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Research Article

Baseline Neutrophil-to-Lymphocyte Ratio is Associated With Poorer Response to Low-Intensity Shockwave Therapy for Erectile Dysfunction: A Two-Centre Retrospective Cohort

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Background: Low-intensity extracorporeal shock wave therapy (Li-ESWT) is explored for erectile dysfunction (ED), yet guideline recommendations remain cautious. Simple blood-count ratios such as neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) may help identify who benefits.
Objective: To evaluate whether baseline NLR/PLR are associated with, and can discriminate, clinical response to Li-ESWT.
Methods: Retrospective, two-centre cohort. We analysed 160 men with ED treated with a standardized 12-session Li-ESWT protocol; 100 men without ED (5-item International Index of Erectile Function [IIEF-5] ≥22) served only for baseline comparisons and were excluded from outcome/prediction analyses. Erectile function (IIEF-5) was recorded at baseline, end of treatment, and Month 6. The primary endpoint was response at Month 6, defined a priori as the minimal clinically important difference (MCID) of ΔIIEF-5 ≥ 4. ROC analyses and multivariable logistic regression were adjusted for age, body mass index (BMI), hypertension, diabetes, and smoking. Preanalytic CBC screening minimized inflammatory confounding.
Results: Response occurred in 110/160 (68.8%). NLR was higher in nonresponders than responders and controls (2.27 ± 0.71 vs. 1.63 ± 0.52 and 1.69 ± 0.60; $p < 0.001$), whereas PLR differences were smaller ($p = 0.032$). NLR discriminated responders from nonresponders with an AUC of 0.752 (95% CI 0.672–0.831); the Youden-optimal cutoff was 1.93 (sensitivity 72%, specificity 71%; PPV 85%, NPV 54). PLR showed weaker discrimination (AUC 0.610, 95% CI 0.520–0.701). In multivariable models, baseline NLR (per 1-SD) independently predicted nonresponse (OR 2.80, 95% CI 1.70–4.62; $p < 0.001$), while PLR did not (OR 1.25, 95% CI 0.83–1.89; $p = 0.29$). Hypertension was also associated with nonresponse (OR 3.74, 95% CI 1.43–9.77; $p = 0.007$).
Conclusions: In this two-centre cohort, baseline NLR, measured on routine CBC, was associated with Li-ESWT nonresponse and provided moderate discrimination, whereas PLR performed weakly. NLR may support pretreatment risk-stratification, but prospective, sham-controlled validation and external threshold calibration are needed before clinical adoption.

Keywords: erectile dysfunction; low-intensity extracorporeal shock wave therapy; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio

1. Introduction

Erectile dysfunction (ED) is described as the inability to attain or keep adequate rigidity for successful vaginal intercourse [1]. ED is a common health issue that adversely affects the quality of life in men and is often considered an early biomarker of serious systemic pathologies, such as cardiovascular diseases [2]. Furthermore, ED is a prevalent health issue affecting ~3%–76% of men worldwide, with this prevalence varying according to age [3]. Globally, about

152 million men were affected by ED in 1995; a widely cited 1999 analysis projected ~322 million by 2025, a figure contemporary reviews still use to indicate scale [4]. The Massachusetts Male Aging Study found that the prevalence of ED in men aged 40–70 years was 52% [5].

ED is a condition associated with fundamental pathophysiological mechanisms, such as endothelial dysfunction, and inflammation has been shown to play a central role in this process [6]. Modern therapeutic approaches, particularly low-intensity extracorporeal shock wave therapy (Li-ESWT), are being explored to modulate these pathways [7]. The mechanism of Li-ESWT in ED is not established; hypotheses include localized microtrauma with downstream angiogenic signaling, but definitive mechanistic endpoints were not assessed in this study [8].

In recent years, multiple clinical studies have evaluated Li-ESWT for ED [9]. Additionally, numerous recent randomized controlled trials involving adult males complaining of mild to moderate ED treated with Li-ESWT have further supported its use for ED [10]. Notwithstanding these reports, professional society guidance remains cautious, with the American Urological Association considering Li-ESWT investigational for ED and the European Association of Urology offering only a weak recommendation limited to well-informed patients with vasculogenic ED [11, 12]. The protocol for Li-ESWT and response to treatment vary significantly in the current literature [13]. Therefore, reliable biomarkers are required to assess treatment response to Li-ESWT and to determine which patient groups may respond better to treatment [14].

In this context, several hematological parameters have been investigated as potential biomarkers for discriminating responders from nonresponders to Li-ESWT [15]. In this regard, hematological parameters such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) may serve as potential guides for estimating the likelihood of response to Li-ESWT [16].

The present study has two primary foci. Firstly, it examines the prognostic role of NLR and PLR while also investigating ED's pathophysiological mechanisms and the therapeutic effects of Li-ESWT. Secondly, it aims to contribute to personalized treatment approaches by investigating the value of these parameters in discriminating responders from nonresponders in patients with ED.

2. Materials and Methods

2.1. Study Design and Setting. This was a retrospective, two-center cohort study evaluating associations between baseline inflammatory ratios (NLR, PLR) and response to Li-ESWT; no randomization or sham control was used. Patients from two urology departments, Medipol University Esenler Hospital, Istanbul, and Sancaktepe Regional Hospital, Istanbul, were included.

2.2. Participants. Participants comprised 260 men, of whom 160 had ED and received Li-ESWT, and 100 were controls without ED (5-item International Index of Erectile Function [IIEF-5] ≥ 22) who did not receive Li-ESWT. Controls had normal erectile function by IIEF-5 ($\geq$22) and contributed baseline CBC and IIEF-5 only; no Li-ESWT or outcomes follow-up was collected for controls. Controls were included only for baseline descriptive comparisons of CBC-derived ratios (NLR, PLR) with the treated cohort and were excluded from response, ROC, and multivariable analyses. Historical PDE5 inhibitors (PDE5i) responsiveness did not preclude inclusion. All patients discontinued PDE5i ≥ 4 weeks before baseline and before each IIEF-5 assessment (end of treatment, Month 6); any use during these windows was an exclusion. Controls were not age-matched to patients and served only to contextualize baseline CBC-derived ratios. A retrospective review of clinical records from January 2023 to June 2024 identified eligible cases. Of the 160 treated patients, 67 were from Medipol University Esenler Hospital and 93 were from Sancaktepe Regional Hospital.

2.3. Eligibility Criteria

2.3.1. Inclusion Criteria. Men aged 18–70 years with ED lasting $\geq$6 months, regular sexual activity, complete medical records, normal testosterone, and who completed 12 sessions of Li-ESWT; available CBC within 30 days of the index visit.

2.3.2. Exclusion Criteria. History of spinal cord injury, concomitant neurologic disorders, severe cardiac disease, penile fibrosis, or prior pelvic radiation; evidence of acute infection or inflammatory flare likely to distort CBC ratios (fever $\geq$ 38°C within 7 days; antibiotic use within 14 days; recent surgery/trauma within 14 days; systemic glucocorticoids > 5 mg prednisone-equivalent for $\geq$3 days within 30 days; active immunosuppressants/chemotherapy within 30 days); use of phosphodiesterase type-5 inhibitors within the prior 4 weeks. Historical responsiveness to PDE5i did not preclude inclusion, provided patients had discontinued PDE5i for at least 4 weeks before baseline and outcome assessments.

2.3.3. Medication Screen. Chart review at the time of CBC captured systemic glucocorticoids, immunosuppressants, chemotherapy, and recent antibiotics (grounds for exclusion as above); statin/NSAID use was recorded as background therapy and was not an exclusion.

2.4. Clinical Data Collection. Medical history, smoking status, age, and body mass index (BMI) were recorded. Before initiating Li-ESWT, patients completed the IIEF-5, using the validated Turkish version [17].

2.5. Hematology and Preanalytic Screening. CBCs were measured on Sysmex XN-1000 analyzers at both centers prior to Li-ESWT initiation. Units are reported as $\times 10^9$/L. To minimize subclinical inflammation bias, CBCs were deferred and repeated if patients reported intercurrent infection symptoms or recent antibiotic use. We excluded CBCs with prespecified flags suggestive of occult inflammation, namely WBC $> 11 \times 10^9$/L, absolute neutrophils $> 7.5 \times 10^9$/L, absolute lymphocytes $< 1.0 \times 10^9$/L, or platelets $< 150 \times 10^9$/L or $> 450 \times 10^9$/L. When CRP was available, values > 10 mg/L prompted repeat sampling rather than analysis. IIEF-5 was also used at baseline to classify ED severity, with categories

defined as 22–25 none; 17–21 mild; 12–16 mild-to-moderate; 8–11 moderate; and 5–7 severe. Because all treated participants had ED at baseline (IIEF-5 $\leq$ 21), the none category did not occur and is not shown in the tables.

2.6. Outcomes and Definitions. Patients were categorized as responders or nonresponders at Month 6 after treatment initiation ($\pm$2 weeks) based on the change in IIEF-5 from baseline. The primary endpoint was response at Month 6, defined a priori as ΔIIEF-5 $\geq$ 4. We treated a 4-point increase in IIEF-5 as the minimal clinically important difference (MCID), the smallest change considered meaningful to patients on this scale. We also report the mean ΔIIEF-5 with 95% confidence intervals. Controls were not evaluated for response; no Month-6 IIEF-5 was collected for controls, and they were excluded from ROC and multivariable analyses. Concomitant PDE5i use was not permitted during the 9-week Li-ESWT course or in the 4 weeks preceding each IIEF-5 assessment used for analysis.

2.7. Li-ESWT Intervention. Li-ESWT was delivered to five regions of the corpus cavernosum twice weekly for 3 weeks, followed by a 3-week rest, for a total of 12 sessions. Erectile function was assessed at baseline ($\leq$14 days before the first session), end of treatment (Week 9 $\pm$ 1 week after session 12), and Month 6 ($\pm$2 weeks) using the IIEF-5. After application of ultrasound gel, the penis was manually stretched, and the probe was held perpendicular to the tunica. Anatomical targeting and shock distribution used 1500 shocks per session, apportioned as 300 shocks to each of five sites (left crus, right crus, proximal shaft, mid-shaft, and distal shaft). Li-ESWT was delivered with a focused Omnispec ED1000 (Medispec Ltd., Gaithersburg, MD, USA) operated at 0.09 mJ/mm^2 and 2 Hz. No analgesia or anesthesia was used, and all sessions were performed in the outpatient setting.

2.8. Statistical Analysis. Normality was assessed using the Kolmogorov–Smirnov test. Age and BMI were approximately normal; NLR, PLR, and ED duration were non-normal. Two analysis sets were prespecified. First, baseline descriptive comparisons were made across three groups (controls, Li-ESWT responders, Li-ESWT nonresponders) using χ^2 or Fisher's exact tests for categorical variables and, for continuous variables, Welch's *t*-test or Welch ANOVA with Games–Howell, or Mann–Whitney *U* or Kruskal–Wallis with Dunn–Bonferroni when distributions were non-normal. Second, primary discrimination analyses were restricted to the treated cohort (responders vs. nonresponders) and included ΔIIEF-5, ROC metrics, and multivariable logistic regression. Controls were not included in these analyses.

Because BMI/obesity, hypertension, diabetes, and smoking can influence NLR/PLR, baseline comparisons of NLR/PLR across clinical groups were also repeated in covariate-adjusted models, ANCOVA with Welch SE for approximately normal data or rank-based ANCOVA (Quade) for non-normal data, using age and BMI as continuous covariates and hypertension, diabetes, and smoking as categorical covariates. In all multivariable models of nonresponse, we adjusted for age, BMI, diabetes, hypertension, and smoking; NLR and PLR were modeled per 1-SD increase. As a sensitivity analysis, we repeated responder versus nonresponder comparisons within the treated cohort, restricting the age range (e.g., 40–60 years); inferences were unchanged.

Normally distributed data are presented as mean $\pm$ standard deviation; non-normal data are summarized as median (interquartile range). For NLR/PLR by baseline ED severity (mild, moderate, severe), we report group n and mean $\pm$ SD, pairwise mean differences with 95% CIs (Welch SE), and Spearman's rank correlation (ρ) with *p*, coding severity as 1–3. Between-group comparisons for normally distributed data with two groups used Student's *t*-test (or Welch's *t*-test when variances were unequal by Levene's test). For more than two groups, the overall test was Welch ANOVA with Games–Howell post hoc; for non-normal data, Mann–Whitney *U* (two groups) or Kruskal–Wallis with Dunn–Bonferroni (more than two groups).

Multivariable logistic regression assessed whether baseline NLR and PLR independently predict nonresponse to Li-ESWT, adjusting for age, BMI, diabetes, hypertension, and smoking; NLR and PLR were modeled per 1-SD increase. AUCs were reported with bootstrap 95% CIs (2000 resamples); optimal thresholds used Youden's *J*. At the Youden-optimal cutoffs, we reported Youden's *J* and PPV/NPV with 95% Wilson CIs calculated at the observed response prevalence in the treated cohort (110/160; 68.8%). Because responders had lower baseline NLR/PLR, ROC was computed on the negated marker, and cutoffs are mapped back to the original scale. Multiple-comparison control used Games–Howell following Welch ANOVA with no additional Bonferroni. For Kruskal–Wallis, we applied Dunn–Bonferroni, and for categorical pairwise comparisons, we reported Bonferroni-adjusted *p*-values. Controls were used for baseline descriptive comparisons only; all outcome (response) and predictive analyses (ROC, models) were restricted to the treated ED cohort. As this was a retrospective cohort, no a priori sample-size/power calculation was performed; instead, precision for effect estimates is reported via 95% confidence intervals (e.g., bootstrap CIs for AUC). Because this is a retrospective, nonrandomized cohort without a sham/control arm, analyses are associational; we do not interpret observed differences as causal effects of Li-ESWT.

3. Results

A total of 260 participants were included, comprising 160 Li-ESWT–treated patients with ED (110 responders and 50 nonresponders) and 100 controls without ED (IIEF-5 $\geq$ 22). Controls were used only for baseline CBC comparisons and were excluded from outcome and prediction analyses.

Kolmogorov–Smirnov tests indicated normality for age and BMI, and non-normality for NLR, PLR, and ED duration; accordingly, Welch's *t*-test/ANOVA with Games–Howell were used for age and BMI, while Mann–Whitney *U*/Kruskal–Wallis with Dunn–Bonferroni were used for NLR, PLR, and ED duration. Variables such as age, BMI, hypertension, hyperlipidemia, smoking, duration of ED, and diabetes were compared between the groups responding and not responding to Li-ESWT (Table 1).

Table 1: Baseline characteristics by group.

Variable	Control ($n = 100$)	Nonresponse ($n = 50$)	Response ($n = 110$)	p
Age (years)[e]	44.41 ± 11.57	49.88 ± 12.42	38.46 ± 8.06	<0.001[a]
BMI (kg/m^2)[e]	26.00 ± 2.95	28.01 ± 2.07	27.03 ± 2.95	<0.001[b]
Hypertension n (%)	23 (23.0%)	18 (36.0%)	16 (14.5%)	0.009[c]
Diabetes n (%)	31 (31.0%)	16 (32.0%)	26 (23.6%)	0.391[c]
Hyperlipidemia, n (%)	28 (28.0%)	28 (56.0%)	12 (10.9%)	<0.001[c]
Smoking n (%)	47 (47.0%)	22 (44.0%)	63 (57.3%)	0.188[c]
ED duration (months)[e]	—	21.00 ± 14.74	18.07 ± 12.03	0.233[d]

Note: Values are mean ± standard deviation unless otherwise indicated. Controls are healthy men without ED (IIEF-5 ≥ 22) used for baseline CBC comparisons only; excluded from outcome and prediction analyses.
Abbreviations: BMI, body mass index; ED, erectile dysfunction.
[a]Welch ANOVA across control/nonresponse/response (Games–Howell post hoc).
[b]Welch ANOVA across control/nonresponse/response.
[c]Pearson χ^2 across control/nonresponse/response (Bonferroni-adjusted pairwise p where reported).
[d]Mann–Whitney U between nonresponse and response (controls excluded).
[e]Continuous variable.

There was a significant difference in age among the Li-ESWT responder group (38.46 ± 8.06 years), the nonresponder group (49.88 ± 12.42 years), and the control group (44.41 ± 11.57 years) ($p < 0.001$). The nonresponder group had higher BMI values (28.01 ± 2.07) than the control group (26.0 ± 2.95) and the responder group (27.03 ± 2.95, $p < 0.001$). The responder group was significantly younger ($p < 0.001$). Hypertension prevalence differed among groups ($\chi^2 p = 0.009$). In Bonferroni-adjusted pairwise tests, nonresponder versus responder remained significant (36% vs. 14.5%, adjusted $p = 0.0099$), whereas nonresponder versus control (36% vs. 23%, adjusted $p = 0.359$) and control vs. responder (23% vs. 14.5%, adjusted $p = 0.464$) were not significant. The frequency of hyperlipidemia was significantly higher in the nonresponder group (56%) than in the control group (28%) and the responder group (11%) ($p < 0.001$).

The duration of ED in the nonresponder group (21.29 ± 15.41 months) was slightly longer compared to the responsive group (18.06 ± 12.42 months); however, the difference was not statistically significant ($p = 0.233$).

The classification and comparison of ED groups of differing baseline severity according to treatment responsiveness were conducted (Table 2). In the mild group, responders improved from 18.2 ± 0.84 to 21.5 ± 1.20, whereas nonresponders changed from 17.8 ± 0.78 to 18.1 ± 1.19 without a significant within-group difference. In the moderate group, responders improved from 13.6 ± 2.38 to 19.2 ± 2.23; nonresponders increased from 12.7 ± 2.86 to 13.8 ± 2.47, which was statistically significant on paired testing but did not meet the MCID threshold ($\Delta < 4$). In the severe group, responders improved from 6.7 ± 0.47 to 14.7 ± 1.18; nonresponders increased from 7.0 ± 0.00 to 7.8 ± 0.92, which was statistically significant on paired testing but again below the MCID threshold ($\Delta < 4$). Responder proportions by baseline severity were 84% (mild: 51/61), 64% (moderate: 39/61), and 53% (severe: 20/38).

The mean NLR was 1.69 ± 0.60 in the control group, 1.63 ± 0.52 in Li-ESWT responders, and significantly higher (2.27 ± 0.71) in Li-ESWT nonresponders ($p < 0.001$). This suggests Li-ESWT nonresponders had a significantly elevated NLR versus the responder and control groups. Although PLR differed among groups, the magnitude of this difference was modest relative to NLR, and this interpretation remained the same after covariate adjustment for age, BMI, hypertension, diabetes, and smoking (Table 3).

ED severity (coded 1–3: mild = 1, moderate = 2, severe = 3) was positively correlated with NLR (Spearman $\rho = 0.363$; $p < 0.001$), but not with PLR ($\rho = 0.049$; $p = 0.537$) (Table 4). Group sizes (treated cohort) were mild $n = 61$, moderate $n = 61$, and severe $n = 38$. NLR mean differences (95% CI) were as follows: moderate–mild +0.15 (−0.06 to +0.36); severe–mild +0.60 (+0.40 to +0.80); severe–moderate +0.45 (+0.25 to +0.65). PLR mean differences (95% CI) were as follows: moderate–mild +4.1 (−6.0 to +14.2); severe–mild +8.9 (−3.2 to +21.0); severe–moderate +4.8 (−8.8 to +18.6). While the increase in NLR was statistically significant, this was not the case for PLR. NLR values increased across the groups as follows: 1.62 ± 0.60 (mild), 1.77 ± 0.60 (moderate), and 2.22 ± 0.40 (severe). Distributions and p-values are shown in Table 4.

The ROC curve analyses demonstrated the sensitivity and specificity of NLR and PLR for discriminating Li-ESWT responders from nonresponders (Figure 1). NLR showed a higher AUC than PLR (0.752 [95% CI 0.672–0.831, $p < 0.001$] vs. 0.610 [95% CI 0.520–0.701, $p = 0.015$]). The optimal cutoffs were 1.93 for NLR and 108.30 for PLR; at these thresholds, sensitivity/specificity were 72%/71% for NLR and 56%/55% for PLR (Table 5).

At the NLR cutoff 1.93 (positive test = NLR ≤ 1.93), Youden's $J = 0.43$; PPV 85% (95% CI 76–91) and NPV 54% (95% CI 42–65). At the PLR cutoff 108.30 (positive test = PLR ≤ 108.30), Youden's $J = 0.11$; PPV 74% (95% CI 64–82) and NPV 37% (95% CI 27–48).

In multivariable logistic regression (adjusted for age, BMI, diabetes, hypertension, and smoking), baseline NLR (per 1-SD) was independently associated with nonresponse (OR 2.80, 95% CI 1.70–4.62, $p < 0.001$), whereas PLR (per 1-SD) was not (OR 1.25, 95% CI 0.83–1.89, $p = 0.29$) (Table 6). Among covariates, hypertension was associated with higher

Table 2: IIEF-5 before/after by treatment response and baseline severity (treated cohort).

Severity	Group	*n*	BL IIEF-5[a]	AT IIEF-5[a]	Δ IIEF[a]	*p*_within (paired)	MCID (Δ ≥ 4), *n*/*N* (%)
Mild	Nonresponse	10	17.80 ± 0.77	18.10 ± 1.17	0.3 ± 0.7	$p = 0.058$	0/10 (0.0%)
Mild	Response	51	18.25 ± 0.84	21.51 ± 1.20	3.3 ± 0.8	$p < 0.001$	28/51 (54.9%)
Moderate	Nonresponse	22	12.77 ± 2.83	13.86 ± 2.45	1.1 ± 1.0	$p < 0.001$	0/22 (0.0%)
Moderate	Response	39	13.62 ± 2.36	19.21 ± 2.22	5.6 ± 0.5	$p < 0.001$	39/39 (100.0%)
Severe	Nonresponse	18	7.00 ± 0.00	7.83 ± 0.91	0.8 ± 0.9	$p < 0.001$	0/18 (0.0%)
Severe	Response	20	6.70 ± 0.46	14.75 ± 1.10	8.1 ± 0.9	$p < 0.001$	20/20 (100.0%)

Note: Within-group *p*: paired *t*-test if the change (Δ) was normally distributed by Shapiro–Wilk ($p \geq 0.05$); otherwise, Wilcoxon signed-rank. Between-group comparisons of Δ (responders vs. nonresponders) within each severity stratum: Welch *t*-test if both Δ distributions were approximately normal; otherwise Mann–Whitney *U*. Responder defined by the minimal clinically important difference (MCID): ΔIIEF-5 ≥ 4; nonresponder if ΔIIEF-5 < 4. A within-group *p*-value may be statistically significant while the MCID is not met; such patients remain nonresponders. Values are mean ± SD. Δ, change.

Abbreviations: AT, after treatment; BL, baseline; IIEF, International Index of Erectile Function.

[a]Indicates within-group statistical significance based on paired testing (paired *t*-test or Wilcoxon signed-rank test, depending on data distribution).

Table 3: Inflammatory ratios among control and Li-ESWT groups.

Inflammatory ratio	Control	Responders	Nonresponders	*p*
NLR	1.69 ± 0.60	1.63 ± 0.52	2.27 ± 0.71	<0.001
PLR	107.9 ± 24.8	105.1 ± 22.1	122.6 ± 40.7	0.032

Note: Numbers are mean ± standard deviation. Comparisons used Kruskal–Wallis with Dunn–Bonferroni post hoc due to non-normality on Kolmogorov–Smirnov testing.

Abbreviations: ED, erectile dysfunction; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 4: NLR and PLR by ED severity in the treated cohort.

Severity	*n*	NLR (mean ± SD)	PLR (mean ± SD)
Mild	61	1.63 ± 0.64	106.94 ± 22.14
Moderate	61	1.80 ± 0.69	111.01 ± 33.41
Severe	38	2.22 ± 0.43	115.89 ± 33.85

Note: Effect sizes (pairwise mean differences with 95% CIs): NLR: mod–mild + 0.17 (−0.06 to 0.41); sev–mild + 0.59 (0.38–0.80); sev–mod + 0.42 (0.20–0.64). PLR: mod–mild + 4.07 (−5.99 to 14.13); sev–mild + 8.95 (−3.16 to 21.07); sev–mod + 4.88 (−8.76 to 18.53). Spearman correlation with baseline severity (coded 1–3): NLR $\rho = 0.363$, $p < 0.001$; PLR $\rho = 0.049$, $p = 0.537$. Overall *p* (Kruskal–Wallis): NLR, $p < 0.001$; PLR, $p = 0.821$. Pairwise mean-difference CIs use Welch SE: $SE = \sqrt{(SD1^2/n1 + SD2^2/n2)}$. Comparisons used Kruskal–Wallis with Dunn–Bonferroni post hoc due to non-normality on Kolmogorov–Smirnov testing.

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

odds of nonresponse (OR 3.74, 95% CI 1.43–9.77, $p = 0.007$); BMI ($p = 0.066$) and smoking ($p = 0.072$) trended but were not significant; diabetes was not significant ($p = 0.86$). The model's discrimination was AUC 0.819.

4. Discussion

Our study evaluates associations between baseline NLR/PLR and response to Li-ESWT in a retrospective cohort; efficacy cannot be determined without a sham-controlled design. The duration of ED was shorter in the responder group (18.07 ± 12.03 months) compared to the nonresponder group (21.00 ± 14.74 months), although this difference was not statistically significant ($p = 0.233$). While previous studies have expressed that patients with a shorter duration of ED tend to respond better to treatment, our findings do not support a significant relationship between the duration of ED and response to Li-ESWT [18–20]. Given the study design, our findings indicate associations between baseline markers and observed response; they do not establish Li-ESWT efficacy or causality.

Various studies have investigated the relationship between NLR and PLR, systemic inflammation markers, in the context of ED. A significant correlation between these biomarkers has been demonstrated. In one study, significantly higher NLR and PLR levels were reported in individuals with ED compared to control groups, emphasizing the pivotal role of inflammation in the pathophysiology of ED [16]. In this study, elevated NLR and PLR levels were observed in Li-ESWT unresponsive patients, suggesting that inflammatory mechanisms may influence the observed response to this treatment modality. A recent cross-sectional study identified a strong relationship between raised NLR levels and an increased risk of ED, highlighting the diagnostic potential of this biomarker [21]. Similarly, a further cross-sectional study exhibited a positive correlation between NLR levels and the severity of ED, with severe ED cases exhibiting NLR values exceeding 3. This establishes NLR as an independent marker of disease severity [22]. These findings are consistent with a systematic review and meta-analysis, further supporting the critical role of inflammatory responses in ED pathogenesis and treatment dynamics [15].

Pharmacotherapy studies likewise link inflammatory ratios with ED. In a prospective cohort, daily tadalafil 5 mg improved erectile function while decreasing NLR and PLR in men with ED. In a randomized controlled study comparing daily tadalafil 5 mg with daily sildenafil 25 mg, both improved erectile function, whereas reductions in NLR/PLR were more pronounced with tadalafil. These findings underscore the biological plausibility that systemic inflammatory tone relates to erectile function and treatment response. Our work differs in focus, baseline

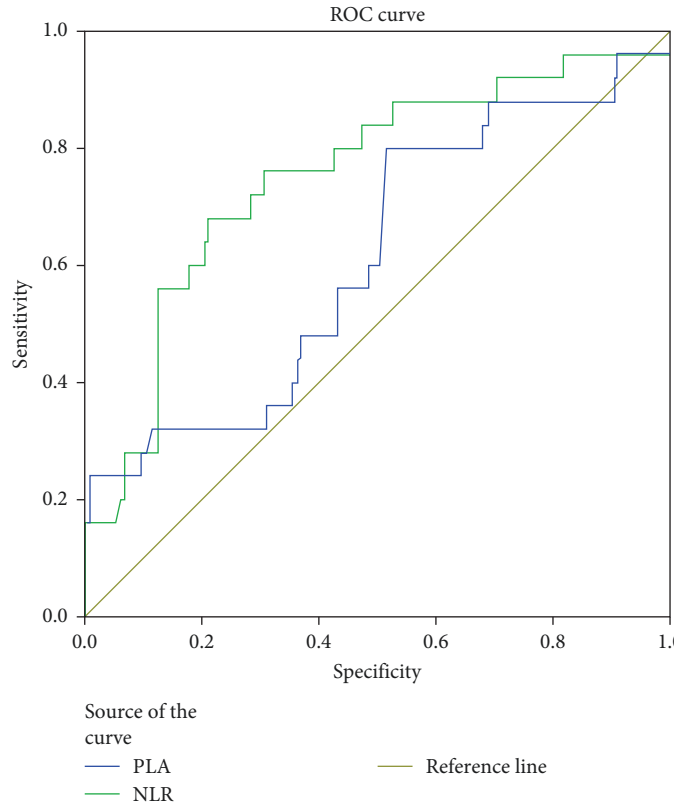

Figure 1: Receiver operating characteristic (ROC) curves for baseline NLR (green) and PLR (blue) discriminating responders vs. nonresponders. AUC (NLR) = 0.752 (95% CI 0.672–0.831); AUC (PLR) = 0.610 (95% CI 0.520–0.701). Youden-optimal cutoffs: NLR = 1.93 (sensitivity 72%, specificity 71%); PLR = 108.30 (sensitivity 56%, specificity 55%). The *x*-axis shows 1-specificity (false-positive rate); the *y*-axis shows sensitivity. The diagonal dashed line indicates no discrimination.

Table 5: ROC metrics in the treated cohort (AUC with 95% CI; PPV/NPV with 95% CI).

Marker	AUC (95% CI)	*p*	Cutoff	Sen	Spec	Youden's *J*	PPV (95% CI)	NPV (95% CI)
NLR	0.752 (0.672–0.831)	<0.001	1.93	72%	71%	0.43	85% (76–91)	54% (42–65)
PLR	0.610 (0.520–0.701)	0.015	108.30	56%	55%	0.11	74% (64–82)	37% (27–48)

Note: AUC is reported with 95% CI; PPV/NPV are reported with 95% CIs (Wilson method at the observed response prevalence, 110/160). Sensitivity/specificity are point estimates at the stated cutoff.

Abbreviations: AUC, area under the curve; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; NPV, negative predictive value; PLR, platelet-to-lymphocyte ratio; PPV, positive predictive value; ROC, receiver operating characteristic; Sen, sensitivity; Spec, specificity.

NLR/PLR as prognostic markers for Li-ESWT response rather than drug-induced changes, yet the directions are consistent and suggest that inflammatory status may inform patient selection and expectations for therapy [23, 24].

Our study corroborates these findings, demonstrating that NLR levels increase proportionally with the severity of ED. The optimal NLR cutoff of 1.93, with sensitivity 72% and specificity 71%, underscores its diagnostic utility. This cutoff value provides a balanced distinction between treatment responders and nonresponders. This observation aligns with the cited study, which emphasizes the role of NLR as a biomarker with discriminative value for observed response to Li-ESWT in ED [25].

Baseline NLR discriminated responders from nonresponders (AUC 0.75, 95% CI 0.67–0.83), whereas PLR showed modest discrimination (AUC 0.61, 95% CI 0.52–0.70). The referred publication reported a weaker association between PLR and treatment outcomes in ED patients [16]. Our study identified the cutoff value for PLR as 108.30, with a sensitivity of 56% and specificity of 55%, suggesting that PLR has weaker discrimination for observed response compared to NLR. Prior studies have suggested that while PLR is related to inflammatory and vascular diseases, its predictive value for ED severity remains limited. Our findings confirm the reduced discriminative value of PLR in assessing response to Li-ESWT, with an AUC of 0.610 and p of 0.015, sensitivity of 56%, and specificity of 55%. The discriminative value of PLR remains uncertain. Several systematic reviews and meta-analyses proposed that PLR may reflect chronic inflammation but cannot predict treatment outcomes [26–28]. A review described PLR as an indirect marker of platelet activation and systemic inflammation but noted its limited discrimination for observed response in ED [29].

Table 6: Multivariable factors associated with nonresponse to Li-ESWT.

Variable	Adjusted OR	95% CI	*p*
NLR (per 1-SD)	2.80	1.70–4.62	<0.001
PLR (per 1-SD)	1.25	0.83–1.89	0.29
Hypertension (yes vs. no)	3.74	1.43–9.77	0.007
BMI (per 1 kg/m^2)	1.15	0.99–1.33	0.066
Smoking (yes vs. no)	0.46	0.20–1.07	0.072
Diabetes (yes vs. no)	1.09	0.44–2.70	0.86

Note: NLR/PLR scaled per 1-SD increase (*z*-scores); model adjusts for age, BMI, diabetes, hypertension, and smoking. Outcome is nonresponse (1) vs. response (0). Exploratory model without internal validation; treat NLR as a candidate predictor pending confirmation.

Abbreviations: BMI, body mass index; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio.

Overall, NLR and PLR reflect inflammatory activity in ED, with NLR showing stronger discrimination in our cohort. Beyond ED, higher NLR has been prospectively linked to all-cause and cause-specific mortality in general population cohorts, underscoring its role as a global inflammatory risk marker [30, 31]. In andrology, preoperative NLR has also been associated with varicocelectomy outcomes, with values near ~ 2.0 predicting less favorable postoperative improvement [32, 33]. Baseline NLR and PLR were higher in nonresponders; the Youden-optimal cutoffs were 1.93 (NLR) and 108.30 (PLR). These findings indicate an association with observed response; NLR is a candidate predictor that requires validation (internal and external) in prospective, controlled studies before clinical application. Because obesity (BMI), hypertension, diabetes, and smoking can elevate NLR/PLR, we incorporated these variables as covariates; the association between baseline NLR and nonresponse persisted after adjustment, whereas PLR remained weaker.

This study adds practical value by evaluating baseline NLR/PLR as prognostic markers in a two-center cohort treated with a standardized 12-session Li-ESWT protocol, using prespecified preanalytic CBC screening and an MCID-based 6-month endpoint (ΔIIEF-5 $\geq$ 4) with multivariable adjustment for age, BMI, diabetes, hypertension, and smoking. We also report severity-stratified outcomes and ROC analyses with bootstrap 95% CIs, yielding an implementable baseline NLR cutoff of 1.93 (sensitivity 72%, specificity 71%, PPV 85%, NPV 54%). NLR increased with baseline ED severity and independently predicted nonresponse, whereas PLR showed weaker discrimination. Together, these features offer low-cost risk stratification for candidate selection and counseling while acknowledging the retrospective, nonsham design.

The present study was subject to several limitations. Firstly, it did not include a control group that was not treated with a sham. We included both historical PDE5i responders and nonresponders to reflect real-world referral patterns; active PDE5i use in the 4 weeks before assessments was excluded. We did not stratify outcomes by historical PDE5i responsiveness, so selection effects related to prior medication response cannot be excluded. A further limitation is that we did not perform subgroup analyses by diabetes, hypertension, smoking, or obesity severity; residual confounding related to disease severity or duration is possible despite covariate adjustment. Finally, the evaluation of EF was based on patients' self-assessment during follow-up, with no objective follow-up assessments, such as penile Doppler studies, being performed. Because the study was retrospective, no a priori power calculation was conducted; findings should be interpreted with attention to the reported 95% confidence intervals. Because the control cohort was not age-matched, baseline group comparisons could be influenced by age; we therefore adjusted for age and restricted outcome and prediction inferences to the treated cohort.

In the case of healthy men experiencing mild-to-moderate ED, lifestyle modifications ought to be considered as a primary treatment option to enhance EF. Li-ESWT may be considered a treatment option for healthy patients with mild-to-moderate ED who have not experienced an improvement in EF following lifestyle changes. In severe ED, response was less frequent (20/38, 53%) and heterogeneous: nonresponders showed minimal change (7.0–7.8), whereas responders improved substantially (6.7–14.7; $p < 0.001$). Given the retrospective, nonsham design, these findings indicate association and heterogeneity, not definitive efficacy.

No internal or external validation of the model was performed; estimates of AUC and cutoffs may be optimistic, and NLR should be considered a candidate predictor pending validation. In this retrospective, nonsham-controlled cohort, Li-ESWT was associated with improvements in some subgroups; causal efficacy cannot be inferred. Our results pertain to clinical response (IIEF-5) only; mechanistic effects (e.g., endothelial function, angiogenesis, or nerve regeneration) were not measured and cannot be inferred from these data.

Additionally, biomarkers such as the NLR and PLR have shown potential for predicting treatment response. High NLR and PLR levels before treatment have been observed to be correlated with a lower likelihood of response to therapy. These biomarkers could aid in personalizing ED treatment and informing risk-stratification and patient selection strategies.

In conclusion, baseline NLR measured on routine CBC was associated with Li-ESWT nonresponse and showed moderate discrimination (AUC 0.75) in this two-center cohort, whereas PLR was weaker (AUC 0.61). These findings support NLR as a candidate prognostic marker that warrants prospective, sham-controlled validation and external threshold calibration before clinical adoption.

Data Availability Statement

The datasets supporting the findings are openly available at https://doi.org/10.5281/zenodo.15379211.

Ethics Statement

This retrospective chart review was approved by the Istanbul Medipol University Ethics Committee for Non-Interventional Clinical Research (Decision Number 133, Date 06.02.2025). The dataset comprised routinely collected records from men

treated with Li-ESWT between January 2023 and June 2024. All data extraction and statistical analyses were performed after ethics approval. The committee waived the requirement for informed consent because only existing, deidentified records were used, and the study posed minimal risk. The study was conducted in accordance with the Declaration of Helsinki and applicable institutional guidelines. The approval document is openly available at https://doi.org/10.5281/zenodo.15392964.

Consent

Clinical informed consent for Li-ESWT was obtained from patients at every treatment step, during which a healthcare professional informed them about the risks, benefits, and alternatives of the procedure.

Disclosure

The originality of the article is asserted by the authors, who further state that the document is not under consideration for publication in other journals and has not already been published. This study does not violate the journal's policies and/or procedures. The authors declare that all material in this assignment is their own work and does not involve plagiarism. The authors reviewed and take full responsibility for all content. The manuscript has been perused and endorsed by all authors. No individuals exist who meet the authorship criteria but are not listed. All authors have approved the order of authors itemized in the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Nuh Aldemir conceived and designed the study, collected data, and wrote the draft. İbrahim Üntan reviewed the literature, performed the analyses, and prepared the manuscript. Akın Demirleğen contributed to data collection. All authors provided critical feedback to each other and contributed to the final manuscript after discussing the results and commenting on the text.

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