients, 16 patients refused conventional chemotherapy or novel agent-based regimens and only received supportive treatment (group A), 65 patients were treated with conventional chemotherapy (group B), 276 patients were treated with novel agent-based regimens (group C), 36 patients were treated with novel agent-based regimens followed by ASCT (group D). The median OS for patients in group A, B, C, and D was 2 months, 25 months, 43 months, and not reached, respectively ($P < .001$ between group A and B; $P < .001$ between group A and C; $P < .001$ between group A and D; $P = .008$ between group B and C; $P < .001$ between group B and D; $P = .002$ between group C and D) (Figure 2). In the 40 early death cases, there were 9, 7, and 24 patients in group A, B, and C, respectively. The early mortality in group A was significantly higher than that in group B or C (all $P < .001$), and there was no significant difference between group B and C.

In a univariable analysis, assessing predictors for OS, RI (eGFR < 40 mL/min), hemoglobin < 100 g/L, LDH ≥ 245 U/L, hyperuricemia, hypercalcemia, ISS stage II and III, RB1 gene deletion, 1q21 amplification, P53 gene deletion, 13q14.3 deletion, IgH rearrangement, and treatment without novel agent were all found to predict for worse OS. However, only severe RI (eGFR < 30 mL/min) (hazard ratio [HR] = 1.89), hemoglobin < 100 g/L (HR = 1.85), LDH ≥ 245 U/L (HR = 1.72), hyperuricemia (HR = 1.56), 1q21 amplification (HR = 2.09), and treatment regimen (HR = 2.07 for novel agent-based regimens, HR = 8.15 in conventional chemotherapy and HR = 26.45 for supportive treatment alone, all vs. novel agent-based regimens followed by ASCT) were significantly associated with decreased OS in a multivariable analysis (Table 2).

3.3 | Renal response and its impact on survival in MM patients with severe RI

Since severe RI was an independent prognostic factor for decreased OS in newly diagnosed MM patients in our study, we further analyzed the renal response of patients with severe RI and investigated the impact of renal response on OS in those patients. In patients with severe RI, 28 patients died within 2 months of diagnosis, so renal response cannot be evaluated in these early death patients. After excluding these patients, we evaluated the renal response of the rest 66 patients with severe RI, 13 (19.7%) had a CR_{renal}, 4 (6.1%) had a PR_{renal}, 22 (33.3%) had a MR_{renal}, and 27 (40.9%) had NR_{renal}.

Next, patients with severe RI were categorized based on their renal function at diagnosis and response to therapy: One was severe RI patients with renal response (n = 39): eGFR < 30 mL/min at diagnosis but achieved renal response after therapy, the other was severe RI patients without renal response (n = 27): eGFR < 30 mL/min at diagnosis but not achieved renal response after therapy. We found that severe RI patients with renal response had a median OS of

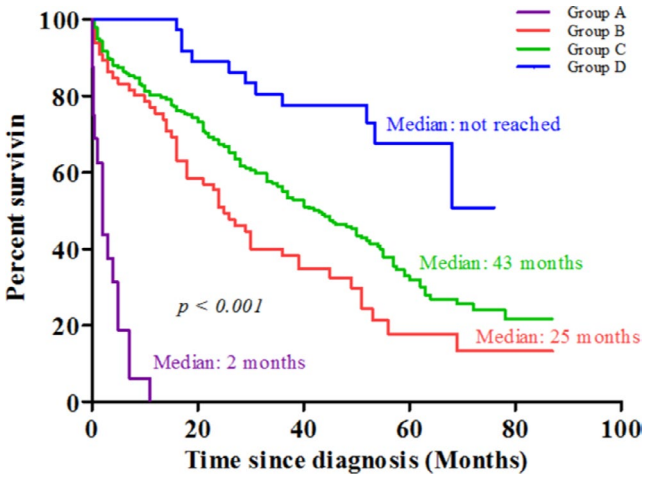

FIGURE 2 Kaplan-Meier plot comparing overall survival between group A, B, C, and D based on the treatment regimens of patients: group A, supportive treatment alone; group B, conventional chemotherapy; group C, novel agent-based regimens, and group D, novel agent-based regimens followed by ASCT

27 months compared with 18 months for severe RI patients without renal response ($P = .030$), but their median OS was still significantly lower than that for patients without severe RI, which was 51 months ($P = .014$; Figure 3).

3.4 | Impact of bortezomib-based regimens on renal response in severe RI patients

In order to explore the impact of bortezomib-based regimens on renal response in severe RI patients, after excluding the patients receiving supportive treatment alone (n = 2) and ASCT (n = 4), we evaluated the renal response in 59 severe RI patients except only one patient receiving carfilzomib-based regimens. Those patients were divided into two groups: bortezomib-based (n = 33) and nonbortezomib-based (n = 26) regimens. There was no significant difference in baseline eGFR between these two groups (data not shown). We found that 27.3%, 9.1%, and 36.4% of severe RI patients receiving bortezomib-based regimens achieved CR_{renal}, PR_{renal}, and MR_{renal}, respectively. The overall renal response rate (CR_{renal} + PR_{renal} + MR_{renal}) in bortezomib-based regimens was significantly higher than that in nonbortezomib-based regimens (72.7% vs. 46.2%, $P = .038$; Table 3).

4 | DISCUSSION

In spite of a high rate of hematological remission in MM patients in the novel agent era, RI, and particularly severe RI, remains associated with poor survival and early mortality.[3,7-10] Moreover, renal function recovery has been one of the main therapeutic goals in MM patients with RI.[3] The incidence of RI ranges between 20% and 40% in newly diagnosed MM patients, depending on different definitions.[3,4,9] The lack of standardization of definitions of RI and severe RI in MM patients was an important shortfall. In 2003, the older IMWG criteria recommended that RI in newly diagnosed MM patients was defined as a sCr >173 μmol/L.[14] However, use of a fixed sCr to define RI leads to patients needing widely different levels of renal dysfunction, based on age, sex, and race, to fulfill the MM diagnostic criteria.[11] Therefore, the 2014 IMWG consensus recommendations suggested that eGFR < 40 mL/min could be used instead of the fixed sCr to fulfill the MM criteria.[11] And severe RI was defined as an eGFR < 30 mL/min in several studies,[7,8,12] but the RI definition from the novel IMWG criteria was not used simultaneously in those studies. Thus, it is necessary to apply the above RI and severe RI definitions together to analyze the outcomes of newly diagnosed MM patients, and investigate the impact of renal function recovery on survival in those patients with RI.

In the present study, we found that the median eGFR in our study was similar to that in the study by Gonsalves et al.[15] Moreover, the result that RI at diagnosis was present in almost 30% of our patients was consistent with the previous reports.[3,4] A study of 1773 consecutive unselected patients has shown that although the increased proportion of older patients, the incidence of severe RI remained unchanged at about 18% over time.[7] However, our frequency of severe RI (24%) was relatively higher than their data. We also found that early mortality in our study was about 10%. This result was close to the previously published study showing that early mortality before day 60 occurred in 299 (10%) of newly diagnosed MM patients.[16]

Our findings indicate that the median OS is significantly different among non-RI, mild, and severe RI groups based on our classification of RI. Furthermore, severe RI is significantly associated with decreased OS in a multivariable analysis. Gonsalves et al also found that the median OS in non-RI patients (112 months) was significantly higher than that in RI patients (43 months) during a median follow-up period of 76 months, but they reported that RI may not be an adverse prognostic marker for OS.[15] However, they did not analyze the OS for patients with severe RI. Nevertheless, studies by de Vries et al and Hsiao et al demonstrated that eGFR < 30 mL/min was significantly associated with decreased OS.[17,18] Moreover, a multicenter study with 198 consecutive patients has shown increased HRs for impaired OS with deteriorating eGFR by univariable analysis and severe RI as the most relevant prognostic factor for OS via multivariable analysis.[8] Collectively, and similar to our study, these studies reported that severe RI was an independent prognostic factor for decreased OS.[8,17,18]

A review by Yadav et al[9] reported that restoration of renal function in MM was correlated with improved clinical outcomes. More recently, the renal response analysis results from ENDEAVOR trial also showed that achievement of renal responses was associated with greater clinical efficacy in MM patients with RI.[19] Since severe RI is an independent risk factor for OS in our study, we further investigated the impact of renal response on OS in severe RI patients. We found that even if MM patients with severe RI experienced a restoration of renal function after therapy, they did not have equivalent survival outcomes to patients without severe RI. However, the restoration of renal function in severe RI remained important, and the median OS was greater in

TABLE 2 Multivariable analysis of clinical and laboratory factors associated with overall survival

	Univariable analysis			Multivariable analysis		
Variate	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Hemoglobin			<.001			.012
≥100 g/L	Ref			Ref		
<100 g/L	2.75	1.99-3.80	<.001	1.85	1.14-2.99	.012
Serum uric acid			<.001			.016
≥430 μmol/L	2.39	1.84-3.10	<.001	1.56	1.09-2.25	.016
<430 μmol/L	Ref			Ref		
Serum corrected calcium			<.001			
>2.75 mmol/L	1.98	1.48-2.66	<.001			
≤2.75 mmol/L	Ref					
LDH			.002			.016
≥245 U/L	1.63	1.19-2.23	.002	1.72	1.11-2.67	.016
<245 U/L	Ref			Ref		
ISS stage			<.001			
I	Ref					
II	2.20	1.36-3.55	.001			
III	3.97	2.40-6.55	<.001			
RB1			.007			
Normal	Ref					
Deletion	1.59	1.14-2.23	.007			
1q21			<.001			.001
Normal	Ref			Ref		
Amplification	2.47	1.76-3.46	<.001	2.09	1.36-3.21	.001
P53			.004			
Normal	Ref					
Deletion	1.82	1.21-2.74	.004			
13q14.3			.022			
Normal	Ref					
Deletion	1.51	1.06-2.14	.022			
IgH			<.001			
Normal	Ref					
Rearrangement	2.00	1.43-2.78	<.001			
eGFR			<.001			.015
≥40 mL/min	Ref			Ref		
<40 mL/min and ≥ 30 mL/min	1.67	1.03-2.70	.036	1.03	0.51-2.08	.928
<30 mL/min	2.83	2.15-3.72	<.001	1.89	1.22-2.93	.004
Treatment regimens			<.001			<.001
Supportive treatment alone	34.10	15.18-76.63	<.001	26.45	9.37-74.62	<.001
Conventional chemotherapy	4.12	2.14-7.94	<.001	8.15	3.79-17.49	<.001
Novel agent-based regimens	2.68	1.45-4.93	.002	2.07	1.06-4.05	.034
Novel agent-based regimens followed by ASCT	Ref			Ref		

Abbreviations: ASCT, autologous stem cell transplantation; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ration; ISS, international staging system; LDH, lactate dehydrogenase; Ref, reference.

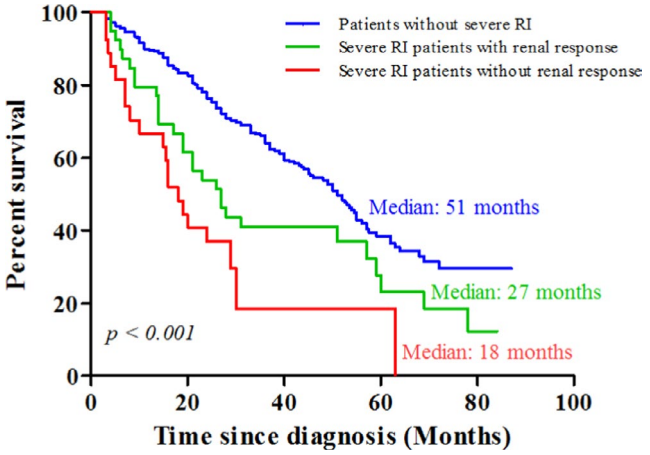

FIGURE 3 Kaplan-Meier plot comparing overall survival between patients without severe RI, and severe RI patients with or without renal response

TABLE 3 Renal response of patients with severe RI received bortezomib-based and nonbortezomib-based regimens

Renal response	Bortezomib-based regimens (N [%])	Nonbortezomib-based regimens (N [%])
CR_{renal}	9 (27.3)	2 (7.7)
PR_{renal}	3 (9.1)	1 (3.8)
MR_{renal}	12 (36.4)	9 (34.6)
NR_{renal}	9 (27.3)	14 (53.8)
Overall renal response	24 (72.7)	12 (46.2)[a]

Abbreviations: CR_{renal}, complete renal response; MR_{renal}, minor renal response; NR_{renal}, no renal response;PR_{renal}, partial renal response.
[a]$P < .05$ compared with the bortezomib-based regimens group.

patients who achieved renal response compared with those who did not. Our study is in agreement with the recent study showing that RI patients with restoration of renal function have improved survival outcomes, but they were still inferior to patients without RI at diagnosis.[15] Therefore, it is important to use prompt and effective treatment to achieve renal response in severe RI patients.

It is known that bortezomib is currently considered the agent of choice for newly diagnosed MM patients with RI.[4,5] A recent review by Fotiou et al[3] reported that bortezomib could induce higher rates of renal response within the first few months of therapy. Dimopoulos et al[20] have demonstrated that novel agent treatments significantly improved renal function, with bortezomib being the most potent agent in restoration of renal function. Roussou et al[21] have shown that the percentage of MM patients with improvement of renal function (MR_{renal} or better) in bortezomib-based regimens, immunomodulator-based regimens, and conventional chemotherapy was 94%, 79% and 59%, respectively (P = .02). Recently, Liu et al[22] have also reported that the percentage of patients with renal response (more than MR_{renal}) in bortezomib-based regimens was noticeably higher than that in nonbortezomib-based regimens in a retrospective study with 134 newly diagnosed MM patients with RI. Those reports were similar to our results that the overall renal response of severe RI patients in bortezomib-based regimens was significantly higher than that in nonbortezomib-based regimens. Thus, we suggest that bortezomib-based regimens may be the cornerstone of the management of MM patients with severe RI.

Many studies have confirmed the beneficial effect of novel agent-based regimens on OS in comparison to conventional chemotherapy in newly diagnosed MM patients,[23-25] consistent with our findings. Moreover, many phase III trials have demonstrated improved OS with the use of ASCT.[26-28] Our study also revealed a significantly better median OS for patients receiving novel agent-based regimens with ASCT than without ASCT. However, there has been increasing debate on the role of ASCT in the current era with the superior efficacy of the novel agent.[29] Therefore, ongoing trials will continue to define the role of ASCT in MM patients in the future. In our study, we also found that 1q21 amplification was associated with poor prognosis. This result was consistent with the data by Grzasko et al.[30] It is known that 1q21 amplification could result in an enhanced expression of cyclin kinase subunit 1B (CKS1B), which regulates myeloma cell growth and survival and might be the responsible gene for adverse outcome.[31,32]

This study has some limitations. First, the retrospective nature of our study increased the risk of bias in data collection. Second, we did not analyze other comorbidities, such as diabetes and hypertension, which can also be associated with a decline in renal function. Third, the number of patients in our study was not large, and some patients were not treated with bortezomib, this was mainly affected by the financial standing of patients because bortezomib was not covered by insurance in our country during those years. Finally, we were unable to analyze the data from severe RI patients receiving carfilzomib-based regimens because of the small number of those patients. Further work is required to compare the patients receiving carfilzomib-based regimens with those receiving bortezomib-based regimens.

5 | CONCLUSION

In summary, our study demonstrates that severe RI (eGFR < 30 mL/min), hemoglobin < 100 g/L, LDH ≥ 245 U/L, hyperuricemia, 1q21 amplification, and treatment without novel agent are significantly associated with decreased OS in newly diagnosed MM patients based on our classification of RI. In addition, severe RI patients who achieved renal response have improved survival outcomes, but they remain inferior to patients without severe RI. And bortezomib-based regimens may be the preferred treatment for newly diagnosed MM patients with severe RI.

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AUTHOR CONTRIBUTIONS

Xuduan Chen analyzed the data and wrote the manuscript. Xiaofeng Luo, Yanping Zu, and Hajji Ally Issa checked and analyzed the data. Linlin Li and Hong Ye prepared figures and tables. Lixin Wei, Jianda Hu, and Ting Yang designed the study and wrote the manuscript.

ORCID

Xuduan Chen https://orcid.org/0000-0003-0488-7035

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