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The relationship of platelet to lymphocyte ratio and neutrophil to monocyte ratio to radiographic grades of knee osteoarthritis

Introduction

Osteoarthritis (OA) is a degenerative joint disease characterized by progressive loss of articular cartilage and osseous overgrowth. Progression of this disease involves changes of bone, ligament, and muscle, leading to joint space narrowing, subchondral sclerosis, and deformity of the bone, which manifest radiographically. OA is considered as the leading cause of lower extremity disability amongst elder adults, and the estimated lifetime risk for knee OA is approximately 40% in men and 47% in women [1]. The clinical manifestations include pain, joint swelling, stiffness, and functional limitation. In an advanced stage, this would result in physical and psychological disability and impact upon quality of life tremendously, patients even having difficulty walking and housekeeping.

In clinical practice, the evaluation of knee OA is mainly based on clinical manifestation and radiographic changes. The Kellgren-Lawrence (KL) grading scale was traditionally used to grade the severity of knee OA on radiographs [2]. Nowadays, researchers have focused on serum markers reflecting the severity of
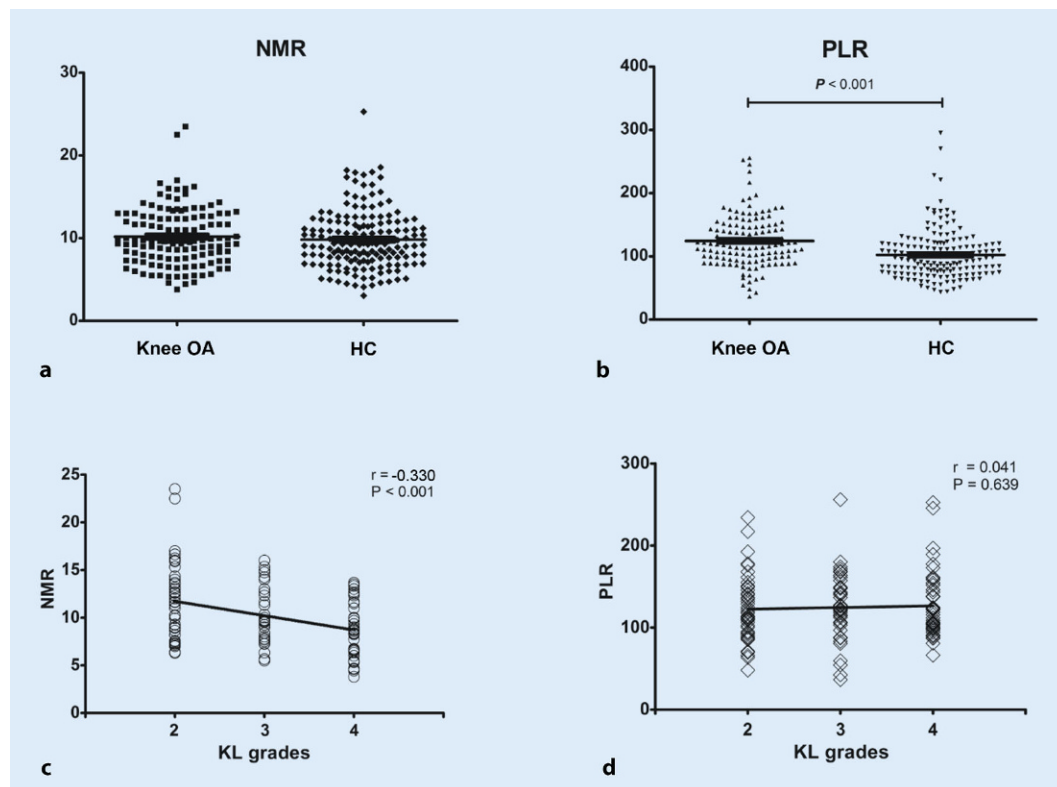

Fig. 1 ◄ PLR and NMR in knee OA patients and HC. **a** The difference in NMR was not significant between knee OA patients and HC; **b** PLR was increased in Knee OA patients compared with HC ($P < 0.001$); **c** NMR was negatively correlated with KL grades in knee OA patients ($r = -0.330, P < 0.001$); **d** PLR showed no correlation with KL grades in knee OA patients ($r = 0.041, P = 0.639$). *NMR* neutrophil to monocyte ratio, *PLR* platelet to lymphocyte ratio, *KL* Kellgren-Lawrence, *OA* osteoarthritis, *HC* healthy control

Table 1	The characteristics of knee OA patients and healthy controls ($n = 294$)		
	Knee OA patients **($n = 132$)**	**Healthy control** **($n = 162$)**	**P-value**
Gender (male/female)	41/91	60/102	0.284
Age (years)	63.36 ± 8.27	63.66 ± 8.75	0.761
WBC ($\times 10^9$/L)	5.91 (5.10, 6.70)	6.64 (5.38, 7.80)	<0.001
Neutrophils ($\times 10^9$/L)	3.46 (2.80, 4.10)	3.81 (2.81, 4.63)	0.107
Lymphocytes ($\times 10^9$/L)	1.92 (1.60, 2.20)	2.25 (1.81, 2.73)	<0.001
Monocytes ($\times 10^9$/L)	0.36 (0.30, 0.40)	0.41 (0.31, 0.50)	0.001
Platelets ($\times 10^9$/L)	225.82 (185.50, 257.75)	213.35 (178.75, 242.75)	0.053
CRP (mg/L)	5.32 (2.20, 4.45)	/	/
ESR (mm/L)	19.46 (9.00, 23.00)	13.57 (5.00, 19.00)	<0.001

Continuous variables were described as medians with interquartile range or mean ± standard deviation (SD), and analyzed by Mann–Whitney test or independent Student's t-test, where appropriate. $P < 0.05$ was considered significant

OA osteoarthritis, *WBC* white blood cell, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

knee OA, such as osteopontin [3], bone morphogenetic protein (BMP)-7 [4], endothelin-1 [5], and calcitonin gene-related peptide [6]. It is important to identify an effective and easily accessibile biomarker to monitor the progress of knee OA.

Recently, PLR was considered as an available marker to determine inflammation in various diseases, such as rheumatoid arthritis [7], systemic lupus erythematosus [8], and epithelial ovarian cancer [9]. It has also been identified as an available marker for the prognostic prediction of diverse diseases [10–13]. Similar to PLR, NMR was also suggested as a potential index for identifying disease or predicting prognosis, such as skin cancer and breast cancer [14, 15]. However, there are few studies of the association of PLR and NMR with knee OA, for which the costs of laboratory tests are much lower and which are much more easily accessible.

In this study, we retrospectively reviewed the medical records of 132 knee OA patients and analyzed the relationship of PLR and NMR to radiographic grades. Furthermore, we attempt to define potential indices of the severity of knee OA and extend our understanding of knee OA.

Patients and methods

Subjects

The ethics were reviewed and approved by the board of Taizhou Hospital (Zhejiang, China) and informed consent was obtained from all individual participants included in the study. According to the American College of Rheumatology (ACR) criteria for diagnosis of knee OA, 132 consecutive patients were enrolled in this cross-sectional study in Taizhou Hospital from January 2011 to December 2015. Their medical records were retrospectively reviewed. Patients with other diseases, such as autoimmune diseases, malignant diseases, cardiovascular diseases, chronic liver diseases, renal diseases, inflammation or other infection, and hematologic diseases or a history of blood transfusion during the past 3 months were excluded. The preoperative laboratory results were selected as the comparison norm from the electronic medical records. Individuals who accepted medical examination and had been confirmed to be in good physical shape were used as healthy controls.

Radiographic grading of knee OA

The disease severity was evaluated according to the Kellgren-Lawrence (KL) grading scale, which uses the following radiographic features: osteophytes, joint space narrowing, subchondral sclerosis,

and subchondral pseudocysts. KL classification: grade 0, no X-ray changes; grade 1, doubtful osteophyte without narrowing of joint space; grade 2, specific slight osteophytes and possible narrowing of joint space; grade 3, moderate multiple osteophytes, specific narrowing of joint space and some sclerosis; grade 4, a great deal of osteophytes, obvious narrowing of joint space, serious sclerosis and specific deformity of bone [2]. Knee OA patients were defined as having radiographic KL ≥ 2.

Statistical analysis

All statistical analyses were performed using SPSS (Version 19.0, IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.) or Graphpad Prism (Version 5.0, GraphPad Software, Inc. USA). The Shapiro–Wilk test was used to examine whether the data were normally distributed. Continuous variables were described as medians with interquartile range or mean ± standard deviation (SD) and analyzed by a Mann–Whitney test or independent Student's t-test, where appropriate. The Spearman rank correlation coefficient was calculated to determine the relationship between PLR and KL grades, and NMR and KL grades. Ordinal polytomous logistic regression was used to determine the factors independently associated with the severity of knee OA. A P value < 0.05 was considered statistical significant.

Results

The demographic characteristics and hematologic parameters of the 132 knee OA patients and 162 HC individuals are given in ◘ Table 1. The age and gender distributions of the OA patients and HC individuals were comparable ($P > 0.05$ for all). The white blood cell (WBC), neutrophil, and monocyte counts were decreased and the erythrocyte sedimentation rate (ESR) was increased in knee OA patients ($P < 0.01$ for all). According to the Kellgren and Lawrence (KL) classification, of 132 knee OA patients, 43 patients were KL grade 2, 43 patients were KL grade 3, and 46 patients were KL grade 4 (shown in ◘ Table 2).

As shown in ◻ **Fig. 1,** knee OA patients had a higher PLR compared to in HC: 124.46 (97.24, 148.63) vs. 102 (75.65, 119.81), $P < 0.001$; whereas NMR did not differ significantly between knee OA patients and HC: 10.18 (7.60, 12.65) vs. 9.81 (7.32, 11.87), $P = 0.251$. Analyzed by the Spearman rank correlation test, we found the correlation of PLR with KL grades was not significant, while NMR was negatively correlated with KL grades ($r = -0.330$, $P < 0.001$) in knee OA patients.

Additionally, in ordinal polytomous logistic regression, the results demonstrated that NMR ($P = 0.003$) and age ($P < 0.001$) were independently associated with KL grades (◻ **Table 2**).

Discussion

It is now widely acknowledged that the circulating WBC classes undergo relative changes under conditions of systemic inflammation. In recent years, WBC and subtype counts have been suggested to be biomarkers of inflammation in various diseases. PLR is an inflammatory index in routine blood tests and changes in it may be related to inflammatory cytokines. The absolute lymphocyte count is usually decreased in autoimmune diseases, while platelet count is increased. An increased PLR had been observed in rheumatoid arthritis [7] and systemic lupus erythematosus [8], and it was positively correlated with rheumatoid arthritis and systemic lupus erythematosus activity. However, the role of PLR in OA remains unknown so far. Our results demonstrate that knee OA patients had a significantly higher PLR than HC individuals; meanwhile, a correlation of NMR with the KL grades was observed in knee OA patients. Similar to PLR, NMR is another biomarker in serum that has been investigated in carcinoma. Among basal cell carcinomas, malignant melanomas, and squamous cell carcinomas, the NMR was significantly different [14]. The finding from LN Saligan's study revealed that elevated fatigue symptoms, especially in women with early stages of breast cancer, were associated with a higher NMR [15]. In knee OA patients, NMR represents particular characteris-

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The relationship of platelet to lymphocyte ratio and neutrophil to monocyte ratio to radiographic grades of knee osteoarthritis

Abstract

Objective. Accumulating data show that platelet to lymphocyte ratio (PLR) and neutrophil to monocyte ratio (NMR) undergo changes during inflammation in various diseases; however, the clinical features remain unclear in knee osteoarthritis (OA) patients. The purpose of our study was to evaluate PLR and NMR in knee OA patients, and assess their relationship to knee OA's radiographic grades. **Methods.** A retrospective study on 132 adult knee OA patients and 162 healthy controls (HC) was performed. All clinical characteristics of the knee OA patients were obtained from their medical records. PLR and NMR were compared between knee OA patients and HC by non-parametric tests. Correlations of PLR and NMR with Kellgren-Lawrence (KL) classification (KL grade 2, KL grade 3, and KL grade 4) were also analyzed through a Spearman correlation test. Ordinal polytomous logistic regression was used to determine independent factors influencing radiographic grades of knee OA patients. **Results.** PLR was increased significantly in knee OA patients, while a statistical difference in NMR was not observed. However, PLR was not relevant to KL grades, while NMR was negatively correlated with these ($r = -0.330$, $P < 0.01$) and was independently associated with KL grades of knee OA. **Conclusion.** PLR could reflect the inflammation response of knee OA. NMR emerged as an independent factor and could be used as a potential marker indicating the severity of knee OA.

Keywords

Platelet to lymphocyte ratio · Neutrophil to monocyte ratio · Knee osteoarthritis · Kellgren-Lawrence grades · Biomarker

Zusammenhang zwischen Thrombozyten-Lymphozyten-Quotient und Neutrophilen-Monozyten-Quotient sowie radiologischem Grad der Gonarthrose

Zusammenfassung

Ziel. Bisher vorhandene Daten zeigen, dass der Thrombozyten-Lymphozyten-Quotient („platelet to lymphocyte ratio", PLR) und der Neutrophilen-Monozyten-Quotient („neutrophil to monocyte ratio", NMR) im Entzündungsprozess bei verschiedenen Erkrankungen Änderungen durchlaufen, dabei bleiben die klinischen Manifestationen der Gonarthose jedoch unklar. Ziel der vorliegenden Studie war es, PLR und NMR bei Gonarthosepatienten zu untersuchen und ihren Zusammenhang mit dem radiologischen Grad der Gonarthose zu ermitteln. **Methoden.** Es wurde eine retrospektive Studie mit 132 erwachsenen Gonarthosepatienten und 162 gesunden Kontrollen durchgeführt. Sämtliche klinischen Daten der Gonarthosepatienten wurden den Krankenakten entnommen. PLR und NMR wurden mittels nichtparametrischer Verfahren zwischen Patienten und Kontrollen verglichen. Die Korrelationen von PLR und NMR mit der Kellgren-Lawrence(KL)-Klassifikation (KL-Grad 2, KL-Grad 3 und KL-Grad 4) wurden auch mit einer Korrelationsanalyse nach Spearman ermittelt. Zur Erfassung unabhängiger Faktoren, die Einfluss auf den radiologischen Grad der Gonarthose haben, wurde die ordinale polytome logistische Regression verwendet. **Ergebnisse.** Der PLR war signifikant bei Gonarthrosepatienten erhöht, während beim NMR kein statistischer Unterschied beobachtet wurde. Allerdings erwies sich der PLR nicht als relevant für den KL-Grad, während der NMR negativ damit korreliert ($r = -0.330$; $p < 0.01$) und unabhängig mit dem KL-Grad der Gonarthose assoziiert war. **Schlussfolgerung.** Der PLR erwies sich als Spiegel der entzündlichen Reaktion bei Gonarthrose. Der NMR stellte sich als unabhängiger Faktor heraus und könnte als potenzieller Marker für den Schweregrad der Gonarthrose Verwendung finden.

Schlüsselwörter

Thrombozyten-Lymphozyten-Quotient · Neutrophilen-Monozyten-Quotient · Gonarthrose · Kellgren-Lawrence-Stadien · Biomarker

Table 2 Variables associated with knee OA severity by Ordinal polytomous logistic regression analysis

	KL grade 2	KL grade 3	KL grade 4	P value
Sex (M/F)	11/32	11/32	19/27	0.153
Age (years)	57.56 ± 7.23	64.70 ± 7.15	67.30 ± 7.29	<0.001
CRP (mg/L)	3.82 (2.35, 5.15)	6.73 (1.40, 4.90)	3.40 (2.10, 3.88)	0.054
ESR (mm/h)	18.53 (9.00, 23.00)	21.51 (11.00, 26.00)	18.41 (6.00, 21.00)	0.088
PLR	122.41 (93.55, 145.65)	124.39 (96.84, 149.38)	126.45 (98.67, 147.64)	0.305
NMR	11.79 (8.92, 13.67)	10.06 (8.00, 12.33)	8.77 (6.46, 11.13)	0.003

Continuous variables were described as medians with interquartile range or mean ± standard deviation (SD), and analyzed by ordinal polytomous logistic regression. $P < 0.05$ was considered significant

KL Kellgren-Lawrence, *M* male, *F* female, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *PLR* platelet to lymphocyte ratio, *NMR* neutrophil to monocyte ratio

tics. There was no statistical difference observed between OA patients and HC individuals. However, in a further analysis we found the phenomenon that neutrophil counts decreased and monocyte counts increased as the KL grades became higher, and NMR negatively correlated with KL grades in knee OA patients. It is recognized that activation of the sympathetic nervous system boots neutrophil mobilization, resulting in increased counts of circulating neutrophil [16]. The decreased neutrophil counts may be caused by the loss of sympathetic nervous fibers in ligament, cartilage, and bone that were damaged by inflammation in knee OA. Marianne Durand et al. [17] had reported that monocyte counts increased in knee OA patients with osteoporosis, and we once speculated that osteoporosis positively correlated with KL grades. However, it has been shown that high bone mineral density increased the prevalence of radiographic knee osteoarthritis [18]. Knee joint space narrowing was also more prevalent in osteoporosis patients [19, 20]. Nevertheless, it has also been demonstrated there is no correlation of bone mineral density and radiographic progression of existing knee OA [21, 22] Recently, Deng ZH et al. revealed that OA grade was strongly correlated with macrophage colony-stimulating factor (M-CSF) [23], which can induce monocyte proliferation [24], and this is one of the important reasons why monocytes increased as the knee OA grades became higher. As well as age, NMR was also independently associated with radiographic knee OA, indicating that NMR is a useful biomarker reflecting the severity of knee OA. To the best of our knowledge, this is the first study in literature to put forward this point. In contrast to KL grades, NMR measurement has a lower cost and is more easily accessible for assessing the severity of knee OA.

Beside PLR and NMR, NLR (neutrophil to lymphocyte ratio) is also an important marker in many diseases [12, 25–27], and Taşoğlu Ö et al. have reported that NLR is an independent predictor of knee osteoarthritis severity [28]. NLR could be also considered as a new inflammatory marker for assessment of inflammation in COPD (chronic obstructive pulmonary disease) patients, as it is quick, cheap, and easy to measure during routine complete blood count analysis [29]. We had also analyzed this in our study, and the differences were not significant—neither between OA patients and HC individuals nor in terms of correlation with KL grades.

Obviously, there are several limitations to the present study. First, the sample size is relatively small and the recruited subjects were from the same place for a quite common disease. Moreover, this study cannot account for the mechanism of the characteristics of NMR in knee OA patients. Finally, this is a retrospective study lacking longitudinal observation, and the influence of treatment on PLR and NMR were not explored on account of limited data. Despite of these limitations, the study has demonstrated that PLR was increased in knee OA patients and NMR was negatively correlated with KL grades of knee OA, indicating that NMR may testify to being an available index for assessing the severity of knee OA.

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Compliance with ethical guidelines

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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Medikamentöse Versorgung der RA: am besten, wenn Haus- und Facharzt gemeinsam behandeln

Mit welchen Medikamenten werden Patienten behandelt, bei denen erstmals eine rheumatoide Arthritis (RA) festgestellt wurde? Eine Studie des Zentralinstituts für die kassenärztliche Versorgung in Deutschland (Zi) untersuchte diese Frage.

Bei der Therapie der RA ist die frühzeitige Kontrolle der Entzündung von zentraler Bedeutung. Entzündungshemmende Medikamente aus der Wirkstoffgruppe der DMARDs nehmen daher eine Schlüsselrolle bei der Therapie ein. Die Zi-Studie mit Daten aus den Jahren 2009 bis 2015 zeigt, dass bei etwa 44 Prozent der RA-Patienten im ersten Jahr nach Diagnosestellung DMARDs eingesetzt werden. Jüngere Patienten erhalten dabei in knapp 53 Prozent der Fälle DMARDS, während ältere Patienten bevorzugt Glukokortikoide erhalten. Unterschiede werden auch bei den Untergruppen der RA deutlich. Während 70 Prozent der Patienten mit seropositiver RA eine DMARD-Verordnung erhalten, liegt die DMARD-Verordnungshäufigkeit für Patienten mit seronegativer RA bei 37 Prozent. Bei gemeinsamer Betreuung neu erkrankter RA-Patienten durch Rheumatologen und Hausärzte wird eine sehr hohe Versorgungsrate mit DMARDs von fast 80 Prozent erreicht. Dies zeigt: Je früher ein Rheumatologe in die Behandlung eingebunden wird, desto eher kommen DMARDs zum Einsatz.

Die Studie basiert auf den bundesweiten vertragsärztlichen Arzneiverordnungsdaten für die Jahre 2009 bis 2015. Es wurden dabei alle gesetzlich krankenversicherten Patienten im Alter von 15 bis 79 Jahren erfasst, die im Untersuchungszeitraum mindestens einen Arztkontakt hatten, unabhängig davon, ob Arzneimittel verordnet wurden oder nicht.

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