ORIGINAL ARTICLE

Clinical Significance of Interleukin-6 (Il-6) Gene Polymorphism and Il-6 Serum Level in Pancreatic Adenocarcinoma and Chronic Pancreatitis

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Abstract The aim of our study was to assess the clinical significance of -174G/C Il-6 gene polymorphism and Il-6 serum level in patients with pancreatic adenocarcinoma (PA) and chronic pancreatitis (CP). The study included 41 with pancreatic adenocarcinoma, 56 with chronic pancreatitis, and 50 healthy volunteers, hospitalized between 2003 and 2006. Il-6 serum levels were measured with an enzyme-linked immunoassay and Il-6 gene polymorphism was studied in DNA isolated from peripheral blood. In PA and CP patients Il-6 serum levels were significantly higher than in the control group ($P < 0.01$). The levels of Il-6 in the patients with tumor size ≥ 3.5 cm were higher than that in patients with smaller tumors ($P < 0.01$). The elevated Il-6 levels were also correlated with the presence of liver metastases ($P < 0.01$). Mean Il-6 serum level was significantly higher in patients homozygous G/G for -174 Il-6 gene compared with patients with at least one C allele. Our findings indicate that -174G/C Il-6 gene polymorphism influences circulating Il-6 levels. Increased Il-6 serum levels may be correlated with tumor size and the presence of liver metastases in patients with pancreatic adenocarcinoma.

Keywords Interleukin-6 · Polymorphism ·
Pancreatic adenocarcinoma · Chronic pancreatitis

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Introduction

Interleukin-6 (Il-6), a phosphorylated glycoprotein containing 185 amino acids, is a cytokine involved in various pathophysiological processes, including inflammation and carcinogenesis. Being produced by a wide variety of cells—macrophages, endothelial cells, hepatocytes, and fibroblasts—Il-6 is the mediator of hepatocyte acute-phase protein synthesis and B, T, and NK cells activation [1]. Serum levels of Il-6 are normally undetectable but are elevated in acute or chronic diseases, such as coronary heart diseases, and after surgical procedures, in sepsis or trauma [2–4]. High Il-6 levels have also been observed in patients with a variety of hematological and solid tumors, including pancreatic, gastric and renal cell cancer, sarcoma, and ovarian cancer [5–8].

The role of Il-6 in cancer biology is still unclear. It has been suggested that increased Il-6 serum levels may enhance the metastatic potential of cancer cells, by upregulating the expression on endothelial cells receptors, and by stimulating the growth factors, such as vascular endothelial growth factor (VEGF) [1, 9]. Il-6 may also mediate host immune response to the disease [10, 11]. In renal cell cancer, gastric, and colorectal cancer high Il-6 levels are associated with advanced stage, short survival, and poor response to additional treatment [5, 7, 12].

The human Il-6 gene is mapped to chromosome 7p21–24 with an upstream promoter containing 303 bp [13]. Polymorphic variants in the promoter region of the Il-6 gene may be responsible for variations in transcription that subsequently affect serum level of this cytokine [4, 14]. The best characterized of these polymorphisms is a single-nucleotide polymorphism at position -174, upstream of the transcription start site, involving substitution of cytosine (C) for guanine (G). A common -174 G/C Il-6 gene

polymorphism has been investigated in a wide variety of diseases, including cancer disease [11, 15, 16].

The polymorphism of other cytokine—interleukin-1β—was observed to influence survival in pancreatic adenocarcinoma patients [17]. In vivo studies have also shown that elevated Il-6 serum level may be correlated with poor prognosis in patients with pancreatic adenocarcinoma, however there is no information available on the value of -174 G/C Il-6 gene polymorphism in pancreatic cancer occurrence and prognosis [6, 18].

The aim of our study was to assess the clinical significance of -174G/C Il-6 gene polymorphism and Il-6 serum level in patients with pancreatic adenocarcinoma (PA) and chronic pancreatitis (CP).

Patients and Methods

The study included 147 Caucasian patients: 41 with pancreatic adenocarcinoma (19 men and 22 women, aged 47–84 years), 56 with chronic pancreatitis (36 men and 20 women, aged 21–73 years), and 50 sex- and age-matched healthy volunteers. Analyzed patients were hospitalized in Department of Digestive Tract Diseases, Medical University of Lodz Hospital between 2003 and 2006. Patients with acute infection, recent myocardial infarction, surgical procedures within 14 days prior or uraemia were excluded from the study because these conditions might be associated with elevated Il-6 serum levels [1]. The study protocol was approved by the ethical committee of Lodz Medical University.

Nine patients (21.9%) with PA underwent Whipple resection or distal pancreatectomy, 10 patients (24.4%) underwent palliative surgery, and 22 patients (53.6%) underwent palliative chemotherapy and/or endoscopic treatment (stent insertion). Only patients with confirmed pathologic diagnosis of ductal adenocarcinoma of pancreatic origin were included into the study. Chronic pancreatitis diagnosis was established based on histopathological confirmation after surgical intervention—in 17 patients (30.3%)—or based on a typical clinical history and characteristic findings on pancreatic imaging. Indications for surgical intervention in chronic pancreatitis were intractable pain (nine patients), suspicion of pancreatic cancer (six patients), and pancreatic pseudocyst (two patients).

Associations of the examined genotypes, Il-6 serum levels, and clinical data at diagnosis were evaluated. The analyzed clinical parameters were age, sex, history of smoking, bilirubin level, and weight loss of more than 10%. To examine the severity of chronic pancreatitis, the Cambridge classification was used [19]. In patients with pancreatic adenocarcinoma additionally tumor size, lymph nodes involvement, and presence of distant metastases were assessed.

Peripheral venous blood samples were obtained from all analyzed patients at the time of hospital admission. Sera were separated by centrifugation at 3000 rpm and were stored at −80°C until the levels of analyzed cytokine were assessed. The serum concentrations of Il-6 were measured with an enzyme-linked immunoassay (Bender MedSystems, Austria). The limit of detection of Il-6 was determined to be 0.92 pg/ml.

Il-6 gene polymorphism was studied in DNA isolated from blood samples. Single-nucleotide polymorphism was discriminated by 5′ nuclease polymerase chain reaction assays. The primers 5′-ATGCCAAGTGCTGAGTCACTA-3′ (in the forward direction) and 5′-CTGCACCTTCTGTC TCGGTTTCTTC-3′ (in the reverse direction) were used to amplify the region containing the Il-6 -174 G/C variant. PCR amplification was performed in a final volume of 25 μl containing 80 ng DNA, 1.5 mM $MgCl_2$, 10 mM Tris–HCl (pH 8.3), 50 mM KCl, 0.2 mM of dNTP, each primer at 1.0 μM, and 1.0 unit Taq polymerase (Qiagen, Germany) in a 2400 Perkin-Elmer Thermocycler.

Ten microliters of the PCR product was digested with 2 units of NlaIII using the manufacturer's recommended protocol. PCR products were visualized on 3% agarose gels with 10% ethidium bromide. PCR products for the Il-6 variants were analyzed by restriction fragment length polymorphism (RFLP) analysis (Fig. 1).

The results were analyzed according to statistical methods by using StatSoft Statistica release 6.0 for Windows (StatSoft, Inc., Tulsa, USA). To determine differences between groups the Mann-Whitney t-test was used. Association between continues variables was analyzed with Pearson's correlation test. P-values <0.05 were considered to be significant.

Results

Serum levels of Il-6 were detected in 33 patients with pancreatic adenocarcinoma (80.5%), 31 with chronic
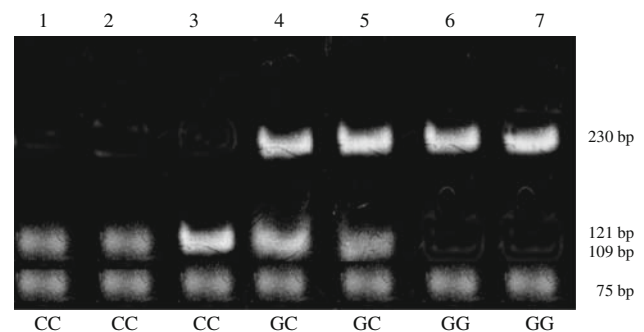

Fig. 1 NlaIII RFLP for IL-6 -174G/C polymorphism of seven pancreatic adenocarcinoma cases. Lanes 1–3 show the typical bands for C/C homozygote variant; lanes 4 and 5 for G/C heterozygote variant; and lanes 6 and 7 for C/C homozygote variant

pancreatitis (55.4%), and in 8 of 50 healthy adults from control groups (16%). In PA and CP patients Il-6 serum levels were significantly higher (respectively, 36.3 ± 2.3 pg/ml and 7.9 ± 1.8 pg/ml) than in the control group (1.7 ± 1.4 pg/ml) ($P < 0.01$). There was also a statistically significant difference between PA and CP Il-6 levels ($P < 0.01$; Fig. 2).

In PA patients, the tumor size ranged from 2 to 6 cm (mean 3.6 ± 1.2 cm). In 14 patients (34.1%) tumor smaller than 3.5 cm was detected. Local lymph node metastases were observed in 19 patients with PA (46.3%) and liver metastases in 8 patients (19.5%). Table 1 summarizes the relation between the Il-6 serum concentration and clinical findings of PA patients. The levels of Il-6 in the patients with tumor size ≥3.5 cm were significantly higher than in those patients with smaller tumors ($P < 0.01$; Fig. 3). The elevated serum concentration of Il-6 correlated also with the presence of liver metastases ($P < 0.01$; Fig. 4). We also observed a trend toward association between Il-6 levels and weight loss of more than 10% ($P = 0.06$; Fig. 5). However, there was no association between examined cytokine serum levels and lymph nodes involvement (Fig. 6). In our study we did not observe a correlation between Il-6 and history of smoking, bilirubin level, sex, and age in the analyzed group of patients (Table 1).

In chronic pancreatitis patients Il-6 serum levels were detectable in 31 subjects (54.4%) and no association between this cytokine level and any clinical factors was observed (Table 2).

The incidence of Il-6 polymorphism was similar in patients with pancreatic adenocarcinoma, chronic pancreatitis, and the control group ($P > 0.5$) (Table 3). In the groups of patients with pancreatic adenocarcinoma and
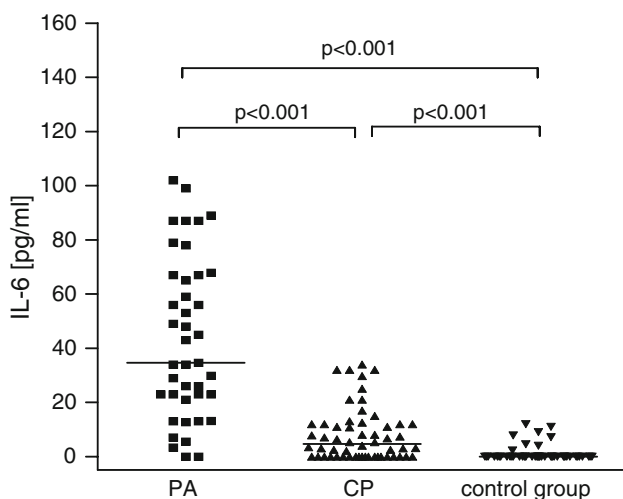
Table 1 Relationship between Il-6 serum levels and clinical findings in patients with pancreatic adenocarcinoma ($n = 41$)

Clinical findings	No. of patients	Mean ± SD (pg/ml)	P-value
Age, years			
<65	18	34.5 ± 9.2	NS
≥65	23	38.7 ± 7.9	
Sex			
Male	19	39.9 ± 10.4	NS
Female	22	33.7 ± 7.0	
Tumor size			
<3.5 cm	14	21.1 ± 6.2	$P < 0.01$
≥3.5 cm	27	63.2 ± 11.2	
Lymph node metastases			
(+)	19	48.2 ± 9.4	NS
(−)	22	31.8 ± 8.8	
Liver metastases			
(+)	8	68.7 ± 9.1	$P < 0.01$
(−)	33	29.1 ± 6.5	
Smoking			
(+)	21	39.7 ± 7.2	NS
(−)	20	23.1 ± 3.7	
Bilirubin level			
<3 mg/dl	17	28.1 ± 6.5	NS
≥3 mg/dl	24	39.7 ± 7.9	
Weight loss			
<10%	15	25.1 ± 4.6	$P = 0.06$
≥10%	26	46.2 ± 11.3	

SD, standard deviation; NS, not significant

Fig. 2 Analysis of Il-6 serum levels in patients with pancreatic adenocarcinoma (PA), chronic pancreatitis (CP), and the control group
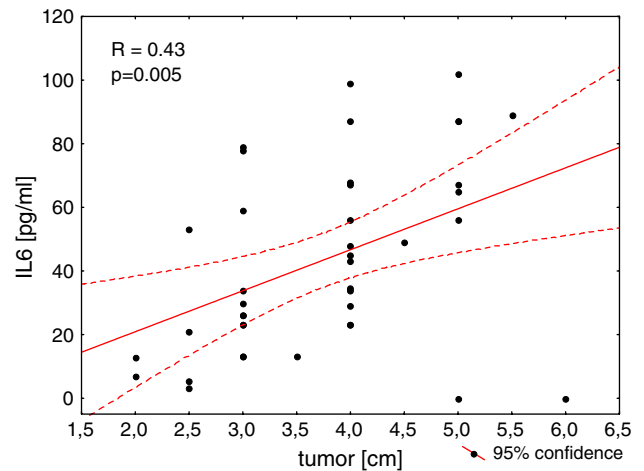

Fig. 3 Relationship between Il-6 serum levels and tumor size in patients with pancreatic adenocarcinoma

chronic pancreatitis mean Il-6 serum level was significantly higher in patients homozygous G/G for -174 Il-6 gene compared with patients with at least one allele C (Figs. 7 and 8). In our study there was no correlation between the
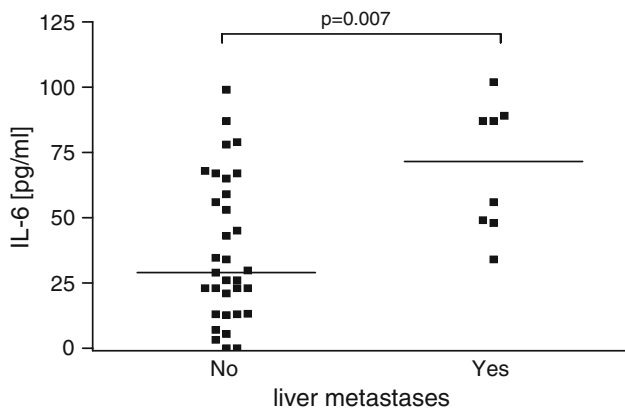
Fig. 4 Relationship between Il-6 serum levels and the presence of liver metastases in patients with pancreatic adenocarcinoma
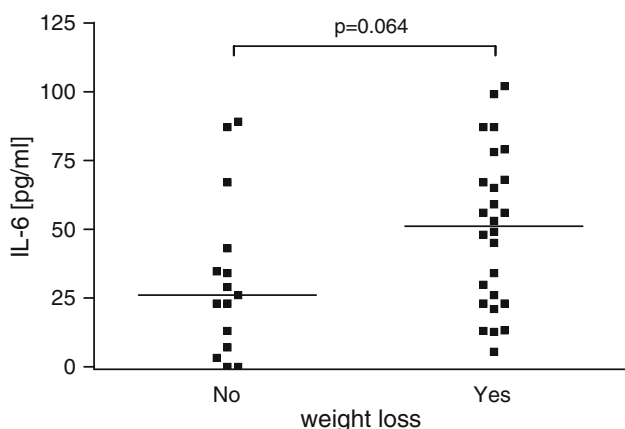

Fig. 5 Relationship between Il-6 serum levels and weight loss of more than 10% in patients with pancreatic adenocarcinoma
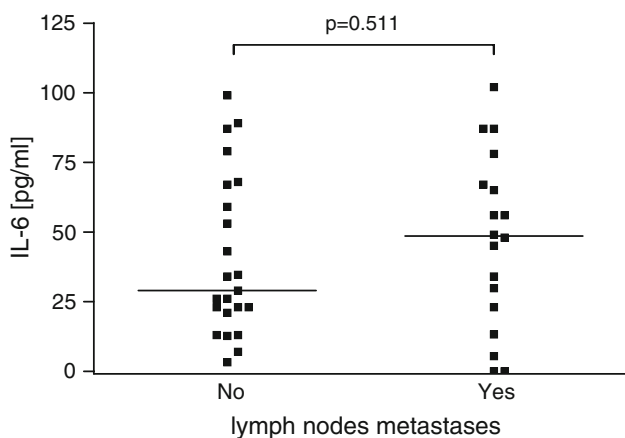

Fig. 6 Relationship between Il-6 serum levels and presence of lymph nodes metastases in patients with pancreatic adenocarcinoma

analyzed gene polymorphism and the clinical findings in patients with pancreatic adenocarcinoma or in those with chronic pancreatitis (data not shown).

Table 2 Relationship between Il-6 serum levels and clinical findings in patients with chronic pancreatitis ($n = 56$)

Clinical findings	No. of patients	Mean ± SD (pg/ml)	P-value
Age, years			
<45	29	9.3 ± 3.6	NS
≥45	27	7.1 ± 4.2	
Sex			
Male	36	6.9 ± 5.2	NS
Female	20	8.8 ± 5.9	
Smoking			
(+)	30	9.6 ± 3.3	NS
(−)	26	6.3 ± 5.1	
Weight loss			
<10%	44	7.3 ± 6.6	NS
≥10%	12	7.9 ± 3.8	
Bilirubin level			
<3 mg/dl	47	10.1 ± 4.7	NS
≥3 mg/dl	9	6.1 ± 3.1	
Cambridge classification			
Grade II	14	7.1 ± 4.4	NS
Grade III	26	5.3 ± 5.0	
Grade IV	16	9.2 ± 6.2	

SD, standard deviation; NS, not significant

Table 3 Il-6 -174 G/C genotypes distributions in the analyzed group of patients

	Pancreatic adenocarcinoma ($n = 41$)	Chronic pancreatitis ($n = 56$)	Control group ($n = 50$)
Il-6-174 G/C			
GG	13 (31.7%)	20 (35.8%)	22 (44%)
GC	19 (46.4%)	24 (42.8%)	19 (38%)
CC	9 (21.9%)	12 (21.4%)	9 (18%)

Discussion

We observed significantly elevated Il-6 serum levels in patients with pancreatic adenocarcinoma, similarly to Okada et al. and Ebrahimi et al. [6, 18]. High Il-6 levels were also detected in patients with a variety of other hematological and solid tumors, including gastric, colorectal, and renal cell cancer [5–8, 20]. On the other hand, Goydos et al. [21] observed high Il-6 levels in patients with cholangiocarcinoma but not with hepatocellular cancer and metastatic colorectal cancer.

Many clinical disorders are known to be associated with elevated serum Il-6 levels. We excluded from this study patients with obvious confounding clinical conditions known to raise Il-6 level. Some authors have suggested that high Il-6 serum levels may also relate to high bilirubin
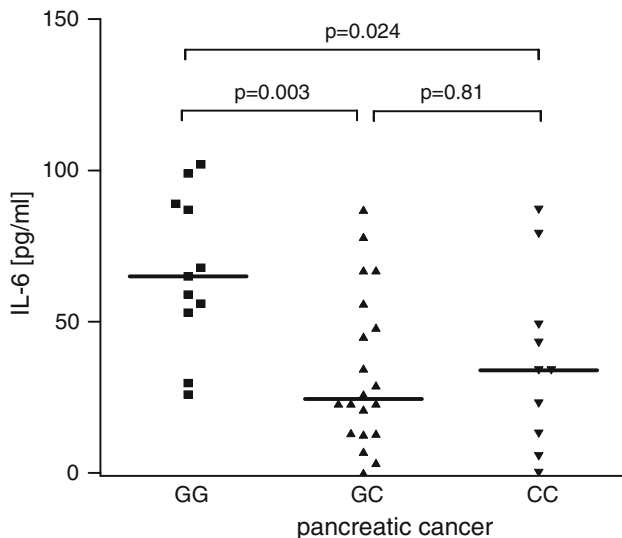
Fig. 7 Relationship between Il-6 serum levels and -174 G/C Il-6 gene polymorphism (genotypes GG, GC, CC) in patients with pancreatic adenocarcinoma
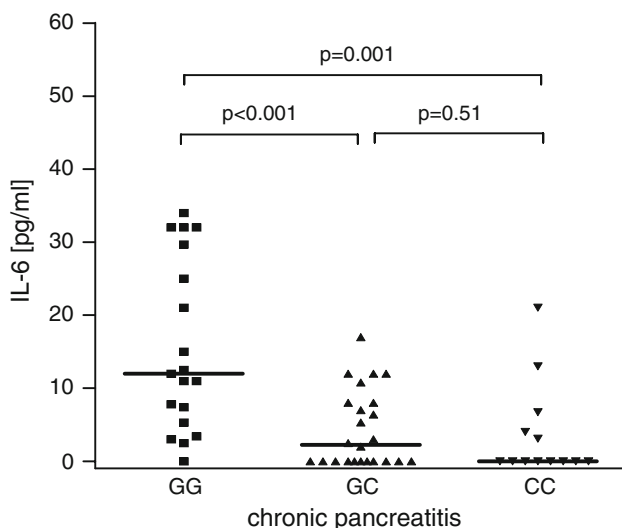

Fig. 8 Relationship between Il-6 serum levels and -174 G/C Il-6 gene polymorphism (genotypes GG, GC, CC) in patients with chronic pancreatitis

levels [22]. However our data, as well as the study of Goydos et al. [21], documented no relation between bilirubin and Il-6 serum levels.

We demonstrated that Il-6 serum levels in patients with tumor size ≥3.5 cm were significantly higher than that in patients with smaller tumors ($P < 0.01$). According to many authors, elevated Il-6 serum levels may be associated with poor prognosis in patients with cancer diseases. This has also been reported in patient with pancreatic adenocarcinoma as well as with other cancers of digestive tract, such as oesophageal squamous cell, gastric, and colorectal cancer [7, 12, 18, 23].

In the current study, there was a trend toward correlation between weight loss and Il-6 serum levels in patients with pancreatic adenocarcinoma. Similarly to in other studies, elevated Il-6 serum concentration was correlated with advanced weight loss, larger tumor size, and metastases development [7, 12, 18, 23]. It was also documented that Il-6 can induce cachexia and fever and that its elevated level may be correlated with poor performance status of patients with PA [18]. Falconer et al. [24] demonstrated that an important component of cachexia is high resting energy expenditure and patients with elevated Il-6 serum levels are markedly hypermetabolic. It has also been proved that Il-6 inhibits hepatic synthesis of albumin and is correlated with hypoalbuminaemia [18].

In our study, the serum concentration of Il-6 correlated with the presence of liver metastases but not with lymph nodes metastases. Kinoshita et al. and Belluco et al. [16, 25] also reported similar results in patients with colorectal carcinoma. The association between Il-6 serum level and hepatic metastases may depend on Il-6 being a potent stimulator of upregulation of the expression of endothelial cells receptors as well as inducing growth factors, such as VEGF. Il-6, in a murine model, has been shown to enhance tumor progression, probably by inhibitory effect on the immune response directed against the tumor, since natural killer functions were impaired by Il-6 and splenic killer cell cytotoxicity was reduced [26]. Wigmore et al. also proved that human pancreatic cancer cell lines themselves elaborate pro-inflammatory cytokines, including Il-6, which have the potential to act as growth factor enhancing cancer cell proliferation [27].

Okada et al. have also suggested a high diagnostic accuracy of Il-6 serum concentration assessment in differential diagnosis between chronic pancreatitis and pancreatic adenocarcinoma. They reported that Il-6 serum levels were detectable only in 54.5% patient with PA, 8% with CP, and 4% of healthy volunteers [6]. In our study there was also difference between Il-6 serum levels in PA and CP patients, however this cytokine was detectable in 54.5% of patients with chronic pancreatitis. According to the results observed by other authors Il-6 serum level may be elevated in CP patients [28, 29]. In contrast, in the study of Bamba et al., patients with chronic pancreatitis showed no change in serum Il-6 levels compared with the group of healthy volunteers [30]. The results of published studies are still controversial, partly because of the limited number of cases and difficulties in obtaining relevant pancreatic material.

Our study suggests that -174G/C Il-6 gene polymorphism influences circulating Il-6 levels. Mean Il-6 serum level was significantly higher in patients homozygous G/G for -174 Il-6 gene compared to patients with at least one allele C. To our knowledge, this is the first available evidence of the effect of this genetic Il-6 variant in PA

patients. In others studies in vivo and in vitro the -174 G/C Il-6 gene polymorphism was also associated with altered Il-6 serum levels [4, 14, 16]. Generally, the G allele probably increases Il-6 expression, both in basal and stimulated conditions [4, 14, 16, 31]. Belluco et al. observed this correlation in patients with colorectal cancer and Haddy et al. in a numerous group of healthy individuals [14, 16].

In our study, the Il-6 genotypes frequency was similar in patients with pancreatic adenocarcinoma, chronic pancreatitis, and control group. The distribution found in healthy subjects was similar to that described in other Caucasian populations [15, 20, 24, 32]. Other authors also did not find differences in the genotypic frequencies of the Il-6 gene between CP patient and healthy volunteers [24, 32]. In contrast, Landi et al. reported that the allele C of Il-6 gene polymorphism at position -174 was associated with increased risk of colorectal cancer development [20]. In addition, Foster et al. reported that men, infected with human immunodeficiency virus, homozygous for allele G of -174 Il-6 gene, had increased risk for the development of Kaposi sarcoma [33].

There is no available data on the role of -174 G/C Il-6 gene polymorphism in patients with pancreatic adenocarcinoma. On the other hand, Hefler et al. observed that -174 G/C or C/C variants were associated with improved disease-free and overall survival in patients with ovarian cancer. Women with two alleles C had the most favourable prognosis: mean 97.6 months compared with 52.5 months in homozygote GG [15]. Similar results have been demonstrated by DeMichele et al. in patients with breast cancer. Women homozygous for the allele G had a significantly increased risk of recurrence and shorter survival time compared with those with the G/C or C/C variant of the -174 Il-6 gene [11]. We have not yet assessed survival time in PA patients, but Il-6 polymorphism certainly merits our further studies.

In conclusion, our findings indicate that -174G/C Il-6 gene polymorphism influences circulating Il-6 level, which was significantly higher in patients homozygous G/G compared with those with at least one allele C. Elevated serum levels of Il-6 in patients with pancreatic adenocarcinoma, especially with larger tumor size and the presence of liver metastases, probably may help to distinguish patients with extremely poor prognosis.

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