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ORIGINAL PAPER

The interplay between neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, erectile dysfunction, and Peyronie's disease: A meta-analysis of observational studies

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Summary ***Introduction: This study aims to investigate the relationship between Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR) with Erectile Dysfunction (ED) and Peyronie's disease (PD). Methods: We conducted a meta-analysis of the observational study by searching for the appropriate keywords in eight databases. The risk of publication bias of the included studies was assessed by Egger's test and Kendall's t. The data extraction was carried out for each study and analysed using Revman 5.0. Results: There were eleven eligible studies out of the 411 studies retrieved. Eight studies were conducted on cases of erectile dysfunction, and three studies on Peyronie's disease. There was a significant relationship between NLR, PLR and ED (SMD: 0.59, 95% CI: 0.33-0.85 and SMD: 0.64, 95% CI: 0.13-1.16, respectively). The same was also found for PD. The active phase of PD tended to have higher NLR (SMD: 0.68, 95% CI: 0.43-0.92) and PLR (SMD: 0.27, 95% CI: 0.06-0.49) compared to the chronic phase. No publication bias was found in both ED and PD studies. Conclusions: NLR and PLR indicate an ongoing inflammatory process in both ED and PD. These findings can be used as markers of treatment and prognosis of both diseases in sexual health care.***

KEY WORDS: *NLR; PLR; Inflammatory; Erectile dysfunction; Peyronie's disease; Sexual health care.*

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INTRODUCTION

Erectile dysfunction (ED) is a condition that is defined as an inability to achieve or maintain an erection sufficient to engage in sexual intercourse (1). In men, ED is the most common cause of sexual dysfunction. The prevalence of ED tends to increase with age. ED occurs in approximately 2% of men under the age of 40, but this rate increases by 15% between the ages of 40 and 50, reaching 45% by age 60 and 70% by age 70 (2). There are many factors contributing to ED, such as obesity, diabetic disease, dyslipidaemia, hypertension, neurological disorder, etc. The most common causes of ED are hypertension, diabetes mellitus, and coronary artery disease. Whatever the reasons, the main problem is a vascular disorder associated with endothelial dysfunction. A dating among ED and extended threat of cardiovascular occasions may be defined through underlying endothelial dysfunction. Endothelial dysfunction is usually defined as impaired nitric oxide bioavailability, decreased vasodilation, and exacerbation of inflammation prior to atherosclerotic lesions. ED itself is not only a strong predictor of CAD, but also of future mortality associated with major cardiovascular events in men with CVD (2, 3).

Blood tests for blood cells are basic tests that are routinely performed in clinical settings, such as *red blood cells* (RBC), *white blood cells* (WBC), and *platelets* (PLT) (4). Studies have shown that these hematologic parameters are closely associated with the development of endothelial dysfunction and atherosclerosis (5). They can be used not only to predict the development of cardiovascular, cerebrovascular, and peripheral vascular diseases, but also to assess the severity and prognosis of such diseases (5). *Neutrophil/lymphocyte ratio* (NLR) has been proposed as a biomarker of subclinical inflammation. In addition, the *platelet/lymphocyte ratio* (PLR) has been found to be an important marker of inflammation (6). Because ED and CVD and other vascular diseases almost share the same pathophysiology, recent studies have found a strong association between atherosclerosis and inflammation, showing that inflammatory markers such as NLR (neutrophil/lymphocyte ratio) and PLR (platelet/lymphocyte ratio) are significantly elevated in CAD and ED (2, 5).

Peyronie's disease (PD) is an acquired pathology of the albuginea of the penis without a clearly established aetiology (7). It is an incurable fibrotic disease of the albuginea that causes penile curvature with loss of sexual function in many patients (8). PD is known as a localized inflammatory disease of the tunica albuginea of the penis. The prevalence of PD in the United States has been estimated at 0.5-9% of the general population. ED is a commonly associated comorbidity of PD, reported in 32% of men (9). There are two phases of PD: active (acute phase) and qui-

escent (chronic phase). "*Acute phase*" of PD is an inflammatory phase characterized by changes in penile curvature, with or without palpable plaques or increased erectile pain. '*Chronic phase*' of PD shows stable penile curvature with or without palpable plaques (8, 9). Nowadays, there are no objective biomarkers used to distinguish between acute and chronic disease stages. Inflammatory parameters such as NLR, the *monocyte-to-eosinophil ratio* (MER), and PLR are simple and actionable markers that can be easily calculated with a *complete blood count* (CBC) (10). Identifying predictive tools for diagnosing PD stages is important for selecting appropriate therapies.

Some of recent studies show significant differences in both NRL and PLR between the acute and chronic stages of PD. In other hands, other studies implicate no relationship between the acute phase ratio values and the penile curvature achieved after stabilization (6, 7). However, there are no validated blood tests on the market that can be used to diagnose or characterise the phases of PD. Based on the considerations above, we conducted a systematic review and meta-analysis to validate the association of NLR, PLR and ED. Indeed, we hoped that the comprehensive conclusions of the meta-analysis would promote the important role of haematological testing in the diagnosis and prediction of ED, especially PD.

Methods

Search strategy and eligibility criteria

This study was conducted following the PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) guidelines (11). The study has been registered with PROSPERO with registration no. CRD42022356840. We conducted a study search on eight databases, including *PubMed, EBSCO, Springer Link, Science Direct, ProQuest, Web of Science, Taylor and Francis, and Google Scholar*. Diseases considered in this review are erectile dysfunction and Peyronie's disease.

We used keywords such as "*neutrophil-lymphocyte ratio*" OR "*NLR*" OR "*platelet-lymphocyte ratio*" OR "*PLR*" AND "*erectile dysfunction*" OR "*erectile*" to search for studies dealing with erectile dysfunction while for Peyronie's disease we used the keyword "*neutrophil -lymphocyte ratio*" OR "*NLR*" OR "*platelet-lymphocyte ratio*" OR "*PLR*" AND "*Peyronie's disease*". The search is not limited by the time of publishing the study. The criteria for the eligible studies in cases of erectile dysfunction and Peyronie's disease were: 1) observational analytical studies, 2) presenting NLR and PLR data, 3) written in English, and (4 available in full text.

Then we excluded studies that were: 1) performed on animals or *in vitro*, 2) case reports or case-series, 3)

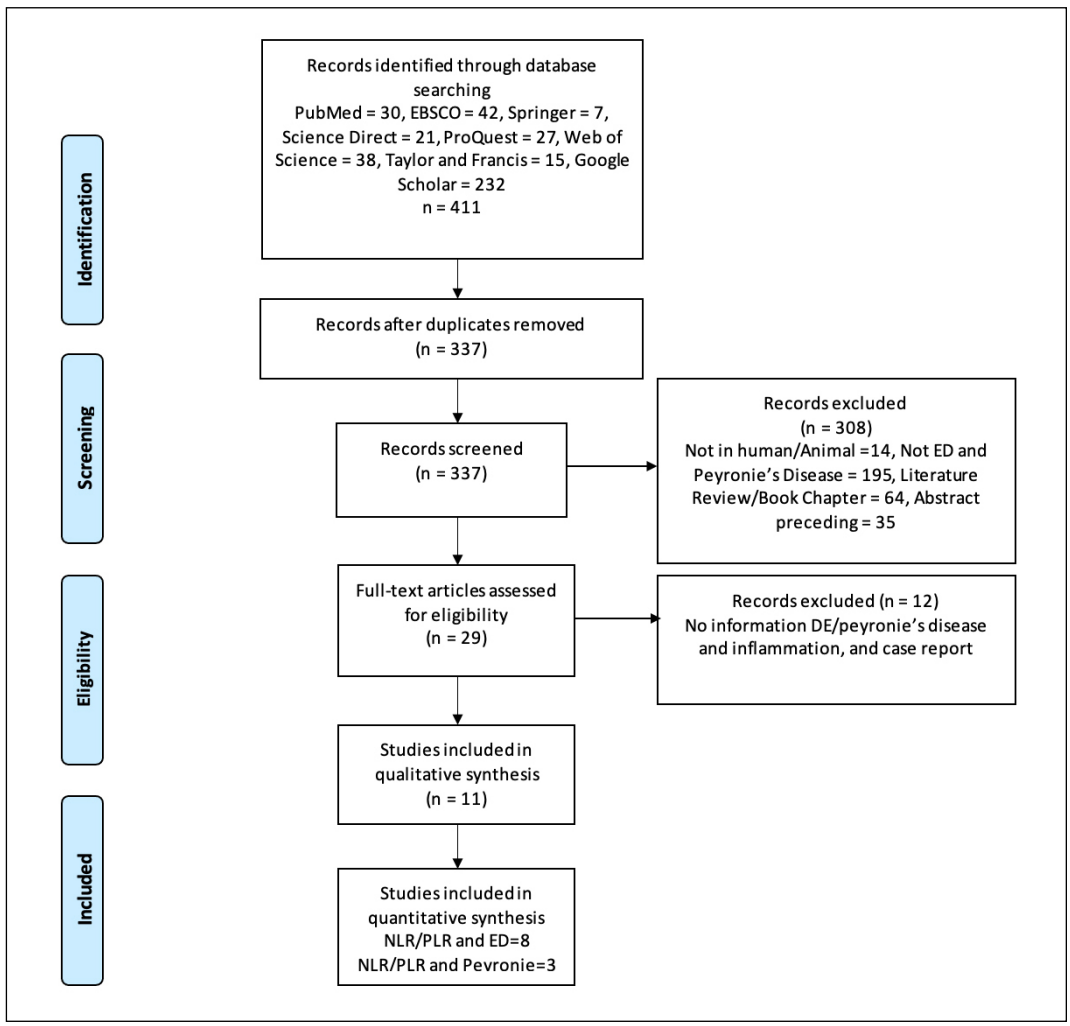


Figure 1.
PRISMA flowchart.

abstract, poster, preceding, review, and 4) articles that had not been published or pre-printed.

Data extraction and study quality analysis

Two authors (CP and II) extracted the studies from the database, and screened through the title and abstract in detail with Mendeley's assistance. Roughly suitable studies were thoroughly read and discussed by the two authors. Data extraction was done if the study met the pre-defined criteria we have set. The data were taken in the form of the author's name, year of publication, population, type of research, number of samples involved, and the statistical size used to see the relationship between NLR, PLR with ED, Peyronie's disease, and age of the sample. Then simultaneously, we assessed the quality of the study with the *Newcastle-Ottawa Scale* (NOS) (12). Any confusion or difference of opinion found during the screening and extraction process was discussed with other authors to reach an agreement.

After completing the data extraction, the data was processed using Revman 5.0 for Mac. The statistical measures we processed were mean and SD of NLR and PLR in the health and ED group in the erectile dysfunction study, and the acute and chronic group in the Peyronie's disease study. Initially, we wanted to assess each study's OR and RR values, but some data needed to be completed, and the author could not be contacted (unresponsive). If the heterogeneity value was $p > 0.05$, we performed a fixed effects model, and if the heterogeneity was $p < 0.05$, we chose a random effects model. Then, we used the regression test for funnel plot asymmetry (Egger's test) and the rank correlation test (Kendall's t) to assess the risk of publication bias using JASP.

Results

Search results and study characteristics

The search for relevant studies is depicted in Figure 1. Out of the eight databases we used, there were 411 studies matching the keywords. But using the Mendeley, there were some duplications found, leaving us with 337 studies matched.

A total of 308 studies were excluded because they did not meet the criteria, leaving only 11 studies eligible for qualitative synthesis (2, 3, 5-7, 9, 10, 13-16). After the review, eight of them were studied in ED cases (*Sambel et al.*, 2018, *Demirci et al.*, 2019, *Demirci et al.*, 2020, *Erdogan et al.*, 2020, *Karabakan et al.*, 2019, *Akbas et al.*, 2016, *Liao et al.*, 2021, *Aslan et al.*, 2019) and three case studies of Peyronie's disease (*Esther et al.*, 2019, *Greenberg et al.*, 2022, *Ozbir et al.*, 2020).

In ED study, eight studies were included, a total sample of 1007 in the control or healthy group and 1221 in the ED group. Of these eight studies, seven were from Turkey, while only one was from China. All studies included were case-control studies. Almost all the patients in the study were confirmed by history, IIEF-5, and some underwent hormone testing.

In Peyronie's disease study, the total sample in the active phase group was 169, and the chronic phase was 217. These three studies came from Turkey, USA, and Spain. The diagnosis of Peyronie's disease, was established by history taking and physical examination, including measuring the penile curvature.

Information on sample age and study quality using NOQS is presented in Table 1.

Table 1.
Baseline characteristics of the included studies.

Author, years of publication	Country origin	Study design	Sample size and allocation	Output variable and measure size	Age in years Mean ± SD, Median (min-max)	NOQS
Study with erectile dysfunction						
Sambel et al, 2018	Turkey	Case-control study	Healthy = 175 ED = 262	Mean ± SD = NLR, PLR	Healthy = 48 (43-65) ED = 49 (40-69)	7/9
Demirci et al, 2019	Turkey	Case-control study	Healthy = 80 ED = 63	Mean ± SD = NLR, PLR	Healthy = 48.8 ± 13.0 ED = 47.45 ± 12.01	7/9
Erdogan et al, 2020	Turkey	Case-control study	Healthy = 44 ED = 148	Mean ± SD = NLR, PLR	Healthy = 52.23 ± 7.6 ED = 52.16 ± 8.6	8/9
Karabakan et al, 2019	Turkey	Case-control study	Healthy = 26 ED = 131	Mean ± SD = NLR, PLR	Healthy = 53.3 ± 8.3 ED = 54.55 ± 8.17	7/9
Akbas et al, 2016	Turkey	Case-control study	Healthy = 175 ED = 262	Mean ± SD = NLR, PLR	Healthy = 53.8 ± 8.4 ED = 54 ± 11.7	7/9
Liao et al, 2021	China	Case-control study	Healthy = 212 ED = 113	Mean ± SD = NLR, PLR	Healthy = 32 (29-37) ED = 33 (29-38)	8/9
Aslan et al, 2019	Turkey	Case-control study	Healthy = 94 ED = 90	Mean ± SD = NLR	Healthy = 59.5 (52.0-68.0) ED = 61.0 (53.0-66.25)	7/9
Demirci et al, 2019	Turkey	Case-control study	Healthy = 201 ED = 152	Mean ± SD = NLR, PLR	Healthy = 45.5 ± 8.6 ED = 46.4 ± 12.9	7/9
Study with Peyronie's disease						
Esther et al, 2019	Spain	Case-control study	Active phase = 42 Chronic phase = 78	Mean ± SD = NLR, PLR	All phase = 55.85 ± 10.71	7/9
Greenberg et al, 2022	USA	Case-control study	Active phase = 27 Chronic phase = 82	Mean ± SD = NLR, PLR	Active phase = 63 (57.0–67.5) Chronic phase = 61 (54.0–66.0)	7/9
Ozbir et al, 2020	Turkey	Case-control study	Active phase = 98 Chronic phase = 57	Mean ± SD = NLR, PLR	Active phase = 54.1 ± 9.2 Chronic phase = 54.1 ± 10.6	8/9

Figure 2.
Forest plot analysis between NLR (a), PLR (b), and erectile dysfunction.

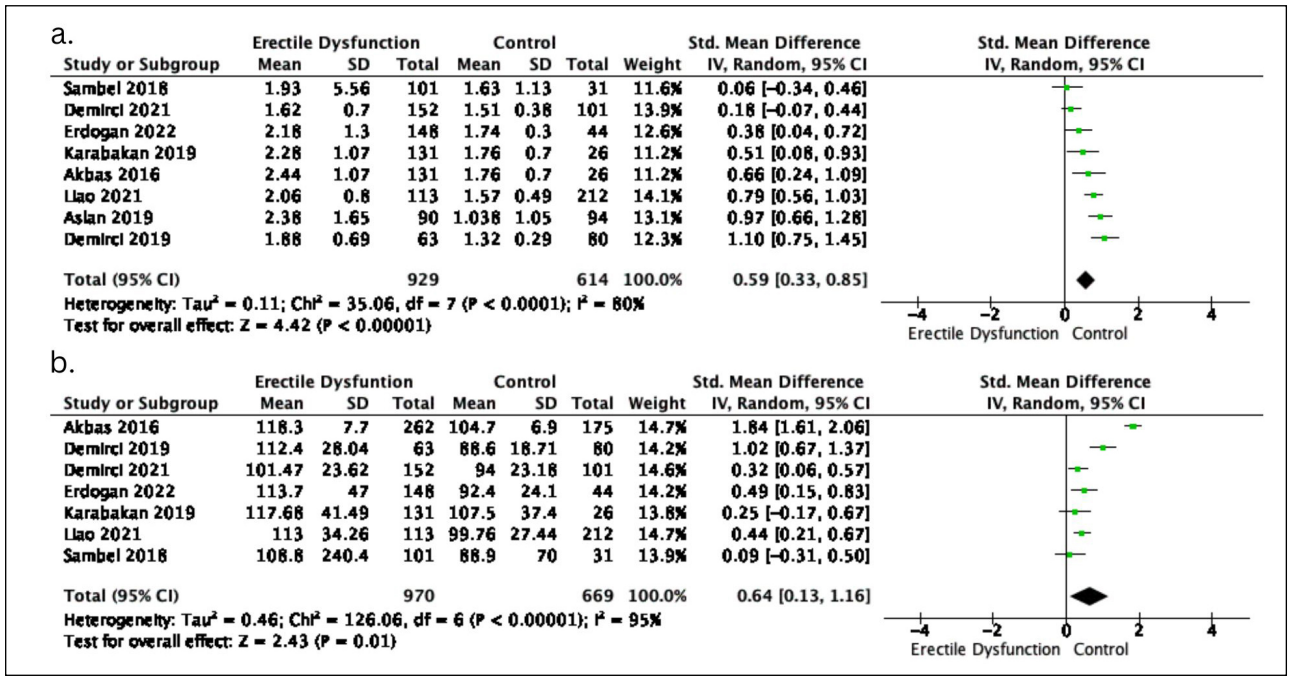
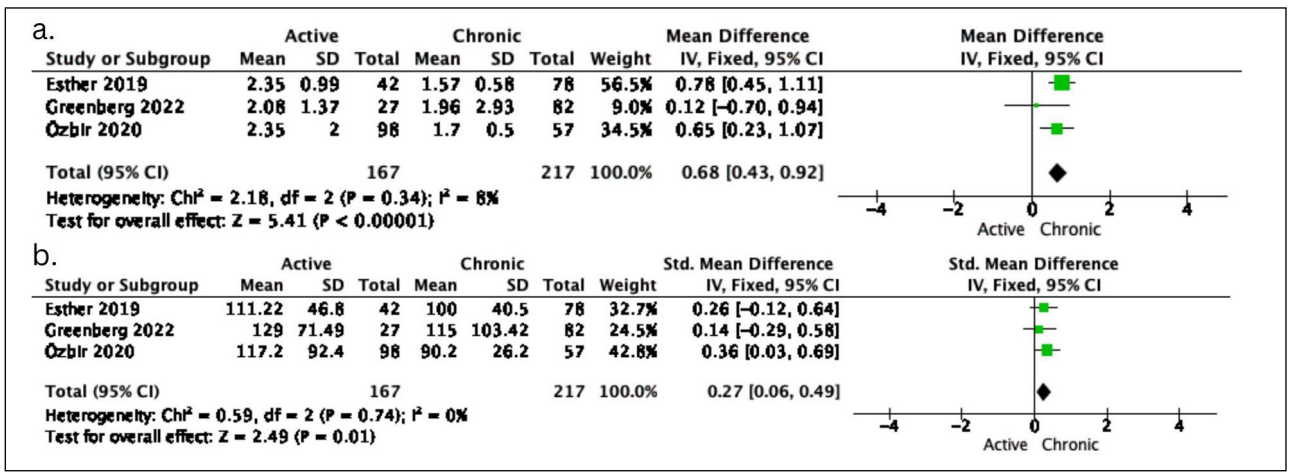


Figure 3.
Forest plot analysis between NLR (a), PLR (b), and Peyronie's disease.



Meta-analysis results

The results of the NLR analysis in relation with ED showed that there were significant differences of ED group compared to the control group (SMD: 0.59, 95% CI: 0.33-0.85). With heterogeneity (I2) = 80% (p < 0.0001), random effects modelling was performed for this variable (Figure 2a). The ED group tended to have higher NLR values than the control group. PLR analysis in relation with ED also showed significant differences of ED group compared to the control group (SMD: 0.64, 95% CI: 0.13-1.16). With heterogeneity (I2) = 95% (p < 0.00001), random effect modelling was performed on this variable (Figure 2b). These results indicated that the PLR value in the ED group tended to be higher than in the control group.

In Peyronie's disease study, significant results were obtained in the NLR test between the active and chronic phase groups. The active group tended to have higher NLR values than chronic (SMD: 0.68, 95% CI: 0.43-0.92). With heterogeneity (I2) = 8% (p = 0.34), fixed effects model was performed for this variable (Figure 3a). For PLR testing in active and chronic phases, significant results were obtained (SMD: 0.27, 95% CI: 0.06-0.49). With heterogeneity (I2) = 0% (p = 0.74), fixed effects model was performed for this variable (Figure 3b). PLR in the active group was higher than in the chronic group.

Risk of Bias assessment

The bias assessment was carried out using the regression test for funnel plot asymmetry (Egger's test) and rank correlation test (Kendall's t). In the study conducted to assess

NLR and PLR for ED, the regression test for funnel plot asymmetry (Egger's test) is z = -0.226, p = 0.822, and the rank correlation test (Kendall's t) is 0.071, p = 0.905. These results indicated no publication bias in those articles (ED). In the NLR and PLR studies with Peyronie's disease phase, the regression test for funnel plot asymmetry (Egger's test) is z = -0.750, p = 0.453, and the rank correlation test (Kendall's t) is -1,000, p = 0.333 indicated that there was no publication bias in those articles.

Discussion

The results of this meta-analysis were in line with previous theories. NLR and PLR were significantly increased in the ED group compared to the control group. This was because the inflammatory process in ED did occur. Several inflammatory mediators (interleukin (IL)-1β, TNF-, IL-6, CRP, IL-10) and endothelial/prothrombotic factors were activated in the ED process (16). So, the increase in NLR and PLR was natural and in sync with the incidence of ED. These findings suggested that NLR and PLR can be used as independent factors in ED cases. Even these two parameters can be used as predictors of ED events. The advantage is that NLR and PLR are two parameters that are easy and inexpensive to check. This can be very promising in terms of diagnosis and management of ED.

The second finding was difference of NLR and PLR in Peyronie's disease between the active and chronic groups. This meta-analysis was the first to analyse the involvement of these two parameters with Peyronie's disease. This showed that active Peyronie's disease was still an inflammatory process. Increased NLR and PLR in the acute phase indicated a traumatic micro-vascular process in Peyronie's disease (17). So, in the acute phase of this disease, patients often complained of pain during erection. Our finding is interesting because until now, there has been no established biomarker for distinguishing the active and chronic phases of Peyronie's disease. So, this finding looked promising, especially in managing Peyronie's disease.

Neutrophils naturally produce many inflammatory agents, such as myeloperoxidase which can cause injury (18). In comparison, lymphocytes are blood components that regulate the number of neutrophils (19). On the other hand, platelets play a role in forming fibrin, commonly found in cases of Peyronie's disease because of injury and inflammation. Fibrin is also a chemoattractant against macrophages, neutrophils, and fibroblasts (20). Then leukocyte and macrophage influx will accumulate and are difficult to degrade, resulting in the production of fiber and collagen (21). This mechanism was in line with the results of this study, showing that NLR and PLR were increased in the acute phase because the inflammatory process was still massive.

A limitation could be that, in the case of ED evaluation, although the number of studies is quite large, surprisingly 7 out of 8 studies were conducted in Turkey. The diversity of study locations is essential to add to the strength of the study's results.

In addition, it was clear that there were significant differences between the ED and control groups. Still, the differences between the degrees of ED were difficult to assess due to data limitations. It is recommended that an analysis should be carried out to explain that the role of inflammation is different in each degree of ED.

As for Peyronie's disease, the number of studies is still minimal. However, this was an excellent start to explain that the active phase of this disease showed ongoing inflammatory activity. So, this can be used as a predictor or even as a consideration in management. In addition, existing studies only compared subjects with Peyronie's disease of different degrees, not with healthy controls. In addition, in the case of either ED or Peyronie's disease, it is crucial to design a cohort study to evaluate NLR and PLR according to disease progression in order to show if determination of NLR and PLR is not only an independent risk factor but can also be a prognostic factor.

Conclusions

This meta-analysis found that NLR and PLR, as markers of inflammation, were significantly different in the ED and control groups. The same finding was also obtained when tested on PD cases in different phase of the disease. This significant finding indicates that the inflammatory process is ongoing in both diseases. This can be the basis for this disease's diagnosis, treatment, and prognosis. However, it cannot be denied that the number of studies and the diversity of the population involved in this study are still small.

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