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ORIGINAL ARTICLE

Significance of Common Blood Test Indexes in the Diagnosis and Prognosis of Multiple Myeloma

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SUMMARY

Background: **The goal of this study is to explore the clinical value of routine tests in multiple myeloma (MM).**
Methods: **A total of 179 MM patients, newly diagnosed in our hospital from January 2010 to December 2018 (case group), as well as 352 cases of healthy individuals (control group) were evaluated. Albumin (Alb), globulin (Glb), albumin/globulin (A/G), creatinine (Cr), calcium (Ca), hemoglobin (Hb), lactate dehydrogenase (LDH), platelet count (Plt), and platelet distribution width (PDW) were compared between the analyzed groups. Respective tests were screened by forward selection. Thereafter, screened out indicators were identified through logistic regression analysis. Risk prediction nomogram, area under curve (AUC), calibration, decision curve analysis (DCA), and clinical impact curve (CIC) were further performed. At the same time, routine test indicators of MM patients for stage and subtype diagnosis, were compared. A correlation analysis between these test indicators and respective disease stages was performed. High stage group and low stage groups were subsequently compared to define the predictive value of single and combined indicators of disease severity.**
Results: **Except for Ca, the difference between the case and control groups for all other blood indicators was statistically significant ($p < 0.05$). Moreover, the difference in positive rate(s) was statistically significant ($p < 0.05$). The receiver operating characteristic (ROC) curve of Alb, Hb, and PDW harbored robust discrimination (AUC = 0.960) and appropriate calibration. The DCA and CIC showed that the resulting nomogram had a superior net benefit in predicting MM. Among all indicators, only LDH was statistically reduced in MM patients at ISS stages I, II, and III ($p < 0.05$). Interestingly, the ISS stage of respective MM patients was positively correlated with Cr ($\tau = 0.392$), while it was negatively correlated with Hb ($\tau = -0.364$). Alb, Glo, A/G, and Hb were significantly distinct between heavy chain (IgG, IgA) and LC, while few significant differences were found between the ISS stages. Lastly, the AUC (0.828) for Cr was greater than that for all other single and combined indicators.**
Conclusions: **The effective application of major indicators measured in routine blood tests can provide important clues for the diagnosis and prognosis of MM.**
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KEY WORDS

multiple myeloma, blood test indexes, diagnosis, International System Staging, subtypes, prognosis

INTRODUCTION

Multiple myeloma (MM) represents the second most common hematologic cancer, accounting for 1.4 percent of all cancers and 10 percent of hematologic malignancy [1,2]. MM is a disease characterized by clonal proliferation of malignant plasma cells in the bone marrow, with some variable clinical presentations including anemia, bone lesions, hypercalcemia, and renal failure [3, 4]. MM is largely diagnosed among older patients, where the median age over 70 years old. With the advance of the aging process, it has been predicted that the number of elders diagnosed with MM will increase remarkably, and MM might become one of the most severe diseases that affect human health in America [5,6]. To date, a number of therapeutic strategies, from autologous hematopoietic stem cell transplantation to novel targeted drug therapy, have evolved and significantly improved the positive clinical outcome of MM. Since a subset of organs is affected by this condition to different degrees and order, MM exhibits very complex and diverse clinical signs and symptoms. In fact, the initial diagnosis of most MM patients is often indicated by non-hematological medical departments, reiterating that the early diagnosis of MM can be challenging.

Routine blood tests are typically considered an initial step of clinical examination performed during hospitalization, thus providing a first impression of the patient's condition and playing an important role in aiding the diagnosis and treatment of MM. Blood/plasma indicators such as albumin (Alb), globulin (Glo), albumin/globulin (A/G), creatinine (Cr), calcium (Ca), hemoglobin (Hb), lactate dehydrogenase (LDH), platelets (Plt) and platelet distribution width (PDW) have been suggested to be relevant to the diagnosis (including subtype and ISS stage) and prognosis of MM [3-5,7-11], as well as complementing each other to reflect the condition. Based on this rationale, we have presently explored the clinical value of routine tests in MM in order to help doctors, especially non-hematologists, to diagnose MM at early stages and, moreover, to gain an initial understanding of this condition in affected patients.

MATERIALS AND METHODS

Patients

Patients were clinically diagnosed with MM at the People's Hospital of Zhejiang Province, between January 1, 2010, and December 31, 2018. Subjects had to meet the following basic exclusion criteria: (1) age < 18 years; (2) presence of primary kidney disease or kidney disease with other causes; (3) use of antiplatelet agents; and (4) detection of secondary tumor(s). All patients conformed to the diagnostic criteria of MM [12], representing a total of 72 females and 107 males with a mean age of 65 years. All patients were newly diagnosed and not previously treated. Data was also collected from 5,000 healthy subjects presenting no malignancies and who underwent routine physical examination during the same period of evaluation. To balance age and gender between MM patients and healthy counterparts, 1:2 propensity score matching (PSM) was utilized with a caliper of 0.2 SD. Finally, 352 healthy individuals were gathered as control by PSM.

Recorded materials

According to medical literature and clinical experience, the age of onset, gender, disease subtype, International Staging System (ISS), in addition to serum test results related to albumin (Alb), globulin (Glo), albumin/globulin (A/G), creatinine (Cr), serum calcium (Ca), hemoglobin (Hb), lactate dehydrogenase (LDH), platelet (Plt) count, and platelet distribution width (PDW) were recorded by data systems for hospitals and analyzed. β2MG was only recorded in MM patients.

Statistics

Statistical analysis was performed using SPSS 26.0 and R 4.0.3 software. Continuous data were tested by *t*-test, while categorical data were tested by chi-squared test (between 2 groups). Continuous data were also evaluated by analysis of variance (ANOVA) in multiple groups. The most important variables identified by the forward selection (likelihood ratio test) were eventually enrolled in multiple logistic regression. In addition, receiver operating characteristic (ROC) curve and calibration curve obtained for the dataset were drawn separately. Area under the curves (AUCs) were calculated with 95% confidence intervals. A nomogram was designed according to the final logistic regression model. Decision curve analysis (DCA) and clinical impact curve

(CIC) were further performed to assess the validation and clinical net benefit of the risk prediction nomogram. The correlation between the test indicators and the ISS stages was performed by Kendall's tau. ISS stage III was selected as the high stage group, while ISS stages I and II were included in the low stage group. Similarly, the most important variables identified, according to a forward selection (likelihood ratio test), were enrolled in multiple logistic regression and, therefore, ROC curves for single and these identified variables were defined. A p-value (p) lower than 0.05 was established as a cutoff for statistical significance.

RESULTS

Comparison of routine tests between the case and control groups

Respective clinical groups were matched according to their age and gender. As indicated in Table 1, the difference in Ca levels (mean value) was not statistically significant. In contrast, other serum tests showed statistical significance, with $p < 0.05$ (Table 1). According to the clinical reference range of the hospital, the routine test indication between the case and control groups was negative within the interval, and positive outside the interval. All tests between groups presented statistical significance (Table 2).

The predictive value of routine tests for MM

According to our previous statistical results, most valuable and independent continuous variables ($p < 0.05$) were selected to define a ROC curve. AUC analysis is presented in Table 3. All eight statistically significant variables were further included according to a forward selection (likelihood ratio test). Finally, three selected variables (Hb, Alb, and PDW) were filtered out and included in the logistic regression analysis. According to the logistic model, Alb, Hb, PDW were defined as protective factors for predicting MM occurrence that OR < 1 (Table 4). These variables were then analyzed to further establish a diagnostic mode. Both ROC and calibration curve were drawn, respectively, in Figure 1 and 2. The AUC for this diagnostic model was 0.960, with a sensitivity of 0.860 and a specificity of 0.957 (Table 3). In order to provide clinicians with a quantitative method to more accurately (and earlier) predict the diagnosis of MM patients, a predictive nomogram was constructed based on a logistic regression analysis that combined Hb, Alb, and PDW (Figure 3). To assess the clinical validity of the risk prediction nomogram, both DCA (Figure 4) and CIC (Figure 5) were performed. Risk prediction nomograms are likely to yield more net clinical benefit on the decision curve as compared to an all-screening or non-screening strategy. Using this risk model, the CIC visualizes the estimated number of people considered to be at high risk and true positives, ranging from 0 to 1.

Comparison of routine test indicators at different ISS stages

Routine test indicators, annotated at distinct ISS stages, were further compared to estimate their clinical value in MM. As shown in Table 5, age was significantly more prominent in patients at ISS stage II when compared to stage I ($p < 0.05$), while A/G and Hb levels were significantly lower ($p < 0.05$). Moreover, age, Cr, and LDH levels were significantly higher in patients at ISS stage III when compared to those at stage I ($p < 0.05$), while A/G and Hb content were significantly lower ($p < 0.05$). In contrast, Cr and Ca were significantly higher ($p < 0.05$), while Hb was significantly lower ($p < 0.05$) in patients at ISS stage III when compared with those at stage II. No statistical difference was detected for all other indicators. Consistently, a significant decrease in LDH levels was observed in patients at all stages (i.e., ISS I, II, and III) in Table 5. Of note, Cr and Hb tended to increase, while Plt and PDW appear to decrease.

Comparison of routine tests between different MM subtypes

Due to the limited number of subjects, patients with MM subtypes other than IgG, IgA, and LC were not statistically analyzed. No statistically significant differences in the clinical MM characteristics were detected, nor in various tests comparing patients with IgG and IgA subtypes (Table 6). The IgG subtype had a significantly lower content of Alb and A/G but, in contrast, a significantly higher level of Glo and Hb when compared to LC. Similarly, IgA was significantly lower than LC in regard to Alb and A/G levels ($p < 0.05$), but significantly higher for Glo and Hb yields ($p < 0.05$). All other indicators were not statistically significantly distinct. The percentage of patients with ISS stage I related to IgG, IgA, and LC subtypes accounted for 44.0%, 36.9%, and 12.0%, while for ISS stage II 44.0%, 37.3%, and 16.0% and for ISS stage III 35.4%, 25.3%, and 30.4%, respectively. When comparing the ISS stages related to IgG, IgA, and LC subtypes in a two by two comparison, the differences were not statistically significant, except for ISS stage III patients with IgA and LC subtypes.

Correlation analysis of various routine test indicators within ISS stages

Table 7 illustrates the correlation analysis performed between various routine test indicators and ISS stages. In MM patients, a mild negative correlation was observed between Hb and ISS stage ($\tau = -0.364$, $p < 0.05$). In addition, a mild positive correlation between Cr and ISS stage was noticed ($\tau = 0.392$, $p < 0.05$). No other tests were significantly correlated with ISS stages.

Standard test indicators to assess MM severity

To properly compare the impact of disease severity, ISS stage III was included as high stage group, while ISS stages I and II were added into the low stage group. Considering that ISS was assessed by β2MG and Alb

Table 1. Baseline characteristics for MM and healthy.

Variable	Patient	Healthy	p
n	179	352	
Age (years)	65.66 ± 11.55	64.79 ± 12.69	0.428
Gender (m/f)	1.49	1.36	0.642
Alb (g/L)	33.91 ± 6.83	43.45 ± 3.43	< 0.001
Glo (g/L)	44.26 ± 22.95	29.08 ± 3.49	< 0.001
A/G	1.03 ± 0.59	1.52 ± 0.23	< 0.001
Cr (μmol/L)	170.85 ± 238.51	82.33 ± 14.84	< 0.001
Ca (mmol/L)	2.30 ± 0.34	2.32 ± 0.10	0.376
Hb (g/L)	94.57 ± 25.90	141.49 ± 17.09	< 0.001
LDH (IU/L)	192.77 ± 73.60	179.81 ± 40.21	< 0.001
Plt (10^9/L)	168.74 ± 82.53	196.24 ± 57.54	< 0.001
PDW (fL)	15.26 ± 11.17	25.05 ± 18.18	< 0.001
β2MG (mg/L)	8.47 ± 11.39		

Alb - albumin, Glo - globulin, A/G - albumin/globulin, Cr - creatinine, Hb - hemoglobin, LDH - lactate dehydrogenase, Plt - platelet count, PDW - platelet distribution width, β2MG - β2-microglobulin.

Table 2. Baseline characteristics for MM and healthy (positive rates).

Variable	Patient	Healthy	p
n	179	352	
Alb (%)	141 (78.8)	47 (13.4)	< 0.001
Glo (%)	179 (100)	2 (0.6)	< 0.001
A/G (%)	110 (61.5)	30 (8.5)	< 0.001
Cr (%)	47 (26.3)	5 (1.4)	< 0.001
Ca (%)	77 (43.0)	14 (4.0)	< 0.001
Hb (%)	160 (89.4)	53 (15.1)	< 0.001
LDH (%)	59 (33)	11 (3.1)	< 0.001
Plt (%)	64 (35.8)	40 (11.4)	< 0.001
PDW (%)	30 (16.8)	130 (36.9)	< 0.001
β2MG (%)	146 (81.6)		

Alb - albumin, Glo - globulin, A/G - albumin/globulin, Cr - creatinine, Hb - hemoglobin, LDH - lactate dehydrogenase, Plt - platelet count, PDW - platelet distribution width, β2MG - β2-microglobulin.

markers, these particular indicators were excluded from the current analysis. As shown in Table 8, the remaining indicators were able to predict the AUC of the high MM stage group. Subsequently, three other indicators - Cr, Ca, and Hb - were screened out by the forward selection (likelihood ratio test). Unfortunately, the AUC of this multivariate model (0.823), while much higher than the AUC of the other univariate variables, is lower than the AUC of Cr (0.828). Finally, it was concluded that Cr provided the highest value in predicting the severity of patients' disease (Table 8, Figure 6).

DISCUSSION

Since 1990, the incidence of MM has shown a consistent increase, especially in countries with intermediate and low socio-demographic indices [13]. The incidence of MM in China is about 1 per 100,000 individuals [14] and, even though it is considered a common hematolog-

Table 3. AUC area for routine tests to diagnose MM.

Variable	Sensitivity	Specificity	AUC
Alb	0.777	0.898	0.890
Glo	0.531	0.960	0.636
A/G	0.553	0.974	0.758
Cr	0.458	0.898	0.650
Hb	0.799	0.943	0.931
LDH	0.330	0.869	0.518
Plt	0.570	0.727	0.646
Pdw	0.939	0.327	0.663
Ca	0.567	0.872	0.689
Alb + Hb + PDW	0.860	0.957	0.960

Alb - albumin, Glo - globulin, A/G - albumin/globulin, Cr - creatinine, Hb - hemoglobin, LDH - lactate dehydrogenase, Plt - platelet count, PDW - platelet distribution width.

Table 4. Logistic regression analysis of Alb, Hb, and PDW to predict the occurrence of MM.

Variable	B	S.E.	Wald	df	Sig.	Exp (B)	95% CI for EXP (B)	
							Lower	Upper
Alb	-0.227	0.037	38.088	1	0.000	0.797	0.741	0.856
Hb	-0.089	0.010	73.619	1	0.000	0.914	0.896	0.933
PDW	-0.039	0.011	13.031	1	0.000	0.961	0.941	0.982

Alb - albumin, Hb - hemoglobin, PDW - platelet distribution width.

Table 5. Characteristics for ISS stage.

ISS	I	II	III	p		
				1 vs. 2	1 vs. 3	2 vs. 3
n (%)	25 (13.97)	75 (41.90)	79 (44.13)			
Age (years)	60.16 ± 13.37	66.21 ± 11.22	66.87 ± 10.88	0.023 *	0.011 *	0.720
Gender (m/f)	1.50	1.14	1.93	0.919	0.941	0.310
Glo (g/L)	36.17 ± 18.36	46.59 ± 21.06	44.61 ± 25.51	0.065	0.210	0.592
A/G	1.37 ± 0.54	0.91 ± 0.52	1.04 ± 0.64	0.002 *	0.043 *	0.389
Cr (µmol/L)	84.78 ± 14.70	103.46 ± 129.75	262.07 ± 314.03	0.534	0.000 *	0.000 *
Hb (g/L)	168.12 ± 36.60	187.25 ± 64.60	205.80 ± 87.15	0.199	0.008 *	0.352
LDH (IU/L)	114.76 ± 20.71	100.27 ± 25.16	82.78 ± 22.26	0.008 *	0.000 *	0.000 *
Plt (10^9/L)	191.40 ± 66.62	172.85 ± 85.23	157.66 ± 83.56	0.330	0.075	0.253
PDW (fL)	20.80 ± 18.83	14.83 ± 8.79	13.93 ± 9.50	0.357	0.247	0.904
Ca (mmol/L)	2.30 ± 0.21	2.20 ± 0.28	2.40 ± 0.39	0.117	0.344	0.001

Glo - globulin, A/G - albumin/globulin, Cr - creatinine, Hb - hemoglobin, LDH - lactate dehydrogenase, Plt - platelet count, PDW - platelet distribution width.

Table 6. Characteristics for different subtypes.

Subtypes	IGG	IGA	Light-chain	Others	p		
					IGG vs. IGA	IGG vs. LC	IGA vs. LC
n (%)	72 (40.22)	57 (31.84)	39 (21.79)	11 (6.15)			
Age (years)	65.75 ± 10.02	66.70 ± 12.73	64.18 ± 12.29		0.644	0.497	0.297
Gender (m/f)	1.00	1.59	2.25		0.733	0.253	0.967
Alb (g/L)	33.49 ± 7.34	32.23 ± 6.44	36.42 ± 5.72		0.290	0.029 *	0.003 *
Glo (g/L)	55.08 ± 23.18	46.30 ± 21.54	25.92 ± 8.83		0.157	0.000 *	0.000 *
A/G	0.80 ± 0.53	0.90 ± 0.52	1.53 ± 0.47		0.296	0.000 *	0.000 *
Cr (µmol/L)	141.41 ± 203.70	134.70 ± 131.47	231.52 ± 312.52		1.000	0.503	0.369
Ca (mmol/L)	2.23 ± 0.34	2.32 ± 0.28	2.33 ± 0.31		0.531	0.563	1.000
Hb (g/L)	185.68 ± 62.76	177.12 ± 74.87	225.85 ± 86.09		0.502	0.005 *	0.001 *
LDH (IU/L)	97.72 ± 27.51	95.28 ± 25.54	88.47 ± 23.83		0.595	0.074	0.207
Plt (10^9/L)	174.57 ± 70.34	160.19 ± 84.08	174.90 ± 99.83		0.329	0.984	0.394
PDW (fL)	15.40 ± 11.12	16.20 ± 13.01	14.03 ± 9.92		0.687	0.541	0.354
β2MG (mg/L)	8.07 ± 14.91	7.69 ± 8.24	9.85 ± 8.14		0.852	0.435	0.365
ISS (%)							
I	11 (44.0)	9 (36,0)	3 (12.0)	2 (8.0)	> 0.05	> 0.05	> 0.05
II	33 (44.0)	28 (37.3)	12 (16.0)	2 (2.7)	> 0.05	> 0.05	> 0.05
III	28 (35.4)	20 (25.3)	24 (30.4)	7 (8.9)	> 0.05	> 0.05	< 0.05 *

Alb - albumin, Glo - globulin, A/G - albumin/globulin, Cr - creatinine, Hb - hemoglobin, LDH - lactate dehydrogenase, Plt - platelet count, PDW - platelet distribution width, β2MG - β2-microglobulin, LC - light chain.

Table 7. Correlation of routine tests with ISS stage.

Variable	ISS	
	τ	p
Age	0.079	0.181
Glo	0.011	0.857
A/G	-0.076	0.195
Cr	0.392	0.000 *
Hb	-0.364	0.000 *
LDH	0.123	0.036 *
Plt	-0.138	0.019 *
PDW	-0.107	0.070
Ca	0.030	0.511

Glo - globulin, A/G - albumin/globulin, Cr - creatinine, Hb - hemoglobin, LDH - lactate dehydrogenase, Plt - platelet count, PDW - platelet distribution width.

ical illness, it is a rare condition to be diagnosed by non-hematology clinicians. Most patients affected by MM are not initially seen by a hematology team but instead in other departments related to the clinical symptoms. Moreover, non-hematologists are often unaware of clinical MM features, which frequently leads to some misdiagnosis and therefore delaying the proper patient treatment. Thus, enhancing the awareness and under-

Table 8. AUC area for tests to assess the severity of the condition.

Variable	Sensitivity	Specificity	AUC
Glo	**0.291**	**0.860**	**0.526**
A/G	**0.304**	**0.850**	**0.504**
Cr	**0.772**	**0.780**	**0.828**
Hb	**0.722**	**0.690**	**0.746**
LDH	**0.506**	**0.740**	**0.417**
Plt	**0.695**	**0.500**	**0.585**
PDW	**0.532**	**0.610**	**0.579**
Ca	**0.316**	**0.900**	**0.625**
Cr + Hb + Ca	**0.633**	**0.880**	**0.823**

Glo - globulin, A/G - albumin/globulin, Cr - creatinine, Hb - hemoglobin, LDH - lactate dehydrogenase, Plt - platelet count, PDW - platelet distribution width.

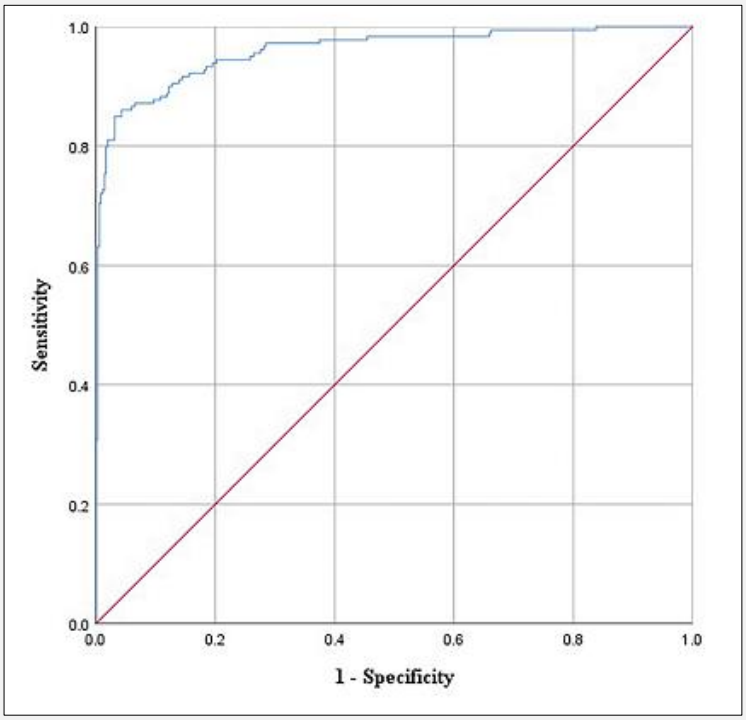

Figure 1. ROC curve of Hb, Alb and Pdw.

tanding of multiple myeloma among non-hematologists is warranted.

Most MM patients are frequently anemic, due to the abnormal proliferation of myeloma cells, accompanied by excessive apoptotic effects on erythroid precursor cells and/or overproduction of hepcidin [15]. Hepcidin, a small peptide mainly produced by hepatocytes, is expressed on many other cells involved in iron metabolism. Ferroportin is the main target of hepcidin. When bound to hepcidin, it prevents iron transport from the in-

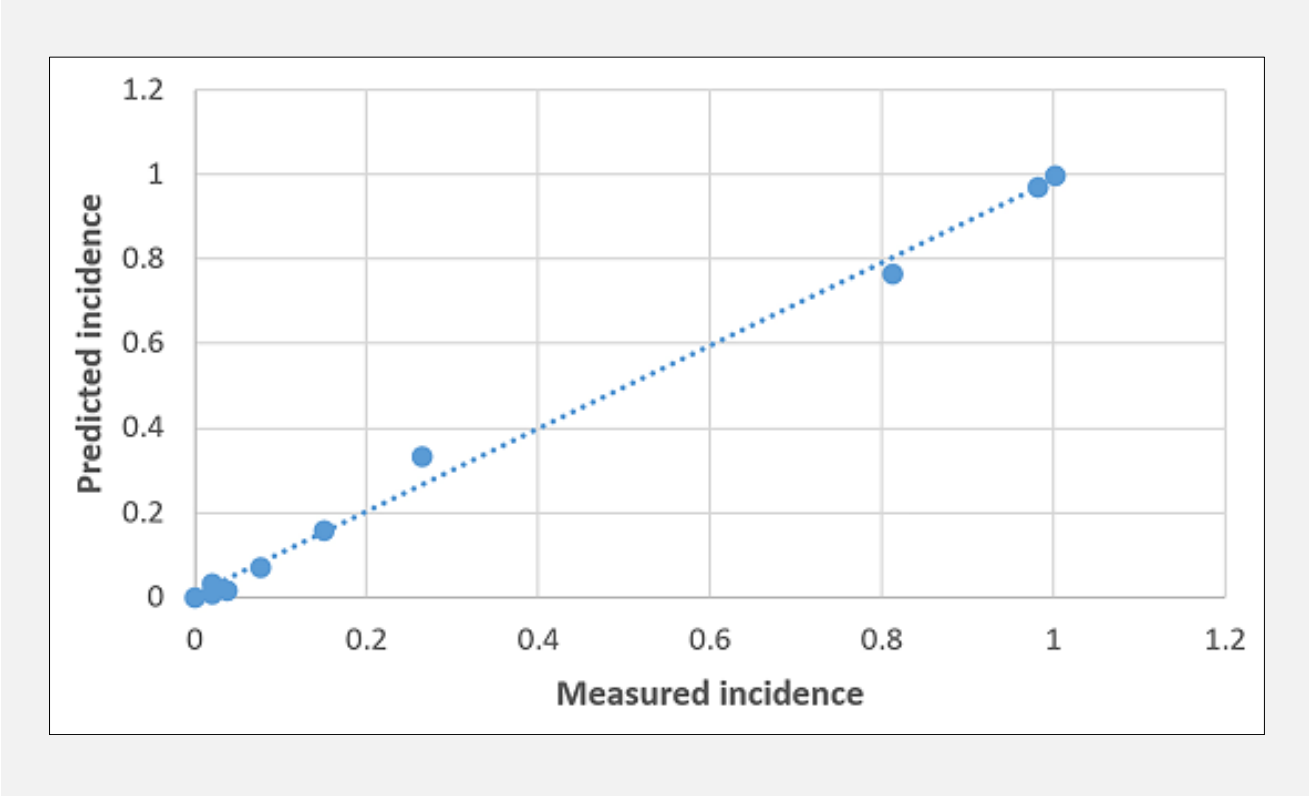

Figure 2. Calibration curve of Hb, Alb and Pdw.

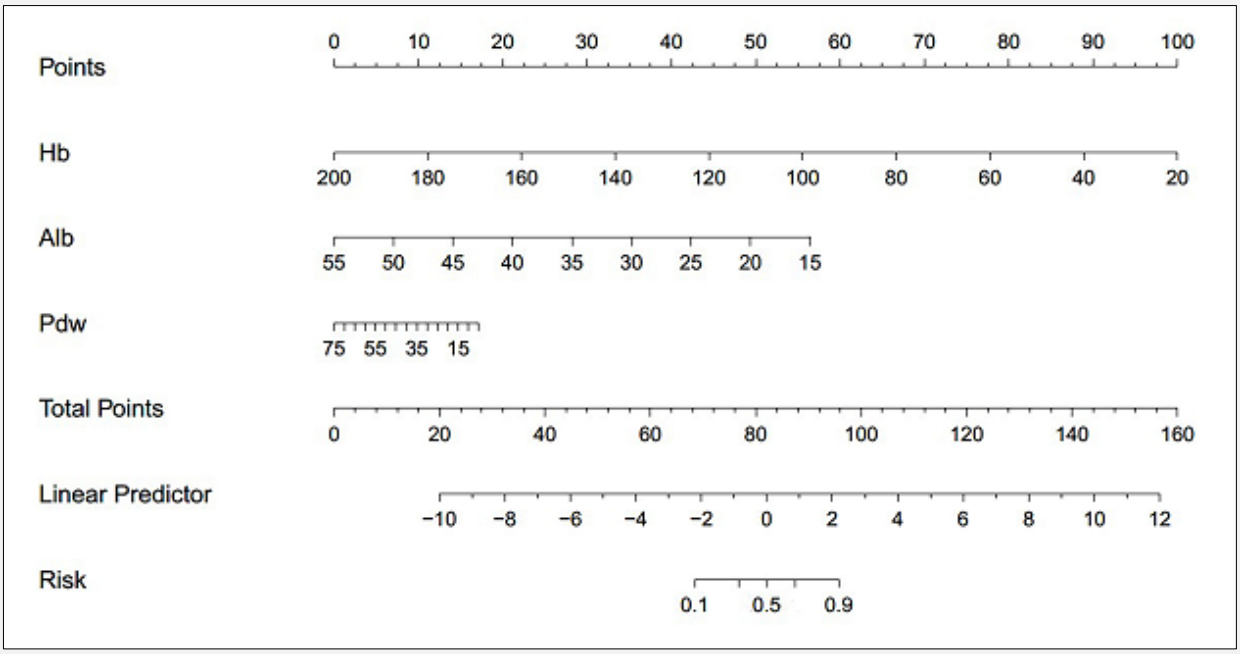

Figure 3. Nomogram for the prediction of the probability of MM.

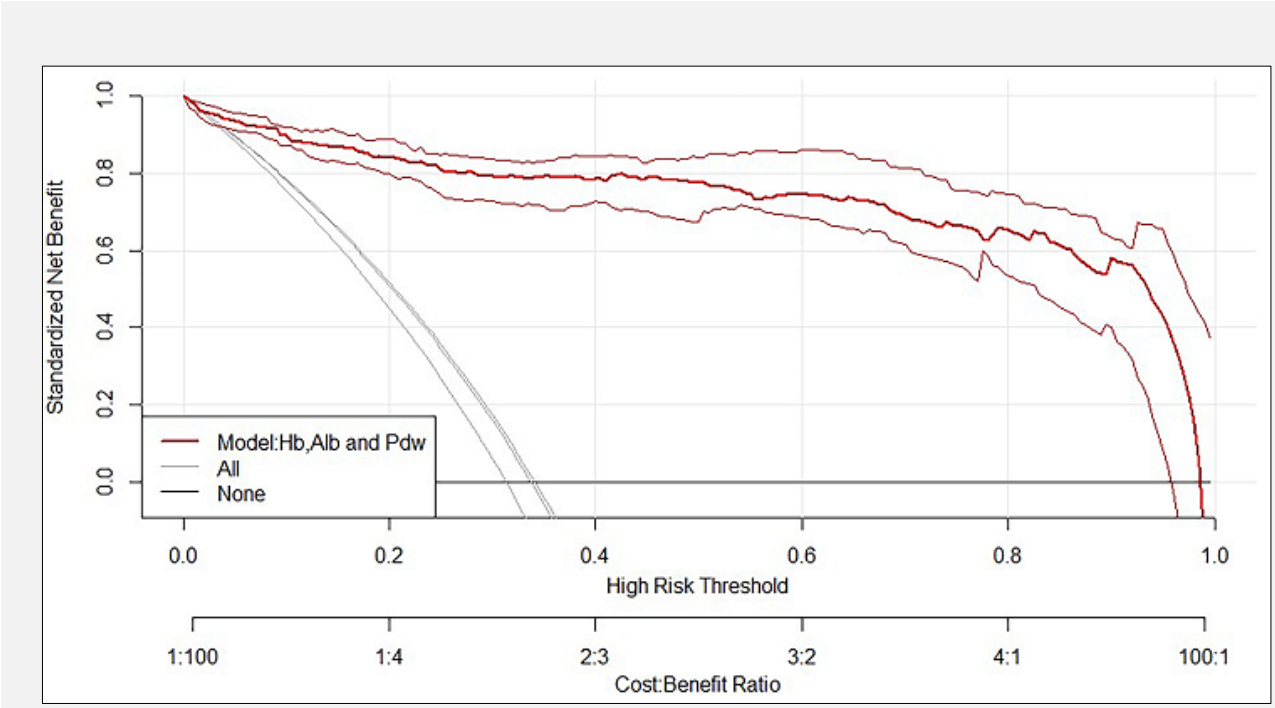

Figure 4. Decision curve analysis.

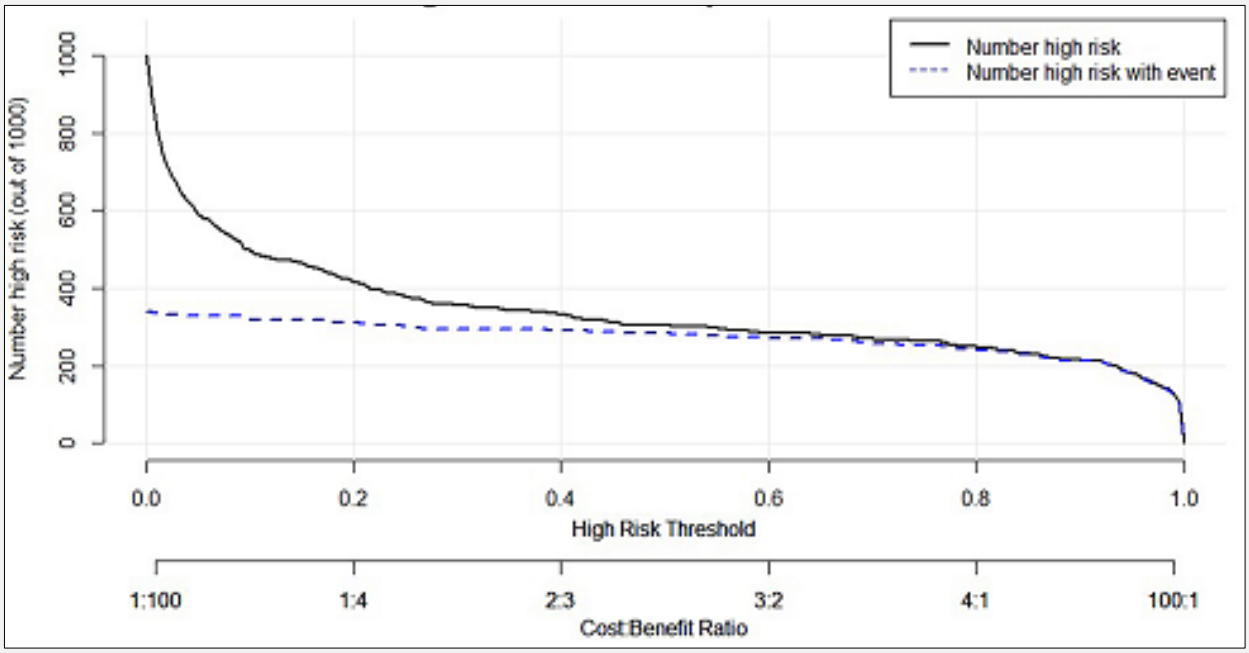

Figure 5. Clinical impact curve.

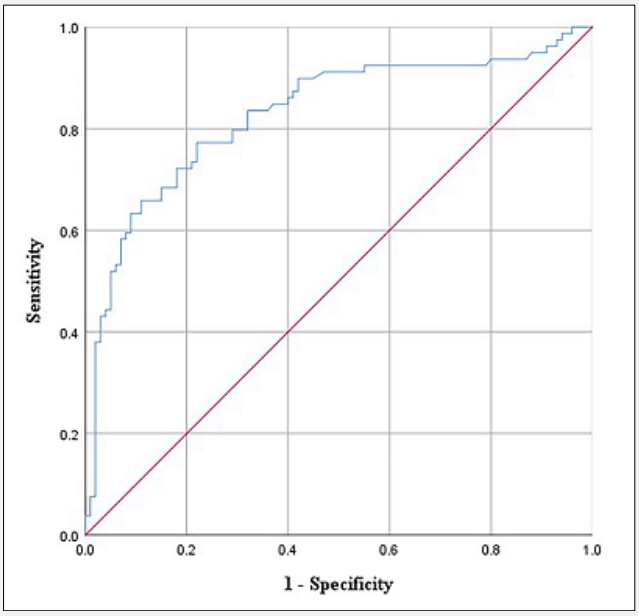

Figure 6. ROC curve of Cr to assess severity of condition.

testinal epithelium and release from the reticuloendothelial cell system, ultimately leading to anemia [16,17]. Hemoglobin (Hb) content, as well as red blood cell counts, are largely reduced, with a mean Hb level of 94.57 ± 25.90 g/L in the case group, which is significantly lower than that in the healthy subjects ($p < 0.05$). A decrease in Hb levels can serve as a valuable indicator. Yet, due to the many diseases that cause anemia, it is clear that reduced Hb alone is not significant enough to predict MM [18-20].

Cr levels are typically elevated in 30 - 50% of myeloma patients at the time of diagnosis, while renal failure requires hemodialysis in 10% of affected patients [21]. Renal insufficiency has been associated with two main conditions: (i) light chain nephropathy and (ii) hypercalcemia [22]. In light chain nephropathy, the light chains exceed the capacity of the tubules to absorb them, resulting in the formation of tubular patterns in the distal convoluted tubule (DCT) of the kidney. These tubular obstructions, derived from precipitated light chains bound to Tamm-Horsfall mucoprotein, can obstruct the DCT and partial ascending medullary loop, triggering a megaloblastic response and leading to interstitial pneumonia. On the other hand, hypercalcemia can lead to the deposition of calcium salts along the renal tubules, increasing the toxicity of the filtered light chains and/or inducing reversible nephrogenic polyuria [23]. In the current study, the mean level of Cr in the case group (170.85 ± 238.51 mmol/L) was significantly higher than that in the healthy group (82.33 ± 14.84 mmol/L). Meanwhile, the positive rate of Cr in the case group was only 26.3%, possibly due to the fact that patients at different stages of the disease were related to different grades of renal injury, which represents one of the reasons for the higher rate of misdiagnosis of MM.

Some MM patients can experience bone destruction, resulting in the release of calcium deposited in the bone [24]. Hypercalcemia relates to a distinctive feature of MM and can be observed in 20 - 40% of newly diagnosed patients [25]. In our work, it is surprising that the positivity rate of Ca was significantly different when comparing the case and the healthy groups, but no statistical difference in regard to concentration was observed. Specifically, the concentration of Ca levels in the case group (2.30 ± 0.34 mmol/L) was lower than that in the healthy group (2.32 ± 0.10 mmol/L), which is inconsistent with other reports [26,27]. Yet, this may be related to the large loss of Alb, which may have masked the hypercalcemia [28].

Hypoproteinemia is a common clinical feature of MM and includes a variety of etiologies including malnutrition, renal insufficiency, and liver damage [29]. In contrast to Alb, Glo is subsequently elevated due to the abnormal increase in immunoglobulin content [30]. In the case of alterations in Alb and Glo levels, a significant decrease in A/G was detected. In fact, A/G has been reported as an independent prognostic factor for MM [9]. The metabolism of tumor cells is mainly supported by anaerobic enzymes [31]. LDH is a very important enzyme in the process of glucose metabolism, which is

widely distributed and also represents a very sensitive indicator of the metabolic state of cells. LDH catalyzes the conversion of L-lactate to pyruvate, during which nicotinamide adenine dinucleotide (NAD) is reduced to NADH [32]. It has been reported that increasing amounts of serum LDH are directly correlated with more progressive tumor malignancy and worse prognosis [33]. Indeed, Barlogie and colleagues [34] have found that elevated serum LDH index levels may affect the survival rate of MM patients.

In MM patients, the cause of thrombocytopenia is not known. Still, this condition may be caused by a decrease in thrombopoietin (TPO) or shortened platelet lifespan, platelet antibodies and other toxic substances [35]. In the current study, the PDW positivity rate was significantly different between the case and the healthy groups, where PDW levels in the patient group (15.26 ± 11.17 fL) were significantly lower than those in the healthy group (25.05 ± 18.18 fL). However, physicians rarely pay attention in the clinic to changes in PDW in MM patients. Moreover, there are a limited number of related studies and the mechanism is not yet clear. PDW is currently being researched more in solid tumors, as it has been identified as an unfavorable factor in cancers such as breast [36], esophageal [37], and colorectal cancers [38].

Presently, the mean values and positivity rates for Hb, Alb, PDW were significantly different between the case and healthy groups. Therefore, these three indicators were screened by the forward selection (likelihood ratio test) to be included in a logistic regression curve as risk factors for predicting MM. A ROC curve was also designed, with an AUC area of 0.960, a sensitivity of 0.860, and a specificity of 0.957. The AUC area of this multivariate model is higher than that of other Univariate models. So, this result indicated that these specific indicators present a high diagnostic value towards MM prediction.

Upon disease progression, various manifestations such as bone pain, anemia, renal insufficiency, infection, and hemorrhage may occur. Therefore, its treatment and prognosis may vary according to the tumor subtype and stage of the diseases. As such, the subtype and stage classification of MM after diagnosis can better guide medical treatment and overall prognosis. Therefore, while establishing a diagnostic model, we also expected to understand whether the conventional tests could be meaningful for predicting the stages and subtypes of MM patients. Correlation analysis showed that the ISS stage in MM patients was positively correlated with Cr levels and, at the same time, negatively correlated with Hb yields. According to our ANOVA results, although many indicators could be significantly different between the two different stages, only LDH was significantly different, where Cr tended to be higher in ISS stages. These results predict the importance of Hb, LDH, and Cr to discriminate the disease stages of MM patients. Since ISS stages are directly related to the prognosis of MM patients [39], while ISS stages are correlated with Hb, LDH, Cr in our study, these three indicators may be prognostic factors for MM patients.

Unfortunately, no significant differences in regard to the presence of certain indicators were found for all MM subtypes. In contrast, Alb, Glo, A/G, and Hb were statistically different when comparing the heavy chain and light chain subtypes of MM, suggesting that this subset of biomarkers may be of some significance in indicating the disease subtype. Yet, no statistically significant differences between the different subtypes were detected, except for the proportion of patients with ISS stage III between IgA and LC types. This means that there is no difference in the progression of the disease between the different subtypes of MM patients.

In summary, here we demonstrate that the analysis of a subset of standard blood/plasma indicators can help the medical community hospitals (particularly those with less clinical experience and/or devoid of hematology specialization). As such, this approach can support more accurate diagnostics, thus achieving the good effect of radiating quality medical resources to community and/or primary hospitals. At the same time, this approach may help doctors strengthen their diagnostic evaluation, allowing experienced clinical hematologists to pay more attention to the diagnosis and treatment of more challenging conditions, as well as reducing the pressure on doctors and enabling a more effective allocation of resources. Moreover, our model may help doctors make rapid diagnoses so that patients can be treated promptly and effectively. In addition, it can also improve the accuracy of doctors' hypothetical reasoning, thereby (i) reducing unnecessary invasive laboratory tests, (ii) causing side effects/intoxication due to overmedication, (iii) increasing unnecessary medical costs and, ultimately, (iv) reducing the burden on families.

The advantage of our study is that MM can be diagnosed by a simple blood test. Nevertheless, this study has several limitations. First, the hospital system has recorded fewer first-episode, first-treatment MM during the specified study period, thus resulting in a smaller total sample size. Second, this study was conducted in only one hospital and did not include other healthcare facilities. Third, no control group for MM related to other blood disorders was accounted. Finally, no follow-up of any patients was provided in this study due to the loss of telephone numbers as a result of the change of medical record system. In conclusion, the value of routine blood tests for MM has high clinical potential but they still require further experimental validation.

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The authors declare no competing financial interests.

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