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REVIEW ARTICLE

Associations between the neutrophil-to-lymphocyte and the platelet-to-lymphocyte ratios and the presence and severity of psoriasis: a systematic review and meta-analysis

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Abstract

The diagnosis of psoriasis, an immune-mediated disease that affects 2% of the population in Western countries, is largely based on history and clinical examination. The aim of this systematic review and meta-analysis was to investigate the associations between the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) and the presence and clinical severity of psoriasis. A systematic literature search was conducted in PubMed, Web of Science, and Scopus, from inception to January 2018. Twelve case–control studies enrolling 1067 psoriasis patients (537 males and 530 females) and 799 healthy controls (404 males and 395 females) were included in the meta-analysis. The NLR was evaluated in all the studies, while the PLR was assessed in four studies. Pooled results showed that both the NLR and the PLR values were significantly higher in patients with psoriasis (SMD = 0.69, 95% CI 0.53–1.85, $p<0.001$, and SMD = 0.40, 95% CI 0.12–0.68, $p=0.006$, respectively). There were no significant differences in NLR values according to the severity of disease ($p=0.52$). The NLR and the PLR are significantly associated with the presence, but not with the severity, of psoriasis. Further studies are required to determine the additional utility of these haematological indexes in the diagnosis of psoriasis.

Keywords Psoriasis · Inflammation · Neutrophils · Platelets · Lymphocytes · NLR · PLR

Introduction

Psoriasis, a chronic disorder which involves the skin, the joints, or both, affects approximately 2% of the population in Western countries [1, 2]. Five clinical types of psoriasis are currently recognized: vulgaris, guttate or eruptive, intertriginous or flexural, pustular, and erythrodermic [3]. Although most patients have mild psoriasis vulgaris at diagnosis [4], the clinical manifestations of the disease (i.e., itch, bleeding, and plaques) significantly affect their quality of life. Additionally, several chronic diseases, such as rheumatoid arthritis, metabolic syndrome, and inflammatory bowel disease, have been reported to be more frequent in patients with psoriasis [3, 5]. Furthermore, the pustular and erythrodermic types are potentially life-threatening [3].

From a pathophysiological point of view, psoriasis is an immune-mediated disease that is characterized by local and systemic inflammation. Locally, inflammatory infiltrates containing T lymphocytes, macrophages, mast cells, and neutrophilic granulocytes are common within the dermis and epidermis of psoriatic lesions; these cells are often organized in subcorneal microabscesses (pustules of Kogoj or Munro's microabscesses) [6]. Nevertheless, inflammation in psoriasis is not merely a local event. The higher rates of chronic inflammatory comorbidities, the triggering effect of several anti-inflammatory drugs, traumas and infections, and the greater disease severity in immunocompromised patients suggest that psoriasis is a systemic inflammatory disease [7, 8]. Genome-wide studies in psoriasis have identified alterations of immune-related genes linked with dysregulation of innate and adaptive components of the immune system with

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resident cutaneous cell types [9]. The interplay between this dysregulation and the pathways causing systemic inflammation is currently a field of active research [10, 11].

Despite the essential role of inflammation in the pathogenesis of psoriasis and the rapidly growing knowledge about interleukins, cytokines, and serum autoantibodies, there is an ongoing need to identify better markers for the diagnosis and the severity of the disease. The available tools in this context, the Psoriasis Area and Severity Index (PASI) and the Psoriasis Global Assessment (PGA) scores, are primarily based on history and clinical examination [12, 13]. Nevertheless, difficulties in the clinical or pathological assessment of psoriasis are not rare, especially in particular forms such as the intertriginous type. Therefore, the identification of simple, low-cost, and widely available biomarkers of systemic inflammation, in addition to clinical data, might be useful for the correct diagnosis, assessment, and treatment of patients with psoriasis.

Several indexes related to systemic inflammation and obtained from routine complete blood count tests have gained interest in recent years, due to their wide availability and low costs, as well as their ability to predict outcomes in several pathological conditions. The most extensively studied are the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR). These indexes have been shown to be useful in the diagnosis and assessment of clinical severity and outcomes in numerous chronic inflammatory diseases and in cancer [14–19]. This is likely due to fact that chronic systemic inflammation activates the white blood cell populations and the platelets during the course of the disease. We conducted a systematic review and meta-analysis of studies investigating the associations between the NLR and/or PLR and the presence and the clinical severity of psoriasis.

Materials and methods

Search strategy, eligibility criteria, and study selection

A systematic search of publications in the electronic databases PubMed, Web of Science, and Scopus, from inception to January 2018, was conducted using the following terms and their combination: "psoriasis," "NLR," "neutrophil-to-lymphocyte ratio," "PLR," and "platelet-to-lymphocyte ratio." Abstracts were screened independently by two investigators to establish relevance. If relevant, the two investigators independently reviewed the full articles. Eligibility criteria were: (1) assessment of NLR and/or PLR, (2) comparison of human subjects with and without psoriasis (case–control design), (3) English language, and (4) full-text publications.

The references of the retrieved articles and reviews were also searched to identify additional studies. Any disagreement between the reviewers was resolved by a third investigator. We used the Newcastle–Ottawa scale (NOS) to assess the quality of each study [20]. The Newcastle–Ottawa scale evaluated the following components: selection of the cohort, comparability of cohorts on the basis of the design or analysis, how the exposure was ascertained, and how the outcomes of interest were assessed. NOS scores of 1–3, 4–6, 7–9 indicated low, intermediate, and high quality, respectively.

Statistical analysis

Standardized mean differences (SMDs) were used to construct forest plots of continuous data and to evaluate differences in NLR and PLR values between healthy controls and patients with psoriasis. $p < 0.05$ was considered statistically significant, and 95% confidence intervals (CIs) were reported. In one study [21], the mean and standard deviation values were extrapolated from the median and IQR values, as previously described [22].

Heterogeneity of SMD across studies was tested using the Q statistic (significance level at $p < 0.10$). The I^2 statistic, a quantitative measure of inconsistency across studies, was also calculated ($I^2 < 25\%$, no heterogeneity; I^2 between 25 and 50%, moderate heterogeneity; I^2 between 50 and 75%, high heterogeneity; and $I^2 > 75\%$, extreme heterogeneity) [23, 24]. Due to the high heterogeneity, a random-effects model was used to calculate the pooled SMD and corresponding 95% confidence intervals.

Sensitivity analysis was conducted to investigate the influence of an individual study on the overall risk estimate, by sequentially excluding one study in each turn [25].

To evaluate the presence of potential publication bias, the associations between study size and magnitude of effect were analyzed by means of Begg's-adjusted rank correlation test and Egger's regression asymmetry test at the $p < 0.05$ level of significance [26, 27]. We also performed the Duval and Tweedie "trim-and-fill" procedure [28] to further assess the possible effect of publication bias. This method considers the possibility of hypothetical "missing" studies that might exist and recalculates a pooled SMD that incorporates the hypothetical missing studies as though they actually existed. Statistical analyses were performed using MedCalc for Windows, version 15.4 64 bit (MedCalc Software, Ostend, Belgium) and Stata 14 (STATA Corp., College Station, TX, USA). The study was fully compliant with the PRISMA statement regarding the reporting of systematic reviews and meta-analyses.

Results

Literature search and study selection

A flowchart describing the screening process is presented in Fig. 1. We initially identified 114 studies. A total of 96 studies were excluded after the first screening because they were either duplicates or irrelevant. After a full-text revision of 18 articles, further six studies were excluded because they did not meet the inclusion criteria. Thus, 12 studies were included in the meta-analysis [21, 29–39]. The characteristics of these studies, published between 2014 and 2017, are presented in Table 1. All studies were, at least, of intermediate quality.

NLR and psoriasis

A total of 1067 psoriasis patients (537 males and 530 females) and 799 healthy controls (404 males and 395 females) were included in the selected studies. The mean ± SD age of participants across all studies was 40.8 ± 2.3 years, in psoriasis patients, and 38.4 ± 1.6 years, in controls. PASI values in psoriasis patients ranged between 5.05 and 20.34, suggesting high heterogeneity in disease severity.

The forest plot for NLR values is shown in Fig. 2. In all studies, NLR values were significantly higher in psoriasis patients when compared to controls. Substantial heterogeneity between studies was observed ($I^2 = 62\%$, $p = 0.002$). Thus, random-effects models were used. Pooled results showed that NLR values were significantly higher in patients with psoriasis (SMD = 0.69, 95% CI 0.53–1.85; $p < 0.001$).

Results stability was evaluated through sensitivity analysis (Fig. 3). The corresponding pooled SMD values were not substantially altered when single studies were sequentially removed, with effect size ranging between 0.62 and 0.74.

The Begg's ($p = 0.24$) and Egger's tests ($p = 0.78$) showed no publication bias. When the trim-and-fill method was used to evaluate the existence of asymmetry in the funnel plot, four potential missing studies were required in the left side to ensure symmetry (Fig. 4). The adjusted SMD was attenuated but remained significant (0.55, 95% CI 0.37–0.74 $p < 0.0001$).

We investigated the effects of disease severity (PASI < 10 or PASI > 10), as well as study type (retrospective or prospective) on the SMD values. SMD of NLR values in subjects with PASI < 10 (0.69, 95% CI 0.46–0.92, $p < 0.0001$; $I^2 = 71\%$, $p = 0.004$) was lower than that of patients with PASI > 10 (0.80, 95% CI 0.61–1.00, $p < 0.0001$; $I^2 = 0.0\%$, $p = 0.68$), although the differences were not statistically significant in meta-regression analysis ($p = 0.52$, Fig. 5). Furthermore, NLR values were higher in prospective studies (0.79, 95% CI 0.59–0.98, $p < 0.001$; $I^2 = 52.3\%$, $p = 0.050$) when compared to retrospective ones (0.56, 95% CI 0.34–0.78, $p < 0.001$; $I^2 = 53.1\%$, $p = 0.073$). However, once again, the differences were not statistically significant in meta-regression ($p = 0.16$, Fig. 6).

PLR and psoriasis

Four studies evaluated PLR in 380 psoriasis patients (203 males and 177 females) and 305 healthy controls (149 males and 156 females). The mean ± SD age of participants across the selected studies was 39.7 ± 6.8 years, in psoriasis patients, and 37.3 ± 5.8 years, in controls. PASI values in psoriasis patients ranged between 7.75 and 16.

The forest plot for PLR values in psoriasis patients and controls is shown in Fig. 7. In all studies, PLR values were higher in psoriasis patients than in controls. Substantial heterogeneity between studies was observed ($I^2 = 66.5\%$, $p < 0.030$). Thus, random-effects models were used. Overall, pooled results showed that PLR values were

Fig. 1 Flowchart of study selection

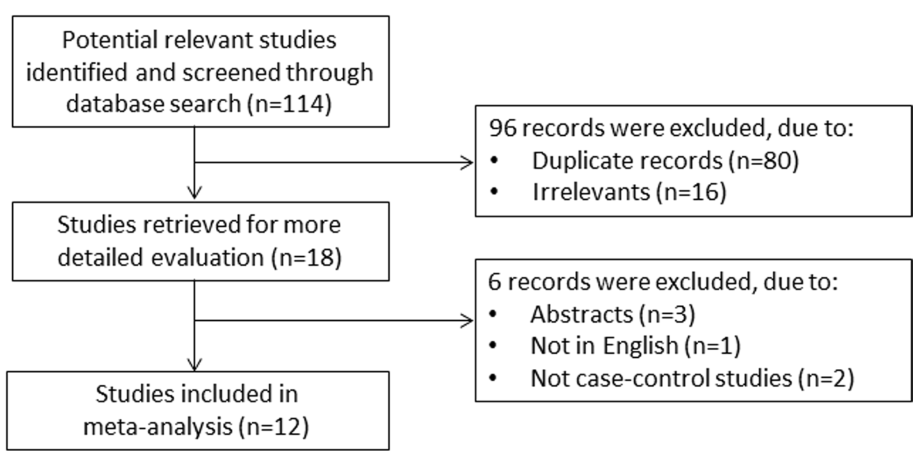

Table 1 Summary of the studies on controls versus psoriasis subjects included in the meta-analysis

			Control					Psoriasis					
First author year, country	Study design	NOS (stars)	*n*	Age Mean ± SD	Gender (M/F)	NLR Mean ± SD	PLR Mean ± SD	*n*	Age Mean ± SD	Gender (M/F)	NLR Mean ± SD	PLR Mean ± SD	PASI Mean or median
Ataseven 2014, Turkey	R	5	70	37.7 ± 13.4	28/42	1.80 ± 0.72		104	39.6 ± 15.8	37/67	2.19 ± 1.11		5.05
Sen 2014, Turkey	P	6	120	38.4 ± 9.8	63/57	1.90 ± 1.07		138	40.4 ± 12.3	78/60	2.71 ± 1.25		8.2
Yildiz 2014, Turkey	P	8	30	36.2 ± 11.0	15/15	1.79 ± 0.52		34	37.4 ± 12.8	18/16	2.66 ± 1.22		16.3
Yurtdas 2014, Turkey	P	7	37	37.0 ± 9.0	20/17	2.60 ± 1.40	101 ± 60	51	39.0 ± 9.0	32/19	4.00 ± 3.00	124 ± 98	16
Sunbul 2015, Turkey	P	6	50	45.0 ± 6.1	33/17	1.82 ± 0.52		50	43.3 ± 13.2	26/24	2.74 ± 1.78		13.7
Kim 2016, South Korea	R	7	94	34.4 ± 13.9	43/51	1.76 ± 0.89	132.3 ± 41.1	111	38.0 ± 16.6	62/49	2.15 ± 1.65	140.7 ± 114.9	NR
Cerman 2016, Turkey	R	5	47	37.8 ± 13.6	24/23	1.60 ± 0.56		49	42.3 ± 15.5	30/19	2.62 ± 1.46		20.34
Pektas 2016, Turkey	P	5	128	40.6 ± 12.7	65/63	1.33 ± 0.66	105.01 ± 45.68	172	42.2 ± 12.0	84/88	2.19 ± 0.83	137.53 ± 61.3	7.75
Toprak 2016, Turkey	P	5	49	38.0 ± 11.0	24/25	1.67 ± 0.44		39	34.0 ± 16.0	17/22	2.42 ± 1.06		11.34
Arisoy 2017, Turkey	P	7	74	37.0 ± 14.0	42/32	1.90 ± 0.70		74	41.0 ± 14.0	40/34	2.40 ± 1.2		8.7
Polat 2017, Turkey	R	7	46	34.0 ± 8.4	21/25	1.75 ± 0.55	125.01 ± 38.14	46	36.6 ± 9.8	25/21	2.78 ± 1.74	159.18 ± 64.22	9.08
Solak 2017, Turkey	R	6	54	43.1 ± 11.3	26/28	1.74 ± 0.56		199	44.1 ± 14.4	88/111	2.19 ± 0.81		8.7

NOS Newcastle–Ottawa quality assessment scale for case–control studies, *PASI* Psoriasis Area and Severity Index, *P* prospective, *R* retrospective, *NR* not reported

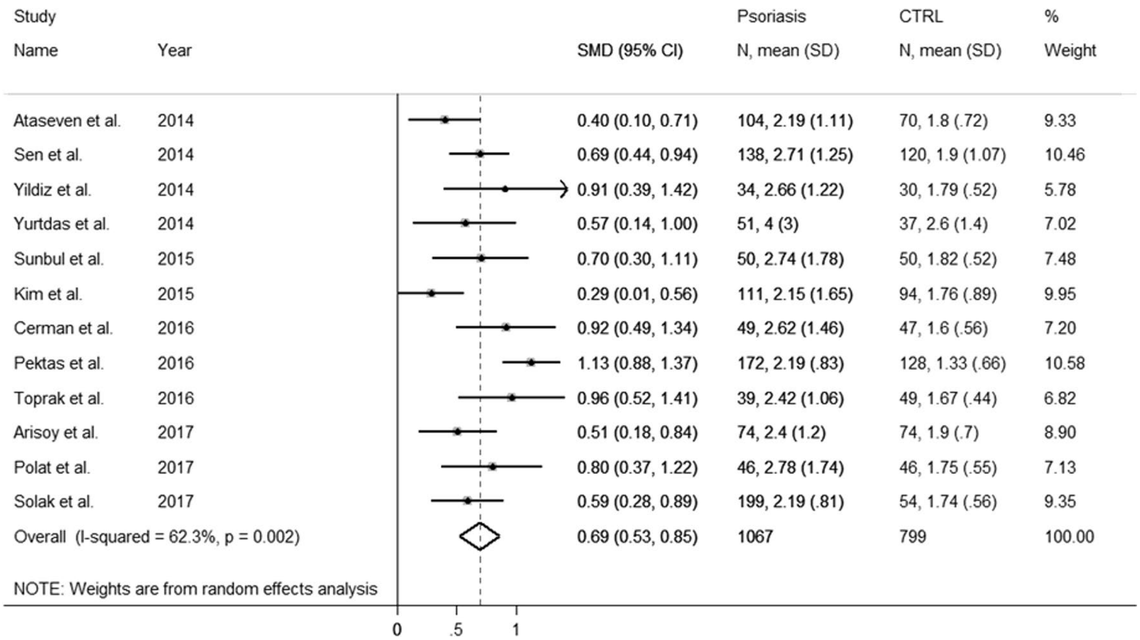

Fig. 2 Forest plot of studies examining NLR and psoriasis

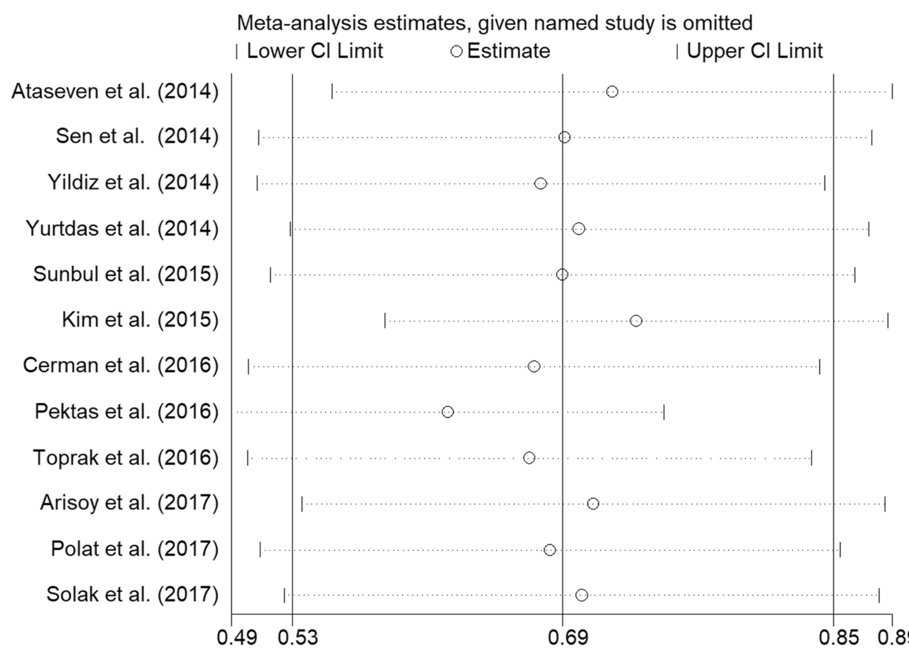

Fig. 3 Sensitivity analysis of the association between NLR and psoriasis. The influence of individual studies on the overall standardized mean difference (SMD) is shown. The middle vertical axis indicates the overall SMD, and the two vertical axes indicate the 95% confidence intervals (CIs). Hollow circles represent the pooled SMD when the remaining study is omitted from the meta-analysis. Two ends of each broken line represent 95% CI

significantly higher in patients with psoriasis (SMD = 0.40, 95% CI 0.12–0.68; $p = 0.006$).

Sensitivity analysis indicated that pooled SMD values were not substantially altered when single studies were removed (effect size ranged between 0.31 and 0.54), suggesting that the results of the meta-analysis were stable. The assessment of publication bias was not possible because of the limited number of studies.

Discussion

Our meta-analysis showed a significant association between the NLR and the presence of psoriasis. NLR is an index that assesses white blood cell populations that are involved in the pathogenesis of several chronic diseases, including psoriasis. Lymphocytes produce tumor

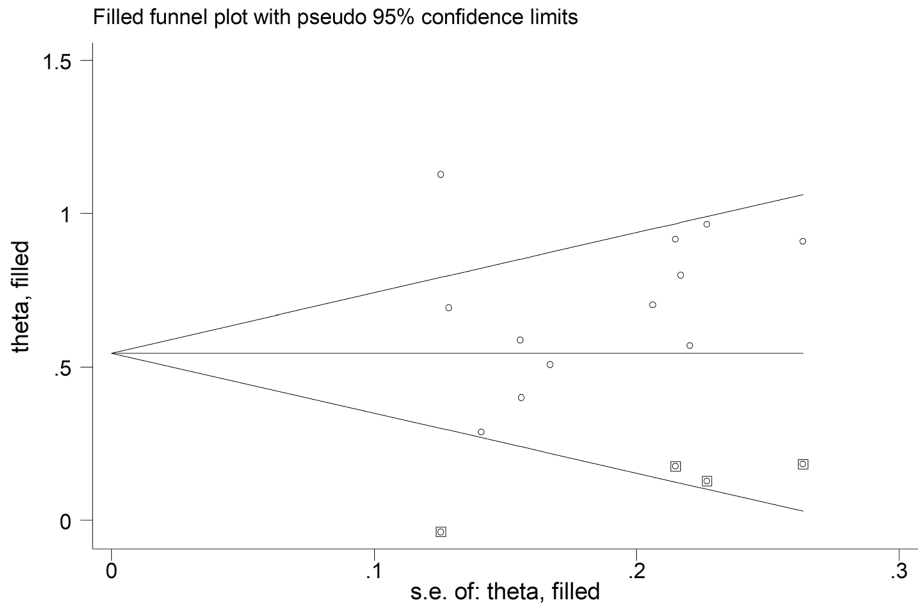

Fig. 4 Funnel plot of studies investigating healthy controls and patients with psoriasis after trimming and filling. Dummy studies and genuine studies are represented by enclosed circles and free circles, respectively

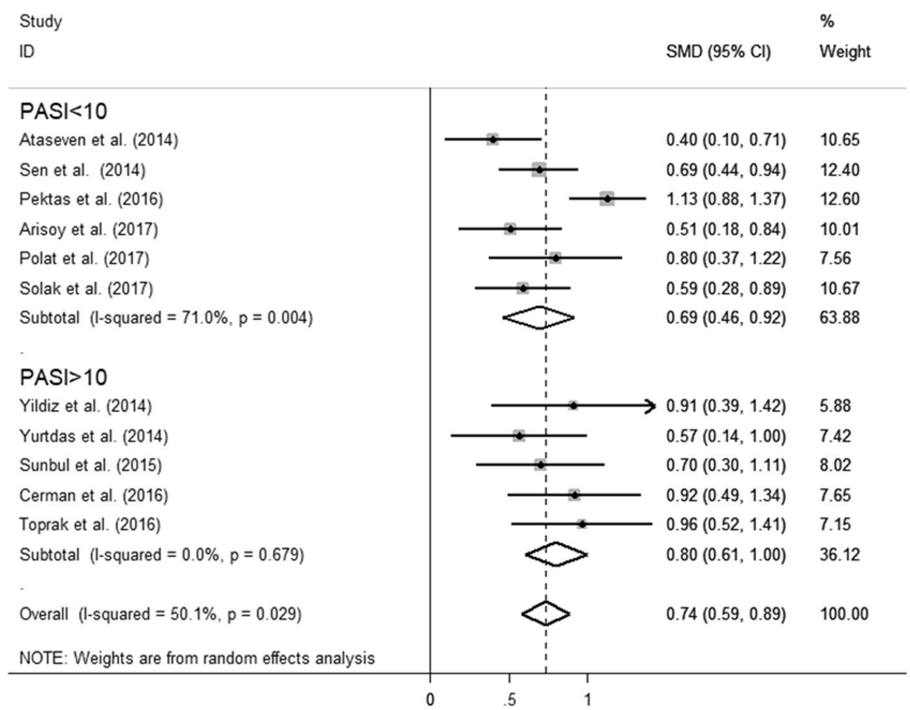

Fig. 5 Forest plot of studies examining NLR and psoriasis according to disease severity evaluated by PASI

necrosis factor α (TNF-α), a pro-inflammatory cytokine which plays a central role in the cross-talk between innate and adaptive immunity and acts through several distinct pathways [40]. TNF-α is also produced by dermal plasmacytoid dendritic cells after stimulation by cathelicidin, keratinocytes, and endothelial cells [41]. Furthermore, Th17 cells, a subset of lymphocytes, produce interleukin-17 (IL-17), which is also produced by neutrophils, mast cells, and macrophages [42]. Both TNF-α and IL-17 stimulate the proliferation of keratinocytes and the production of inflammatory mediators, which further enhance the involvement of circulating cells. The NLR seems to adequately reflect this involvement and, therefore, systemic inflammation in patients with psoriasis. This concept is supported by the observed alterations in the relative number of circulating neutrophils and lymphocytes although the exact pathogenetic mechanisms are unclear. On the other hand, when we studied the NLR in patients with high PASI (greater than 10) in comparison with those with lower values, no statistically significant associations

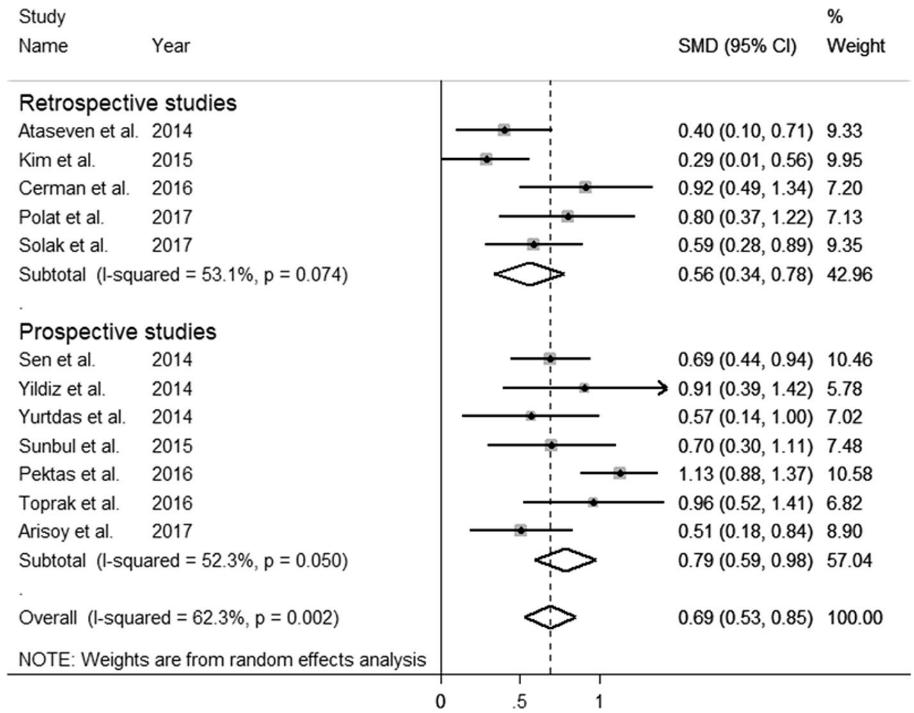

Fig. 6 Forest plot of studies examining NLR and psoriasis according to study design (retrospective or prospective)

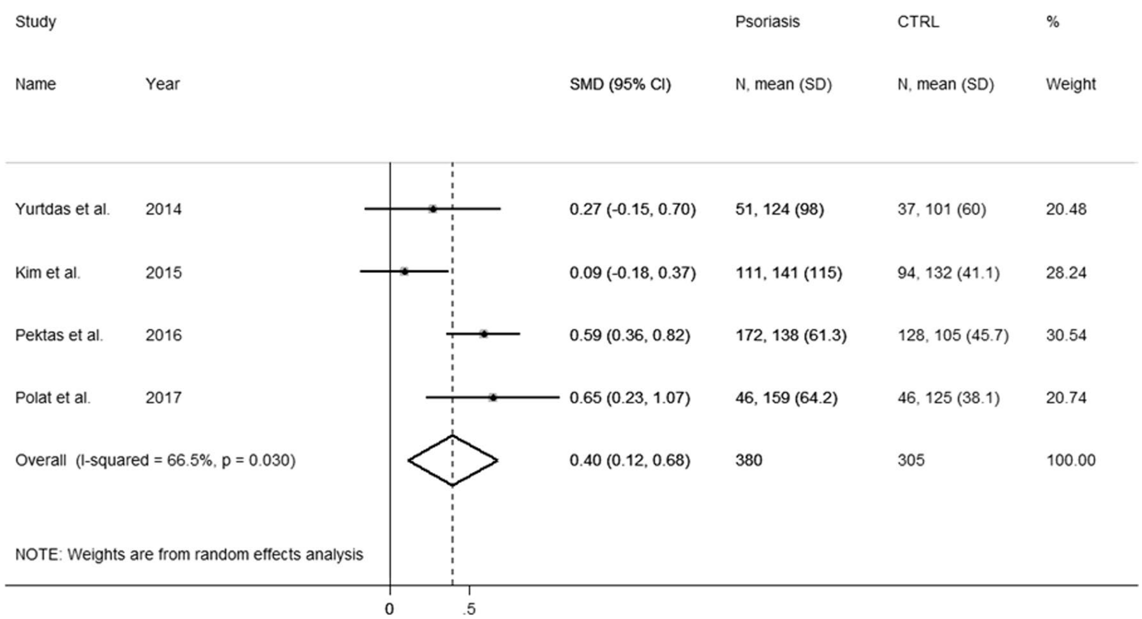

Fig. 7 Forest plot of studies examining PLR and psoriasis

were found in meta-regression analysis, despite a trend toward increased NLR levels in patients with PASI > 10. Interestingly, this subgroup did not show significant heterogeneity, differently from the PASI < 10 group that was characterized by high heterogeneity. Heterogeneity in the studies of patients with mild psoriasis may be due to a certain degree of diagnostic inaccuracy, caused by less overt clinical manifestations in those patients; by contrast, the diagnosis would likely be easier and more accurate in patients with severe psoriasis, thus reducing the heterogeneity in this subset. Overall, our findings suggest that NLR correlates with the presence of the disease, but not its severity.

PLR was also significantly associated with the presence of psoriasis. The role of the platelets in the pathophysiology of several chronic inflammatory diseases is currently under investigation. Zamora et al. demonstrated an anti-inflammatory role of platelets, mediated by platelet–leukocyte cell-to-cell interactions via P-selectin, platelet glycoprotein Ibα (GPIbα) and CD40L. By contrast, Boilard et al. reported pro-inflammatory effects mediated by leukocyte recruitment in the synovial vascular compartment in rheumatoid arthritis [43, 44]. In psoriasis, alterations in platelet activity creating a pro-thrombotic state and favouring leukocyte rolling in the skin microvasculature have been described [45, 46]. Although our results suggest a significant association between the PLR and the presence of the disease, the relatively small number of studies did not allow the conduct of meta-regressions to investigate further associations with the severity of psoriasis.

Although meta-analyses generally enhance the quality of the available evidence, inherent limitations of our study should be acknowledged. First, we could not rule out between-study differences in the analytical assessment of complete blood count testing and in the reference intervals used. Furthermore, the impact of specific immunosuppressive drugs (i.e., nonsteroidal anti-inflammatory drugs or glucocorticoids) on NLR and PLR was not assessed due to the lack of data presented in individual studies. In addition, these indexes are likely influenced by other skin or systemic comorbidities of psoriasis, which might limit their clinical use in patients suffering from concomitant disorders. Finally, considering that 11 out of the 12 studies included were performed in Turkey, a possible bias linked to race could not be excluded. On the other hand, this is the first meta-analysis to our knowledge which investigates associations between blood count cell indexes and presence and severity of psoriasis. The relatively high number of cases and controls, the quality of the studies selected, and the rigorous methodological approach are further strengths of our work.

In conclusion, this meta-analysis shows significant associations between the NLR and PLR and the presence, but not the severity, of psoriasis. Further studies are required to determine the additional utility of these haematological indexes in the diagnosis of psoriasis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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