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Review

Prognostic role of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in patients with non-metastatic and metastatic prostate cancer: A meta-analysis and systematic review

Stefano Salciccia [a], Marco Frisenda [a,*], Giulio Bevilacqua [a], Pietro Viscuso [a], Paolo Casale [b], Ettore De Berardinis [a], Giovanni Battista Di Pierro [a], Susanna Cattarino [a], Gloria Giorgino [a], Davide Rosati [a], Francesco Del Giudice [a], Alessandro Sciarra [a], Gianna Mariotti [a], Alessandro Gentilucci [a]

[a] *Department of Urology, Sapienza Rome University, Policlinico Umberto I, 00161 Rome, Italy*
[b] *Department of Urology, Humanitas, 20089 Rozzano, MI, Italy*

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Abstract *Objective:* To analyze data available in the literature regarding a possible prognostic value of the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) in prostate cancer (PCa) patients stratified in non-metastatic and metastatic diseases.
Methods: A literature search process was performed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines. In our meta-analysis, the pooled event rate estimated and the pooled hazard ratio were calculated using a random effect model.
Results: Forty-two articles were selected for our analysis. The pooled risk difference for non-organ confined PCa between high and low NLR cases was 0.06 (95% confidence interval [CI]: −0.03–0.15) and between high and low PLR cases increased to 0.30 (95% CI: 0.16–0.43). In non-metastatic PCa cases, the pooled hazard ratio for overall mortality between high and low NLR was 1.33 (95% CI: 0.78–1.88) and between high and low PLR was 1.47 (95% CI: 0.91–2.03), whereas in metastatic PCa cases, between high and low NLR was 1.79 (95% CI: 1.44–2.13) and between high and low PLR was 1.05 (95% CI: 0.87–1.24).
Conclusion: The prognostic values of NLR and PLR in terms of PCa characteristics and responses after treatment show a high level of heterogeneity of results among studies. These two ratios

* Corresponding author.
E-mail address: marco.frisenda@uniroma1.it (M. Frisenda).
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can represent the inflammatory and immunity status of the patient related to several conditions. A higher predictive value is related to a high NLR in terms of risk for overall mortality in metastatic PCa cases under systemic treatments.

1. Introduction

Prostate cancer (PCa) is an extremely heterogeneous tumor. Clinical decisions continue to depend upon serum prostate-specific antigen levels, tumor stages, risk classes, and pathologic Gleason scores [1,2]. Predictive nomograms mainly including these clinical parameters are also used to evaluate the risk of advanced stage, undifferentiated tumors, and progression after treatments [3,4].

Different research sustains the hypothesis that chronic inflammation and immune environment can condition carcinogenesis and tumor progression. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) can be easily obtained from routine blood counts and they have been proposed as marker of the relationship between inflammation or immune responses and tumor growth or progression [5,6]. Low lymphocyte counts while increased platelet counts have been associated with adverse prognostic features for different diseases, including PCa [7]. The prognostic roles for NLR and PLR have been underlined for several solid tumors [8]. In PCa, the significance of NLR or PLR has been investigated in different settings, more frequently in advanced metastatic PCa submitted to systemic therapies. In two recent meta-analysis, heterogeneously combining localized, metastatic, and castration resistant PCas, either a high PLR or a high NLR, were correlated with poor disease-free survival and overall survival (OS) [9,10]. On the contrary, a retrospective analysis on localized PCa submitted to radical prostatectomy (RP) concluded that neither PLR nor NLR can correlate with the presence of a clinically significant PCa or predict an increased risk of biochemical recurrence [7,8].

The primary aim of this systemic review and meta-analysis was to analyze data available in the literature regarding a possible prognostic value of NLR and PLR in PCa patients. Differently to previous data, we distinguished our analysis in different settings (initial diagnosis, primary therapies for localized tumors, and systemic therapies for metastatic tumors) and we stratified our evaluation between non-metastatic and metastatic tumors, in terms of PCa staging, histologic aggressiveness, and risk of progression after treatments.

2. Method

2.1. Search strategy

A literature search using electronic databases, such as PubMed, Medline, Web of Science, Scopus, and the Cochrane library was performed from January 2000 to July 2021. The search process was performed on a combination of the items ("prostatic cancer" AND "platelet" and "lymphocyte" AND/OR "platelet to lymphocyte ratio" OR "neutrophil" AND "lymphocyte" AND/OR "neutrophil to lymphocyte ratio") without language restrictions and following the Preferred Reporting Items for Systematic review and Meta-Analyses guidelines. Original and review articles were included and critically considered. We have not included abstracts or reports from meetings.

2.2. Selection of the studies and inclusion criteria

Entry into the analysis was restricted to data collected from original studies on clinical retrospective or prospective trials including patients with a histological diagnosis of prostatic adenocarcinoma. Two authors (Frisenda M, Giorgino G) independently screened titles and abstracts of all articles using predefined inclusion criteria. The full-text articles were independently examined by three authors (Frisenda M, Giorgino G, and Bevilacqua G) to determine whether they met the inclusion criteria. Then two authors (Frisenda M, Giorgino G) extracted data from the selected articles. Final inclusion was determined by discussion of all investigators' evaluation.

Studies selected for inclusion met the following criteria: (I) patients with a histological diagnosis of PCa; (II) serum NLR or PLR determination; (III) investigation on the association between NLR or PLR and PCa characteristics or survival outcomes.

Articles were excluded if: (I) multiple reports were published on the same population; (II) data provided were insufficient for the outcomes described in the aim section; (III) failed to meet inclusion criteria; (IV) mixed populations without possibility of data extraction.

The following data were extracted: population characteristics (sample size and age), PCa variables (stage and grading), and outcomes from treatments (progression and survival).

2.3. Statistical analysis

Risk of bias was assessed at the study level for each of the cohort included in full agreement with the Cochrane Collaboration's "risk of bias" tool (Supplementary Table 1). According to predetermined endpoints, we compared the available populations using standardized mean difference, event rate, and risk difference (RD) with 95% confidence interval (CI).

Moreover, a pooled hazard ratio (HR) with 95% CI obtained from multivariate analysis in the different studies was used to evaluate the prognostic value in terms of risk of

progression and mortality. Evaluation for presence of heterogeneity was done using: (1) Cochran's Q test with $p<0.05$ signifying heterogeneity; (2) Higgins I^2 test with inconsistency index. The pooled standardized mean difference, event rate, RD, and HR estimates for each group were calculated using a random effects model, and the results are graphically displayed as forest plots.

Possible prognostic value for PNL or NLR was estimated regarding PCa staging, histologic aggressiveness, and risk of progression and mortality after treatment distinguishing between initial diagnosis and primary treatment in localized or systemic treatment in metastatic PCa. NLR and PLR prognostic values were evaluated either in terms of mean values or cut-off values calculated from area under the curve using the Youden's index. HR and corresponding 95% CI at multivariate analysis were considered to evaluate the importance of prognostic value for the two ratios. Calculations were accomplished using Stata version 1.7 (Stata Corporation, College Station, TX, USA) with all tests being two sided, and statistical significance was set at <0.05.

3. Results

3.1. Studies included in the meta-analysis

Database searches initially yielded 104 article references. Of these, 45 were subsequently removed due to either duplication or meeting the exclusion criteria. Full-text articles were then re-evaluated and critically analyzed for the remaining 59 references. Of these, 17 did not meet the inclusion criteria. The remaining 42 articles were considered for our critical review and meta-analysis (Fig. 1).

3.2. Quality of studies and sample size

Of the 42 articles selected for the review [8,11–51], 24 studies considered NLR, eight studies PLR, and 10 studies both NLR and PLR. Moreover, 40 studies were retrospective and only two were prospective, either mono- or multicenter clinical trials (Supplementary tables 2, 3, 4 and 5).

Sample size of the populations ranged from 47 to 7426 cases across all the studies (from 47 to 7426 cases in studies on NLR and from 59 to 1826 cases in studies on PLR). All these studies defined the patient population in terms of clinical (age and prostate-specific antigen values), pathologic characteristics (staging and histologic grading), biochemical progression (BCP) and radiological clinical progression rates, cancer-specific survival, and OS after treatments. Of all 34 studies considering NLR, 18 focused on non-metastatic PCa and 16 on metastatic PCa; six studies considered the prognostic value in terms of initial diagnosis of PCa; 20 considered differences between pre- and post-treatment; 21 considered the prognostic value in terms of progression or survival (Tables 1 and 2, Supplementary Tables 1 and 2). Of all 18 studies considering PLR, 13 focused on non-metastatic PCa and five on metastatic PCa; five studies considered the prognostic value in terms of initial diagnosis of PCa; seven considered differences between pre- and post-treatment; nine considered the prognostic value in terms of progression or survival (Tables 3 and 4, Supplementary Tables 4 and 5).

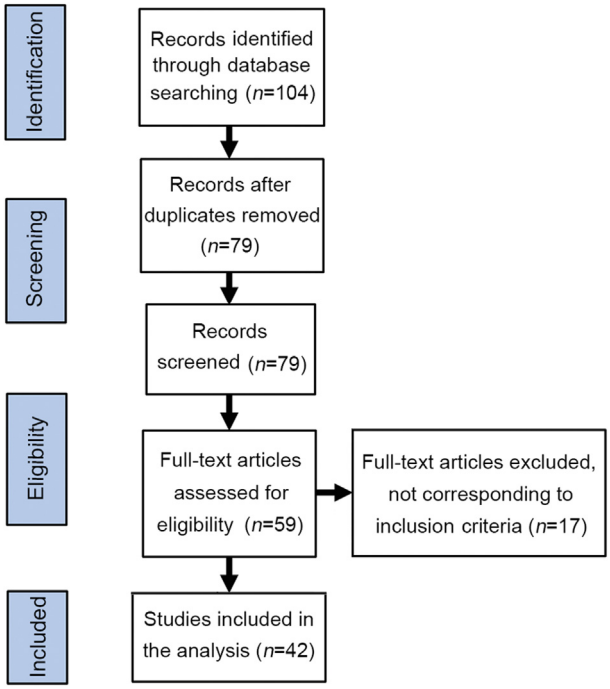

Figure 1 Flow chart for meta-analysis.

3.3. Identification of the optimal cut-off for NLR and PLR

Thirty-one studies identified an optimal cut-off value for NLR and 16 studies for PLR to stratify the population between low and high NLR or PLR groups. Cut-off values were determined by receiver operating characteristics curve analysis using the Youden's index and the optimal cut-off values in the different courts varied ranging from 1.7 to 5.0 for NLR and from 100.7 to 253.9 for PLR (Supplementary tables 2, 3, 4, and 5).

3.4. NLR and PLR prognostic value in terms of initial diagnosis of PCa

3.4.1. NLR

Six studies considered NLR in populations submitted to prostatic biopsy for the initial diagnosis of PCa (clinically significant PCa). Mean NLR value varied from 1.6 to 3.6 in benign prostatic hyperplasia and from 1.6 to 4.2 in clinically significant PCa at initial diagnosis. Considering a cut-off value for NLR, an elevated NLR was associated to a significantly higher HR for an initial diagnosis of clinically significant PCa ($p<0.01$; range 1.29–2.86) when compared to low NLR (Table 1).

3.4.2. PLR

Five studies considered PLR in populations submitted to prostatic biopsy for the initial diagnosis of PCa (clinically significant PCa). Mean PLR value ranged from 101.3 to 150.0 in benign prostatic hyperplasia and from 104.3 to 169.5 in clinically significant PCa at initial diagnosis. Considering a cut-off value for PLR, an elevated PLR was not associated to a significantly higher HR for an initial diagnosis of clinically

Table 1 Clinical trials on non-metastatic PC included in the analysis: results on the basis of NLR groups.

Study	Cut-off groups	Treatment	HR (95% CI) for BPH *vs.* PC	Cases on the basis of T stage, *n* (%)	OR (95% CI) for PCa diagnosis	Cases on the basis of N stage, *n* (%)	HR or OR (95% CI) for N+ disease	Cases on the basis of ISUP, *n* (%)	HR (95% CI) for ISUP 4–5	HR (95% CI) for progression after treatment	HR (95% CI) for OM or CSM
Sun et al. [11]	• NLR<2.31 • NLR≥2.31	Initial biopsy	NA	NA	NA	NA	NA	• NLR<2.31 - 1: 33 (30.8) - 2–5: 74 (69.2) • NLR ≥ 2.31 - 1: 22 (18.5) - 2–5: 97 (81.5)	NA	NA	• CSM: 2.0 (1.0–3.8) • OM: 2.0 (0.8–5.4)
Zanaty et al. [8]	• NLR<3 • NLR≥3	RP	NA	NA	NA	NA	NA	NA	NA	0.9 (0.721–1.384)	NA
Shelton et al. [12]	• Low NLR: 2 (±0.67) • High NLR: 5.15 (±2.62)	Active surveillance	NA	NA	NA	NA	NA	• Low NLR - 1: 66 (89.2) - 2: 8 (10.8) • High NLR - 1: 23 (95.8) - 2: 1 (4.2)	NA	NA	NA
Vidal et al. [13]	• No cut-off	RP	NA	NA	NA	NA	NA	NA	NA	1.06 (0.97–1.17)	• CSM: 1.15 (0.81–1.65) • OM: 1.04 (0.91–1.17)
Cao et al. [14]	• NLR<2 • NLR≥2	RP	NA	• NLR<2 - pT2: 362 (69.9) - pT3: 148 (28.6) - pT4: 8 (1.5) • NLR≥2 - pT2: 298 (67.7)	NA	• NLR<2 - N0: 395 (92.3) - N1: 33 (7.7) • NLR≥2 - N0: 326 (93.1) - N1: 24 (6.9)	NA	• NLR<2 - 1: 99 (19.6) - 2: 185 (36.6) - 3: 95 (18.8) - 4–5: 126 (25.0) • NLR≥2	NA	0.600 (0.413–0.871)	• OM: 1.466 (0.607–3.542)

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Table 1 (*continued*)

Study	Cut-off groups	Treatment	HR (95% CI) for BPH *vs.* PC	Cases on the basis of T stage, *n* (%)	OR (95% CI) for PCa diagnosis	Cases on the basis of N stage, *n* (%)	HR or OR (95% CI) for N+ disease	Cases on the basis of ISUP, *n* (%)	HR (95% CI) for ISUP 4–5	HR (95% CI) for progression after treatment	HR (95% CI) for OM or CSM
				- pT3: 126 (28.6) - pT4: 16 (3.6)				- 1: 81 (18.6) - 2: 145 (33.3) - 3: 75 (17.2) - 4–5: 134 (30.8)			
Nkengurutse et al. [15]	• NLR<2 • NLR≥2	RP	NA	NA	NA	NA	NA	NA	NA	1.131 (0.633–2.021)	NA
Taussky et al. [16]	• NLR>3 • NLR≤3	Brachytherapy	NA	NA	NA	NA	NA	NA	NA	0.37 (0.15–0.92)	NA
Langsenlehner et al. [17]	• NLR≥5 • NLR<5	Radiotherapy	NA	NA	NA	NA	NA	NA	NA	3.09 (1.64–5.82)	• OM: 2.16 (1.17–3.99)
Lee et al. [18]	• NLR<2.5 • NLR≥2.5	RP	NA	• NLR<2.5 - pT2: 836 (69.2) - pT3a: 252 (20.9) - ≥pT3b: 120 (9.9) • NLR≥2.5 - pT2: 78 (49.4) - pT3a: 47 (29.7) - ≥pT3b: 33 (20.9)	NA	NA	HR: 0.819 (0.303–2.216)	• NLR<2.5 - 1: 616 (51.0) - 2–3: 429 (35.5) - 4–5: 163 (13.5) • NLR≥2.5 - 1: 63 (39.9) - 2–3: 48 (30.4) - 4–5: 47 (29.7)	1.750 (0.960–3.189)	1.358 (1.008–1.829)	NA
Jang et al. [19]	• NLR<1.76 • NLR≥1.76	RP	NA	• NLR<1.76 - pT2: 484 (47.3) - pT3: 540 (52.7) • NLR≥1.76 - pT2: 476 (45.6) - pT3: 567 (54.4)	NA	NA	NA	• NLR<1.76 - 1–3: 812 (79.3) - 4–5: 212 (20.7) • NLR≥1.76 - 1–3: 802 (76.9) - 4–5: 241 (23.1)	NA	1.099 (0.944–1.278)	• CSM: 2.012 (1.222–3.310) • OM: 1.650 (1.127–2.416)

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Table 1 (*continued*)

Study	Cut-off groups	Treatment	HR (95% CI) for BPH *vs.* PC	Cases on the basis of T stage, *n* (%)	OR (95% CI) for PCa diagnosis	Cases on the basis of N stage, *n* (%)	HR or OR (95% CI) for N+ disease	Cases on the basis of ISUP, *n* (%)	HR (95% CI) for ISUP 4–5	HR (95% CI) for progression after treatment	HR (95% CI) for OM or CSM
Jang et al. [20]	• NLR<3.5 • NLR≥3.5	RP	NA	• NLR<3.5 - pT2: 708 (44.8) - pT3: 871 (55.2) • NLR≥3.5 - pT2: 227 (50.1) - pT3: 226 (49.9)	NA	NA	NA	• NLR<3.5 - 1–3: 483 (30.6) - 4–5: 1096 (69.4) • NLR≥3.5 - 1–3: 138 (30.5) - 4–5: 315 (69.5)	NA	1.270 (1.066–1.514)	NA
Zhang et al. [21]	• NLR<2.36 • NLR≥2.36	RP	NA	• NLR<2.36 - pT2: 127 (78.9) - pT3–4: 34 (21.1) • NLR≥2.36 - pT2: 43 (56.6) - pT3–4: 33 (43.4)	NA	• NLR<2.36 - N0: 152 (94.4) - N1: 9 (5.6) • NLR≥2.36 - N1: 15 (19.7) - N0: 61 (80.3)	NA	• NLR<2.36 - 1: 34 (21.1) - 2–3: 75 (46.6) - 4–5: 52 (32.3) • NLR≥2.36 - 1: 13 (17.1) - 2–3: 31 (40.8) - 4–5: 32 (42.1)	NA	1.388 (0.909–2.118)	NA
Özsoy et al. [22]	• NLR≥3 • NLR<3	RP	NA	• NLR≥3 - cT1: 1565 (91.7) - cT2: 114 (6.7) - cT3: 1 (0.1) • NLR<3 - cT1: 5320 (93.0) - cT2: 302 (5.3) - cT3: 2 (0.1)	1.60 (1.30–1.95)	NA	OR: 1.43 (1.20–1.72)	• NLR≥3 - 1: 344 (20.2) - 2–3: 1116 (65.4) - 4–5: 247 (14.5) • NLR<3 - ISUP 1: 1888 (33.0) - ISUP 2–3: 3487 (61.0)	2.32 (1.90–2.83)	NA	NA

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Table 1 (*continued*)

Study	Cut-off groups	Treatment	HR (95% CI) for BPH *vs.* PC	Cases on the basis of T stage, *n* (%)	OR (95% CI) for PCa diagnosis	Cases on the basis of N stage, *n* (%)	HR or OR (95% CI) for N+ disease	Cases on the basis of ISUP, *n* (%)	HR (95% CI) for ISUP 4–5	HR (95% CI) for progression after treatment	HR (95% CI) for OM or CSM
								- ISUP 4–5: 339 (5.9)			
Adhyatma et al. [23]	• NLR≥3.08 • NLR<3.08	Initial biopsy	2.856 (1.734 – 4.702)	NA	NA	NA	NA	NA	NA	NA	NA
Masuda et al. [24]	• NLR≤1.92 • NLR>1.92	Biopsy	2.44 (1.19 –5.17)	NA	NA	NA	NA	NA	NA	NA	NA
Huang et al. [25]	• NLR<2.44 • NLR≥2.44	Initial biopsy	1.640 (1.045 –2.573)	NA	NA	NA	NA	• NLR<2.44 - 1–2: 47 (33.1) - 3–4: 95 (66.9) • NLR≥2.44 - 1–2: 61 (34.9) - 3–5: 114 (65.1)	NA	NA	NA
Oh et al. [26]	• No cut-off	Initial biopsy	1.372 (1.017 –1.850)	NA	NA	NA	NA	NA	NA	NA	NA
Hashimoto et al. [27]	• No cut-off	Biopsy	1.29 (0.874 –1.9)	NA	NA	NA	NA	NA	NA	NA	NA

RP, radical prostatectomy; BCP, biochemical progression; BCR, biochemical recurrence; BPH, benign prostatic hyperplasia; NLR, neutrophil-to-lymphocyte ratio; CSM, cancer specific mortality; OM, overall mortality; HR, hazard ratio; CI, confidence interval; PCa, prostate cancer; ISUP, International Society of Urological Pathology; IQR, interquartile range; NA, not available.

Table 2 Clinical trials on metastatic CRPC included in the analysis: results on the basis of NLR groups.

Study	Cut-off groups	Treatment	HR (95% CI) for pretreatment *vs.* posttreatment	Cases on the basis of ISUP, *n* (%)	Cases on the basis of progression after treatment, *n* (%)	HR (95% CI) for progression after treatment	HR (95% CI) for OM
Lolli et al. [28]	• NLR<3 • NLR≥3	Abiraterone	NA	NA	NA	NA	• Low–High (<3–≥3): 1.49 (0.84–2.63) • High–Low (≥3–<3): 3.22 (1.89–5.49)
Onal et al. [29]	• NLR<3.1 • NLR≥3.1	Abiraterone	• Low–high: 1.55 (0.64–3.74) • High–low: 3.96 (1.26–12.47)	• 1–3: - NLR<3.1: 25 (54.3) - NLR≥3.1: 21 (45.7) • 4–5: - NLR<3.1: 25 (44.6) - NLR≥3.1: 31 (55.4)	NA	• 2.25 (1.44–3.51)	• 3.13 (1.67–5.88)
Bauckneht et al. [30]	• NLR<4.8 • NLR≥4.8	Radium-223	NA	NA	NA	NA	• 1.09 (1.00–1.20)
Bauckneht et al. [31]	• NLR<3.1 • NLR≥3.1	Radium-223	NA	NA	NA	NA	• 2.70 (2.06–3.56)
Pei et al. [32]	• NLR≤3.3 • NLR>3.3	Docetaxel	NA	NA	NA	• 1.831 (1.087–3.085)	• 2.056 (1.007–4.200)
Sonpavde et al. [33]	• NLR<2.5 • NLR 2.5 to <5 • NLR≥5	Sunitinib	NA	NA	NA	NA	• 1.55 (1.32-1.83)
Buttigliero et al. [34]	• NLR≤3 • NLR>3	Docetaxel	NA	NA	• NLR≤3: 39/46 (84.8) • NLR>3: 57/64 (89.1)	• 1.57 (0.84–2.92)	• 3.16 (1.50–6.65)
Kawahara et al. [35]	• NLR>3.02 • NLR≤3.02	Abiraterone and/ or enzalutamide	NA	NA	NA	NA	• 2.115 (1.540–2.906)
Chong et al. [36]	• NLR<2.65 • NLR≥2.65	ARTA and docetaxel	NA	NA	• NLR<2.65: 14/21 (66.7) • NLR≥2.65: 31/42 (73.8)	• 1.65 (0.87–3.12)	• 3.27 (1.11–9.63)
Lorente et al. [37]	• NLR>3 • NLR<3	Mitoxantrone and cabazitaxel	NA	NA	NA	• BCP: 1.35 (1.12–1.62) • RCP: 1.42 (1.15–1.76)	• 1.55 (1.30–1.84)
Uemura et al. [38]	• NLR<3.83 • NLR≥3.83	Cabazitaxel	NA	NA	NA	NA	• 3.01 (1.06–8.49)
Templeton et al. [39]	• NLR<3 • NLR>3	Docetaxel	NA	NA	NA	NA	• 1.89 (1.27–2.82)
Boegemann et al. [40]	• NLR<5 • NLR>5	Abiraterone	NA	• 4–5: - NLR<5: 46 (60.5) - NLR>5: 9 (56.3)	NA	• 3.4 (0.8–15.2)	• 1.6 (0.5–5.6)

(*continued on next page*)

Table 2 (*continued*)

Study	Cut-off groups	Treatment	HR (95% CI) for pretreatment *vs.* posttreatment	Cases on the basis of ISUP, *n* (%)	Cases on the basis of progression after treatment, *n* (%)	HR (95% CI) for progression after treatment	HR (95% CI) for OM
Conteduca et al. [41]	• NLR<3 • NLR≥3	Abiraterone and/or enzalutamide	NA	NA	NA	• 1.98 (1.54–2.56)	• 2.04 (1.54–2.70)
Yasui et al. [42]	• NLR<3.76 • NLR≥3.76	Abiraterone	NA	• NLR<3.76: - 1: 1 (2.0) - 2–3: 7 (14.0) - 4–5: 42 (84.0) • NLR≥3.76: - 1: 0 (0) - 2–3: 6 (20.0) - 4–5: 24 (80.0)	NA	NA	• 2.506 (1.106–5.68)
Fan et al. [43]	• NLR≥3 • NLR<3	Abiraterone and docetaxel	NA	• NLR≥3: - 1–3: 25 (40.3) - 4–5: 37 (59.7) • NLR<3: - 1–3: 23 (54.8) - 4–5: 19 (45.2)	NA	NA	NA

ARTA, new generation androgen receptor target agents; BCP, biochemical progression; CI, confidence interval; CRPC, castration resistant prostate cancer; CSM, cancer-specific mortality; NLR, neutrophil-to-lymphocyte ratio; OM, overall mortality; RCP, radiological clinical progression; NA, not available.

Table 3 Clinical trials on non-metastatic PCa included in the analysis: results on the basis of PLR groups.

Study	Cut-off groups	Treatment	HR (95% CI) for BPH *vs.* PCa	HR (95% CI) for pretreatment *vs.* posttreatment	Cases on the basis of T stage, %	Cases on the basis of ISUP, %	Cases on the basis of treatment, *n* (%)	HR (95% CI) for progression after treatment	HR (95% CI) for OM or CSM
Sun et al. [11]	• Low PLR<134 • High PLR≥134	Initial biopsy	NA	NA	NA	• Low PLR - 1: 31.6 - 2–5: 68.4 • High PLR - 1: 16.5 - 2–5: 83.5	NA	NA	• CSM: 1.30 (0.60–2.80) • OM: 2.10 (0.80–4.90)
Zanaty et al. [8]	• Low PLR<190 • High PLR≥190	RP	NA	NA	NA	NA	NA	BCP: 0.997 (0.988–1.006)	NA
Shelton et al. [12]		Active surveillance	NA	NA	NA	• Low PLR - 1: 90.0 - 2: 10.0 • High PLR - 1: 92.0 - 2: 8.0	NA	NA	NA
Ferro et al. [44]	• Low PLR<118 • High PLR≥118	RP and active surveillance	NA	NA	NA	• 2–5 - PLR<118: 29.9 - PLR≥118: 44.2	NA	NA	NA
Vidal et al. [13]	NA	RP	NA	NA	NA	NA	NA	NA	• CSM: 1.00 (0.99–1.01) • OM: 1.00 (0.98–1.03)
Shu et al. [45]	• Low PLR<100.7 • High PLR≥100.7	RP	NA	NA	NA	NA	• BCP: - Low PLR: 184/380 (48.4) - High PLR: 196/380 (51.6)	NA	NA
Nkengurutse et al. [15]	• Low PLR<120.4 • High PLR≥120.4	RP	NA	NA	NA	NA	NA	BCP: 1.020 (0.575–1.811)	NA
Lee at al. [46]	NA	Initial biopsy	0.094 (0.003–2.900)	NA	NA	NA	NA		NA

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Table 3 (*continued*)

Study	Cut-off groups	Treatment	HR (95% CI) for BPH *vs.* PCa	HR (95% CI) for pretreatment *vs.* posttreatment	Cases on the basis of T stage, %	Cases on the basis of ISUP, %	Cases on the basis of treatment, *n* (%)	HR (95% CI) for progression after treatment	HR (95% CI) for OM or CSM
Wang et al. [47]	• Low PLR<117.58 • High PLR≥117.58	ADT	NA	NA	NA	• Low PLR<117.58 - ≤7: 52.0 - >7: 48.0 • High PLR≥117.58 - ≤7: 47.0 - >7: 53.0	NA	RCP: 1.581 (1.100−2.272)	• CSM: 1.768 (1.036−3.015) • OM: 1.650 (1.013−2.687)
Li et al. [48]	• Low PLR<150 • High PLR ≥150	Initial biopsy	NA	2.67 (1.73−4.92)	• PCa: T3 - Low PLR: 41.8 - High PLR: 75.0	• 4−5 - Low PLR: 53.7 - High PLR: 58.3	NA	NA	NA
Langsenlehner et al. [49]	• Low PLR<190 • High PLR≥190	Radiotherapy	NA	NA	NA	NA	NA	NA	• CSM: 3.99 (1.19−13.4) • OM: 1.87 (1.02−3.42)
Adhyatma et al. [50]	• Low PLR<143 • High PLR≥143	Initial biopsy	1.152 (0.648−2.049)	NA	NA	NA	NA	NA	NA
Masuda et al. [24]	• Low PLR<101.3 • High PLR≥101.3	Initial biopsy	1.710 (0.810−3.630)	NA	NA	NA	NA	NA	NA

RP, radical prostatectomy; CI, confidence interval; ISUP, International Society of Urological Pathology; PCa, prostate cancer; PLR, platelet-to-lymphocyte ratio; HR, hazard ratio; BPH, benign prostatic hypertrophy; ADT, androgen deprivation therapy; CSM, cancer specific mortality; OM, overall mortality; BCP, biochemical progression; RCP, radiological clinical progression; NA, not available.

Table 4 Clinical trials on metastatic CRPC included in the analysis: results on the basis of PLR groups.

Study	Cut-off groups	Treatment	HR (95% CI) for pretreatment *vs.* posttreatment	Cases on the basis of ISUP, %	Cases on the basis of progression after treatment, *n* (%)	HR (95% CI) for progression after treatment	HR (95% CI) for OM
Onal et al. [29]	• Low PLR<163 • High PLR≥163	ARTA (abiraterone)	• Low–high: 0.90 (0.38–2.13) • High–low: 1.39 (0.49–3.92)	• PLR<163 - ≤7: 59 - >7: 41 • PLR≥163 ≤7: 41 >7: 59	NA	0.88 (0.56–1.37)	• 1.02 (0.56–1.87)
Shi et al. [51]	• Low PLR<104.275 • High PLR≥104.275	Chemotherapy (docetaxel)	NA	NA	NA	NA	• Poor *vs.* favorable: 28.606 (9.390–87.144) • Poor *vs.* intermediate: 7.412 (2.406–22.808)
Bauckneht et al. [30]	• Low PLR<241 • High PLR≥241	Radium-223	NA	NA	NA	NA	• 1.03 (0.90–1.18)
Chong et al. [36]	• Low PLR<155.54 • High PLR≥155.54	ARTA and chemotherapy	NA	NA	• Low PLR<155.54: 14/23 (60.9%) • High PLR≥155.54: 31/40 (77.5%)	1.72 (0.91–3.24)	• 2.38 (0.88–6.43)
Lolli et al. [28]	• Low PLR<210 • High PLR≥210	ARTA (abiraterone)	NA	NA	NA	NA	• Low–high (<210– ≥210): 1.54 (0.71–3.33) • High–low (≥210– <210): 1.46 (0.91–2.36)

CRPC, castration resistant prostate cancer; PLR, platelet-to-lymphocyte ratio; ARTA, new generation androgen receptor target agents; HR, hazard ratio; CI, confidential interval; OM, overall mortality; NA, not available.

significant PCa ($p=0.176$; range 0.094–1.710) when compared to low PLR (Table 3).

3.5. Association between NLR or PLR and pathologic features

3.5.1. NLR

According to T stage, mean±standard deviation of NLR was 2.40±2.35 in T2 localized PCa and 2.30±1.90 in T3 locally advanced PCa. Considering a cut-off value for NLR, elevated NLR had a significantly higher HR for non-organ confined disease ($p<0.001$; range 1.600–1.851) when compared to low NLR (Table 1). According to N stage, elevated NLR had a significantly higher HR for N1 PCa ($p<0.001$; range 0.819–1.661) when compared to low NLR (Table 1). According to ISUP grading, considering a cut-off value for NLR, elevated NLR was associated to a significantly higher HR for ISUP 4–5 PCa ($p<0.001$; rang 1.75–2.32) when compared to low NLR (Table 1).

3.5.2. PLR

According to T stage, very few data are available, and only one trial [48] observed a low PLR and a high PLR associated with T3 stage in 41.8% and 75.0% of cases, respectively (Table 3). In the same study [48], according to histopathological grading, ISUP scores 4–5 was observed in 58.3% of the high PLR and in 53.7% of low PLR patients (Table 3).

3.5.3. Meta-analysis on NLR or PLR and pathologic features

A meta-analysis was implemented in order to examine the distribution of cases according to pathologic staging between high and low values in NLR and PLR groups. Considering a random effect model among eligible studies, the pooled RD for non-organ confined PCa between high NLR and low NLR cases was 0.06 (95% CI: −0.03–0.15) and between high PLR and low PLR increased to 0.30 (95% CI: 0.16–0.43). The pooled RD for lymph node involvement between high and low NLR was 0.37 (95% CI: −0.37–1.11) whereas it was not analyzed according to PLR in the selected studies (Fig. 2).

According to ISUP grading distribution, considering a random effect model among eligible studies for our meta-analysis, the pooled RD for ISUP scores 4–5 PCa between high NLR and low NLR cases was similar in non-metastatic (0.07; 95% CI: −0.02–0.16) and metastatic (0.08; 95% CI: 0.01–0.15) PCa, whereas between high PLR and low PLR changed from 0.07 (95% CI: −0.01–0.14) in non-metastatic to 0.18 (95% CI: 0.04–0.32) in metastatic PCa (Fig. 2). Deeks' funnel plots are displayed in Supplementary Fig. 1 and meta-regression plots are presented in Supplementary Fig. 2. A high rate of heterogeneity either among studies on PLR ($I^2=71.49\%$; test of group differences $p<0.001$), or on NLR ($I^2=95.87\%$; test of group differences $p=0.72$) was found (Fig. 2).

3.6. Association between NLR or PLR and progression or survival after treatment

3.6.1. Non-metastatic PCa

Results in terms of BCP rates were reported in 13 analyses on non-metastatic PCa submitted to RP or radiotherapy [8,13–22,45,49], and five of them analyzed results in terms of cancer-specific survival and OS [13,14,17,19,49].

A meta-analysis was implemented in order to examine the pooled HR to progression and mortality after treatment between high and low values in NLR and PLR groups obtained from a multivariate analysis in the different studies. Considering a random effect model among eligible studies, the pooled HR for BCP after treatment between high and low NLR cases was 0.99 (95% CI: 0.77–1.20) and between high and low PLR was 1.02 (95% CI: 0.84–1.21). The pooled HR for overall mortality (OM) between high and low NLR was 1.33 (95% CI: 0.78–1.88) and between high PLR and low PLR was 1.47 (95% CI: 0.91–2.03). Low rates of heterogeneity ($I^2<60\%$) among studies (test of group differences $p>0.05$) are presented (Fig. 3). Deeks' funnel plots are displayed in Supplementary Fig. 3 and meta-regression plots are presented in Supplementary Fig. 4.

3.6.2. Metastatic PCa

All the studies considered metastatic castration resistant PCa [28–43,51]. Results in terms of BCP rates were reported in seven analyses on the metastatic PCa submitted to systemic treatments. Sixteen studies analyzed results in terms of cancer-specific mortality and OM (Table 2 and Table 4).

A meta-analysis was implemented in order to examine the pooled HR to progression and mortality after treatment between high and low values in NLR and PLR groups obtained from multivariate analyses in the different studies. Considering a random effect model among eligible studies, the pooled HR for BCP after treatment between high and low NLR cases was 1.59 (95% CI: 1.27–1.90) and between high and low PLR was 1.01 (95% CI: 0.47–1.55). The pooled HR for OM between high and low NLR was 1.79 (95% CI: 1.44–2.13) and between high and low PLR was 1.05 (95% CI: 0.87–1.24). Low rates of heterogeneity ($I^2<50\%$) among studies (test of group differences $p>0.05$) are presented (Fig. 3). Deeks' funnel plots are displayed in Supplementary Fig. 3 and meta-regression plots are presented in Supplementary Fig. 4.

4. Discussion

To our knowledge, this is the first meta-analysis evaluating the predictive value of either NLR or PLR in PCa cases stratified in terms of non-metastatic and metastatic populations, regarding initial diagnosis, local staging, histologic aggressiveness and progression, or mortality risk after treatments. In the present meta-analysis, following the Preferred Reporting Items for Systematic reviews and Meta-Analyses statements, we found 40 retrospective studies and two prospective studies corresponding to our inclusion criteria. The quality of data from these trials is high. Sample sizes reaching 7426 cases were significant and most of these trials accurately defined the patient population in terms of pre-operative characteristics, pathologic results, and survival after treatments. Thirteen out of the 42 selected trials [8,13–22,45,49] considered non-metastatic PCa cases selected for surgery (RP) or radiotherapy, and 17 [28–43,51] considered metastatic PCa cases selected for systemic treatments. Serum determination of NLR or PLR is

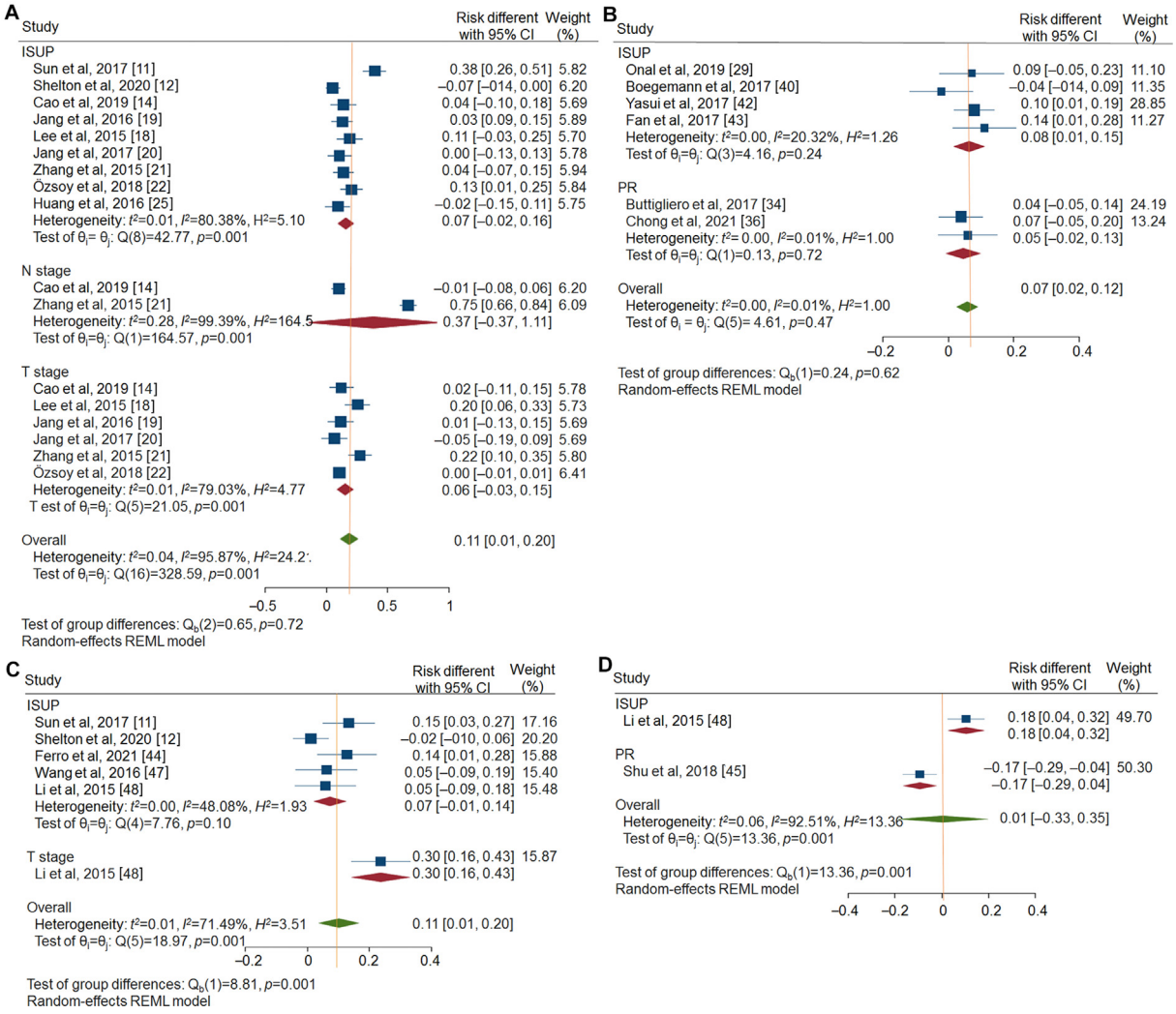

Figure 2 Forrest plot assessing risk differences with 95% CI for non-organ confined PCa (T stage), lymph node involvement (N stage), ISUP grading 4–5, PR (biochemical and clinical) between high and low NLR or PLR groups. (A) NLR in non-metastatic PCa; (B) NLR in metastatic PCa; (C) PLR in non-metastatic PCa; (D) PLR in metastatic PCa. I^2 for heterogeneity and test of group differences are reported. ISUP, International Society of Urological Pathology; PR, progression; CI, confidence interval; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; REML, residual maximum likelihood.

a very simple method to be used in our clinical practice, and it can be related to the inflammatory or immunity status of the patient. However, different limits must be underlined. Most of the studies identified a cut-off value for NLR and PLR to stratify results between Low and High groups. NLR and PLR cut-off values were determined by receiver operating characteristics curve analysis, but the optimal cut-off values in the different courts strongly varied, ranging from 1.7 to 5.0 for NLR and from 100.7 to 253.9 for PLR. The majority of studies concluded with positive outcomes in favor of a clinically significant prognostic values of NLR and PLR in terms of risk for progression or cancer-specific mortality, less in terms of risk for advanced stage or high aggressiveness of PCa. However, heterogeneity of results is significantly high, in particular for the analysis in terms of staging and aggressiveness, underlying a low specificity of these two ratios for PCa staging and grading. Several situations related to the inflammatory and immunity condition of the subject, as well as PCa, often expressed in the population, can influence the variability in NLR or PLR.

Our meta-analysis found a high rate of heterogeneity either among studies on PLR ($I^2=71.49\%$; test of group differences, $p<0.001$), or on NLR ($I^2=95.87\%$; test of group differences, $p=0.72$) regarding the analyses on tumor stage and aggressiveness, whereas a low rate of heterogeneity ($I^2<60\%$) among studies (test of group differences, $p>0.05$) is present regarding analyses on progression and mortality.

A low predictive value of both ratios was found in terms of T staging or PCa aggressiveness. The pooled RD for non-organ confined PCa between high and low NLR cases was 0.06 (95%CI: −0.03–0.15) and between high and low PLR increased to 0.30 (95% CI: 0.16–0.43). According to ISUP grading distribution, the predictive value of NLR was similar comparing non-metastatic; metastatic PCa groups (pooled RD for ISUP scores 4–5 PCa in non-metastatic PCa: 0.07, 95%

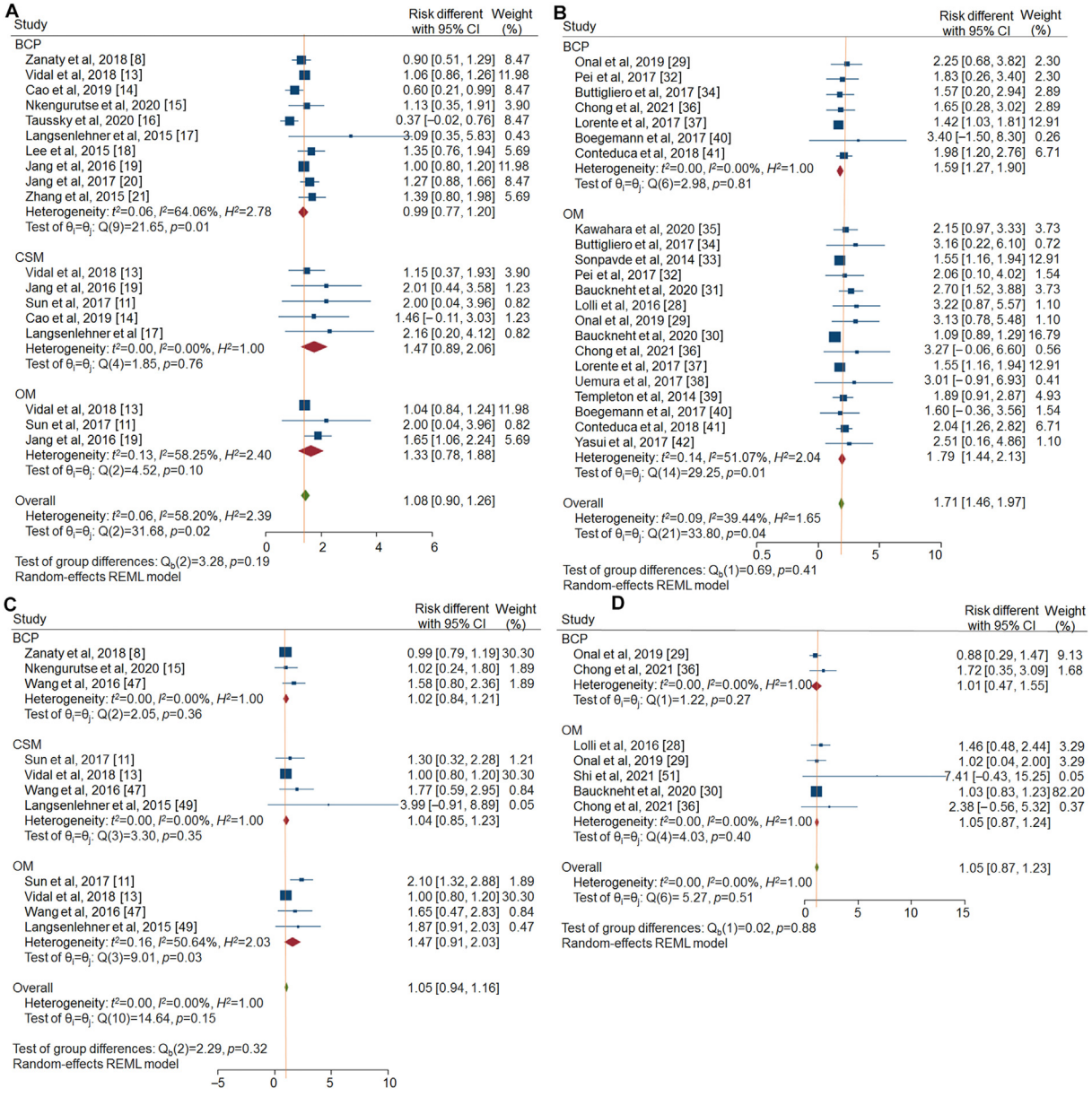

Figure 3 Forrest plot assessing pooled HR with 95% CI for BCP, CSM, and OM between high and low NLR or PLR groups. (A) NLR in non-metastatic PCa; (B) NLR in metastatic PCa; (C) PLR in non-metastatic PCa; (D) PLR in metastatic PCa. I^2 for heterogeneity and test of group differences are reported. CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; BCP, biochemical progression; CSM, cancer-specific mortality; OM, overall mortality; PCa, prostate cancer; REML, residual maximum likelihood.

CI: −0.02–0.16 and in metastatic PCa: 0.08, 95% CI: 0.01–0.15), whereas for PLR changed from 0.07 (95% CI: −0.01–0.14) in non-metastatic PCa to 0.18 (95% CI: 0.04–0.32) in metastatic PCa.

A higher predictive value was found in terms of risk for mortality. In particular, considering values obtained from multivariate analyses in the different studies, a higher pooled HR for OM in the metastatic PCa population was related to a high NLR (1.79, 95% CI: 1.44–2.13) when compared to a high PLR (1.05, 95% CI: 0.87–1.24). In non-metastatic PCa populations, the pooled HR for OM was similar between high NLR (1.33, 95% CI: 0.78–1.88) and high PLR (1.47, 95% CI: 0.91–2.03).

5. Conclusions

The prognostic values of NLR and PLR in terms of PCa characteristics and responses after treatments show a high level of heterogeneity of results among studies. These two ratios can represent the inflammatory and immunity status of the patient related to several conditions, as well as PCa. A higher predictive value is related to a high NLR in terms

of risk for OM in metastatic PCa cases under systemic treatments.

Author contributions

Study concept and design: Alessandro Sciarra, Stefano Salciccia, Gianna Mariotti.
Data acquisition: Marco Frisenda, Giulio Bevilacqua, Gloria Giorgino, Davide Rosati.
Data analysis: Marco Frisenda, Giulio Bevilacqua, Gloria Giorgino, Francesco Del Giudice, Pietro Viscuso, Susanna Cattarino.
Drafting of manuscript: Alessandro Sciarra, Stefano Salciccia, Marco Frisenda, Giulio Bevilacqua, Gloria Giorgino, Francesco Del Giudice, Alessandro Gentilucci.
Critical revision of the manuscript: Alessandro Sciarra, Stefano Salciccia, Marco Frisenda, Giulio Bevilacqua, Gloria Giorgino, Francesco Del Giudice, Ettore De Berardinis, Giovanni Battista Di Pierro, Paolo Casale.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajur.2023.01.002.

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