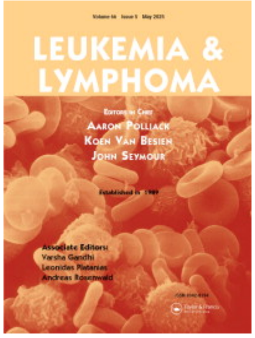

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ORIGINAL ARTICLE

Evidence of the modified staging system and comparative performance of IPSS and revised IPSS in a Single-Center Asian cohort with Waldenström macroglobulinemia

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ABSTRACT

Waldenström macroglobulinemia (WM), a rare incurable low-grade B-cell lymphoma, exhibits heterogeneous survival outcomes. We evaluated the prognostic performance of a novel modified staging system of WM (MSS-WM) through comparison with existing models in a single-center cohort of 294 symptomatic WM patients. MSS-WM demonstrated significant stratification capacity ($p < 0.0001$), with 5-year overall survival rates of 89% (low-risk), 84% (low-intermediate), and 52% (intermediate/high-risk). All MSS-WM factors, including age, serum albumin, and LDH demonstrated independent prognostic impact. In addition, high beta-2 microglobulin level also showed negative prognostic impacts ($p = 0.0002$). While high concordance of MSS-WM and the revised IPSS (rIPSS-WM) was confirmed, the rIPSS-WM exhibited better predictive accuracy. However, MSS-WM's simplified structure enhances clinical utility, enabling rapid risk stratification: 89% 5-year survival in low-risk vs 52% in high-risk groups. This practical staging system requires no complex calculations, making it preferable for routine clinical implementation while maintaining comparable prognostic discrimination.

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KEYWORDS
Waldenström macroglobulinemia; modified staging system; international prognostic scoring system

Introduction

Waldenström macroglobulinemia (WM) has been recognized as a rare subtype of low-grade B-cell lymphoma [1]. Although WM mostly has an indolent course and the prognosis has improved during the last decades [2], WM remains incurable and perpetually relapse and most patients succumb to disease progression [3,4]. Approximately one-third to two-thirds of the WM patients die from WM-related reasons [5,6]. The firstline therapies for WM mostly rely on the use of immunochemotherapy or alkylating drugs [7], while proteasome inhibitors and Bruton tyrosine kinase (BTK) inhibitors have recently been introduced in the front-line treatment regimens [8,9]. The use of these new therapies has improved the progression-free survival and overall survival of WM.

In order to predict the prognosis of symptomatic WM, the International Prognostic Scoring System for WM (IPSS-WM) has been formulated to stratify patients into three risk groups with 5-year survival rates of 87%, 68%, and 36%, respectively [10]. However, the IPSS-WM was based on data of WM patients primarily treated with alkylating agents and did not account for non-WM-related deaths [11]. A revised version of IPSS-WM (rIPSS-WM) based on age, lactate dehydrogenase (LDH), beta-2 microglobulin (β2-MG), and albumin, was developed in 2019 to address some of the deficiencies. The rIPSS-WM stratifies WM patients into five risk groups with 10-year survival rates of 84%, 59%, 37%, 19%, and 9%, respectively [5]. However rIPSS-WM contains more biomarkers which might add difficulties in clinical use and requires further validation in Asian population.

In 2024, the modified staging system of WM (MSS-WM) [12] was developed to identify and validate clinical prognostic factors and categorize patient into

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distinct risk groups. As a simplified risk stratification model for WM, MSS-WM was derived from data of over 800 patients with WM treated in accordance with the current treatment consensus [7]. It stratifies patients into four risk groups with 5-year survival rates of 93%, 82%, 69%, and 55%, respectively. However, the survival difference was not significantly in the high-risk and intermediate-risk groups in the validation cohort. There is a lack of data regarding its performance in Asian population.

The purpose of our current study was to provide evidence for MSS-WM and compare the performance of MSS-WM, rIPSS-WM, and IPSS-WM in symptomatic WM patients in Asia.

Methods

Patient cohort

We identified symptomatic WM patients diagnosed between January 2000 and December 2023 from the Department of Hematology, Peking Union Medical College Hospital, Beijing, China. Patients with available clinical data were included. All diagnoses were reviewed based on the 2003 diagnostic criteria in the Second International Workshop on Waldenström Macroglobulinemia [13]. In accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Ethical approval and waivers of informed consent were obtained from the Peking Union Medical College Hospital Ethics Committee.

Clinical data and specimens

Medical records were reviewed to collect baseline clinical features, physical examination results, biological data, radiological data, treatment, and survival for analysis. Unsorted bone marrow samples were collected at screening. MYD88^{L265P} and CXCR4^{S338X} mutations were assayed by real-time allele-specific polymerase chain reaction [14,15]. Genomic DNA of some patients were also sequenced by targeted gene sequencing panel of 76 genes in relation to lymphoproliferative disorders, including MYD88 and CXCR4 (Table S1). Treatment regimens were categorized into chemotherapy, immunochemotherapy (rituximab combined with chemotherapy), proteasome inhibitor-based therapy, and BTK inhibitors [16].

Risk stratification system and outcome parameters

Prognosis stratification was analyzed based on the 2024 modified staging system for WM (MSS-WM, using age ≤65 years (0 point), 66-75 years (1 point), >75 years (2 points), serum albumin <3.5 g/dL (1 point), and LDH > upper limit of normal (2 points). Prognosis of WM patients calculated by MSS-WM was grouped into low-risk (score 0), low-intermediate risk (score 1), intermediate-risk (score 2), and high-risk (score ≥3) [12]. Staging predicted by MSS-WM were compared with the results calculated by the 2009 prognostic scoring system for WM (IPSS-WM) [10] and the 2019 revised international prognostic scoring system (rIPSS-WM) [5]. Time to next treatment (TTNT) was defined as the interval from the date of initiation of a treatment to the date of the next line of therapy [17]. Overall survival (OS) was defined as the duration from diagnosis to death. WM-related death includes those occurring due to progressive disease, transformation, infections during therapy and post-therapy period, or treatment-related complications [5,6]. Patients without a recorded date of death or documented events were censored on the date of their last follow-up contact with the medical center. The final follow-up date was May 31, 2024.

Statistical analysis

Patient clinical and demographic characteristics were reported using descriptive statistics. MSS-WM scores were available in all patients, while IPSS-WM and rIPSS-WM scores were vacant in some patients because of the missing data in serum β2-MG or serum monoclonal protein levels. Student's t-test or the Mann–Whitney U-test was used for continuous outcomes. Categorical data were analyzed with the chi-square test or Fisher's exact test. Spearman's correlation analysis was applied to measure the monotonic relationship between biomarkers. Univariate and multivariate regression analysis were employed to analyze the predictors of OS and TTNT. Kaplan–Meier analysis and a log-rank test and Cox regression model characterized the OS and TTNT of patients stratified according to MSS-WM, rIPSS-WM, or IPSS-WM. Competing events are non-WM-related death occurring in the remission of WM, such as cardiovascular event, COVID-19 infection, other malignancies, and trauma. A competing risk analysis was used to validate the model on the basis of the cause of death (cmprsk package, version 2.2.12,R) [6,18]. Statistical analyses were performed using SPSS (version 25, IBM Corp., Armonk, NY, USA), and GraphPad Prism (version 5.01). All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

Patient clinical characteristics

A total of 294 symptomatic WM patients were identified, and the demographics and baseline characteristics are summarized in Table 1. The median age was 64 years old (29-92 years old), and the majority (71.4%) were male. *MYD88* mutations were found in 174 (84.4%) patients and *CXCR4* mutations were present in 30 (14.6%) patients in bone marrow. $MYD88^{L265P}$ mutations were detected in 173 of 174 patients, while the other patient had $MYD88^{T294P}$. $CXCR4^{S338X}$ mutations were detected in 25 of 30 patients, while other patients had $CXCR4^{S343fs}$, $CXCR4^{c.1021\_1022delTC}$, $CXCR4^{c.952dupA}$, and $CXCR4^{c.976dupC}$. WM-Related complications included peripheral neuropathy (9.5%), amyloidosis (8.5%), cold agglutinin disease (7.1%), cryoglobulinemia (6.1%) and Bing-Neel syndrome (2.4%).

Indications for therapy included anemia (63.6%), fatigue (47.3%), liver/spleen/lymph node enlargement (46.6%), B-symptoms (38.4%), WM-related complications (30.3%), and hyperviscosity (20.1%) (Table 1). At baseline, the median hemoglobin level was 91 g/L (42-157 g/L). The median serum β2-MG level was 4.3 mg/L (0.2-36.6 mg/L). The median serum M-protein and IgM level was 21.1 g/L (0.14-75.7g/L) and 35.0 g/L (1.23-118.0g/L), respectively. A subset of patients (68/294, 23%) exhibited difference between serum M-protein and IgM levels exceeding 10 g/L, likely due to polyclonal IgM elevation or laboratory methodological differences. Most of the patients received systemic first-line therapy including chemotherapy (37.1%), rituximab-based immunochemotherapy (33.0%), proteasome inhibitor-based therapy (12.9%), BTK inhibitors (11.6%), while 16 patients were not treated because of patients will. The median year of treatment initiation within our cohort was 2018.

Survival outcomes

The median follow-up period was 48 months (0.3-241 months). Eighty-three patients died during the follow-up, including 46 (55.4%) patients died of WM disease progression, 21 (25.3%) patients died of infections, four (4.8%) patients died of stroke, three (3.6%) patients died of unrelated second primary malignancies, one (1.2%) patient died of trauma, and eight (9.6%) patients died of unknown causes. Among them, 64 WM patients (77.1%) were deemed to die of WM-related causes. The estimated 5-year and 10-year OS rates of all patients were 74.2% and 58.2%, respectively, and the median OS was 192 months (Figure 1(A)). On univariate analysis of all of the 294 patients, independent prognostic impacts were revealed with hazard ratios 2.44 for age 66-75 years old ($p = 0.0003$), 3.83 for age older than 75 years old ($p < 0.0001$), 2.21 for albumin lower than 35 g/L ($p = 0.0017$), 2.06 for LDH higher than upper limit of normal ($p = 0.0345$), and 2.10 for hemoglobin level lower than 115 g/L ($p = 0.0225$). Univariate analysis in 236 patients available of data of β2-MG showed independent prognostic impact of β2-MG higher than 4 mg/L with hazard

Table 1. Patients baseline characteristics.

Baseline Characteristics		$N = 294$
Gender (Male, n, %)		210 (71.4%)
Age (median, range)		64 (29-92)
Manifestations	Fatigue (n, %)	139 (47.3%)
	Fever/Sweat/Weight Loss (n, %)	113 (38.4%)
	Liver/Spleen/Lymph node enlargement (n, %)	137 (46.6%)
	Hyperviscosity (n, %)	59 (20.1%)
	Bleeding (n, %)	37 (12.6%)
Laboratory features	Hemoglobin (g/L, median, range) $n = 294$	91 (42-157)
	Platelet (x10^9/L, median, range) $n = 294$	210 (14-1113)
	LDH (U/L, median, range) $n = 294$	138 (43-722)
	β2-MG (mg/L, median, range) $n = 236$	4.3 (0.2-36.6)
	Serum M-protein (g/L, median, range) $n = 252$	21.1 (0.14-75.7)
	Serum IgM (g/L, median, range) $n = 294$	35.0 (1.23-118.0)
Bone marrow genotype	MYD88mut (n, %)	174/206 (84.4%)
	CXCR4mut (n, %)	30/206 (14.6%)
IgM-related clinical complications	Peripheral neuropathy (n, %)	28 (9.5%)
	Amyloidosis (n, %)	25 (8.5%)
	Cryoglobulinemia (n, %)	18 (6.1%)
	Cold agglutinin disease (n, %)	21 (7.1%)
	Bing-Neel syndrome (n, %)	7 (2.4%)
First-line therapy	Chemotherapy (n, %)	109 (37.1%)
	R + Chemotherapy (n, %)	97 (33.0%)
	Proteasome inhibitor (n, %)	38 (12.9%)
	BTK inhibitor (n, %)	34 (11.6%)
	not treated (n, %)	16 (5.4%)

LDH: Lactate dehydrogenase; β2-MG: beta-2 microglobulin

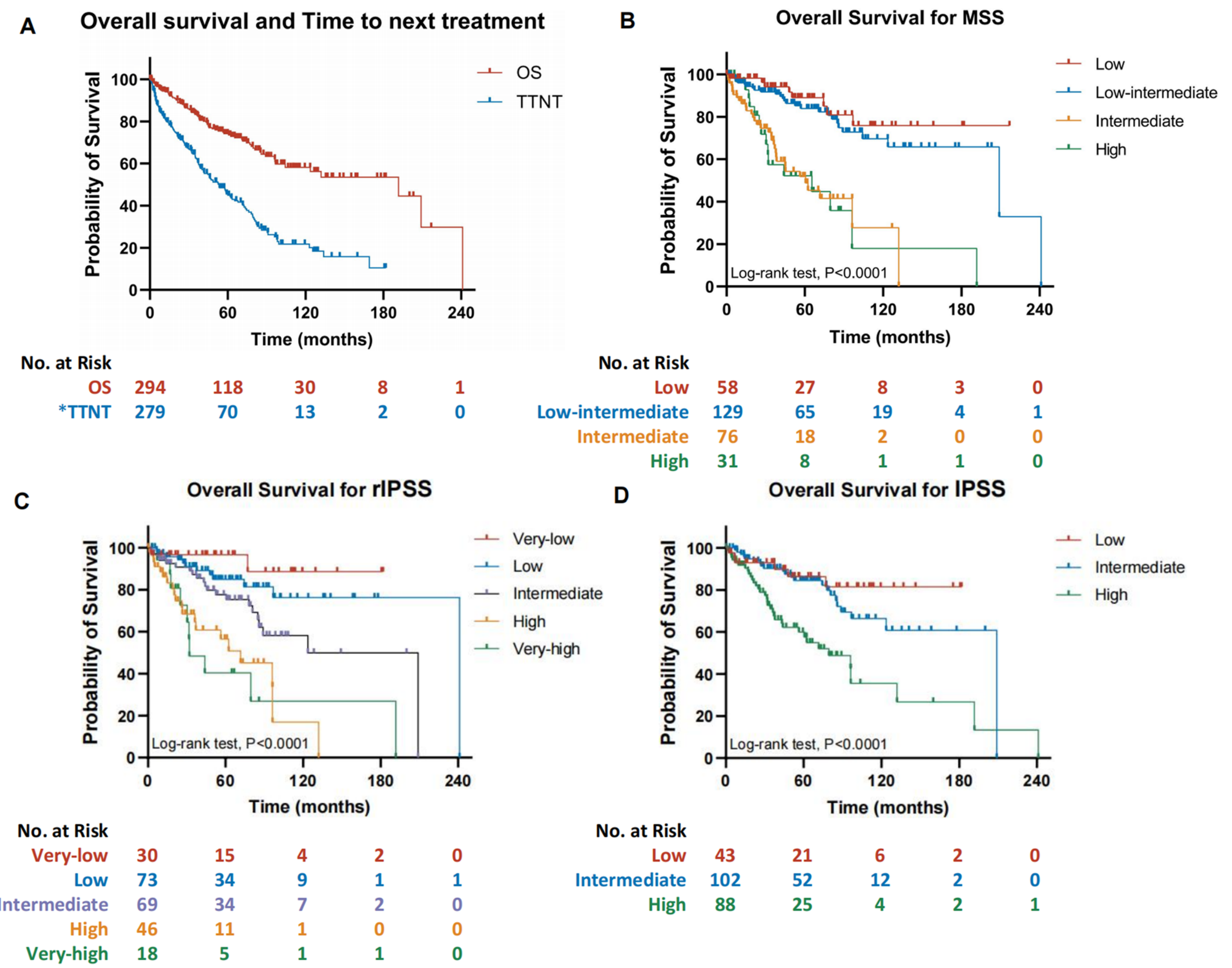

Figure 1. Survival outcome in the cohort. (A) Overall survival (OS) and time to next treatment (TTNT) in the cohort. (B) OS of patients grouped by MSS-WM; MSS-WM staging model: age ≤65 years (0 point), 66-75 years (1 point), >75 years (2 points), serum albumin <3.5 g/dL (1 point), and LDH > upper limit of normal (2 points); low-risk (score 0), low-intermediate risk (score 1), intermediate-risk (score 2), and high-risk (score ≥3). (C) OS of patients grouped by rIPSS-WM. (D) OS of patients grouped by IPSS-WM.*TTNT: time to next treatment or death (whichever comes first).

ratio of 3.07 ($p = 0.0002$) (Table 2). The prognostic impacts of MYD88 mutation ($p = 0.4705$) or CXCR4 mutation ($p = 0.9450$) were not significant. In the multivariate analysis of 236 patients available of data in age, albumin, LDH, β2-MG and hemoglobin levels, hazard ratios were 2.34 ($p = 0.002$) for age 66–76 years old, 2.7 ($p = 0.0126$) for age older than 75 years old, 1.94 ($p = 0.0636$) for albumin, 2.16 ($p = 0.0636$) for LDH, and 2.12 ($p = 0.0277$) for β2-MG.

One hundred and sixty-five patients had disease progression or relapse during the follow-up. The estimated 5-year TTNT rate of all treated patients was 44.9%, and the median TTNT was 53 months (Figure 1(A)). Univariate analysis revealed independent prognostic impact of age 66-75 years old, albumin lower than 35 g/L, β2-MG, and hemoglobin levels on TTNT with hazard ratios of 1.61 (95% CI, 1.15–2.23, $p = 0.0052$), 1.81 (95% CI, 1.31–2.54, $p = 0.0004$), 2.47 (95% CI, 1.71–3.65, $p < 0.0001$), and 1.62 (95% CI, 1.10–2.48, $p = 0.0188$). The multivariate analysis showed hazard ratio of 1.58 ($p = 0.0162$) for age 66-75 years old, 1.61 ($p = 0.0337$) for albumin, 1.96 ($p = 0.0239$) for LDH, and 2.20 ($p = 0.0004$) for β2-MG level.

Performance of MSS-WM

The MSS-WM scores were available in all 294 patients. According to MSS-WM, 58 (19.7%) patients were classified as low risk (MSS-LR), 129 (43.9%) as low-intermediate risk (MSS-LIR), 76 (25.8%) as intermediate risk (MSS-IR), and 31 (10.5%) as high risk (MSS-HR). The 5-year OS rates were 89%, 84%, 52%, 52% in the low to high risk groups, respectively ($p < 0.0001$, Figure 1B). The 10-year OS rates were 75%, 70%, 28%, 18% in the low to high-risk groups, respectively. The hazard ratios were 1.49 (95% CI, 0.71–3.53, $p = 0.3205$) for MSS-LIR versus

Table 2. Univariate and multivariate analysis of prognostic factors affecting OS of WM.

	Univariate Analysis			Multivariate Analysis		
Variable	*n	HR (95% CI)	P value	n	HR (95% CI)	P value
Overall Survival, potential factors						
Age 66-75ys vs ≤65ys	294	2.44 (1.51–3.94)	0.0003	236	2.34 (1.36–4.03)	0.0020
>75ys vs ≤65ys		3.83 (1.98–7.04)	< 0.0001		2.70 (1.17–5.67)	0.0126
Albumin < 35g/L	294	2.21 (1.37–3.72)	0.0017	236	1.94 (1.00–4.09)	0.0636
LDH > ULN	294	2.06 (0.99–3.83)	0.0345	236	2.16 (0.89–4.53)	0.0597
β2-MG > 4mg/L	236	3.07 (1.74–5.78)	0.0002	236	2.12 (1.12–4.32)	0.0277
IgM > 70g/L	294	1.52 (0.87–2.52)	0.1164			
HGB ≤ 115g/L	294	2.10 (1.16–4.19)	0.0225	236	1.18 (0.50–3.19)	0.7195
PLT ≤ 100×10^9/L	294	1.10 (0.58–1.92)	0.3002			
MYD88mut	206	0.72 (0.39–1.69)	0.4705			
CXCR4mut	206	0.90(0.43–1.91)	0.9450			
Overall Survival, MSS-WM groups						
MSS LIR vs LR		1.49 (0.71–3.53)	0.3205			
IR vs LIR	294	3.99 (2.36–6.84)	<0.0001			
HR vs IR		1.03 (0.54–1.87)	0.9182			

LDH: Lactate dehydrogenase; β2-MG: beta-2 microglobulin
*n: number of patients with available data for univariate analysis.

Table 3. Cumulative incidence of disease-specific death and overall survival of WM.

		WM-related death		WM-unrelated death		Overall survival	
Model	Risk group	5-year	10-year	5-year	10-year	5-year	10-year
MSS	Low	6.30%	19.50%	4.60%	4.60%	89.10%	75.90%
	Low-Intermediate	15.10%	27.30%	1.10%	3.10%	83.80%	69.60%
	Intermediate	36.90%	61.00%	11.30%	11.30%	51.80%	27.70%
	High	34.10%	43.00%	13.70%	39.10%	52.20%	17.90%
	P value	<0.0001		0.0004		<0.0001	
rIPSS	Very Low	3.30%	11.40%	0%	0%	96.70%	88.60%
	Low	11.40%	20.00%	3.80%	3.80%	84.80%	76.20%
	Intermediate	17.00%	32.70%	5.40%	9.10%	77.60%	58.20%
	High	27.90%	56.20%	15.60%	26.90%	56.50%	16.90%
	Very High	43.50%	57.00%	16.10%	16.10%	40.40%	26.90%
	P value	0.0023		0.0040		<0.0001	
IPSS	Low	13.70%	18.50%	0%	0%	86.30%	81.50%
	Intermediate	11.90%	27.30%	3.70%	6.30%	84.40%	66.40%
	High	25.10%	43.30%	15.00%	21.10%	59.90%	35.60%
	P value	0.0281		0.0073		0.0001	

MSS-LR, 3.99 (95% CI, 2.36–6.84, $p<0.0001$) for MSS-IR versus MSS-LIR, and 1.03 (95% CI, 0.54–1.87, $p=0.9182$) for MSS-HR versus MSS-IR. According to competing risk analysis, the MSS-WM demonstrated significantly different cumulative incidence of WM-related death ($p<0.0001$) and WM-unrelated death ($p=0.0004$) (Table 3).

Performance of rIPSS-WM

The rIPSS-WM scores were available in 236 (80.3%) patients. Among them, 30 (12.7%) patients were classified as very-low risk (rIPSS-VLR), 73 (30.9%) were low risk (rIPSS-LR), 69 (29.2%) were intermediate risk (rIPSS-IR), 46 (19.5%) were high risk (rIPSS-HR), and 18 (7.6%) were very-high risk (rIPSS-VHR). The 5-year OS rates were 97%, 85%, 78%, 56%, and 40% in the very-low to very-high risk groups, respectively ($p<0.0001$, Figure 1(C)). The 10-year OS rates were 89%, 76%, 58%, 17%, 27% in the low to high risk groups, respectively. The hazard ratios were 2.35 (95% CI, 0.63–15.23, $p=0.2600$) for rIPSS-LR versus rIPSS-VLR, 2.06 (95% CI, 1.01–4.44, $p=0.0425$) for rIPSS-IR versus rIPSS-LR, 2.46 (95% CI, 1.31–4.60, $p=0.0046$) for rIPSS-HR versus rIPSS-IR, and 1.16 (95% CI, 0.51–2.44, $p=0.7100$) for rIPSS-VHR versus rIPSS-HR. Based on competing risk analysis, the rIPSS-WM demonstrated significantly different cumulative incidence of WM-related death ($p=0.0023$) and WM-unrelated death ($p=0.0040$) (Table 3).

Performance of IPSS-WM

In 233 (79.3%) patients with scores of IPSS-WM, 43 (18.5%) of them were classified as low risk (IPSS-LR), 102 (43.8%) as intermediate risk (IPSS-IR), and 88 (37.8%) as high risk (IPSS-HR). The 5-year OS rates were 86%, 84%, and 60% in the low- to high-risk groups, respectively ($p=0.0001$) (Figure 1(D)). The 10-year OS rates were 81%, 66%, 36% in the low to high-risk groups, respectively. The hazard ratios were 1.62 (95% CI, 0.70–4.41, $p=0.2942$) for IPSS-IR versus IPSS-LR, and

2.64 (95% CI, 1.56–4.59, $p = 0.0004$) for IPSS-HR versus IPSS-IR. Based on competing risk analysis, the IPSS-WM demonstrated significantly different cumulative incidence of WM-related death ($p = 0.0281$) and WM-unrelated death ($p = 0.0073$) (Table 3).

Comparison of MSS-WM, IPSS-WM, and rIPSS-WM

Overall survival analysis performances using Concordance Index (C-index) were 0.68 (95% confidence interval [CI] 0.63–0.74) in MSS-WM, 0.69 (95% CI 0.62–0.76) in rIPSS-WM, and 0.64 (95% CI 0.57–0.71) in IPSS-WM. The majority of patients had comparable performance between MSS-WM and IPSS-WM or rIPSS-WM. Based on IPSS-WM (Figure 2(A)), a proportion of high risk patients (11/88, 12.5%) were down-staged in MSS-WM, and a few patients in low risk (2/43, 4.6%) and in intermediate risk group (3/102, 2.9%) were up-staged in MSS-WM. Based on rIPSS, a small fraction of rIPSS low-risk patients (5/73, 6.8%) were up-staged as MSS-WM IR (Figure 2(B)). Subgroup analysis of the re-staged IPSS-IR, IPSS-HR, rIPSS-LR, and rIPSS-IR showed that the overall survival was significantly different (Figure S1, P value 0.0003 ~ 0.0217), which the patients who were re-staged into MSS-IR or MSS-HR tend to have shorter overall survival compared to MSS-LR and MSS-LIR (Figure S1).

Discussion

The results of the present study provided evidence for the prognostic value of MSS-WM for WM on an independent patient cohort in Asia, and compared it to the existing prognostic models including IPSS-WM and rIPSS-WM. In newly diagnosed WM of all ages treated according to recognized standards, the MSS-WM discriminated four groups of LR, LIR, IR, and HR, with 5-year OS rates of 89%, 84%, 52%, and 52%. Although the survival rates were not significantly different between LR vs LIR, and IR vs HR, the MSS-WM largely grouped patients into relatively low and high-risk groups as a simplified and modified stratification model. MSS-WM was initially developed in a cohort of 341 symptomatic WM patients and subsequently validated in an external cohort of 335 patients by the Mayo Clinic [12]. In their validation cohort, the 5-year OS rates were close in LR and LIR groups (93% vs 90%), which aligns with our findings.

The majority of our patients demonstrated comparable risk level among MSS-WM and IPSS-WM or rIPSS-WM, while the survival stratification predicted by rIPSS-WM appeared to perform the best in our cohort. The IPSS-WM has long served as a cornerstone for risk stratification among WM patients [19]. However, it did not account for alternate causes of death and requires validation by competing risk analysis. Therefore, the rIPSS-WM attempted to overcome these limitations and identified stratified age and albumin, LDH, and β2-MG levels as independent prognostic factors [5]. Despite the advancement, the rIPSS-WM has not been fully validated and remains underutilized in routine clinical practice. We performed competing risk analysis and validated all of the three stratification models in an Asian cohort. The MSS-WM contains less biomarkers and was available in all of the 294 patients, while IPSS-WM and rIPSS-WM were not available in a few patients, reinforcing the simplified and practical value of the MSS-WM.

The discrepancy in survival prediction of these stratification models comes from the included biomarkers. In the development of MSS-WM, stratified age, elevated LDH level, and low serum albumin level were found to be independently prognostic [12]. These

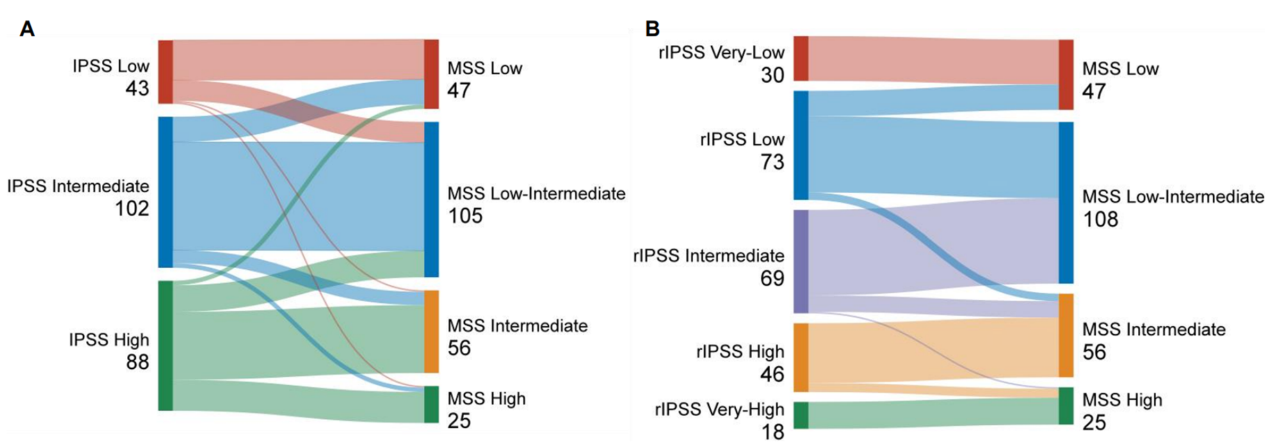

Figure 2. Sankey diagram showing concordance between MSS-WM, rIPSS-WM, and IPSS-WM. (A) Sankey diagram of IPSS-WM and MSS-WM. (B) Sankey diagram of rIPSS-WM and MSS-WM.

three biomarkers have been consistently observed in the reported stratification models and have been shown to be independently associated with short-term survival of WM [19–21]. Advance age at diagnosis has been identified as the most substantial risk factor for survival, with increasing age being consistently correlating with inferior outcomes [5,22]. MSS-WM places greater emphasis on prognostic value of advance age and elevated LDH level while weakens the role of β2-MG compared to rIPSS-WM [12]. Nonetheless, our results indicated that β2-MG retained significant prognostic value in both the univariate and multivariate analyses of overall survival. And it might be more appropriate to assign only one point to the elevated LDH level in our results. Consequently, the survival stratification predicted by rIPSS-WM appeared to perform better than that of MSS-WM in our cohort.

The prognostic value of $MYD88^{L265P}$ mutation remains controversial. In symptomatic WM, some studies have reported a higher risk of disease transformation and shorter overall survival in patients with wild-type MYD88 ($MYD88^{WT}$) [23,24], while other studies found no significant difference in survival between patients with $MYD88^{L265P}$ and $MYD88^{WT}$ [12,25,26]. In asymptomatic WM, the presence of the MYD88 mutation confers a negative impact in progression-free survival [27,28]. Since mutated MYD88 promote malignant survival of lymphoplasmacytic cells through downstream Bruton tyrosine kinase (BTK) [29], the $MYD88^{L265P}$ mutation may be associated with better treatment responses and longer progression-free survival in WM patients treated with BTK inhibitors [30]. In our cohort, only 34 patients received BTK inhibitor as first-line treatment. Similar to previous study [12], the prognostic significance of MYD88 mutations was not observed in the overall cohort or in patients treated with BTKi in our study. Other clinical and laboratory factors associated with overall survival of WM include somatic variations in CXCR4 and SP1 [31], TP53 mutations [32], hepatosplenomegaly [22], extramedullary involvement [33]. However, the prognostic impact of these factors was not significant in our study. Additionally, higher CXCL13 and CRP levels have been reported to be associated with poor survival outcome in WM, as highlighted in previous studies [16,34,35]. Unfortunately, serum CXCL13 and CRP levels were not included in the univariate analysis for overall survival in this cohort due to a lack of data in the majority of patients.

There are several limitations of our study. There was potential variability in the time between diagnosis and treatment start. About 12.5% of the patients received treatment after one month after diagnosis. This could introduce confounding if biomarkers fluctuated significantly during this period. Another potential limitation is the relatively short median follow-up duration of 48 months after first treatment, given the long diagnostic period (2000–2023). This may limit the accurate assessment of long-term overall survival, particularly for patients treated in later years. Extended follow-up might be necessary to validate these findings.

The majority of patients in our cohort died of WM-related causes, for over half succumbing to disease progression and approximately a quarter experiencing death from infectious complications. A small group of patients died of WM-unrelated causes such as trauma and other malignancies. However, there is a lack of the detailed information on the relationships between the rest of death events and WM disease status. Therefore, we did not evaluate prognostic models based solely on WM-related deaths, which is one of the limitations of our study. In the existing prognostic models, the IPSS-WM was derived in the WM patients where 20%-40% succumb to WM-unrelated causes [10,19]. The rIPSS-WM model was formulated with a focus on early WM-related death in a cohort that included about 22% of patients who died of WM-unrelated causes, demonstrating good performance for overall survival concerning all causes of death [5,7,36,37]. The MSS-WM model was initially proposed based on the overall survival, and a competing risk analysis was performed to assess the WM-related mortality [6,12]. Our study validated these prognostic models by performing competing risk analyses in an Asian WM cohort. In our results, the rIPSS-WM appeared to demonstrate better performance on OS than the MSS-WM concerning WM-related causes and across all causes. However, as a simplified model, MSS-WM employs fewer clinical biomarkers than both rIPSS-WM and IPSS-WM which might facilitate its implementation in clinical use.

Conclusion

In conclusion, our study validates the prognostic utility of the MSS-WM serve in an Asian WM cohort treated according to current standards and compares its performance with the established scoring system IPSS-WM and rIPSS-WM. The MSS-WM demonstrates greater accessibility and effectively discriminates low-risk patients (89% 5-year OS) from intermediate/high-risk cohorts (52% OS). Importantly, MSS-WM's reliance on routinely available clinical parameters (age, serum albumin, LDH) makes it immediately applicable in clinical practice. Multicenter validation is needed across diverse populations, particularly in different treatment patterns.

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Not applicable.

Ethics approval and consent to participate

In accordance with the ethical standards of the Declaration of Helsinki, informed consent was obtained from all patients, and the study was approved by the Peking Union Medical College Hospital Ethics Committee.

Consent for publication

Not applicable.

Authors' contributions

XXC, DBZ, and JL contributed to study conception and design; JC contributed to patient follow-up; JC, and XXC contributed to data analysis and interpretation; JC retrospectively reviewed patient records and contributed to data collection; JC and XXC wrote the paper; and all authors revised the paper and approved the submitted version.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

[1] Castillo JJ, Advani RH, Branagan AR, et al. Consensus treatment recommendations from the tenth International Workshop for Waldenström Macroglobulinaemia. Lancet Haematol. 2020;7(11):e827–e37. doi:10.1016/S2352-3026(20)30224-6

[2] Dhodapkar MV, Hoering A, Gertz MA, et al. Long-term survival in Waldenstrom macroglobulinemia: 10-year follow-up of Southwest Oncology Group-directed intergroup trial S9003. Blood. 2009;113(4):793–796. doi:10.1182/blood-2008-07-172080

[3] Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. N Engl J Med. 2012;367(9):826–833. doi:10.1056/NEJMoa1200710

[4] Kapoor P, Ansell SM, Fonseca R, et al. Diagnosis and Management of Waldenstrom Macroglobulinemia: Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) Guidelines 2016. JAMA Oncol. 2017;3(9):1257–1265. doi:10.1001/jamaoncol.2016.5763

[5] Kastritis E, Morel P, Duhamel A, et al. A revised international prognostic score system for Waldenström's macroglobulinemia. Leukemia. 2019;33(11):2654–2661. doi:10.1038/s41375-019-0431-y

[6] Kastritis E, Kyrtsonis M-C, Morel P, et al. Competing risk survival analysis in patients with symptomatic Waldenström macroglobulinemia: the impact of disease unrelated mortality and of rituximab-based primary therapy. Haematologica. 2015;100(11):e446–e9. doi:10.3324/haematol.2015.124149

[7] Gertz MA. Waldenström macroglobulinemia: 2023 update on diagnosis, risk stratification, and management. Am J Hematol. 2023;98(2):348–358. doi:10.1002/ajh.26796

[8] Castillo JJ, Meid K, Gustine JN, et al. Long-term follow-up of ibrutinib monotherapy in treatment-naive patients with Waldenstrom macroglobulinemia. Leukemia. 2022;36(2):532–539. doi:10.1038/s41375-021-01417-9

[9] Buske C, Dimopoulos MA, Grunenberg A, et al. Bortezomib-dexamethasone, rituximab, and cyclophosphamide as first-line treatment for waldenström's macroglobulinemia: a prospectively randomized trial of the European Consortium for Waldenström's Macroglobulinemia. J Clin Oncol. 2023;41(14):2607–2616. doi:10.1200/JCO.22.01805

[10] Morel P, Duhamel A, Gobbi P, et al. International prognostic scoring system for Waldenstrom macroglobulinemia. Blood. 2009;113(18):4163–4170. doi:10.1182/blood-2008-08-174961

[11] Hivert B, Tamburini J, Vekhoff A, et al. Prognostic value of the International Scoring System and response in patients with advanced Waldenstrom macroglobulinemia. Haematologica. 2011;96(5):785–788. doi:10.3324/haematol.2010.029140

[12] Zanwar S, Le-Rademacher J, Durot E, et al. Simplified risk stratification model for patients with Waldenstrom macroglobulinemia. J Clin Oncol. 2024;42(21):2527–2536. doi:10.1200/JCO.23.02066

[13] Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's macroglobulinemia. Semin Oncol. 2003;30(2):110–115. doi:10.1053/sonc.2003.50082

[14] Xu L, Hunter ZR, Yang G, et al. MYD88 L265P in Waldenström macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. Blood. 2013;121(11):2051–2058. doi:10.1182/blood-2012-09-454355

[15] Xu L, Hunter ZR, Tsakmaklis N, et al. Clonal architecture of CXCR4 WHIM-like mutations in Waldenström macroglobulinaemia. Br J Haematol. 2016;172(5):735–744. doi:10.1111/bjh.13897

[16] Chen J, Jia MN, Cai H, et al. Serum CXCL13 level is related to treatment response and predicts disease prognosis in Waldenstrom macroglobulinemia. Ann Hematol. 2024;103(9):3667–3675. doi:10.1007/s00277-024-05690-3

[17] Campbell BA, Scarisbrick JJ, Kim YH, et al. Time to next treatment as a meaningful endpoint for trials of primary cutaneous lymphoma. Cancers (Basel). 2020;12(8):2311. doi:10.3390/cancers12082311

[18] Latouche A, Allignol A, Beyersmann J, et al. A competing risks analysis should report results on all cause-specific hazards and cumulative incidence functions. J Clin Epidemiol. 2013;66(6):648–653. doi:10.1016/j.jclinepi.2012.09.017

[19] Kastritis E, Kyrtsonis M-C, Hadjiharissi E, et al. Validation of the International Prognostic Scoring System (IPSS) for Waldenstrom's macroglobulinemia (WM) and the importance of serum lactate dehydrogenase (LDH). Leuk Res. 2010;34(10):1340–1343. doi:10.1016/j.leukres.2010.04.005

[20] Dimopoulos MA, Hamilos G, Zervas K, et al. Survival and prognostic factors after initiation of treatment in Waldenstrom's macroglobulinemia. Ann Oncol. 2003;14(8):1299–1305. doi:10.1093/annonc/mdg334

[21] Ruan G, Zanwar S, Abeykoon JP, et al. Predictors of short-term survival in Waldenström Macroglobulinemia. Leuk Lymphoma. 2020;61(12):2975–2979. doi:10.1080/10428194.2020.1789625

[22] Ghobrial IM, Fonseca R, Gertz MA, et al. Prognostic model for disease-specific and overall mortality in newly diagnosed symptomatic patients with Waldenstrom macroglobulinaemia. Br J Haematol. 2006;133(2):158–164. doi:10.1111/j.1365-2141.2006.06003.x

[23] Treon SP, Gustine J, Xu L, et al. MYD88 wild-type Waldenstrom macroglobulinaemia: differential diagnosis, risk of histological transformation, and overall survival. Br J Haematol. 2018;180(3):374–380. doi:10.1111/bjh.15049

[24] Treon SP, Sarosiek S, Castillo JJ. How I use genomics and BTK inhibitors in the treatment of Waldenström macroglobulinemia. Blood. 2024;143(17):1702–1712. doi:10.1182/blood.2022017235

[25] Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 trial of ibrutinib plus rituximab in Waldenström's macroglobulinemia. N Engl J Med. 2018;378(25):2399–2410. doi:10.1056/NEJMoa1802917

[26] Abeykoon JP, Paludo J, King RL, et al. MYD88 mutation status does not impact overall survival in Waldenström macroglobulinemia. Am J Hematol. 2018;93(2):187–194. doi:10.1002/ajh.24955

[27] Moreno DF, Jiménez C, Escalante F, et al. Prognostic risk and survival of asymptomatic IgM monoclonal gammopathy: results from a Spanish Multicenter Registry. Hemasphere. 2024;8(11):e70029. doi:10.1002/hem3.70029

[28] Moreno DF, López-Guerra M, Paz S, et al. Prognostic impact of MYD88 and CXCR4 mutations assessed by droplet digital polymerase chain reaction in IgM monoclonal gammopathy of undetermined significance and smouldering Waldenström macroglobulinaemia. Br J Haematol. 2023;200(2):187–196. doi:10.1111/bjh.18502

[29] Yang G, Zhou Y, Liu X, et al. A mutation in MYD88 (L265P) supports the survival of lymphoplasmacytic cells by activation of Bruton tyrosine kinase in Waldenström macroglobulinemia. Blood. 2013;122(7):1222–1232. doi:10.1182/blood-2012-12-475111

[30] Treon SP, Xu L, Hunter Z. MYD88 mutations and response to ibrutinib in Waldenström's macroglobulinemia. N Engl J Med. 2015;373(6):584–586. doi:10.1056/NEJMc1506192

[31] Krzisch D, Guedes N, Boccon-Gibod C, et al. Cytogenetic and molecular abnormalities in Waldenström's macroglobulinemia patients: correlations and prognostic impact. Am J Hematol. 2021;96(12):1569–1579. doi:10.1002/ajh.26339

[32] Poulain S, Roumier C, Bertrand E, et al. TP53 mutation and its prognostic significance in Waldenstrom's macroglobulinemia. Clin Cancer Res. 2017;23(20):6325–6335. doi:10.1158/1078-0432.CCR-17-0007

[33] Cao X, Ye Q, Orlowski RZ, et al. Waldenstrom macroglobulinemia with extramedullary involvement at initial diagnosis portends a poorer prognosis. J Hematol Oncol. 2015;8(1):74. doi:10.1186/s13045-015-0172-y

[34] Debureaux P-E, Forgeard N, Elessa D, et al. Inflammation is predictive of outcome in Waldenström macroglobulinemia treated by Bruton tyrosine kinase inhibitors: a multicentric real-life study. Haematologica. 2024;109(1):325–330. doi:10.3324/haematol.2023.283141

[35] Debureaux P-E, Poulain S, Harel S, et al. Inflammatory Waldenström macroglobulinemia is associated with clonal hematopoiesis: a multicentric cohort. Blood. 2025;145(4):450–454. doi:10.1182/blood.2024025738

[36] Castillo JJ, Sarosiek SR, Gustine JN, et al. Response and survival predictors in a cohort of 319 patients with Waldenstrom macroglobulinemia treated with ibrutinib monotherapy. Blood Adv. 2022;6(3):1015–1024. doi:10.1182/bloodadvances.2021006106

[37] Dimopoulos MA, Kastritis E, Delimpassi S, et al. The International Prognostic Scoring System for Waldenstrom's macroglobulinemia is applicable in patients treated with rituximab-based regimens. Haematologica. 2008;93(9):1420–1422. doi:10.3324/haematol.12846