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Research Article

The Clinical Significance of the Derived Neutrophil-to-Lymphocyte Ratio in Differentiating Occult Psoriatic Arthritis from Psoriasis Alone

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Background. Occult psoriatic arthritis (PsA) refers to a subset of psoriasis patients showing lesions on imaging but do not exhibit arthritis symptoms. *Objective*. This study was aimed to discover a simple biomarker that could be easily incorporated in clinical practice to identify occult PsA patients, defined as psoriasis patients with lesions on imaging but without arthritis symptoms, among silent psoriasis (PsO) patients, defined as psoriasis patients without any arthritis symptoms. *Methods*. A total of 149 silent PsO patients, including 83 PsO alone patients, defined as psoriasis patients without any arthritis symptoms and evidence of lesions on imaging, and 66 occult PsA patients, were enrolled in this cross-sectional study, and they all underwent blood tests to determine hematological inflammation biomarkers. *Results*. Occult PsA patients had a higher derived neutrophil-to-lymphocyte ratio (dNLR) (1.6 (1.3–2.2) vs. 1.3 (0.9–1.8), $p < 0.001$), body mass index (BMI) (25.2 (23.7–28.1) vs. 24.0 (21.9–26.0), $p = 0.002$), diabetes mellitus (DM) rate (30.3% vs. 7.2%, $p < 0.001$), and nail involvement rate (65.2% vs. 41.0%, $p = 0.003$) than patients with PsO alone. A prediction nomogram was established, and the area under the curve (AUC) was 0.843. The sensitivity and specificity of the model for identifying occult PsA patients were 77.3% and 81.9%, respectively. *Conclusion*. Our findings suggest that dNLR is a valuable diagnostic biomarker for occult PsA, and our prediction nomogram could provide clinicians with a useful tool for differentiating occult PsA patients from PsO alone patients.

1. Introduction

Psoriasis is a prevalent chronic inflammatory skin disease that affects 3% of the global population. Approximately, one-third of patients with psoriasis will eventually develop psoriatic arthritis (PsA) [1].

The presence of occult forms of PsA has been recognized since the 1970s, its definition is any patient with psoriasis who has evidence of lesions on imaging but without arthritis symptoms [2]. Haroon et al. found a delay in diagnosing PsA by more than 6 months can lead to poor radiological and functional outcomes [3]. Furthermore, before progression to clinically evident PsA, the production of inflammatory factors such as interleukin- (IL-) 23, IL-17, and tumor necrosis factor- (TNF-) α has been activated [1]. Occult PsA patients already have imaging abnormalities indicating that their joints have been compromised. Occult PsA has not received sufficient attention compared to PsA and is more difficult to identify due to the absence of symptoms. Therefore, there is an urgent need for biomarkers that can facilitate the early identification of occult PsA.

Several immune-related biomarkers have been demonstrated to be associated with certain inflammatory diseases. The neutrophil-to-lymphocyte ratio (NLR), derived NLR (dNLR), and platelet-to-lymphocyte ratio (PLR) have been associated with arthritis inflammation, such as rheumatoid arthritis (RA) [4, 5]. Both NLR and PLR are found to be higher in patients with a high impact of PsA [6]. Yorulmaz

et al. found that the systemic immune-inflammation (SII) index was higher in patients with PsA than in those without, and it might serve as an independent prognostic indicator for patients with psoriasis and PsA [7]. In the study conducted by Zeng et al. on elderly patients with COVID-19, it was observed that NLR, PLR, and SII are associated with the severity of COVID-19 [8]. NLR is elevated in Sjogren's syndrome patients, while PLR was found to be correlated with disease activity [9]. The above results suggest that these biomarkers may have the potential for identifying occult PsA.

Therefore, we assessed four immune-related biomarkers based on blood cell counts: NLR, dNLR, PLR, and SII index and explored the difference between occult PsA and PsO alone patients. We attempted to develop a diagnostic nomogram for differentiating occult PsA from PsO alone.

2. Materials and Methods

2.1. Study Design. All psoriasis patients were recruited from Shanghai Skin Disease Hospital, between October 2020 and February 2023. A total of 149 silent PsO patients meeting the inclusion and exclusion criteria were enrolled in this cross-sectional study (Figure 1). The patients underwent dermatologist evaluation and ultrasound (US) examination of 60 joints, 38 tendons, and 40 entheses. Patients with evidence of synovio-enthesitis in the US were classified into the occult PsA group, while the patients with no evidence of synovio-enthesitis in the US belong to the PsO alone group. The diagnostic method of US was consistent with that of detailed in our previous publication [10]. The study was conducted in accordance with the Declaration of Helsinki, and all participants provided signed consent.

2.2. Classification of Psoriasis Patient Groups. The classification of psoriasis patient groups and the recruitment process of psoriasis participants are shown in Figure 1. Silent PsO was defined as psoriasis patients without any arthritis symptoms. PsO alone was defined as psoriasis patients without any arthritis symptoms and evidence of lesions on imaging. Occult PsA was defined as psoriasis patients with evidence of lesions on imaging but without arthritis symptoms [2].

2.3. Definition of Hematological Inflammation Biomarkers. The following hematological inflammation biomarkers were defined: NLR = absolute neutrophil count (ANC)/absolute lymphocyte count (ALC), dNLR = ANC/(white blood cell (WBC) − ANC), PLR = absolute platelet count (APC)/ALC, and SII = APC × NLR. [5, 11].

2.4. Statistical Analysis. Skewed distributed variables were presented as medians and interquartile ranges (IQRs). Qualitative variables were presented as frequency counts and percentages (%). The Mann–Whitney U test was used to compare skewed distributed quantitative variables between two groups. Logistic regression with L1 regularization (LASSO) was used to select significant predictors. Potential confounding factors were selected, and the multivariate logistic regression method was used to construct the diagnostic model. The receiver operating characteristic (ROC) curve was used for sensitivity analysis and to calculate the Youden index. A p value <0.05 was considered statistically significant. All data analysis was performed using SPSS version 23.0 and R version 4.2.1.

3. Results

3.1. Differences in Clinical Characteristics between Occult PsA and PsO Alone Patients. A total of 149 patients were enrolled in the study, including 83 PsO alone patients and 66 occult PsA patients (Figure 1). Table 1 presents the baseline demographics, disease characteristics, comorbidities, and four inflammation indexes of patients with PsO alone and occult PsA. Compared to PsO alone patients, occult PsA patients had a higher BMI score (25.2 (23.7–28.1) vs. 24.0 (21.9–26.0), $p = 0.002$), while PsO alone patients had a higher smoking history rate (51.8% vs. 22.7%, $p < 0.001$) and drinking history rate (25.3% vs. 9.1%, $p = 0.011$). Occult PsA patients had a higher PASI score (17.0 (12.5–25.2) vs. 12.8 (10.2–19.4), $p = 0.002$) and BSA score (32.0 (17.9–47.8) vs. 18.5 (10.5–32.5), $p < 0.001$) than PsO alone patients. In addition, occult PsA patients had higher rates of diabetes mellitus (DM) (30.3% vs. 7.2%, $p < 0.001$), hypertension (39.4% vs. 18.1%, $p = 0.004$), and nail involvement (65.2% vs. 41.0%, $p = 0.003$) than PsO alone patients. Conversely, PsO alone patients had a higher rate of nonalcoholic fatty liver disease (9.6% vs. 1.5%, $p = 0.044$). Regarding inflammation indexes, occult PsA and PsO alone patients exhibited similar NLR, PLR, and SII indexes. However, occult PsA patients had a higher dNLR than PsO alone patients (1.6 (1.3–2.2) vs. 1.3 (0.9–1.8), $p < 0.001$).

3.2. Identification of Significant Predictors for Occult PsA. A total of 19 potential predictors were enrolled in LASSO regression, and candidate predictors were selected, including dNLR, DM, nail involvement, BMI, smoking history, BSA, and hyperlipidemia (Figures 2(a) and 2(b)). These seven predictors were then entered into the univariate logistic regression, and five predictors were significantly correlated with occult PsA (Figure 2(c)). These predictors were enrolled in multivariate logistic regression to adjust the effects of covariates (Figure 2(d)). We used predictors with $p < 0.05$ to create the multivariate model, and five factors were found to be significant by multivariate analysis, of which four were identified as risk factors: dNLR (OR: 1.780, 95% CI: 1.067–2.971, $p = 0.027$), DM (OR: 3.981, 95% CI: 1.224–12.944, $p = 0.022$), nail involvement (OR: 2.784, 95% CI: 1.142–6.879, $p = 0.024$), and BMI (OR: 1.202, 95% CI: 1.069–1.353, $p = 0.002$).

Based on the significant predictors, we established a predictive nomogram, which incorporated dNLR, DM, nail involvement, BMI, and smoking history for occult PsA diagnosis (Figure 3(a)). The AUC value of this nomogram was 0.843. The prediction model was constructed as follows:

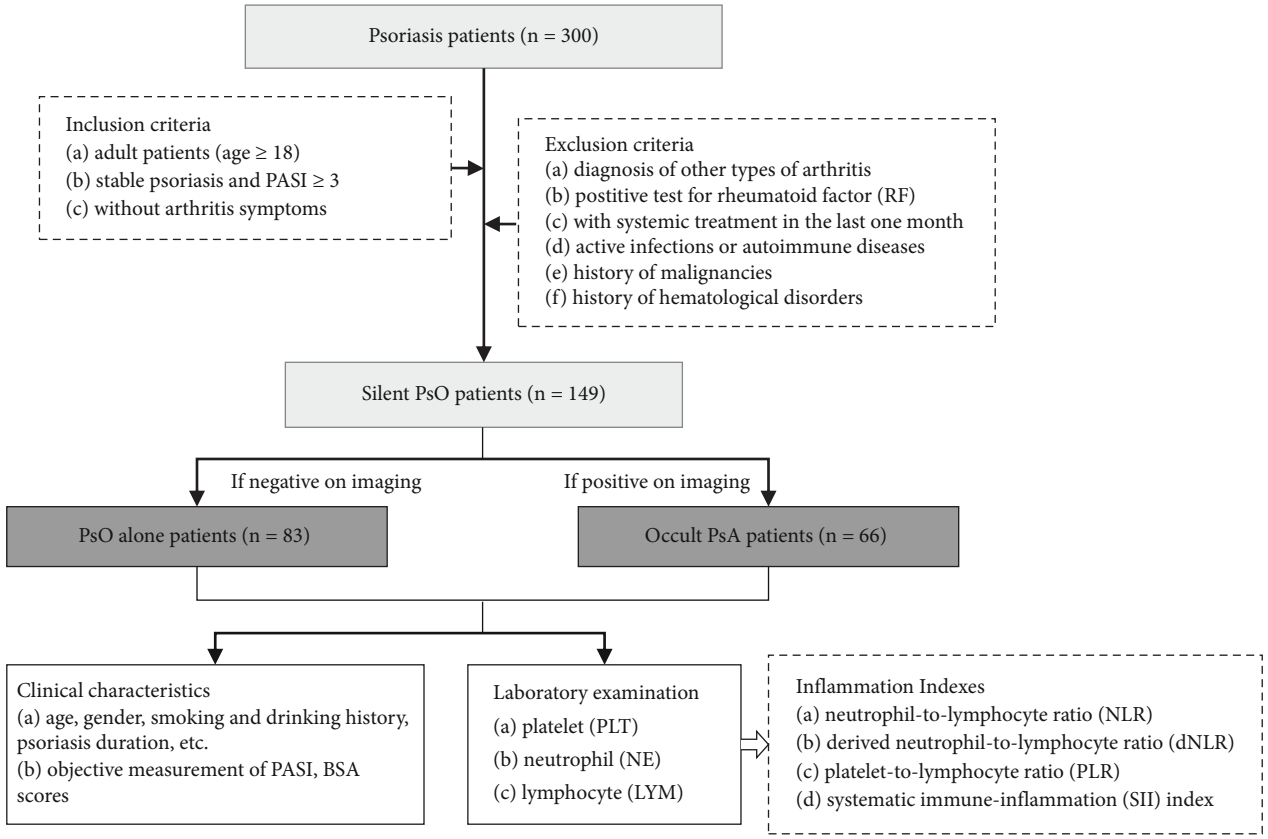
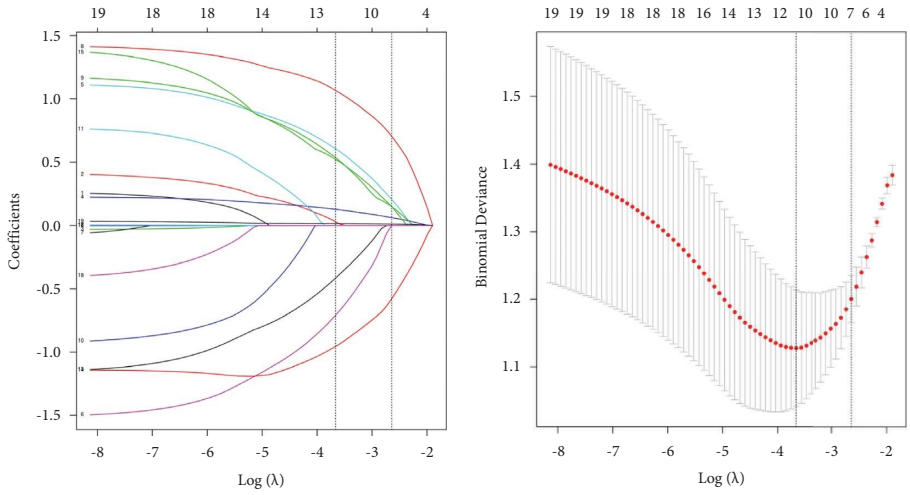


Figure 1: Study design. Silent PsO, psoriasis patients without any arthritis symptoms; PsO alone, psoriasis patients without any arthritis symptoms and evidence of lesions on imaging; occult PsA, psoriasis patients with evidence of lesions on imaging but without arthritis symptoms.

Table 1: Comparison of characteristics between PsO alone patients and occult PsA patients ($n = 149$).

Patient characteristics	PsO alone ($n = 83$)	Occult PsA ($n = 66$)	p value
Demographics			
Women, n (%)	21 (25.3)	13 (19.7)	0.418
Age ≥65, n (%)	21 (25.3)	33 (34.8)	0.204
BMI, median (IQR), kg/m^2	24.0 (21.9–26.0)	25.2 (23.7–28.1)	0.002
Duration of disease, y	11.0 (6.0–18.0)	13.5 (7.0–20.0)	0.318
Smoking history, n (%)	43 (51.8)	15 (22.7)	<0.001
Drinking history, n (%)	21 (25.3)	6 (9.1)	0.011
Disease characteristics			
PASI score, median (IQR)	12.8 (10.2–19.4)	17.0 (12.5–25.2)	0.002
BSA score (%), median (IQR)	18.5 (10.5–32.5)	32.0 (17.9–47.8)	<0.001
Nail involvement, n (%)	34 (41.0)	43 (65.2)	0.003
Psoriasis comorbidities			
Hypertension, n (%)	15 (18.1)	26 (39.4)	0.004
Diabetes mellitus, n (%)	6 (7.2)	20 (30.3)	<0.001
Cardiometabolic disease, n (%)	5 (6.0)	7 (10.6)	0.307
Nonalcoholic fatty liver disease, n (%)	8 (9.6)	1 (1.5)	0.044
Hyperlipidemia, n (%)	3 (3.6)	2 (3.0)	1.000
Cerebral stroke, n (%)	1 (1.2)	3 (4.5)	0.322
Inflammation indexes			
NLR, median (IQR)	2.3 (1.7–3.1)	2.3 (1.9–3.3)	0.551
dNLR, median (IQR)	1.3 (0.9–1.8)	1.6 (1.3–2.2)	<0.001
PLR, median (IQR)	136.4 (100.0–165.8)	122.1 (102.4–154.6)	0.305
SII, median (IQR)	610.4 (451.7–926.1)	504.4 (357.6–718.2)	0.056

PsO alone: psoriasis alone; occult PsA: occult psoriatic arthritis. BMI: body mass index; PASI: psoriasis area and severity index; BSA: body surface area; NLR: neutrophil-to-lymphocyte ratio; dNLR: derived neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systematic immune-inflammation index; IQR: interquartile range.



(a) (b)

Univariate analysis

Characteristics	Total (N)	OR (95% CI)	p
dNLR	149	1.794 (1.079-2.982)	0.024
BMI	149	1.186 (1.058-1.328)	0.003
Diabetes mellitus	149		
No	123	Reference	
Yes	26	4.590 (1.433-14.706)	0.010
Nail involvement	149		
No	72	Reference	
Yes	77	2.471 (1.043-5.855)	0.040
Smoking history	149		
No	91	Reference	
Yes	58	0.220 (0.090-0.533)	0.001
BSA		1.021 (0.999-1.044)	0.061
Hyperlipidemia	149		
No	108	Reference	
Yes	41	2.377 (0.902-6.263)	0.080

0 1 2 3 4 5

(c)

Multivariate analysis

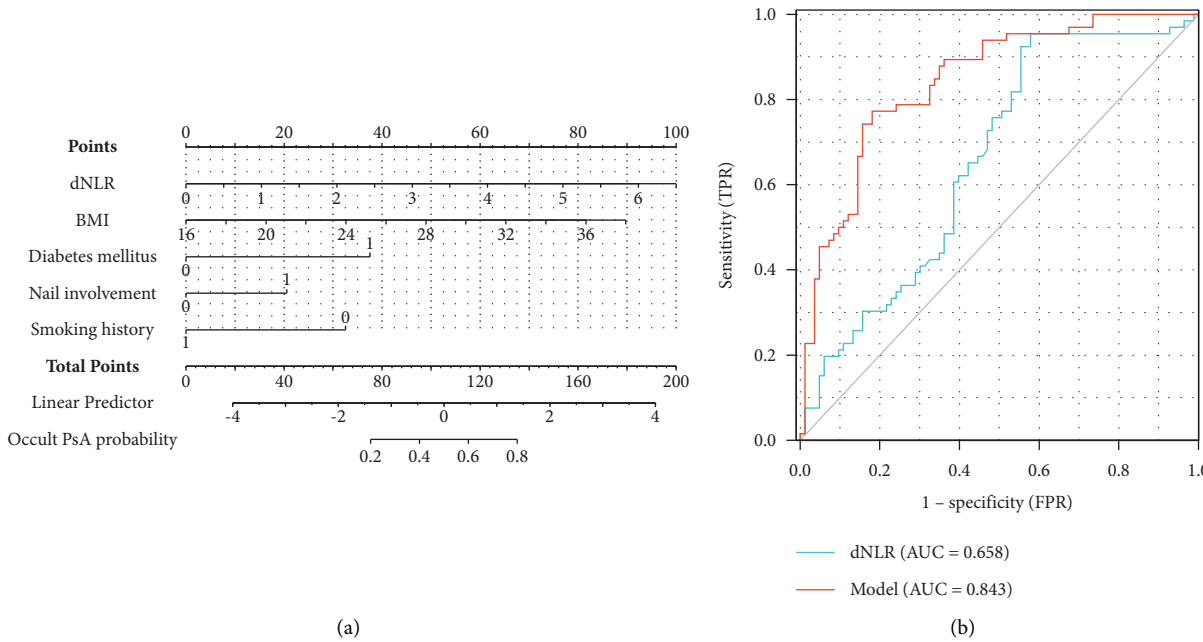
Characteristics	Total (N)	OR (95% CI)	p
dNLR	149	1.780 (1.067-2.971)	0.027
BMI	149	1.202 (1.069-1.353)	0.002
Diabetes mellitus	149		
No	123	Reference	
Yes	26	3.981 (1.224-12.944)	0.022
Nail involvement	149		
No	72	Reference	
Yes	77	2.784 (1.142-6.879)	0.024
Smoking history	149		
No	91	Reference	
Yes	58	0.260 (0.097-0.699)	0.008

0 1 2 3 4

(d)

Figure 2: Logistic regression with L1 regularization (LASSO) regression and forest plot of candidate predictors for occult psoriatic arthritis (PsA). (a) Coefficient profiles of candidate predictors. (b) Selection of the optimal penalization coefficient in the LASSO regression. (c) Forest plot for the factors of occult PsA (univariate analysis). (d) Forest plot for factors of occult PsA (multivariate analysis).

logit (occult PsA) = −6.396 + 1.739 × 1 (if: have DM) + 0.953 × 1(if: nail changes present) + 0.713 × dNLR + 0.189 × BMI + (−1.511) × 1 (if: smoking history present). The ROC analysis revealed that the cutoff value of dNLR, which demonstrated the maximum sensitivity and specificity for differentiating occult PsA patients from PsO alone patients, was 0.932 and that the area under the curve (AUC) for dNLR was 0.658. Using the cutoff value, the sensitivity and specificity of dNLR for identification were 95.5% and 42.2%, respectively. The AUC for the nomogram was 0.843, the



(a) (b)

Figure 3: The nomogram and the receiver-operating characteristic (ROC) analyses for predicting occult psoriatic arthritis (PsA) patients. (a) The nomogram for occult PsA patient prediction. (b) ROC curves showing the performance of the multiple factor model. dNLR, derived neutrophil-to-lymphocyte ratio; OR, odds ratio; 95% CI, 95% confidence interval; AUC, area under the receiver operating characteristic curve. Model: dNLR + diabetes mellitus + nail involvement + BMI + smoking history.

cutoff value of the model that demonstrated the maximum sensitivity and specificity for distinguishing occult PsA patients was 0.452, and using the cutoff value, the sensitivity and specificity of the model for identification were 77.3% and 81.9%, respectively (Table 2 and Figure 3(b)).

4. Discussion

Early detection of PsA is crucial for clinicians to initiate appropriate treatment, which can prevent or delay joint damage, improve quality of life, and avoid joint deformation and dysfunction associated with PsA [12]. There were some reported biomarkers for PsA including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anticyclic citrullinated peptide (anti-CCP) antibodies, osteoprotegerin (OPG), matrix metallopeptidase-3 (MMP-3), the ratio of C-propeptide of type II collagen (CPII) to collagen fragment neoepitopes Col2–3/4 (C2C), and chemokine (C-X-C motif) ligand-10 (CXCL-10) [13]. Although these biomarkers are associated with PsA, there is no mature serum-based screening biomarker for PsA, let alone occult PsA [14]. Moreover, since occult PsA patients do not exhibit arthritis symptoms, diagnosing it is more difficult than diagnosing PsA. Therefore, the development of a tool for screening occult PsA in patients with psoriasis is valuable for its diagnosis.

Neutrophils play an essential role in frontline defense against pathogens by initiating and amplifying inflammatory reactions. T-helper (Th17) cells promote neutrophil recruitment, and neutrophils can drive cytokine-mediated inflammatory precursors in PsA [15]. Poorly differentiated and immature neutrophils can be released into a proinflammatory environment that rapidly increases neutrophil production [16]. dNLR has mainly been studied in the field of cancers, and it has shown diagnositic and prognostic values for multiple cancers [17–19]. dNLR incorporates the total number of WBC into its calculation, making it a potentially more comprehensive indicator of inflammation compared to NLR [16]. In inflammatory diseases such as COVID-19, dNLR can not only reflect the severity of the disease but also predict mortality of the disease [16], and dNLR displays a better predictive performance than NLR in prognosis of COVID-19 infected patients [20, 21]. Our research findings suggest that dNLR can also be an indicator of occult PsA, and this single factor has an extremely high sensitivity of 95.5%.

Diabetes mellitus was the first observed comorbidity in psoriasis [22], and our results suggest that DM is a risk factor for occult PsA. Patients with PsA have a higher risk of DM than the general population (with an incidence rate of 7.3 cases versus 4.3 cases per 1000 person years) [23]. DM can lead to complications related to a chronic inflammatory environment, such as oral microbiome, periodic inflammation, and bone loss. The two diseases share some possible pathogenic mechanisms such as TNF-α and adipokine [24]. Nail involvement was found to be an independent risk factor for occult PsA. Nail dystrophy is also an important part of the Criteria for Psoriatic Arthritis (CASPAR) criteria, which considered the gold standard for PsA [1]. The percentage of nail dystrophy in PsA patients ranges from 41% to 93%, which is higher than the prevalence in psoriasis patients (ranging from 15% to 50%) [1]. The nail matrix and the musculoskeletal system are connected by an enthesis network fused with the extensor tendon crossing

Table 2: Multiple factor model with dNLR and risk factors.

	AUC	CI	Cutoff	SE	SP	Youden J
dNLR	0.658	0.570–0.745	0.932	0.955	0.422	0.376
Model	0.843	0.780–0.906	0.452	0.773	0.819	0.592

AUC: area under the receiver operating characteristic curve; SE: sensitivity; SP: specificity; Youden J (sensitivity + specificity − 1). Model: dNLR + diabetes mellitus + nail involvement + BMI + smoking history.

the distal interphalangeal joint [25]. Nail involvement may be an external manifestation of joint involvement. Obesity has been demonstrated to be a risk factor for the development of PsA [26]. In PsA patients, obesity is thought to be a consequence of the patient's reluctance to do physical activity because of joint dysfunction. However, in our study, obesity has been found to contribute to the characterization of occult PsA patients, even though they had no arthritis symptoms. This could be due to the low-grade inflammatory state promoted by chronic inflammation stimulated by obesity [27]. In our study, we found an inverse association between smoking and occult PsA. The relationship between smoking, psoriasis, and PsA is complex. While smoking is generally considered a risk factor for PsA development in the general population, there is a "smoking paradox" with PsA, where smoking is negatively associated with PsA in patients with psoriasis [28]. However, we cannot conclude that smoking is a protective factor against occult PsA, as a convincing study has demonstrated that the "smoking paradox" is actually due to the effect of a collider bias [29, 30].

We successfully created a nomogram that predicts the possibility of occult PsA based on dNLR, DM, nail involvement, BMI, and smoking history. As described above, all included factors have a basis as a possible explanation for their association with the occurrence of occult PsA. dNLR is a simple, inexpensive, and readily available inflammatory biomarker. Our model achieved an AUC of 0.843, a sensitivity of 0.773, and a specificity of 0.819. Though the study population was small, this nomogram may become useful for predicting the probability of occult PsA. Therefore, further validation in routine clinical practice is necessary.

One limitation of the study is that scalp lesions and intergluteal/perianal lesions, which are known risk factors [31] for the development of PsA, were not investigated in this study. Another limitation of the study is that dNLR is involved in various inflammatory and malignant diseases [9, 16–19]. Therefore, when interpreting dNLR values and considering its application as a diagnostic tool, more consideration of the wider clinical context is needed. Future research should elucidate the impacts of these confounding factors, thereby underscoring the practical effectiveness and dependability of dNLR in clinical practice.

5. Conclusions

This study successfully established a predictive nomogram for occult PsA utilizing the inflammation value score, dNLR, which can be routinely assessed and observed. This model is valuable for distinguishing occult PsA patients from PsO alone patients and has the potential to improve clinical management of psoriasis patients.

Data Availability

The data that used to support the findings of this study are available from the corresponding author on request.

Ethical Approval

This study was approved by the Medical Ethical Committee of Shanghai Skin Disease Hospital (approval #2020−31).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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