

# The ultimate preoperative 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 ratio (CRP/albCAR) 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 ultimate preoperative CRP/albCAR 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/albCAR 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/albCAR ratio  $\geq 0.2$  was associated with decreased overall survival (16 vs. 26 months,  $P = 0.003$ ).

*Conclusion* We demonstrated that an ultimate preoperative elevated CRP/albCAR ratio is an independent indicator of decreased overall survival after resection for PDAC. The preoperative CRP/albCAR 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  $\geq 3$ ), 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.(3, 7–11) Serum elevation of C-reactive protein (CRP), an acute-phase protein, has been shown to be a prognostic indicator in a variety of neoplasms.(12–15) Moreover, hypoalbuminemia brought about by malnutrition and related to cachexia has been reported to be correlated with an unfavourable prognosis of gastrointestinal tumours.(RW.ERROR - Unable to find reference:doc:5db2e1a0e4b044ff33679ba3)

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.(RW.ERROR - Unable to find reference:doc:5db2b004e4b02d4c96af2fee) 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.(RW.ERROR - Unable to find reference:doc:5da7252ee4b03d8801e716e2) 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.(17) Patients' preoperative physical performance was determined according to the Eastern Cooperative Oncology Group (ECOG)(18) 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/albumin 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/albumin ratio (chi-square test, Fisher'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/albumin ratios ( $\geq 0.2$ ) are also presented in Table 1. Mean haemoglobin was lower in patients with high CRP/albumin ratios ( $P < 0.001$ ), and patients with high CRP/albumin ratios had a higher metastatic lymph node ratio. Although the type of resection appeared to be different between patients with high and low CRP/albumin 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.

	<b>Total n = 163</b>	<b>CRP/Alb &lt; 0.2 n = 90 (55%)</b>	<b>CRP/Alb &gt; 0.2 n = 73 (45%)</b>	<b>P- value</b>
Sex	87	49	38 (44%)	0.875
Male	76	41	35 (46%)	
Female				
Age, years (mean, SD)	66 (± 9.7)	65 (± 9.7)	67 (± 9.7)	0.591
ASA	12	7	5 (42%)	0.055
I	121	73	48 (40%)	
II	29	10	19 (66%)	
III	1	0	1 (100%)	
IV				
ECOG grade	<i>11 unknown</i>	45	31 (41%)	0.380
0	76	29	27 (48%)	
1	56	7	7 (50%)	
2	14	1	4 (80%)	
3	5	1	0	
4	1			
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	<i>38 unknown</i>	39	22 (36%)	0.398
No	61	31	26 (46%)	
Enteral	57	3	4 (57%)	
Parenteral	7			
Neoadjuvant therapy	157	86	71 (45%)	0.692
No	6	4	2 (33%)	
Yes				

	<b>Total n = 163</b>	<b>CRP/Alb &lt; 0.2 n = 90 (55%)</b>	<b>CRP/Alb &gt; 0.2 n = 73 (45%)</b>	<b>P- value</b>
Approach	154	85	69 (45%)	1.000
Open or conversion	9	5	4 (44%)	
Laparoscopy				
Type of resection	106	59	47 (44%)	0.043 *
PPPD	24	9	15 (63%)	
PD (Whipple's)	22	17	5 (23%)	
Distal pancreas resection	2	0	2 (100%)	
Central pancreas resection	9	5	4 (44%)	
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	<i>25 unknown</i>	49	39 (44%)	0.861
Well or moderate	88	27	23 (46%)	
Poorly	50			
Metastatic lymph nodes	108	64	44 (41%)	0.183
< 5	55	26	29 (53%)	
≥ 5				
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	36	24	12 (33%)	0.005
0	26	20	6 (23%)	
> 0.10	101	46	55 (55%)	
≥ 0.10				

	Total n = 163	CRP/Alb < 0.2 n = 90 (55%)	CRP/Alb > 0.2 n = 73 (45%)	P-value
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	1	0.432–0.923	0.018 *	1	1.191–3.282	0.001
Female	0.632			1.977		
Male						
Age (years)	1.034	1.011–1.059	0.004 *	1.062	1.030–1.094	< 0.001
ASA	1	0.923–2.044	0.117			
I - II	1.374					
III - IV						
ECOG grade	1	0.971–2.748	0.064 *			
0–1	1.634					
2–4						
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	1	0.946–2.128	0.090			
0	1.419		0.061			
1	1.953	0.971–3.929				
2						
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	0.264			
No	1.264		0.272			
Enteral	1.612	0.588– 3.789				
Parenteral						
Neoadjuvant therapy	1	0.171– 1.710	0.296 **			
No	0.541					
Yes						
Approach	1	0.380– 2.306	0.887			
Open or conversion	0.937					
Laparoscopy						
Type resection	1	0.756– 1.865	0.456 **			
Pancreas head	1.187					
Pancreas other						
Complication	1	0.778– 2.059	0.342			
Clavien Dindo 0–2	1.266					
Clavien Dindo 3–5						
Tumor size	1.007	0.996– 1.018	0.237 **			
Differentiation grade	1	0.837– 1.931	0.261 **	1	1.627–4.861	< 0.001
Well or moderate	1.271			2.812		
Poorly						
Metastatic lymph node ratio	2.946	1.154– 7.521	0.024 *			
Para-aortic lymph node	3.299	1.738– 6.262	< 0.001 *	1	1.883– 10.702	< 0.001
No metastasis				4.489		
One or more metastases						
Radicality	1	0.952– 2.018	0.089 *			
R0	1.386					
R1 – R2						

## Univariate analysis

## Multivariate analysis

\* Included in stepwise cox regression because  $p < 0.1$ ; \*\* Included in stepwise cox regression because of prognostic value in literature; ASA = American Society of Anesthesiologists ; ECOG = Eastern Cooperative Oncology Group scale of performance; CEA = Carcinoembryonic antigen; CA 19 - 9 = carbohydrate antigen 19 - 9

# 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 ( $\geq 0.2$ ) 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. (RW.ERROR - Unable to find reference:doc:5da7252ee4b03d8801e716e2) This has also been demonstrated in patients with advanced pancreatic cancer.(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,(RW.ERROR - Unable to find reference:doc:5db2b004e4b02d4c96af2fee) 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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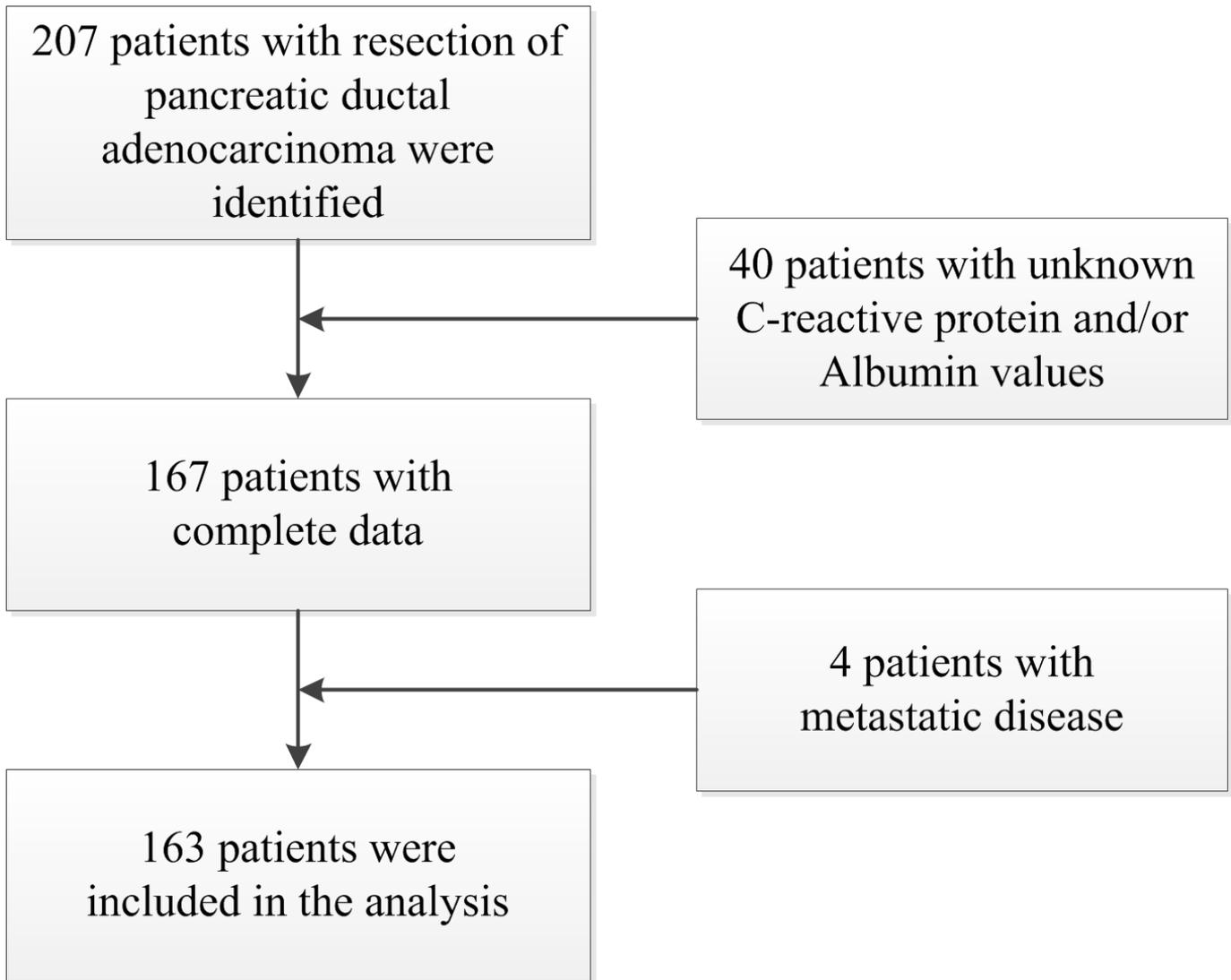
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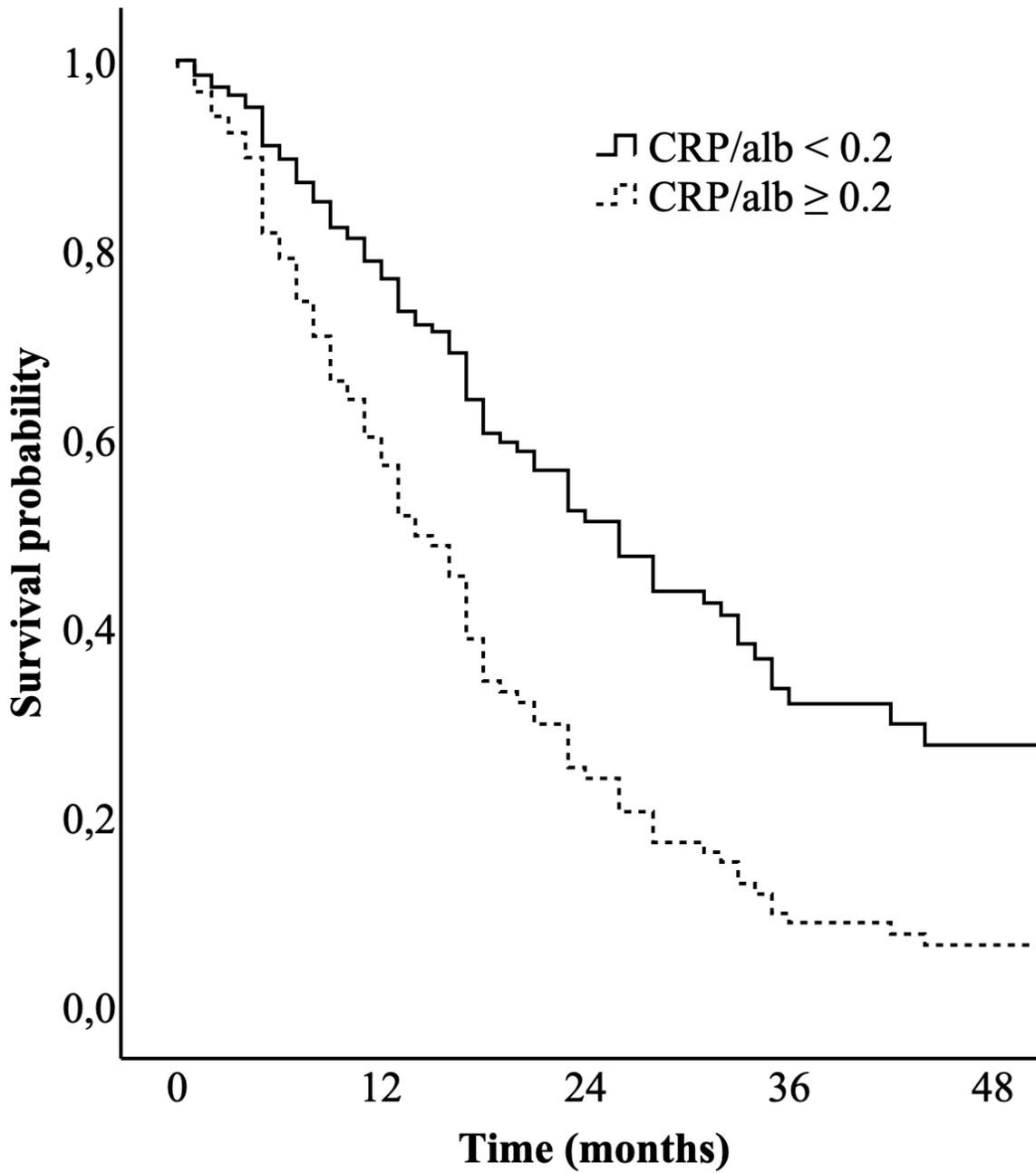
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## Figures



**Figure 1**

Flowchart of patient inclusion PDAC = Pancreatic ductal adenocarcinoma; CRP = C-reactive Protein



		<b>Number at risk</b>				
		0	12	24	36	48
<b>&lt; 0.2</b>	90	78	66	54	42	
<b>≥ 0.2</b>	73	61	49	37	25	

**Figure 2**

Overall survival of patients with low (< 0.2) and high (≥ 0.2) CRP/albumin ratios, corrected for age, sex, differentiation grade, and positive para-aortic lymph nodes using Cox regression