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# Diagnostic Usefulness of Serum Interleukin 6 (IL-6) and C-Reactive Protein (CRP) in the Differentiation Between Pancreatic Cancer and Chronic Pancreatitis

**Barbara Mroczko,[1]* Magdalena Groblewska,[1] Mariusz Gryko,[2] Bogusław Kędra,[2] and Maciej Szmitkowski[1]**

[1]*Department of Biochemical Diagnostics, Medical University, Białystok, Poland*
[2]*Second Department of General Surgery, Medical University, Białystok, Poland*

Previous studies have shown elevated serum levels of interleukin 6 (IL-6) and C-reactive protein (CRP) in patients with pancreatic cancer (PC). The aim of this study was to assess the diagnostic usefulness of pretreatment serum levels of IL-6 and CRP to differentiate between PC and chronic pancreatitis (CP) patients. Serum levels of CRP, IL-6, carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA 19-9) were determined in 78 patients with PC before surgery, in 45 patients with CP, and in 70 healthy controls. Serum levels of all the proteins tested were significantly higher in cancer patients when compared with CP and healthy subjects, and increased in more advanced tumor stages. Concentrations of IL-6 were significantly higher in nonresectable tumors and in patients who died during the 2-year observation period. Area under receiver operating characteristic curve for IL-6 was higher than for other substances tested in the differentiation between PC and CP. Cox's univariate analysis revealed serum IL-6 as a significant prognostic factor of patients' survival. Our findings suggest higher diagnostic usefulness of serum IL-6 than CRP, CEA, and CA 19-9 in the diagnosis and prognosis of patients with PC and in the differentiation with CP. J. Clin. Lab. Anal. 24:256–261, 2010. © 2010 Wiley-Liss, Inc.

**Key words:** interleukin 6; C-reative protein; pancreatic cancer; chronic pancreatitis; tumor markers

## INTRODUCTION

Pancreatic cancer (PC) is a highly lethal and malignant disease. The reported 5-year survival rate is estimated as low as 0.2% (1). Only 10–20% of PC patients are eligible for a curative surgery (2). The life expectancy in patients with occult metastasis or locally nonresectable PC found during surgery is limited. The majority of PC patients with advanced cancer do not respond well to chemotherapy. As this type of treatment is of limited value, especially in metastatic PC, careful selection of patients is required. An enhancement of our knowledge of the mechanisms of the disease progression and prognostic factors might improve the choice of PC treatment.

C-reactive protein (CRP) is an essential acute-phase reactant that is synthesized in the hepatocytes. It has been reported that CRP is related to cancer cachexia and malignant potential of the tumor (3). It has been proved that the proinflammatory cytokines, interleukin 6 (IL-6), and to a lesser extent interleukin 1 and tumor necrosis factor alpha (TNF-α), can stimulate synthesis of this acute-phase protein (4). It is also known that the interaction of CRP with Fc receptors can stimulate synthesis of IL-6 and enhance the inflammatory response. Previous studies have shown elevated concentrations of TNF-α, IL-6, interleukin 8, and acute-phase proteins in the sera of patients with pancreatic adenocarcinoma and other malignancies (5–9). Talar-Wojnarowska et al. (10) have found that serum levels of IL-6 were significantly higher in patients with PC than in

*Correspondence to: Barbara Mroczko, Department of Biochemical Diagnostics, Medical University, Białystok, Waszyngtona 15 a, 15-269 Białystok, Poland. E-mail: mroczko@umwb.edu.pl

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subjects with chronic pancreatitis (CP). Some authors have suggested that serum CRP or IL-6 might be possible negative prognostic factors for survival of PC patients (2,11–13). Therefore, to further evaluate the clinical value of serum IL-6 and CRP, we determine the diagnostic usefulness of these proteins.

The objective of this study was to compare the pretreatment serum levels of IL-6 and CRP with classical tumor markers in PC patients in relation to clinicopathological features of tumor and survival rates, as well as to assess the prognostic significance of these proteins for PC patients. We investigated the levels of IL-6 and CRP in the sera of CP patients and determined their diagnostic usefulness to differentiate between PC and CP patients. In addition, the areas under receiver operating characteristic (ROC) curves for all the proteins tested were estimated.

## MATERIAL AND METHODS

### Patients

The study included 78 previously untreated PC patients (25 women and 53 men, aged 42–88 years) diagnosed from September 2003 to May 2006 and operated on in the Second General Surgery Department of the University Hospital in Białystok, 45 patients with CP (19 women and 26 men, aged 27–84 years), and 70 healthy subjects (53 women and 15 men, aged 20–69 years). Physical examination, blood tests, chest x-rays, abdominal ultrasound, and computed tomography were used in the clinical diagnosis of the patients. In addition, radioisotopic bone scans and brain computed tomography were also performed. The clinical diagnosis of PC was confirmed by microscopic examination of the material obtained during surgery and/or biopsy. Twenty-four PC patients underwent surgical tumor resection, whereas 54 patients had nonresectable tumors. The staging was based on a routine postoperative histopathological analysis and clinical assessment, according to the standard TNM classification. The tumors were classified in accordance with the staging of the 5th International Union Against Cancer (14). For the statistical analysis, the PC patients were divided into three groups: eight cancer patients in stage II, 19 patients in stage III, and 51 patients in stage IV, and then sub-divided into three groups depending on tumor size (T2, T3, and T4), two groups depending on nodal involvement (N0 and N1), and two groups depending on the presence of distant metastases (M0 and M1). Forty-one PC patients died of malignancy during the 2-year observation period, whereas 15 patients were still alive. In 22 PC patients, the data of survival were not available and those patients were excluded from survival analysis. The numbers of patients in all study subgroups are presented in Table 1. The study was approved by the Ethical Committee of Białystok Medical University, and all the patients gave their informed consent to participate.

**TABLE 1. Characteristics of Pancreatic Cancer Patients**

| | |
|---|---|
| Pancreatic cancer patients | 78 |
| Gender | |
| Female | 25 |
| Male | 53 |
| Age (yr) | |
| $<65$ | 33 |
| $\geq 65$ | 45 |
| Median | 66.5 |
| Range | 42–88 |
| Tumor stage | |
| II | 8 |
| III | 19 |
| IVa | 18 |
| IVb | 33 |
| Tumor size | |
| T2 | 12 |
| T3 | 22 |
| T4 | 44 |
| Lymph node metastases | |
| N0 | 11 |
| N1 | 67 |
| Distant metastases | |
| M0 | 45 |
| M1 | 33 |
| Survival of patients | |
| Alive | 15 |
| Dead | 41 |
| Tumor respectability | |
| Resectable | 24 |
| Nonresectable | 54 |

### Biochemical Analyses

None of the PC patients received chemo- or radiotherapy before blood sample collection. Blood samples from all the patients were drawn before treatment. All sera were separated within 1 hr after blood collection and stored at $-80^{\circ}$C until assayed.

Serum concentrations of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) in the patients and healthy controls were measured by microparticle enzyme immunoassay kits (Abbott, Chicago, IL). The intra-assay CV for CEA is reported by the manufacturer of the assay kits to be 4.9% at a mean concentration of 2.2 ng/ml, SD = 0.11 and the intra-assay CV% for CA 19-9 to be 4.7% at a mean concentration of 38.2 U/ml, SD = 1.80.

Serum levels of IL-6 were measured using enzyme-linked immunosorbent assay kits (R&D Systems, Abingdon, England), according to the manufacturer's instructions. The intra-assay coefficient of variation (CV%) is reported by the manufacturer to be 4.2% at a mean concentration of 16.8 pg/ml, SD = 0.7.

Concentrations of CRP in the sera were determined using immunoturbidimetric Protiline® CRP assay kits (bioMerieux, Lyon, France), according to the manufacturer's instructions. The intra-assay coefficient of variation (CV%) is reported by the manufacturer to be 2.49% at a mean concentration of 10 mg/l.

The reference cut-off values (the 95th percentile) were established previously in our department (9). The cut-off points were 13.1 pg/ml for IL-6, 9.7 mg/l for CRP, 4.0 ng/ml for CEA, and 30.0 U/ml for CA 19-9.

### Statistical Analysis

The distribution of IL-6, CRP, CEA, and CA 19-9 levels did not follow a Gaussian curve in preliminary statistical analysis ($\chi^2$ test). Consequently, the comparisons between two groups were performed by the Mann–Whitney *U*-test, and for three groups or more, the one-way ANOVA Kruskal–Wallis test was used. The method of Kaplan and Meier was used for the calculation of the survival curves. The log-rank test for univariate analyses of survival as well as the Cox proportional hazards model for multivariate analyses were employed. Differences were considered statically significant with *P* values below 0.05. Moreover, we calculated the area under the ROC curve (AUC) for the IL-6, CRP and tumor markers. Statistical analyses were carried out using the STATISTICA 5.1 PL program (StatSoft Inc., Tulsa, OK). Diagnostic criteria were calculated using Med-Calc statistical software (MedCalc Software, Mariakerke, Belgium) and Microsoft Office Excel program (Microsoft Corporation, Redmond, WA).

## RESULTS

### Serum IL-6, CRP, and Tumor Markers (CEA and CA 19-9) in PC Patients Versus CP Patients and Controls

The median and range of serum levels of IL-6, CRP, and tumor markers (CEA and CA 19-9) in PC and CP patients before treatment and in healthy subjects (control group) are presented in Table 2. The serum levels of IL-6, CRP, CEA, and CA 19-9 in PC patients were significantly higher than in healthy subjects and in CP patients. The serum concentrations of IL-6, CRP, and tumor markers in cancer patients increased with tumor stage and were the highest in patients with stage IV, although the differences between stages were statistically significant only for IL-6 ($P = 0.005$) and CEA ($P = 0.033$) in the Kruskal–Wallis test. In addition, based on the Mann–Whitney test, the serum levels of IL-6 in patients with stages II and III and the concentrations of CEA in stage III were significantly lower than in stage IV.

### The Relationship Between Serum Levels of IL-6, CRP, CEA, CA 19-9, and Clinicopathological Features in PC Patients

Table 3 shows the medians and ranges of serum levels of IL-6, CRP, and tumor markers in cancer patients in relation to clinicopathological features of PC (TNM score, tumor resectability and survival of patients). Serum concentrations of all the proteins measured were the highest in patients in T4 subgroup. The differences between T2, T3, and T4 subgroups were significant for serum levels of IL-6 ($P = 0.008$) and CEA ($P = 0.009$), based on the Kruskal–Wallis test. Moreover, in the Mann–Whitney test, the serum levels of IL-6 were significantly higher in T4 subgroup than in T2 patients, CRP levels were significantly higher in T3 patients when compared with T2 tumors, whereas CEA concentrations were significantly higher in T3 and T4 subgroups than in T2 patients. The serum levels of all the proteins tested in patients with nodal metastases (N1) were higher than in N0 patients, although these differences were significant only for serum IL-6 ($P = 0.009$) and CRP ($P = 0.030$). The concentrations of all the proteins were higher in patients with distant metastases (M1 subgroup) than those in M0 group and the differences were statistically significant for IL-6 ($P < 0.001$) and CEA ($P = 0.002$). Median concentrations of all the proteins examined

**TABLE 2. Serum Levels of IL-6, CRP, and Tumor Markers in Pancreatic Cancer Patients**

| | IL-6 (pg/ml) | | CRP (mg/l) | | CEA (ng/ml) | | CA19-9 (U/ml) | |
|---|---|---|---|---|---|---|---|---|
| Group tested | Median | Range | Median | Range | Median | Range | Median | Range |
| Pancreatic cancer patients ($n = 78$) | $10.9^{AB}$ | 0.9–304.0 | $17.7^{AB}$ | 1.0–263.0 | $3.5^{AB}$ | 0.6–884.0 | $174.4^{AB}$ | 0.0–50000.0 |
| Chronic pancreatitis patients ($n = 45$) | 1.8 | 0.0–88.9 | $7.7^{A}$ | 0.0–282.0 | $1.4^{A}$ | 0.1–7.4 | $4.7^{A}$ | 0.0–114.2 |
| Control group ($n = 70$) | 1.3 | 0.0–26.7 | 5.0 | 0.0–9.0 | 0.7 | 0.0–3.9 | 2.0 | 0.0–24.0 |
| Tumor stage | | | | | | | | |
| II ($n = 8$) | $6.7^{ABC}$ | 2.8–17.5 | $12.1^{A}$ | 2.0–23.0 | $1.6^{A}$ | 0.7–7.4 | $56.1^{AB}$ | 0.0–724.5 |
| III ($n = 19$) | $7.2^{ABC}$ | 1.6–33.4 | $14.7^{A}$ | 2.0–92.0 | $2.3^{ABC}$ | 0.9–110.7 | $168.8^{AB}$ | 0.0–44800.0 |
| IV ($n = 51$) | $18.2^{AB}$ | 0.9–304.0 | $23.0^{AB}$ | 1.0–263.0 | $4.5^{AB}$ | 0.6–884.0 | $261.7^{AB}$ | 0.0–50000.0 |

A, statistically significant compared with control group; B, statistically significant compared with chronic pancreatitis; C, statistically significant compared with pancreatic cancer stage IV.

**TABLE 3. Serum Levels of IL-6, CRP, and Tumor Markers in Pancreatic Cancer Patients in Relation to Clinicopathological Features of Tumor**

| | IL-6 (pg/ml) | | CRP (mg/l) | | CEA (ng/ml) | | CA19-9 (U/ml) | |
|---|---|---|---|---|---|---|---|---|
| Group tested | Median | Range | Median | Range | Median | Range | Median | Range |
| Tumor size | | | | | | | | |
| T2 ($n = 12$) | $4.8^{ABD}$ | 1.6–17.5 | $7.6^{AC}$ | 2.0–26.0 | $1.6^{AD}$ | 0.7–7.4 | $48.6^{AB}$ | 0.0–724.5 |
| T3 ($n = 22$) | $9.6^{AB}$ | 2.6–75.8 | $20.9^{A}$ | 1.0–155.0 | $2.2^{ABD}$ | 0.7–110.7 | $192.4^{AB}$ | 13.5–44800.0 |
| T4 ($n = 44$) | $18.3^{AB}$ | 0.9–304.0 | $22.1^{A}$ | 1.0–263.0 | $4.7^{AB}$ | 0.6–884.0 | $269.6^{AB}$ | 0.0–50000.0 |
| Nodal metastases | | | | | | | | |
| N0 ($n = 11$) | $4.2^{AB}$ | 1.2–17.5 | $8.7^{A}$ | 1.0–23.0 | $1.7^{A}$ | 0.7–14.6 | $46.8^{AB}$ | 0.0–724.5 |
| N1 ($n = 67$) | $14.9^{ABE}$ | 0.9–304.0 | $21.9^{ABE}$ | 1.0–263.0 | $3.7^{AB}$ | 0.6–884 | $216.1^{AB}$ | 0.0–50000.0 |
| Distant metastases | | | | | | | | |
| M0 ($n = 45$) | $7.2^{AB}$ | 0.9–213.8 | $14.7^{A}$ | 1.0–144.0 | $2.3^{AB}$ | 0.7–884.0 | $147.2^{AB}$ | 0.0–44800.0 |
| M1 ($n = 33$) | $19.5^{ABF}$ | 2.4–304.0 | $31.6^{AB}$ | 1.0–263.0 | $6.1^{ABF}$ | 0.6–320.5 | $310.1^{AB}$ | 0.0–50000.0 |
| Tumor resectability | | | | | | | | |
| Resectable ($n = 24$) | $4.9^{AB}$ | 0.9–75.8 | $14.8^{A}$ | 1.0–155.0 | $1.8^{A}$ | 0.7–17.9 | $70.1^{AB}$ | 0.0–724.5 |
| Nonresectable ($n = 54$) | $16.2^{ABG}$ | 1.6–304.0 | $22.0^{AB}$ | 1.0–263.0 | $4.6^{ABG}$ | 0.6–884.0 | $316.4^{ABG}$ | 0.0–50000.0 |
| Survival of patients | | | | | | | | |
| Alive ($n = 15$) | $5.0^{AB}$ | 1.2–65.1 | $19.9^{A}$ | 1.0–138.0 | $1.3^{A}$ | 0.7–197.2 | $65.4^{AB}$ | 0.0–50000.0 |
| Dead ($n = 41$) | $17.0^{ABH}$ | 0.9–267.4 | $21.2^{AB}$ | 2.0–263.0 | $4.5^{ABH}$ | 0.6–884.0 | $310.1^{AB}$ | 0.0–44800.0 |

A, statistically significant compared with control group; B, statistically significant compared with chronic pancreatitis patients; C, statistically significant compared with T3; D, statistically significant compared with T4; E, statistically significant compared with N0; F, statistically significant compared with M0; G, statistically significant compared with patients with resectable tumors; H, statistically significant compared with patients who survived.

were higher in patients with nonresectable tumors in comparison with those with the resectable ones. The differences were statistically significant for IL-6 ($P = 0.002$), CEA ($P = 0.002$), and CA 19-9 ($P = 0.004$). The levels of IL-6, CRP, and the tumor markers—CEA and CA 19-9—were higher in the sera of patients who died of PC during the 2-year observation period when compared with patients who survived, although the differences were significant for serum IL-6 ($P = 0.026$) and CEA ($P = 0.012$) only (Table 3).

## The Diagnostic Usefulness of IL-6, CRP, and Tumor Markers (CA 19-9 and CEA) in PC and CP Patients

The area under the ROC curve (AUC) indicates the clinical usefulness of a tumor marker—the larger AUC, the better the tumor marker. We showed that the IL-6 AUC (0.9439) was higher than the AUC for CEA (0.8937), CA 19-9 (0.8622), and CRP (0.8440) in the diagnosis of PC versus healthy subjects (Fig. 1). In addition, the area under ROC curve for IL-6 (0.8433) was higher than for CA 19-9 (0.8097), CEA (0.7390), and CRP (0.6073) in the differentiation between PC and CP patients (Fig. 2).

## Correlations Between Pretreatment Serum Levels of Proteins Tested and PC Patients Prognosis

The Kaplan–Meier method was used to evaluate the relationship between the survival of cancer patients and

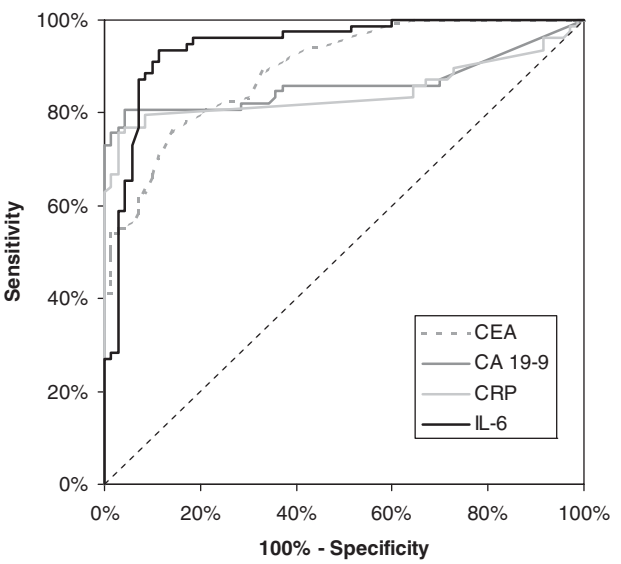


**Fig. 1.** Areas under ROC curves for IL-6 (0.9439), CEA (0.8937), CA 19-9 (0.8622) and CRP (0.8440) in the differentiation between pancreatic cancer patients and healthy subjects. IL-6, interleukin-6; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; CRP, C-reactive protein; ROC, receiver operating characteristic.

the serum levels of the proteins tested. The patients were followed-up for 2 years. The univariate log-rank analysis showed that the presence of nodal ($P = 0.028$) and distant metastases ($P < 0.001$), tumor resectability ($P = 0.003$), and the serum levels of IL-6 ($P = 0.004$) were the significant factors affecting the overall survival

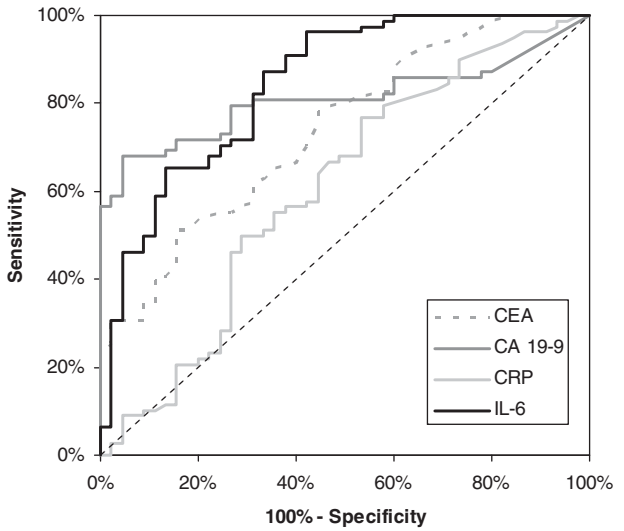


**Fig. 2.** Areas under ROC curves for IL-6 (0.8433), CA 19-9 (0.8097), CEA (0.7390) and CRP (0.6073) in the differentiation between pancreatic cancer and chronic pancreatitis patients. IL-6, interleukin-6; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; CRP, C-reactive protein; ROC, receiver operating characteristic.

**TABLE 4. Results of Cox's Univariate Analysis in Pancreatic Cancer Patients**

| | Odds ratio | *P* |
|---|---|---|
| Tumor stage | | 0.120 |
| TNM III versus TNM II | 2.166 | 0.376 |
| TNM IV versus TNM II | 3.863 | 0.066 |
| Tumor size (T factor) | | 0.131 |
| T3 versus T2 | 3.645 | 0.227 |
| T4 versus T2 | 5.922 | 0.081 |
| Lymph node metastases (N factor) | 4.952 | 0.028* |
| Distant metastases (M factor) | 3.694 | <0.001* |
| Resectability of tumor | 0.256 | 0.003* |
| CEA | 1.001 | 0.249 |
| CA19-9 | 1.000 | 0.291 |
| IL-6 | 1.009 | 0.004* |
| CRP | 1.004 | 0.133 |

IL-6, interleukin-6; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; CRP, C-reactive protein.
*Statistically significant at $P<0.05$.

(Table 4). Multivariate regression analysis with the Cox's proportional hazards model revealed that only tumor resectability ($P = 0.038$) and the presence of distant metastases ($P = 0.018$) were independent prognostic factors for the survival of PC patients.

## DISCUSSION

PC is an aggressive malignancy of the gastrointestinal tract and one of the most lethal human cancers. It has been estimated that PC is the cause of approximately 30,000 deaths per year in the United States (15) and the majority of cancer-related deaths in patients with pancreatic adenocarcinoma result from aggressive growth and metastases. There is currently no commonly accepted prognostic factor in PC. Some authors have proposed that tumor size (T factor) and/or the presence of distant metastases (M factor) (16,17) as well as serum levels of IL-6 (13) and CRP (12,16) might predict the survival of PC patients.

In this study, we analyzed the serum levels of the proinflammatory cytokine, IL-6, and acute-phase (C-reactive) protein in PC and CP patients. The clinical significance of the measurement of these inflammatory markers in the diagnosis and prognosis of PC as well as in the differentiation between PC and CP was assessed. We demonstrated that the preoperative serum levels of IL-6 and CRP as well as CEA and CA 19-9 were significantly higher in the cancer group than in healthy subjects. In addition, the concentrations of CRP and both classical tumor markers in CP patients increased significantly when compared with the control group. These findings are in line with a report of Barber et al. (18), who showed higher concentrations of IL-6 and CRP in PC patients in comparison with healthy subjects; however, the researchers did not include CP patients in their study. In this paper, the levels of IL-6, CRP, CEA, and CA 19-9 increased with tumor stage, although the differences were significant only for serum IL-6 and CEA concentrations. Our findings are in agreement with a study of Okada et al. (19), who found that serum levels of IL-6 were higher in PC patients than in healthy subjects and CP patients, and increased in more advanced tumor stage. The opposite results were shown in a study of Bellone et al. (6), who failed to establish any significant differences in serum IL-6 levels between PC patients and healthy subjects.

In addition, in our study, preoperative serum levels of all the proteins tested increased with tumor size (T factor), the presence of nodal (N factor), and distant metastases (M factor). The differences were significant for CEA and IL-6 when T and M factors were analyzed and for CRP and IL-6 in the assessment of nodal involvement. Similar results were obtained by Wenger et al. (20) who found that plasma concentrations of IL-6 rose with increasing tumor dimension, but not with involvement of lymph nodes. Moreover, we revealed that the concentrations of IL-6, CEA and CA 19-9 were significantly higher in subjects with nonresectable tumors in comparison with the resectable cancer group.

In this study, the concentrations of IL-6 and CEA in the patients who died of PC were significantly higher than in those who survived in the course of the 2-year follow-up. Serum concentration of IL-6 was the significant prognostic factor of PC patients' survival in Cox's univariate analysis, but only tumor resectability and the presence of distant metastases were independent predictors of PC

patients' survival. This finding seems to confirm earlier observations of Ebrahimi et al. (13), who demonstrated that elevated preoperative levels of this protein may predict unfavorable prognosis in PC patients.

IL-6 is a multi-functional and complex cytokine. The increased pretreatment levels of IL-6 might reflect the synthesis of acute-phase proteins during tumor progression. We have currently found that elevated concentrations of IL-6 can be detected in early stages of PC—there were increased serum levels of this protein in patients with stage II of cancer as well as in patients with T2 tumors. Therefore, the measurement of serum IL-6 in PC patients before treatment may be helpful for performing a successful surgery or other curative measures for this disease. Moreover, serum IL-6 may be considered as an appropriate predictor of PC patients' prognosis and might be helfpul for the choice of treatment strategy.

According to our knowledge, this is the first study comparing diagnostic usefulness of IL-6 and CRP with tumor markers in PC. We proved—especially based on the ROC analysis—the advantage of IL-6 measurement over assessment of CRP and classical tumor markers (CEA and CA 19-9) in the diagnosis of PC patients and in differentiation between PC and CP patients. We found that the IL-6 areas under the ROC curves (PC versus healthy subjects and PC versus CP) were larger than the AUC of other proteins tested. Moreover, in this study the area under ROC curve of IL-6 (PC versus healthy subjects) was higher than those of other biomarkers of PC from our previous study (21), i.e., hematopoietic cytokines, such as macrophage colony-stimulating factor (AUC = 0.7191) and granulocyte colony-stimulating factor (AUC = 0.6576) (21).

In conclusion, this study objective was to compare the serum levels of IL-6 and CRP with tumor markers in PC patients in relation to clinicopathological features of tumor and to estimate the prognostic significance of these proteins for patients' survival. Moreover, we analyzed serum levels of IL-6 and CRP in nonmalignant disease of the pancreas, i.e., CP, and assessed diagnostic usefulness of these substances to differentiate between PC and CP. Our findings suggest higher usefulness of serum IL-6 than CRP and classical tumor markers in the diagnosis of PC, in the differentiation with nonmalignant disease of the pancreas, and in the prognosis of PC patients' survival.

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