BMC Gastroenterology

SYSTEMATIC REVIEW

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Long-term prognostic value of postoperative C-reactive protein in gastric cancer patients: a systematic review and meta-analysis

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Abstract

Background C-reactive protein (CRP) has begun to be used in clinical practice to predict the prognosis of cancer patients, but evidence on its prognostic role remains inconsistent. We performed a systematic review and meta-analysis to investigate the prognostic value of postoperative CRP among patients with gastric cancer.

Methods We systematically searched PubMed, Embase, Web of Science, the Cochrane Library, Scopus, the Chinese National Knowledge Infrastructure (CNKI), Wan Fang Data, and the VIP Database for studies published from inception to April 30, 2025. Studies investigating the association between postoperative CRP and overall survival (OS) or recurrence-free survival (RFS) were included. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for these outcomes were extracted for meta-analysis.

Results Twelve eligible cohort studies, involving 9246 patients, were included in the meta-analyses. Elevated postoperative CRP was a significant predictor of OS and RFS in gastric cancer patients (HR:1.51, 95% CI:1.38–1.66; HR:1.44, 95% CI:1.27–1.63, respectively). CRP measured at a specific postoperative time point showed stronger prognostic value (HR:1.74, 95% CI:1.37–2.19), despite substantial heterogeneity, whereas peak postoperative CRP during hospitalization yielded a highly consistent and significant effect (HR:1.53, 95% CI:1.34–1.76). Notably, peak CRP measured within the first week after surgery served as an independent prognostic factor for both worse OS (HR:1.80, 95% CI:1.38–2.34) and RFS (HR:1.63, 95% CI:1.29–2.06) after multivariable adjustment, without heterogeneity.

Conclusion This study identifies postoperative CRP as a powerful and readily available prognostic indicator for patients undergoing radical gastrectomy for gastric cancer, with its peak level within the first postoperative week being of particular prognostic value. Future prospective studies should aim to establish the optimal timing and specific thresholds for postoperative CRP measurement, thereby facilitating its effective integration into routine clinical practice.

Keywords Prognosis, C-reactive protein, Biomarkers, Gastric Cancer

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Introduction

Gastric cancer (GC) ranks as the fifth most commonly diagnosed malignancy worldwide and represents the fourth leading cause of cancer-related mortality. In 2020, approximately 1.08 million new cases were reported globally, resulting in 770,000 deaths attributable to the disease [1–3]. Although comprehensive treatment strategies centered on radical surgery have significantly reduced the mortality of gastric cancer, the surgical trauma itself induces systemic inflammatory responses and reshapes the tumor microenvironment [4–6]. This may lead to elevated levels of postoperative inflammatory biomarkers, thereby potentially affecting patient prognosis. Accumulating evidence suggests that the host inflammatory response, both locally and systemically, plays a critical role in tumor progression and is strongly associated with poor prognosis in gastric cancer [7–9]. Consequently, identifying readily measurable inflammatory biomarkers has become a pivotal objective for prognostic prediction.

The clinical imperative for accurate prognostic stratification is evident across the entire disease spectrum. For instance, in the management of recurrent disease, studies have demonstrated that predictive factors for post-recurrence survival are not uniform but vary substantially between early recurrence and late recurrence patients [10, 11]. Collectively, these findings underscore the imperative to refine prognostic models based on specific clinical contexts and timelines.

Arguably, the most critical window for initial prognosis and treatment planning is immediately following curative surgery. The ability to identify high-risk patients at this juncture can significantly influence decisions regarding adjuvant therapy and surveillance intensity. Among various biomarkers, C-reactive protein, an acute-phase protein produced by the liver that rapidly elevates in response to inflammation, has gained increasing attention as a readily measurable prognostic indicator in peripheral blood [12]. Consequently, it has been widely applied by researchers, either alone or in combination with other biomarkers, for prognostic evaluation in cancer patients [13]– [14]. In gastric cancer, a high preoperative CRP/albumin ratio significantly predicts both short- and long-term surgical outcomes in elderly patients [15], while CRP-based multiple predictors are effective for assessing early and late mortality in those with early-stage disease [16]. Moreover, postoperative CRP plays a significant role in predicting long-term prognostic outcomes for patients with colorectal cancer [17].

Despite these valuable insights, the specific value of postoperative CRP for predicting long-term survival among broader populations of gastric cancer patients remains to be comprehensively synthesized. Therefore, in this systematic review and meta-analysis, we aim to evaluate and summarize the long-term prognostic value of postoperative CRP.

Methods

Registration

The protocol of this systematic review was registered in the international prospective register of systematic reviews (PROSPERO, registration no. CRD42024554859). This meta-analysis was performed according to the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; see Table S1).

Literature searches and study selection

A systematic search of published literature was conducted using comprehensive databases including PubMed, Embase, Web of Science, the Cochrane Library, Scopus, CNKI, Wan Fang Data, and VIP Database, with a cutoff date of April 30, 2025. For database searches, we employed medical subject headings, keywords, free-text words, and synonyms related to the concepts of "stomach neoplasms," "C-reactive protein," "prognosis," and "postoperative" conditions. The search strategy results are presented in Table S2.

Inclusion and exclusion criteria

Inclusion Criteria: (i) patients who underwent gastric tumor resection and were diagnosed with gastric cancer through postoperative histopathological examination; (ii) postoperative serum CRP levels were measured using routine laboratory techniques; (iii) studies must be full-text cohort studies, with prognosis assessed based on CRP-based inflammatory biomarkers; and (iv) sufficient information must be provided to calculate the hazard ratio (HR) and 95% confidence intervals (CIs).

Exclusion criteria: (i) literature types including reviews, case reports, conference abstracts, letters, academic dissertations, editorials, and clinical guidelines; (ii) blood biochemical examination conducted prior to surgery; (iii) the full text lacks the corresponding predictive indicators, or fails to conduct a correlation study between these indicators and prognostic outcomes.

Data extraction and risk of bias assessment

Two researchers (D.Y.S and X.Y.) independently imported the retrieved relevant literature into EndNote version 9, a literature management software, and subsequently screened and identified articles eligible for inclusion. All studies were subjected to a double-checking process, and any disagreements arising from data extraction were resolved by discussion or consultation with a third reviewer. Microsoft Excel spreadsheet was used to record data.

The following information was independently extracted by the researchers (D.Y.S, S.Z., and X.Y.) : first author's

name, publication year, country of origin, number of participants, sex ratio, time of postoperative blood collection, specific biomarkers, cut-off values, hazard ratios (HRs) for biomarkers in relation to prognostic outcomes (along with their corresponding 95% confidence intervals [CIs] and P-values), median follow-up time, and study design. The prognostic outcomes of interest in this meta-analysis were overall survival (OS) and recurrence-free survival (RFS). For each included study, results from multivariate analyses were preferentially extracted to assess the association between postoperative CRP and prognostic outcomes. In cases where studies did not directly report results for the association between CRP and prognostic outcomes, data provided in the supplementary files of these studies were utilized to perform univariate and multivariate analyses of prognostic risk factors, thereby estimating the effect of CRP on OS while adjusting for other potential prognostic factors. See Table S3for details.

The risk of bias for included studies was assessed using the Quality in Prognosis Studies (QUIPS) tool [18]–[19]. Two researchers (D.L, X.Y) separately conducted a bias risk assessment on six domains within the included studies: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis, and reporting. To evaluate the overall risk, studies in which all six bias domains were assessed as having a low risk of bias were identified as low-risk bias studies; studies were deemed high-risk if high bias risk was present in at least one domain; and studies with one or more moderate risk domains were deemed moderate risk.

Statistical analysis

Meta-analysis was performed for a predictor when it was assessed in at least two studies examining its relationship with the outcome. The pooled hazard ratio (HR) with 95% confidence interval (CI) was used to assess the association between postoperative CRP and prognostic outcomes. Testing for heterogeneity was performed using the I^2 statistic and the Cochran's Q-test. A fixed-effects model was used for meta-analysis in the presence of low heterogeneity (I^2 < 50%), while a random-effects model was used when I^2 >50%. To comprehensively evaluate the prognostic impact of CRP, subgroup meta-analyses were stratified based on biomarker evaluation method (serum CRP level measured at a specific postoperative time point or maximum serum CRP level during postoperative hospital stay). Furthermore, sensitivity analyses were undertaken to assess the robustness of CRP effect on prognostic outcomes and to investigate the impact of each single study on the overall effect. Where possible, publication bias was comprehensively evaluated using Egger's test, and funnel plots. All meta-analyses were conducted with STATA 17.0 and Review Manager 5.3. A P value < 0.05 was considered statistically significant.

Results

Search results

The PRISMA study flow diagram is provided in Fig. 1. A total of 24,841 individual studies were reviewed: 5487 from PubMed, 6352 from Embase, 3669 from Web of Science, 156 from the Cochrane Library, 2826 from Scopus, 5398 from CNKI, 786 from Wan Fang Data, and 167 from VIP Database. After removing duplicates, studies not relevant to the topic, and those with full text unavailable, 179 studies were identified for full-text screening. Ultimately, following the application of inclusion and exclusion criteria, we identified twelve studies eligible for the meta-analysis. The included and excluded studies were shown in Table S4.

Study characteristics

The general information about the included studies is provided in Table 1. A total of twelve studies involving 9246 patients were included in this meta-analysis. Five studies were completed in China, and seven came from Japan. All studies provided an association between CRP and prognosis in GC patients, of which ten were retrospective studies and two were prospective studies. Five studies used serum CRP measured at a specific postoperative time point as a prognostic predictor, and eight utilized the maximum serum CRP level (CRP max) during the hospital stay. Notably, one study (Migita et al.) employed both methods. The risk of bias for the included studies was assessed using QUIPS, and the results are presented in Table 1 and Fig. S1. A high risk of bias was identified in the study confounding domain for two studies [20, 29], as detailed in Table S5.

The prognostic value of CRP for OS in gastric cancer

Studies evaluating the relationship between postoperative CRP and survival showed that an elevated CRP was positively correlated with poor OS in GC patients [HR (95% CI): 1.51(1.38–1.66)] (Fig. 2A). Low heterogeneity was observed in the meta-analysis of ten cohort studies examining the relationship between CRP and OS.

The pooled results from five studies, which assessed the relationship between elevated CRP measured at a specific postoperative time point and OS, revealed a remarkable prognostic effect, albeit with substantial heterogeneity [HR (95% CI): 1.74 (1.37–2.19), I^2=58%] (Fig. 2B). In contrast, the maximum postoperative CRP during hospitalization demonstrated a more conservative and highly consistent effect [HR (95% CI): 1.53 (1.34–1.76), I^2=1%] (Fig. 2C). Further analysis revealed that although a specifically measured CRP on postoperative day 3 showed a high hazard ratio for prognostic assessment, suggesting

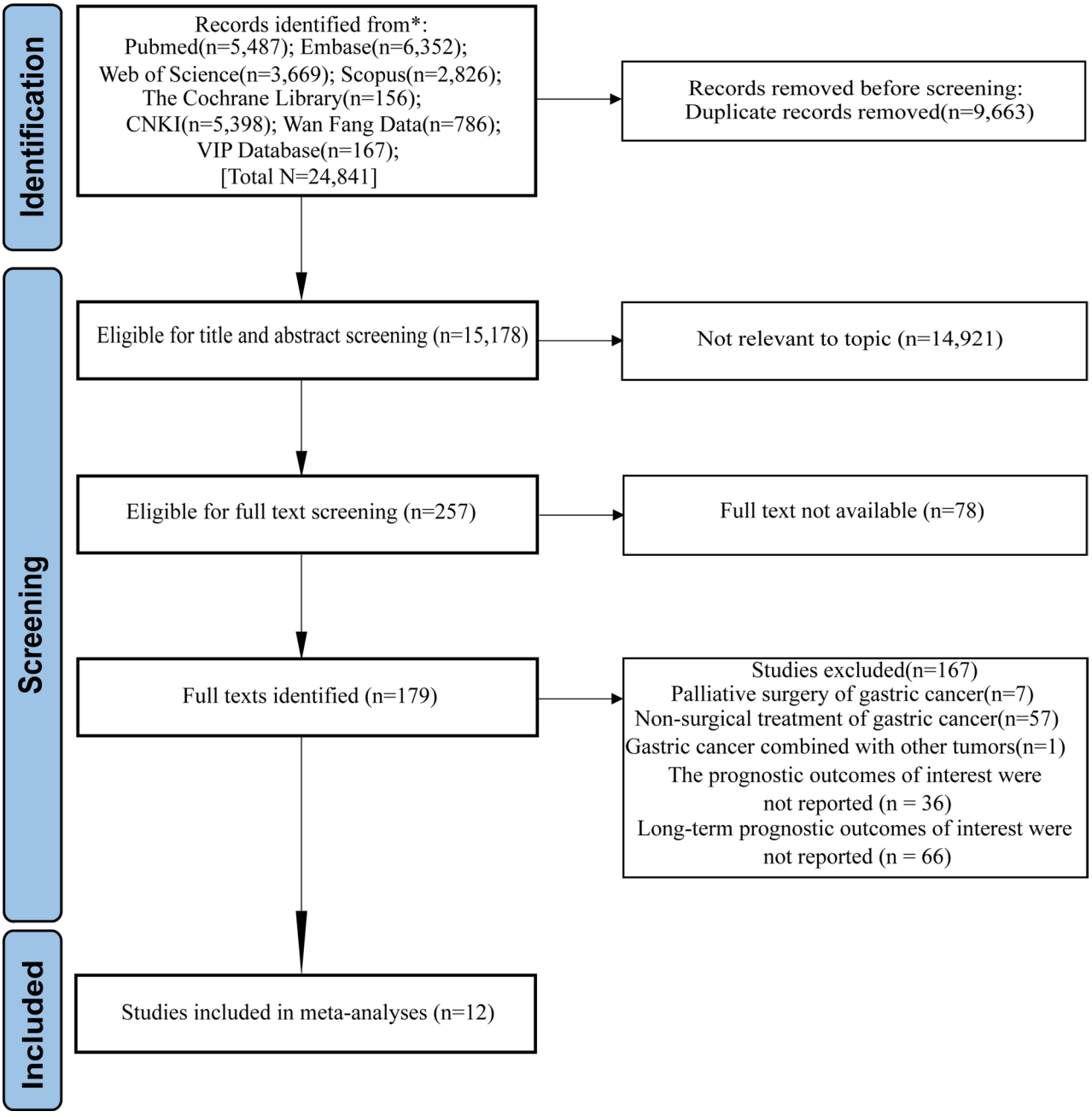

Fig. 1 The PRISMA study flow diagram

a potential strong clinical association, the pooled results did not reach statistical significance [HR (95% CI): 1.88 (0.87–4.07), $P > 0.05$] (Fig. 2D).

The prognostic value of CRP for RFS in gastric cancer

In a pooled analysis of six studies, elevated CRP was significantly associated with worse recurrence-free survival, with moderate heterogeneity observed [HR (95% CI): 1.44 (1.27–1.63), $I^2 = 46\%$] (Fig. 3A).

Independent prognostic value of peak CRP within the first week after surgery

After adjustment for multiple clinical covariates, elevated peak CRP measured within one week after surgery was independently associated with markedly poorer OS and RFS [HR (95% CI): 1.80 (1.38–2.34); 1.63 (1.29–2.06), respectively]. No significant heterogeneity was observed in the meta-analyses of OS and RFS from the three cohort studies (Fig. 3B-C).

Table 1. Characteristics of Included Studies

Study		Population	Predictor (mg/L)			Long-term outcomes	Median follow-up time (months)	Cohort studies	Risk assessment
First Author	Country	Male/Female	Time	Biomarker	Cut-off	HR (95% CI)			
Kong,2016[20]	China	55/17	Postop	CRP	8	MOS: 1.765(1.159–2.687.159.687)	55	P	High
Kuroda,2022[21, a]	Japan	304/140	POD 1,3,6,7	CRP max	92	MOS:1.68(1.19–2.36.19.36) MRFS:1.56(1.12–2.18.12.18)	88	R	Low
Kurokawa,2020[22, a]	Japan	1007/449	Postop	CRP max	120	UOS:1.43(1.18–1.72.18.72) MRFS:1.21(1.01–1.47.01.47)	61	R	Low
Li,2023[23]	China	331/99	1 month	CRP	10	MOS:2.15(1.37–3.39.37.39) MRFS:2.11(1.49–3.00.49.00)	107.1	R	Low
Lu,2020[24, a]	China	271/130	POD 1,3,5	CRP max	77.1	MRFS: 1.631(1.019–2.611.019.611)	42	R	Moderate
Matsui,2025[25]	Japan	3027/1691	POD 3	CRP	114	MOS:1.356(1.168–1.576.168.576)	66	R	Low
Migita,2019[26, a]	Japan	324/146	POD 3	CRP	139	MOS:3.026(1.505–6.084.505.084);	61.4	R	Moderate
			POD 1,3,7	CRP max	139	MOS:2.578(1.280–5.191.280.191);		R	
Nagata,2021[27,a,b]	Japan	135/62	≤ 3 weeks	CRP max	93.5	MOS:2.020(1.177–3.466.177.466);	39.1	R	Moderate
Saito,2015[28, a]	Japan	213/92	POD 1,3,5,7	CRP max	120	MRFS: 1.77(1.11–2.82.11.82)	57	R	Moderate
Urakawa,2019[29, a]	Japan	194/84	POD 0,1,3,7	CRP max	114	UOS: 1.28(0.86–1.89.86.89); URFS: 1.30(0.90–1.86.90.86)	NR	P	High
Yuan,2017[30]	China	210/174	Postop	CRP	10	UOS: 1.72(1.30–2.27.30.27)	9.77	R	Moderate
Zang, 2021[31, a]	China	62/29	POD 2–5	CRP max	300	MOS: 1.741(1.050–2.888.050.888)	47.74	R	Low

Notes: a Study reported the relationship between prognosis and maximum serum CRP level during the postoperative hospital stay (CRP max). b Univariate and multivariate analyses were performed to assess the impact of CRP and other factors on overall survival (OS)

Abbreviations: *M* male, *F* female, POD 1,3,4,5,6 or7, blood tests were performed on postoperative days 1,3,4,5,6 or 7; Postop, post-operation; *CRP* C-reactive protein, *CRP max* maximum serum CRP level, *OS* overall survival; *RFS* recurrence-free survival, *HR* hazard ratio, *CI* confidence interval, *NR* not reported, *U* univariate analysis, *M* multivariate analysis, *P* prospective study, *R* retrospective study

Sensitivity analysis

Sensitivity analysis confirmed the robustness of our findings, as the pooled hazard ratios for both OS and RFS remained stable and significant upon the sequential exclusion of individual studies. This indicates that postoperative CRP is a reliable predictor of survival outcomes (Fig. S2).

Publication bias

As shown in Table S6 and Fig. S3, in evaluating the long-term prognostic value of postoperative CRP, significant small-study effects were detected by Egger's test for OS outcomes ($P < 0.05$), with corresponding funnel plot asymmetry suggesting potential publication bias. In contrast, both Egger's test ($P > 0.05$) and symmetrical funnel plot indicated no evidence of publication bias for RFS outcomes.

Discussion

Gastric cancer (GC) remains a formidable global health challenge, ranking as a leading cause of cancer-related mortality worldwide [32, 33]. Despite the availability of multimodal therapeutic strategies, including surgery, chemotherapy, and targeted therapy, the prognosis for advanced-stage disease remains poor [34]. A critical factor driving tumor progression and therapeutic resistance is the tumor microenvironment (TME), of which inflammation is a well-established hallmark [35]. Systemic

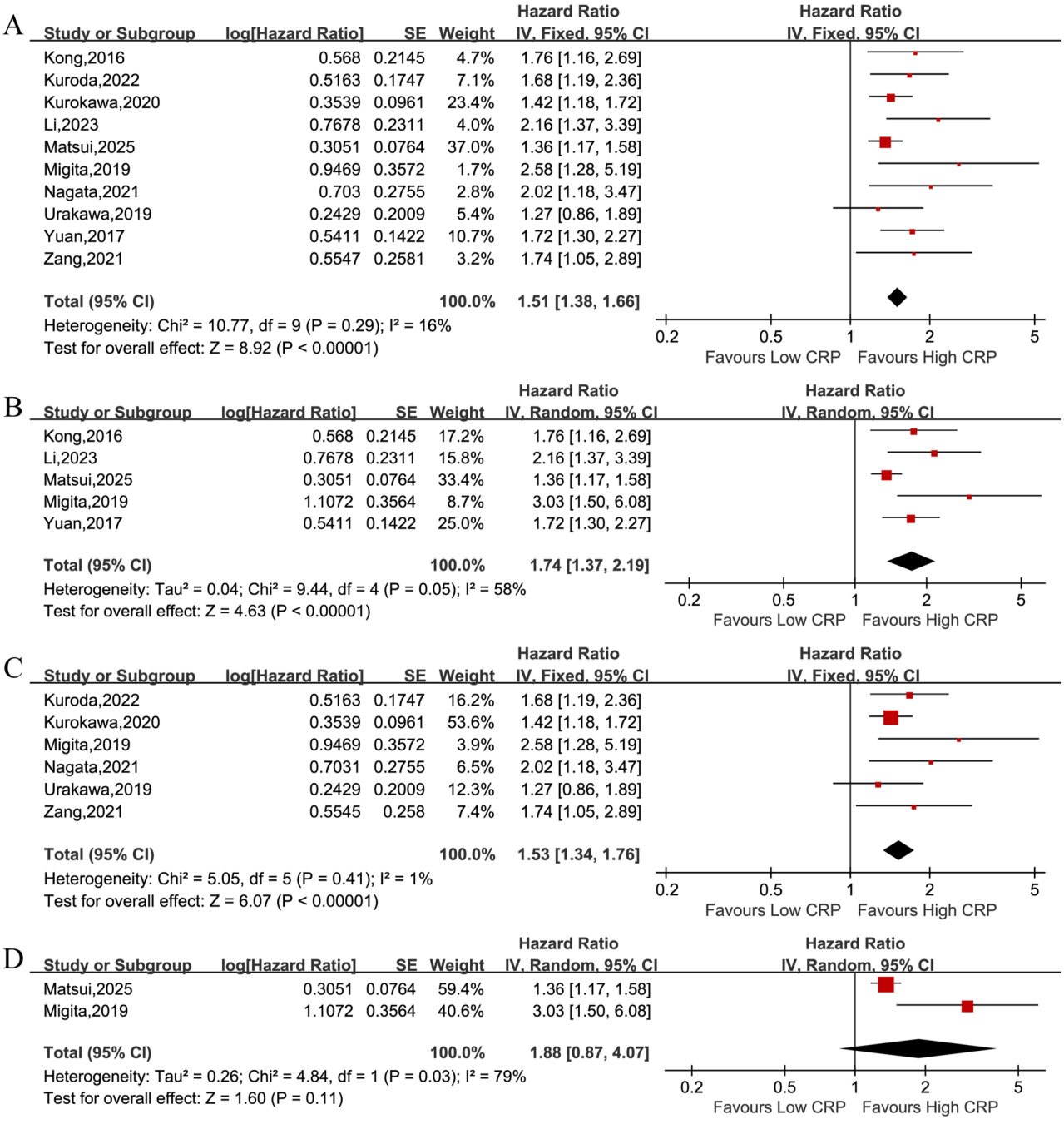

Fig. 2 Meta-analysis of postoperative C-reactive protein and overall survival in gastric cancer. Forest plot showing the pooled association between CRP and overall survival (A), along with subgroup analyses stratified by biomarker evaluation method: (B) CRP at a specific postoperative time point, (C) maximum CRP during postoperative hospital stay, and (D) CRP on postoperative day 3

inflammation, in particular, plays a pivotal role in tumor occurrence, malignant development, and metastasis.

Acute-phase reactive proteins, such as CRP and albumin, are synthesized by hepatocytes in response to cytokine stimulation and serve as key biomarkers of the systemic inflammatory response [10, 12]. Elevated CRP levels can amplify local inflammation by enhancing the secretion of inflammatory cytokines and recruiting immune cells, thereby fostering an early TME conducive to tumor growth [36]. Within this TME, the interplay between tumor cells and stromal components leads to the overexpression of oncogenes and inflammatory mediators, which collectively mediate malignant processes such as immune evasion, angiogenesis, and metastasis [37].

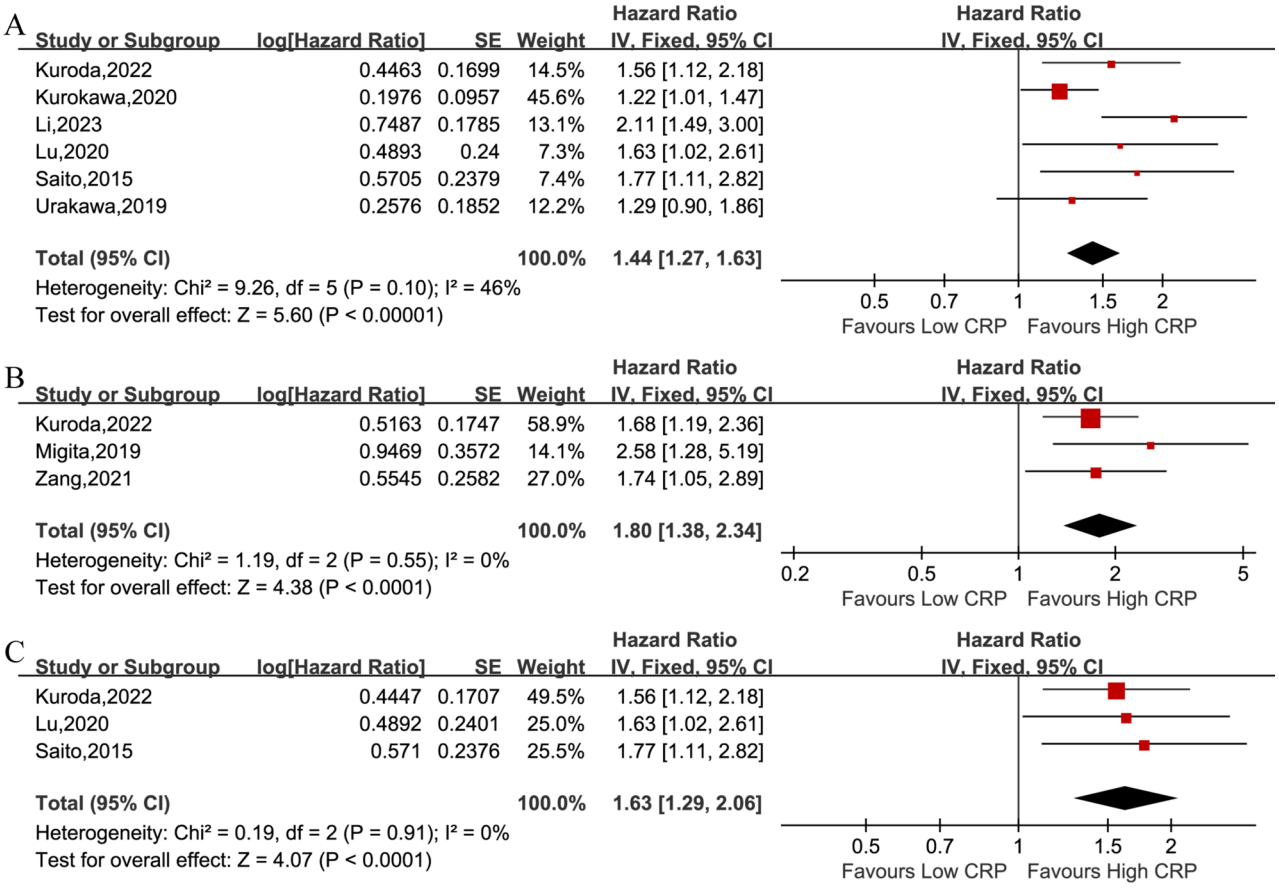

Fig. 3 Meta-analysis of the association between postoperative C-reactive protein and survival outcomes in gastric cancer. Forest plot for the association between CRP and recurrence-free survival (A). Forest plot showing the association between peak postoperative CRP within one week and overall survival (B) and recurrence-free survival (C), adjusted for multiple clinical covariates

Given the central role of systemic inflammation, numerous studies have investigated the prognostic value of inflammatory biomarkers in GC. Multiple studies have indicated that prognostic scores based on elevated preoperative CRP are considered independent indicators of poor survival [38, 39]. A large-scale pan-cancer analysis further demonstrated that CRP positively correlates with overall cancer risk, highlighting its potential for cancer risk stratification [40].

However, while the prognostic significance of preoperative inflammatory markers is well-documented, the prognostic value of postoperative CRP dynamics remains less clear. The postoperative period is a critical window where inflammatory responses reflect the physiological stress of surgery and may also indicate minimal residual disease or early recurrence. To better guide clinical decision-making—such as tailoring adjuvant therapies and optimizing follow-up strategies—it is critical to investigate the association between postoperative CRP and long-term survival, which could ultimately improve patient outcomes. Therefore, this systematic review and meta-analysis aims to comprehensively evaluate the prognostic value of postoperative CRP, with a specific focus on comparing different measurement strategies to identify the most reliable prognostic indicator.

The present meta-analysis comprehensively demonstrated the prognostic significance of postoperative CRP, with a specific focus on OS and RFS. Our pooled results demonstrate that elevated postoperative CRP is consistently associated with poorer survival outcomes, reinforcing the role of systemic inflammation as a key determinant of cancer progression.

In the analysis of OS, elevated CRP was significantly correlated with increased mortality risk, with low heterogeneity across ten cohort studies. This suggests that CRP, as a marker of inflammatory response, may reliably reflect tumor aggressiveness or host immune dysfunction in GC. Notably, when CRP was measured at a specific postoperative time point, the effect size was more pronounced, albeit with substantial heterogeneity. This variability may stem from differences in the timing of measurement or patient characteristics, highlighting the need for standardized protocols in postoperative biomarker assessment. Interestingly, the maximum CRP

during hospitalization exhibited a more conservative yet highly consistent prognostic effect. This implies that peak CRP, capturing the highest inflammatory burden during the early recovery phase, may serve as a more robust and reproducible predictor than single time-specific measurements. Although CRP on postoperative day three showed a numerically high hazard ratio, the lack of statistical significance was likely due to the limited sample size, underscoring the need for larger prospective studies to validate its utility.

With respect to RFS, elevated CRP was similarly associated with an increased risk of recurrence. The moderate heterogeneity observed may reflect variations in adjuvant treatment regimens or tumor staging among included studies. Importantly, when focusing on peak CRP within the first postoperative week, we found that it remained an independent prognostic factor for both OS and RFS after multivariable adjustment, with minimal heterogeneity. This underscores the potential of peak CRP as a clinically feasible and integrative indicator of postoperative inflammatory stress, which may enhance existing prognostic models.

Strengths and limitations

To our knowledge, this is the first meta-analysis to systematically evaluate the prognostic value of postoperative CRP for survival outcomes in gastric cancer. The clinical relevance of our findings is strengthened by the fact that the included studies predominantly provided results from multivariate analyses, confirming that the prognostic value of CRP is independent of other established clinical covariates. Our findings advocate for the integration of routine postoperative CRP monitoring into clinical practice. Specifically, tracking peak CRP during postoperative hospitalization offers a clinically feasible and highly reproducible strategy to identify patients at the highest risk for mortality and recurrence. Such risk stratification could inform decisions regarding the intensity of adjuvant therapy and follow-up schedules. Future research should focus on establishing standardized, evidence-based cutoff values for peak CRP and exploring its synergistic value when combined with other biomarkers to construct more powerful predictive models.

Despite the systematic retrieval of authoritative databases and the inclusion of high-quality studies in this meta-analysis, there was still a possibility of missing other studies, which might result in publication bias. This meta-analysis is limited by the observational design of the included studies, which precludes any causal inference regarding the relationship between postoperative CRP and survival outcomes. Despite adjustments in some original studies, residual confounding cannot be entirely ruled out. A significant constraint was our inability to perform extensive subgroup analyses to dissect how the prognostic impact of postoperative CRP might be modified by key clinicopathological factors. This constraint stems primarily from the lack of granular, patient-level data in the included primary studies, which prevented us from stratifying outcomes by key variables such as tumor stage, histological subtype, or the presence of postoperative complications. Furthermore, the variability in CRP cutoff values across the included studies may limit the generalizability of our findings. While our meta-analysis confirms the prognostic significance of postoperative CRP in gastric cancer, the evidence base is constrained by the limited number of included studies. Therefore, large-scale, prospective studies are warranted to establish standardized measurement timings and evidence-based cutoff values, ultimately enhancing the predictive accuracy for poor prognosis after radical gastrectomy.

Conclusions

In summary, postoperative CRP is a robust prognostic marker in gastric cancer. Peak CRP value within the first postoperative week emerges as a particularly strong, independent, and consistent predictor of both overall and recurrence-free survival, advocating for its incorporation into future prognostic scoring systems for guiding personalized patient management.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-04481-y.

Additional file 1. Table S3: Analysis of prognostic risk factors

Additional file 2. Table S6: Publication bias

Additional file 3. Table S2: Search strategy

Additional file 4. S2 Fig: Sensitivity analysis

Additional file 5. S3 Fig: Funnel plot

Additional file 6. S1 Fig: Risk of bias

Additional file 7. Table S1: PRISMA 2020 Checklist

Additional file 8. Table S4: Included studies, excluded studies and reasons for exclusion

Additional file 9. Table S5: QUIPS Risk of Bias Assessment

Acknowledgements

The authors would like to acknowledge all the authors of the articles that were reviewed in preparing this manuscript.

Authors' contributions

Design, conceive and write papers: Dong yang ShenConceptualization: Dong yang Shen, Wen Bo Xia, Zhi Yong LiLiterature search and data extraction: Dong Yang Shen, Shuai Zhao, Xu YangFormal analysis: Dan Li, Xu YangReview and editing: Yun Ning HuangAll authors read and approved the final manuscript, and ensured that this is the case.

Funding

None.

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.

Received: 4 June 2025 / Accepted: 13 November 2025
Published online: 26 November 2025

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