ORIGINAL ARTICLE

Male Health

Role of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in Peyronie's disease: a new diagnostic approach to predict the stage of the disease?

Esther García Rojo[1], Borja García Gómez[1,2], Rocio Santos-Pérez de la Blanca[1], Celeste Manfredi[1], Manuel Alonso Isa[1,2], José Medina Polo[1,2], Alfredo Rodríguez Antolín[1], Javier Romero Otero[1,2]

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been associated with multiple entities and several types of cancers. They can be assumed as markers of inflammatory imbalance. The objective of this study is to evaluate the NLR and PLR in Peyronie's disease (PD) and to establish a comparison of its values in the acute and chronic stages. We recruited patients with PD from March 2018 to March 2019. The patients enrolled underwent medical and sexual history as well as a physical examination. The values of blood count of each patient were collected both in the acute and chronic stages. Wilcoxon test was used to compare the acute and chronic stage ratios. Kruskal–Wallis test was carried out to evaluate the impact of treatments on the ratios. To identify cutoff values, we used sensibility and specificity tables and receiver operating characteristic (ROC) curves. A total of 120 patients were enrolled. Their mean age was 55.85 (range: 18–77) years and the mean penile curvature was 48.43° (range: 10°–100°). In the acute stage, the mean NLR was 2.35 and the mean PLR was 111.22. These ratios, in the chronic stage, were 1.57 and 100.00, respectively. Statistically significant differences between acute and stable stages for both indices were found (NLR: $P < 0.0001$; PLR: $P = 0.0202$). The optimal cutoff for classification in acute or stable stage was 2 for NLR and 102 for PLR. According to our results, with an ordinary blood count, we could have important indications regarding the disease stage of the patient, and consequently on the most appropriate type of therapy to choose.

INTRODUCTION

Peyronie's disease (PD) is an acquired pathology of the tunica albuginea of the penis without clearly established etiopathogenesis.[1] PD has been associated with different comorbidities, such as diabetes mellitus, hypertension, hyperlipidemia, inflammatory genital diseases, connective tissue disease, surgery of the genital tract, or even hormonal factors such as hypogonadism.[2]

The natural history of the disease is variable, though it is classically subdivided into two stages of inconstant duration: first active or inflammatory, which is usually accompanied by pain in erections and in which the inflammatory plaque develops and causes the commonly associated malformations (curvatures, shortening, or narrowing), and second chronic or stable, where inflammation decreases, pain subsides, and anatomical deformities stabilize.[3]

Historically, the gold standard of PD treatment was a surgical approach. Many nonsurgical treatments have been proposed for PD, such as oral drugs, intraplaque injections, iontophoresis, or low-intensity shockwaves. None of them has shown a clear benefit against placebo in curvature correction.[4–7] In contrast, in 2013, the Food and Drug Administration (FDA) approved the use of collagenase from *Clostridium histolyticum* (CCH; Xiapex®, Swedish Orphan Biovitrum AB, Stockholm, Sweden) along with penile modeling, as a therapeutic alternative to some patients with PD in stable stage, which was once demonstrated in the IMPRESS I and II trials to be safe and effective.[8,9] Although this therapy is not yet indicated for the acute phase of PD, there are preliminary results that suggest the effectiveness of this minimally invasive option by improving penile curvature at this stage.[10,11] With an effective conservative treatment, the stage classification of the disease becomes even more important.

The blood count is a cost-effective, easy-to-perform, and straightforward method of wide availability that allows evaluating the presence of an ongoing inflammatory process.[12]

Neutrophils are immature phagocytes with a short half-life. Their ability to release proteolytic enzymes and oxygen free radicals

is well known, actively contributing to the damage produced during inflammatory processes. Furthermore, the proteins present in their granules generate molecular instructions to recruit and activate other inflammatory cells. These actions trigger a significant immunoregulatory effect.[13] The lymphocytes are a subtype of white blood cells whose primary function is the adaptive (or specific) immune response regulation, reacting against foreign antigens. For this purpose, they are differentiated into the following three cell lines: T lymphocytes, B lymphocytes, and natural killer (NK) cells. Lastly, platelets are nonnucleated cell fragments derived from megakaryocytes. Their hemostatic and prothrombotic role was widely recognized, although an important pro-inflammatory function has recently been suggested.[14] They interact with numerous immune cells, with their relationship with endothelial cells and leukocytes being of great importance.[12,14]

Among the different hematological parameters, the neutrophil-to-lymphocyte ratio (NLR) is significantly associated with pro-inflammatory cytokine levels and systemic inflammation development and progression.[15] This ratio, together with the platelet-to-lymphocyte ratio (PLR), was associated with multiple entities, such as cardiovascular,[16] rheumatological,[17] or gynaecological[18] diseases. It was also shown that they are biomarkers associated with the aggressiveness of numerous tumors (*e.g.*, breast, lung, gastrointestinal, melanoma, and urological cancers).[15,19] In this context, some studies suggested that the NLR can be used as an independent prognostic factor in a wide spectrum of cancers.[20] Based on these findings, it can be assumed that NLR and PLR represent a marker of inflammatory imbalance characterized by a predominance of effector cells (pro-inflammatory effect), headed by neutrophils and activated platelets, over regulatory cells (anti-inflammatory effect), particularly CD4 T lymphocytes.[16]

The hypothesis of the current study is that these systemic inflammatory parameters are higher in the active phase of the disease and could predict the stage of PD. There is just one previous paper linking these ratios with PD.[21] They found statistically significant differences in NLR and PLR between acute and chronic groups. The aim of this study is to corroborate these results evaluating the NLR and PLR in PD patients and comparing their values in the acute and chronic stages.

PATIENTS AND METHODS

Study design and patient enrollment

We designed an observational descriptive study, in which patients with PD who arrived at our center (University Hospital 12 de Octubre, Madrid, Spain) were recruited from March 2018 to March 2019.

The study has been approved by the Ethics Committee at University Hospital 12 de Octubre (N° CEIm 18/332). All patients were informed of the study features and signed an informed consent.

We calculated the sample size to detect differences between the acute and chronic ratios, assuming a deviation of the differences of 0.7 (according to a preanalysis with thirty patients), and to detect a difference of 0.5 units in NLR. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, the needed sample size was 25 patients.

Patient assessment: variables and measurement methods

Each patient enrolled underwent medical and sexual history as well as a physical examination. The variables collected were age, body mass index (BMI), comorbidities (hypertension, diabetes mellitus, dyslipidemia, smoking, and connective tissue diseases), previous endoscopic urologic surgery or intracavernous injections, penile curvature, plaque characteristics, and stretched penis length (SPL). The penile curvature was evaluated by Kelami method,[22] whereas SPL was assessed using a caliber, from the base (pubo-penile junction) to

the tip of the glans (meatus) on the dorsal aspect of the penis. Every type of treatment for PD the patients underwent before and during the study was recorded.

The PD stage at the time of consultation was also evaluated (acute or chronic). The classification was clinical; patients in the acute stage were classified as those who presented any of the following: painful erections, palpable penile plaque, and/or progressive penile deformity; whereas for the chronic stage, patients had to report a painless disease with a nonworsening penile deformity for at least 3 months.[23] In all patients, time from the onset of symptoms was recorded and in patients with a chronic disease, the time from stabilization was also collected.

A full blood count, reporting the absolute number of neutrophils, lymphocytes, and platelets values, was collected for each patient both in the acute and chronic stages of the disease. In patients enrolled in the acute stage, the data corresponding to the chronic stage were collected prospectively when the disease stability was confirmed; vice versa in patients recruited in the chronic stage, the data corresponding to the acute stage were obtained retrospectively. The data of patients enrolled in the acute stage were recorded before any type of treatment. NLR and PLR were calculated as the ratio between the absolute number of neutrophils and lymphocytes and of platelets and lymphocytes, respectively.

The comparison between ratios in the acute and chronic stages was performed comparing each patient with himself to minimize possible bias related to different comorbidities or medical conditions in different groups. Patients with no available data in the acute or chronic stage were excluded from the analysis.

Statistics

The statistical analysis was performed with the statistical software SAS® version 9.4 (SAS Institute, Cary, NC, USA). The categorical variables were described as frequencies and percentages, whereas the quantitative variables were presented as means and standard deviations (s.d.). The comparison between the acute and chronic stage ratios was performed with the Wilcoxon test and the Spearman's correlation. Subsequently, regression analysis was carried out with univariate models, adjusted between the difference of the values of acute and chronic stages ratios as dependent variables and the rest of the relevant variables as independent ones. A confidence level of 95% ($P < 0.05$) was established for all analyses. In order to evaluate the possible impact of treatments on the ratios, we selected the patients who were recruited in the acute stage, and we used the Kruskal–Wallis test to evaluate the variation differences between the acute and chronic ratios after the different treatments. To identify the optimal cutoff ratios to predict acute or chronic disease, we used sensibility and specificity tables and receiver operating characteristic (ROC) curves.

RESULTS

A total of 120 patients with a mean age of 55.85 (s.d. = 10.71) years were enrolled. The general clinical features of the patients are shown in **Table 1**.

PD: penile characteristics, stage, and treatments

The mean penile curvature of all population was 48.43° (s.d. = 22.06°). Ninety patients (75.0%) had a dorsal curvature, while 20 (16.7%) and 10 patients (8.3%) showed a lateral and ventral curvature, respectively. Eight patients (6.7%) had also an hourglass deformity associated.

The plaque was palpable in 109 patients (90.8%); however, the data regarding its location were available only in 86 cases: 43 (50.0%) in the middle third of penis, 31 (36.0%) in the distal third, and 12 (14.0%) in the proximal third. The mean SPL was 145 (s.d. = 17.7) mm.

At the time of the first visit, 78 (65.0%) patients were in the chronic stage of disease and 42 (35.0%) in the acute stage.

Concerning the initial treatment offered to patients, no treatment was performed in 23 (19.2%) patients; 30 (25.0%) patients received intraplaque injection of collagenase; in 47 cases (39.2%), the use of a penile traction device was the first treatment proposed; 9 (7.5%) patients received verapamil injections; and 11 (9.2%) patients underwent surgery.

NLR and PLR: values and clinical correlations

The mean NLR and PLR were 2.35 (s.d. = 0.99) and 111.22 (s.d. = 46.8) in the acute stage, whereas in the chronic stage, they were 1.57 (s.d. = 0.58) and 100.00 (s.d. = 40.5), respectively (**Figure 1**). The blood count data were available for both stages in 71 patients. Comparing each patient with himself, using the values of NLR in the acute and chronic stages, and in the same way the PLR, we obtained a statistically significant difference for both ratios between the two stages (NLR: $P < 0.0001$; PLR: $P = 0.0202$). We found the same statistically significant differences (NLR: $P < 0.0001$; PLR: $P < 0.0001$) comparing the means of both ratios in the acute and chronic stage groups.

Regarding the difference of NLR in the acute and chronic stages, in the univariate models of regression analysis, a statistically significant positive correlation was found only with dyslipidemia ($P = 0.02$). No correlation was found with the rest of the variables evaluated. Analyzing the difference of PLR in the acute and chronic stages, we found similarly a significant correlation only with dyslipidemia ($P = 0.04$; **Table 2**).

In the univariate model of regression analysis, no correlation was found with the penile curvature (NLR: $P = 0.80$; PLR: $P = 0.055$). In addition, excluding patients whom in the active stage underwent procedures that could modify the curvature, we did not find a statistically significant relationship between NLR ($P = 0.80$) or PLR ($P = 0.09$) in the acute stage and the penile curvature reached after stabilization. No statistically significant association was found between the ratios and the presence of greater deformities, such as those with hourglass deformity (NLR: $P = 0.62$; PLR: $P = 0.76$).

When the analysis to evaluate the possible impact of treatments for PD on the ratios was performed, selecting the patients who were recruited in the acute stage ($n = 42$), no statistically significant differences were found between the acute and chronic stages for both ratios (NLR: $P = 0.29$; PLR: $P = 0.35$; **Table 3**).

Finally, we calculated the optimal cutoff values of NLR and PLR to distinguish the acute and chronic stages of the disease. The optimal cutoff was 2 for NLR (sensitivity: 62.0%, specificity: 85.0%, area under the curve [AUC]: 0.77) and 102 for PLR (sensitivity: 56.0%, specificity: 66.0%, AUC: 0.59; **Figure 2**).

DISCUSSION

Several theories have been proposed about the PD pathogenesis, although its exact etiology remains unclear.[1] Currently, the most
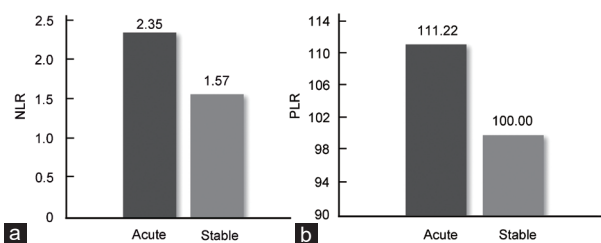
Table 1: General clinical characteristics of the study population (*n*=120)

Variable	Value
Age (year), mean±s.d.	55.85±10.71
BMI (kg m^{-2}), mean±s.d.	26.5±3.81
Arterial hypertension, *n* (%)	27 (22.5)
Diabetes mellitus, *n* (%)	19 (15.8)
Dyslipidemia, *n* (%)	31 (25.8)
Connective tissue disease, *n* (%)	3 (2.5)
Current smokers, *n* (%)	15 (12.5)
Intracavernous injections, *n* (%)	1 (0.8)
Endoscopic surgery, *n* (%)	2 (1.7)
Penis surgery, *n* (%)	10 (7.5)
Circumcision	5 (4.2)
Plicature	4 (3.3)
Others	1 (0.8)

s.d.: standard deviation; BMI: body mass index

Table 2: Regression analysis

Variable	P (NLR)	P (PLR)
Age	0.96	0.50
BMI	0.38	0.79
Arterial hypertension	0.88	0.78
Diabetes mellitus	0.31	0.59
Dyslipidemia	0.02	0.04
Connective tissue disease	0.79	0.79
Current smokers	0.45	0.64
Intracavernous injections	0.99	0.86
Endoscopic surgery	0.62	0.61
Penis surgery	0.11	0.93

NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; BMI: body mass index

Table 3: Treatments of patients enrolled in the acute stage of Peyronie's disease (*n*=42)

Treatment	Patient, n (%)	NLR		PLR	
		A	C	A	C
None	10 (23.8)	1.59	1.43	85.35	84.63
Intraplaque collagenase (CCH)	5 (11.9)	2.4	1.69	99.25	94.20
Penile traction device	18 (42.8)	1.99	1.37	103.51	103.91
Intraplaque verapamil	8 (19.9)	2.13	1.63	120.29	104.57
Surgery	1 (2.4)	2.94	1.99	111.23	109.67
P (Kruskal–Wallis test)	–	0.29		0.35	

PD: Peyronie's disease; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; A: acute stage; C: chronic stage; CCH: collagenase clostridium histolyticum; –: no result
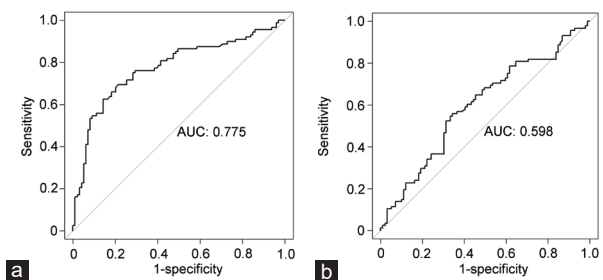

Figure 1: Mean (**a**) NLR and (**b**) PLR in the acute and chronic stages of the disease. NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

Figure 2: ROC curves for Peyronie's disease stages. (**a**) Neutrophil-to-lymphocyte ratio curve. (**b**) Platelet-to-lymphocyte ratio curve. ROC: receiver operating characteristic; AUC: area under the curve.

accepted theory is the occurrence of a trauma or microtrauma in the tunica albuginea during intercourse in susceptible individuals.[24] The repeated injury in the albuginea tissue causes inflammation, alteration of the elastic fibers, and deposition of fibrin.[3] Fibrin is a potent chemoattractant which promotes the influx of inflammatory cells such as macrophages, neutrophils, and fibroblasts.[26] Leukocyte and macrophage influx results in large amounts of cytokine production that cannot be easily degraded, resulting in excessive production of matrix fiber and collagen.[3,27] During the early stage of the disease, inflammation irritates the nerve endings, causing pain, which gradually decreases with the inflammation maturation and nerve fiber degeneration. During the chronic stage, the erectile tissues can be affected, leading to erectile dysfunction (ED). Therefore, in the acute stage, we found the classic triad of pain, plaque and progressive penile deformity, and ED, plaque and stable deformity in the chronic stage.[3]

Antibodies against elastin are present in all individuals; however, patients with PD show elevated levels of anti-tropoelastin (which reflects the elastin synthesis) and anti-α-elastin (which reflects elastin destruction), suggesting a possible related autoimmune mechanism.[28] On the other hand, PD has been linked to transforming growth factor beta-1 (TGF-β1), which is a growth factor synthesized by inflammatory cells, which binds to specific receptors on the cell surface, triggering the activation of transduction cascade signals with profibrotic effects and cell proliferation and inhibition of the collagenase enzyme.[29] This evidence suggests that PD plaques and the related symptoms develop due to a pro-inflammatory stage on the surface of the penile tunica albuginea.

Multiple studies in recent years linked the NLR and PLR to a pro-inflammatory stage and with numerous conditions and pathologies.[17–21] There is just one published paper relating these ratios with PD. They analyzed 156 patients with PD and NLR and PLR were calculated. They found statistically significant differences in NLR and PLR between acute and chronic groups ($P = 0.008$ and $P = 0.008$, respectively). Multivariate regression analysis revealed that NLR was the only independent risk factor for discrimination of the phases of PD. ROC analysis revealed a cutoff value of 1.8 (AUC: 0.712, $P < 0.001$; sensitivity: 61.1%; specificity: 75.0%) for the NLR. They studied neither the relationships between the ratios and penile curvature nor the impact of different treatments on the ratios.

In our study, we also found statistically significant differences between the acute and chronic stages in both ratios (NLR and PLR). This seems to support the hypothesis of a possible pro-inflammatory state during the acute stage of the disease. To avoid possible bias, we compared each patient's ratio with himself in different phases, in addition to comparing the whole groups based on the disease stage.

Currently, there are specific blood tests neither for the diagnosis of PD nor to assess its aggressiveness/evolution. Only a correlation with a higher expression of the antigen human leukocyte antigen-B7 (HLA-B7), TGF-β1, anti-DNA, and antinuclear and anti-elastin antibodies was demonstrated, but they cannot be considered specific markers and cannot be used on a regular practice basis.[28]

According to these results, with a simple, quick, and inexpensive blood count, we could have important indications regarding disease stage (acute or chronic), confirming the clinical suspicion of the stage and consequently on the most appropriate type of therapy to select in each case, such as the use of collagenase or surgery (which are often offered only in the setting of chronic disease).

However, we did not find statistically significant relationships between the value of the ratios in the acute stage and the penile curvature reached after stabilization or the presence of an hourglass deformity, which seems to suggest that the severity of the disease and the degree of penile curvature at the end of its evolution remain unpredictable. Regarding the evaluation of the impact on the ratios of PD treatments, no statistically significant differences were found, and this makes sense because the treatments investigated only act locally without any impact on the systemic inflammatory state. In the regression analysis, a statistically significant positive correlation was found only with dyslipidemia variable in both ratios. This is reasonable because atherosclerosis has been related with the proliferation of inflammatory cells and platelet aggregation.[16]

In our study, the mean NLR in the chronic stage of PD was 1.57, a similar value was found by Lee *et al.*;[30] indeed, they demonstrated a mean NLR of 1.65 in a sample of more than 12 000 healthy patients. These data seem to suggest that in the chronic stage of the disease, there is a reduction of the inflammatory process. However, the mean PLR in the chronic stage of our sample was lower than the PLR found in the previously mentioned study (100 *vs* 132); in other words, the value recorded in our acute patients (111) was closer.

The cutoff of NLR to establish the disease stage in our cohort was 2 (above, the disease was classified as acute, and below as chronic). With this cutoff, we had very high specificity (85.0%) with an acceptable sensitivity (62.0%) and an AUC of 0.77. On the other hand, with a PLR cutoff of 102, the AUC was 0.59, indicating that PLR is a worse predictor of stage compared to NLR (less specificity and sensitivity). This suggests that in the case of discordant classification, NLR should have a greater weight to establish the stage of the disease. The NLR cutoff value is similar to that of the other published paper: 1.8 with an AUC of 0.712, a sensitivity of 61.1%, and a specificity of 75.0%.

We are aware of the limitations of our study. First, the absence of a control group and the retrospective collection of some analytical data. Second, the low specificity of the blood parameters evaluated, which therefore may present an important fluctuation due to multiple medical conditions.[15] Third, we did not use ultrasonography for PD diagnosis, so we could not accurately evaluate the plaque calcification. Our preliminary results need to be confirmed in larger prospective studies, with subgroup analyses to exclude potential confounders, and different intakes should be extracted to be able to make an accurate evaluation of the evolution of ratios during the course of the disease. Furthermore, the impact of the routine use of these ratios in clinical practice will need to be evaluated in subsequent studies.

CONCLUSION

We found a statistically significant difference in both NLR and PLR between acute and chronic stages of PD, with optimal cutoff points of 2 and 102, respectively. No relationships were found between the value of the ratios in the acute stage and the penile curvature reached after stabilization, and no impact of PD treatments on the ratios was reported. These findings could be helpful in the diagnosis of PD stages. Further studies are necessary to confirm our results.

AUTHOR CONTRIBUTIONS

EGR, BGG, MAI, JMP, and JRO conceived the study and designed the methodology; EGR and RSPB collected the data; EGR and CM performed the statistical analysis and drafted the manuscript; BGG, MAI, JMP, ARA, and JRO revised and edited the final version of the manuscript; and ARA and JRO supervised the whole process. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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