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Validation of C-reactive protein levels as a prognostic indicator for survival in a large cohort of pancreatic cancer patients

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Background: Recent evidence indicates that the host inflammatory response has an important role in the tumour progression. Elevated C-reactive protein (CRP) levels have been previously associated with poor prognosis in several cancer types including small-scale studies in pancreatic cancer (PC) patients. The purpose of the present study was to validate the prognostic impact of plasma CRP levels at date of diagnosis on cancer-specific survival (CSS) in a large cohort of PC patients.

Methods: Data from 474 consecutive patients with adenocarcinoma of the pancreas, treated between 2004 and 2012 at a single centre, were evaluated retrospectively. CSS was analysed using the Kaplan–Meier method. To evaluate the prognostic significance of plasma CRP levels, univariate and multivariate Cox analyses were applied.

Results: High plasma CRP levels at diagnosis were significantly associated with well-established prognostic factors, including high tumour stage and tumour grade and the administration of chemotherapy ($P<0.05$). In univariate analysis, we observed that a high plasma CRP level was a consistent factor for poor CSS in PC patients (hazard ratio (HR) = 2.21; 95% confidence interval (CI) = 1.68–2.92, $P<0.001$). In multivariate analysis, tumour stage, grade, administration of chemotherapy, a high neutrophil–lymphocyte ratio and the highest quartile of CRP levels (HR = 1.60, 95% CI = 1.16–2.21; $P=0.005$) were identified as independent prognostic factors in PC patients.

Conclusion: In conclusion, we confirmed a significant association of elevated CRP levels with poor clinical outcome in PC patients. Our results indicate that the plasma CRP level might represent a useful marker for patient stratification in PC management.

Pancreatic cancer (PC) is a very aggressive tumour, which is reflected by the second most common cause of death from cancer within all gastrointestinal malignancies (Siegel *et al*, 2012). In more detail, the prognosis for PC has been nearly unchanged over the last 25 years, with an overall poor 5-year survival rate of only 1–4% (Richter *et al*, 2003). Despite developments in novel diagnostic techniques and modalities, the lack of early symptoms results in delayed diagnosis. The majority of patients initially diagnosed have locally advanced or metastatic disease and only approximately 15% of the patients are amenable to resection (Niederhuber *et al*, 1995). Adjuvant chemotherapy and palliative treatment have slightly improved the clinical outcome results and neoadjuvant treatment approaches are under clincial investigation (Sultana *et al*, 2012; Tinchon *et al*, 2013). Several prognostic factors have been

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identified that predict survival in PC patients, such as tumour size, histologic grade, vascular invasion, lymph node metastases and perineural invasion (Griffanti-Bartoli *et al*, 1994; Fortner *et al*, 1996; Ozaki *et al*, 1999; Raut *et al*, 2007). Nevertheless, the majority of these established histological predictors is only amenable for assessment after surgery. Other novel molecular biomarkers are associated with high costs, time-consuming procedures and laboratory efforts. Therefore, there is a clear need for the establishment of easily determinable and cheap pre-treatment prognostic markers that can be used for a better risk stratified treatment approach. Recent studies suggest that not only the intrinsic properties of tumour cells determine tumour spread, but also systemic factors, in the shape of cytokines and other chemical messengers, have an important role in cellular proliferation and the ability to metastasize (Coussens and Werb, 2002; Mantovani *et al*, 2008). C-reactive protein (CRP) is an acute phase protein produced by the liver as part of the systemic inflammatory response. Several studies have demonstrated a prognostic role of CRP in numerous cancer types including soft tissue sarcoma, small-cell lung cancer, renal cell cancer and colorectal cancer (Hashimoto *et al*, 2005; Karakiewicz *et al*, 2007; Nakamura *et al*, 2013). However, with respect to PC, the results are mainly derived from small-scale studies with controversially reported results (Falconer *et al*, 1995; Ueno *et al*, 2000; Jamieson *et al*, 2005; Tingstedt *et al*, 2007; Papadoniou *et al*, 2008; Pine *et al*, 2009; Garcea *et al*, 2011; Sanjay *et al*, 2012). In the present study, we aimed at validating the prognostic significance of pre-treatment plasma CRP levels on cancer-specific survival (CSS) in a large cohort of 474 PC patients.

MATERIAL AND METHODS

This retrospective analysis included data from 474 consecutive patients who were treated at the Division of Clinical Oncology, Medical University of Graz, between 2004 and 2012. All patients had histological confirmed pancreatic ductal adenocarcinoma and available CRP levels at the time of diagnosis. All clinico-pathological data were retrieved from medical records at the Division of Clinical Oncology, as well as from pathology records from the Institute of Pathology at the same institution.

As the TNM classification system for PC changed during the study period, tumour stages were uniformly adjusted according to the 7th edition of this system (Edge *et al*, 2010). Other documented clinico-pathological parameters included administration of chemotherapy with gemcitabine, gender and age. The laboratory data, CRP levels, bilirubin levels, numbers of neutrophils, lymphocytes and platelets were obtained by exploration within 7 days before treatment or histological-proven diagnosis. The neutrophil–lymphocyte ratio (NLR) and the platelet–lymphocyte ratio (PLR) were calculated as previously described (Wang *et al*, 2012). Based on our previously published smaller study, a NLR of >3.25 was selected as the cutoff value for validation (Stotz *et al*, 2013). In addition, we evaluated the prognostic value of the PLR as previously described (Proctor *et al*, 2011; Wang *et al*, 2012). PLR was categorised into three groups according to previously published cutoff values (Wang *et al*, 2012). Follow-up evaluations were performed every 3 months within the first 3 years, 6 months for 5 years and annually thereafter for curative resected tumour stages. For deceased patients, dates of death were obtained from the central registry of the Austrian Bureau of Statistics or telephone calls to their families. A complete follow-up was available for all patients in this retrospective analysis. The study was approved by the local ethical committee of the Medical University of Graz (No. 25-458 ex 12/13).

Statistical analyses. Cancer-specific survival was defined as the time (in months) from date of surgery or date of histological-proven diagnosis to cancer-related death. The association between the plasma CRP levels and clinico-pathological parameters was evaluated by non-parametric tests (Mann–Whitney U and χ^2 test). We seek an ideal cutoff value for the continuous CRP variable by applying receiver operating curve analysis as previously reported (Absenger *et al*, 2013). Patients' clinical end point was calculated using the Kaplan–Meier method and compared by the log-rank test. Backward stepwise multivariate Cox proportion analysis was performed to determine the influence of different clinico-pathological parameters and plasma CRP levels on CSS. Hazard ratios (HRs) estimated from the Cox analysis were reported as relative risks with corresponding 95% confidence intervals (CIs). All statistical analyses were performed using the Statistical Package for Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA). A two-sided $P<0.05$ was considered statistically significant.

RESULTS

Overall, 256 male and 218 female patients with PC were included in the study cohort. The mean age at diagnosis was 64.6 ± 10.4 years. Median survival was 7 months (range: 0–79 months) and 406 (85.7%) patients died by their most recent follow-up visit. The tumour stage was defined as stage I in 5 (1%) patients, stage IIa in 18 (3.8%) patients, stage IIb in 85 (17.9%) patients, stage III in 33 (7%) patient and stage IV in 333 (70.3%) patients. Three hundred and forty-five (72.6%) patients received a chemotherapy. Of the 474 patients, 126 (26.6%) underwent a tumour resection, 93 (19.6%) patients underwent a laparoscopic/laparotomy and consecutive biopsy and 255 (53.8%) were diagnosed by fine needle biopsy.

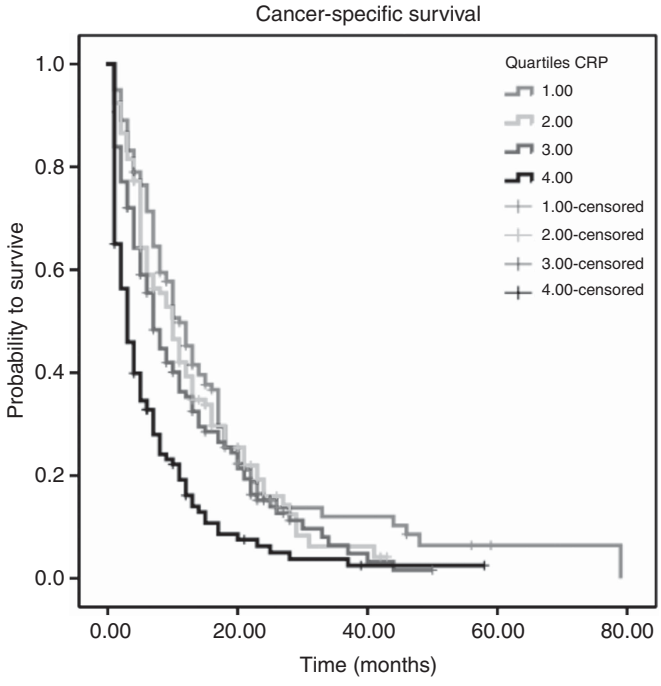

Figure 1. Kaplan–Meier curve stratified by quartiles of C-reactive protein (CRP) levels regarding cancer-specific survival for patients with pancreatic cancer ($n=474$, $P<0.001$).

The mean pre-treatment plasma CRP level was $23.2 \pm 36\,mg\,l^{-1}$. In an attempt to test whether increasing CRP levels influence the clinical outcome of PC patients, we first subdivided the patients into four groups according to their CRP levels. Kaplan–Meier curves for CSS, which comprises groups according to quartiles of the CRP levels are shown in Figure 1. Pairwise log-rank test indicates significant differences between the highest quartile (plasma CRP level $>27.1\,mg\,l^{-1}$) compared with the lowest ($0–2.4\,mg\,l^{-1}$; $P<0.001$), low ($2.1–7.5\,mg\,l^{-1}$; $P<0.001$) and third ($7.5–27.1\,mg\,l^{-1}$, $P<0.001$) quartiles. After performing receiver operating curve analysis, an optimal cutoff value of $>4.5\,mg\,l^{-1}$ (area under the curve: 0.59, 95% CI: 0.54–0.62) was identified to differentiate between survival and death. Consequently, we separated patients into two groups according to low CRP levels ($<4.5\,mg\,l^{-1}$) or high CRP levels ($\geqslant 4.5\,mg\,l^{-1}$) and tested the associations between preoperative plasma CRP levels and other clinical-pathological factors. An elevated plasma CRP level significantly correlated with high tumour stage, unresectable tumours, poor Karnofsky index, high NLR, high PLR and elevated bilirubin ($P<0.05$), whereas no association with age, gender, tumour grading, administration of chemotherapy could be found (Table 1).

To investigate whether plasma CRP level and other clinical-pathological factors are associated with clinical outcome of PC patients, univariate and multivariate Cox proportional models for CSS were calculated. Among the 474 PC patients, death occured in 134 of 177 (77.9%) patients with a low plasma CRP level and in 272 of 302 (90.1%) patients with a high plasma CRP level ($P<0.001$). Figure 2 shows the Kaplan–Meier curves for CSS and reveals that a high plasma CRP level is a consistent factor for poor prognosis in PC patients ($P<0.001$, log-rank test).

Univariate analysis identified older age (<65 *vs* $\geqslant 65$ years, $P=0.011$), a high tumour stage (stage I + II *vs* III *vs* IV, $P<0.001$), a high tumour grade (G1, G2 *vs* G3, G4, $P=0.011$), no administration of chemotherapy (chemotherapy *vs* no treatment, $P<0.001$), no surgical resection ($P<0.001$), a high NLR ($P<0.001$) and a high plasma CRP level ($P<0.001$) as poor prognostic factors for CSS in this study cohort. Gender, PLR and elevated bilirubin levels were not significantly associated with clinical outcome (Table 2).

To determine the independent prognostic value of the plasma CRP levels for CSS, a multivariate analysis using a Cox proportional hazard model was performed. In the multivariate analysis that included age, gender, tumour grade, tumour stage, administration of chemotherapy, surgical resection, NLR, PLR, bilirubin levels and plasma CRP levels, we identified tumour grade, tumour stage, administration of chemotherapy, high NLR and plasma CRP level within the highest quartile as independent prognostic factors for CSS (HR = 1.60, 95% CI = 1.16–2.21; $P=0.005$; Table 2).

Table 1. The relation between clinico-pathological parameters and pre-treatment plasma CRP levels of patients with pancreatic carcinoma ($n=474$)

Characteristics	CRP level $<4.5\,mg\,l^{-1}$ number of pts	CRP level $\geqslant 4.5\,mg\,l^{-1}$ number of pts	*P*-value
Age at operation (years)			
<65	83	137	0.544
⩾65	89	165	
Gender			
Female	85	133	0.259
Male	87	169	
Tumour stage			
Stage I–II	53	55	0.002
Stage III	15	18	
Stage IV	104	229	
Tumour grade			
G1 + G2	113	178	0.146
G3 + G4	59	124	
Chemotherapy			
No	38	92	0.050
Yes	134	210	
Curative resection			
No	113	235	0.004
Yes	59	67	
Karnofsky index			
Missing cases	4	2	0.001
<80	85	201	
90–100	83	99	
Neutrophil–lymphocyte ratio			
<3.25	124	103	<0.001
⩾3.25	48	199	
Platelet–lymphocyte ratio			
0–150	80	88	<0.001
150–300	75	149	
>300	16	62	
Bilirubin			
Normal	102	144	0.005
Elevated	60	148	

Abbreviations: CRP = C-reactive protein; pts = patients.

DISCUSSION

In the present study, we confirmed an association between elevated CRP levels at the time of PC diagnosis and decreased CSS on a large cohort of patients with PC. Many efforts have been previously made to investigate the relationship between CRP and prognosis in various types of cancer (Hashimoto *et al*, 2005; Karakiewicz *et al*, 2007; Nakamura *et al*, 2013). Regarding PC, the previously reported data are conflicting and mainly relies on small-scale studies. An early study conducted by Falconer *et al* (1995) proposed a prognostic value for elevated CRP levels ($>10\,mg\,l^{-1}$) in 102 patients with unresectable PC. Ueno *et al* (2000) found an independent prognostic significance for elevated CRP ($>5\,mg\,l^{-1}$) in 103 metastatic PC patients. In a smaller study, including 65 patients with surgically resected PC, Jamieson *et al* (2005) reported that patients with elevated ($>10\,mg\,l^{-1}$) post-operative CRP values had a poor clinical outcome. Papadoniou *et al* (2008) retrospectively evaluated 215 patients and showed that elevated plasma CRP was an independent factor of poor prognostic outcome in patients with advanced or metastatic PC. Pine *et al* (2009) reported in 199 patients that raised plasma CRP concentration ($>5\,mg\,l^{-1}$) at the time of presentation of advanced PC carries a poor prognosis independent of biliary tract obstruction.

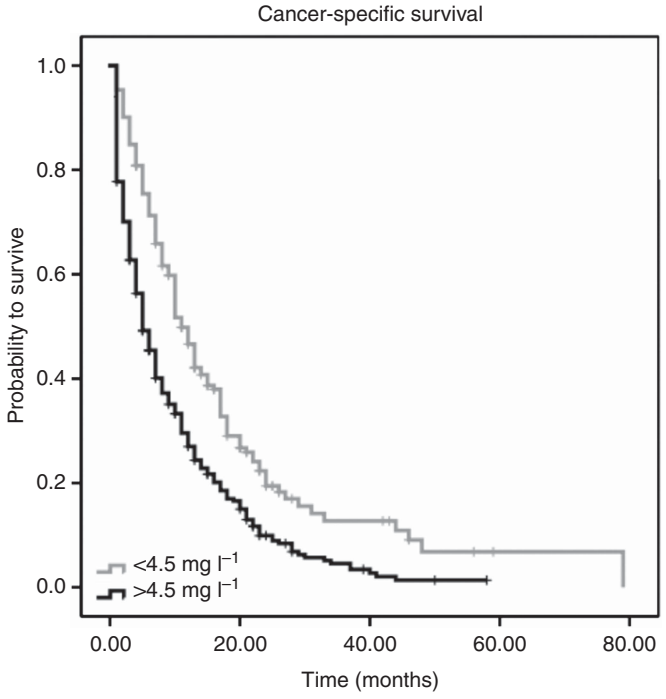

Figure 2. Kaplan–Meier curve stratified by C-reactive protein according to an optimal cutoff value regarding cancer-specific survival for patients with pancreatic cancer ($P<0.001$).

Table 2. Univariate and multivariate Cox proportional analysis regarding cancer-specific survival in pancreatic cancer patients ($n=474$)

	Univariate analysis		Multivariate analysis	
Parameter	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Age at operation (years)				
<65	1 (reference)	0.011	1 (reference)	0.954
⩾65	1.29 (1.06–1.58)		0.99 (0.80–1.23)	
Gender				
Female	1 (reference)	0.206	1 (reference)	0.841
Male	1.14 (0.93–1.38)		1.02 (0.82–1.27)	
Tumour stage				
Stage I–II	1 (reference)	<0.001	1 (reference)	0.007
Stage III	3.03 (1.88–4.88)	<0.001	2.16 (1.24–3.76)	<0.001
Stage IV	3.90 (2.95–5.16)		3.24 (2.00–5.26)	
Tumour grade				
G1 + G2	1 (reference)	0.011	1 (reference)	<0.001
G2 + G4	1.30 (1.06–1.58)		1.67 (1.34–2.07)	
Chemotherapy				
No	1 (reference)	<0.001	1 (reference)	<0.001
Yes	0.42 (0.34–0.52)		0.34 (0.26–0.43)	
CRP levels				
Quartile 1	1 (reference)	0.427	1 (reference)	0.658
Quartile 2	1.12 (0.84–1.48)	0.065	1.07 (0.79–1.44)	0.888
Quartile 3	1.29 (0.98–1.71)	<0.001	0.98 (0.73–1.32)	0.005
Quartile 4	2.21 (1.68–2.92)		1.60 (1.16–2.21)	
Resection				
No	1 (reference)	<0.001	1 (reference)	0.098
Yes	0.37 (0.26–0.43)		0.69 (0.45–1.07)	
Neutrophil–lymphocyte ratio				
<3.25	1 (reference)	<0.001	1 (reference)	0.003
⩾3.25	1.78 (1.46–2.17)		1.47 (1.15–1.89)	
Platelet–lymphocyte ratio				
0–150	1 (reference)	0.436	1 (reference)	0.055
150–300	0.91 (0.73–1.14)	0.236	0.79 (0.62–1.01)	0.680
>300	1.18 (0.89–1.58)		0.93 (0.66–1.31)	
Bilirubin				
Normal	1 (reference)	0.778	1 (reference)	0.151
Elevated	0.97 (0.80–1.19)		1.17 (0.95–1.44)	

Abbreviation: NYCRIS = Northern and Yorkshire Cancer Registry Information Service.

In line with these findings, Tingstedt *et al* (2007) reported that raised plasma CRP concentrations ($\geqslant 5\,mg\,l^{-1}$) were independently associated with decreased overall survival in 119 PC patients. Furthermore, in a smaller study including 51 patients from Japan, elevated preoperative plasma CRP levels ($>3\,mg\,l^{-1}$) were demonstrated to predict poor prognosis in patients undergoing curative resection for PC (Sanjay *et al*, 2012). In contrast to these mentioned studies, in a recent report by Garcea *et al* (2011), no association between plasma CRP levels and tumour recurrence was identified in 74 PC patients. However, many of these studies included rather small number of investigated cases and differ in terms of inclusion criteria and clinical end points. In our study, we validated the prognostic impact of plasma CRP levels on CSS as the end point and clearly demonstrated that an elevated plasma CRP level was independently associated with CSS in a large cohort of 316 PC patients. In our study, which is currently the largest one reported, we found also an association of elevated CRP levels and other clinico-pathological parameters. Regarding this association, different factors might explain the prognostic value of CRP. For instance, a higher tumour stage can lead to a greater extend of systemic inflammation by secretion of cytokines and release of tumour-degradation products, which in turn increase the CRP production in the liver. The association with elevated bilirubin levels and reduced Karnofsky index also indicate to a higher rate of PC-related cholestasis/cholangitis and impaired performance status in patients with high CRP levels. Thus, elevated CRP levels can be regarded as a surrogate biomarker for poor tumour biology as well as adverse individual-related medical conditions. Besides the role of CRP as a simply indicative circulating biomarker, its independent prognostic role might also be explained by its discrete influence on tumour progression. In this context, a number of theories have been postulated to explain why an elevated plasma CRP level could influence the biological properties of cancer cells. Previous studies indicate that tumour cells recruit endothelial cells, fibroblasts and inflammatory cells into the tumour bed to shape their unique microenvironment. The inflammatory response to tumour cells, reflected by an elevated plasma CRP level, results in a tumour microenvironment enriched with proinflammatory cytokines, angiogenic and lymphogenic factors and chemokines that promote tumour growth, angiogenesis and metastasis (Coussens and Werb, 2002; Miki *et al*, 2004). Alternatively, elevated plasma CRP may represent a response secondary to tumour necrosis and local tissue damage, which is caused by the tumour–host cell interaction and reflects a high tumour burden (McMillan *et al*, 2003). On the other hand, IL-6 may also indirectly help the binding of CRP to phospholipides on tumour cells, activating the complement system and acting as an opsonin, augmenting tumour cell phagocytosis (Black *et al*, 2004). Thus, CRP may not only

represent a response to tumour microenvironment, but also contribute to opsonisation and elimination of tumour cells. Taken together, CRP has a fundamental role in a wide range of inflammatory processes and provides a link between the innate and adaptive immune system.

There are a few limitations to the present study. CRP is known to be a non-specific marker of inflammation, and it is also possible that the presence of other systemic diseases could influence CRP concentrations in the plasma. Furthermore, for head of pancreas tumours the associated clinical condition of jaundice (with an associated bactobilia) may be a confounding factor in assessing CRP levels but we were not able to evaluate this feature in our study. Moreover, our study is limited by its retrospective nature and a heterogenous group of patients. Based on the results of our study, one can propose that higher CRP levels at the date of diagnosis of PC are associated with a higher risk for earlier death because of the disease. Whether patients can be selected for resection or increase the chances of curative resection can only be evaluated in a controlled prospective clinical trial. However, to the best of our knowledge, our study represents to date the largest one validating the prognostic value of plasma CRP levels in PC patients.

In conclusion, in the present study, elevated CRP levels before initial treatment were demonstrated to represent a poor prognostic factor for CSS in PC patients. This simple, highly repitable, inexpensive and easily available marker shows a potential to select patients at high risk for poor clinical outcome for appropriate treatment strategies.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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