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Relationship between NLR and penile squamous cell carcinoma: a systematic review and meta-analysis

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Abstract

Objective We conducted this study to summarize the results of studies reporting the role of NLR (neutrophil to lymphocyte ratio) in PSCC (penile squamous cell carcinoma).

Methods This meta-analysis was conducted using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria. A systematic search was conducted on PubMed, Scopus, and web of science up to March 10, 2023. Fourteen studies were included in the review. The NOS (Newcastle–Ottawa Scale) was used to determine the quality of the included studies. This meta-analysis was conducted on the studies reporting the relationship between NLR and survival using HR (hazard ratio) and 95% CI (confidence interval).

Results There was a significant association between NLR levels and the prognosis, nodal stage, and anatomical tumor stage of PSCC patients. In the meta-analysis of the association of NLR with survival, NLR level was significantly associated with lower cancer-specific survival (HR = 3.51, 95% CI = 2.07–5.98, $p < 0.001$) and lower disease-free survival (HR = 2.88, 95% CI = 1.60–5.20, $p < 0.001$). However, NLR was found to have no association with the stage, grade, location, and size of the tumor.

Conclusion NLR has a significant diagnostic and prognostic value in PSCC.

Keywords Neutrophil to lymphocyte ratio, NLR, Penile squamous cell carcinoma, Systematic review, Meta-analysis

Introduction

PSCC (penile squamous cell carcinoma) is a relatively uncommon form of cancer in developed countries [1]. In contrast, in developing countries in Africa, Asia, and South America PSCC remains a pertinent public health problem, where its incidence ranges from 3 to 8.3 cases per 100,000 individuals [2]. Universally, numerous risk factors for PSCC have been identified and include HPV (human papillomavirus) infection, large number of sexual partners, and phimosis [3–5]. Prognostic factors for PSCC include but are not limited to grade of tumor differentiation, T-stage, LVI (lymphovascular invasion), N-stage, visceral metastasis, and perineural invasion (Hu) [6–9]. A growing body of evidence supports the

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association of systematic inflammation with the development of solid organ malignancies [10–12]. As such, inflammatory markers are being identified to help predict patients with cancer. The NLR (neutrophil to lymphocyte ratio) has demonstrated an association with PSCC prognosis [13]. Notably, the NLR can be calculated from routine CBCs (complete blood counts) in peripheral blood samples [13]. In their study evaluating the utility of NLR as a prognosticator for patients with PSCC, Kasuga et al., found that determining the NLR before a radical penectomy can help with determining the prognosis of PSCC patients. Numerous studies reported that PSCC patients with a high NLR have worse OS (overall survival), recurrence-free survival, and CSS (cancer-specific survival) [2, 7–9, 13–21]. Recently, there has been a significant increase in the number of studies reporting NLR as a prospective biomarker for PSCC. Consequently, there is a need for an analysis that can illustrate whether the evidence surrounding the diagnostic and prognostic role of NLR in PSCC is consistent or inconsistent. Subsequently, a systematic review was conducted to bring together publications associated with the role of NLR in PSCC patients, intended to help clinicians understand the pathogenesis of PSCC, differential diagnosis, staging and predicting progression and survival.

Methods

Literature search strategy

The systematic review was conducted using the criteria outlined by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). A literature search was conducted using PubMed, Scopus, and Web of Science without any language limitations. The search was conducted using the following key words: (neutrophil AND lymphocyte AND ratio) OR (neutrophil-to-lymphocyte) OR (NLR) AND (penile OR penis) AND (cancer OR carcinoma). Only studies published before March 06, 2023, were considered for this review. Search formulas were adjusted with respect to the characteristics of each database. Table 1 presents the search strategies used for this systematic review.

Criteria for inclusion and exclusion

Studies included in this review satisfied the following inclusion criteria: (1) reporting NLR value in peripheral blood; (2) evaluating the diagnostic and prognostic role of NLR in penile cancer; (3) including human subjects; and (4) the full-text article was available. The criteria for exclusion were as follows: (1) unsuitable publication types (case reports, meetings, abstracts, reviews); (2) animal experiments or non-clinical reports studies; (3) incomplete data without original text; and (4) studies that overlapped the included studies (such as studies from the same study group, institution, and with the same results).

Primary endpoint

Primary endpoint was the association of NLR with prognosis, stage, survival, grade, location, and size of the tumor in patients with PSCC.

Data extraction

Two independent reviewers screened the literature and extracted the data. First author, year of publication, country, sample size, treatment, and the main results related to the diagnostic and prognostic role of NLR data were extracted. Additional data were obtained on the NLR value, including the mean, SD (standard deviation), HR (hazard ratio), correlation coefficient, OR (odds ratio), the results of ROC (receiver operating characteristic), and the Kaplan–Meier survival analysis. The NLR level was presented as mean ± SD or median (interquartile range). Due to the heterogeneity of these studies, a meta-analysis was not appropriate. Missing data were supplemented via contact with the authors to the best possible degree. The NOS (Newcastle–Ottawa Scale), which includes three sections: selection, comparability, and outcome, and quality assessment, and a total score from 0 to 9, was used by two independent reviewers to determine the quality of the studies included in this systematic review. In cases of disagreements between the reviewers, a third reviewer was consulted, and the disagreement was settled through multilateral discussion.

Table 1 Systematic review search strategies

Database	Key words	Number of articles
PubMed	(("neutrophil"[All Fields] AND "lymphocyte"[All Fields] AND "ratio"[All Fields]) OR "neutrophil-to-lymphocyte"[All Fields] OR "NLR"[All Fields]) AND "penile"[All Fields] AND ("cancer"[All Fields] OR "tumor"[All Fields])	12
Scopus	((ALL ((neutrophil AND lymphocyte AND ratio) OR (neutrophil-to-lymphocyte) OR NLR))) AND ((TITLE-ABS-KEY (cancer)) OR (TITLE-ABS-KEY (tumor))) AND (TITLE-ABS-KEY (penile))	241
Web of Science	All = ((neutrophil AND lymphocyte AND ratio) OR (neutrophil-to-lymphocyte) OR NLR) AND All = (cancer OR tumor) AND ALL = (penile)	15

Statistical analysis

HR was reported with a 95% CI (confidence interval) for the association of NLR level with survival. Heterogeneity was assessed by I^2 statistic and χ2 (chi-squared) test. $P_{\chi 2}$ test < 0.05 and I^2 > 75% were considered as significant heterogeneity; In such a case, a random effect model was used. Otherwise, the fixed-effect model was used. STATA 12.0 software (Stata Corporation, College Station, TX, USA) was used for statistical analyses. A $p \leq 0.05$ was conceived as statistically significant.

Results

Search and selection of literature

In this systematic review, the search and selection of studies is depicted in Fig. 1. Initial searches yielded a total of 281 related articles. After the exclusion of duplicates and not relevant records, 14 studies were included in the systematic review (Fig. 1).

Characteristics of the included studies

The systematic review included a total of 14 studies, all of which were in English and retrospective in nature. Of these, thirteen studies evaluated the role of NLR in predicting patient survival (CSS, OS, RFS, PFS (progression-free survival), DSS (disease-specific survival)), six studies assessed the association between NLR and PSCC staging, six studies evaluated the association between NLR and lymph node and distant metastasis, five studies evaluated the correlation between NLR and cancer grade, four studies evaluated the association between NLR and response to cancer treatment, two studies reported the role of NLR in differentiating tumor size and location, and a single study assessed the correlation between the absolute neutrophil count and metastasis. Table 2 lists the characteristics of the studies included in this review.

NLR and survival in PSCC

In 13 studies [2, 7–9, 13–21], NLR levels were evaluated to determine patient survival. In a 2016 study conducted by Kasuga et al., 41 patients underwent CBC with differential, and subsequent radical penectomy was analyzed [1]. The median and mean (± SD) NLRs in the 41 PSCC patients were 3.42 and 5.03 ± 4.99, respectively. Based on the AUC (area under the curve) for the ROC curve, the cut-off value of NLR was determined to be 2.82. Subsequently, patients with a high NLR (≥ 2.82) showed a significantly poorer CSS ($p = 0.02$) and OS ($p = 0.07$) than those with a low NLR. Li et al. reported similar results with a study population of 228 PSCC patients in 2019. Using a multivariate analysis, the NLR had an independent effect on DFS (disease-free survival) before ILND (inguinal lymph node dissection) (HR = 2.13, $p = 0.03$). Additionally, Li et al. carried out an exploratory data analysis wherein the results indicated that NLR ($p = 0.02$)

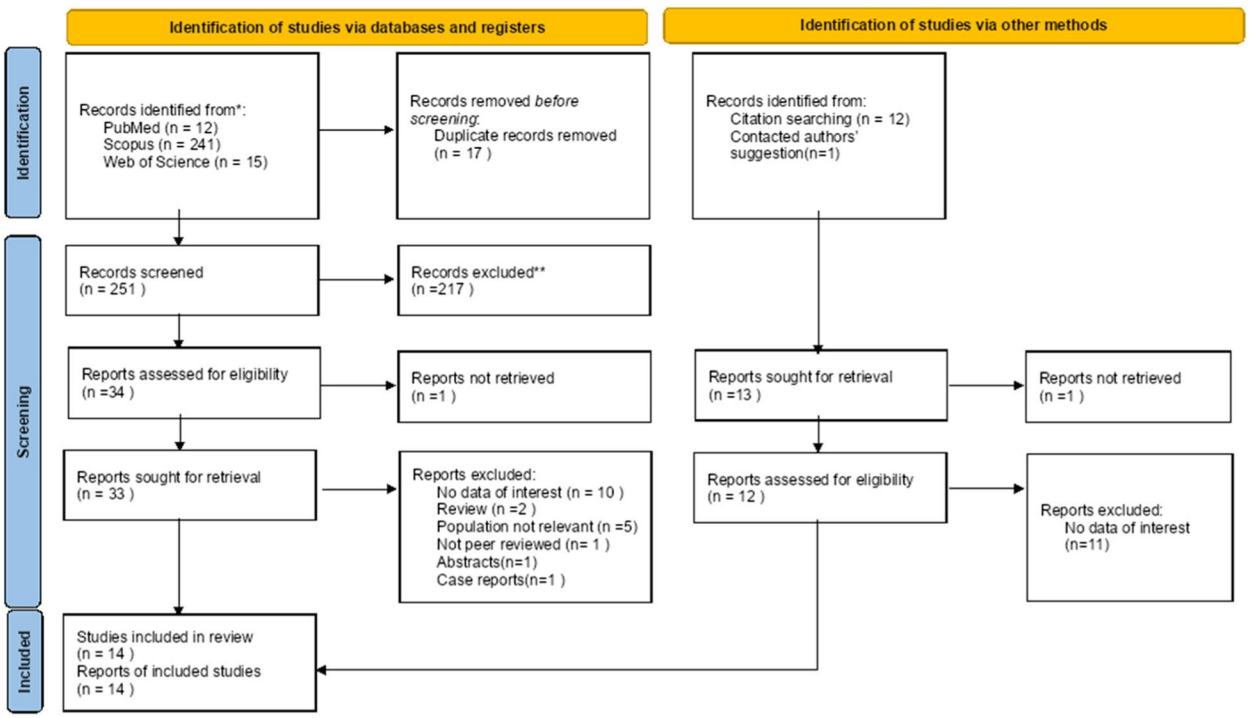

Fig. 1 PRISMA 2020 Flow diagram for new systematic reviews which includes searches of databases, registers and other sources

Table 2 Characteristics of studies included in this systematic review

First author	Sample size	Study design	Year	Country	NLR Cut off	Mean age(year)	Treatment	Outcome	NOS score
Kasuga	41	Retrospective cohort	2016	Japan	2.82	68.5 ± 11.4	radical penectomy	Higher NLR value was associated with poorer CSS, OS and lymph node metastasis	7
Azizi	84	Retrospective cohort	2018	USA	3	64.8 (53.4–69.3)	Inguinal Lymph Node Dissection	The correlation between NLR with disease stage, Pathologic N stage, extranodal extension, and OS was significant	7
Hu	225	Retrospective cohort	2020	China	_	54.95 ± 10.60	Inguinal Lymph Node Dissection	higher rates of metastasis, recurrence, higher nodal and anatomical stage, higher tumor grade, pathologically positive inguinal lymph nodes, and response to initial cancer treatment were seen in patients with higher NLR	8
Tan	39	Retrospective cohort	2017	Singapore	2.8	65.1 (59–72.5)	5.1%: radiotherapy, 25.6%: partial penectomy, 30.8%: excisional biopsy, 38.5%: total penectomy	Higher NLR had a significant correlation with worse CSS and T-stage	7
Li	228	Retrospective cohort	2019	China	_	52.0 (24–85)	bilateral inguinal lymph node dissection	NLR was an independent prognostic variable for DSS and DFS	8
Pond	140	Retrospective cohort	2013	North America, Europe, and India	_	57.0 ± 11.4	first-line systemic therapy	Higher NLR was significantly predictive of the poorer OS	8
Buonerba	65	Retrospective cohort	2016	America	5	61.3 ± 8.7	second or later lines of systemic treatment	There was no significant correlation between NLR and OS and response to systemic treatment	6
Jindal	69	Retrospective cohort	2021	India	3	_	bilateral inguinal lymph node dissection	NLR was significantly associated with the presence of pathological inguinal node involvement, type of surgery and T-stage	7
Jiao Hu	134	Retrospective cohort	2020	China	3.59	54.95 ± 10.60	bilateral inguinal lymphadenectomy after local treatment of primary penile cancer	NLR was an independent predictor of LNM and advanced tumor grade	7
Albuquerque	230	Retrospective cohort	2019	Brazil	3.0	-	Inguinal Lymph Node Dissection	NLR was associated with worse RFS, CSS, and OS	7
Kawahara	122	Retrospective cohort	2016	Japan	2.82	-	radical penectomy	NLR was significantly higher in patients with poorer CSS	6
Zhou	114	Retrospective cohort	2019	China	3.25	54 (24–86)	partial or radical penectomy with or without bilateral inguinal lymphadenectomy	NLR had a significant correlation with DSS	6
Pond	26	Retrospective cohort	2014	Europe and UAS	_	60.3 ± 12.4	concurrent chemotherapy and radiotherapy	Higher NLR was significantly associated with poorer OS	6

Table 2 (continued)

First author	Sample size	Study design	Year	Country	NLR Cut off	Mean age(year)	Treatment	Outcome	NOS score
Hou	101	Retrospective cohort	2019	China	2.42	55 (26–84)	Not declared	Absolute neutrophil value ($P < 0.043$) was an independent predictor of LNM	7

Data was presented as mean ± standard deviation or median (interquartile range)

NLR Neutrophil to lymphocyte ratio, *OS* overall survival, *CSS* Cancer-specific survival, *PFS* Progression-free survival, *DSS* Disease-specific survival, *LNM* lymph node metastasis, *DFS* Disease-free survival

was an independent prognostic variable for DSS. In Tan et al.'s 2017 study of 39 PSCC patients, the median NLR was 2.99 (0.76 – 5.22) [3]. In the same study, the NLR cut-off was determined to be 2.8, with respect to the AUC operator characteristic curve. Patients with a high NLR (≥2.8) had significantly worse CSS ($p<0.001$) than those with a low NLR. These results matched a 2013 study done by Pond et al. which showed that higher NLR was significantly ($p=0.05$) predictive of poorer OS [9]. Furthermore, in 2019, Albuquerque et al. evaluated 230 penile cancer patients from Brazil [15]. On multivariable Cox regression, adjusted for age, staging T, histological grade, lymphovascular invasion, and perineural invasion, and before ILND, patients with NLR≥3.0 was associated with worse RFS ($p<0.001$, 95% CI: 1.99—17.03, HR=5.82), OS ($p<0.001$, 95% CI:1.99—10.77, HR=4.63) and CSS ($p=0.001$, 95% CI: 1.835—10.434, HR=4.376). Kawahara et al. conducted a study on 122 patients from Japan who underwent radical penectomy and reported a similar result in 2016 [16]. CBCs were performed on forty patients (33%) prior to pathological diagnosis. At a NLR cut-off of 2.82, patients with a high NLR showed significantly poorer CSS ($p=0.02$) than those with low NLR. In Zhou et al.'s study, the data of 114 PSCC patients from China were analyzed in 2019 [17]. Using a multivariate Cox regression analysis for DSS, patients with NLR≥3.25 had shorter DSS than those with NLR<3.25 (HR=2.780, 95% CI: 1.06–7.21, $p=0.04$). Pond et al. retrieved the data of 26 PSCC patients from Canada and America in 2014 [18]. They highlighted that baseline NLR was significantly associated with OS, although no p-value was reported. In a 2018 study where 84 patients treated with ILND for non-metastatic (M0) PSCC, Azizi et al. on median OS was significantly shorter for patients with NLR≥3 than NLR<3 ($p<0.001$) [19]. Also, in a univariate analysis, NLR≥3 was associated with shorter CSS ($p<0.001$) and RFS ($p<0.01$). Interestingly however, in a multivariable analysis, only the association between NLR and OS was significant (HR=2.48; 95% CI: 1.02 – 6.06, $p=0.04$), and there was no correlation between NLR with CSS (HR=2.58; 95% CI: 0.79 – 8.41, $p=0.1$) and RFS (HR=1.66; 95% CI: 0.73 – 3.76, $p=0.2$).

Concurrently, other studies could not demonstrate an association between NLR and PSCC cancer survival. In a 2021 study done by Jindal et al., 69 PSCC patients were analyzed using Kaplan–Meier analysis determined the NLR cut-off to be 3 and found no statistically significant association with CSS using a multivariate analysis ($p=0.9$) [20]. Similarly, in an evaluation of 225 PSCC patients by Hu et al., a multivariate analysis revealed NLR was not a significant independent factor for OS (95% CI: 0.605—2.718, HR=1.28, $p=0.5$) and PFS (95% CI: 0.67 -1.97, HR=1.12, $p=0.6$) [8]. With respect to an association between NLR and RFS, Tan et al. reported similar findings [13]. These findings are further supported by Jiao Hu et al.'s study of 134 PSCC patients in 2020 [21]. With a cutoff value of NLR being 3.59, patients were divided into NLR positive (41%) and NLR negative (59%) groups. They conducted a significant correlation between NLR and CSS. Those with negative and positive NLR had 61% and 22% had 5 years CSS, respectively ($p<0.001$). However, the results of the multivariate analysis indicated no significant correlation between NLR and CSS. In the study by Buonerba et al., the data of 65 PSCC patients from North America and Europe were analyzed in 2016 [7]. At a NLR cut off of 5, there was no significant correlation between NLR and OS (HR=0.81 (0.45–1.45), $p=0.4$), PFS (HR=0.80 (0.47, 1.38), $p=0.4$) and response to systemic treatment (HR=3.36 (0.84, 13.44), $p=0.09$).

Meta-analysis of the association of NLR with CSS

In the meta-analysis of the association of NLR with CSS, NLR level was significantly associated with lower CSS (HR=3.51, 95% CI=2.07–5.98, $p<0.001$). Fixed-effects model was applied to the pooled meta-analysis, as heterogeneity did not exist ($I^2=0\%$, P-value=0.8) (Fig. 2).

Meta-analysis of the association of NLR with OS

NLR level was not associated with OS (HR=1.78, 95% CI=0.82–3.86, $p=0.1$). Random-effects model was applied to the pooled meta-analysis, because statistical heterogeneity existed among studies ($I^2=76\%$, P-value<0.01) (Fig. 3).

Meta-analysis of the association of NLR with DFS

In the meta-analysis of the association of NLR with DFS, NLR level was significantly associated with lower CSS (HR=2.88, 95% CI=1.60–5.20, $p<0.001$). Because there was no significant heterogeneity between studies, we used Fixed-effects model ($I^2=58\%$, P-value=0.1) (Fig. 4).

Meta-analysis of the association of NLR with PFS

The association of NLR with PFS was not significant (HR=0.94, 95% CI=0.64–1.38, $p=0.7$). Fixed-effects model was applied to the pooled meta-analysis, because the heterogeneity was not significant ($I^2=0\%$, P-value=0.3) (Fig. 5).

NLR and lymph nodal and distant metastasis

In 7 studies, the association between NLR and lymph node and distant metastasis was characterized, and a single study assessed the correlation between absolute neutrophil count and metastasis [2, 8, 15, 19–22]. Hu et al. reported higher rates of metastasis and recurrence for patients with a high NLR (>2.94) when compared to those with those that had a lower NLR (<2.94) [8].

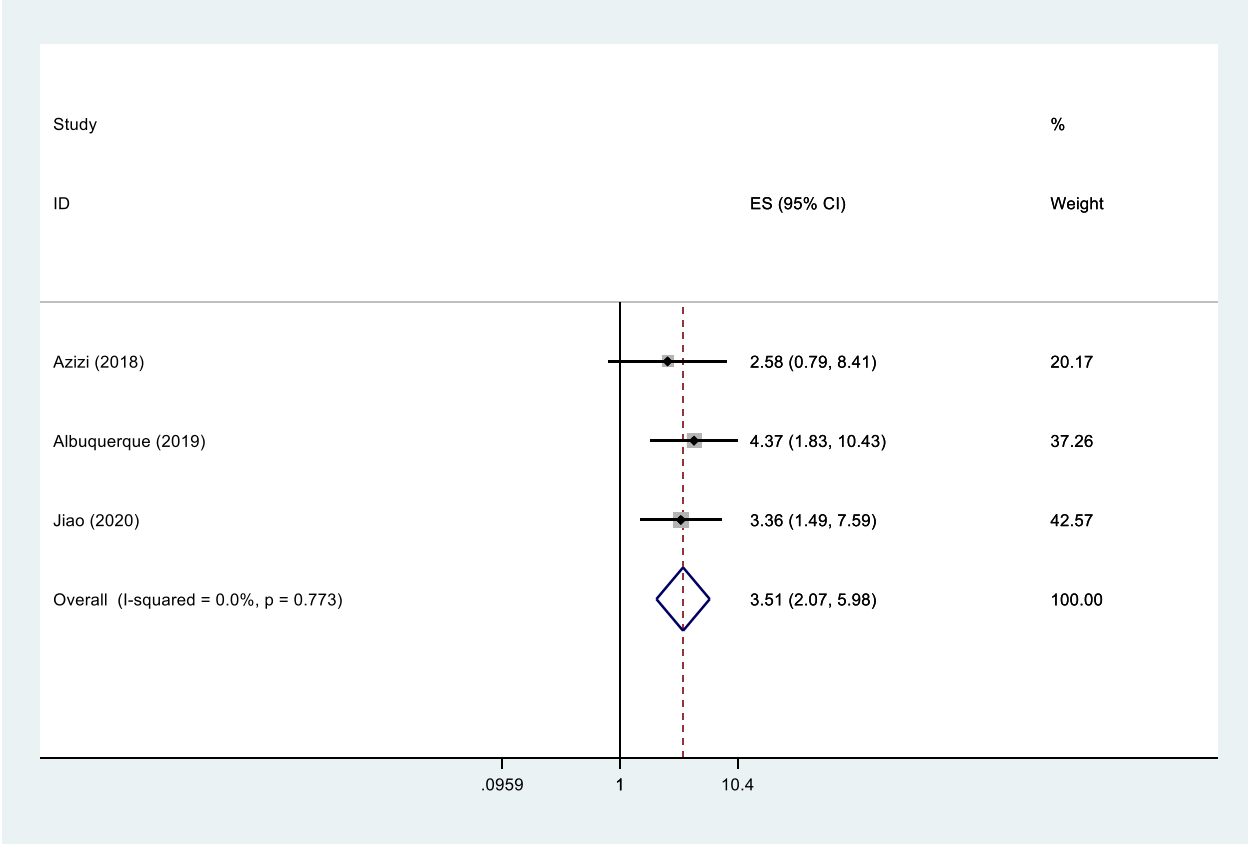

Fig. 2 Meta-analysis of the association of NLR with CSS

Additionally, the study found that higher levels of NLR had a significant correlation with pathologically positive inguinal lymph nodes after ILND ($p=0.02$). This conclusion is further supported by a study conducted by Jindal et al., wherein a high NLR (>3) was significantly associated with the presence of pathological inguinal node involvement [20]. This study also found that 78% of patients with positive pathological nodal status and 36% of those without pathologic nodal status expressed a high NLR (>3) ($p=0.001$). Similar results were reported by Jiao Hu et al., which showed the NLR was an independent predictor of LNM (lymph node metastasis) [21]. In their study, 78% patients with positive NLR had positive LNM, while 34% of patients with negative NLR ($p<0.01$). Moreover, in a study with 101 PSCC patients, Hou et al. reported the absolute neutrophile value ($p<0.04$) as an independent predictor of LNM using both a univariate and multivariate logic regression analyses [22].

In contrary to the previous studies, numerous studies reported no significant correlation between NLR and distant metastasis. Kausga et al. did report that that patients with an NLR≥2.82 had significant LNM ($p=0.04$) than those with a low NLR, however no significant correlation was found ($p=0.3$) [2]. In a univariable analysis, Azizi et al. found an association between a NLR≥3 and an increased risk of pN+(pathologic node-positivity) (OR=3.75; 95% CI: 1.30– 10.81, $p=0.01$) [19]. However, this association became insignificant when a multivariable analysis adjusted for primary tumor grade, lymphovascular invasion, clinical N stage, and neoadjuvant treatment receipt was conducted (OR=3.66, 95% CI: 0.82 – 16.42, $p=0.09$). Likewise, using a univariable model, Albuquerque et al. found that a NLR≥3.0 was an independent predictor of LN+(HR=5.96; 95% [CI]: 1.24–28.74, $p=0.03$) [15]. However, when using a multivariable model, this correlation was no longer significant.

Based on these findings, NLR in PSCC patients may be associated with metastasis and lymph node involvement. As indicated, patients with higher NLR values experience a higher rate of metastasis and lymph node involvement.

NLR and PSCC staging

In 6 studies [2, 8, 13, 19–21], the relationship between NLR and PSCC staging were evaluated. In their study, Azizi et al. characterized patients in 1 of 6 stages of cancer: stage 0, stage I, stage II, stage IIIA, stage IIIB,

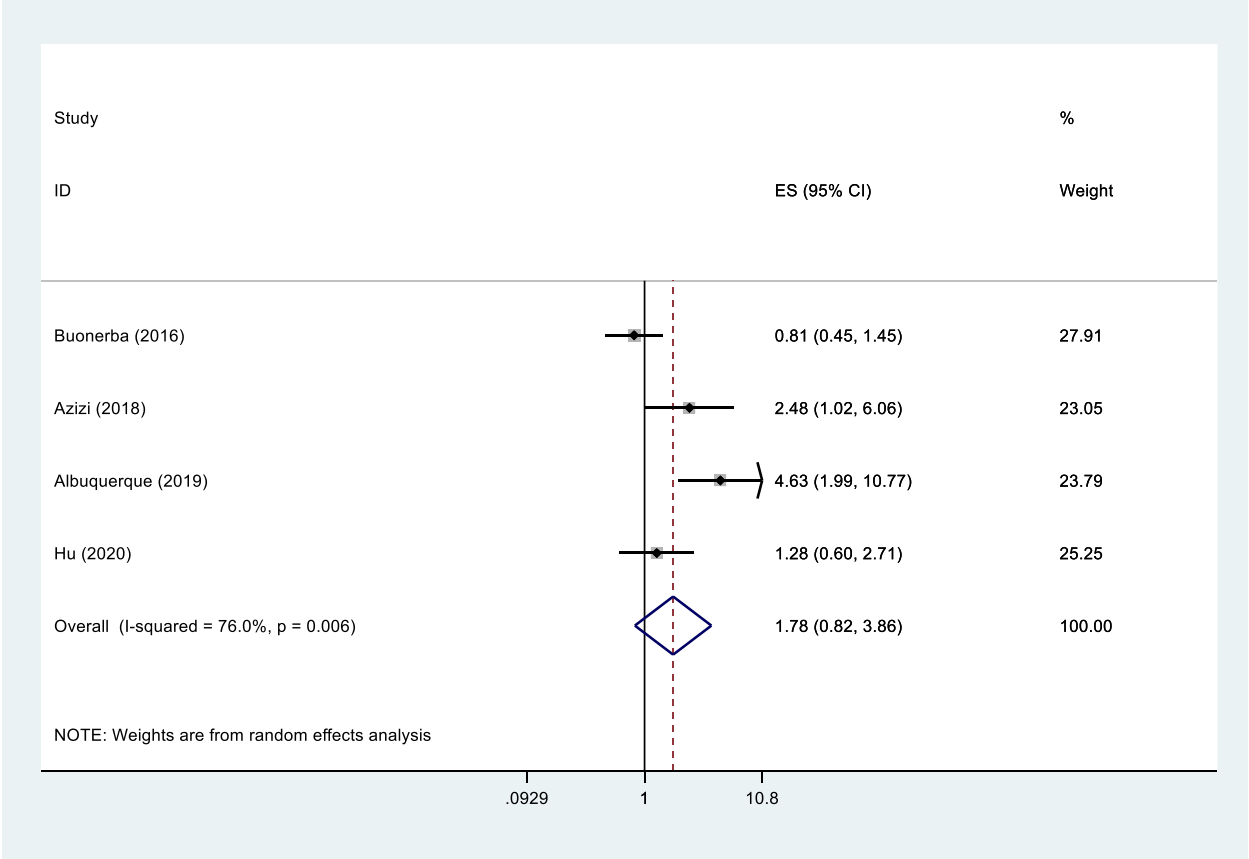

Fig. 3 Meta-analysis of the association of NLR with OS

and stage IV [19]. Their study found that patients with NLR ≥ 3 expressed a higher stage in their disease (3%, 3%, 13%, 5%, 24%, and 53%) versus those with NLR < 3 (0%, 0%, 47%, 17%, 10% and 23%) ($p = 0.003$). Importantly, a higher pathologic N stage was reported for patients with NLR ≥ 3 than patients with NLR < 3 (79% and 50% respectively) ($p = 0.02$) even though this correlation was not significant between the clinical N stage and pathologic T stage of patients and respective NLR values ($p = 0.2$ and 0.6, respectively). These findings are further supported by Tan et al.'s study, wherein the NLR cut-off was determined to be 2.8 with respect to the AUC operator characteristic curve [13]. Patients with a high NLR (≥ 2.8) also had significantly higher T-stage ($p = 0.006$) compared to those with a low NLR (< 2.8). Similarly, Jindal et al. observed patients with NLR > 3 also reported higher tumor stages (40%, 54%, 81%, and 100% in T1, T2, T3, and T4, respectively). When assessing NLR values with the nodal stage, Jindal et al. found 36%, 100%, 67%, and 72% of patients with pN0, pN1, pN2, and pN3 had NLR > 3 (p value was not reported) [20]. These findings seem consistent with Hu et al.'s research, which found that based on NLR cut-off of 2.94, patients with NLR > 2.94 showed higher nodal stage and anatomical stage of tumor than those with lower NLR [8].

However, Kasuga et al. found no significant correlation between NLR and Pathological T stage [1–4] ($p = 0.3$), and anatomic stage (I-IV) ($p = 0.2$) [2]. Likewise, Jiao Hu et al. found that 46.66% patients NLR positive and 38% NLR negative expressed a tumor stage ≥ T1b ($p = 0.4$), which was not significant [21].

Based on the findings, it can be inferred that NLR is a prognostic factor of patients' nodal stage and anatomical tumor stage, however, NLR has no association with the tumor stage.

NLR and *cancer* grade

In 5 studies, the correlation between NLR and cancer grade was evaluated [2, 8, 19–21]. In the study of Hu et al., for tumor types: benign, well, moderate, poor, and other tumor type, PSCC patients with NLR > 2.94 had an incident rate of 20%, 28%, 34%, 50% and 100% for respectively, and for PSCC patients with NLR ≤ 2.94 experienced an incident rate of 80%, 72%, 66%, 50% and 0%, respectively ($p = 0.03$) [8]. These results are further supported by Jindal et al.'s study, wherein they demonstrated

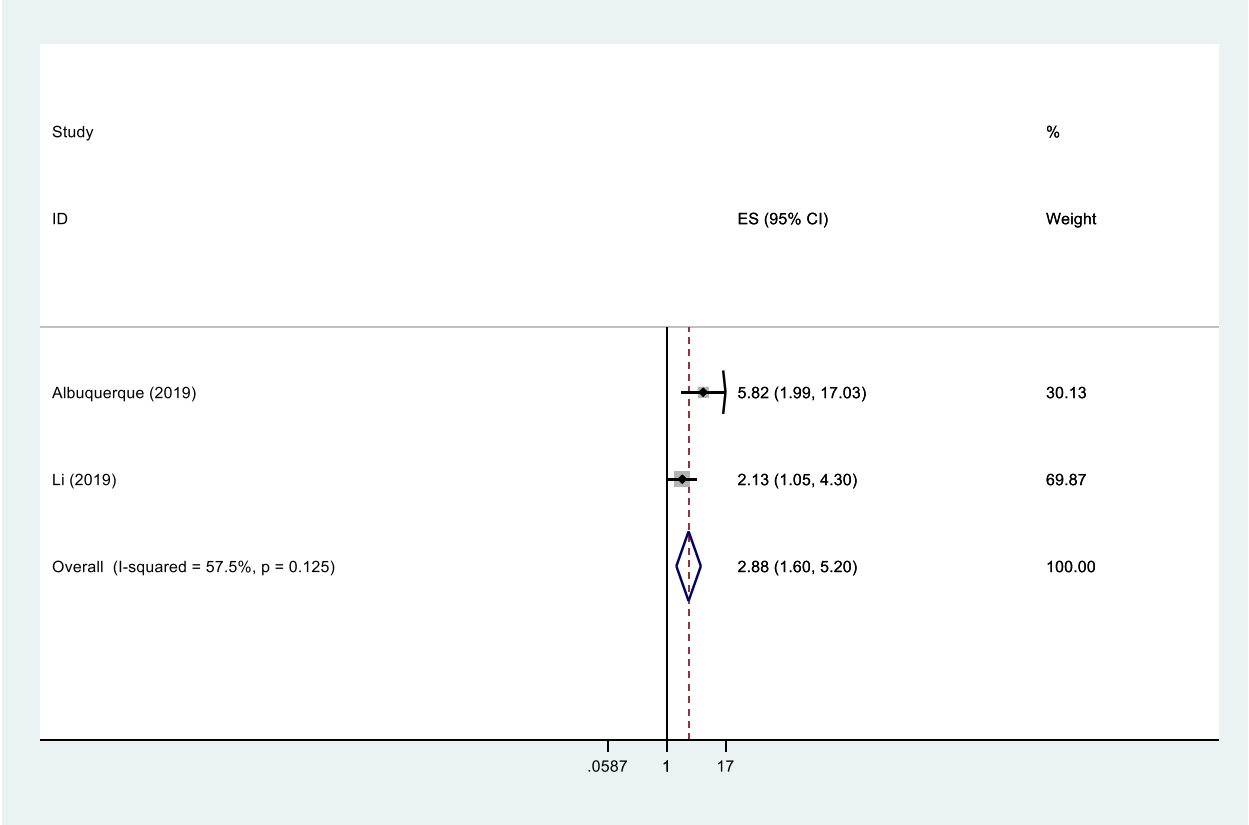

Fig. 4 Meta-analysis of the association of NLR with DFS

that patients with NLR > 3 had higher tumor grades (25%, 52%, and 79% in Grade I, II, and III respectively), although no *p*-value was reported [20]. These findings remain consistent with the study done by Jiao Hu et al. which showed that NLR was positively related to advanced tumor grade [21]. In their study, 64% and 36% of patients with negative NLR, and 38% and 63% of those with positive NLR had Grade1 and Grade2 tumor respectively ($p = 0.02$).

However, the findings of the Kasuga et al. study do not support the aforementioned results ($p = 0.3$) [2]. This conclusion is supported by Azizi et al.'s study, which showed 50% and 47% of patients with NLR < 3, and 66% and 32% of patients with NLR ≥ 3.0 had G1/G2 and G3/G4 tumor types which was not statistically significant ($p = 0.2$) [19].

According to results above, NLR could potentially be indicative of cancer grade.

NLR and tumor size and location

In 2 studies reported the role of NLR in differentiating tumor size and location [2, 21]. Jiao Hu et al. found no significant correlation between NLR and tumor size ($p = 0.9$). In a similar assessment, Kasuga et al. reported no significant correlation between the tumor's location (gland, foreskin, and shaft) and NLR ($p = 0.3$) [2]. As such, NLR does not demonstrate to be an independent predictor for tumor size and location.

NLR and response to cancer treatment

In 4 studies, the association between NLR and the patients' response to cancer treatment was assessed [7, 8, 19, 20]. In the study of Azizi et al., the optimal threshold of NLR to assess treatment efficacy in PSCC patients was determined to be 3 [19]. No statistically significant difference in receipt of neoadjuvant or adjuvant treatments between NLR groups was reported ($p > 0.05$). Additionally, Buonerba et al. evaluated NLR as a predictive factor of response to treatment but found no significant correlation with an NLR cut-off of 5 (OR: 3.36; 95% CI: 0.84, 13.44; $p = 0.09$) [7].

Contrarily, Jindal et al. found a correlation between NLR values and the type of surgery a PSCC patient experienced [20]. Of the PSCC patients with an NLR > 3, 47% underwent a partial penectomy, and 79% underwent a total penectomy (no *p*-value was reported). Moreover, Hu et al. reported a significant difference in receiving initial treatment for patients with varying values of NLR

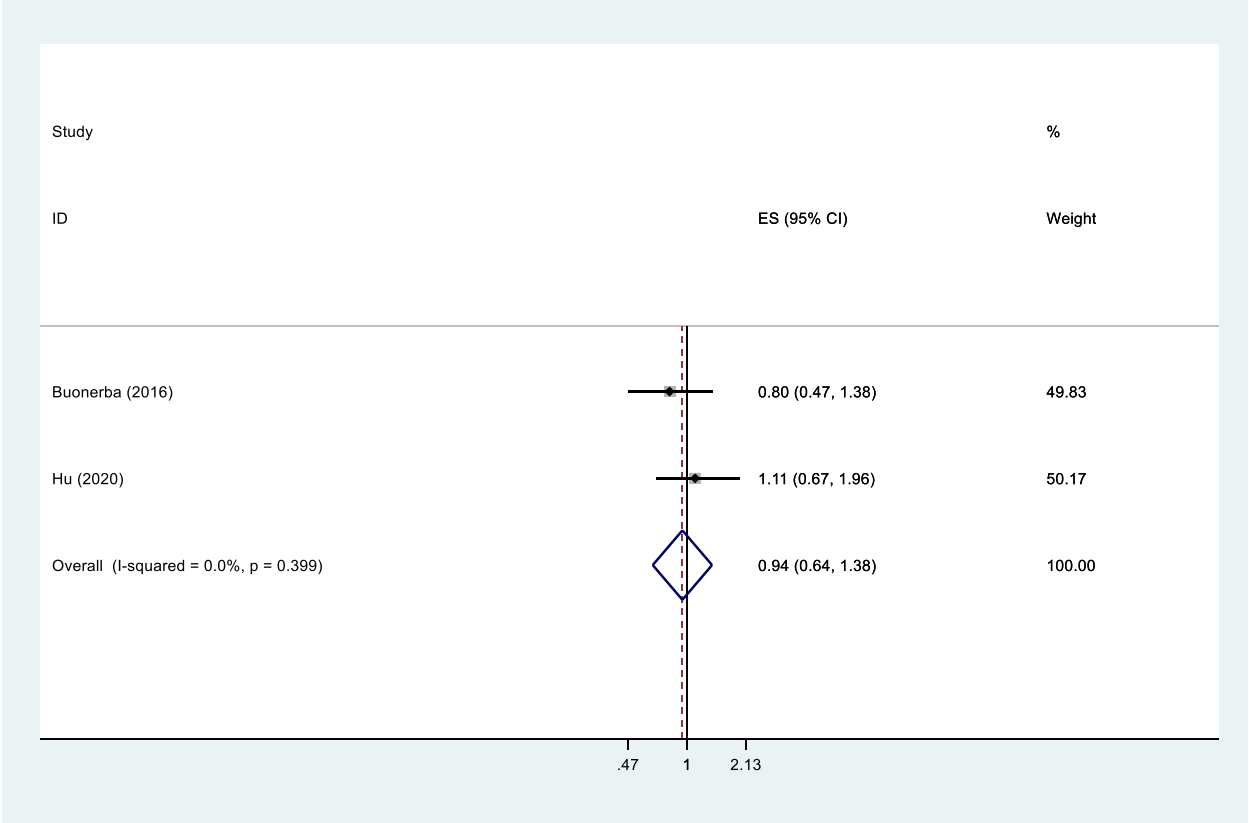

Fig. 5 Meta-analysis of the association of NLR with PFS

[8]. For patients with NLR ≤ 2.94, 6% underwent surveillance and 97% underwent surgery treatment. Likewise, for patients with NLR > 2.94, 19% underwent surveillance and 80.88% underwent surgery treatment ($p = 0.004$).

Due to ongoing controversy, the debate continues about the association between NLR and cancer treatment. Further research which specifically takes this variable into consideration needs to be conducted. According to results above, NLR could potentially be indicative of cancer grade.

Discussion

Our systematic review had three findings. Firstly, an elevated NLR level was a strong prognostic determinant for lower CSS, and DFS. Secondly, patients with higher NLR values experienced a higher rate of metastasis and lymph node involvement. Thirdly, NLR was not an independent determinant for predicting PFS, OS, RFS, or tumor stage. An elevated NLR has been associated with unfavorable survival outcomes in numerous urologic cancers including renal cell carcinoma and urothelial carcinoma [19]. Pond et al. were the first to report an association between NLR and outcomes in PSCC [18]. In this context, our systematic analysis highlights prospective studies that show varying degrees of support for the prognostic capability of the NLR in predicting OS, CSS, and other variables.

The majority of the studies included assess the relationship between NLR and patient survival, with respect to OSS, CSS, DSS, and DFS, and reported a strong link between NLR and patient could be inferred. Kasuga et al. explored the role of NLR before a radical penectomy as a possible prognostic indicator for 41 men diagnosed with PSCC [2]. From that study, the authors show that patients with higher NLR (≥ 2.8) have worse CSS ($p = 0.023$) when compared with those patients with a lower NLR (< 2.8) using a univariate analysis. Additionally, the authors performed a multivariable analysis that did not demonstrate any significant prognostic factor. These findings are in agreement with Tan et al. ($p < 0.001$), Azizi et al. ($p < 0.001$), Zhou et al. ($p = 0.04$) [13, 17, 19]. Also, a number of researchers sought to establish a relationship between NLR and lymph nodal and distant metastasis. Hu et al. reported higher rates of metastasis and recurrence for patients with high NLR (> 2.94) ($p = 0.02$) [8]. Their results agree with the findings of Jindal et al. which shows a high NLR was significantly associated with the presence of pathological inguinal node involvement ($p = 0.001$) [20]. In accordance with their results, Jiao Hu

et al. and Hou et al. revealed NLR was an independent prediction of LNM ($p < 0.01$, $p = 0.04$, respectively) [21, 22].

The underlying mechanisms between the association of high NLR and poor outcome of PSCC patients is poorly understood. To begin to elucidate possible mechanisms, it is imperative to identify the role of the individual components of the NLR, neutrophils and lymphocytes, in this context. Peripheral blood neutrophil counts are increased in patients with cancer. Tumors secrete G-CSF (granulocyte colony-stimulating factor) which alters the neutrophil release and retention balance in the bone marrow, which is ultimately responsible for this increase in blood neutrophils [23]. One mechanism by which increased neutrophil count and subsequent increased NLR may lead to worse PSCC outcomes is through immunosuppression in the tumor microenvironment. It has been demonstrated that neutrophilia inhibits the immune system by suppressing the cytolytic activity of numerous immune cells such as activated T cells, natural killer cells, and lymphocytes [24]. Neutrophils have been demonstrated to mediate this effect in the tumor microenvironment through modulation of several pathways, including through the induction of nitric oxide synthase and upregulation of TGF-β (transforming growth factor-β) [25–27]. In addition, neutrophils also have been shown to contribute to tumor propagation through the production of reactive oxygen species and enzymes such as proteases within the tumor microenvironment [28, 29]. They may even contribute to metastasis through production of cytokines [30, 31]. A mediating mechanism by which these substances that are produced by neutrophils contribute to tumor propagation and metastasis is through chronic inflammation, a process already demonstrated to be prevalent in the pathogenesis of PSCC [32, 33]. Neutrophils have also been reported to produce tumor growth promoting compounds such as vascular endothelial growth factor, and thus may contribute to stimulating the tumor microenvironment [24]. As such, another possible mechanism driving increased neutrophil count leading to worse PSCC outcomes is through the induction of angiogenesis. Neutrophils have been shown to produce several different substances that ultimately induce angiogenesis within the tumor microenvironment, including proMMP-9 (pro-matrix metalloproteinase-9) and protein Bv8 [34–36]. Indeed, a 2012 study by Al-Najar examined the density of microvessels in patients with PSCC and discovered a widely variable degree of microvessel density found across 64 PSCC patients [37]. This suggests that angiogenesis, which is at least partially mediated by neutrophils, has been found to be present and variable in patients with PSCC. Gunia et al. further demonstrated that overexpression of periostin, which has been previously shown to increase angiogenesis and invasion in SCCs (squamous cell carcinomas), correlated with increase tumor size and histologic grade of PSCCs [38]. Thus, increased neutrophil-induced angiogenesis leading to worse prognostic factors in PSCCs is one explanation for increased NLR leading to poor outcomes of PSCC consistent with the results of the present study.

Further, the role of lymphopenia in this context is less clear in the literature, with results from studies indicating a variability in isolated peripheral lymphocyte count in cancer patients [39, 40]. Results from these studies generally focus on variabilities in lymphocyte subsets [41, 42]. Porcellato et al. conducted a preclinical study focusing on isolating components of the tumor microenvironment in equine PSCCs. Results indicated a significantly increased amount of CD3 + and FoxP3 + lymphocytes in the tumor microenvironment compared to healthy tissue [43]. A 2012 study examined similar tumor microenvironment constituents in patients with PSCC, finding that increased lymphocyte migration into the tumor microenvironment was associated with a significantly higher rate of groin metastasis ($p < 0.01$) [33]. More recently, FoxP3 + lymphocyte expression in the tumor microenvironment has also been demonstrated to correlate with increased thickness of tumors in patients with PSCC [44]. Additionally, in a 2018 retrospective study that examined constituents of the tumor microenvironment in 213 PSCC patients, increased T-cell expression of programmed death ligand-1 (PD-L1) was observed within the tumor microenvironment that was attributed to significantly decreased DSS [45].

Taken together, it follows that measured peripheral lymphopenia may be a function of increased migration of lymphocytes into the tumor microenvironment in PSCC, potentially accounting for increased NLR seen in these patients, as the results of our present study suggest. As it currently stands, the evidence for the significance of lymphopenia as a driving factor behind the diagnostic utility of NLR for PSCC is less convincing than the evidence for the role of neutrophilia as explained above. However, increased migration of several subtypes of lymphocytes into the tumor microenvironment have now been demonstrated in both preclinical and clinical models and have been postulated to contribute to several poor prognostic factors, including increased tumor size and potential for metastasis. This likely confounds the magnitude of increased NLR found in these patients, adding to its significance in this context. Thus, the efficacy of the NLR on prognosis of PSCC may well be a function of the various pro-tumorigenic effects of neutrophilia and lymphopenia, making this a potentially useful diagnostic and prognostic marker for clinical use in PSCC patients. In recent years, there has been an increased amount of effort and

resources dedicated to the development of biomarkers which can help customize the therapeutic approach to the need of a specific patient with cancer. Altered levels of NLR in the blood may be useful in this attempt to tailor therapy for patients with PSCC, where there is a lack of reliable biomarkers for diagnostic purposes and subsequent prognostication.

Limitations

The systematic review had three major limitations. Firstly, due to the absence of prospective research on this topic, all studies included were retrospective. To verify the findings presented in this systematic review, further prospective analysis should be conducted in the future. Secondly, a meta-analysis could not be performed due to significant heterogeneity of the studies included, conflicting results in the literature, and the lack of a significant number of studies suitable for a meta-analysis. Also, the variation in NLR cut-offs among the studies is the third limitation of our study.

Conclusion

In conclusion, this systematic review highlights the potential NLR has to be a critical diagnostic and prognostic factor in PSCC. As it currently stands, the data collected from these retrospective studies exhibit variable levels of support for NLR as a predictive indicator for PSCC. There was a significant association between NLR levels and the prognosis, nodal stage, and anatomical tumor stage of PSCC patients. Furthermore, an elevated NLR can indicate lower CSS, worse OS, shorter DSS and DFS, and a higher rate of metastasis and lymph node involvement. Notably, NLR was found to have no association with the stage, grade, location, and size of the tumor. Prospective trials are needed to establish a more definitive role of NLR in the management of PSCC.

Abbreviations

NLR	Neutrophil to lymphocyte ratio
PSCC	Penile squamous cell carcinoma
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
NOS	Newcastle–Ottawa Scale
HR	Hazard ratio
CI	Confidence interval
HPV	Human papillomavirus
LVI	Lymphovascular invasion
CBCs	Complete blood counts
OS	Overall survival
CSS	Cancer-specific survival
SD	Standard deviation
OR	Odds ratio
ROC	Receiver operating characteristic
PFS	Progression-free survival
DSS	Disease-specific survival
DFS	Disease-free survival
ILND	Inguinal lymph node dissection
LNM	Lymph node metastasis
pN+	Pathologic node-positivity
G-CSF	Granulocyte colony-stimulating factor
TGF-β	Transforming growth factor-β
proMMP-9	Pro-matrix metalloproteinase-9
SCCs	Squamous cell carcinomas
PD-L1	Programmed death ligand-1

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Authors' contributions

ShKh contributed to the conception of the study, performed the data analyses, and supervised the project; S.S searched the articles; S.F.N and Ar.B reviewed all identified articles for eligibility; A.C and B.L-W assessed the quality of studies; S.B reviewed all identified articles for eligibility; A.Gh and A.B assessed the quality of studies; S.B and Sh.Kh wrote the manuscript. M.M.S revised the manuscript. All of the authors read and approved the final manuscript.

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Declarations

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