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ORIGINAL ARTICLE

Association between Mean Corpuscular Hemoglobin and Platelet Distribution Width Ratio and Knee Osteoarthritis Severity

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SUMMARY

Background: **The goal was to simply and efficiently predict the indicators of disease severity in knee osteoarthritis (KOA) patients.**
Methods: **One hundred eighty-four patients with KOA and 126 healthy subjects were included. WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) was used as a reference index for disease severity in KOA patients, in which WOMAC < 80 was classified as mild and WOMAC ≥ 80 as moderate and severe. Blood routine parameters of the KOA and the healthy groups were analyzed by the Mann Whitney U test. Receiver operating characteristic curves were used to analyze the sensitivity and specificity of mean corpuscular hemoglobin and platelet distribution width ratio (MPR) and monocyte and hemoglobin ratio (MHR) indicators. The correlation between MPR and MHR and disease severity of KOA was determined by bivariate regression analysis. Independent predictors of disease severity in patients with KOA were assessed by multivariate regression analysis.**
Results: **MPR, MHR, and WOMAC were significantly higher in the KOA group. The ROC curve indicated that the cutoff values of MPR and MHR were 2.09 and 0.0030, respectively, with sensitivity of 86.4% and 68.5% and specificity of 99.2% and 79.4%. Bivariate regression analysis found that MPR was better correlated with disease severity than MHR. The results of multivariate regression analysis demonstrated that the MPR values of moderate and severe patients were more than 19 times that of mild patients, and the OR values were 21.695 and 19.558, respectively.**
Conclusions: **MPR and MHR demonstrated a good correlation with disease severity in patients with KOA. MPR is a potential independent predictor of disease severity in patients with KOA.**
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KEY WORDS

knee osteoarthritis, mean corpuscular hemoglobin and platelet distribution width ratio, monocyte and hemoglobin ratio, WOMAC

INTRODUCTION

Osteoarthritis (OA) is a common orthopedic degenerative chronic disease with changes dominated by articular cartilage damage accompanied by varying degrees of osteo proliferation and synovial inflammation [1,2]. The clinical symptoms are mainly characterized by joint pain, hypertrophy, stiffness, and limited joint movement [3,4]. OA tends to occur in the hands, hips and even whole-body weight-bearing joints, and especially most commonly in the knee joint. KOA mostly occurs in the elderly over 65 years of age, but the pathogenesis of KOA is still unclear. Its occurrence may be related to pathological changes of articular cartilage, incorrect walking posture, and excessive weight [5]. The main clinical manifestations were joint motion disorders and pain, which seriously affect the quality of life of patients. In the early stage of KOA, patients generally have unrestricted joint movement and insignificant pain sensation, thereby aggravating the progression of the disease [6,7]. The previous studies showed that the prevalence rate of osteoarthritis in China is as high as 27.18%, while the estimated prevalence rate of KOA in the global elderly over 65 years old is 3.8% [8-10]. At present, the treatment of clinical KOA is mainly to relieve patients' pain, delay disease progression, protect joint function, and adopt more surgical methods for patients with severe joint and ineffective medical treatment [6,11]. However, the side effects of long-term use of drugs cannot be ignored. There are fewer patients with postoperative recurrence, which seriously affects the quality of life of patients [12]. Thereby, it is important to find an effective detection index to predict the trend and severity of KOA.

Recently, neutrophil/lymphocyte ratio and lymphocyte/monocyte ratio have been widely recognized as effective indicators of inflammatory disease activity and prognosis, for example, breast cancer, systemic lupus erythematosus, acute myocardial infarction, etc. [13-16]. Platelet distribution width has also been found to have an important relationship with the occurrence of osteoarthritis [17]. However, these indicators can only reflect the acute attack phase of inflammatory diseases and have little significance for the prediction of the chronic phase. Therefore, we hope to identify the relationship between mean corpuscular hemoglobin and platelet distribution width ratio (MPR), monocyte and hemoglobin ratio (MHR), and the severity of KOA through our study and whether they can be used as independent factors to predict KOA severity.

MATERIALS AND METHODS

Study subjects

We reviewed the medical records of 184 patients who were diagnosed with KOA at Zhujiang Hospital of Southern Medical University between January 2020 and December 2020, including 18 males and 166 females with a mean age of 67.41 years. We also collected 126 healthy individuals as controls, with 59 males and 67 females with a mean age of 66.82 years.

Inclusion criteria

The patients fulfilled the diagnostic criteria of KOA by the American College of Rheumatology in 1995: i) history of knee pain; ii) age $\geq$ 40 years; iii) morning stiffness $\leq$ 30 minutes; iv) bone friction; v) X-ray with osteophyte formation; vi) joint fluid examination was consistent with osteoarthritis. i and v were satisfied. i, ii, iv, i, iii, iv could be diagnosed with KOA and included in our study cases [18]. vii) The age of the healthy group was $\geq$ 40 years.

Exclusion criteria

Knee or hip infection; 2) Various inflammatory diseases, malignancies, hematological diseases; 3) Rheumatoid arthritis, gout, immune arthritis, septic arthritis; 4) Liver and kidney dysfunction, heart disease, psychiatric disease, HIV and other infectious diseases. The study protocol first obtained informed consent from the relevant study subjects and was approved by the ethics committee affiliated with Zhujiang Hospital, Southern Medical University.

Outcome measures

WOMAC was used to evaluate the severity of disease in KOA patients [19,20]. The knee joint structure and function of the patients were mainly assessed from three major aspects: pain, stiffness, and joint function. In total, there are 24 assessment items containing the basic symptoms and signs of osteoarthritis with 5 items in the pain section, 2 items in the stiffness section, and 17 items in the joint function section. Each item is rated on a scale of 0 - 10, with higher scores representing more intense pain. A higher index of WOMAC indicates more severe OA, and the severity of OA was assessed according to the total score according to the following criteria: mild < 80, moderate and severe $\geq$ 80.

Biochemical and hematological measurements

After fasting for 12 hours, we used ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes to extract 3 mL of peripheral venous blood from 184 patients with KOA and 126 healthy subjects. Within 2 hours, the Japanese Symsex2100 automatic blood analyzer was used to detect the red blood cells, white blood cells, monocytes, platelets, hemoglobin, platelet distribution width, mean corpuscular hemoglobin and other items of the KOA and healthy groups. The normal range of mean corpuscular hemoglobin is 27 - 34 pg, the range of

platelet distribution width is 9.8 - 16.2 fL, the range of monocytes is 0.1 - 0.6 G/L, and the normal range of hemoglobin is 115 - 150 g/L. MPR was calculated by the ratio of mean hemoglobin content to platelet distribution width, and MHR was calculated by the ratio of monocytes to hemoglobin.

Demographic data

Typical clinical manifestations and clinical trials related to KOA were collected, including morning stiffness, knee pain (left/right/bilateral), osteophyte, grinding test, flexion test, extension test and floating patella test.

Statistics

All statistical data were processed by SPSS version 23.0 software. The values of quantitative or counting variables are mainly expressed as mean ± SD (standard deviation), and the percentage is mainly used to express the classification variables. ROC curve was used to analyze the sensitivity and specificity of MPR, MHR, hemoglobin, mean corpuscular hemoglobin, monocyte and platelet distribution width. Bivariate regression analysis was used to evaluated the correlation between MPR, MHR and disease severity in patients with KOA. Multivariate regression analysis was mainly used to assess the potential independent predictors of KOA severity. $p < 0.05$ represents statistical significance.

RESULTS

Basic characteristics of patients with osteoarthritis of knee joint

Table 1 shows the demographic, laboratory results, and clinical manifestations of 184 patients with knee osteoarthritis and 126 healthy physical examination patients. The average age of KOA patients was 67.41 years old, which was significantly higher than that of the health examination (66.82 years old), and the gender distribution of KOA was 166 (90%) compared with that of male patients 18 (10%), while the gender distribution of health subjects accounted for nearly 50% of men and women, the difference was statistically significant. Table 1 shows the proportion of female patients in the KOA group (166 (90%) vs. 67 (53%), $p < 0.001$), lymphocyte count (2.20 ± 0.81 vs. 2.10 ± 0.50, $p = 0.019$), monocyte count (0.34 ± 0.48 vs. 0.09 ± 0.28, $p < 0.001$), MPR (2.55 ± 0.54 vs. 1.99 ± 0.09, $p < 0.001$), MHR (0.0037 ± 0.0012 vs. 0.0026 ± 0.0006, $p < 0.001$), WOMAC (92.96 ± 35.93 vs. 0.00 ± 0.00, $p < 0.001$) were significantly higher than that of the healthy group. In contrast, erythrocyte in patients with KOA (4.32 ± 0.58 vs. 4.80 ± 0.55, $p < 0.001$), hemoglobin (127.27 ± 14.03 vs. 146.52 ± 12.55, $p < 0.001$), mean corpuscular hemoglobin (MCH, 29.58 ± 2.62 vs. 30.32 ± 1.53, $p = 0.012$), platelet count (246.28 ± 67.46 vs. 253.46 ± 48.19, $p = 0.008$), platelet distribution width (PDW, 11.89 ± 1.74 vs. 16.01 ± 0.16, $p < 0.001$) were significantly lower than that of the healthy group. There were no significant differences in other parameters such as age, leukocyte count, neutrophil count, hematocrit, mean red blood cell volume (MCV), mean hemoglobin concentration (MCHC), coefficient of variation of red blood cells (RDW-CV), mean platelet volume (MPV), and procalcitonin (PCT) in KOA group and healthy group.

Our results also showed that the typical clinical manifestations of KOA patients were morning stiffness (49, 27%), knee pain (71, 39%), osteophyte (47, 26%), and clinical positive patella grinding test (84, 46%), flexion test (78, 42%), over extension test (62, 34%), floating patella test (39, 21%) were significantly higher than that of the healthy group (Table 1, $p < 0.001$).

The ROC curve analysis of MPR and MHR

ROC curve was mainly used to analyze the sensitivity and specificity of MPR and MHR in patients with KOA. The area under the curve (AUCs) of MPR, MHR, MCH, PDW, hemoglobin (HB), and monocytes were 0.923, 0.800, 0.417, 0.027, 0.148, and 0.628, respectively. The area under the curve of MPR, MHR, and monocytes was statistically significant ($p < 0.001$, Figure 1B, C). However, the area under the curve of MCH, PDW, and Hb was less than 0.5, which was not statistically significant ($p < 0.001$, Figure 1A, B). The results of Figure 1C showed that the area under the curve of MPR in KOA patients was significantly larger than that of MHR, and the difference was statistically significant. The cutoff value of MPR was 2.09 (sensitivity 86.4%, specificity 99.2%, AUCs 0.923, $p < 0.001$), that of MHR was 0.0030 (sensitivity 68.5%, specificity 79.4%, AUCs 0.800, $p < 0.001$), and that of monocytes was 0.5 (sensitivity 34.2%, specificity 91.3%, AUCs 0.628, $p < 0.001$, in Table 2).

Comparison between the severity of disease in patients with KOA by cutoff values of MPR and MHR

KOA patients with MPR values above 2.09 had statistically significantly higher mean hemoglobin (MCH, 30.11 ± 1.90 vs. 26.31 ± 3.85, $p = 0.001$), mean corpuscular volume (MCV, 91.33 ± 4.87 vs. 81.69 ± 10.25, $p < 0.001$), mean hemoglobin concentration (MCHC, 329.60 ± 9.20 vs. 320.35 ± 11.25, $p = 0.01$) as well as WOMAC (94.28 ± 35.80 vs. 84.96 ± 36.32, $p = 0.023$) level (Table 3). Conversely, values for red blood cell count, coefficient of variation of red blood cells, platelet distribution width, and mean platelet volume were significantly lower in patients with KOA compared with MPR ≤ 2.09. However, there were no significant differences in white blood cell ($p = 0.247$), neutrophil ($p = 0.945$), lymphocyte ($p = 0.207$), monocytes ($p = 0.858$), hemoglobin ($p = 0.290$), hematocrit ($p = 0.657$), platelet ($p = 0.692$), and platelet ($p = 0.302$) counts at MPR greater or less than 2.09 (Table 3). For KOA patients, when the MHR was greater than 0.0030, the WBC count (7.35 ± 1.75 vs. 5.98 ± 1.64, $p < 0.001$), neutronphil count (4.25 ± 1.51 vs. 3.36 ± 1.47, $p < 0.001$), lymphocyte count (2.36 ± 0.88 vs. 2.01 ± 0.69, $p = 0.002$),

Table 1. Basic characteristics of KOA patients and healthy group.

	All objects n = 310	Health n = 126	KOA n = 184	p-value
Gender (female)	223 (72%)	67 (53%)	166 (90%)	< 0.001
Age (years)	67.17 ± 6.36	66.82 ± 3.50	67.41 ± 7.74	= 0.399
Leukocyte (G/L)	6.55 ± 1.61	6.33 ± 1.21	6.70 ± 1.83	= 0.422
Neutrophil (G/L)	3.75 ± 1.36	3.63 ± 1.00	3.83 ± 1.55	= 0.059
Lymphocyte (G/L)	2.15 ± 0.70	2.10 ± 0.50	2.20 ± 0.81	= 0.019
Monocyte (G/L)	0.24 ± 0.43	0.09 ± 0.28	0.34 ± 0.48	< 0.001
Erythrocyte (T/L)	4.51 ± 0.62	4.80 ± 0.55	4.32 ± 0.58	< 0.001
Hemoglobin (g/L)	135.10 ± 16.43	146.52 ± 12.55	127.2 ± 14.03	< 0.001
Hematocrit (%)	0.01 ± 0.11	0.02 ± 0.15	0.01 ± 0.08	= 0.668
MCH (pg)	29.88 ± 2.27	30.32 ± 1.53	29.58 ± 2.62	= 0.012
MCV (fL)	90.77 ± 5.88	91.94 ± 3.98	89.97 ± 6.78	= 0.174
MCHC (g/L)	328.86 ± 8.70	329.70 ± 6.22	328.29 ± 10.02	= 0.216
RDW-CV (%)	12.88 ± 1.08	12.68 ± 0.70	13.02 ± 1.26	= 1.121
platelet (G/L)	249.20 ± 60.39	253.46 ± 48.19	246.28 ± 67.46	= 0.008
PDW (%)	13.56 ± 2.43	16.01 ± 0.16	11.89 ± 1.74	< 0.001
MPV (fL)	10.32 ± 0.93	10.20 ± 1.01	10.40 ± 0.86	= 0.160
PCT (%)	0.00 ± 0.06	0.00 ± 0.00	0.01 ± 0.07	= 0.849
MPR	2.32 ± 0.50	1.99 ± 0.09	2.55 ± 0.54	< 0.001
MHR	0.0032 ± 0.0012	0.0026 ± 0.0006	0.0037 ± 0.0012	< 0.001
WOMAC (scores)	55.18 ± 53.44	0.00 ± 0.00	92.96 ± 35.93	< 0.001
Morning stiffness	-	-	49 (27%)	< 0.001
Knee pain	-	-	71 (39%)	< 0.001
Osteophyte	-	-	47 (26%)	< 0.001
Patella grinding test	-	-	84 (46%)	< 0.001
Over bend test	-	-	78 (42%)	< 0.001
Over extension test	-	-	62 (34%)	< 0.001
Floating patella test	-	-	39 (21%)	< 0.001

MCH: mean corpuscular hemoglobin; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; RDW-CV: coefficient of variation of red blood cell distribution width; PDW: platelet distribution width; MPV: mean platelet volume; PCT: platelet hematocrit; MPR: mean corpuscular hemoglobin and platelet distribution width ratio; MHR: monocyte and hemoglobin ratio; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2. Sensitivity and specificity of MCH, PDW, HB, monocytes, MPR, and MHR.

	MPR	MHR	MCH	PDW	HB	Monocytes
Cutoff value	2.09	0.0030	-	-	-	0.5
AUCs	0.923	0.800	0.417	0.027	0.148	0.628
Sensitivity	86.4%	68.5%	-	-	-	34.2%
Specificity	99.2%	79.4%	-	-	-	91.3%
p-value	< 0.001	< 0.001	0.013	< 0.001	< 0.001	< 0.001

MPR: mean hemoglobin content and platelet distribution width ratio; MHR: monocyte and hemoglobin ratio; MCH: mean corpuscular hemoglobin; PDW: platelet distribution width; HB: hemoglobin; AUC: area under the curve.

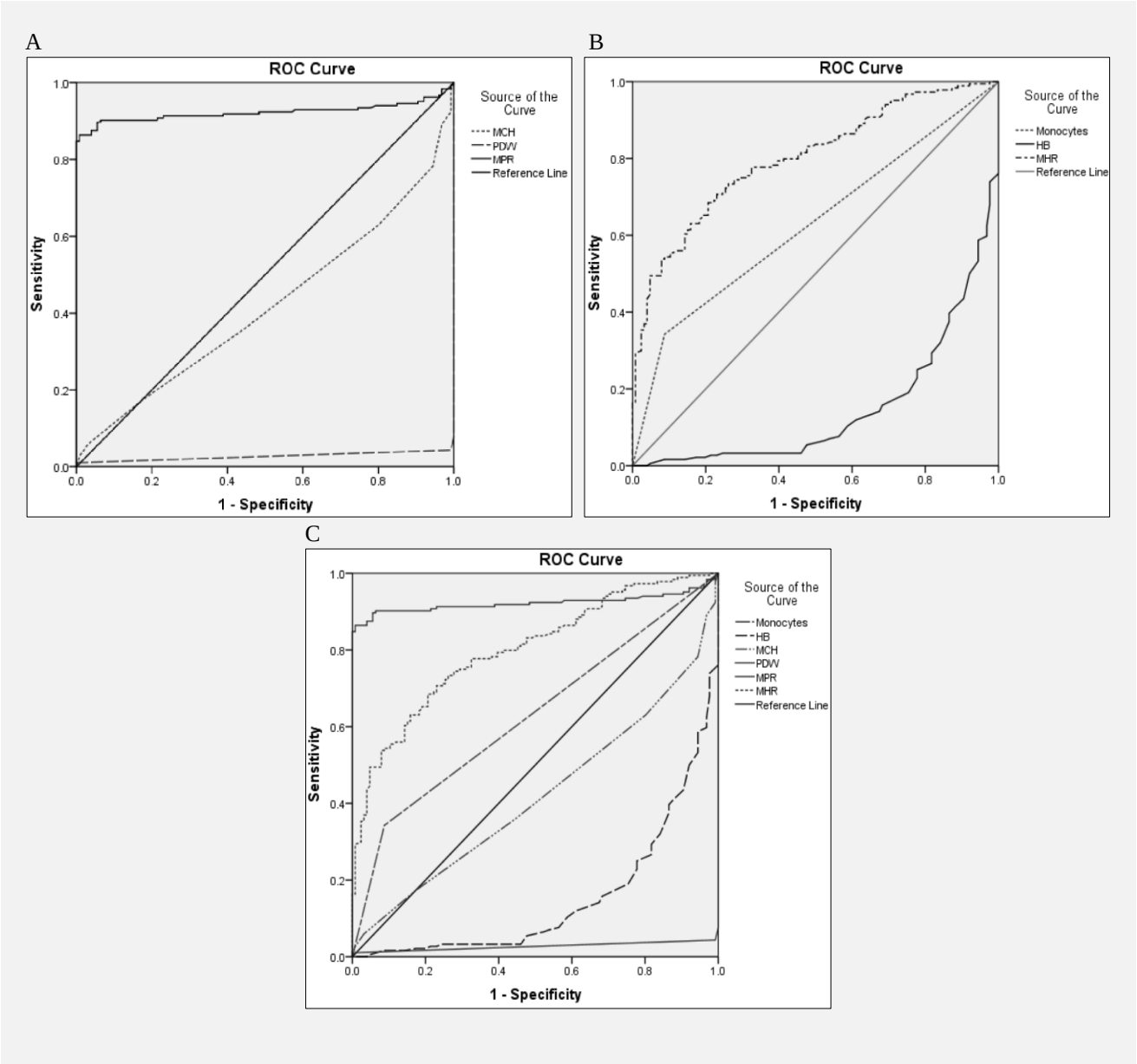

Figure 1. The ROC curve analysis of monocytes, HB, MCH, PDW, MPR, and MHR. (A) The ROC curve analysis of MCH, PDW, and MPR. (B)The ROC curve analysis of monocytes, HB, and MHR. (C) The ROC curve analysis of monocytes, HB, MCH, PDW, MPR, and MHR.

monocyte count (0.65 ± 0.48 vs. 0.00 ± 0.000, $p < 0.001$), coefficient of variation in RBCs (13.31 ± 1.48 vs. 12.69 ± 0.84, $p = 0.003$) as well as WOMAC (94.18 ± 36.44 vs. 91.61 ± 35.50, $p = 0.008$) values were all elevated. Conversely, mean platelet volume (10.28 ± 0.86 vs. 10.53 ± 0.85, $p = 0.031$) was reduced. However, the RBC count ($p = 0.885$), HB ($p = 0.555$), hematocrit ($p = 0.526$), mean HB content ($p = 0.254$), mean corpuscular volume ($p = 0.533$), mean HB concentration ($p = 0.192$), platelet distribution width ($p = 0.076$) and platelet specific volume ($p = 0.956$) levels in KOA patients had no significant difference with MHR greater than 0.0030 or less than 0.0030 (Table 4).

Correlation between MPR and MHR and disease severity in KOA patients

Table 5 shows the relationship between MPR, MHR, monocytes, hemoglobin, mean hemoglobin content as well as platelet distribution width and disease severity in KOA patients. Bivariate regression analysis indicated that MPR ($R = 0.481$, $p < 0.001$), MHR ($R = 0.320$, $p < 0.001$) as well as monocytes ($R = 0.244$, $p < 0.001$) were significantly correlated with WOMAC. Similarly, MPR correlated significantly with MHR ($R = 0.265$, $p < 0.001$) as well as monocytes ($R = 0.209$, $p < 0.001$), and MHR correlated significantly with monocytes ($R = 0.559$, $p < 0.001$), mean hemoglobin content with plate-

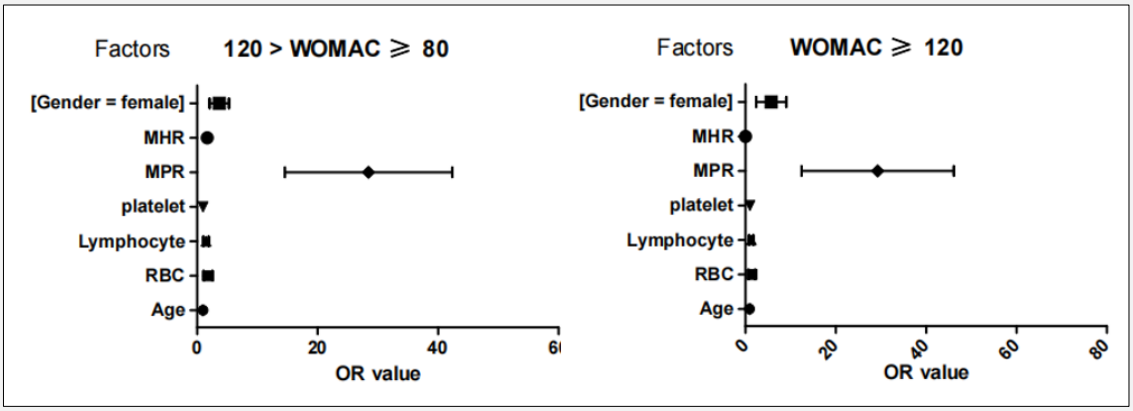

Figure 2. The metanalysis plot analysis of MHR, MPR, platelet, lymphocyte, and RBC.

(A) The metanalysis plot analysis of MHR, MPR, platelet, lymphocyte, and RBC in 120 > WOMAC ≥ 80. (B)The metanalysis plot analysis of MHR, MPR, platelet, lymphocyte, and RBC in WOMAC ≥ 120.
MHR: monocyte and hemoglobin ratio; MPR: mean hemoglobin content and platelet distribution width ratio; RBC: red blood cell.

let distribution width (R = 0.058, p = 0.198) and hemoglobin (R = 0.148, p < 0.001). There was a significant positive correlation between PDW and hemoglobin (R = 0.433, p < 0.001). But there were significant correlations between MPR and MCH (R = -0.299, p < 0.001), PDW (R = -0.749, p < 0.001) and hemoglobin (R = -0.299, p < 0.001), MHR and PDW (R = -0.346, p < 0.001) and Hb (R = -0.290, p < 0.001), MCH and WOMAC (R = -0.108, p = 0.014), PDW and monocytes (R = -0.254, p < 0.001) and WOMAC (R = -0.603, p < 0.001). There was a significant inverse correlation between monocytes and hemoglobin (R = -0.092, p = 0.049) as well as hemoglobin and WOMAC (R = -0.380, p < 0.001). In contrast, there were no significant statistical differences between MCH and MHR (R = -0.065, p = 0.118), PDW (R = 0.058, p = 0.198) as well as monocytes (R = -0.002, p = 0.965, in Table 5).

Multivariate logistic regression analysis of ROA patients (grouped by WOMAC)

According to the statistical results of WOMAC, we divided all patients into three groups: severe severity (WOMAC ≥ 120), moderate severity (120 > WOMAC ≥ 80), and mild severity (WOMAC < 80). The reference standard was mild severity. Combined with clinical experience, gender and age were correlated with the severity of KOA. At the same time, gender, red blood cell count, lymphocyte count, platelet count, MPR, and MHR were included in the regression analysis according to meaningful indicators in Table 1, excluding collinearity. Table 6 and Figure 2A, 2B regression analysis results showed that MPR and gender had statistical significance for the severity of KOA. In the analysis of moderate severity (120 > WOMAC ≥ 80), MPR (OR = 21.695, p < 0.001), and gender (OR = 2.987, p = 0.008). In terms of severe severity (WOMAC ≥ 120), MPR (OR = 19.558, p < 0.001) and gender (OR = 3.744, p = 0.029). Therefore, the MPR value of moderate and severe patients was more than 19 times that of mild patients, and the red blood cell count (RBC), lymphocyte count, platelet count, and MHR were not statistically significant (Table 6).

DISCUSSION

This study mainly analyzed the correlation between MPR and MHR and disease severity in patients with KOA. The results of the present study show that both MPR and MHR are also significantly increased with the increase of disease severity. Therefore, MPR and MHR are potential independent predictors of disease severity in patients with KOA. The main pathogenesis of KOA is clinical manifestations such as pain and even deformity caused by articular cartilage injury. Generally, we do not consider KOA as an inflammatory disease [21, 22]. At present, numerous studies have shown that the serum levels of TNF, IL-6 as well as IL-8 are significantly decreased in severe KOA patients [23-26]. Although many inflammatory factors, cytokines are currently used as markers for OA, few effective indicators can be applied in the clinic to predict the severity of the disease in patients with KOA [27]. At present, the clinical treatment mode for KOA is to relieve the joint pain of patients as well as the progress of the disease with nonsteroidal anti-inflammatory drugs [28,29]. However,

with the continuous research, it is discovered that long-term administration of NSAIDS (nonsteroidal anti-inflammatory drugs) will cause damage to the gastric mucosa of patients as well as unwanted side effects such as anemia [30]. Therefore, it is particularly important that efficient detection indicators can accurately predict the degree of KOA disease progression.

Some researchers have found that the platelet distribution width and higher neutrophil to lymphocyte ratio have an important relationship with the severity of KOA disease, that is, the higher the platelet distribution width and neutrophil/lymphocyte, the more severe the disease progression in KOA patients [17]. Platelet mean volume and platelet distribution width have also been found to have important predictive value for the development of arthritis [31,32]. Ozturk et al. found that platelet distribution width is significantly elevated in inflammatory bowel disease [33]. Platelet volume and platelet distribution width have also been studied as predictors of inflammatory diseases [34,35]. Our study identified a significant increase in MPR and a decrease in PDW in patients with KOA compared with controls. The study found that the disease severity of KOA patients increased when the MPR was greater than 2.09. Juping Du et al. [36] found a significant correlation between the lymphocyte to monocyte ratio and rheumatoid arthritis disease activity. Our study found that the more severe the disease tension was in patients with KOA, the higher the level of MHR.

Although an increasing number of indicators have been used for the prediction of inflammatory disease activity, severity, prognosis, many can only reflect a feature of the acute phase of the patients, and predictors for chronic diseases have not been found. Therefore, we hope to find a specific relationship between KOA disease severity through the analysis of clinical data, so as to find economical, easy, and effective detection indicators to predict the disease progression of KOA, and thus guide clinicians to the early intervention treatment of patients, so as to improve the quality of life of patients.

Although we found that MPR and MHR were independent predictors of disease severity in patients with KOA, our study also had significant deficiencies. First, our study is retrospective, which cannot exclude the subjectivity of data collection and processing, so our conclusions are inaccurate. Second, our data is only about 300 cases. In order to further draw accurate conclusions and verify our conjecture, we need to collect a large amount of data for prospective study.

Institutional Review Board Statement:

The study protocol first obtained informed consent from the relevant study subjects and was approved by the ethics committee affiliated with Zhujiang Hospital, Southern Medical University.

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Declaration of Interest:

No potential conflicts of interest with regard to the research, authorship, and publication of this article were disclosed.

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