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Association of inflammatory markers with the disease & mutation status in pancreatic cancer

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***Background & objectives*: Inflammation has been studied to be an important contributory factor to carcinogenesis through pro-inflammatory markers such as interleukin (IL)-6 and C-reactive protein (CRP). Furthermore, *K-ras* mutation is an important genetic alteration in the pathogenesis of pancreatic cancer. This study aimed to compare these inflammatory markers in pancreatic ductal adenocarcinoma (PDAC) with the diseased and healthy controls (HCs) and to check for any association between IL-6 and CRP serum levels with the disease status, survival and *K-ras* mutation status of PDAC patients.**

***Methods*: The study included 135 PDAC, 25 chronic pancreatitis (CP) patients and 25 HCs. The serum levels of IL-6 and CRP were detected by enzyme-linked immunosorbent assay and *K-ras* mutations were detected by polymerase chain reaction-restriction fragment length polymorphism technique.**

***Results*: The serum levels of both these markers were elevated in PDAC cases than that in HCs. High IL-6 levels and higher CRP levels were found to be associated with locally advanced disease, lymphatic invasion, metastasis and advanced stage of the PDAC. In patients with unresectable PDAC, higher IL-6 levels were found to be associated with the presence of *K-ras* mutations.**

***Interpretation & conclusions*: Higher IL-6 and CRP levels in patients with advanced PDAC suggest an important role of these inflammatory markers in tumour progression. Furthermore, the association of mutations in the *K-ras* gene with serum IL-6 indicates cross-talks that may contribute to the progression of the PDAC.**

Key words C-reactive protein - interleukin-6 - *K-ras* mutation - pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal disease owing to its unspecific symptoms and rapid metastasis. At the time of diagnosis, only 15-20 per cent of patients are typically found to have resectable disease[1]. Due to delayed diagnosis and aggressiveness of this disease, the overall five-year survival rate is as low as nine per cent[2].

Genetic changes such as over-activation of oncogenes and silencing of tumour suppressor genes are responsible for various processes in tumourigenesis[3]. *K-ras* mutations have long been associated with pancreatic tumours and are also found at high frequencies in pancreatic tumour tissue, which has also been confirmed through sequencing[4].

In our earlier study[5], the presence of this mutation in circulating DNA as well as in tumour tissue DNA in patients with PDAC was found. Although mutations in the *K-ras* gene is an important event in early tumourigenesis, these mutations have also been found in the healthy pancreas as well as in pancreatitis patients[5,6]. Thus, these mutations are not sufficient and depend on the various underlying processes in the tumour microenvironment. One such phenomenon is inflammation, which over a long period, may lead to cancer[7]. The role of inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) has been studied in various types of cancers.

IL-6 is produced from many cells, including tumour cells. This pleiotropic pro-inflammatory cytokine has been found to be an important link between inflammation and cancer[8]. Elevated levels of IL-6 in pancreatic cancer patients have been reported earlier[9] and higher levels of IL-6 were found to be associated with poor prognosis in pancreatic cancer patients as an independent prognostic marker[10]. Higher serum IL-6 has also been found to be associated with liver metastasis, high carcinoembryonic antigen (CEA), advanced stage of the disease in patients with advanced pancreatic cancer without treatment[11].

CRP is a marker of systemic inflammation. Certain pro-inflammatory cytokines such as IL-6, participate in the synthesis of CRP in hepatocytes through the nuclear factor kappa B and STAT3 inflammatory pathways[12]. In a systematic review, elevated CRP levels were found to predict prognosis in 90 per cent of the solid tumours[13]. In the case of pancreatic cancer also, CRP has been shown to predict prognosis by a number of studies[14,15]. In a study on colorectal cancer, the presence of allele-specific polymorphism in the *CRP* gene and mutations in *K-ras/BRAF* genes emerged as independent prognostic markers[16].

Oncogenic Ras was previously found to induce secretion of IL-6 in mouse model, and ablation of IL-6 was reported to retard tumour progression[8]. Zhang *et al*[17] reported that IL-6 synergizes with *K-ras* mutation to activate downstream MAPK/ERK signalling, which induces tumourigenesis, and ablation of IL-6 was found to completely ablate the tumour *in vivo*. Conversely, IL-6 was also shown to induce activation of *K-ras* in myeloma cell lines[18].

In this study, the levels of serum IL-6 and CRP levels in PDAC patients were compared with chronic pancreatitis (CP) patients and healthy controls (HCs) and checked for any association of these markers with clinicopathological parameters, survival and *K-ras* mutation status (in plasma) of PDAC patients.

Material & Methods

Patients: One hundred and thirty five consecutive confirmed PDAC patients, who presented to the departments of Gastroenterology and Gastrointestinal Surgery, All India Institute of Medical Sciences, New Delhi, India, were recruited over four years after approval by the Institutional Ethics Committee, and obtaining written informed consent from all the patients. The diagnoses of PDAC patients were confirmed on the basis of computed tomography (CT) scan and histopathologic (biopsy or fine-needle aspiration cytology) evaluation. PDAC patients with the only confirmed diagnosis were included in the study while patients who were found to have neuroendocrine tumour, periampullary carcinoma, or insulinoma (other than PDAC) were excluded from the study. 5 ml of blood was drawn from the patients and collected in vacutainers. The blood samples of 25 HCs and 25 CP patients were also collected as controls. The plasma was separated from the blood samples as per the protocol described previously[5]. The separated plasma was divided into aliquots (200 µl) and stored at −80°C till further use.

Enzyme-linked immunosorbent assay (ELISA) for interleukin-6 (IL-6) and C-reactive protein (CRP): The serum IL-6 and CRP levels in the PDAC, CP patients, and HCs were determined using commercial ELISA kits (Thermo Scientific, USA and BioChek, Inc., CA, respectively) following the manufacturer's instructions. For IL-6, standards of concentrations – 400, 160, 64, 25.6 and 10.24 pg/ml, and for CRP standards of concentrations – 0, 0.005, 0.010, 0.025, 0.050 and 0.100 mg/l were used. For measuring IL-6, 50 µl of undiluted serum samples were analyzed, while for measuring CRP, serum samples were diluted 100 times and 50 µl of diluted samples were analyzed. Standard curves for IL-6 and CRP were plotted and concentrations of these proteins in serum samples of patients were extrapolated from this curve. CRP levels obtained from the standard curve were multiplied by 100 (dilution factor) to get the actual concentration of the protein in the serum.

DNA extraction and K-ras mutation assessment: Of 135 PDAC cases analyzed for IL-6 and CRP, DNA was extracted from the plasma of 122 patients (as

part of our earlier study). Mutation status in the *K-ras* gene at codon 12 was assessed using PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) using Mva I restriction enzyme. The results were interpreted from the different band sizes on agarose gel electrophoresis[4].

Statistical analysis: For comparing variables between the groups, Student's t test and Mann–Whitney U test were used. Kaplan–Meier method and Log Rank test were used for assessing survival. A $P< 0.05$ was considered significant. The STATA 11.0 software (Statacorp., Texas, USA) was used for carrying out all the statistical analysis.

Results

Demographic, clinical and biochemical investigations: The mean age of the PDAC patients recruited in the study was 55.7 ± 10.9 yr. Of the 135 patients recruited in the study, 97 were male. The clinical parameters of the patients are summarized in Table I. Serum CA19.9 levels were recorded for 86 patients, and the median level was 677.5 (2-26057) U/ml.

Fifty two (38.5%) patients were found to have the tumour at the resectable stage at the time of presentation. However, after further investigations, namely biopsy or fine-needle aspiration cytology, and during surgery, the actual number of patients who had resectable tumour was 26 (19.2%). The rest of the patients having unresectable tumours were offered other palliative or chemotherapeutic procedures.

Survival data: For all the PDAC patients taken together, the median overall survival time was six months (range 1-41 months). The overall survival time was calculated from the day the sample collected from the patient to the day of the death of the patient. Of the 135 patients, 108 patients died of disease, eight patients were found living until the last follow up (3 yrs), six patients died due to reasons other than pancreatic cancer while 13 patients were lost to follow up. Patients who were lost to follow up were considered alive, and their survival time was recorded until the last follow up.

Circulating levels of IL-6 and CRP: The median value for IL-6 in PDAC patients was 9.4 (0-21) pg/ml (n=135). This was significantly higher than in CP patients [4.5 (0-28) pg/ml; n=25, (P=0.012)] as well as from levels in healthy individuals [3.4 (0-16.1) pg/ml; n=25] (P=0.02). The median value of CRP in PDAC patients was 18.1 (1-412) mg/l (n=133). This was significantly higher than in CP patients [9.5 (0-54) mg/l; n=25] (P=0.122) as well as from levels in healthy individuals [4.5 (0-10.3) mg/l; n=25] (P=0.04).

Table I. Clinical parameters of the patients with pancreatic cancer (n=135)

Clinical parameters	Number of patients, n (%)
Pain	112 (82.9)
Jaundice	102 (75.5)
Anorexia	106 (78.5)
Weight loss	107 (79.2)
Diabetes	38 (28.1)
Chronic pancreatitis history	17 (12.6)
Common bile duct dilated	84 (62.2)
Main pancreatic duct dilated	98 (72.6)
Locally advanced disease	89 (65.9)
Lymphatic invasion	56 (41.4)
Vascular encasement	70 (51.8)
Metastasis	56 (41.4)
Resectability	26 (19.2)
Chemotherapy	81 (60.0)

Clinical significance of IL-6 and CRP levels: Significant associations of serum IL-6 levels were found with vascular encasement (P=0.048), locally advanced disease (P=0.004), lymphatic invasion (0.028) and metastasis (P=0.001) and the advanced stage of the disease (P=0.003) (Table II). Similarly, serum CRP levels were also found to associate with locally advanced disease (P=0.014) and metastasis (P=0.031) as well as the stage of the disease (P=0.03) (Table II).

The strength of the statistical association of both the pro-inflammatory cytokines levels in plasma with prognosis was assessed by Kaplan–Meier survival analysis. The median levels of serum IL-6 *i.e.,* 10.8 pg/ml and serum CRP *i.e.* 27.7 mg/l, in surviving patients (at the time of completion of the study), were taken as cut-off values for survival analysis.

IL-6 and CRP levels did not correlate with survival of pancreatic cancer patients (Table III). Among the other clinicopathological parameters, shorter survival correlated with patients having vascular encasement (P=0.017), locally advanced disease (P=0.002), metastasis (P=0.001) and advanced stage of the disease (P=0.001) as expected (Table III).

Table II. Comparison of serum IL-6 and CRP levels between groups of clinicopathological parameters

Parameters	n[#]	IL-6 (pg/ml)		n[δ]	CRP (mg/l)	
		Median (range)	*P*[*]		Median (range)	*P*
Vascular encasement						
Yes	70	9.9 (0-21)	0.048	69	40 (1-389)	0.241
No	65	7.1 (0-17)		64	16.2 (1.2-412)	
Tumour mass (cm)						
≥2	108	9.0 (0-21)	0.872	106	31.4 (1-399)	0.054
<2	27	6.8 (0-17)		27	15.1 (1.2-412)	
Lymphatic invasion						
Yes	56	10.3 (0-21)	0.028	56	42.8 (1-389)	0.089
No	79	7.5 (0-16.2)		77	16.8 (1.2-418)	
Locally advanced						
Yes	89	10.3 (0-21)	0.004	89	34 (1-399)	0.014
No	46	5.5 (0-17)		44	15.3 (1.2-412)	
Metastasis						
Yes	56	11.1 (0-21)	0.001	57	31.4 (4-399)	0.031
No	79	7.5 (0-17)		76	16.5 (1-412)	
Surgery						
Yes	26	5.6 (0-14.5)	0.122	85	27.8 (1-399)	0.239
No	109	9.8 (0-21)		48	16.9 (1.2-412)	
Stage						
I+II	49	5.6 (0-17)	0.003	26	104.5 (9-412)	0.030
III+IV	86	10.3 (0-21)		107	17.3 (1-389)	
Chemotherapy						
Yes	81	9.8 (1-21)	0.195	81	22.5 (1.2-399)	0.703
No	54	7.5 (0-16.3)		52	17.7 (1-412)	

[*]Wilcoxon rank sum test, [#]number of cases in whom IL-6 was analysed (total 135 cases); [δ]number of cases in whom CRP was analysed (total 133 cases). CRP, C-reactive protein; IL-6, interleukin-6

K-ras mutations: Out of 135 patients, DNA was amplified in 122 patients. Of these 122 plasma DNA samples, 35 (28.6%) cases were found to have mutation in the *K-ras* gene. However, from the previous work in our laboratory, the presence and absence of mutations in the *K-ras* gene were not found to be associated with any of the clinicopathological parameters and/or survival of patients[5].

K-ras mutation versus IL-6 and CRP: *K-ras* mutation status of all 122 above-mentioned PDAC cases was not found to associate with pro-inflammatory cytokines – IL-6 and CRP. However, when this association was checked among only unresectable cases (n=109), serum IL-6 levels were found to be significantly elevated in patients with *K-ras* mutation (n=21) than in patients without *K-ras* mutation (n=88) (*P*=0.032). However, no such correlation was found between *K-ras* mutation status in plasma and serum CRP levels (*P*=0.06).

Discussion

Long-term inflammation has an important role to play in tumourigenesis. On the other hand, genetic alterations also get accumulated over time to give way to tumourigenesis. Thus, in this study, we not only analyzed comparative levels of IL-6 and CRP in pancreatic cancer, HCs, diseased controls, and their association with clinicopathological parameters and survival but also assessed if any correlation exists between pro-inflammatory cytokines- IL-6 and CRP levels and mutation status in *K-ras* gene in patients with pancreatic cancer.

Table III. Comparison of survival between groups in patients with pancreatic cancer (n=135)

Parameters	Number of cases	Death (%)	Median survival in months (95% CI)	*P**	Univariate analysis	
					Unadjusted hazard ratio (95% CI)	*P*
Vascular encasement						
Yes	70	62	6.0 (3.7-8.2)	0.017	1.5	0.025
No	65	45	5.0 (2.7-7.2)		1.0 (1.05-2.2)	
Tumour mass (cm)						
≥2	108	88	6.0 (5.1-6.9)	0.173	1.3	0.020
<2	27	19	8.0 (5.0-10.9)		1.0 (0.8-2.2)	
Lymphatic invasion						
Yes	56	45	6.0 (3.7-8.2)	0.408	1.2	0.436
No	79	62	6.0 (4.6-7.3)		1.0 (0.79-1.7)	
Locally advanced						
Yes	89	75	5.0 (3.3-6.7)	0.002	1.8	0.004
No	46	33	9.0 (4.8-13.1)		1.0 (1.2-2.8)	
Metastasis						
Yes	56	51	3.0 (2.1-3.8)	0.001	2.3	0.001
No	79	57	9.0 (6.8-11.1)		1.0 (1.6-3.5)	
Stage						
I+II	49	34	9.0 (6.5-11.4)	0.001	1.0	0.003
III+IV	86	74	5.0 (3.3-6.6)		1.9 (1.2-2.8)	
Surgery						
Yes	26	20	6.0 (4.0-7.9)	0.272	1.3	0.301
No	109	88	6.0 (4.1-7.8)		1.0 (0.8-2.1)	
Chemotherapy						
Yes	81	65	6.0 (4.2-7.7)	0.419	0.86	0.447
No	54	43	5.0 (2.1-7.8)		1.0 (0.6-1.8)	
IL-6						
High	57	43	5.0 (2.6-7.3)	0.723	1.06	0.738
Low	78	65	6.0 (4.6-7.3)		1.0 (0.72-1.5)	
CRP						
High	61	59	6.0 (3.7-8.2)	1.00	0.99	1.00
Low	72	48	6.0 (4.3-7.6)		1.0 (0.67-1.4)	

*Log rank test. CI, confidence interval

In the present study, the median levels of IL-6 were found to be 9.3 pg/ml in serum of patients with pancreatic tumour (PDAC), which is comparable to that reported by Feng *et al*[10]. In our study, median levels of IL-6 in serum of PDAC patients were found to be significantly higher than that of HCs and CP patients. This increase of IL-6 is in agreement with earlier studies on pancreatic cancer[11].

Higher IL-6 has been found to be associated with the severity of the disease[19]. In the present study also, higher IL-6 was found to be associated with vascular encasement, locally advanced disease, lymphatic invasion, metastasis and advanced stage of the disease and survival. Similar trends have emerged from other studies as well which emphasize the correlation of higher levels of serum IL-6 with liver metastasis and poor outcomes of the disease[10,20]. Miura *et al*[11] have even suggested that higher IL-6 production in patients with liver metastasis is by monocytes in the tumour. CEA-induced production of IL-6 from Kupffer cells[21] and direct release of IL-6 from not only tumour cells

themselves[22] but also from tumour macrophages[23], are some of the mechanisms thought to be involved in raising the concentration of IL-6 in serum of cancer patients.

The fact that IL-6 has been reported to associate with aggressive disease parameters and poor survival indicates its extent of involvement within the tumour and moving the tumour microenvironment towards advanced stage of disease. One of the molecular events which is induced by IL-6 is *K-ras* activation. *In vitro* studies have reported that IL-6 along with mutation in the *K-ras* gene give rise to precursor lesions and subsequent progression of cancer[17] via MAPK signalling. This study for the first time, reported that higher levels of IL-6 in the serum of pancreatic cancer (PDAC) patients were associated significantly with the presence of mutation in the *K-ras* gene in circulating DNA, although in patients with unresectable disease.

Similarly, the median levels of CRP were also increased in PDAC cases as compared to HCs, which are in agreement with the earlier studies[24], but there was no difference in CRP levels in PDAC patients and CP patients. Possible mechanisms for increased CRP in pancreatic cancer cases may be firstly due to an increased secretion of inflammatory cytokines such as IL-6 in cancer, which is in turn responsible for the production of CRP[25]; secondly in response to tumour antigens[26]; thirdly due to tumour growth giving rise to inflammation in tissue and thus an increase in CRP[27], and fourthly as a result of chronic inflammation[28]. This fourth mechanism might explain the increase in CRP levels in CP patients, as evident in the present study. However, there are studies[9] which report lower levels of CRP in CP patients than that in PDAC patients.

Higher CRP levels were found to associate with locally advanced disease, metastasis and advanced stage of the disease. A study by Mitsunaga *et al*[29] also found that increased CRP concentrations indicate aggressive disease at an advanced stage. Serum levels of CRP did not associate significantly with the *K-ras* mutation status in the circulating DNA of PDAC patients. Despite the serum CRP levels showing association with the aggressiveness of the disease[30] and prognosis[30], to the best of our knowledge, no study has so far commented on the possible association between serum CRP levels and *K-ras* mutation status. However, *CRP* gene polymorphism was found to be unrelated to *K-ras* and *p53* gene mutations in a study on colorectal cancer[31].

The main limitation in this study was that, different cytokines contribute to inflammation and tumourigenesis, other different types of cytokines need to be assessed to get a more comprehensive assessment of cytokines and disease progression. Despite this limitation, this study suggests that higher serum IL-6 has been found to associate with aggressive disease status and the presence of *K-ras* mutation in patients with unresectable PDAC. The *in vitro* study by Zhang *et al*[17] suggesting the role of IL-6 in the activation of *K-ras*, together with the findings of the present study indicate that the association between these two molecules may be an important mechanism in pancreatic cancer pathogenesis.

Higher IL-6 and CRP serum levels have been found to predict the advanced stage of the disease, so these inflammatory markers may emerge as non-invasive way of predicting the stage of the disease. Also, this study, for the first time, reports that in advanced or unresectable patients, cases with higher serum levels of IL-6 have mutated *K-ras* gene, which indicates that there may be some mechanistic link between mutated *K-ras* and cytokine IL-6, and this may be an important aspect to be considered in developing therapeutics against PDAC.

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***Conflicts of Interest*:** None.

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