Systematic Review and Meta-Analysis

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Pretreatment C-reactive protein/albumin ratio for predicting overall survival in pancreatic cancer

A meta-analysis

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Abstract

Background: Inconsistent findings have been reported regarding the association of C-reactive protein to albumin ratio (CAR) with survival outcome in patients with pancreatic cancer. We conducted the current meta-analysis to assess the prognostic utility of elevated baseline CAR in predicting overall survival (OS) in pancreatic cancer patients.

Methods: A comprehensively literature search was performed in the PubMed and Embase database until February 10, 2019. Studies evaluating the association between pretreatment CAR and OS among pancreatic cancer were selected. Study quality was evaluated by using the Newcastle-Ottawa Scale.

Results: Nine retrospective studies involving 1534 pancreatic cancer patients were identified. A meta-analysis using a random-effect model indicated that elevated CAR was associated with poor OS (hazard ratio 1.98; 95% confidence interval 1.58–2.48). Subgroup analysis produced similar prognostic values for OS in different geographical regions, sample sizes, thresholds of CAR, treating methods, and Newcastle-Ottawa Scale points.

Conclusion: Elevated pretreatment CAR may independently predict poor OS in pancreatic cancer patients. Pretreatment CAR is possibly a simple and cost-effective blood-derived indicator for predicting survival outcome in patients with pancreatic cancer.

Abbreviations: CAR = C-reactive protein to albumin ratio, CI = confidence intervals, GPS = Glasgow prognostic score, HR = hazard ratio, mGPS = modified Glasgow prognostic score, NLR = neutrophil-to-lymphocyte ratio, NOS = Newcastle–Ottawa Scale, OS = overall survival, PLR = platelet-lymphocyte ratio.

Keywords: C-reactive protein/albumin ratio, meta-analysis, overall survival, pancreatic cancer

1. Introduction

Pancreatic cancer remains the sixth most frequent malignancy.[1] Inoperable advanced pancreatic cancer accounts for approximately 80% to 85% of patients.[2] Despite great advancement in chemotherapy and surgery, the 5-year survival rate of advanced pancreatic cancer is less than 5%.[3] Therefore, identification of new prognostic markers is very crucial for improved risk stratification in advanced pancreatic cancer patients.

Cancer-related inflammation play an important role in carcinogenesis and tumor progression.[4,5] Chronic systemic inflammation markers, such as Glasgow prognostic score (GPS) or modified GPS (mGPS), platelet-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) have been linked to the survival of cancer patients.[6] The mGPS established on the C-reactive protein (CRP) and albumin level is recognized as a useful prognostic score for predicting the prognosis of cancer patients.[7] CRP/albumin ratio (CAR), a new developed predictive indicator, reflects both inflammatory and nutritional status of cancer patients. Both inflammation and malnutrition contribute to poor outcomes in cancer patients. An elevated CAR indicates a worse general condition for cancer patients.[8] CAR has been identified as an independent prognostic marker for survival outcomes in patients with solid tumors.[9] However, conflict results[10–15] have been reported regarding the association of elevated baseline CAR with survival outcome in pancreatic cancer patients. Thus, the predicting role of CAR in these patients remains inconclusive.

Among pancreatic cancer patients, no previous meta-analysis has specially focused on the use of pretreatment CAR in the prediction of overall survival (OS). We therefore performed the current meta-analysis to investigate the prognostic utility of elevated baseline CAR in predicting OS in patients with pancreatic cancer.

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2. Materials and methods

2.1. Literature search

The current meta-analysis was followed by the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis.[16] Ethical approval was not necessary because this study is a study-level analysis. A comprehensively literature search was performed in the PubMed and Embase database from their inceptions to February 10, 2019. The literature search applied the following strategy: C-reactive protein/albumin ratio or C-reactive protein to albumin ratio and pancreatic cancer or pancreatic tumor or pancreatic carcinoma or "pancreatic ductal adenocarcinoma". Additionally, the reference lists of pertinent articles were also manually searched for any possible missing studies.

2.2. Inclusion and exclusion criteria

Studies satisfying the following inclusion criteria were eligible:

(1) observational studies enrolling patients with confirmed diagnosis of pancreatic cancer;
(2) exposure was baseline CAR;
(3) reported multivariable adjusted hazard ratio (HR) and 95% confidence interval (CI) for OS associated with elevated CAR.

Exclusion criteria included

(1) reported unadjusted risk estimates;
(2) post-treatment CAR as exposure; and
(3) meeting abstracts, reviews, or comments.

2.3. Data extraction and study quality

The following items were independently extracted by 2 authors from the included studies: surname of the first author, publication year, country, design of study, sample sizes, gender, mean/median age, cancer stage, type of treatment, cutoff value for CAR, duration of follow-up, multivariable adjusted risk HR with 95% CI, and variables in the adjustment model. Methodological quality was evaluated using the Newcastle–Ottawa Scale (NOS) for cohort studies by 2 independent authors.[17] Studies with NOS scores of 7 points or over were recognized as high-quality. Disagreement between 2 authors was resolved through consensus.

2.4. Data synthesis and analyses

The prognostic value of elevated baseline CAR was pooled by the multivariable adjusted HR and 95% CI. The Cochrane Q test and the I^2 statistic were used to check the presence of heterogeneity between studies.

P value $<.1$ of Cochrane Q test or I^2 statistic $\geq 50\%$ indicates the presence of statistical significant heterogeneity. A random-effect model was selected for the pooling analysis in the presence of significant heterogeneity. Otherwise, a fixed-effect model was selected. Publication bias was quantitatively examined using the Begg rank correlation[18] and Egger linear regression test,[19] with significance level set at $P<.10$. Furthermore, a trim-and-fill approach was used to explore the influence of possible missing studies. Furthermore, we conducted the subgroup analysis according to sample sizes (≥ 100 vs <100), country (Japan vs South Korea vs China), treating methods (chemotherapy vs resection), thresholds of CAR (≤ 0.5 vs >0.5), and NOS points (<7 vs ≥ 7). Sensitivity analysis was conducted by sequentially omitting 1 study at each turn from the meta-analysis. All statistical analyses were carried out with STATA 12.0 (Stata Corp LP, TX).

3. Results

3.1. Search results and study features

Initially, 361 potentially pertinent articles were identified by searching the above-mentioned databases. Of which, 255 duplicates were removed. Eighty-six records were removed after scanning the titles or abstracts. The remaining 22 articles were retrieved for full-text assessment. Finally, 9 studies[10–13,20–24] were included in the meta-analysis (Fig. 1).

Table 1 shows the main feature of included studies. All eligible studies were retrospective designs. These included studies were published from 2016 to 2019 and conducted in China,[11,13,20,23] South Korea,[10,22] and Japan.[12,21,24] The patients number of included studies varied from 43 to 386, with a total of 1534 pancreatic cancer patients. Five studies only included surgical resection patients, 2 studies enrolled patients undergoing chemotherapy, and the remaining studies enrolled patients receiving multiple treatments. The thresholds of elevated baseline CAR varied between 0.03 and 3.85. Seven studies[11–13,20,22–24] achieving 7 to 8 NOS points were defined as high quality.

3.2. Impact of CAR on overall survival

All the included studies reported results on serum CAR and OS in pancreatic cancer patients. As shown in Figure 2, there was significant heterogeneity across studies ($I^2=56.7\%$; $P=.018$). A random effect model meta-analysis indicated that elevated baseline CAR was associated with poor OS (HR 1.98; 95% CI 1.58–2.48) than those with lower CAR group. In the sensitivity analyses, removal of any individual studies had minimal impact on the pooled results (HR ranged from 1.76 to 2.10). P values of the Egger and Begg test were 0.585 and 0.466, respectively, which revealed no evidence of publication bias. In the trim-and-fill approach, there was 1 possible missing study in the funnel plot (Fig. 3). However, imputing this potential missing study did not significantly alter the original prognostic significance (HR 1.76; 95% CI 1.07–2.89; $P=.027$). Moreover, the significant prognostic roles were consistently observed in each named subgroup (Table 2).

4. Discussion

Current results were obtained by analyzing data on 1534 pancreatic cancer patients in 9 retrospective studies. The main finding of this meta-analysis suggests that elevated pretreatment CAR may be independently predicted poor OS among pancreatic cancer patients. Pancreatic cancer patients with elevated CAR had a 98% higher risk of death compared with those with lower CAR level. Our subgroup analysis further confirmed the statistically significant prognostic value of elevated CAR in each named subgroup. Therefore, determination of CAR may be better defining the baseline risk in pancreatic cancer patients.

Several scoring systems based on the systemic inflammation have been developed to investigate the prognosis of pancreatic cancer patients.[25] Both mGPS and NLR are promising prognostic biomarkers for pancreatic cancer but PLR is less predictive than others.[26–28] In our analysis, the prognostic role of elevated baseline CAR in prediction of OS was superior to

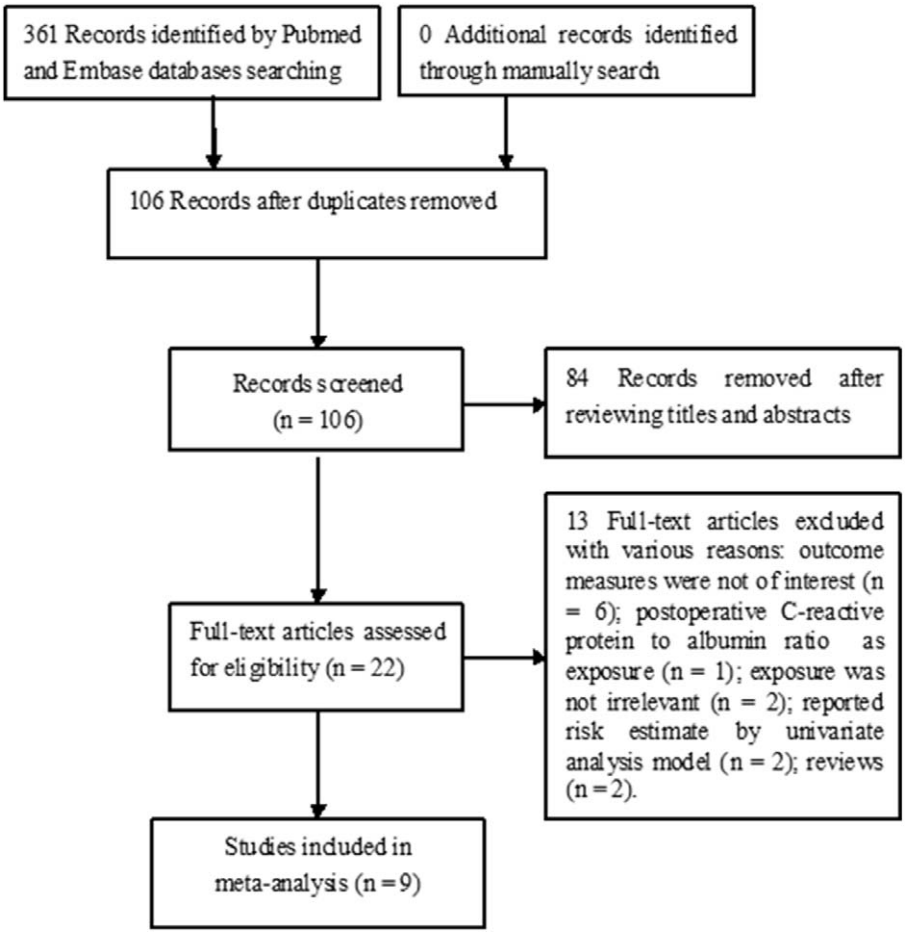

Figure 1. Flowchart showing the study selection process.

those of NLR and PLR. Jaundice is frequently observed in pancreatic cancer patients.[29] Malignant obstructive jaundice increases the circulation of inflammatory biomarkers.[30] Pancreatic cancer patients with jaundice may present high CAR and subsequently affect the prognostic value.

CAR was significantly associated with poor OS of pancreatic cancer patients, which is similar to the findings in lung cancer,[31] nasopharyngeal carcinoma,[32,33] colorectal cancer,[34] and various solid tumors.[35] In addition to OS, CAR also independently predicted the progression-free survival (HR 1.48; 95% CI 1.17–1.88)[22] and disease-free survival (HR 1.66; 95% CI 1.19–2.29)[15] in pancreatic cancer patients. There was no significant association between elevated baseline CAR and recurrence-free survival (HR 1.12; 95% CI 0.73–1.71).[14]

Table 1

Summary of clinical studies included in meta-analysis.

Author/yr	Country	Study design	Patients (%men)	Mean/median age (years)	Cancer stage	Treatment	Cutoff value for CAR	OS/RR or HR (95% CI)	Follow-up (mo)	Total NOS
Lee 2016[10]	South Korea	Retrospective	Advanced PC 82 (60)	63.5±10.7	NR	Chemotherapy	>0.5 vs≤ 0.5	1.60 (0.84–3.04)	Up to 24	6
Wu 2016 [11]	China	Retrospective	Advanced PC 233 (67)	Median 62 (26–85)	III or IV	Multiple	≥0.54 vs<0.54	4.00 (2.64–6.03)	Up to 12	7
Haruki 2016[12]	Japan	Retrospective	PC 113 (61.9)	66.8±10.5	0 (7), I (3), II (19), III (55), IV (29)	Resection	≥0.03 vs<0.03	1.73 (1.04–2.87)	>60	8
Liu 2017[13]	China	Retrospective	PDA 386 (61.7)	Median 61 (34–83)	I (39), II (89), III (84), IV (174)	Resection	≥0.18 vs<0.18	2.07 (1.59–2.70)	Median 8.7	8
Hang 2017[20]	China	Retrospective	Locally advanced or metastatic PC 142 (64.8)	Median 61 (34–86)	III (41), IV(101)	Chemotherapy	≥0.156 vs <0.156	1.63 (1.10–2.42)	Up to 45	7
Ikeguchi 2017[21]	Japan	Retrospective	PDA 43 (69.8)	Median 71.6 (37–88)	I A (3), IB (2), IIA (7), IIB (25), III (6)	Resection	>0.04 vs≤ 0.04	2.90 (1.14–7.34)	Median 25	6
Kim 2018[22]	South Korea	Retrospective	Advanced PC 302 (62.6)	Median 64 (38–82)	NR	Multiple	≥3.85 vs<3.85	1.45 (1.11–1.91)	Median 6.7	7
Luo 2018[23]	China	Retrospective	PC 97 (66)	Median 63.8 (42–81)	I–IIA (57), IIB– III (40)	Resection	≥0.109 vs <0.109	1.83 (1.07–3.14)	Median 18	7
Ikuta 2019[24]	Japan	Retrospective	PDA 136 (55.9)	Median 68 (33–86)	I–II (99), III–IV (37)	Resection	>0.09 vs≤ 0.09	1.98 (1.05–3.72)	16.8	8

CAR = C-reactive protein (CRP)-to-albumin, CRP = C-reactive protein, HR = hazard ratio, NOS = Newcastle–Ottawa Scale, NR = not reported, OS = overall survival, PC = pancreatic cancer, PDA = pancreatic ductal adenocarcinoma, RR = risk ratio.

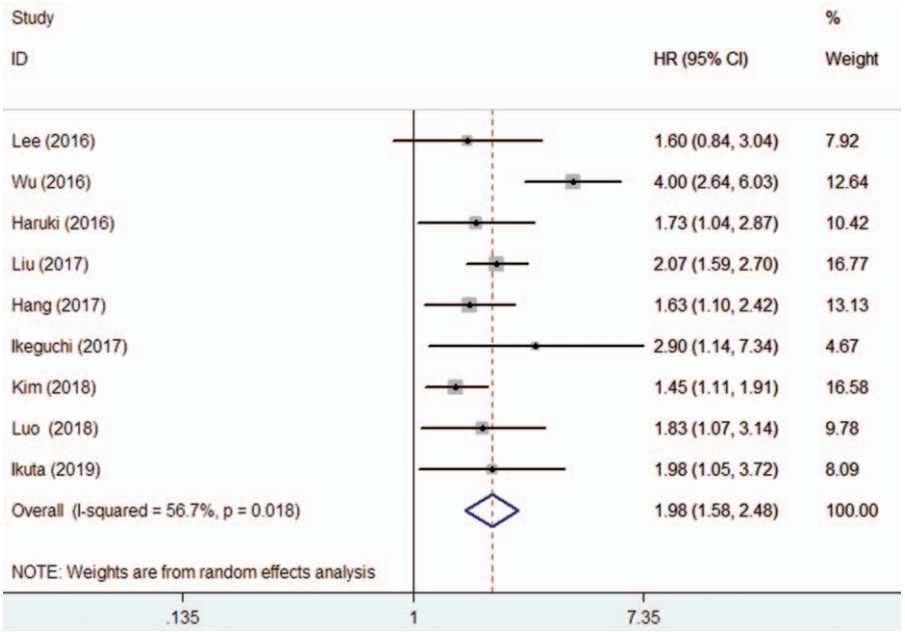

Figure 2. Forest plots showing HR and 95% CI of overall survival for high versus low C-reactive protein to albumin ratio in a random effect model. CI = confidence intervals, HR = hazard ratio.

However, elevated CAR at post-surgery day 14 but not baseline CAR independently predicted recurrence-free survival and OS.[14]

The cut-off values of CAR were lower in patients with surgical resection than in those without. This finding may be partly explained the better nutritional status in patients who received the resection. The prognostic mechanisms of CAR in pancreatic cancer are largely unknown. Cancer-related inflammatory responses may be associated with tumor progression and recurrence.[36] CRP has been demonstrated to independently predict poor survival in patients with pancreatic cancer.[37] Serum albumin level is an important biomarker of nutritional state. Meanwhile, serum level albumin also reflects a consequence of inflammatory status. Pretreatment hypoalbuminemia is also linked with poor survival in cancer patients.[38] CAR combined with the effects of CRP and albumin may continuously reflect the inflammatory and nutritional status of patients with different stages of pancreatic cancer. Therefore, CAR can improve the prognostic value than the single use of CRP or albumin.

Nevertheless, several limitations should be noted in this meta-analysis. First, all eligible studies were retrospective nature, which was more susceptible to recall bias and selection bias. Second, CRP is a non-specific inflammatory marker, and the coexistence of other systemic inflammatory diseases could influence CRP level. Third, cutoff values of high CAR were not unified and ranged between 0.04 and 3.85 across the included studies, which

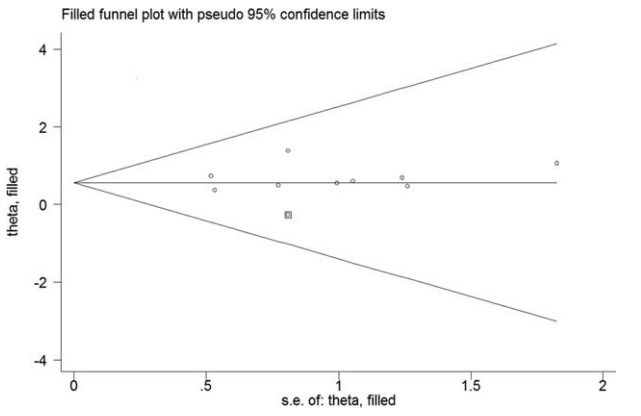

Figure 3. Funnel plot of high C-reactive protein to albumin ratio with overall survival. The circles alone are real studies and the circle enclosed in box is "filled" study.

Table 2

Subgroup analyses of overall survival.

Subgroup	Number. of studies	Pooled hazard ratios	95% confidence interval	Heterogeneity between studies
Sample sizes				
≥100	6	2.00	1.49–2.68	P=.004; I^2=71.2%;
<100	3	1.88	1.29–2.75	P=.582; I^2=0.0%
Country of origin				
China	4	2.23	1.54–3.24	P=.012; I^2=72.5%
Japan	3	1.96	1.36–2.82	P=.633; I^2=0.0%
South Korea	2	1.47	1.15–1.89	P=.782; I^2=0.0%
Type of cancer				
Advanced PC	3	2.11	1.05–4.24	P<.001; I^2=87.9%;
PDA	3	2.10	1.66–2.66	P=.776; I^2=0.0%
Treatment methods				
Chemotherapy	2	1.62	1.16–2.27	P=.962; I^2=0.0%
Resection	5	2.00	1.64–2.44	P=.895; I^2=0.0%
Cutoff value of CAR				
>0.5	3	2.11	1.05–4.24	P<.001; I^2=87.9%
≤0.5	6	1.92	1.61–2.29	P=.859; I^2=0.0%
NOS points				
≥7	7	1.98	1.53–2.56	P=.008; I^2=65.6%;
<7	2	1.95	1.13–3.38	P=.303; I^2=5.7%

CAR = C-reactive protein (CRP)-to-albumin, PC = pancreatic cancer, PDA = pancreatic ductal adenocarcinoma.

prevented us from determining the optimal cutoff value of CAR in predicting adverse outcomes. Fourth, we failed to perform a subgroup analysis based on tumor stages because the included studies did not report the risk estimate according to these characteristics. Future studies should investigate the prognostic utility of CAR according to the tumor stages. Fifth, all selected studies were from Asia, and the current results should be interpreted with caution in Western countries. Finally, the risk summary was established on the pooling multivariable adjusted risk estimates. Thus, prognostic value of CAR may have been overestimated because the lack of statistical significant risk estimate in the univariate analysis may be not included in the multivariable analysis.

5. Conclusions

In conclusion, the current meta-analysis indicates that elevated pretreatment CAR may independently predict poor OS in pancreatic cancer patients. Baseline CAR is possibly a simple and cost-effective blood-derived indicator for predicting survival outcome in patients with pancreatic cancer.

Author contributions

ZJ Gao contributed to study conception and design; Y Zang and Y Fan contributed to the literature search, data extraction, quality assessment, and statistical analysis. Y Zang drafted the manuscript.

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