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Evaluation of C-reactive protein levels in patients with penile cancer: a systematic review and meta-analysis

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Abstract

Background C-reactive protein (CRP) is an essential biomarker for evaluating penile cancer prognosis. Previous studies have reported conflicting outcomes concerning the correlation between CRP levels and penile cancer prognosis. This study aimed to investigate this relationship by conducting a meta-analysis of published literature.

Methods A systematic literature search was conducted using the Cochrane Library, PubMed, and Embase databases to analyze the prognostic significance of serum CRP levels in individuals diagnosed with penile cancer. Pooled risk estimates were calculated using fixed-effects or random-effects models, depending on the degree of interstudy heterogeneity.

Results Sixty-eight articles were reviewed, identifying 8 articles and 989 patients that met the inclusion criteria for the meta-analysis. The pooled analysis revealed a significant association between serum CRP levels and adverse outcomes in penile cancer cases (hazard ratio [HR] = 2.37, 95% confidence interval [CI] = 1.46–3.858). Additional meta-analysis findings showed a negative correlation between elevated CRP levels and overall survival (HR = 1.97, 95% CI = 1.23–3.16, $p<0.01$), cancer-specific survival (HR = 3.42, 95% CI = 1.38–8.47, $p<0.01$), and disease-specific survival (HR = 3.23, 95% CI = 1.79–5.8, $p<0.01$) in patients with penile cancer. In the subgroup analysis, the HRs (95% CI) were 1.66 (0.61–4.48) in Europeans, 3.08 (2–4.74) in Asians, 3.04 (1.93–4. 77) in Chinese, 2.07 (1.21–3.53) in the group of cutoff value ≥ 5 mg/L, 2.43 (1.44–4.12) in the group of cutoff value ≥ 10 mg/L, 2.12 (1.04–4.32) in the group of surgical intervention, and 3.07 (1.76–5.37) in the group of multitherapy. This study also found a significant relationship between serum CRP levels and lymph node metastasis in patients with penile cancer (relative risk = 2.27, 95% CI = 1.61–3.2, $p<0.01$).

Conclusion This meta-analysis indicates that increased CRP levels were associated with a poorer prognosis in penile cancer. Therefore, CRP levels could potentially serve as a prognostic indicator of penile cancer.

Keywords C-reactive protein, Penile cancer, Meta-analysis

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Introduction

Penile cancer is a rare malignant tumor of the male reproductive system with a poor prognosis among patients with an advanced stage. According to the International Agency for Cancer Research, the number of new penile cancer cases in 2020 was 36,068 globally, with the highest incidence occurring in the age group > 60 years [1]. Regional lymph node metastasis (LNM) at all stages (pN1-3) is associated with a lower survival rate (approximately 46%). The presence of extranodal extension and lymphatic infiltration significantly increases the risk of death and tumor recurrence in patients with advanced-stage penile cancer [2]. Therefore, identifying the potential predictors of therapeutic efficacy and long-term prognosis in patients with advanced penile cancer is crucial.

Previous studies have found that tumor stage, histological grade, lymphatic and vascular infiltration, and histological subtypes are closely associated with poor prognosis in advanced penile cancer [3, 4]. Recent studies indicated that inflammatory processes within the tumor microenvironment (TME) could also be pivotal in the initiation, growth, advancement, and spread of penile carcinomas [5]. Inflammatory reactions, such as leukocytosis, neutropenia, and thrombocytopenia, commonly occur due to the growth and spread of cancer cells in advanced penile cancer. C-reactive protein (CRP), a widely used marker for systemic inflammation in standard clinical diagnostics, has been identified as being correlated with unfavorable prognosis in a range of cancers, including breast [6], bladder [7], and lung [8] cancers. Higher CRP levels may correlate with more aggressive cancers or advanced diseases, reflecting the extent or severity of the malignancy. CRP can participate in inflammatory processes within the TME, influencing tumor progression and metastasis.

Elevated CRP levels in patients with cancer may indicate that malignant tumor cells have invaded the surrounding tissues and organs, potentially leading to metastasis. Additionally, CRP can influence the immune function of patients and contribute to related complications [9]. Chen et al. [10] found a significant correlation between elevated circulating CRP levels, LNMs, and survival rates in patients with oral squamous cell carcinoma. Multivariate analysis has revealed that high CRP levels serve as indicators or predictive factors for lymph node and distant metastases in T3 colorectal cancer [11]. Some researchers have suggested that elevated CRP levels are associated with poor prognosis in patients with advanced penile cancer and that monitoring changes in CRP levels during treatment may aid in assessing treatment response and clinical management decisions [12, 13]. However, other researchers have argued that there may be no significant correlation between CRP levels and prognosis in patients with advanced penile cancer. Ghoshal et al. [14] conducted a serological assessment of inflammatory markers in 50 men with penile cancer and found no statistically significant correlation between CRP levels and the risk of penile cancer. They noted limitations due to technical constraints that prevented quantifying any CRP level < 10 mg/L, potentially leading to underestimating the relationship between serum CRP levels and penile cancer. Therefore, our investigation undertook a comprehensive meta-analysis of all reputable scholarly literature to estimate the correlation between CRP levels and the prognosis of penile carcinoma.

Materials and methods

Literature search strategy

We assessed the Cochrane Library, PubMed, and Embase databases from inception to August 1, 2024. The heading terms and keywords were "C-reactive protein," "C reactive protein," or "CRP," combined with "Penile Cancer." Additionally, we evaluated other eligible articles among the retrieved articles to identify potential articles that met the criteria. This study was registered in Prospero (registration number: CRD 42023432350).

Inclusion and exclusion criteria

The study selection process included an independent review of all papers by two authors (S.Du and T.Qin). Uncertainties and discrepancies were resolved through consensus discussions with senior researchers. For inclusion in the meta-analysis, studies were required to meet the following criteria: (a) using a cohort or case-control study design, (b) reported results on serum CRP levels, (c) using penile cancer survival rate as the outcome of interest, and (d) reported estimates of relative risk (RR) (or OR [odds ratio] and HR [hazard ratio] estimates in case-control and cohort studies, respectively) and their corresponding 95% confidence intervals (CI). When duplicate studies were identified, we included the subsequent publication or one that provided more detailed information. Review articles and editorials that contained original data were included in the analysis, whereas abstracts were excluded.

Search strategy and data abstraction

After identifying the studies that met the inclusion criteria, we extracted standardized data from the literature, including the following: name of the first author, year of publication, nationality, study design (cohort or case study), time of enrollment, duration of follow-up for cohort studies, subjects and cancer cases, subject characteristics, CRP threshold (mg/L), CRP markers, and method of clinical outcome assessment (RR, OR, or HR estimates, and their corresponding 95% CI for continuous variables). We also extracted adjusted risk estimates

for each study, considering the maximum number of potential confounders [15].

Literature quality evaluation and statistical analysis

We evaluated the quality of the included literature on treatment using the Newcastle-Ottawa Quality Rating Scale (NOS). This scale assesses the selection of study populations, the comparability between groups, and the exposure factors. Only studies with scores of >5 were included in the meta-analysis. The NOS evaluation was completed independently and cross-blinded by two researchers. Any disagreements were resolved by a third person. Stata software was used to calculate the combined results of elevated CRP levels and penile cancer risk using RR, OR, or HR for each natural log unit change in CRP, along with their corresponding 95% CI. We assessed statistical heterogeneity among eligible studies by performing the Cochran's Q test ($p<0.1$ indicating high statistical heterogeneity) and I^2 (with values of 25%, 50%, and 75% representing low, medium, and high heterogeneity, respectively). Studies were considered homogeneous if $p>0.1$ and $I^2 \leq 50\%$, and effect values were combined using a fixed effects model. Sensitivity analyses were conducted to assess the stability of the combined effect values by changing the data analysis model to account for the heterogeneity between studies. Finally, we conducted funnel plot analysis and statistical tests to detect publication bias.

Results

Characteristics of the included studies

A preliminary search yielded 68 publications. Among these, 46 papers were retrieved using EndNote software, and an additional 20 papers were selected based on a preliminary screening of their titles and abstracts. Twelve papers were excluded because they did not meet the specified inclusion and exclusion criteria, resulting in the final selection of eight retrospective cohort studies (Fig. 1). The essential characteristics of the selected studies with a total cumulative sample size of 989 cases are detailed in Table 1. The characteristics of the eight studies are summarized in Table 1. One study was conducted in Japan, four in China, one in Sweden, and two in Germany. These studies collectively involved 989 patients, with five focusing solely on surgical intervention, while the remaining three implemented a combination of treatments, such as chemotherapy, radiation, and surgery. The CRP cutoff values varied across studies, ranging from 2.1 mg/L to 15 mg/L, with the majority opting for 5 mg/L or 10 mg/L as the standard threshold. All eight studies provided documented HR. The NOS scores of the included studies were ≥7 points, indicating a high quality. The quality assessments of these studies are summarized in Table 1.

Meta-analysis

The eight studies yielded $I^2=58.5\%$ (>50%) for the heterogeneity test and $p=0.019$ (<0.1) for the Q test, suggesting a strong heterogeneity among the studies. Thus, the random effects model was selected for the meta-analysis. The forest plot is shown in Fig. 2. The meta-analysis results given by random effects showed that elevated CRP caused penile cancer adverse outcomes in the control group (HR = 2.37, 95% CI = 1.46–3.85), implying that elevated CRP might increase the risk of poor prognosis in penile cancer.

A subgroup analysis was conducted to explore further the correlation between elevated CRP levels and poor prognosis in penile cancer. Eight studies were categorized based on "country," "cutoff value," and "treatment style."

Upon stratification by "country," the analysis comprised three studies from European countries (HR = 1.66, 95% CI 0.61–4.48), five from Asian countries (HR = 3.08, 95% CI = 2–4.74), and four specifically from China (HR = 3.04, 95% CI = 1.93–4.77) (Fig. 3).

When segregated by "cutoff value," four studies fell into the "≥ 10 mg/L" group (HR = 2.43, 95% CI = 1.44–4.12) and six into the "≥ 5 mg/L" group (HR = 2.07, 95% CI = 1.21–3.53) (Fig. 4). One study [19] selected "≥ 2.1 mg/L" as their threshold, resulting in their exclusion from the subgroup analysis, leaving just seven studies in this subgroup.

Categorized by "treatment style," the "surgical intervention" category comprised five studies (HR = 2.12, 95% CI = 1.04–4.32), and the "multitherapy" group included three studies (HR = 3.07, 95% CI = 1.76–5.37 (Fig. 5).

In the overall survival (OS) analysis, a random model was employed to determine the combined HR and the corresponding 95% CI. The results indicated a significant association between CRP levels and OS, with an observed combined HR of 1.97 (95% CI, 1.23–3.16). Regarding cancer-specific survival (CSS) and disease-specific survival (DSS), elevated CRP levels were found to be a predictor of adverse outcomes, yielding combined HRs of 3.42 (95% CI, 1.38–8.47) for CSS and 3.23 (95% CI, 1.79–5.80) for DSS. Therefore, CRP level has emerged as a noteworthy prognostic biomarker for OS, CSS, and DSS (Fig. 6).

The T, N, and M grades play pivotal roles in the prognosis of penile cancer. However, only two studies have explored the association between serum CRP levels and LNM. Thus, our analysis investigated the correlation between serum CRP levels and the N grade. These two studies examined the correlation between increased serum CRP levels and N staging (specifically N0 versus N1–3), yielding an RR of 2.27 (95% CI = 1.61–3.2) (Fig. 7).

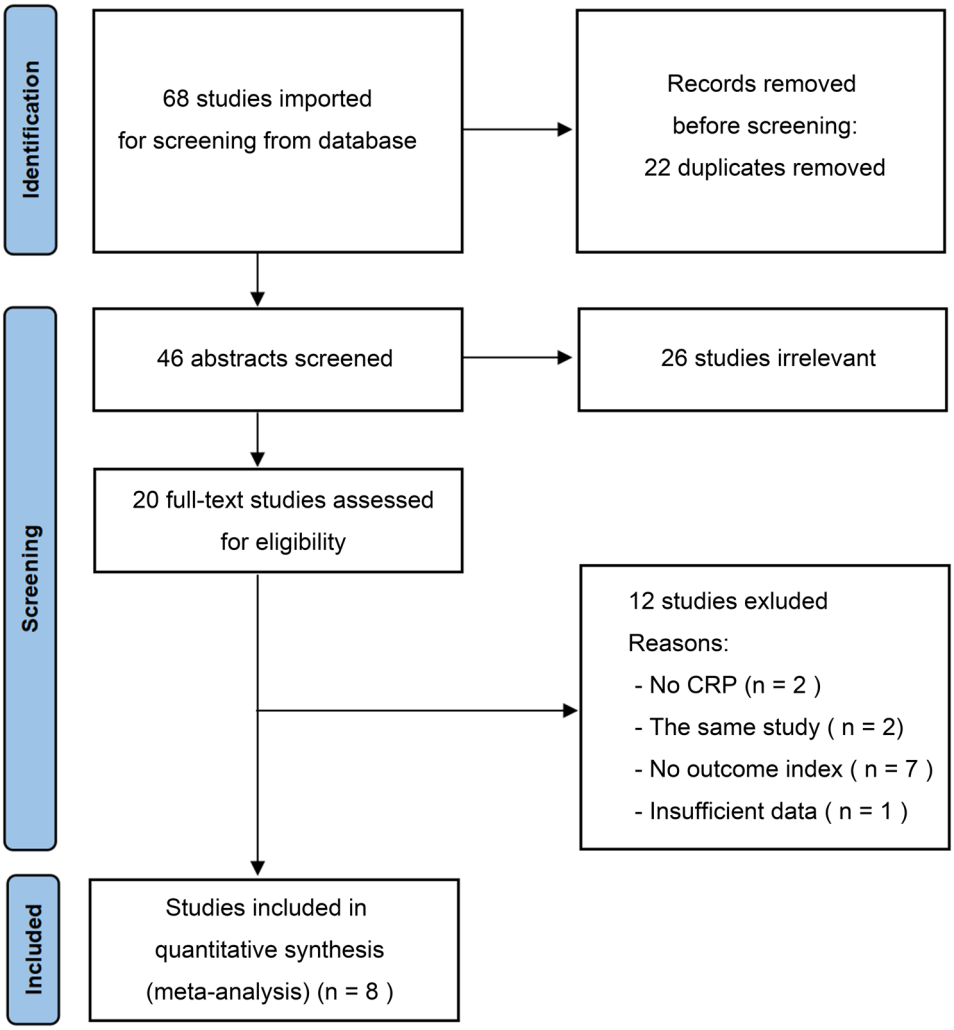

Fig. 1 Flow diagram of systematic literature search

Publication bias and sensitivity analysis

Sensitivity analyses were conducted to mitigate potential heterogeneity stemming from variations in the quality of the included studies and assess their ramifications on the overall effect. We observed substantial heterogeneity arising from the study by Gholshal (2017), which significantly affected the combined data (Supplementary Fig. 1). After excluding this particular study, heterogeneity within the pooled data markedly decreased (Supplementary Fig. 2). The elevated heterogeneity observed in the study by Gholshal might stem from the sample size in the original article or variances in the detection methodologies employed.

As depicted in Fig. 8, Begg's funnel plots revealed evidence of publication bias, whereas Egger's test indicated no significant publication bias in the prognosis of penile cancer ($p = 0.173$). The trim-and-fill method [21] maintained the reliability of the analysis (Supplementary Fig. 3) by incorporating four studies with small sample sizes. The corrected HR (95% CI) was 2.65 (1.89–4.44).

Discussion

Penile cancer, a rare yet highly aggressive form of malignancy, has a profound and deleterious effect on the well-being of men. This condition, characterized by its rapid progression and potential for severe complications, poses a significant threat to the health and quality of life of affected individuals. Owing to insufficient awareness of this disease, many patients delay seeking medical attention. Therefore, identifying reliable prognostic factors is crucial for recognizing high-risk patients with poor outcomes. In this study, we conducted a systematic review and meta-analysis of 989 patients from Western and Eastern countries to evaluate the prognostic value of CRP expression levels in patients with penile cancer. The findings revealed a significant correlation between elevated CRP levels and diminished survival probabilities among

Table 1 Characteristics of the included studies

First author	Year	Study Year of recruitment	Country	Study design	Age, y	Tumor stage *N*(%)	LNM *N*(%)	CRP thresh-old (mg/L)	No. of Subjects/Cases	Outcome assessment	Hs-CRP/CRP	HR(95%CI)	Qual-ity scores
Steffens, S. [13]	2013	1990–2010	Germany	PC	65.4(33–92)	≥T2:36 (45.6%)	16 (25%)	15	79/34 (43%)	Institution	CRP	5.58(1.79 ~ 17.42)	8
Li, Z.S. [16]	2016	2007–2014	China	PC	50(25–86)	T2:68 (54.8%) ≥T3:14 (11.3%)	60 (48.4%)	4.5	124/54 (43%)	Institution	CRP	8.416(0.976 ~ 72.583)	8
Li, Z. [17]	2016	2005–2014	China	PC	52 (25–86)	≤T1:57(33.1%); T2:90(52.3%); ≥T3:25(14.5%)	84 (48.8%)	8.7	172/59 (34.3%)	Institution	CRP	3.706(1.531–8.972)	8
Ghoshal, A. [14]	2017	Not given	Sweden	PC	51(10.6)	Not given	Not given	10	50/8(12%)	Laboratory examinations	CRP	0.59(0.25 ~ 1.41)	7
Zhou, Q. [18]	2018	2009–2015	China	PC	54	T2-4:77 (97.5%)	47 (59.5%)	5.0	79/22(28%)	UCC	CRP	2.465(1.064 ~ 5.712)	7
Draeger, D. [2]	2021	2005–2019	Germany	PC	65.4 (13.8)	T2:107 (69%) T3:43 (28%) T4:6 (4%)	All;100%	10	156/74(47%)	Department	CRP	1.66(1.11 ~ 2.53)	8
Kawase, M. [19]	2022	2008–2019	Japan	PC	74 (63–82)	Tis:1(1.6%); T1: 21(32.8); T2:14(21.9%); T3:17(26.6%); T4: 11(17.2%)	26 (40.7%)	2.1	58/28 (48%)	Department	CRP	3.536 (0.86–14.52)	7
Xue, T. [20]	2023	2006–2021	China	PC	55	T1:100(36.9%);T2:44(16.2%);T3:115(42.4%);T4:12(4.4%)	104(38.3%)	10	271/56 (20.7%)	Department	CRP	2.77(1.36–5.64)	8

PC: prospective cohort; UCC: University Cancer Center; LNM = lymph node metastasis: CRP = C-reactive protein; Hs-CRP = high-sensitivity C-reactive protein

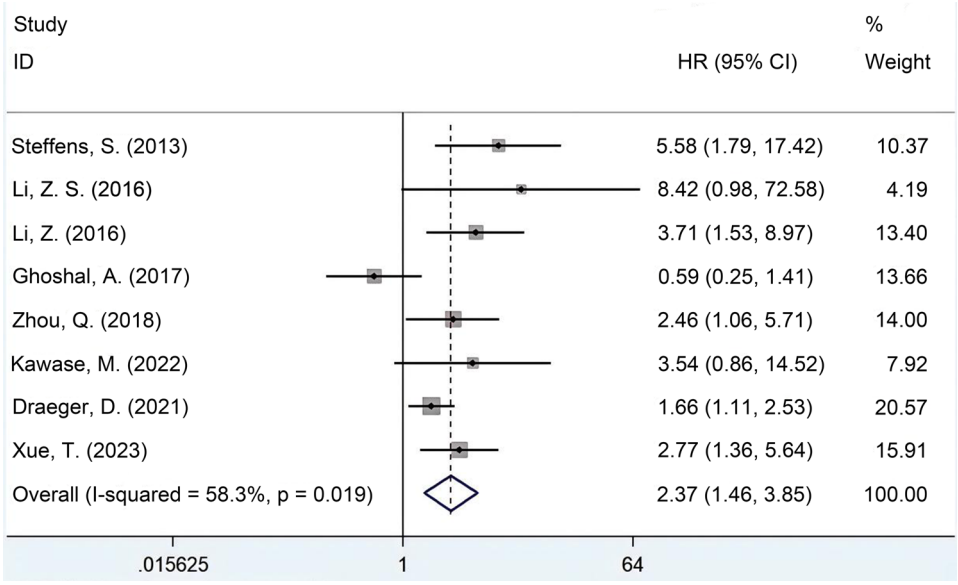

Fig. 2 Forest plots for the estimate of CRP associated with the risk of poor prognosis for penile cancer in the meta-analysis

individuals with penile carcinoma. This association has been observed to affect the OS, CSS, and DSS metrics, underscoring the prognostic implications of CRP as a biomarker in this patient population. Subgroup analyses demonstrated the persistent impact of elevated CRP levels on survival rates, considering factors such as country, treatment method, CRP cutoff values, and lymph node metastasis.

Tumor initiation and progression constitute a multifaceted process intricately linked to the conditions and biological attributes of tumor cells. Inflammation contributes substantially to cancer progression and dissemination. This is achieved by releasing bioactive factors into the tumor microenvironment, including growth factors that stimulate cell proliferation and proangiogenic factors that induce neovascularization, thereby accelerating tumor cell invasion and metastasis [22]. Peripheral blood inflammatory assays offer a convenient and cost-effective means for discerning the extent of inflammatory response. Prior studies have reported inflammatory mediators as prognostic markers in penile cancer, specifically the neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios [23]. Our meta-analysis further confirmed that CRP level holds considerable predictive value for the prognosis of patients with penile cancer.

High CRP levels are associated with poor prognosis and can predict the survival time and recurrence rate of malignant tumors [24]. Postoperative CRP levels are closely related to the prognosis of breast [25], gastric [26], and colorectal [27] cancers. A comprehensive study [17] that specifically concentrated on the surgical management of metastatic penile cancer revealed a significant association between elevated CRP levels and an increased risk of tumor recurrence after surgical intervention. In the prognostic indicators for penile cancer, our data demonstrate that CRP levels are statistically significant predictors of OS, CSS, and DSS ($p < 0.05$). An HR > 2 is currently considered a strong predictive factor threshold. In our meta-analysis, elevated CRP levels are reliable predictors of adverse outcomes related to CSS and DSS, with combined HRs of 3.42 (95% CI, 1.38–8.47) for CSS and 3.23 (95% CI, 1.79–5.80) for DSS.

Similarly, changes in CRP levels can serve as valuable biomarkers reflecting the response of patients with malignant tumors to anticancer therapy. Several studies have demonstrated a close relationship between decreased CRP levels and treatment response in lung cancer [28, 29], lymphoma [30], and other malignant tumors. Niklas et al. conducted both retrospective and prospective validation cohort studies. They found that early CRP kinetics strongly predicted immunotherapy response in patients with lung cancer, regardless of the histological subtype. Specifically, CRP kinetics within the first four weeks of treatment is a cost-effective and easily identified biomarker that can predict the response to immunotherapy [29]. Other factors, such as infection and inflammation, may influence CRP levels. It is highly advisable to incorporate biomarkers into a comprehensive prognostic assessment system to enhance the precision and reliability of prognostic evaluations. Recently, significant advancements have been made with the introduction of the modified Glasgow Prognostic Score (mGPS), specifically designed to evaluate the prognosis of metastatic penile cancer using inflammation-based scoring. The mGPS meticulously assesses elevated CRP levels > 10 mg/L and hypoalbuminemia falling < 35 g/L

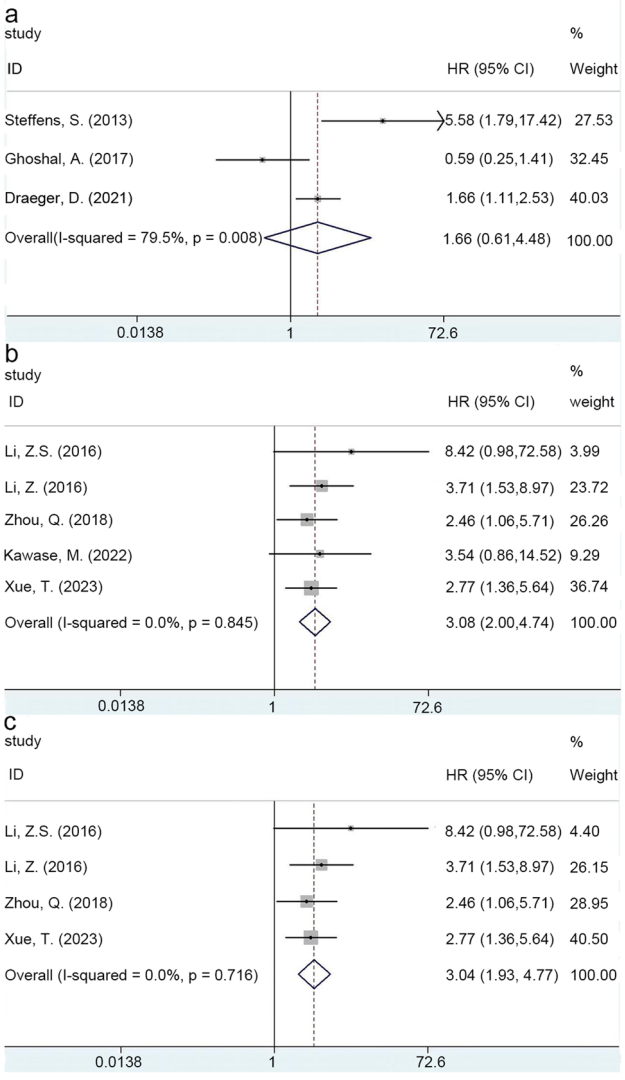

Fig. 3 Subgroup Analyses of Pooled HR for High Serum CRP Expression and the risk of poor prognosis for penile cancer. (**a**) European subgroup (**b**) Asian subgroup (**c**) Chinese subgroup

[2]. It has emerged as a valuable indicator for determining prognosis and treatment responsiveness in patients with metastatic penile cancer .

Studies on using potential indicators to predict penile squamous cell carcinoma metastasis to the inguinal lymph nodes are crucial in clinical practice. Inflammation is key in developing and spreading primary penile squamous cell carcinoma to lymph nodes [31]. CRP levels are associated with poor outcomes in patients with penile squamous cell carcinoma, although there is mixed evidence regarding their ability to predict LNM specifically [32]. In the subgroup analysis, elevated serum CRP levels were closely associated with LNM, indicating a potential correlation (RR = 2.27, 95% CI = 1.61–3.2). This meta-analysis had several limitations, such as methodological differences and restrictions in the patient populations included in the original articles and systematic reviews/meta-analyses. Despite these limitations, by synthesizing current clinical research data, it has been further validated that elevated CRP levels may be valuable in predicting LNM in patients with penile cancer. Further clinical data and studies are required to validate and strengthen this conclusion. This emphasizes the need for further research to explore additional indicators that can enhance the predictive accuracy of metastasis in penile squamous cell carcinoma to improve patient outcomes.

There are some limitations in evaluating the results of this research. First, there was heterogeneity in the relevant data provided by different researchers involved in the meta-analysis, including different source countries, CRP diagnostic methods, and CRP biomarkers. Second, the subgroup analysis only presented the relationship between the source country, LNM, CRP concentration, and prognosis of patients with penile cancer. This was mainly because not all relevant studies provided comprehensive information. Owing to the limitations of the available data, it was not possible to evaluate the

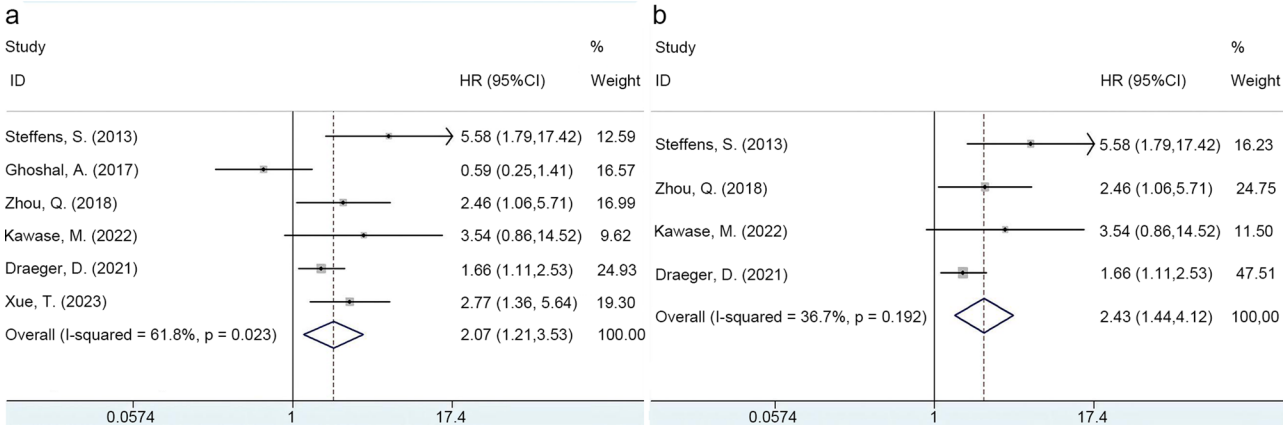

Fig. 4 Subgroup Analyses of Pooled HR for High Serum CRP Expression and the risk of poor prognosis for penile cancer. (**a**) cut-off = 5 mg/L; (**b**) cut-off = 10 mg/L

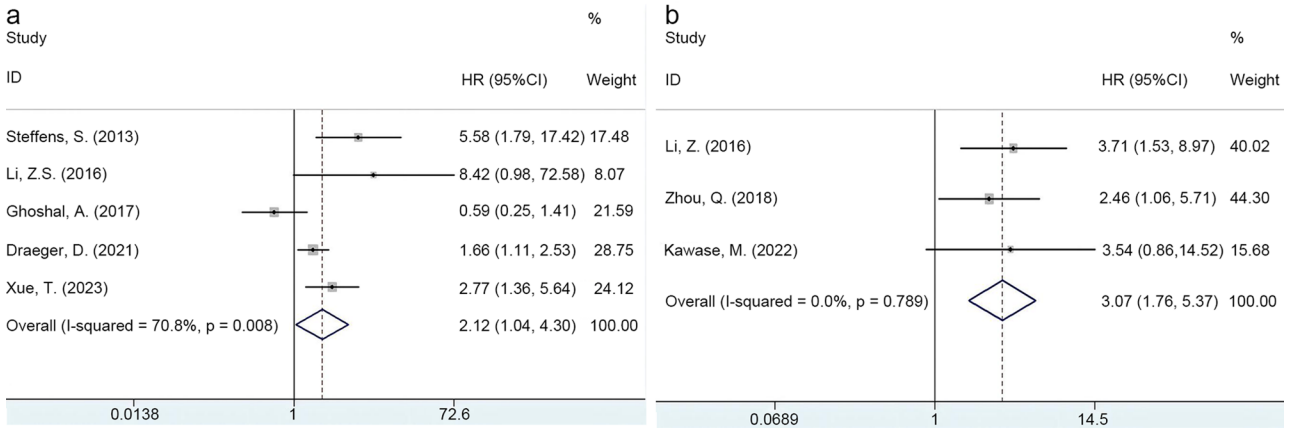

Fig. 5 Subgroup analyses of Pooled HR for High Serum CRP Expression and the risk of poor prognosis for penile cancer. (**a**) "surgical intervention" category (**b**) "multi-therapy" category

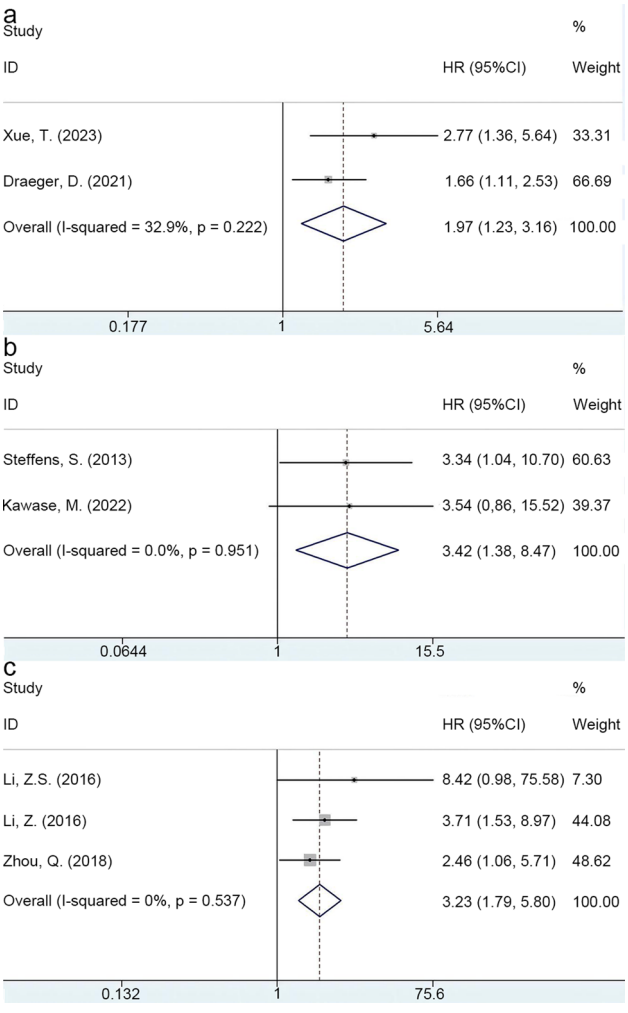

Fig. 6 Forrest plots of studies evaluating hazard ratios with 95% confidence interval (95% CI) for high CRP levels as compared with low levels. Survival data are reported as overall survival (**a**), cancer-specific survival (**b**), and disease specific survival (**c**)

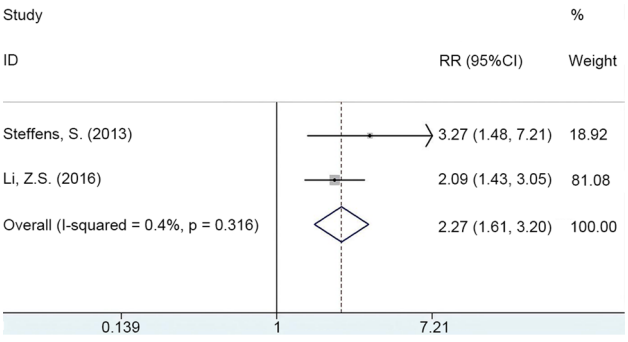

Fig. 7 Subgroup Analyses of Pooled RR for serum CRP levels associated with lymph node metastasis in patients with penile cancer

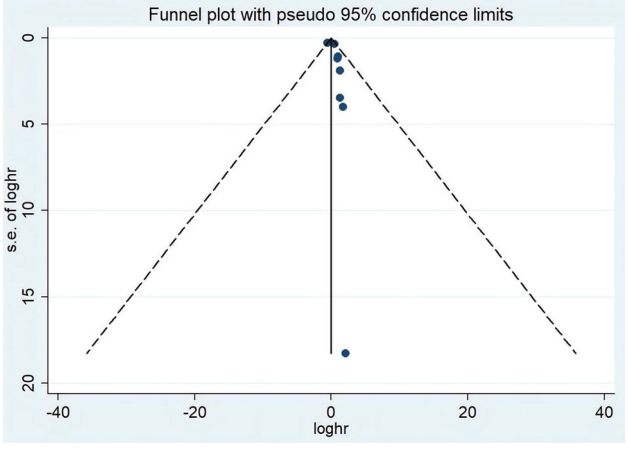

Fig. 8 Funnel plot for analysis results of publication bias

correlation between CRP levels and the risk of penile cancer stratified by TNM staging. Further large prospective studies are necessary to validate the prognostic value of serum CRP levels in patients with penile cancer and its predictive potential for assessing the efficacy of antitumor therapy. Finally, there was a publication bias in this systematic review, which may be attributed to several

factors. Current research articles on penile cancer are relatively limited. We only included articles published in English and Chinese during the literature collection process, potentially overlooking unpublished studies with insignificant results. However, after incorporating the four missing studies into the funnel plot, no significant changes were observed in the overall results. We believe that this meta-analysis is reliable.

Conclusions

Our meta-analysis indicates that CRP expression is associated with an unfavorable prognosis in penile cancer. CRP is a significant predictor of survival outcomes, with a notable impact on CSS and DSS. Our comprehensive findings indicate that CRP is promising as a biomarker for the prognostic evaluation of patients with penile cancer.

Abbreviations

CRP	C-reactive protein
CI	Confidence interval
CSS	Cancer-specific survival
DSS	Disease-specific survival
FIGO	International Federation of Gynecology and Obstetrics
HR	Hazard ratio
NOS	Newcastle-Ottawa Quality Assessment Scale
LNM	Lymph node metastasis
OR	Odds ratio
OS	Overall survival
PFS	Progression-free survival
RR	Relative risk

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

S.Du analyzed the data and T.Qin wrote the manuscript. K.Zhang, L.Wang, L.Zong and W.Yu conceived the study and stastics analysis; L.Wang assisted in revising the manuscript; All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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