The C-reactive protein to albumin ratio is a prognostic factor for survival after pancreatic cancer resection

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Research

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Abstract

Background Emerging evidence indicates that an elevated C-reactive protein-to-albumin (CRP/alb) ratio may be associated with a poor prognosis in pancreatic ductal adenocarcinoma (PDAC). Further evidence showing that this ratio has significant prognostic value could contribute to current prediction models and clinical decision-making.

Methods Data were analysed of consecutive patients who underwent curative pancreatic resection between 2013 and 2018 and were histologically diagnosed with PDAC. We investigated the relation between the preoperative CRP/alb ratio and overall survival.

Results A total of 163 patients were analysed. Median overall survival was 18 months (IQR 9–36). Multivariate analysis demonstrated that a higher CRP/alb ratio (HR 1.745, P = 0.004), a higher age (HR 1.062, P < 0.001), male sex (HR 1.977, P = 0.001), poor differentiation grade (HR 2.812, P < 0.001), and positive para-aortic lymph node(s) (HR 4.489, P < 0.001) were associated with a lower overall survival. Furthermore, a CRP/alb ratio ≥ 0.2 was associated with decreased overall survival (16 vs. 26 months, P = 0.003).

Conclusion We demonstrated that an elevated CRP/alb ratio is an independent indicator of decreased overall survival after resection for PDAC. The preoperative CRP/alb ratio may be of additional value to the current prediction models.

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths worldwide, with a 5-year survival rate of 9% for all stages combined.(1) Within the group of pancreatic tumours, pancreatic ductal adenocarcinoma (PDAC) is the most common.(2) As most patients with pancreatic cancer are asymptomatic, the disease is often at an advanced stage at the time of diagnosis.(3) Tumour biology of pancreatic cancer contributes to a rapid clinical decline in patients, culminating in a 1-year survival rate of only 24%.(2, 4) For pancreatic tumours, surgical resection is the mainstay of treatment while (neo-)adjuvant therapy is gaining ground. However, morbidity and mortality rates after surgery are high. According to a nationwide audit, the current outcome after pancreatic surgery is now characterised by 30% minor complications (Clavien-Dindo 1 or 2) and 30% major complications (Clavien-Dindo ≥ 3), with an in-hospital mortality of 4.2%.(5) Thus, it is important to identify prognostic factors that could assist in advising patients which type of treatment is recommended.

Currently, the most reliable prognostic factors for survival after PDAC are tumour size, lymph node status, resection margin and differentiation grade.(6) However, these prognostic factors rely on surgical exploration.(RW.ERROR - Unable to find reference:doc:5db15ed6e4b025c0dd88b732) There is therefore a need for identifying preoperative biomarkers that would enable better stratification of patients who may benefit from surgery.
In recent years, emerging evidence has shown the potential value of a variety of systemic inflammation-based prognostic scores in pancreatic cancer. Serum elevation of C-reactive protein (CRP), an acute-phase protein, has been shown to be a prognostic indicator in a variety of neoplasms. Moreover, hypoalbuminemia brought about by malnutrition and related to cachexia has been reported to be correlated with an unfavourable prognosis of gastrointestinal tumours.

An elevated C-reactive protein-to-albumin (CRP/alb) ratio or a composite score such as the modified Glasgow Prognostic Score (mGPS) seem to be potentially useful biomarkers for survival, but the evidence remains controversial. The mGPS combines the serum elevation of CRP and the decrease in albumin concentration, whereas the CRP/alb ratio is a continuous and more quantitative measure. Further evidence demonstrating that the CRP/alb ratio can predict survival may contribute to current prediction models and support clinical (shared) decision-making. The aim of our study was to investigate the prognostic value of the CRP/alb ratio after resection for PDAC as compared with several established prognostic factors.

## Methods

### Patients

Between January, 2013, and December, 2018, all consecutive patients who underwent pancreatic resection and were pathologically diagnosed with PDAC at the University Medical Centre Groningen, the Netherlands, or the Isala clinics, the Netherlands, were included in the present study. All medical records were retrospectively reviewed. Patients were excluded if data relating to their preoperative CRP or albumin were missing or if they already had metastatic disease at the time of resection. All patients were followed up until October, 2019, or death. Survival status was assured using the national Personal Records Database. This study was approved by the Institutional Review Boards of the University Medical Centre Groningen and Isala Zwolle (research registration number: 201900699).

### Data collection

Baseline characteristics were collected from the electronic medical record system. Laboratory tests were routinely conducted for each patient preoperatively. The laboratory results closest to the date of surgery were used for analysis. The following laboratory tests were conducted: CA 19–9, CEA, Haemoglobin, Bilirubin, CRP and Albumin. The CRP/alb ratio was calculated by dividing the serum-CRP level by the serum-albumin level. The mGPS was calculated according to the following method: Patients with an albumin level greater than 35 g/L and a CRP level less than < 10 mg/L were scored 0; patients with only an elevated CRP (> 1 mg/dL) were scored 1; and patients with low albumin (< 3.5 g/dL) and high CRP (> 1 mg/dL) were scored 2. Patients’ preoperative physical performance was determined according to the Eastern Cooperative Oncology Group (ECOG) scale and the ASA-score. The type of pancreatic resection was selected based on tumour location and was classified into two groups: pancreatic head resections (pylorus...
preserving pancreatoduodenectomy, or Whipple procedure) and other types of pancreatic resection (distal pancreatectomy, central pancreatectomy, total pancreatectomy). Postoperative complications were categorised into minor (Clavien-Dindo 1–2) and major complications (Clavien-Dindo 3–5). Overall survival time was defined as the time between date of surgery and date of the final follow-up or date of death.

Statistical analysis

Discrete variables were described as total and percentage, and continuous variables as median and interquartile range (IQR). The primary outcome was overall survival after pancreatic resection with curative intention. Univariate Cox regression was used to identify possible prognostic factors (i.e., when the $P$-value was below 0.1). These variables, along with known prognostic factors in pancreatic cancer, were included in a stepwise multivariable Cox proportional-hazard regression analysis to ascertain independent prognostic factors. For the CRP/alb ratio, the optimal cut-off point was estimated with a receiver operating characteristic (ROC) curve using Youden’s index. The resulting bivariate variable (high or low ratio) was also tested for prognostic value in overall survival. Additionally, baseline and clinicopathological characteristics were tested on difference in patients with low and high CRP/alb ratio (chi-square test, Fischer’s exact test, Mann–Whitney U test, as appropriate). $P$-values under the significance level of 0.05 were considered significant. For all statistical analyses, SPSS version 24 (IBM, Armonk, NY) was used.

Results

Study population

A total of 207 patients underwent resection of histologically confirmed PDAC at our institutes from 2013 to 2018. In 40 patients, CRP or albumin were not determined preoperatively. Additionally, four patients were retrospectively found to have metastatic disease at the time of resection (two pulmonary, one hepatic, and one omental metastasis). This left 163 individuals resected with curative intent for our study population (Fig. 1).

Baseline and clinicopathological characteristics

Baseline and clinicopathological characteristics are presented in Table 1. Postoperative major morbidity occurred in 26 patients (16%), and the mortality rates within 30 and 90 days were one (0.6%) and nine (5.5%), respectively. Differences in baseline and clinicopathological characteristics between patients with low (< 0.2) and high CRP/alb ratios ($\geq 0.2$) are also presented in Table 1. Mean haemoglobin was lower in patients with high CRP/alb ratios ($P < 0.001$), and patients with high CRP/alb ratios had a higher metastatic lymph node ratio. Although the type of resection appeared to be different between patients with high and low CRP/alb ratios, when grouping the resections into pancreatoduodenectomy (pancreas-head tumours) and other pancreatectomy, no significant difference was observed ($P = 0.112$).
Table 1
- Baseline and clinicopathological characteristics in relation to CRP/alb ratio with cut-off at 0.2. Percentages represent proportion within group.

|                         | Total (n = 163) | CRP/Alb < 0.2 (n = 90 (55%)) | CRP/Alb > 0.2 (n = 73 (45%)) | P-value |
|-------------------------|-----------------|-------------------------------|-------------------------------|---------|
| **Sex**                 |                 |                               |                               |         |
| Male                    | 87              | 49                            | 38 (44%)                      | 0.875   |
| Female                  | 76              | 41                            | 35 (46%)                      |         |
| **Age, years (mean, SD)** | 66 (± 9.7)    | 65 (± 9.7)                    | 67 (± 9.7)                    | 0.591   |
| **ASA**                 |                 |                               |                               |         |
| I                       | 12              | 7                             | 5 (42%)                       | 0.055   |
| II                      | 121             | 73                            | 48 (40%)                      |         |
| III                     | 29              | 10                            | 19 (66%)                      |         |
| IV                      | 1               | 0                             | 1 (100%)                      |         |
| **ECOG grade**          |                 |                               |                               |         |
| 0                       | 11 unknown      | 45                            | 31 (41%)                      | 0.380   |
| 1                       | 76              | 29                            | 27 (48%)                      |         |
| 2                       | 56              | 7                             | 7 (50%)                       |         |
| 3                       | 14              | 1                             | 4 (80%)                       |         |
| 4                       | 5               | 1                             | 0                             |         |
| **Haemoglobin, g/dL (mean, SD)** | 12.9 (± 1.6) | 13.4 (± 1.5)                  | 12.1 (± 1.6)                  | < 0.001 |
| **CEA, ng/ml (median, IQR)** | 4.1 (2.2–6.7) | 4.5 (2.2–6.6)                 | 3.2 (2.2–7.5)                 | 0.577   |
| **CA 19–9, U/ml (median, IQR)** | 246 (60–936) | 342 (54–867)                  | 133 (62–1092)                 | 0.800   |
| **Supplementary nutrition** | 38 unknown    | 39                            | 22 (36%)                      | 0.398   |
| No                      | 61              | 31                            | 26 (46%)                      |         |
| Enteral                 | 57              | 3                             | 4 (57%)                       |         |
| Parenteral              | 7               |                               |                               |         |
|                          | Total n = 163 | CRP/Alb < 0.2 n = 90 (55%) | CRP/Alb > 0.2 n = 73 (45%) | P-value |
|--------------------------|---------------|-----------------------------|-----------------------------|---------|
| Neoadjuvant therapy      |               |                             |                             | 0.692   |
| No                       | 157           | 86                          | 71 (45%)                    |         |
| Yes                      | 6             | 4                           | 2 (33%)                     |         |
| Approach                 |               |                             |                             | 1.000   |
| Open or conversion       | 154           | 85                          | 69 (45%)                    |         |
| Laparoscopy              | 9             | 5                           | 4 (44%)                     |         |
| Type of resection        |               |                             |                             | 0.043 * |
| PPPD                     | 106           | 59                          | 47 (44%)                    |         |
| PD (Whipple's)           | 24            | 9                           | 15 (63%)                    |         |
| Distal pancreas resection| 22            | 17                          | 5 (23%)                     |         |
| Central pancreas resection| 9            | 0                           | 2 (100%)                    |         |
| Total pancreatectomy     |               |                             |                             |         |
| Complication             | 137           | 76                          | 61 (45%)                    | 1.000   |
| Clavien Dindo 0–2        | 26            | 14                          | 12 (46%)                    |         |
| Clavien Dindo 3–5        |               |                             |                             |         |
| Tumor size in mm (median, IQR) | 30 (25–40) | 30 (25–40)                  | 35 (25–40)                  | 0.477   |
| Differentiation grade    | 25 unknown    | 49                          | 39 (44%)                    | 0.861   |
| Well or moderate         | 25            | 49                          | 39 (44%)                    |         |
| Poorly                   | 68            | 27                          | 23 (46%)                    |         |
| Metastatic lymph nodes   |               |                             |                             | 0.183   |
| < 5                      | 108           | 64                          | 44 (41%)                    |         |
| ≥ 5                      | 55            | 26                          | 29 (53%)                    |         |
|                                | Total (n = 163) | CRP/Alb < 0.2 (n = 90 (55%)) | CRP/Alb > 0.2 (n = 73 (45%)) | P-value |
|--------------------------------|-----------------|-----------------------------|-----------------------------|---------|
| Metastatic lymph node ratio    | 0.16 (0.06–0.26) | 0.13 (0.04–0.25)            | 0.19 (0.01–0.29)            | 0.007   |
| Metastatic lymph node ratio    |                 |                             |                             |         |
| 0                              | 36              | 24                          | 12 (33%)                    | 0.005   |
| > 0.10                         | 26              | 20                          | 6 (23%)                     |         |
| ≥ 0.10                         | 101             | 46                          | 55 (55%)                    |         |
| Para-aortic lymph node         | 152             | 85                          | 67 (44%)                    | 0.543   |
| No metastasis                  | 11              | 5                           | 6 (55%)                     |         |
| One or more metastases         |                 |                             |                             |         |
| Radicality                     | 2 unknown       | 53                          | 41 (44%)                    | 0.726   |
| R0                             | 94              | 35                          | 39 (45%)                    |         |
| R1                             | 64              | 1                           | 2 (67%)                     |         |
| R2                             | 3               |                             |                             |         |
| Adjuvant therapy               | 5 unknown       | 28                          | 28 (50%)                    | 0.246   |
| No                             | 56              | 61                          | 41 (40%)                    |         |
| Yes                            | 102             |                             |                             |         |

* pancreatoduodenectomy vs. other pancreas resections: p = 0.171; ASA = American Society of Anesthesiologists; ECOG = Eastern Cooperative Oncology Group scale of performance; CEA = Carcinoembryonic antigen; CA 19–9 = carbohydrate antigen 19–9; PPPD = pylorus-preserving pancreatoduodenectomy; PD = pancreatoduodenectomy; SD = standard deviation; IQR = interquartile range

**Univariate and multivariate analysis using Cox multiple regression for overall survival**

Median overall survival was 18 months (IQR 9–36) in the study population. Univariable Cox proportional-hazard regression was used to identify variables that were possibly associated with overall survival (Table 2). Stepwise multivariable Cox regression was performed using the variables sex, age, ECOG performance grade, haemoglobin, CRP/alb ratio, neo-adjuvant therapy, type of resection, tumour size, tumour differentiation grade, metastatic lymph node ratio, para-aortic lymph node status, and radicality. The ultimate proportional-hazards model was significant (P < 0.001) and consisted of sex, age, CRP/alb ratio, differentiation grade, and para-aortic lymph node status. Higher CRP/alb ratios were independently
associated with lower survival; the hazard ratio was 1.745 (95% CI 1.200–2.539, \( P = 0.004 \)). Due to significant collinearity with CRP and albumin, haemoglobin level was analysed separately, and stepwise Cox regression demonstrated that haemoglobin was not significantly associated with survival. Furthermore, when analysing CRP and albumin separately in multivariate analysis, only CRP was independently associated with survival (HR 1.006, 95% CI 1.006–1.027, \( P = 0.002 \)). Additionally, when replacing the CRP/alb ratio by the mGPS, the variable mGPS ended in the ultimate regression model, but was non-significant (\( P = 0.077 \))
Table 2
Univariate and multivariate analysis using Cox multiple regression for overall survival. Variables presented under Multivariate analysis represent the final model after stepwise exclusion.

| Covariate       | Univariate analysis | Multivariate analysis |
|-----------------|---------------------|-----------------------|
|                 | HR                  | 95% CI                | P-value | HR                  | 95% CI                | P-value |
| Sex             |                     |                       |         |                     |                       |         |
| Female          | 1                   | 0.432–0.923           | 0.018 * | 1                   | 1.191–3.282           | 0.001   |
| Male            | 0.632               |                       |         | 1.977               |                       |         |
| Age (years)     | 1.034               | 1.011–1.059           | 0.004 * | 1.062               | 1.030–1.094           | <0.001  |
| ASA             |                     |                       |         |                     |                       |         |
| I - II          | 1                   | 0.923–2.044           | 0.117   |                     |                       |         |
| III - IV        | 1.374               |                       |         |                     |                       |         |
| ECOG grade      |                     |                       |         |                     |                       |         |
| 0–1             | 1                   | 0.971–2.748           | 0.064 * |                     |                       |         |
| 2–4             | 1.634               |                       |         |                     |                       |         |
| Hemoglobin      | 0.961               | 0.805–1.148           | 0.661   |                     |                       |         |
| Bilirubin       | 1.000               | 0.999–1.001           | 0.833 **|                     |                       |         |
| CRP             | 1.011               | 1.002–1.020           | 0.022   |                     |                       |         |
| Albumin         | 0.952               | 0.920–0.986           | 0.006   |                     |                       |         |
| CRP/Albumin ratio | 1.406             | 1.038–1.905           | 0.028 * | 1.745               | 1.200–2.539           | 0.004   |
| mGPS            |                     |                       |         |                     |                       |         |
| 0               | 1                   | 0.946–2.128           | 0.090   |                     |                       |         |
| 1               | 1.419               | 0.971–3.929           | 0.061   |                     |                       |         |
| 2               | 1.953               |                       |         |                     |                       |         |
| CEA             | 1.011               | 0.999–1.022           | 0.074   |                     |                       |         |
| CA 19.9         | 1.215               | 0.940–1.570           | 0.138   |                     |                       |         |
|                                | Univariate analysis | Multivariate analysis |
|--------------------------------|---------------------|-----------------------|
| **Supplementary nutrition**    | 1                   | 0.838–1.905           |
| **Enteral**                    | 1.264               | 0.588–3.789           |
| **Parenteral**                 | 1.612               | 0.264                 |
| **Neoadjuvant therapy**        | 1                   | 0.171–1.710           |
| **Yes**                        | 0.541               | 0.296 **              |
| **Approach**                   | 1                   | 0.380–2.306           |
| **Open or conversion**         | 0.937               | 0.887                 |
| **Laparoscopy**                | 1                   | 0.756–1.865           |
| **Type resection**             | 1.187               | 0.456 **              |
| **Pancreas head**              | 1.187               |                       |
| **Pancreas other**             | 1.187               |                       |
| **Complication**               | 1                   | 0.778–2.059           |
| **Clavien Dindo 0–2**          | 1.266               | 0.342                 |
| **Clavien Dindo 3–5**          |                     |                       |
| **Tumor size**                 | 1.007               | 0.996–1.018           |
| **Differentiation grade**      | 1                   | 0.837–1.931           |
| **Well or moderate**           | 1.271               | 0.261 **              |
| **Poorly**                     | 1                   | 1.627–4.861           |
|                                |                     | < 0.001               |
### Determination of the cut-off point for the CRP/alb ratio

The mean CRP/alb ratio was 0.38 (SD 0.54); the median CRP/alb ratio was 0.16 (IQR 0.07–0.42). The optimal cut-off for the CRP/alb ratio in predicting overall mortality was estimated using a ROC curve. Maximum sensitivity and specificity was found at a ratio of 0.2, which corresponded with a sensitivity of 54% and a specificity 69%.

### Overall survival

Median overall survival in patients with low CRP/alb ratios was 26 months (IQR 11–56), and in patients with high CRP/albumin ratios, 16 months (IQR 7–24). The final model using a bivariate variable of low (< 0.2) and high (≥ 0.2) CRP/alb ratio revealed that this variable was an independent prognostic factor as well ($P < 0.001$, HR 2.129, 95% CI 1.395–3.251). Survival was lower in patients with high CRP/alb ratios (Fig. 2).

### Discussion

Our results demonstrated that a higher CRP/alb ratio together with a higher age, male sex, poor differentiation grade and positive para-aortic lymph node(s) was associated with a lower overall survival. A CRP/alb ratio above 0.2 is associated with a decreased overall survival in patients with PDAC after curative pancreatic resection. In accordance with Haruki et al., the CRP/alb ratio was an independent
prognostic factor for overall survival in patients after resection for PDAC. (3) In addition, previous studies have shown the prognostic value of the mGPS on overall survival of patients with PDAC. (19–21) In our cohort, however, the mGPS was not an independent prognostic factor for overall survival, which was consistent with some previous studies, (22) although a prognostic trend was present. This might indicate that the CRP/alb ratio, being a continuous variable, may be a superior predictor if it is not condensed into a score. Furthermore, both high CRP and low albumin were associated with poor survival, but only CRP was an independent prognostic factor for overall survival, indicating that the prognostic value of CRP/alb is mainly driven by CRP. There is increasing understanding of the mechanism of the relation between the CRP/alb ratio and survival in patients with cancer. C-reactive protein is a marker of inflammation, and an elevated serum level might be caused by tumour necrosis or local tissue damage. (13) In addition, an elevated CRP could be a marker for a beneficial environment for the origin and growth of metastases. An elevated CRP gives an upregulation of the vascular endothelial growth factor, which promotes the growth and proliferation of tumours. (11) In addition, CRP is produced in response to elevated interleukin-6 levels. (12) Interleukin-6 promotes tumour growth by inducing multiple signalling pathways, including proliferation, angiogenesis and metabolism. (22) Hypoalbuminemia is often thought to reflect malnutrition in patients. However, emerging evidence shows that a low albumin level may also be a reflection of an inflammatory state. (23, 24) The exact cause of low albumin levels in patients with cancer is unclear. The literature suggests that it is a combination of several mechanisms. One explanation is that high interleukin-6 levels produced by cancer cells inhibit the synthesis of albumin. (25) Alternatively, it may be the result of an increase in vascular permeability, which causes a redistribution of albumin, leading to lower serum levels and high extra vascular fluid levels. (26, 27) In accordance with the literature, men had a lower overall survival than women did. (28–30) It is well known that pancreatic cancer occurs more frequently in men. The underlying cause remains unclear. Possible explanations include differences in environmental or occupational risk-factors, but other lifestyle factors, such as heavy smoking and high alcohol intake in men, may also contribute. (2) Alternatively, undiscovered genetic factors may play a role. These possible factors were assumed to also contribute to a higher mortality risk. In a recent review of clinical prediction models for survival after pancreatic cancer surgery, it was found that tumour size, lymph node status, resection margin and differentiation grade were most often included in the final prediction models. (6) In this study, all these variables were analysed, and the multivariate analysis showed that, of these variables, only differentiation grade and para-aortic lymph node status were significantly associated with overall survival. In the same review, it was also suggested to include neo-adjuvant therapy in the analyses. In our study, neo-adjuvant therapy had no significant predictive value, probably due to the small number (n = 6) of patients receiving neo-adjuvant therapy. However, the role of neo-adjuvant therapy is currently being investigated in the PREOPANC II trial and the CRP/alb ratio in these patients could be the subject of research in the near future. Moreover, Strijker and others have recommended to include the location of the tumour in the pancreas as a variable, since previous studies have demonstrated differences in tumour biology between tumours in the head and corpus/tail. (31, 32) In our study, no statistical difference in overall survival was observed between head or
distal pancreatic resections. The authors of the review have also commented that to objectively predict the outcome for pancreatic tumours, a distinction between different types of pancreatic and periampullary tumours should be made. Our study had several important strengths: we included only PDACs; we made a distinction between tumour locations; and we confirmed patients’ survival status using the national Personal Records Database. Our study was limited, however, by its retrospective nature, which among other consequences, resulted in the limited availability of laboratory results and confounding factors like preoperative pancreatitis, cholangitis or biliary drainage. Since biliary drainage might influence CRP, it may have been appropriate to include this variable. We did, however, include in the analyses the bilirubin level, which had no significant association with overall survival and did not influence the outcome. Over the last decades, variables used to assess the immune system and inflammation have gained interest as prognostic biomarkers for the prediction of outcomes for pancreatic cancer.(3, 7–11) Since immunotherapy may play an important role in the future treatment of pancreatic cancer, our study and future research concerning prognostic systemic inflammatory variables could be of significant value.(33) In conclusion, this study showed that an elevated CRP/alb ratio was independently and significantly associated with decreased overall survival in patients with PDAC after pancreatic resection. The CRP/alb ratio may therefore be of additional value to current prediction models and may be helpful in clinical decision-making.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Boards of the University Medical Centre Groningen and Isala Zwolle (research registration number: 201900699). Informed consent was exempted due to the policy or the law of the government or the type of the research.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions
(I) Conception and design: LW, GAP, JMK

(II) Administrative support: not applicable

(III) Provision of study materials or patients: GAP, JMK

(IV) Collection and assembly of data: LVW, GWK, MAK

(V) Data analysis and interpretation: All authors

(VI) Manuscript writing: All authors

(VII) Final approval of manuscript: All authors

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin 2019 January. 2019;01(1):7–34.
2. Rawla P, Sunkara T, Gaduputi V. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. World J Oncol 2019 February 01;10(1):10–27.
3. Wu M, Guo J, Guo L, Zuo Q. The C-reactive protein/albumin ratio predicts overall survival of patients with advanced pancreatic cancer. Tumour Biol 2016 September 01;37(9):12525–12533.
4. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. Lancet 2016 July 02;388(10039):73–85.
5. van Rijssen LB, Zwart MJ, van Dieren S, de Rooij T, Bonsing BA, Bosscha K, et al. Variation in hospital mortality after pancreatoduodenectomy is related to failure to rescue rather than major complications: a nationwide audit. HPB (Oxford) 2018 August 01;20(8):759–767.
6. Strijker M, Chen JW, Mungroop TH, Jamieson NB, van Eijck CH, Steyerberg EW, et al. Systematic review of clinical prediction models for survival after surgery for resectable pancreatic cancer. Br J Surg 2019 March 01;106(4):342–354.
7. Haruki K, Shiba H, Shirai Y, Horiuchi T, Iwase R, Fujiwara Y, et al. The C-reactive Protein to Albumin Ratio Predicts Long-Term Outcomes in Patients with Pancreatic Cancer After Pancreatic Resection. World J Surg 2016 September 01;40(9):2254–2260.
8. Shirai Y, Shiba H, Sakamoto T, Horiuchi T, Haruki K, Fujiwara Y, et al. Preoperative platelet to lymphocyte ratio predicts outcome of patients with pancreatic ductal adenocarcinoma after pancreatic resection. Surgery 2015 August 01;158(2):360–365.
9. Aziz MH, Sideras K, Aziz NA, Mauff K, Haen R, Roos D, et al. The Systemic-immune-inflammation Index Independently Predicts Survival and Recurrence in Resectable Pancreatic Cancer and its Prognostic Value Depends on Bilirubin Levels: A Retrospective Multicenter Cohort Study. Ann Surg 2019 July 01;270(1):139–146.

10. Wang DS, Luo HY, Qiu MZ, Wang ZQ, Zhang DS, Wang FH, et al. Comparison of the prognostic values of various inflammation based factors in patients with pancreatic cancer. Med Oncol 2012 December 01;29(5):3092–3100.

11. Chen J, Gu Z, Wu M, Yang Y, Zhang J, Ou J, et al. C-reactive protein can upregulate VEGF expression to promote ADSC-induced angiogenesis by activating HIF-1alpha via CD64/PI3k/Akt and MAPK/ERK signaling pathways. Stem Cell Res Ther 2016 August 16;7(1):114–1.

12. Thomsen M, Kersten C, Sorbye H, Skovlund E, Glimelius B, Pfeiffer P, et al. Interleukin-6 and C-reactive protein as prognostic biomarkers in metastatic colorectal cancer. Oncotarget 2016 November 15;7(46):75013–75022.

13. Wong VK, Malik HZ, Hamady ZZ, Al-Mukhtar A, Gomez D, Prasad KR, et al. C-reactive protein as a predictor of prognosis following curative resection for colorectal liver metastases. Br J Cancer 2007 January 29;96(2):222–225.

14. Mitsunaga S, Ikeda M, Shimizu S, Ohno I, Takahashi H, Okuyama H, et al. C-Reactive Protein Level Is an Indicator of the Aggressiveness of Advanced Pancreatic Cancer. Pancreas 2016 January 01;45(1):110–116.

15. Pine JK, Fusai KG, Young R, Sharma D, Davidson BR, Menon KV, et al. Serum C-reactive protein concentration and the prognosis of ductal adenocarcinoma of the head of pancreas. Eur J Surg Oncol 2009 June 01;35(6):605–610.

16. 10.1111/ecc.12403
Chiang JM, Chang CJ, Jiang SF, Yeh CY, You JF, Hsieh PS, et al. Pre-operative serum albumin level substantially predicts post-operative morbidity and mortality among patients with colorectal cancer who undergo elective colectomy. Eur J Cancer Care (Engl) 2017 March 01;26(2):10.1111/ecc.12403. Epub 2015 Nov 3.

17. Proctor MJ, Morrison DS, Talwar D, Balmer SM, O'Reilly DS, Foulis AK, et al. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow Inflammation Outcome Study. Br J Cancer 2011 Feb 15;104(4):726–734.

18. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649–55.

19. La Torre M, Nigri G, Cavallini M, Mercantini P, Ziparo V, Ramacciato G. The glasgow prognostic score as a predictor of survival in patients with potentially resectable pancreatic adenocarcinoma. Ann Surg Oncol 2012 September 01;19(9):2917–2923.

20. Jamieson NB, Denley SM, Logue J, MacKenzie DJ, Foulis AK, Dickson EJ, et al. A prospective comparison of the prognostic value of tumor- and patient-related factors in patients undergoing
potentially curative surgery for pancreatic ductal adenocarcinoma. Ann Surg Oncol 2011 August 01;18(8):2318–2328.

21. Numata K, Morinaga S, Katayama Y, Sawazaki S, Numata M, Godai T, et al. Combining the Glasgow Prognostic Score and Serum Carbohydrate Antigen 19–9 Level Improves the Ability to Predict Early Recurrence in Resected Pancreatic Cancer Patients Receiving Adjuvant Gemcitabine. Anticancer Res 2016 May 01;36(5):2467–2474.

22. Kumari N, Dwarakanath BS, Das A, Bhatt AN. Role of interleukin-6 in cancer progression and therapeutic resistance. Tumour Biol 2016 September 01;37(9):11553–11572.

23. Don BR, Kaysen GA. Assessment of inflammation and nutrition in patients with end-stage renal disease. J Nephrol 2000 August 01;13(4):249–259.

24. McMillan DC, Watson WS, O’Gorman P, Preston T, Scott HR, McArdle CS. Albumin concentrations are primarily determined by the body cell mass and the systemic inflammatory response in cancer patients with weight loss. Nutr Cancer. 2001;39(2):210–3.

25. Barber MD, Ross JA, Fearon KC. Changes in nutritional, functional, and inflammatory markers in advanced pancreatic cancer. Nutr Cancer. 1999;35(2):106–10.

26. Fleck A, Raines G, Hawker F, Trotter J, Wallace Pl, Ledingham IM, et al. Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. Lancet 1985 April 06;1(8432):781–784.

27. Fanali G, di Masi A, Trezza V, Marino M, Fasano M, Ascenzi P. Human serum albumin: from bench to bedside. Mol Aspects Med 2012 June 01;33(3):209–290.

28. Wahi MM, Shah N, Schrock CE, Rosemurgy AS, Goldin SB. Reproductive factors and risk of pancreatic cancer in women: a review of the literature. Ann Epidemiol 2009 February 01;19(2):103–111.

29. van der Geest LG, Besselink MG, van Gestel YR, Busch OR, de Hingh IH, de Jong KP, et al. Pancreatic cancer surgery in elderly patients: Balancing between short-term harm and long-term benefit. A population-based study in the Netherlands. Acta Oncol. 2016;55(3):278–85.

30. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013 April 01;49(6):1374–1403.

31. van Erning FN, Mackay TM, van der Geest LGM, Groot Koerkamp B, van Laarhoven HWM, Bonsing BA, et al. Association of the location of pancreatic ductal adenocarcinoma (head, body, tail) with tumor stage, treatment, and survival: a population-based analysis. Acta Oncol 2018 December 01;57(12):1655–1662.

32. Sheng W, Dong M, Wang G, Shi X, Gao W, Wang K, et al. The diversity between curatively resected pancreatic head and body-tail cancers based on the 8th edition of AJCC staging system: a multicenter cohort study. BMC Cancer 2019 October 22;19(1):981-z.

33. Kunk PR, Bauer TW, Slingluff CL, Rahma OE. From bench to bedside a comprehensive review of pancreatic cancer immunotherapy. J Immunother Cancer 2016 March 15;4:14-z. eCollection 2016.
Figures

207 patients with resection of pancreatic ductal adenocarcinoma were identified

167 patients with complete data

40 patients with unknown C-reactive protein and/or Albumin values

4 patients with metastatic disease

163 patients were included in the analysis

Figure 1

Flowchart of patient inclusion PDAC = Pancreatic ductal adenocarcinoma; CRP = C-reactive Protein
Overall survival of patients with low (< 0.2) and high (≥ 0.2) CRP/alb ratios, corrected for age, sex, differentiation grade, and positive para-aortic lymph nodes using Cox regression