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*Original Article*

# Prognostic value of serum C-reactive protein in pancreatic cancer: a meta-analysis

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**Abstract:** Background: The prognostic value of pretreatment C-reactive protein in pancreatic carcinoma patients remains controversial. This meta-analysis was performed to evaluate that prognostic value. Purpose: Systemic review and meta-analysis was used to evaluate the prognostic value of C-reactive protein in pancreatic cancer. Methods: PubMed, EMBASE, and CNKI were searched. There were no eligible studies in CNKI. Therefore, PubMed and EMBASE were searched to identify eligible studies reporting the prognostic role of pretreatment C-reactive protein in patients with pancreatic cancer. Statistical analyses were performed using STATA software (Version 12.0; Stata Corporation). Hazard ratio (HR) with its 95% confidence interval (CI) was used to estimate effect size. Results: A total of 9 studies, including 1,084 patients, were identified. Pooled results showed that elevated C-reactive protein levels were associated with poor overall survival (HR: 1.74, 95% CI: 1.49-2.04) in pancreatic cancer and (HR: 1.70, 95% CI: 1.42-2.04) in advanced pancreatic cancer patients. In addition, high C-reactive protein levels tended to be an independent prognostic factor for overall survival in patients with pancreatic cancer (HR: 3.93, 95% CI: 2.35-6.59). Conclusion: This meta-analysis indicated that elevated C-reactive protein levels were associated with poor outcomes in pancreatic carcinoma patients and may be an independent prognostic indicator for pancreatic cancer.

**Keywords:** Pancreatic cancer, C-reactive protein, prognosis, survival, meta-analysis

## Introduction

Pancreatic cancer is one of the most aggressive tumors and a leading cause of cancer-related deaths worldwide, with a median survival time of less than 6 months and 5-year overall survival rate under 6% [1-3]. Incidence of pancreatic cancer in China has increased dramatically over the past several decades [4]. Despite advances in surgical techniques and incorporation of new therapeutic approaches, pancreatic cancer remains a highly devastating disease with poor prognosis. A variety of evidence has shown that some clinical parameters, such as CA19-9 [5-8] and the neutrophil to lymphocyte ratio (NLR), [9-11] can be used as both diagnostic and prognostic factors for pancreatic carcinoma. Although some researchers have reported that C-reactive protein (CRP) could serve as a risk factor in tumorigenesis, the current opinion on the prognostic role of pretreatment and elevated serum CRP levels in pancreatic cancer remains controversial.

CRP is a representative acute phase reactant, accepted as one of the most widely used systemic inflammatory markers *in vivo* [12]. In addition, CRP has been examined frequently with respect to predicting survival [13]. Preoperative serum elevation of CRP has been identified as a significant prognostic factor in various malignancies, such as colorectal cancer [14], small cell lung cancer [15] and hepatic carcinoma [16].

To date, 9 studies have investigated association between elevated CRP and prognosis for pancreatic cancer. Three studies [17-19] reported that elevated CRP was a poor independent prognostic factor for pancreatic cancer. Six studies [20-25] found that elevated CRP is not a poor independent prognostic factor.

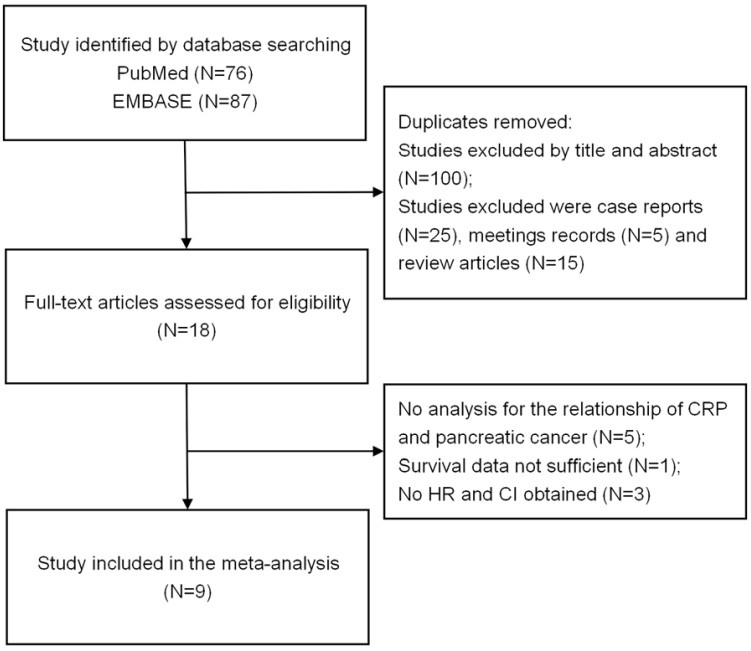


**Figure 1.** Detailed overview of literature search. A total of 163 articles were identified through database search. After titles and abstracts were reviewed, 18 were eligible for further evaluation. Finally, 9 studies were eligible for meta-analysis.

As these results were inconsistent, a meta-analysis was needed to evaluate the prognostic value of CRP in pancreatic cancer.

## Materials and methods

*Search strategy and selection criteria*

This study was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [26]. PubMed and EMBASE databases were searched for studies showing the prognostic value of CRP in pancreatic cancer, before December 31, 2015, using the following terms: 'pancreatic cancer' or 'pancreatic carcinoma', 'C-reactive protein', and 'prognostic'. Only studies published in English were included.

All potentially eligible studies were retrieved. Studies were included if they met the following criteria: (1) Measured pretreatment serum CRP levels and reported the number of patients with normal CRP and elevated CRP levels; (2) Evaluated the potential association between pretreatment serum CRP levels and overall survival (OS) of patients with pancreatic carcinoma; (3) Provided hazard ratio (HR) and 95% confidence intervals (95% CI); and (4) Included a minimum sample size of 50.

Two authors, independently, evaluated the potential eligibility of all studies retrieved from the databases according to predetermined selection and exclusion criteria.

*Data extraction*

Data were extracted, independently, by two authors according to inclusion criteria. The following data were collected from each study: first author, publication year, location of the study, sample size, median age, cut-off value of the CRP, analysis, and outcomes reported. Overall survival (OS) was calculated from the date of diagnosis to date of the last follow up or death from cancer.

*Statistical analyses*

The objective of this study was to evaluate the prognostic role of pretreatment CRP in pancreatic carcinoma patients. Hazard ratios (HRs) of overall survival (OS) and their 95% CIs were used to quantitatively aggregate survival data. HRs were collected directly from the journal articles. Heterogeneity was assessed using Higgins $I^2$, which measures the percentage of total variation across studies that is due to heterogeneity rather than change [27]. Fixed-effects models were used to analyze the relationship of CRP with survival of PC patients and the relationship between elevated CRP levels and OS in advanced PC patients, as heterogeneity did not exit. Next, 2 studies were found to lead to heterogeneity when analyzing the independent prognostic value of CRP for OS in patients with pancreatic carcinoma. After dropping those 2 studies, the fixed-effects model was used again, finding no heterogeneity. Begg's funnel plot was employed to examine publication bias, considered to be statistically significant with $P \leq 0.1$. Significance of pooled HR was determined by Z-test and $P<0.05$ was considered statistically significant. Stata soft-

**Table 1.** Characteristics of studies in the meta-analysis

| Study | Country | Sample size | Median age (range) | Cut-off point | Outcome Reported | Selection | Comparability | Outcome | Score |
|---|---|---|---|---|---|---|---|---|---|
| Jamieson 2005 [21] | UK | 65 | <65 | 10 mg/l | OS | ★★★ | ★ | ★★ | 6 |
| Nakachi 2007 [18] | Japan | 74 | 61.5 (37-90) | 5.0 mg/dl | OS | ★★★ | ★ | ★★★ | 7 |
| Muller 2008 [23] | Germany | 136 | 63 (31-83) | 50 mg/l | OS | ★★★ | ★ | ★★ | 6 |
| Wang 2012 [24] | China | 177 | <65 | 10 mg/l | OS | ★★★ | ★ | ★★ | 6 |
| Sanjay 2012 [19] | UK | 51 | 70 (49-85) | 3 mg/l | OS | ★★ | ★ | ★★★ | 6 |
| Haas 2013 [20] | Germany | 155 | 63 (31-78) | 1.0 mg/dl | OS | ★★ | ★ | ★★★ | 6 |
| Miura 2014 [17] | Japan | 50 | 64 (48-85) | 0.4 mg/dl | OS | ★★★ | ★ | ★★ | 6 |
| Xue 2014 [25] | Japan | 252 | >65 | 0.5 mg/dl | OS | ★★ | ★ | ★★★ | 6 |
| Martin 2014 [22] | Australia | 124 | 68.5 (35-90) | 10 mg/l | OS | ★★★ | ★ | ★★ | 6 |

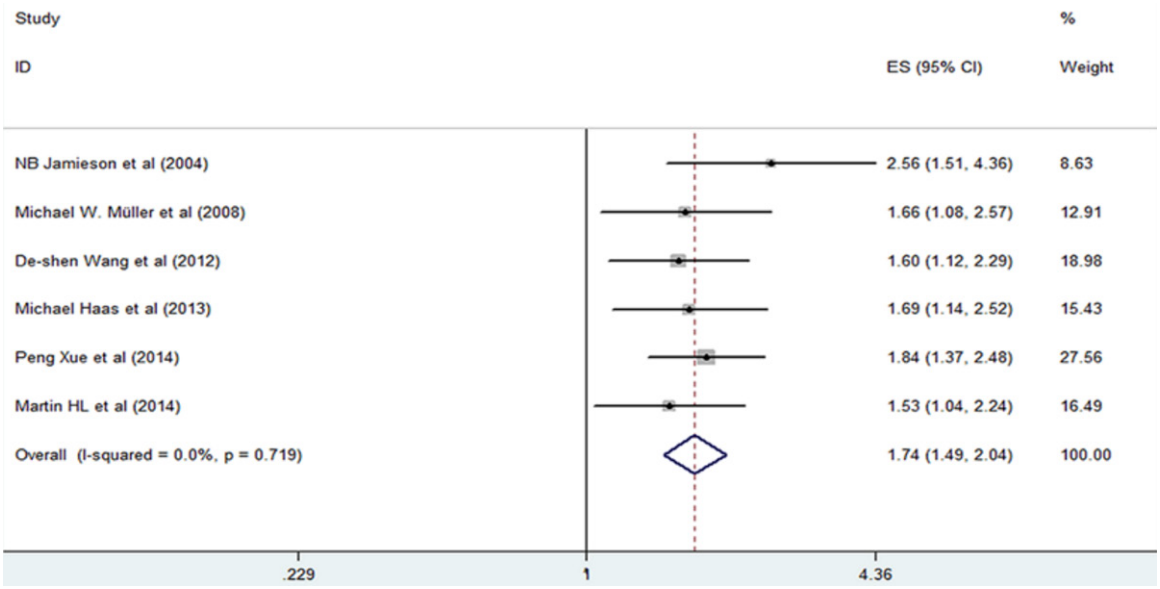


**Figure 2.** Overall survival associated with CRP in six studies. Six studies analyzed the relationship of CRP with survival of PC patients and presented the HR. It appeared that an elevated CRP level was associated with worse OS. Furthermore, an increased serum CRP level was significantly correlated to OS. The pooled HR was 1.74 (95% CI: 1.49-2.04). No heterogeneity existed ($I^2$=0.0%, P=0.719).

ware (Version 12.0, Stata Corporation, USA) was used for all analyses.

## Results

### *Study characteristics*

A total of 163 articles were identified through the database search. After titles and abstracts were reviewed, 18 were eligible for further evaluation. Finally, 9 studies were eligible for the meta-analysis. A detailed overview of the literature search is shown in **Figure 1**.

Major characteristics of the retained studies are listed in **Table 1**. Among these nine studies, two studies were performed in the UK, three in Japan, two in Germany, one in Australia, and one in China. A total of 1,084 patients were included in this study.

### *Meta-analysis*

*Overall survival associated with CRP:* Six studies analyzed the relationship of CRP with survival of PC patients and presented the HR. It appeared that elevated CRP levels were associated with worse OS. Furthermore, increased serum CRP levels were significantly correlated to OS. Pooled HR was 1.74 (95% CI: 1.49-2.04). No heterogeneity existed ($I^2$=0.0%, P=0.719). Results are listed in **Figure 2**.

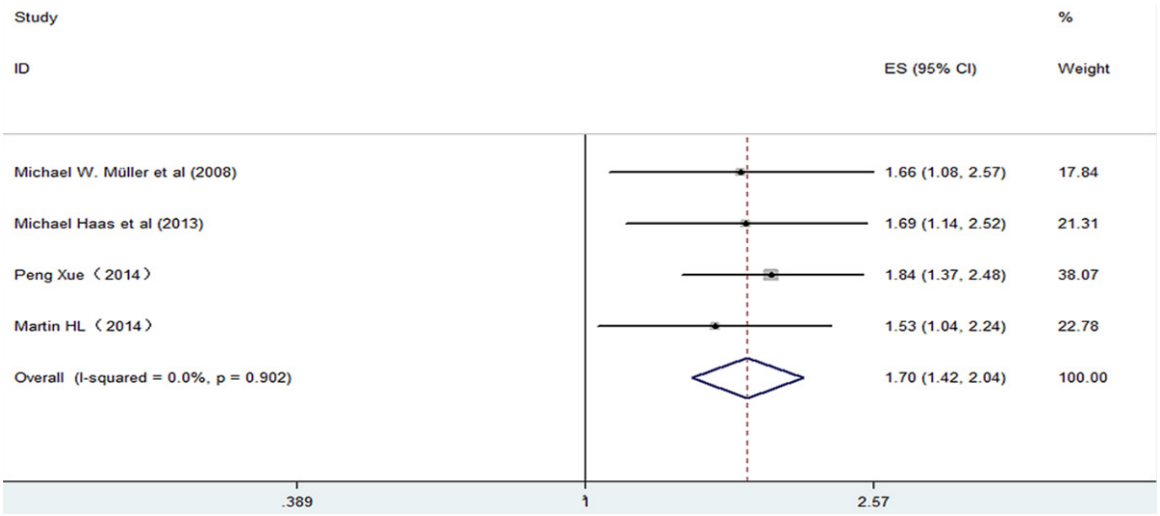


**Figure 3.** Overall survival associated with CRP in four advanced PC studies. Four studies provided data regarding the relationship between an elevated CRP level and OS in advanced PC patients. In patients with advanced PC, an elevated CRP was obviously associated with worse OS, with an estimated HR of 1.70 (95% CI: 1.42-2.04). No heterogeneity existed ($I^2$=0.0%, P=0.902) and results are listed in the picture.

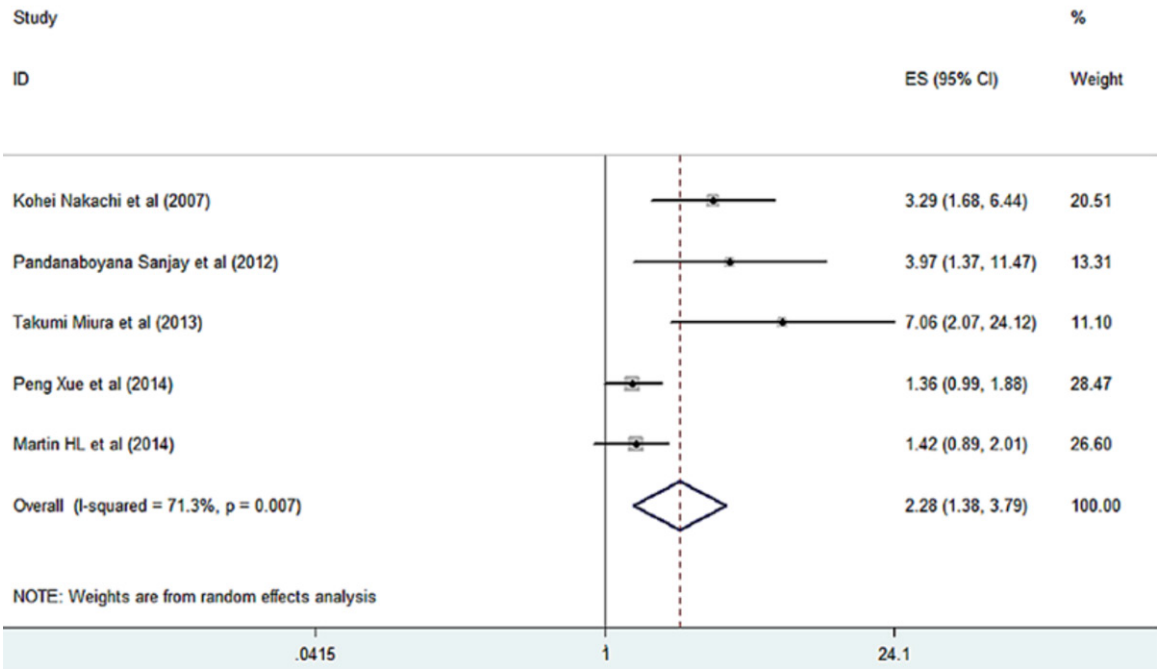


**Figure 4.** Independent prognostic value of CRP for OS. There were only five studies that reported the independent prognostic value of CRP for OS in patients with pancreatic carcinoma. Three concluded that elevated CRP was an independent prognostic factor for OS in patients with pancreatic cancer, while two studies gave a different result. The combined HR was 2.28 (95% CI: 1.38-3.79), which showed that a high CRP level was an independent prognostic factor for OS in patients with PC. There was heterogeneity between the 5 studies ($I^2$=71.3%, P=0.007).

*Overall survival associated with CRP in advanced PC:* Four studies provided data regarding the relationship between elevated CRP levels and OS in advanced PC patients. In patients with advanced PC, elevated CRP was obviously associated with worse OS, with an estimated HR of 1.70 (95% CI: 1.42-2.04). No heterogeneity existed ($I^2$=0.0%, P=0.902). Results are listed in **Figure 3**.

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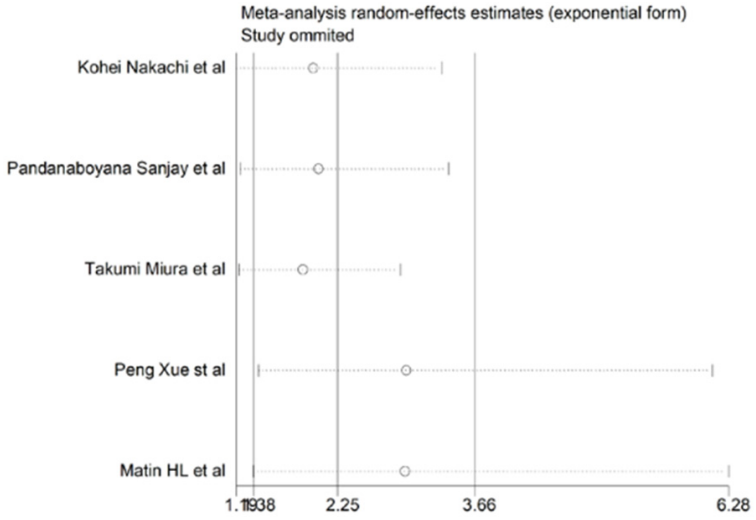


**Figure 5.** Result of sensitivity analysis. According to results of sensitivity analysis, it was found that there were 2 studies leading to heterogeneity.

pendent prognostic value of CRP for OS in patients with pancreatic carcinoma. Three concluded that elevated CRP was an independent prognostic factor for OS in patients with pancreatic cancer, while two studies gave a different result. Combined HR was 2.28 (95% CI: 1.38-3.79), which showed that a high CRP level was an independent prognostic factor for OS in patients with PC. There was heterogeneity between the 5 studies ($I^2$=71.3%, $P$=0.007). Results are listed in **Figure 4**. Next, sensitivity analysis was performed. According to the results of sensitivity analysis (**Figure 5**), it was found that there were 2 studies [22, 25] that led to heterogeneity. After removing those 2 studies, meta-analysis was performed again. There was no heterogeneity between the last 3 studies [17-19] ($I^2$=0.0%, $P$=0.564). Combined HR was 3.93 (95% CI: 2.35-6.59) and results are listed in **Figure 6**.

*Publication bias*

Begg's funnel plot was presented to assess publication bias. Results of Begg's test in the survival analysis showed no evidence of publication bias (P=0.086) (**Figure 7**).

## Discussion

Elevated CRP has been investigated for its prognostic value in pancreatic cancer patients for several years. However, whether it is an independent factor for poor prognosis in pancreatic cancer patients remains controversial. Thus, this meta-analysis was conducted. Overall, elevated serum CRP was found to be an independent indicator of poor prognosis.

It has been over 80 years since CRP was identified and used as a traditional inflammatory marker [12], however, its prognostic value in pancreatic carcinoma has only been reported in recent years. In this study, elevated CRP was a good predictor of poor OS (HR=1.74, 95% CI: 1.49-2.04) of pancreatic cancer patients. In addition, Szkandera reported that poor cancer-specific survival (CSS) in patients was associated with elevated CRP levels and an HR of 1.60 (95% CI: 1.16-2.21) [28].

This study was implemented to evaluate the prognostic role of CRP in advanced PC. Results revealed that those with lower CRP levels probably have a more optimistic likelihood of survival, while higher CRP levels tend to show association with worse survival. Combined HR and its 95% CI indicated that an elevated CRP level was an independent prognostic factor for a poor OS (HR=3.93, 95% CI: 2.35-6.59) in patients with pancreatic cancer.

CRP is a representative acute-phase reactant, due to its rapid production and short half-life in circulation. CRP is mainly produced by hepatocytes in the liver in response to inflammatory cytokines. Elevated CRP is considered the hallmark of underlying malignancy or premalignancy tissue inflammation associated with tumor growth [29]. Extrahepatic production of CRP has been found in tumor cells, monocytes, lymphocytes, and neurons as a part of local inflammation, but the amount is not sufficient to affect serum CRP [30]. Induced by infectious and non-infectious processes, including cancer and tissue damage, CRP is a sensitive but not a specific serum biomarker [31]. In addition to its role as a very sensitive indicator of current inflammation status, serum CRP has recently been re-evaluated for extending its clinical use to diagnosis of cardiovascular diseases and prediction of cancer risk [30].

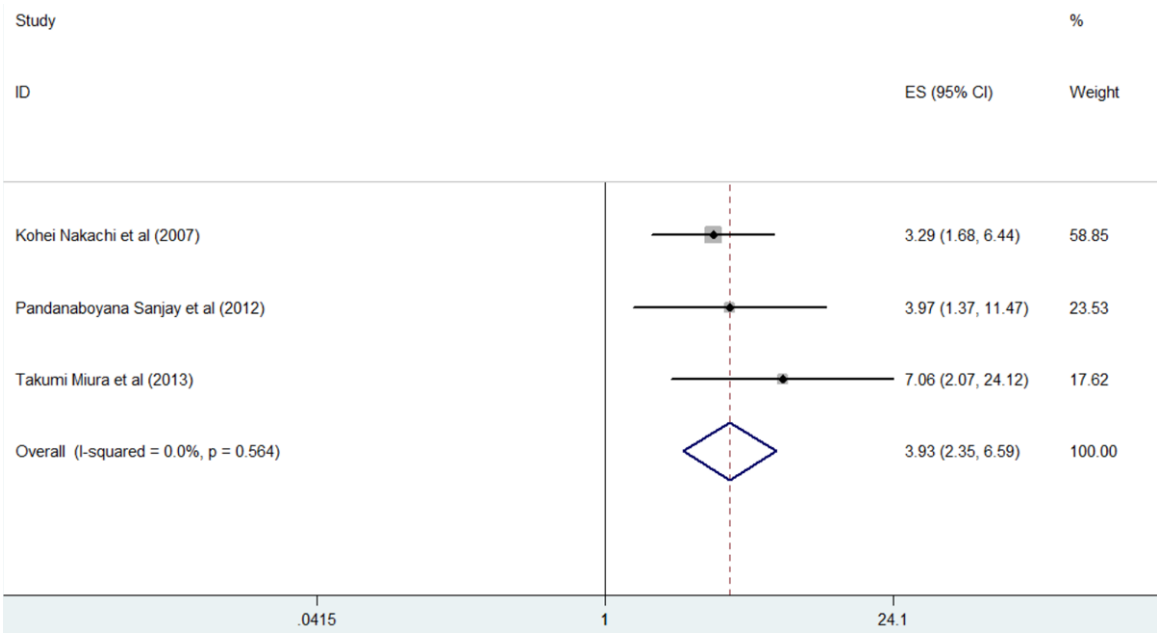


**Figure 6.** Results of heterogeneity analysis. After removing those 2 studies, meta-analysis was performed again. There was no heterogeneity between the last 3 studies ($I^2$=0.0%, P=0.564). Combined HR was 3.93 (95% CI: 2.35-6.59).

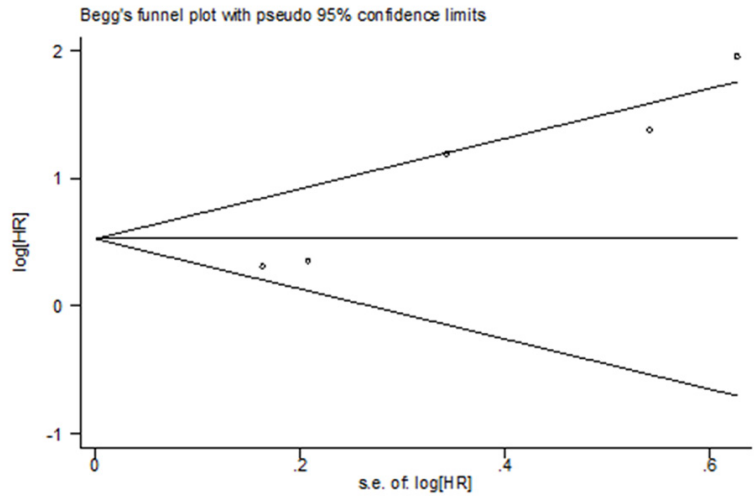


**Figure 7.** Results of publication bias. Begg's test results showed no evidence of publication bias (P=0.086).

The mechanisms connecting CRP levels with survival in advanced disease are not clear. However, there is a release of inflammatory cytokines and growth factors as part of the systemic inflammatory response to tumors. This could not only stimulate tumor growth but also exert profound catabolic effects on host metabolism [32]. CRP expression is associated with increased weight loss, reduced performance status, and increased fatigue, ultimately resulting in poor survival. According to these indicators, elevated CRP values may produce poor survival in patients with pancreatic cancer.

This present study had limitations. A key point of this meta-analysis was that the cut-off value of CRP in the original documents was not absolute. It ranged from 3 to 50 mg/L, as different methods and kits were used to assay CRP in respective hospitals. Stratifying cases by absolute CRP values was not possible. Therefore, all cases were classified according to the original research. This could inevitably cause heterogeneity and bias. Additionally, studies included in this analysis differed considerably in carcinoma subtypes, selection criteria, and methodology. This may have introduced heterogeneity and bias. Therefore, the validity of this present analysis might be weakened.

## Conclusion

In conclusion, the present meta-analysis suggests that elevated serum CRP is significantly associated with poor outcomes in pancreatic

carcinoma patients. In addition, CRP may be an independent prognostic indicator for pancreatic cancer. However, additional research is necessary to provide more powerful evidence, confirming the present results.

## Disclosure of conflict of interest

None.

## Abbreviations

PC, Pancreatic cancer; CRP, C-reactive protein; HR, Hazard ratio; CI, Confidence interval; OS, Overall survival; CSS, Cancer-specific survival.

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