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RESEARCH ARTICLE

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Prognostic and clinicopathological value of C-reactive protein in patients with bladder cancer: a meta-analysis

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ABSTRACT

Background: The prognostic value of C-reactive protein (CRP) in patients with bladder cancer (BCa) has been widely analysed; however, the results remain conflicting. Therefore, we performed this meta-analysis to identify the precise role of CRP level in predicting BCa prognosis.

Methods: PubMed, Web of Science, Embase and Cochrane Library databases were comprehensively searched until 19 April 2024. The impact of CRP level on predicting the prognosis of patients with BCa was examined using combined hazard ratios (HRs) and 95% confidence intervals (CIs). The relationship between CRP level and BCa clinicopathological characteristics was investigated by combining the odds ratios (ORs) with 95%CIs.

Results: Twenty studies with 7276 patients were enrolled in this study. As revealed by pooled data, elevated CRP levels were markedly related to poor overall survival (OS) (HR = 2.02, 95%CI = 1.41–2.90, $p < .001$), inferior cancer-specific survival (CSS) (HR = 1.46, 95%CI = 1.29–1.66, $p < .001$), shortened recurrence-free survival (RFS) (HR = 1.25, 95%CI = 1.17–1.33, $p < .001$) and dismal progression-free survival (PFS) (HR = 2.28, 95%CI = 1.80–2.90, $p < .001$) in BCa patients. Nevertheless, there was no significant relationship between CRP level and sex, tumour size, tumour grade or lymph node metastasis (LNM) in BCa.

Conclusions: Elevated CRP levels were significantly related to poor OS, CSS, RFS and PFS of BCa patients with BCa. CRP could act as a reliable biomarker for predicting the short- and long-term survival of patients with BCa in clinical practice.

KEY MESSAGES

- As far as we know, this work is the first to investigate the effect of C-reactive protein (CRP) on predicting bladder cancer (BCa) prognosis.
- The combined data demonstrated the elevated CRP level was notably related to poor overall survival (OS), cancer-specific survival (CSS), recurrence-free survival (RFS) and progression-free survival (PFS) of BCa patients.
- CRP could act as a reliable biomarker for predicting short- and long-time survival of BCa patients in clinical practice.

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C-reactive protein; bladder cancer; meta-analysis; prognosis; biomarker

Introduction

Bladder cancer (BCa) has the highest prevalence among all urinary tract cancers. BCa ranks 10th among malignant tumours worldwide in 2020 [1]. It was estimated that 573,278 new cases of BCa were diagnosed and 212,536 deaths due to BCa occurred in 2020 globally [1]. There is an estimated 75% rate of non-muscle invasive BCa (NMIBC) (Ta/T1) in the general population, and it represents a heterogeneous group with varying risks of recurrence and progression to muscle invasive BCa (MIBC) (T2–T4) [2]. NMIBC has favourable prognostic outcomes, with a 5-year overall survival (OS) rate of >90% [3]. The gold standard treatment for localized MIBC is radical cystectomy and pelvic lymph node dissection, with an OS rate of approximately 60% over 5 years [4]. BCa is multicentric in nature, with a high rate of recurrence after surgery, requiring frequent review and long-term follow-up, which is a great burden on healthcare systems. Thus, identifying prognostic indicators for patients with BCa would be helpful for predicting survival and recurrence.

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C-reactive protein (CRP), first detected in the serum of patients with pneumococcal pneumonia in 1930 [5], is a typical acute-phase protein that is primarily generated in the liver. CRP is an indicator of inflammation and a frequently used systemic inflammation marker [6]. As a 'robust biomarker', CRP measurement is one of the most requested laboratory tests because it may provide valuable information in a wide range of clinical conditions [7]. The significance of CRP in various cancers, including breast cancer [8], oesophageal squamous cell carcinoma [9], hepatocellular carcinoma [10], head and neck cancer [11] and pancreatic ductal adenocarcinoma [12], has been explored previously. The prognostic impact of CRP on BCa has been extensively analysed, but the results remain conflicting [13–32]. In certain studies, high CRP served as a significant marker to predict the prognosis of BCa patients [13,17,22,23,27,29], while in others, CRP was not significantly related to the prognosis of BCa [21,28,30,31]. Therefore, we performed the present meta-analysis to identify the precise significance of CRP level in predicting BCa prognosis. Moreover, the relationship between CRP level and BCa clinicopathological features was examined in this meta-analysis.

Materials and methods

Study guideline

This meta-analysis was performed following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [33].

Ethics statement

This meta-analysis relied on previously published data, which exempted the requirement for informed consent and ethical approval.

Literature retrieval

PubMed, Web of Science, Embase and Cochrane Library databases were comprehensively searched until 19 April 2024, using the following strategies: (C-reactive protein or CRP) and (bladder cancer or bladder carcinoma or bladder tumour or urinary bladder cancer or urinary bladder neoplasm or urothelial carcinoma). Only publications published in English were included. In addition, reference lists of the retrieved studies were manually searched to identify other relevant studies.

Eligibility criteria

Studies satisfying the following criteria were included: (1) BCa was confirmed through pathology; (2) studies exploring the relationship between CRP levels and BCa prognosis; (3) studies with available or calculable (by Tierney's method) hazard ratios (HRs) with 95% confidence intervals (CIs) of survival outcomes [34]; (4) studies with identified CRP thresholds; and (5) English studies. The following studies were excluded: (1) case reports, meeting abstracts, reviews, comments and letters, (2) duplicate patients and (3) animal studies.

Data collection and quality evaluation

Data were collected in qualified studies by two researchers (X.F. and Z.Z.) independently, and any discrepancy was settled through negotiation with a third investigator (S.M.) until consensus was reached. The following data were collected: first author, publication year, country, sample size, age, sex, study design, study period, study centre, cT stage, treatment, threshold, threshold determination approach, survival endpoints, survival analysis types, follow-up and HRs with 95%CIs. The survival endpoints included OS, cancer-specific survival (CSS), recurrence-free survival (RFS) and progression-free survival (PFS). As the metric of discernment, the Newcastle-Ottawa Scale (NOS) [35] was employed to evaluate the incorporated literature. NOS evaluates study quality from three domains: selection, comparability and outcomes. In addition, the total score is 0–9, with NOS scores ≥6 indicating high-quality studies.

Statistical analysis

The effect of CRP level on predicting BCa prognosis was analysed based on the combined HRs and 95%CIs. The Cochrane Q test and I^2 statistics were used to assess among-study heterogeneity. $p < .10$ or $I^2 > 50\%$ was identified as indicators of significant heterogeneity, so a random-effects model should be adopted; otherwise, a fixed-effects model should be applied. We also conducted subgroup analyses based on various clinical factors for further investigation. The relationship between CRP and BCa clinicopathological factors was investigated by combining the odds ratios (ORs) with 95%CIs. Publication bias was assessed using Begg's and Egger's tests. Stata version 12.0 software (Stata Corp., College Station, TX) was used for the statistical analysis. Statistical significance was set at $p < .05$.

Results

Search results

Altogether 1023 studies were obtained through primary retrieval, among which duplicates were removed, yielding 818 articles (Figure 1). After reading the title and abstract, we eliminated 751 articles due to irrelevance and animal studies. The full texts of the remaining 67 studies were read, and 47 were discarded due to unavailable survival information (n = 15), irrelevance to CRP (n = 28), non-English study (n = 1), duplicate patients involved (n = 1) and reviews (n = 2). Finally, 20 studies with 7276 patients were included in the present work [13–32] (Figure 1; Table 1).

Enrolled study features

Table 1 presents the fundamental characteristics of all the enrolled studies. These articles were published between 2005 and 2023 and were all English publications. Eight studies were performed in Japan [14,16–18,25,28,31,32], four in China [21,23,27,29], three in Germany [15,19,26] and one each in UK [13], Austria [20], Belgium [22], Italy [24] and Turkey [30], respectively. The sample sizes were 26–1709 (median, 182). Two were prospective trials [22,26], 18 with a retrospective design [13–21,23–25,27–32]. Thirteen studies used 0.5 mg/dL as CRP cut-off value [14–20,23,26,27,30–32] and seven studies adopted cutoff values other than 0.5 mg/dL [13,21,22,24,25,28,29]. Nine articles

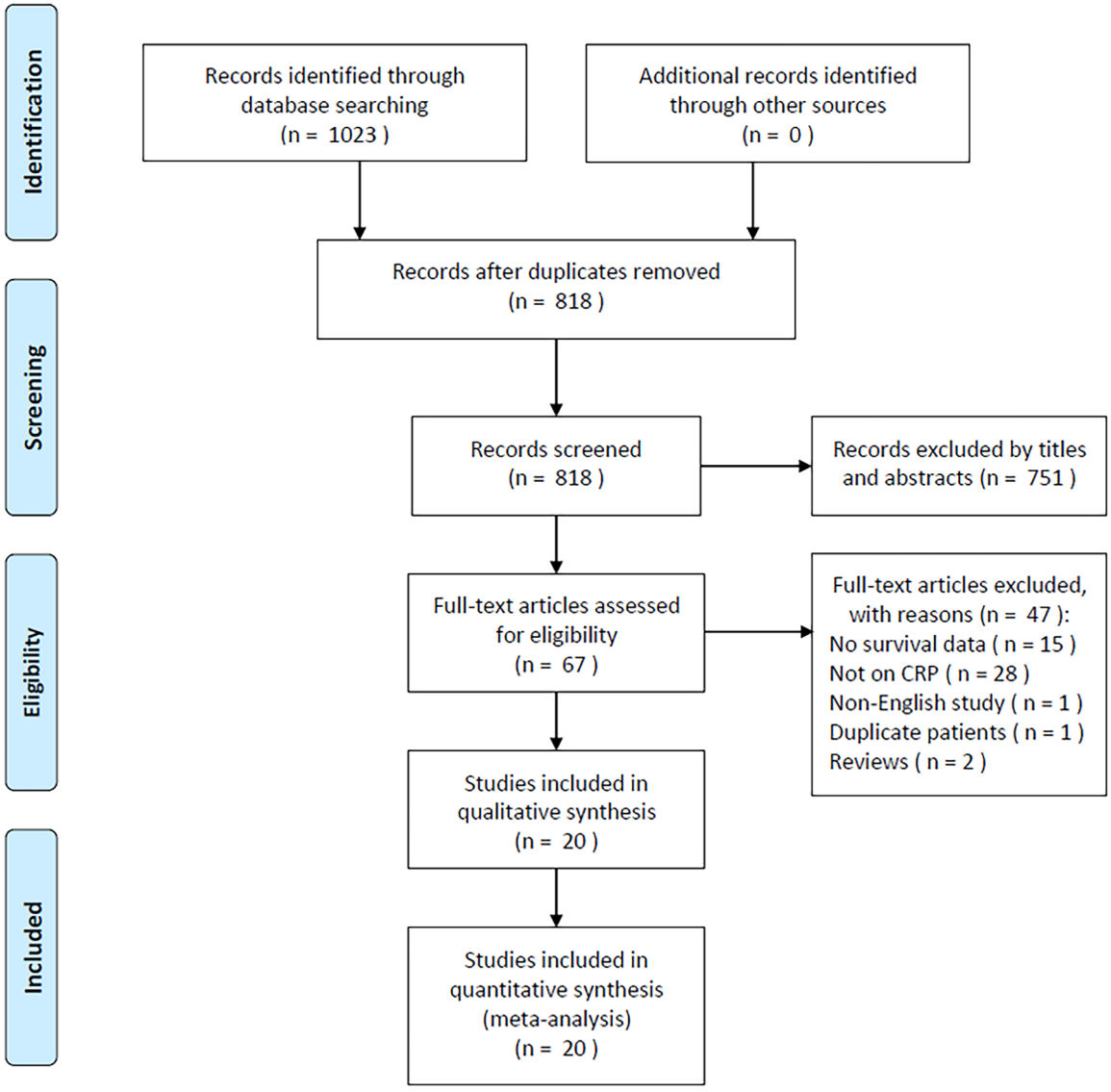

Figure 1. PRISMA flow diagram of study selection.

Table 1. Baseline characteristics of included studies in this meta-analysis.

Author	Country	Sample size	Age (years) Median (range)	Gender (M/F)	Study design	Study period	Study center	cT stage	Treatment	Cut-off value (mg/dL)	Cut-off determination	Survival endpoints	Survival analysis	Follow-up (months) Median (range)	NOS score
Hilmy et al. [13]	UK	105	≤65 y: 37 >65 y: 68	75/30	Retrospective	1992–1999	Single center	T1–T4	Mixed	1	Literature	OS, CSS	Multivariate	To Sep 2004	7
Yoshida et al. [14]	Japan	88	70 (63–75)	63/25	Retrospective	1997–2006	Single center	T2–T4	Mixed	0.5	Literature	CSS	Multivariate	33 (3–117)	8
Gakis et al. [15]	Germany	246	65 (43–84)	191/55	Retrospective	1999–2009	Single center	T1–T4	Mixed	0.5	Literature	CSS	Multivariate	30 (6–116)	8
Gondo et al. [16]	Japan	189	68 (38–85)	158/31	Retrospective	2000–2009	Single center	T1–T4	Surgery	0.5	Literature	CSS	Univariate	25.1 (2.1–127.9)	8
Nakagawa et al. [17]	Japan	114	67 (32–84)	92/22	Retrospective	1990–2010	Single center	Recurrent/ metastatic	Surgery	0.5	Literature	OS	Multivariate	11.0 (0.2–206.7)	8
Sejima et al. [18]	Japan	249	72 (47–91)	214/35	Retrospective	2003–2011	Multicentre	T1–T4	Surgery	0.5	Literature	CSS	Multivariate	24.8 (0.7–110.1)	9
Grimm et al. [19]	Germany	664	70 (35–97)	511/153	Retrospective	2004–2013	Single center	T1–T4	Surgery	0.5	Median value	CSS	Multivariate	24 (3–108)	7
Mbeutcha et al. [20]	Austria	1117	67	855/262	Retrospective	1996–2007	Multicentre	Ta–T1	Surgery	0.5	Literature	RFS, PFS	Univariate	64	9
Mao et al. [21]	China	207	66	169/38	Retrospective	2010–2012	Single center	Ta–T1	Surgery	0.34	ROC curve	RFS, PFS	Multivariate	1–48	8
Albisinni et al. [22]	Belgium	134	72	110/24	Prospective	2013–2018	Multicentre	T1–T4	Surgery	0.91	ROC curve	CSS, RFS	Univariate	21.1 (5–37)	9
Ma et al. [23]	China	169	66.6 (32–87)	245/24	Retrospective	2009–2018	Single center	T1–T4	Surgery	0.5	X-tile	OS, CSS, PFS	Multivariate	32.3 (2–108)	8
Mari et al. [24]	Italy	694	79	212/43	Retrospective	2008–2015	Single center	T1–T4	Surgery	0.3	ROC curve	OS, CSS, RFS	Univariate	1–60	7
Ogawa et al. [25]	Japan	26	91 (77–101)	11/15	Retrospective	2012–2019	Single center	T2–T4	No anti-cancer treatment	2.0	ROC curve	OS	Univariate	9.5 (1–25)	8
Tamalunas et al. [26]	Germany	1049	70	793/250	Prospective	2004–2018	Single center	T1–T4	Surgery	0.5	Median value	OS, CSS	Multivariate	22 (1–170)	9
Gui et al. [27]	China	175	59.5	124/51	Retrospective	2005–2016	Single center	T2–T4	Surgery	0.5	ROC curve	OS	Univariate	1–100	8
Tomioka et al. [28]	Japan	27	71	25/2	Retrospective	2015–2019	Multicentre	T2–T4	Chemotherapy	0.475	ROC curve	PFS	Multivariate	1–60	9
Wang et al. [29]	China	199	66	174/25	Retrospective	2010–2019	Single center	T1–T4	Surgery	0.68	ROC curve	OS, PFS	Multivariate	20	8
Caglayan and Horsanali [30]	Turkey	74	67.4	64/10	Retrospective	2016–2020	Single center	Ta–T1	Surgery	0.5	Literature	OS, CSS, RFS	Univariate	38.7	8
Iemura et al. [31]	Japan	41	72 (52–88)	35/5	Retrospective	2007–2017	Single center	T2–T4	Surgery	0.5	Literature	CSS	Multivariate	14	7
Nishikawa et al. [32]	Japan	1709	72 (65–78)	1402/307	Retrospective	2000–2019	Multicentre	Ta–T1	Surgery	0.5	Literature	CSS, RFS, PFS	Multivariate	1–200	9

OS: overall survival; CSS: cancer-specific survival; RFS: recurrence-free survival; PFS: progression-free survival; NOS: Newcastle-Ottawa Scale; ROC: receiver operating characteristics.

mentioned the significance of CRP for predicting OS [13,17,23–27,29,30], 13 studies analysed the relationship of CRP with CSS [13–16,18,19,22–24,26,30–32], six studies presented the relationship between CRP and RFS [20–22,24,30,32] and six studies showed the prognostic role of CRP for PFS [20,21,23,28,29,32]. Seven articles provided HRs and 95%CIs from univariate regression [16,20,22,24,25,27,30] and 13 studies applied multivariate analysis [13–15,17–19,21,23,26,28,29,31,32]. The NOS scores were 7–9, revealing high-quality studies (Table 1).

CRP and OS

Altogether, nine articles involving 2605 cases [13,17,23–27,29,30] reported the role of CRP in predicting OS of BCa patients. Owing to the obvious heterogeneity (I^2 = 89.5%, p < .001), we selected the random-effects model. As shown in Figure 2 and Table 2, the pooled results indicated that CRP significantly predicted the prognosis of dismal OS of BCa (HR = 2.02, 95%CI = 1.41–2.90, p < .001). Subgroup analysis revealed that CRP level still significantly predicted OS, regardless of the study design (Table 2). Moreover, elevated CRP significantly predicted dismal OS in Asian countries, sample size <200, in cT stage T1–T4, T2–T4, and recurrent/metastatic, treatment with surgery and systemic treatments, threshold of 0.5 mg/dL, and multivariate survival analysis subgroups (p < .05; Table 2).

CRP and CSS

Thirteen articles enrolling 5411 cases [13–16,18,19,22–24,26,30–32] provided the data on association between CRP and CSS in BCa. We applied the random-effects model and obtained HR = 1.46, 95%CI = 1.29–1.66, p < .001, which indicated a significant relation between a high CRP level and dismal CSS of BCa patients with BCa (Figure 3; Table 3). As demonstrated by the subgroup analysis, CRP still remarkably predicted CSS regardless of geographical region, sample size, study design, study centre or survival analysis type (Table 3). Furthermore, CSS significantly predicted BCa in the cT stage of T1–T4 and T2–T4, treatment of surgery, threshold of 0.5 mg/dL, threshold determination methods of literature, median value and X-tile software subgroups (p < .05; Table 3).

CRP and RFS

Six articles comprising 3935 patients showing the prognostic efficiency of CRP for RFS [20–22,24,30,32] in BCa. The heterogeneity was non-significant (I^2 = 0, p = .473); thus, the fixed-effects model was adopted to obtain HR = 1.25, 95%CI = 1.17–1.33, p < .001), which suggested that a high CRP level was markedly related to inferior RFS of BCa (Figure 4; Table 4). As revealed by the subgroup analysis, CRP still significantly predicted RFS regardless of geographical region, sample size, study centre, study design, threshold, threshold determination approach or survival analysis type (Table 4).

CRP and PFS

A total of six studies involving 3428 cases [20,21,23,28,29,32] showed the impact of CRP on the PFS of BCa. As indicated by the pooled data, a high CRP level was significantly associated with dismal PFS of BCa (HR = 2.28, 95%CI = 1.80–2.90, p < .001; Figure 5, Table 5). Subgroup analysis showed that the significance of CRP level in predicting PFS was not influenced by geographical region, sample size, study centre, threshold, threshold determination method or survival analysis type (Table 5).

The relation of CRP with clinicopathological features of BCa

Seven studies involving 3815 patients [14,15,18,20,21,29,32] reported the relationship between CRP and BCa clinicopathological features. Based on the combined data, there was a non-significant relationship between CRP and sex (OR = 1.22, 95%CI = 0.84–1.78, p = .297), tumour grade (OR = 0.90, 95%CI = 0.59–1.38, p = .637), tumour size (OR = 1.29, 95%CI = 0.84–2.00, p = .244) or lymph node metastasis (LNM) (OR = 1.37, 95%CI = 0.68–2.75, p = .384) in patients with BCa (Figure 6; Table 6).

Publication bias

Publication bias was analysed using Begg's and Egger's tests in the current study (Figures 7 and 8). Publication bias was not detected for OS, CSS, RFS and PFS (Figures 7 and 8).

Discussion

The efficiency of CRP in predicting BCa prognosis has been previously analysed, but there are no consistent findings. In this study, we synthesized data from 20 articles involving 7276 cases. Our pooled data showed that CRP level significantly predicted the dismal OS,

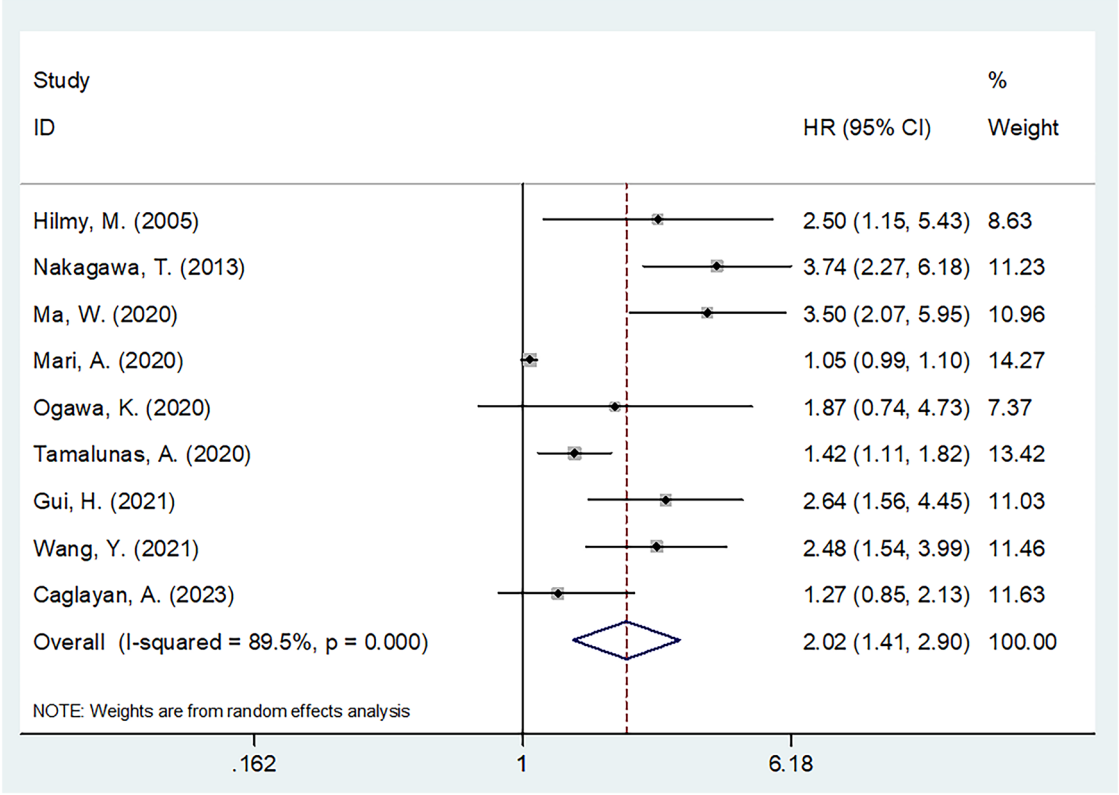

Figure 2. Meta-analysis of the association between elevated CRP and OS in patients with BCa.

Table 2. Subgroup analysis of prognostic value of CRP for OS in patients with BCa.

Subgroups	No. of studies	No. of patients	Effects model	HR (95%CI)	*p*	Heterogeneity I^2 (%)	Heterogeneity Ph
Total	9	2605	Random	2.02 (1.41–2.90)	<.001	89.5	<0.001
Geographical region							
Asian countries	6	757	Random	2.45 (1.72–3.49)	<.001	60.8	0.026
Non-Asian countries	3	1848	Random	1.33 (0.95–1.86)	.100	80.2	0.006
Sample size							
<200	7	862	Random	2.46 (1.80–3.36)	<.001	53.0	0.047
≥200	2	1743	Random	1.19 (0.89–1.59)	.241	81.7	0.019
Study design							
Prospective	1	1049	–	1.42 (1.11–1.82)	.005	–	–
Retrospective	8	1556	Random	2.16 (1.35–3.45)	.001	90.3	<0.001
cT stage							
Ta–T1	1	74	–	1.27 (0.80–2.01)	.308	–	–
T1–T4	5	2216	Random	1.87 (1.21–2.89)	.005	90.2	<0.001
Recurrent/metastatic	1	114	–	3.74 (2.27–6.17)	<.001	–	–
T2–T4	2	201	Fixed	2.43 (1.54–3.83)	<.001	0	0.526
Treatment							
Surgery	7	2474	Random	1.99 (1.34–2.97)	.001	91.5	<0.001
Mixed	1	105	–	2.50 (1.15–5.43)	.021	–	–
No anti-cancer treatment	1	26	–	1.87 (0.74–4.73)	.186	–	–
Cut-off value (mg/dL)							
0.5	5	1581	Random	2.22 (1.42–3.50)	.001	81.8	<0.001
≠0.5	4	1024	Random	1.78 (0.98–3.23)	.060	83.7	<0.001
Cut-off value determination							
Literature	3	293	Random	2.25 (1.10–4.64)	.027	79.7	<0.001
ROC curve	4	1094	Random	1.84 (0.99–3.40)	.052	88.1	<0.001
Median value	1	1049	–	1.42 (1.11–1.82)	.005	–	–
X-tile	1	169	–	3.50 (2.07–5.95)	<.001	–	–
Survival analysis							
Univariate	4	969	Random	1.50 (0.95–2.36)	.081	78.3	0.003
Multivariate	5	1636	Random	2.51 (1.60–3.95)	<.001	78.7	<0.001

OS: overall survival; BCa: bladder cancer; ROC: receiver operating characteristics.

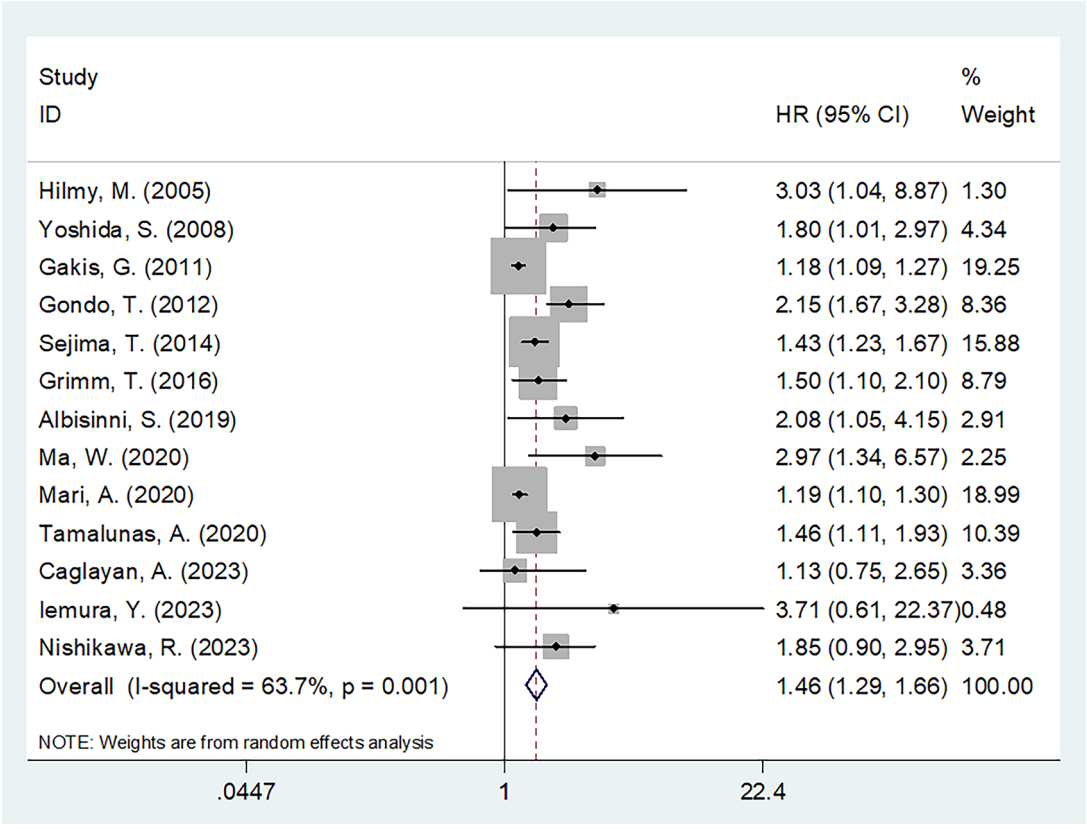

Figure 3. Meta-analysis of the association between elevated CRP and CSS in patients with BCa.

Table 3. Subgroup analysis of prognostic value of CRP for CSS in patients with BCa.

Subgroups	No. of studies	No. of patients	Effects model	HR (95%CI)	*p*	Heterogeneity I^2 (%)	Heterogeneity Ph
Total	13	5411	Random	1.46 (1.29–1.66)	<.001	63.7	0.001
Geographical region							
Asian countries	7	2519	Fixed	1.58 (1.39–1.79)	<.001	37.4	0.143
Non-Asian countries	6	2892	Fixed	1.21 (1.15–1.28)	<.001	45.9	0.100
Sample size							
<200	7	4611	Fixed	2.01 (1.60–2.52)	<.001	0	0.488
≥200	6	800	Random	1.29 (1.17–1.41)	<.001	51.5	0.067
Study design							
Prospective	2	1183	Fixed	1.53 (1.19–1.98)	.001	0	0.349
Retrospective	11	4228	Random	1.45 (1.26–1.66)	<.001	66.5	0.001
Study center							
Single center	10	3319	Random	1.44 (1.24–1.66)	<.001	65.4	0.002
Multicentre	3	2092	Fixed	1.48 (1.28–1.71)	<.001	0	0.441
cT stage							
Ta–T1	2	1783	Fixed	1.47 (0.95–2.26)	.083	18.9	0.267
T1–T4	9	3499	Random	1.44 (1.26–1.65)	<.001	71.6	<0.001
T2–T4	2	129	Fixed	1.91 (1.14–3.20)	.014	0	0.451
Treatment							
Surgery	10	4972	Random	1.54 (1.30–1.82)	<.001	63.3	0.004
Mixed	3	439	Random	1.54 (0.97–2.43)	.068	61.7	0.074
Cut-off value (mg/dL)							
0.5	10	4478	Random	1.53 (1.30–1.81)	<.001	64.5	0.002
≠0.5	3	933	Random	1.65 (0.95–2.88)	.074	62.6	0.069
Cut-off value determination							
Literature	8	2701	Random	1.55 (1.25–1.91)	<.001	68.8	0.002
ROC curve	2	828	Random	1.41 (0.85–2.34)	.180	60.0	0.114
Median value	2	1713	Fixed	1.48 (1.20–1.82)	<.001	0	0.901
X-tile	1	169	–	2.97 (1.34–6.57)	.007	–	–
Survival analysis							
Univariate	4	1091	Random	1.53 (1.04–2.26)	.031	77.6	0.004
Multivariate	9	4320	Random	1.49 (1.26–1.76)	<.001	58.6	0.031

CSS: cancer-specific survival; BCa: bladder cancer; ROC: receiver operating characteristics.

CSS, RFS and PFS of patients with BCa. Moreover, the prognostic power of CRP was stable in the subgroup analysis. Nonetheless, CRP levels were not significantly related to sex, tumour grade, tumour size or LNM of BCa. Collectively, CRP levels significantly and reliably predicted the short- and long-term prognosis of patients with BCa. To the best of our knowledge, this is the first study to investigate the effect of CRP level on predicting BCa prognosis.

The precise mechanisms underlying the significance of CRP in predicting BCa prognosis have not been comprehensively analysed. These results are

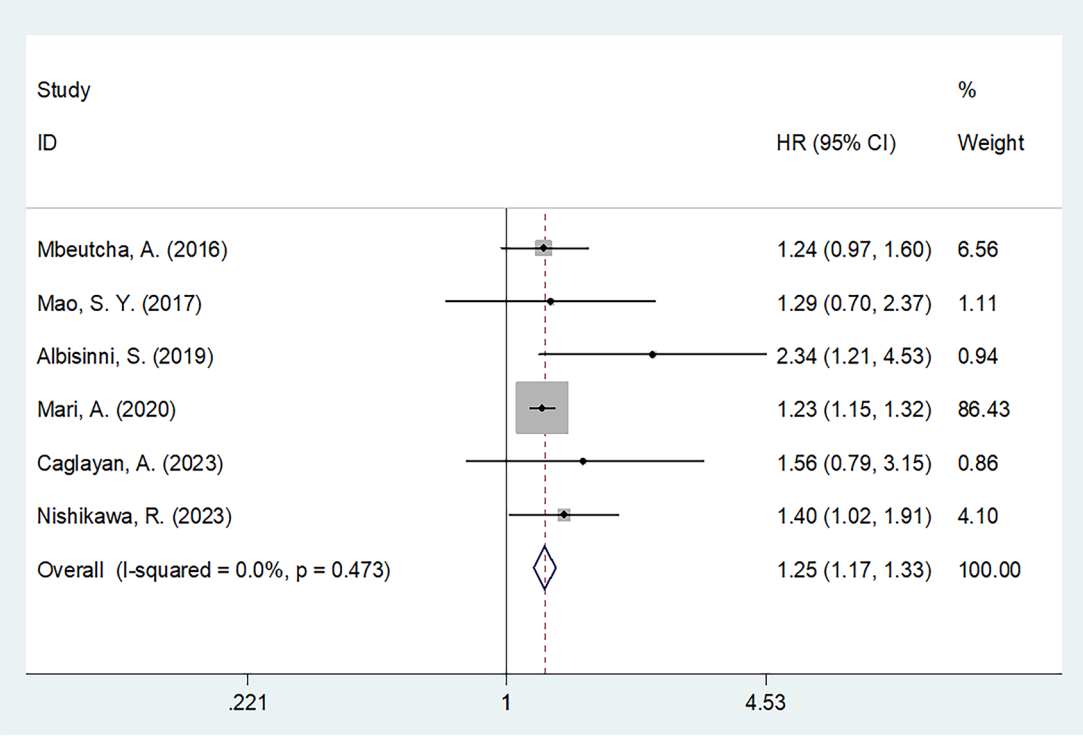

Figure 4. Meta-analysis of the association between elevated CRP and RFS in patients with BCa.

Table 4. Subgroup analysis of prognostic value of CRP for RFS in patients with BCa.

Subgroups	No. of studies	No. of patients	Effects model	HR (95%CI)	*p*	Heterogeneity	
						I^2 (%)	Ph
Total	6	3935	Fixed	1.25 (1.17–1.33)	<.001	0	0.473
Geographical region							
Asian countries	3	1990	Fixed	1.40 (1.08–1.81)	.012	0	0.923
Non-Asian countries	3	1945	Fixed	1.24 (1.16–1.32)	<.001	44.6	0.165
Sample size							
<200	2	208	Fixed	1.93 (1.20–3.11)	.007	0	0.406
≥200	4	3727	Fixed	1.24 (1.16–1.32)	<.001	0	0.895
Study design							
Prospective	1	134	–	2.34 (1.21–4.53)	.012	–	–
Retrospective	5	3801	Fixed	1.24 (1.16–1.32)	<.001	0	0.905
Study center							
Single center	3	2960	Fixed	1.23 (1.15–1.32)	<.001	0	0.790
Multicentre	3	975	Fixed	1.36 (1.13–1.64)	.001	36.4	0.207
cT stage							
Ta–T1	4	3107	Fixed	1.31 (1.10–1.57)	.003	0	0.900
T1–T4	2	828	Random	1.55 (0.85–2.85)	.154	72.3	0.058
Cut-off value (mg/dL)							
0.5	3	2900	Fixed	1.32 (1.09–1.59)	.004	0	0.747
≠0.5	3	1035	Fixed	1.24 (1.16–1.33)	<.001	44.8	0.163
Cut-off value determination							
Literature	3	2900	Fixed	1.32 (1.09–1.59)	.004	0	0.747
ROC curve	3	1035	Fixed	1.24 (1.16–1.33)	<.001	44.8	0.163
Survival analysis							
Univariate	4	2019	Fixed	1.24 (1.16–1.33)	<.001	25.6	0.258
Multivariate	2	1916	Fixed	1.37 (1.04–1.82)	.027	0	0.825

RFS: recurrence-free survival; BCa: bladder cancer; ROC: receiver operating characteristics.

interpreted as follows: first, acute-phase proteins such as CRP are produced by the liver when stimulated by cytokines, such as interleukin-6 (IL-6) [36]. The presence of chronic inflammation may contribute to carcinogenesis and cancer occurrence or progression [37]. The circulating concentration of vesicular endothelial growth factor (VEGF) and CRP is directly related, so an elevated circulating CRP level may indicate a tumour's aggressiveness or phenotype [38]. Second, high serum levels of IL-6 are

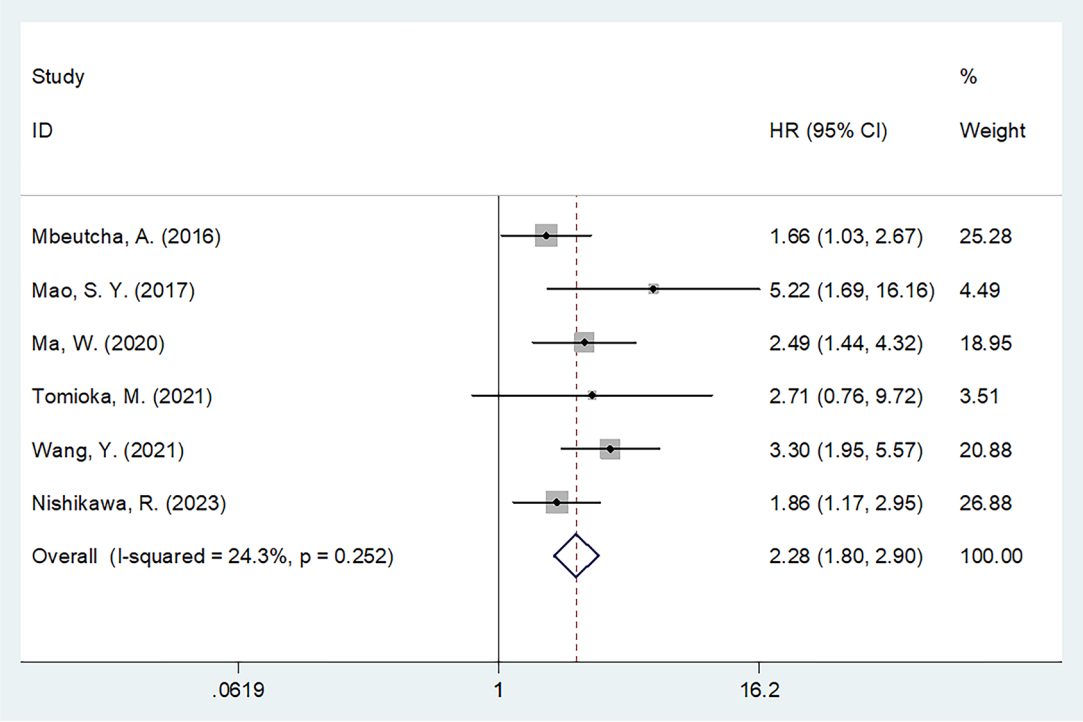

Figure 5. Meta-analysis of the association between elevated CRP and PFS in patients with BCa.

Table 5. Subgroup analysis of prognostic value of CRP for PFS in patients with BCa.

Subgroups	No. of studies	No. of patients	Effects model	HR (95%CI)	*p*	Heterogeneity	
						I^2 (%)	Ph
Total	6	3428	Fixed	2.28 (1.80–2.90)	<.001	24.3	0.252
Geographical region							
Asian countries	5	2311	Fixed	2.54 (1.93–3.36)	<.001	6.9	0.367
Non-Asian countries	1	1117	–	1.66 (1.03–2.67)	.037	–	–
Sample size							
<200	3	395	Fixed	2.87 (2.00–4.13)	<.001	0	0.768
≥200	3	3033	Fixed	1.92 (1.39–2.64)	<.001	41.0	0.183
Study center							
Single center	3	575	Fixed	3.07 (2.14–4.39)	<.001	0	0.479
Multicentre	3	2853	Fixed	1.81 (1.31–2.49)	<.001	0	0.771
cT stage							
Ta–T1	3	3033	Fixed	1.92 (1.39–2.64)	<.001	41.0	0.183
T1–T4	2	368	Random	2.89 (1.98–4.22)	<.001	0	0.471
T2–T4	1	27	–	2.71 (0.75–9.72)	.126	–	–
Treatment							
Surgery	5	3401	Fixed	2.27 (1.78–2.90)	<.001	38.8	0.163
Chemotherapy	1	27	–	2.71 (0.75–9.72)	.126	–	–
Cut-off value (mg/dL)							
0.5	2	1286	Fixed	1.76 (1.26–2.45)	.001	0	0.740
≠0.5	4	2142	Fixed	3.04 (2.15–4.29)	<.001	0	0.681
Cut-off value determination							
Literature	2	2826	Fixed	1.76 (1.26–2.45)	.001	0	0.740
ROC curve	3	433	Fixed	3.46 (2.21–5.40)	<.001	0	0.711
X-tile	1	169	–	2.49 (1.44–4.32)	.001	–	–
Survival analysis							
Univariate	1	1117	–	1.66 (1.03–2.67)	.037	–	–
Multivariate	5	2311	Fixed	2.54 (1.93–3.36)	<.001	6.9	0.367

PFS: progression-free survival; BCa: bladder cancer; ROC: receiver operating characteristics.

associated with elevated CRP levels in the blood. Because of its role in regulating the JAK–STAT signalling pathway, IL-6 regulates the expression of genes that are related to proliferation [39]. Third, patients with elevated CRP concentrations may have impaired T-lymphocytic responses to tumours, which may lead to the development of BCa 40. Tumor antigens may trigger an increase in CRP levels because of innate and adaptive immune responses.

This meta-analysis indicated that elevated CRP was significantly associated with diverse survival outcomes of BCa. Notably, integrating additional biomarkers with CRP or providing a weighted nomogram for CRP usage has been crucial for enhancing clinical decision-making and care delivery. However, due to the inherent nature of meta-analysis study, a weighted nomogram cannot be performed in the current study. A panel incorporating CRP with other biomarkers is also important for clinical decision-making of BCa. Because of limited data in this meta-analysis, prognostic panels are not performed in this study. Current evidence showed that panels with acute phase proteins were novel and reliable tools for prognostication and response evaluation in various cancers [40] including non-small cell lung cancer [41], pancreatic ductal adenocarcinoma [42] and diffuse large B-cell lymphoma [43]. Therefore, prognostic nomograms and panels incorporating CRP should be investigated and developed in future studies.

Moreover, identifying CRP status at the moment of transurethral resection of bladder tumour (TURBT)

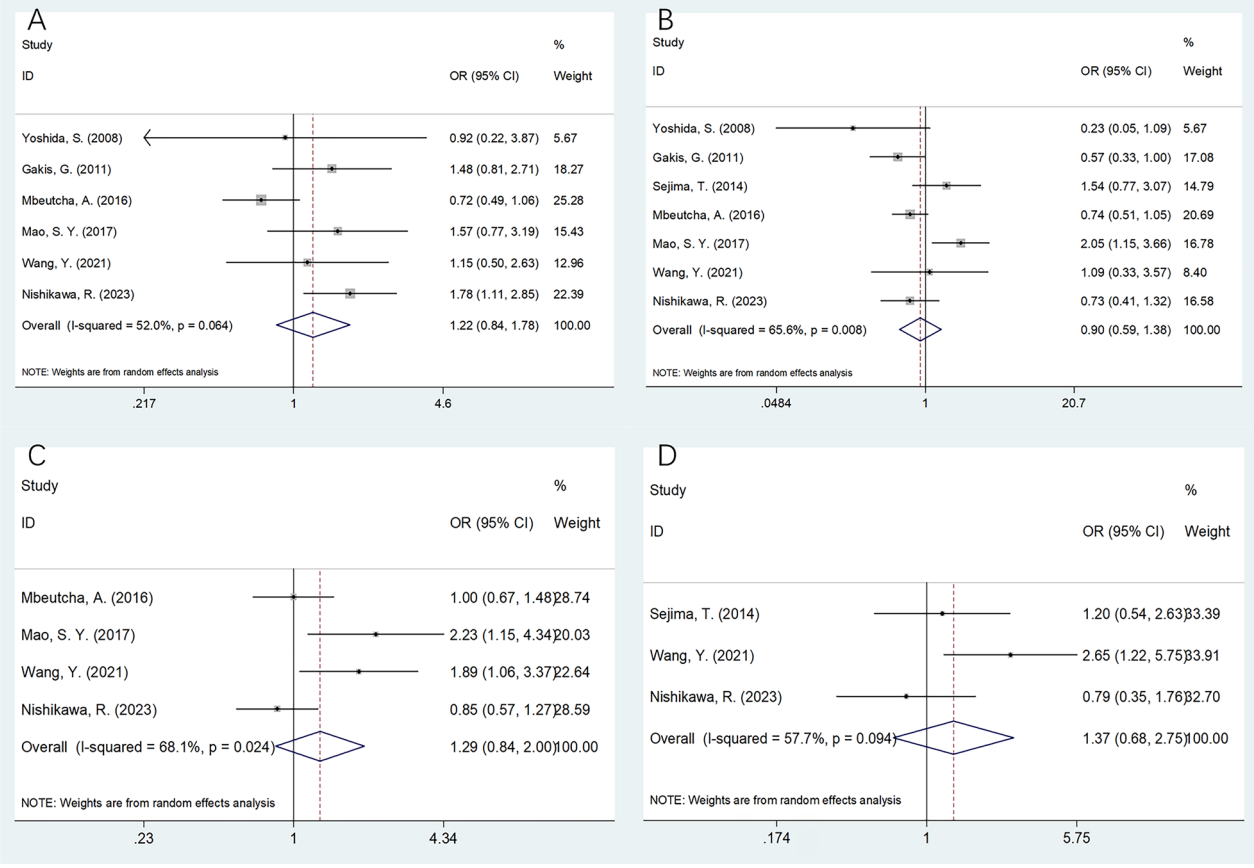

Figure 6. Meta-analyses of the correlation between CRP and clinicopathological parameters in patients with BCa. (A) Gender (male vs. female); (B) tumor grade (G3 vs. G1–G2); (C) tumor size (cm) (≥3 vs. <3); and (D) LNM (yes vs. no).

Table 6. The correlation between CRP and clinicopathological features in patients with BCa.

Variables	No. of studies	No. of patients	Effects model	OR (95%CI)	*p*	Heterogeneity	
						I^2 (%)	Ph
Gender (male vs. female)	6	3566	Random	1.22 (0.84–1.78)	.297	52.0	0.064
Tumor grade (G3 vs. G1–G2)	7	3815	Random	0.90 (0.59–1.38)	.637	65.6	0.008
Tumor size (cm) (≥3 vs. <3)	4	3232	Random	1.29 (0.84–2.00)	.244	68.1	0.024
LNM (yes vs. no)	3	2157	Random	1.37 (0.68–2.75)	.384	57.7	0.094

CRP: C-reactive protein; LNM: lymph node metastasis; BCa: bladder cancer.

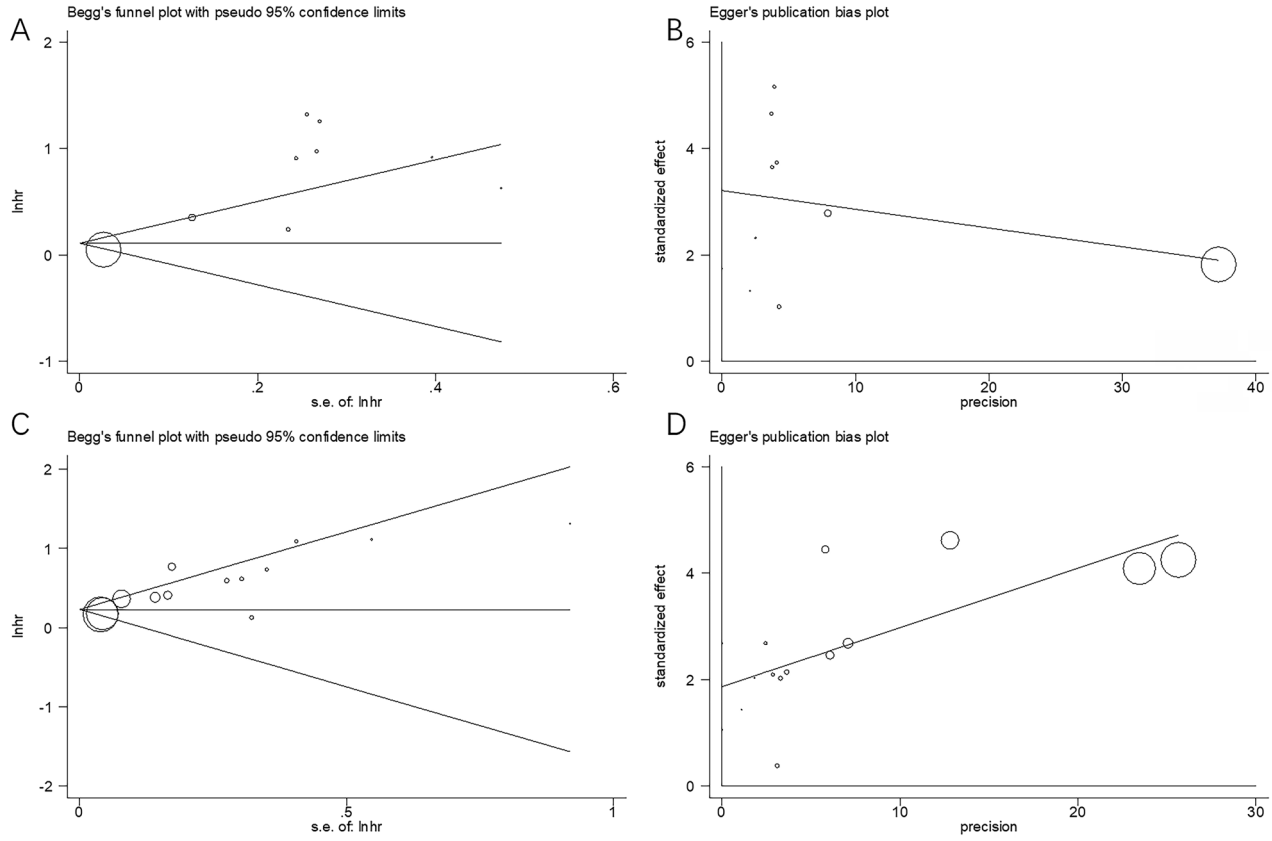

Figure 7. Publication bias of the studies. (A) Begg's test for OS, $p = .466$; (B) Egger's test for OS, $p = .182$; (C) Begg's test for CSS, $p = .127$; and (D) Egger's test for CSS, $p = .907$.

would be novel. In this meta-analysis, the majority of BCa patients were treated with surgery. Our results showed that CRP remained a significant prognostic marker for BCa patients receiving surgery.

The cut-off values of CRP were not consistent in included studies. Interestingly, when we searched the literatures including urothelial carcinoma, a total of 47 studies were finally eligible (Supplementary Table S1). The cut-off values (mg/dL) ranged from 0.13 to 4.2, with a median value of 0.5. Moreover, 0.5 (mg/dL) was still the most prevalently selected cut-off value, which was used in 26 studies out of the 47 studies. The above-mentioned results on cut-off value were in consistent with the data in the current meta-analysis.

Recently, many studies have also reported the significance of CRP in predicting the prognosis of different cancers by conducting meta-analysis [44–47]. As shown by Zhang et al. in their meta-analysis comprising 3202 cases, a high serum CRP level was closely related to poor OS and PFS in ovarian cancer [44]. According to Yu and Zhang in their meta-analysis incorporating 2149 cases, higher CRP levels were significantly related to dismal OS in Asian patients with endometrial cancer [45]. Zhou et al. conducted a meta-analysis of 16 articles and based on their results, a high CRP level was associated with poor OS, CSS and PFS in prostate cancer cases [46]. In a recent meta-analysis encompassing 2204 cases, Yang et al. discovered a significant association between high CRP levels and poor OS and shortened PFS in cervical cancer [47]. Another recent meta-analysis of 2314 patients indicated that CRP level significantly predicted the dismal OS of patients with diffuse large B-cell lymphoma patients [48].

The present study had some limitations. First, many enrolled articles had a retrospective design. Therefore, heterogeneity may exist because of the retrospective nature of the studies. Second, the CRP threshold was nonuniform in the included articles, although the majority of these studies used 0.5 mg/dL. The CRP cut-off is the most compelling to us, even though there are multiple CRP cut-off values. Third, some studies only reported univariate HRs during raw data extraction, which may have led to an overestimation of effect sizes in the pooled results. Therefore, large-scale trials applying a standard CRP threshold should be conducted for further validation.

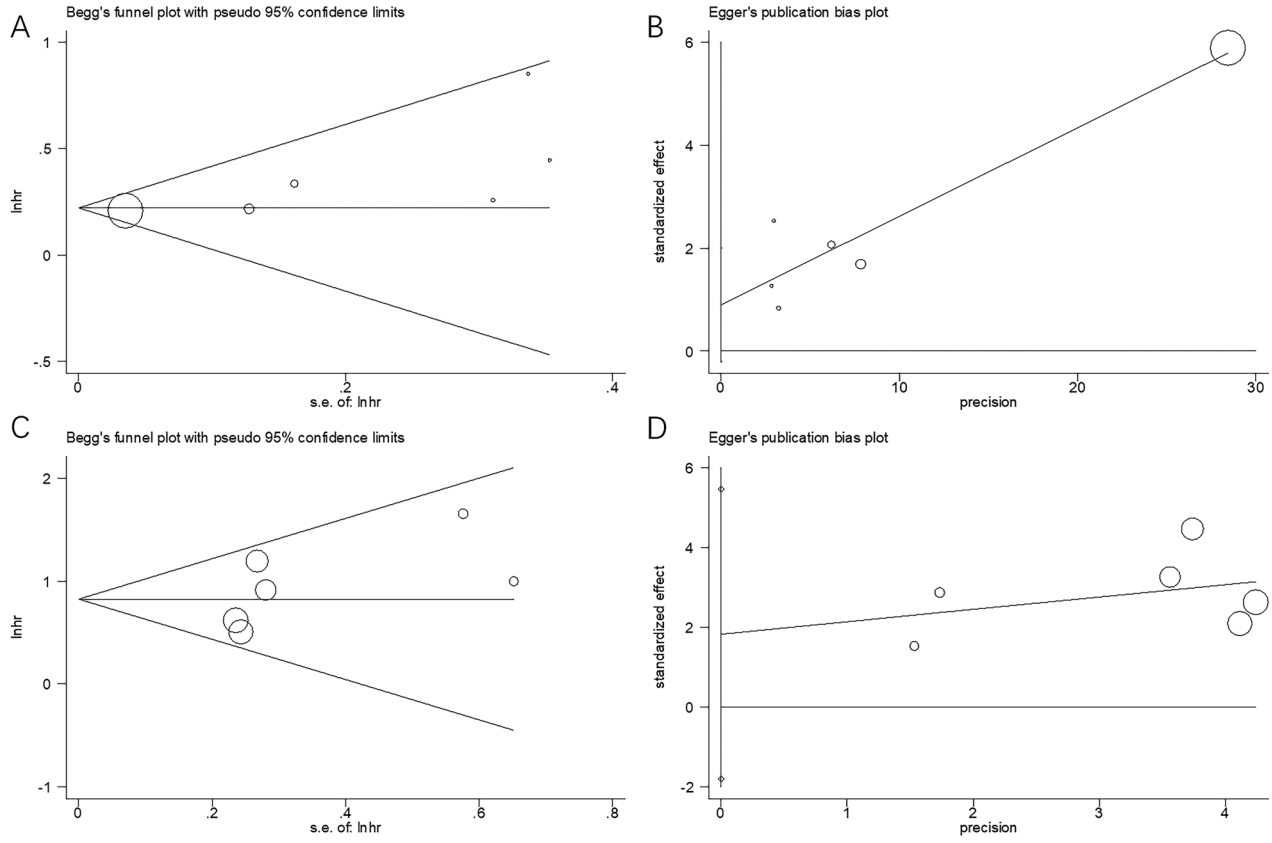

Figure 8. Publication bias of the studies. (A) Begg's test for RFS, $p = .133$; (B) Egger's test for CSS, $p = .086$; (C) Begg's test for PFS, $p = .707$; and (D) Egger's test for PFS, $p = .234$.

Conclusions

In summary, elevated CRP levels were notably related to poor OS, CSS, RFS and PFS of BCa patients with BCa. CRP could serve as a reliable biomarker for predicting short- and long-term BCa prognoses in clinical practice.

Author contributions

XF and ZZ performed the article search and selection. XF, ZZ and SM collected relevant data. XF and ZZ performed the analyses, and ZZ and SM interpreted the results and drafted this paper. XF, ZZ and SM revised the manuscript and provided some critical suggestions. All authors have approved the final version of the manuscript.

Ethical approval

Not applicable.

Consent form

Not applicable.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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