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ORIGINAL ARTICLE

Establishment of Multiple Myeloma Diagnostic Model Based on Logistic Regression in Clinical Laboratory

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SUMMARY

Background: **Due to the insidious onset of multiple myeloma (MM), missed diagnosis and misdiagnosis have a serious impact on the health of MM patients. Simple, rapid, and valid laboratory screening is critical for MM clinical diagnosis.**

Methods: **We used routine laboratory tests to establish a simple, inexpensive, and non-invasive diagnostic model for MM based on logistic regression. In the retrospective analysis, a total of 273 newly diagnosed MM inpatients and 288 non-MM participants, from January 2016 to December 2018 in Beijing Chaoyang hospital, Capital Medical University, were divided into training set and validation set. Age, gender, and the related routine laboratory tests for MM, including albumin (ALB), globulin (GLB), lactate dehydrogenase (LDH), creatinine (Cr), calcium ($Ca2^+$), hemoglobin (Hb) and platelet (PLT), were analyzed by multivariate logistic regression to develop a diagnostic model.**

Results: **A diagnostic model was calculated using the formula $MM\ index = -(\frac{-18\times gender-3\times ALB-Hb}{10})$, based on the logistic regression. The MM index [22 (20 - 25)] of MM patients was significantly lower than that of non-MM [30 (29 - 31)] in the training set ($p < 0.001$). It showed an excellent diagnostic performance in diagnosing MM through a receiver operating characteristic (ROC) curve, and its corresponding sensitivity, specificity, and area under the curve (AUC) were 95.6%, 96.7%, and 0.982 (0.968, 0.997), respectively. At a diagnostic risk threshold of 28, the model identified MM with a sensitivity of 95.6% and a specificity of 98.1% by using independent validation data. There was a significant positive correlation ($r = 0.845$, $p < 0.001$) between the DS grading and the MM index among all the participants.**

Conclusions: **The established diagnostic model of MM index can successfully identify newly diagnosed MM from healthy controls. The diagnostic model of MM index may also act as a predictor of the severity of MM without therapy.**

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KEY WORDS

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INTRODUCTION

Multiple myeloma (MM) is a malignant tumor of plasma cells. It is one of the most common hematological malignancies. It is characterized by clonal proliferation and accumulation of plasma cells in the bone marrow [1], secretion of monoclonal immunoglobulin or its fragments (M protein), accompanied by extensive osteolysis or osteoporosis and anemia, infection, renal function damage and other clinical manifestations [2,3]. It has been reported that there are approximately 86,000 new invasive cases of MM, accounting for approximately 0.8% of all new cancer cases, and 63,000 related deaths, which represent 0.9% of all cancer deaths every year [4]. There are 159,985 (0.9% of all cancers) new cases and 106,105 deaths (1.1% of all cancer deaths), increasing markedly with age and with a male predominance [5]. The incidence of MM in China is about 1/100,000, lower than that in western industrialized countries (about 4/100,000), with an increasing trend year by year. Due to the insidious onset of MM and its diverse clinical symptoms, it may lead to misdiagnosis and missed diagnosis. Many patients are often diagnosed at the late stage of the disease, which causes patients to miss the optimal stage of treatment. In the treatment of MM, the prognosis is poor and the genetic and molecular mechanisms concerning MM remain unclear.

The standard screening workup includes bone marrow aspirate and biopsy, serum and urine protein electrophoresis, immunofixation electrophoresis, quantitation of immunoglobulins in serum or urine, routine laboratory tests, and image studies of the skeleton [6,7]. As the current laboratory tests for MM diagnosis are generally invasive and costly, a new non-invasive, inexpensive, and convenient method is desired that can diagnose MM with high sensitivity and specificity. Wang et al. [8] established a multiple myeloma diagnostic model using magnetic bead-based MALDI-TOF mass spectrometry of serum and pattern recognition software, which was suitable for preliminary assessment of MM with high sensitivity and specificity. MALDI-TOF MS is a highly sensitive and reproducible analytical platform for proteome profiling of human blood; however, it is not widely available in the laboratory, and it is also not suitable for wide screening in population. In this study, we developed a diagnostic model with the formula based on multivariate logistic regression for MM in the training set and subsequently validated the accuracy of this model by use of the other independent set of data.

MATERIALS AND METHODS

Study design

This is a retrospective case-control study. The inclusion criteria were as follows: the patients were newly diagnosed MM according to the Durie-Salmon staging system during their hospitalization. The exclusion criteria used for the final selection of cases were as follows: (1) the MM patients had been treated; (2) the clinical data were incomplete; (3) patients who were outpatients. The 273 patients (male/female 144/129, median age 61 years, age range 53 - 67) were newly diagnosed according to the diagnostic criteria for MM from the International Myeloma Working Group [9]. The non-MM participants, which served as healthy controls, were apparently healthy population from physical examination center. A total of 561 subjects were finally selected from Beijing Chaoyang Hospital from January 2016 to December 2018. Among them, the data of 344 subjects from 2016 to 2017 were used to develop the diagnostic model for MM, and the remaining data in 2018 were used for model validation.

Data collection

Clinical data were collected from hospital medical records. Laboratory data collected from the laboratory information system included ALB, GLB, lactate dehydrogenase (LDH), creatinine (Cr), calcium ($Ca2^{+}$), Hb, and PLT.

Ethical approval

The study was approved by the Ethics Committee of Beijing Chaoyang Hospital (2017-2-17-17). Owing to the anonymous and retrospective nature of the study, patient consent was not required.

Statistical analyses

Statistical analyses were performed using SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism software vision 6 (GraphPad Software Inc., San Diego, CA, USA). Statistical significance was defined when p-value was < 0.05. The normally distributed data are expressed as the mean ± standard deviation (SD) and were compared using Independent-Samples *t*-test. The non-normally distributed data are expressed as medians with the corresponding 25th and 75th percentiles (interquartile range) and compared using Mann-Whitney *U* tests. The risk factors of MM were obtained by binary logistic forward stepwise regression analyses using related variables. A new diagnostic model for MM was generated based on the B coefficient of the chosen variables of multivariate logistic regression. Receiver operating characteristic (ROC) analysis was performed to set the diagnostic cutoff value of the related clinical variables. Correlativity between the MM DS grades and the variables was performed by the nonparametric correlation analysis.

Table 1. Differences in the clinical characteristics and blood parameters between MM and control groups.

Items	All subjects	MM	Non-MM	p
Patients (n, %)	344 [100]	160 [47]	184 [53]	-
Gender (male, n, %)	191 [55]	86 [54]	105 [57]	0.538
Age (years)	59 (52 - 65)	60 (53 - 65)	58 (52 - 65)	0.433
ALB (g/L)	42.7 (36.1 - 45.1)	35.7 (30.0 - 39.7)	44.9 (43.4 - 46.4)	0.000
GLB (g/L)	31.1 (27.7 - 41.0)	43.7 (26.6 - 72.0)	29.7 (27.7 - 32.4)	0.000
LDH (U/L)	182 (150 - 212)	157 (133 - 215)	191 (173 - 211)	0.000
Cr (μmol/L)	69.2 (58.5 - 83.1)	72.1 (60.0 - 120.3)	67.9 (58.4 - 74.8)	0.000
Ca^{2+} (mmol/L)	2.34 (2.23 - 2.44)	2.25 (2.13 - 2.41)	2.38 (2.31 - 2.45)	0.000
Hb (g/L)	131 (98 - 147)	94 (74 - 111)	145 (136 - 154)	0.000
PLT (x 10^9/L)	211 (169 - 256)	180 (134 - 235)	225 (194 - 267)	0.000

Values are expressed as mean ± standard deviation, number, or median (Q1 - Q3).

Table 2. Multivariate logistic regression analysis of risk factors associated with MM.

Items	B	OR	95% CI	p-value
Gender	-2.608	0.074	(0.018, 0.297)	0.000
ALB (g/L)	-0.409	0.664	(0.549, 0.803)	0.000
H b(g/L)	-0.149	0.861	(0.821, 0.904)	0.000

RESULTS

A flow diagram of the participants selected for the study is presented in Figure 1.

Characteristics of study participants

According to the Durie-Salmon staging system, there were 20 cases in stage I, 27 cases in stage II and 113 cases in stage III. According to the results of immunofixation electrophoresis, there were 16 cases of Ig A κ, 20 cases of Ig A λ, 40 cases of Ig G κ, 33 cases of Ig G λ, 3 cases of Ig D λ, 19 cases of light chain κ, 11 cases of light chain λ, 5 cases of none secretory type, and 13 cases without clear typing.

The clinical characteristics and hematological parameters between the two groups are shown in Table 1. According to Independent-Samples *t*-test, there were seven significantly different hematological parameters between MM and non-MM, including ALB, GLB, LDH, Cr, Ca^{2+}, Hb, and PLT. However, age and gender were not statistically different between the two groups.

Development of the diagnostic model based on logistic regression analysis

Multivariate logistic regression analysis was used to establish the diagnostic model for MM (Table 2). Three influencing factors, including gender, ALB, and Hb, were found significantly correlated with MM after performing multivariate logistic regression analysis. A diagnostic model for MM was developed by the formula $MM\ index = -(\frac{-18\times gender-3\times ALB-Hb}{10})$, based on the B coefficient of related variables in the logistic model. As shown in Figure 2, the MM index of MM and control groups were 22 (20 - 25) and 30 (29 - 31), respectively. There was significant difference between the two groups ($p < 0.001$). Furthermore, MM patients also exhibited significantly lower ALB and Hb [35.7 (30.0 - 39.7) g/L; 94 (74 - 111) g/L, n = 160, $p < 0.001$] compared to non-MM [44.9 (43.4 - 46.4) g/L; 145 (136 - 154) g/L, n = 184, $p < 0.001$].

ROC analysis for diagnostic performance

ROC analysis was performed to evaluate the diagnostic value for MM of the three different influencing factors. The area under the curves (AUCs) were 0.944 [0.918, 0.971], 0.960 [0.939, 0.982], and 0.982 [0.968, 0.997] for ALB, Hb, and MM index, respectively (Table 3). Based on the optimum sensitivity and specificity, MM index showed the best diagnostic performance with a sensitivity and specificity of 95.6% and 96.7%, and its diagnostic threshold value was 28. Therefore, MM index was chosen as the diagnostic model for MM. The

Table 3. Parameters of ROC curves between MM and non-MM in training set.

	AUC	95% CI	p-value	Cutoff	Specificity	Sensitivity
ALB	**0.944**	**(0.918, 0.971)**	**0.000**	**41.4**	**94.6**	**86.3**
Hb	**0.960**	**(0.939, 0.982)**	**0.000**	**124**	**97.3**	**86.3**
MM index	**0.982**	**(0.968, 0.997)**	**0.000**	**28**	**96.7**	**95.6**

Table 4. The correlation between MM index and D-S clinical staging.

Item	r	p-value
MM index	**-0.845**	**0.000**
ALB	**-0.778**	**0.000**
Hb	**-0.822**	**0.000**

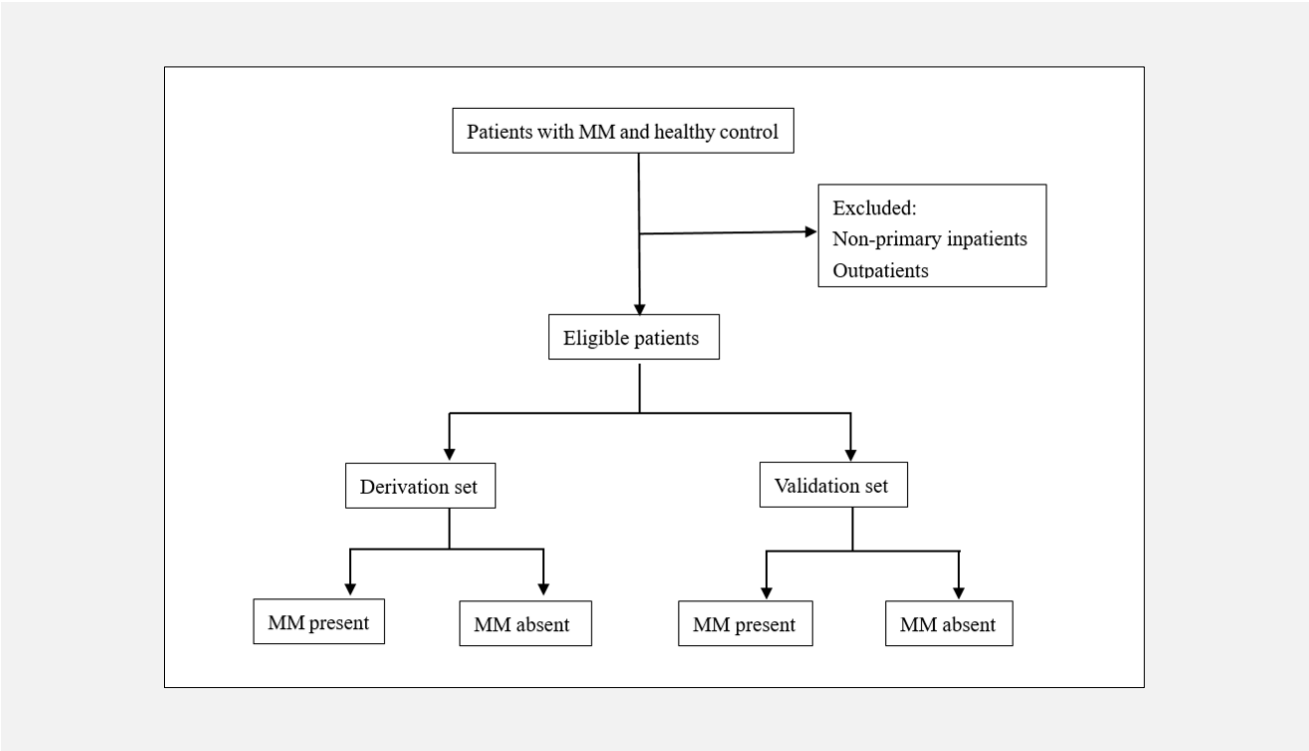

Figure 1. Flow diagram of study participants.

ROC curve for MM index for predicting the onset of MM was shown in Figure 3.

Model Validation in an independent set

To further validate these findings, the corresponding items were obtained in an independent set of 217 eligible participants with MM (n = 113) and non-MM (n = 104). The MM index was calculated according to the established diagnostic model based on the multivariate logistic regression model. The MM index was significantly lower in MM compared to non-MM groups [23 (21 - 25), vs. 29 (30 - 31), $p < 0.001$]. With the cutoff value of 28, the sensitivity and the specificity of the MM index were 95.6% and 98.1%, respectively.

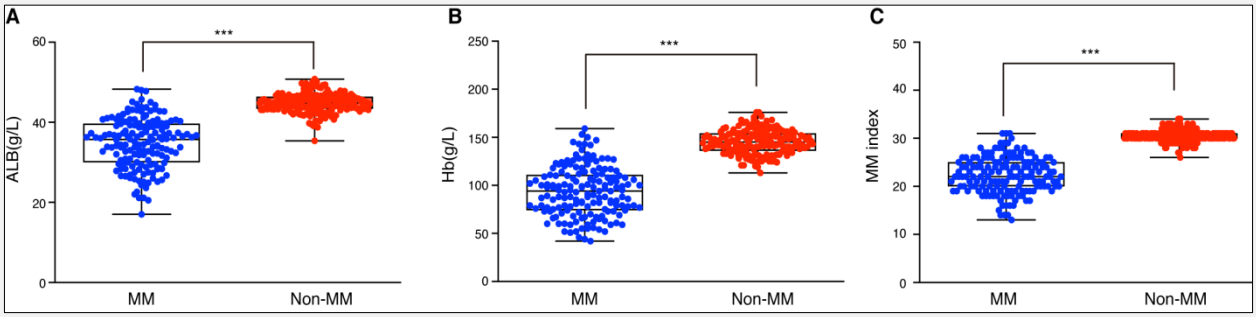

Figure 2. Comparison between MM and non-MM, ALB, and Hb levels were significantly lower in patients with MM than non-MM patients (95% CI [33.8 - 35.8], 95% CI [90 - 98], n = 160 vs. 95% CI [44.5 - 45.2], 95% CI [143 - 147], n = 184; p < 0.001), and MM index levels of MM patients were significantly lower than that of non-MMs (95% CI [22 - 23], n = 160 vs. 95% CI [30 - 31], n = 184; p < 0.001).

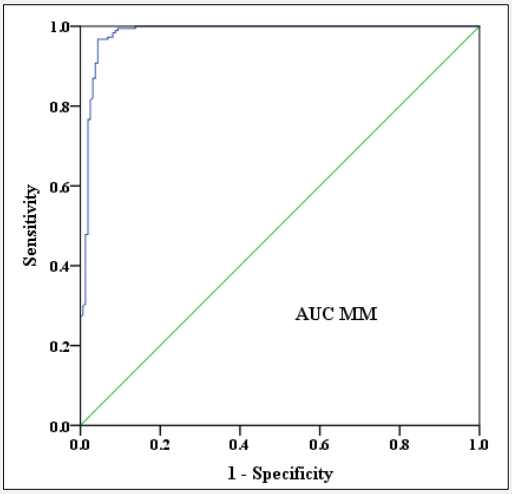

Figure 3. Diagnostic value of MM index in MM was examined through ROC analysis. The ROC curve revealed that MM index could be used to distinguish between patients with MM and patients without MM with an AUC value of 0.982, a cutoff value of 28, a sensitivity of 95.6%, and a specificity of 96.7%.

Correlativity between the DS grades and the MM index

The nonparametric correlation analysis was performed between the DS grades and the MM index among all the participants. There was an excellent negative correlation between the two parameters, with a correlation coefficient of -0.845, $p < 0.001$, which was higher than that of ALB and Hb (-0.778 and -0.822, respectively).

DISCUSSION

In the current study, based on the multivariate logistic regression analysis, a simple diagnostic model, composed of gender, ALB, and Hb, was established for MM. We found that the cutoff value for diagnosis (MM index = 28) can effectively distinguish MM patients from non-MMs. The MM index was negatively correlated with the severity of MM D-S clinical staging.

MM is an incurable malignancy of plasma cells with characteristics of excessive secretion of monoclonal immunoglobulin or light chains and lytic bone lesions [10]. Clinically, the patients with MM often present with bone pain, renal failure, anemia, hypercalcemia and susceptibility to infections and venous thromboembolism [11, 12]. As MM has non-specific clinical symptoms, especially in the early stage, it becomes difficult to make an accurate diagnosis and easy to commit a misdiagnosis or missed diagnosis [7]. Early diagnosis in clinical practice plays a key role to improve the prognosis of MM. The discovery of tumor biomarkers specific to MM will be of great significance to the early diagnosis and prognosis evaluation. Du et al. [13] and Puchades et al. [14] identified the specific metabolic profiles as MM biomarkers. Jiang et al. [15] demonstrated that circulating miR-125b-5p levels can be used as a diagnostic and predictive biomarker to discriminate individuals with and without MM and monitor response to treatment. Though these biomarkers were novel and non-invasive, they were not suitable for population screening for the quantitative formula or diagnostic threshold, owning to their high cost and operational complexity. The development of a diagnostic model specific to MM will be of great significance to the early diagnosis and prognosis evaluation and may play an important role for clinical treatment in order to delay the disease progression. Wang et al. [8] and He et al. [16] constructed diagnostic models for identifying individuals with MM based on MALDI-TOF mass spectrometry by several biomarkers. Both researchers laid a solid foundation for further studies by identification of some MM possible biomarkers. However, there were some limitations in the unconventional techniques and clinical application for people who appear to be healthy. Based on these problems, we assumed there were differences in routine laboratory tests between MM and non-MM. In our study, we compared the baseline of age, gender, and seven laboratory tests closely related to MM diagnosis and found those seven laboratory tests had significant differences between the two groups (Table 1). Therefore, we analyzed all these variables by the multivariate logistic regression analysis and hoped to establish a simple and available diagnostic model to identify MM patients from apparently healthy population. Based on the B coefficient of logistic model, a formula, composed of the screened influencing factors of gender, ALB, and Hb, was developed as a new risk index for MM. We identified the three influencing factors by multivariate logistic regression analysis (Table 2) and established a formula of $MM\ index = -(\frac{-18\times gender-3\times ALB-Hb}{10})$ as the diagnostic model of MM. We validated the diagnostic performance of the model by ROC analysis (Table 3). The AUCs of the 3 predictors, including ALB, Hb, and MM index, were 0.944, 0.960, and 0.982, respectively. However, considering the optimal diagnostic performance of the sensitivity and specificity, the MM index showed outstanding results.

The limitation of this study is that we did not include different types of disease controls in the research design, which probably narrows the clinical application of our novel diagnostic model.

CONCLUSION

The diagnostic model of MM index can successfully identify newly diagnosed MM from healthy controls. There was a negative correlation between MM index and the severity of MM. The established diagnostic model showed a potential value for clinical applications in differentiating primary MM from healthy controls and provided reliable evidence supporting the feasibility of non-invasive diagnosis of MM. The indicators involved in the model were inexpensive, convenient, and routinely available parameters in physical examination. The established diagnostic model for MM may offer an effective tool to help doctors optimize the diagnosis workflow, reduce workload, and improve diagnostic efficiency.

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Declaration of Interest:
The authors declare that they have no conflict of interest

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