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

J Szkandera¹, M Stotz¹, G Absenger¹, T Stojakovic², H Samonigg¹, P Kornprat³, R Schaberl-Moser⁴, W AlZoughbi⁴, C Lackner⁴, A L Ress¹, F S Seggewies¹, A Gerger¹,⁵, G Hoefler⁴ and M Pichler *,¹

¹Division of Clinical Oncology, Department of Medicine, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria; ²Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria; ³Division of General Surgery, Department of Surgery, Medical University of Graz, Graz, Austria; ⁴Institute of Pathology, Medical University of Graz, Graz, Austria and ⁵Research Unit Genetic Epidemiology and Pharmacogenetics, Division of Clinical Oncology, Department of Medicine, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria

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 clinical investigation (Sultana et al, 2012; Tinchon et al, 2013). Several prognostic factors have been
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 χ² 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).](image-url)
The mean pre-treatment plasma CRP level was 23.2 ± 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 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 (> 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, and 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 occurred 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 ≥ 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).

### 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 rely 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.

Table 1. The relation between clinicopathological 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 ≥ 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.
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)

| Parameter                      | Univariate analysis | Multivariate analysis |
|-------------------------------|---------------------|-----------------------|
| Age at operation (years)      |                     |                       |
| <65                           | 1 (reference)       | 1 (reference)         |
| ≥65                           | 1.29 (1.06–1.58)    | 0.99 (0.80–1.23)      |
| Gender                        |                     |                       |
| Female                        | 1 (reference)       | 1 (reference)         |
| Male                          | 1.14 (0.93–1.38)    | 1.02 (0.82–1.27)      |
| Tumour stage                  |                     |                       |
| Stage I–II                    | 1 (reference)       | 1 (reference)         |
| Stage III                     | 3.03 (1.88–4.88)    | 2.61 (1.24–4.76)      |
| Stage IV                      | 3.90 (2.95–5.16)    | 3.24 (2.00–5.26)      |
| Tumour grade                  |                     |                       |
| G1 + G2                       | 1 (reference)       | 1.07 (1.34–2.07)      |
| G2 + G4                       | 1.30 (1.06–1.58)    | 1.67 (1.34–2.07)      |
| Chemotherapy                  |                     |                       |
| No                            | 1 (reference)       | 1 (reference)         |
| Yes                           | 0.42 (0.34–0.52)    | 0.34 (0.26–0.43)      |
| CRP levels                    |                     |                       |
| Quartile 1                    | 1 (reference)       | 1 (reference)         |
| Quartile 2                    | 1.12 (0.84–1.48)    | 1.07 (0.79–1.44)      |
| Quartile 3                    | 1.29 (0.98–1.71)    | 1.08 (0.73–1.32)      |
| Quartile 4                    | 2.21 (1.68–2.92)    | 1.60 (1.16–2.21)      |
| Resection                     |                     |                       |
| No                            | 1 (reference)       | 1 (reference)         |
| Yes                           | 0.37 (0.26–0.43)    | 0.69 (0.45–1.07)      |
| Neutrophil–lymphocyte ratio   |                     |                       |
| <3.25                         | 1 (reference)       | 1 (reference)         |
| ≥3.25                         | 1.78 (1.46–2.17)    | 1.47 (1.15–1.89)      |
| Platelet–lymphocyte ratio     |                     |                       |
| 0–150                         | 1 (reference)       | 1 (reference)         |
| 150–300                       | 0.91 (0.73–1.14)    | 0.79 (0.62–1.01)      |
| >300                          | 1.18 (0.89–1.58)    | 0.93 (0.66–1.31)      |
| Bilirubin                     |                     |                       |
| Normal                        | 1 (reference)       | 1 (reference)         |
| Elevated                      | 0.97 (0.80–1.19)    | 1.17 (0.95–1.44)      |

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| Stage IV                      | 3.90 (2.95–5.16)    | 3.24 (2.00–5.26)      |
| Tumour grade                  |                     |                       |
| G1 + G2                       | 1 (reference)       | 1.07 (1.34–2.07)      |
| G2 + G4                       | 1.30 (1.06–1.58)    | 1.67 (1.34–2.07)      |
| Chemotherapy                  |                     |                       |
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| Bilirubin                     |                     |                       |
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Abbreviation: NYCRIS = Northern and Yorkshire Cancer Registry Information Service.
C-reactive protein in pancreatic cancer

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