INTRODUCTION
Peyronie’s disease (PD) is an acquired pathology of the tunica albuginea of the penis without clearly established etiopathogenesis. 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.

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.

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. 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.

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.

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.

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.

Keywords: diagnosis; inflammation; neutrophil-to-lymphocyte ratio; Peyronie’s disease; platelet-to-lymphocyte ratio
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. 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. They interact with numerous immune cells, with their relationship with endothelial cells and leukocytes being of great importance. 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. This ratio, together with the platelet-to-lymphocyte ratio (PLR), was associated with multiple entities, such as cardiovascular, rheumatological, or gynaecological 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). In this context, some studies suggested that the NLR can be used as an independent prognostic factor in a wide spectrum of cancers. 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. 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 inflammatory parameters are higher in the active phase of the disease. In patients enrolled 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. Currently, the most

![Figure 1](image1.png)

**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](image2.png)

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

| 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)     |
| Intraplaque injections, n (%) | 1 (0.8)     |
| Endoscopic surgery, n (%) | 2 (1.7)      |
| Penis surgery, n (%) | 10 (7.5)       |
| Circumcision | 5 (4.2)     |
| Plication | 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           |
| Intraplaque 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 (19.2) | 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
accepted theory is the occurrence of a trauma or microtrauma in the tunica albuginea during intercourse in susceptible individuals. The repeated injury in the albuginea tissue causes inflammation, alteration of the elastic fibers, and deposition of fibrin. Fibrin is a potent chemoattractant which promotes the influx of inflammatory cells such as macrophages, neutrophils, and fibroblasts. 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. 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.

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. 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. 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. 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 \( (P = 0.008 \text{ and } P = 0.008, \text{ respectively}) \). 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, sensitivity: 61.1%; specificity: 75.0%) for the NLR. They studied neither the relationships between the acute and chronic stages in both ratios (NLR and PLR). Further studies are necessary to confirm our results. These findings could be helpful in the diagnosis of PD stages. 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. 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.
REFERENCES

1. Al-Thakafi S, Al-Hathal N. Peyronie's disease: a literature review on epidemiology, genetics, pathophysiology, diagnosis and work-up. *Transl Androl Urol* 2016; 5: 280–9.

2. Rhoden EL, Riedner CE, Fuchs S, Ribeiro EP, Helmenschlager G. A cross-sectional study for the analysis of clinical, sexual and laboratory conditions associated to Peyronie's disease. *J Sex Med* 2010; 7: 1529–37.

3. El-Sakka AI, Salabas E, Dinçer M, Kadioglu A. The pathophysiology of Peyronie's disease. *Arab J Urol* 2013; 11: 272–7.

4. Levine LA. Peyronie's disease: a contemporary review of non-surgical treatment. *Arab J Urol* 2013; 11: 278–83.

5. Russell S, Steers W, McMurry KT. Systematic evidence-based analysis of plaque injection therapy for Peyronie's disease. *Eur Urol* 2007; 51: 640–7.

6. Yafi FA, Pinsky MR, Sangkum P, Hellstrom WJ. Therapeutic advances in the treatment of Peyronie's disease. *Andrology* 2015; 3: 650–62.

7. Levine LA. Seeking answers on the quest for effective nonsurgical treatment of Peyronie's disease. *Eur Urol* 2007; 51: 601–3.

8. Abdel Raheem A, Johnson M, Abdel-Raheem T, Capece M, Ralph D. Collagenase clostridium histolyticum in the treatment of Peyronie's disease – a review of the literature and a new modified protocol. *Sex Med Rev* 2017; 5: 529–35.

9. Gelbard M, Goldstein I, Hellstrom WJ, McMahon CG, Smith T, et al. Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of Peyronie disease in 2 large double-blind, randomized, placebo controlled phase 3 studies. *J Urol* 2013; 190: 199–207.

10. Nguyen HM, Yousif A, Chung A, Virasoro R, Tapscott A, et al. Safety and efficacy of collagenase clostridium histolyticum in the treatment of acute phase Peyronie's disease: a multi-institutional analysis. *Urology* 2020; 145: 280–9.

11. Cacci A, Di Maida F, Russo G, Capogrosso P, Francesco L, et al. Efficacy of collagenase clostridium histolyticum (Xiape®) in patients with the acute phase of Peyronie's disease. *Clin Drug Investig* 2020; 40: 583–8.

12. Kaplan ZS, Jackson SP. The role of platelets in atherothrombosis. *Hematology* 2011; 2011: 51–61.

13. Soehnlein O. Multiple roles for neutrophils in atherosclerosis. *Circ Res* 2012; 110: 875–88.

14. Ruggeri ZM. Platelet adhesion under flow. *Microcirculation* 2009; 16: 58–83.

15. Templeton AJ, McNamara MG, Senuga B, Vera-Badillo FE, Aneja P, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst* 2014; 106: dju124.

16. Afari ME, Bhat T. Neutrophil to lymphocyte ratio (NLR) and cardiovascular diseases: an update. *Expert Rev Cardiovasc Ther* 2016; 14: 573–7.

17. Sargin G, Senturk T, Yavasoglu I, Kose R. Relationship between neutrophil-lymphocyte, platelet-lymphocyte ratio and disease activity in rheumatoid arthritis treated with rituximab. *Int J Rheum Dis* 2018; 21: 2122–7.

18. Ghelfi AM, Lassus MN, Diodati S, Hails EA. Utility of the neutrophil/lymphocyte ratio and the polymorphonuclear/mononuclear ratio, in the prediction of preeclampsia. *Hypertens Res* 2019; 36: 63–9. [Article in Spanish].

19. Guthrie GI, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, et al. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. *Crit Rev Oncol Hematol* 2013; 88: 218–30.

20. Socorro Faría S, Fernandes PC Jr, Barbosa Silva MJ, Lima VC, Fontes W, et al. The neutrophil-to-lymphocyte ratio: a narrative review. *Eur Urol* 2016; 10: 702.

21. Özbur S, Değirmenetepe RB, Atalay HA, Alkan İ, Çakır SS, et al. The role of inflammatory parameters (neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to- eosinophil ratio) in patients with Peyronie's disease. *Andrologia* 2020; 8: 348–52.

22. Kelâmi A. Classification of congenital and acquired penile deviation. *Urol Int* 1983; 38: 223–33.

23. Hatzimouratidis K, Eardley I, Giuliano F, Hatzichristou D, Moncada I, et al. EAU guidelines on penile curvature. *Eur Urol* 2012; 62: 543–52.

24. Bjekic MD, Vlajinac HD, Pipetic SB, Marinkovic JM. Risk factors for Peyronie's disease: a case-control study. *BJU Int* 2006; 97: 570–4.

25. Diegelmann RF. Cellular and biochemical aspects of normal and abnormal wound healing: an overview. *J Urol* 1997; 157: 298–302.

26. Devine CJ, Somers KD, Jordan SG, Schlossberg SM. Proposal: trauma as the cause of the Peyronie's lesion. *J Urol* 1997; 157: 285–90.

27. Mühall JP. Expanding the paradigm for plaque development in Peyronie's disease. *Int J Impot Res* 2003; 15 Suppl 5: S93–102.

28. Al-Thakafi S, Al-Hathal N. Peyronie's disease: a literature review on epidemiology, genetics, pathophysiology, diagnosis and work-up. *Transl Androl Urol* 2016; 5: 280–9.

29. Baiza E, Borsi L, Allemanni G, Zardi L. Transforming growth factor β regulates the levels of different fibronectin isoforms in normal human cultured fibroblasts. *FEBS Letters* 1988; 228: 42–4.

30. Lee JS, Kim NY, Na SH, Youn YH, Shin CS. Reference values of neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, and mean platelet volume in healthy adults in South Korea. *Medicine* 2018; 97: e11383.