



# Plasma IFN- $\gamma$ -inducible chemokines CXCL9 and CXCL10 correlate with survival and chemotherapeutic efficacy in advanced pancreatic ductal adenocarcinoma

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## ABSTRACT

**Objectives:** Recent studies have suggested that the CXCL9, 10, 11/CXCR3 axis is significant in immune regulation and therapeutic efficacy in human cancers; however, its role in pancreatic ductal adenocarcinoma (PDAC) remains unknown. This study serves to evaluate the prognostic prediction value of plasma IFN- $\gamma$ -inducible chemokines, CXCL9 and CXCL10, in advanced PDAC.

**Methods:** Two hundred patients with advanced PDAC receiving palliative chemotherapy were retrospectively recruited. The association between Plasma CXCL9/CXCL10 levels and survival time was first analyzed in a test group of 110 patients and then confirmed in a validation group of 90 patients.

**Results:** High levels of CXCL9 and CXCL10 were significantly correlated with longer overall survival (OS) in advanced PDAC patients (314 vs. 136 days for CXCL9,  $P < 0.0001$ , and 374 vs. 163 days for CXCL10,  $P < 0.0001$ , respectively) in the test group, which was consistent with the results derived from the validation group. In addition, high levels of CXCL9 and CXCL10 were associated with longer time to progression (TTP) in patients receiving chemotherapy (100 vs. 60 days for CXCL9,  $P = 0.0021$ , and 104 vs. 67 days for CXCL10,  $P = 0.0057$ , respectively). Multivariate analyses confirmed that CXCL9 and CXCL10 were independent prognostic predictors for OS (hazard ratio [HR]: 0.452,  $P < 0.001$  for CXCL9; and HR: 0.586,  $P = 0.007$  for CXCL10, respectively) and TTP (HR: 0.656,  $P = 0.015$  for CXCL9; and HR: 0.687,  $P = 0.040$  for CXCL10, respectively).

**Conclusions:** Plasma CXCL9 and CXCL10 can be used to predict survival of advanced PDAC patients receiving chemotherapy, allowing clinicians to potentially improve treatment outcomes by identifying candidates for aggressive therapy.

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## Introduction

The CXCL9, 10, 11/CXCR3 axis has recently become a major focus of research, as it mainly regulates immune cell migration, differentiation, and activation. For example, the axis increases immune reactivity via the recruitment of immune cells to focal sites and activates immune cells in response to gamma interferon (IFN- $\gamma$ ) by promoting the polarization of T helper 1 (Th1) cells [1]. As ELR-negative CXC chemokines, CXCL9 (known as monokine induced by IFN- $\gamma$ ) and CXCL10 (known as IFN- $\gamma$ -induced protein)

generally induce lymphocytic migration and attenuate angiogenesis, leading to anti-tumor effects [2,3]. Studies confirmed the association between CXCL9 and CXCL10 expression and longer survival or positive response to existing therapies in cancers [4–7]. However, studies have also shown that these chemokines may play tumorigenic roles [8–11], considering their abilities to promote tumor proliferation and metastasis. In total, all of these studies suggest significant roles of IFN- $\gamma$ -induced chemokines in human cancers, although the observations seem to conflict.

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers around the world, with an overall 5-year survival rate of approximately 8% when considering all stages [12]. The median survival of patients with advanced PDAC is only 5–6 months [13], but it varies considerably among patients [14]. Furthermore, as the only curative treatment option, only 15–20% of PDAC patients are

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eligible for curative resection because they are often diagnosed at an advanced stage [15]. Gemcitabine-based chemotherapy, utilizing gemcitabine monotherapy or couplets, has been approved and employed as a treatment regimen for advanced patients worldwide [13,16,17]. However, most PDAC patients do not respond to treatment, and only a minority of patients achieve stabilization of the disease or a partial response to treatment [13,17]. Therefore, it is important to identify a prognostic tool that can predict patient survival and chemotherapeutic efficacy, thus tailoring future therapies for those patients who would experience relatively poor outcomes.

As the role of the IFN- $\gamma$ -inducible chemokines CXCL9 and CXCL10 seems to be context- and tissue-dependent [4–11] and their possible clinical significance in PDAC remains unknown, in this study, we measured plasma CXCL9 and CXCL10 levels in 200 patients with advanced PDAC receiving palliative chemotherapy. We discovered that patients with high plasma levels of CXCL9 and CXCL10 exhibited longer time to progression (TTP) and overall survival (OS) after chemotherapy. Furthermore, both CXCL9 and CXCL10 are independent prognostic predictors of patient survival.

## Methods and materials

### Patients and clinical specimens

This study was approved by the Ethics Committee of the Fudan University Shanghai Cancer Center (Shanghai, China), and written informed consent was obtained from each participant in accordance with institutional guidelines.

We retrospectively recruited (from January 2011 to August 2013) 200 patients who had pathologically confirmed locally advanced or metastatic pancreatic adenocarcinoma from the Fudan University Shanghai Cancer Center, Shanghai, China. The criteria for locally advanced disease included tumor invasion of the celiac trunk, superior mesenteric artery, or both, which corresponded to stage III PDAC according to the International Union Against Cancer TNM Classification of Malignant Tumors (6th edition). Standard radiological studies, including contrast-enhanced abdominal CT scans, magnetic resonance imaging (MRI), and/or MR-cholangiopancreatography (MRCP), were performed. Clinical variables such as demographic data, tumor location, stage and CA 19-9 were collected.

Among the 200 recruited retrospective patients [18], 75 (37.5%) were male, and 125 (62.5%) were female. The tumors were located within the pancreatic head-neck in 78 (39%) of the patients and within the pancreatic body-tail in 122 (61%) of the patients. According to American Joint Committee on Cancer staging, 73 (36.5%) patients were diagnosed with stage III PDAC; the remaining patients (127, 63.5%) were diagnosed with stage IV PDAC. Additionally, 106 (53%) of the patients had CA 19-9  $\geq 1000$  IU/mL, whereas 94 (47%) of the patients had CA 19-9  $< 1000$  IU/mL. The patients were treated with gemcitabine monotherapy (gemcitabine 1000 mg/m<sup>2</sup> weekly for 7 weeks and, after a 1-week rest, on days 1, 8, and 15 every 4 weeks) or gemcitabine based combination chemotherapy, including GEMOX (gemcitabine 1000 mg/m<sup>2</sup> on day 1 plus oxaliplatin 100 mg/m<sup>2</sup> on day 2 every 14 days) or GP (gemcitabine 1000 mg/m<sup>2</sup> plus cisplatin 25 mg/m<sup>2</sup> on days 1, 8, and 15 every 4 weeks). The patients were randomly divided into two groups, with 110 patients in the test group and the remaining 90 patients in the validation group. Detailed clinicopathological characteristics are summarized in Table 1.

### CXCL9/CXCL10 measurements

The blood samples were collected in tubes with ethylene

**Table 1**  
Clinical Characteristics of the different PDAC patient groups.

Variables	Test Cohort (n = 110)	Validation Cohort (n = 90)	P <sup>a</sup>
Age, mean $\pm$ SD, y	60.1 $\pm$ 11.7	62.5 $\pm$ 9.46	0.072 <sup>b</sup>
Sex, n (%)			
Male	43 (39.1)	32 (35.6)	0.607
Female	67 (60.9)	58 (64.4)	
Location, n (%)			
Head-neck	44 (40)	34 (37.8)	0.749
Body-tail	66 (60)	56 (62.2)	
Cancer stage, n (%)			
III	37 (33.6)	36 (40)	0.352
IV	73 (66.4)	54 (60)	
CA 19-9, n (%)			
<1000 IU/mL	60 (54.5)	46 (51.1)	0.628
$\geq 1000$ IU/mL	50 (45.5)	44 (47.9)	
CXCL9 level	83.9 (35.3–145.5)	65.9 (32.6–130.6)	0.311 <sup>c</sup>
Median (P25–P75)			
CXCL10 level	68.2 (42.7–99.0)	65.1 (34.3–114.1)	0.593 <sup>c</sup>
Median (P25–P75)			

Abbreviations: CA19-9, cancer antigen 19-9; SD, standard deviation.

<sup>a</sup> P values were obtained using Pearson's  $\chi^2$  tests; b: Comparison was performed with the T-test; c: Comparison was performed with the Wilcoxon rank sum test.

diamine tetraacetic acid anticoagulant, stored at room temperature for 30 min, centrifuged ( $\times 12,000$  g) for 15 min, and then separated into plasma and cellular fractions. The plasma samples were then cryopreserved at  $-80^\circ\text{C}$  until analysis. The concentrations of plasma CXCL9 and CXCL10 were measured using a sandwich ELISA kit (DuoSet; R&D Systems, Minneapolis, MN, USA).

### Statistical analyses

Our primary outcome of interest was OS, and our secondary outcome of interest was TTP. OS was defined as the interval between the initiation of chemotherapy and death. For patients who had not died at the time of last follow-up, OS was censored at the date of the last follow-up. TTP was defined as the time from the start of chemotherapy to the first report of progression. Progression was defined as an increase of  $\geq 20\%$  in the sum of diameters of target lesions or the appearance of any new lesion. Patients who had not experienced progression at the time of death or last follow-up were censored. T-tests, Wilcoxon rank sum tests, and Pearson Chi-square tests were used to assess any associations between variables. The Kaplan–Meier method was used to compare OS and TTP between patients in different groups, and the log-rank test was used to estimate differences in survival. Univariate and multivariate Cox regression analyses using a backward stepwise approach were performed to determine whether CXCL9 and CXCL10 were independent prognostic indicators of TTP and OS. All of the statistical calculations were performed with the Statistical Package for the Social Sciences (SPSS) for Windows version 22 (SPSS Inc., Chicago, IL) and GraphPad Prism for Windows version 5 (GraphPad Software, Inc.). Hazard ratios (HRs) estimated from the Cox analysis are reported as relative risks with corresponding 95% confidence intervals (CIs). Receiver operating characteristic (ROC) analyses were used to determine the optimal cutoff points of CXCL9 and CXCL10 for OS. A P value  $< 0.05$  was considered statistically significant.

## Results

### Plasma CXCL9 and CXCL10 levels were associated with OS in patients with advanced PDAC

We first examined the correlation between OS and chemokines CXCL9 and CXCL10 in the test cohort of 110 patients. Characteristics of these 110 patients are shown in Table 1. The optimal cutoff values of CXCL9 and CXCL10 for OS in the test cohort were calculated via

ROC analysis. The Youden index (sensitivity + specificity-1) was used to select the threshold to estimate sensitivity and specificity. The results of the ROC analyses revealed that the optimal cutoff points of CXCL9 and CXCL10 levels in the test cohort were 78.03 pg/mL and 88.28 pg/mL, respectively. Therefore, 78.03 pg/mL was selected as the cut-off between high and low CXCL9 levels, and 88.28 pg/mL as the cut-off between high and low CXCL10 levels. Kaplan-Meier analyses showed that high levels of CXCL9 (314 days vs. 136 days, log rank = 27.92,  $P < 0.0001$ , Fig. 1A) and CXCL10 (374 days vs. 163 days, log rank = 18.61,  $P < 0.0001$ , Fig. 1B) were significantly correlated with longer OS in patients with advanced PDAC.

The prognostic value of CXCL9 and CXCL10 were further confirmed in the validation cohort. Patients in this cohort who had high CXCL9 and CXCL10 levels experienced significantly longer OS than those who had low CXCL9 (289 days vs. 168 days, log rank = 12.17,  $P = 0.0005$ , Fig. 1C) and CXCL10 (287 days vs. 174.5 days, log rank = 5.308,  $P = 0.0212$ , Fig. 1D) levels. Taken together, these results suggest that plasma levels of both CXCL9 and CXCL10 are positively associated with OS in patients with advanced PDAC.

#### Plasma CXCL9 and CXCL10 levels were correlated with TTP in patients with advanced PDAC receiving palliative chemotherapy

We then calculated the correlation between chemokines CXCL9 and CXCL10 and TTP in the test cohort. Here, 78.03 pg/mL and 88.28 pg/mL were still used as the cutoff values of CXCL9 and CXCL10, respectively. Kaplan-Meier analyses showed that high levels of either CXCL9 (100 days vs. 60 days, log rank = 9.470,  $P = 0.0021$ , Fig. 2A) or CXCL10 (104 days vs. 67 days, log rank = 7.648,  $P = 0.0057$ , Fig. 2B) were correlated with prolonged TTP in patients with advanced PDAC.

The prognostic values of CXCL9 and CXCL10 for TTP were subsequently confirmed in the validation cohort. Patients in this cohort who had high CXCL9 and CXCL10 levels had longer TTP than those who had low CXCL9 (109 days vs. 64.5 days, Fig. 2C) and CXCL10 (110.5 days vs. 66.5 days, Fig. 2D) levels, but neither the distinction of plasma CXCL9 (log rank = 2.665,  $P = 0.1026$ ) nor CXCL10 (log rank = 2.826,  $P = 0.0927$ ) showed statistical significance.

#### Plasma CXCL9 and CXCL10 levels are prognostic predictors for OS and TTP

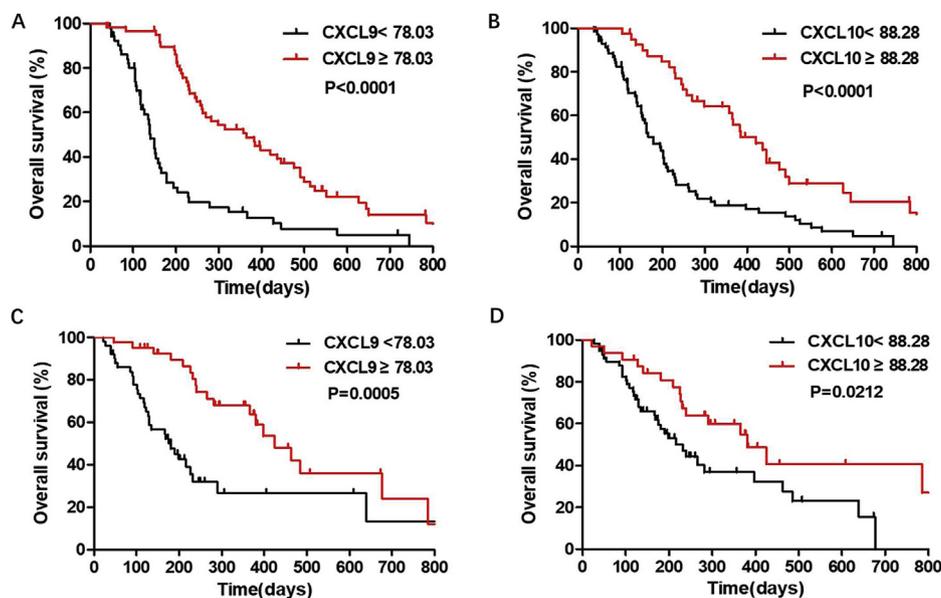
Next, we performed univariate analyses to determine the prognostic value of plasma CXCL9 and CXCL10 levels for OS in all patients. We found that advanced tumor stage (stage IV,  $P < 0.001$ ), as well as high CA19-9 (CA 19-9  $\geq 1,000$  IU/mL,  $P < 0.001$ ) levels, were prognostic predictors for poor OS, whereas high plasma CXCL9 levels ( $P < 0.001$ ) and high CXCL10 levels ( $P < 0.001$ ) predicted longer OS. Given that tumor stage and CA 19-9 affect prognosis, we performed multivariate analyses using Cox proportional hazards regression. The multivariate analysis confirmed that plasma CXCL9 (HR: 0.452, 95% CI: 0.314–0.650,  $P < 0.001$  for OS, Table 2) and CXCL10 (HR: 0.586, 95% CI: 0.396–0.866,  $P = 0.007$  for OS, Table 2) levels were independent prognostic predictors for OS.

We further performed univariate analyses to evaluate the prognostic value of plasma CXCL9 and CXCL10 levels for TTP. We discovered that tumor stage ( $P = 0.002$ ), CA 19-9 levels ( $P < 0.001$ ), CXCL9 levels ( $P = 0.001$ ), and CXCL10 levels ( $P = 0.001$ ) were also prognostic predictors for TTP. Cox regression multivariate analyses indicated that CXCL9 (HR: 0.656, 95% CI: 0.467–0.922,  $P = 0.015$  for TTP, Table 2) and CXCL10 (HR: 0.687, 95% CI: 0.480–0.984,  $P = 0.040$  for TTP, Table 2) levels were independent prognostic predictors for TTP as well.

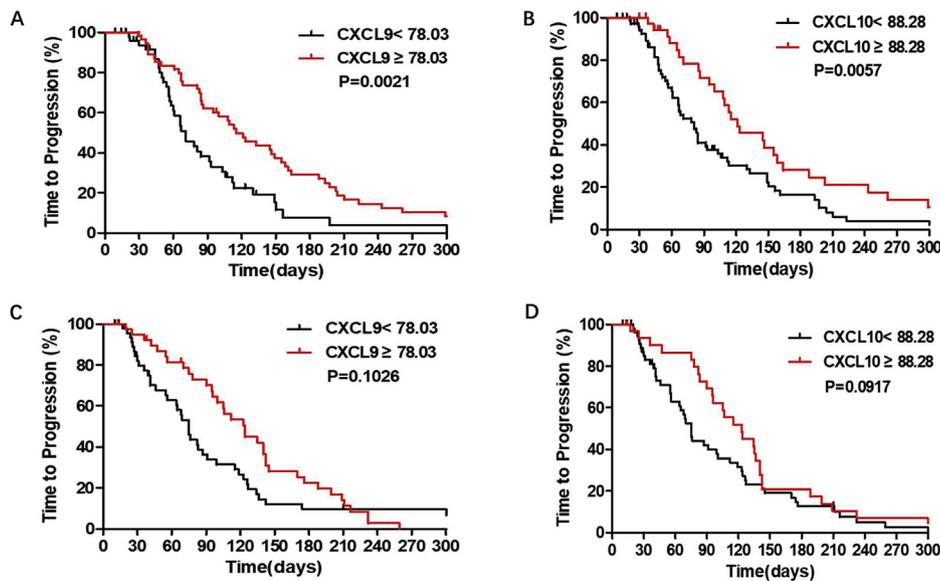
#### Predictive value of plasma CXCL9 and CXCL10 level for OS and TTP

To evaluate the prognostic value of plasma CXCL9 and CXCL10 levels for OS, we performed subgroup survival analyses by grouping patients according to baseline stratification factors. The results showed that plasma CXCL9 level was significantly associated with OS in all subgroups except in the stage III subgroup (Fig. 3A), while plasma CXCL10 was positively correlated with OS in all but the head-neck subgroup (Fig. 3B).

Subgroup analyses were also performed to estimate the prognostic value of CXCL9 and CXCL10 for TTP. We found that plasma CXCL9 level was associated with OS in most subgroups (Fig. 3C) and that plasma CXCL10 level was also associated with TTP in most subgroups (Fig. 3D).



**Fig. 1.** Plasma CXCL9 and CXCL10 levels were associated with OS in patients with advanced PDAC. A, Kaplan-Meier curves of CXCL9 for OS in the test group. B, Kaplan-Meier curves of CXCL10 for OS in the test group. C, Kaplan-Meier curves of CXCL9 for OS in the validation group. D, Kaplan-Meier curves of CXCL10 for OS in the validation group. Receiver operating characteristic (ROC) analysis was used to determine the optimal cutoff points of CXCL9 and CXCL10 levels for OS. The P value was determined using the log-rank test.



**Fig. 2.** Plasma CXCL9 and CXCL10 levels were associated with TTP in patients with advanced PDAC. A, Kaplan-Meier curves of CXCL9 for TTP in the test group. B, Kaplan-Meier curves of CXCL10 for TTP in the test group. C, Kaplan-Meier curves of CXCL9 for TTP in the validation group. D, Kaplan-Meier curves of CXCL10 for TTP in the validation group. Receiver operating characteristic (ROC) analysis was used to determine the optimal cutoff points of CXCL9 and CXCL10 levels for TTP. The P value was determined using the log-rank test.

**Table 2**

Univariate and multivariate Cox regression analyses of CXCL9 and CXCL10 levels for predicting OS and TTP of patients with advanced PDAC in all samples (N = 200).

Variables	Case number	OS		TTP	
		HR (95% CI)	P value	HR (95% CI)	P value
<b>Univariate analysis</b>					
Age ( $\geq 60$ years vs. $< 60$ years)	104/96	0.962 (0.692–1.338)	0.817	1.005 (0.736–1.371)	0.976
Sex (male vs. female)	75/125	0.960 (0.685–1.346)	0.814	1.120 (0.814–1.540)	0.893
Location (head vs. body-tail)	78/122	0.821 (0.585–1.151)	0.252	0.949 (0.691–1.303)	0.745
Cancer stage (IV vs. III)	127/73	2.033 (1.430–2.891)	$< 0.001$	1.694 (1.209–2.371)	0.002
CA 19-9 ( $\geq 1000$ vs. $< 1000$ IU/mL)	94/106	2.331 (1.649–3.294)	$< 0.001$	2.062 (1.489–2.855)	$< 0.001$
CXCL9 (high vs. low)	101/99	0.371 (0.265–0.521)	$< 0.001$	0.577 (0.422–0.790)	0.001
CXCL10 (high vs. low)	128/72	0.420 (0.292–0.606)	$< 0.001$	0.583 (0.419–0.812)	0.001
<b>Multivariate analysis</b>					
Cancer stage (IV vs. III)	127/73	1.638 (1.137–2.361)	0.008	1.983 (1.417–2.775)	$< 0.001$
CA 19-9 ( $\geq 1000$ vs. $< 1000$ IU/mL)	94/106	2.151 (1.509–3.066)	$< 0.001$	1.352 (0.950–1.923)	0.094
CXCL9 (high vs. low)	99/101	0.452 (0.314–0.650)	$< 0.001$	0.656 (0.467–0.922)	0.015
CXCL10 (high vs. low)	72/128	0.586 (0.396–0.866)	0.007	0.687 (0.480–0.984)	0.040

**Abbreviations:** CA19-9, cancer antigen 19-9; CI, confidence interval; OS, overall survival; TTP, time to progression; HR, hazard ratio.

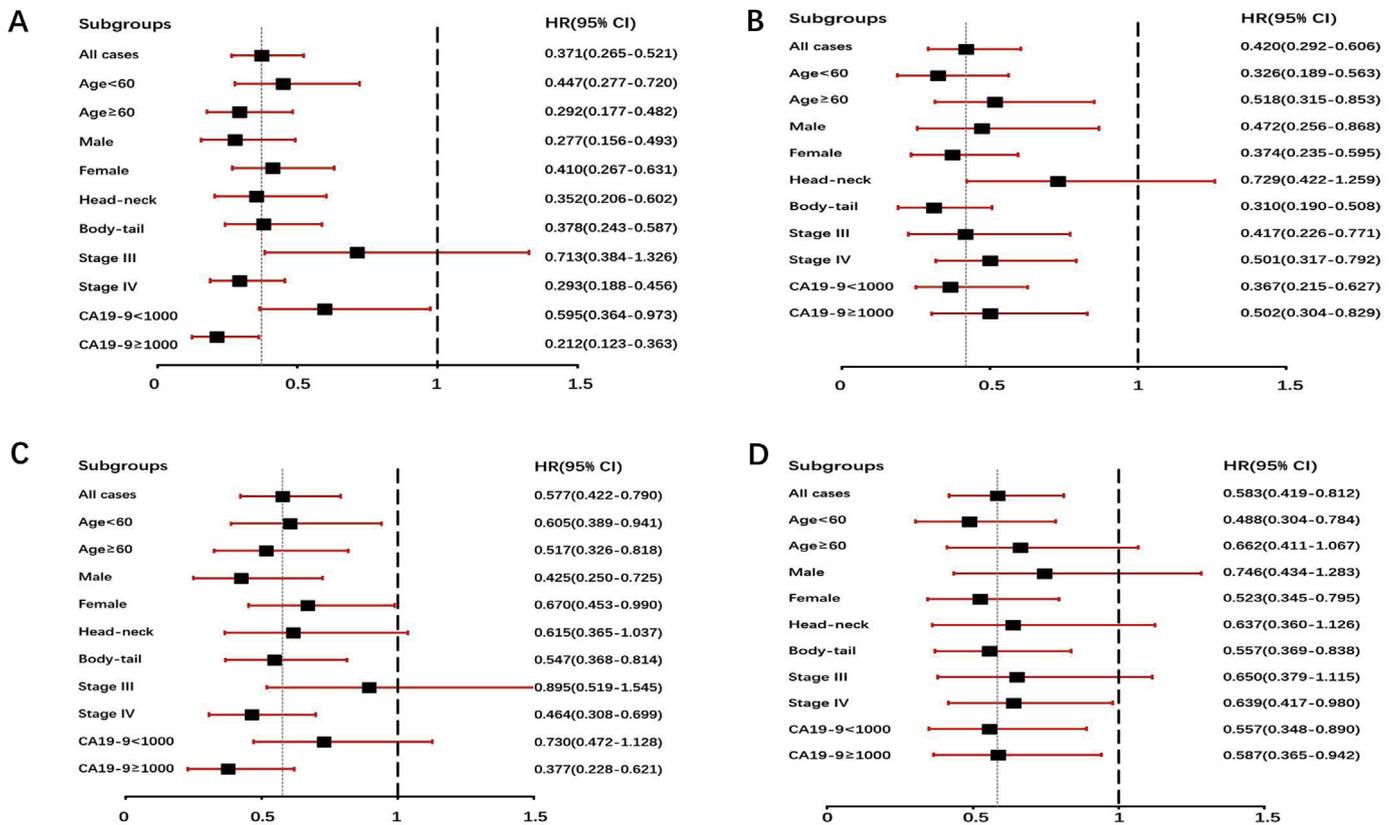
## Discussion

In this study, we examined plasma levels of CXCL9 and CXCL10 in patients with advanced PDAC in order to explore the correlation of these factors with patient survival. The results indicated that high levels of both CXCL9 and CXCL10 were significantly associated with longer OS and longer TTP in two groups. In addition, we also found that plasma CXCL9 and CXCL10 levels were independent prognostic predictors for OS in patients with metastatic PDAC. They are also independent prognostic biomarkers for TTP in advanced patients after palliative chemotherapy.

Chemokines, the largest subfamily of cytokines, are small proteins (8–15 kDa) that serve key roles in inducing chemotaxis, facilitating proliferation and differentiation of leukocytes, and initiating tissue differentiation through interaction with a subset of G protein-coupled seven-transmembrane signaling receptors [19,20]. They can be divided into 4 main classes based on the position of the conservative cysteine residues in their sequence: CXC (alpha), CC (beta), C (gamma), CXC3 (delta) [21,22]. Among these classes, the CXC subfamily can be further classified into two groups

according to the existence of a glutamic acid-leucine-arginine (ELR) motif near the N-terminus [2,3]. ELR-negative CXC chemokines, such as CXCL9 (known as monokine induced by IFN- $\gamma$ ), CXCL10 (known as IFN- $\gamma$ -induced protein 10 [IP10]), and CXCL11 (known as IFN-inducible T-cell alpha chemoattractant or IP 9), are all located on chromosome 4 and are closely related to each other [23–25]. Normally, they are undetectable in most non-lymphoid tissues, but they can be strongly induced by IFN- $\gamma$  through the CXCL9, 10, 11/CXCR3 axis [3,26].

Recent studies demonstrated that chemokines also affect proliferation, stemness and angiogenesis of cancer cells by targeting tumor cells and stromal cells within the tumor microenvironment, directly or indirectly, thereby causing tumor metastasis and altering patient clinical outcomes [27–35]. Notably, most studied chemokines, such as CCL2 [35], CCL18 [34], CCL25 [33], CXCL8 [27], CXCL12 [32], and CXCL17 [31], have been shown to have pro-tumor effects in various cancers; however, the ELR-negative CXC chemokines CXCL9, CXCL10, and CXCL11 were found to exert anti-tumor effects in cancers [28–30], as they primarily allow lymphocytic migration and attenuate angiogenesis [2]. However, some studies



**Fig. 3. Predictive value of plasma CXCL9 and CXCL10 levels for OS and TTP.** A, Hazard ratios (HRs) of plasma CXCL9 levels were calculated for OS in different patient subgroups in all cases. B, HRs of plasma CXCL10 levels were calculated for OS in different patient subgroups in all cases. C, HRs of plasma CXCL9 levels were calculated for TTP in different patient subgroups in all cases. D, HRs of plasma CXCL10 levels were calculated for TTP in different patient subgroups in all cases. Receiver operating characteristic (ROC) analysis was used to determine that the optimal HRs <1.0 indicate a better outcome.

reported that IFN- $\gamma$ -inducible chemokines were associated with poor prognosis [9,11]. The discrepancy in the roles of CXCL9, 10, 11 can be attributed to the different variants of their receptor CXCR3 with unique properties: namely, CXCR3A, CXCR3B, and CXCR3-alt. More specifically, the function of CXCL9, 10, 11/CXCR3 axis consists of two major directions: the paracrine signaling axis and the autocrine signaling axis. The paracrine axis exerts anti-tumor effects against cancer cells through recruiting immune cells, such as Th1, cytotoxic lymphocytes, and natural killer cells, to focal sites [36–38]; the autocrine axis is responsible for proliferation and metastasis of cancer cells via tumor-derived CXCR3A ligand activity [39,40]. In PDAC, we found that both CXCL9 and CXCL10 predict the survival of advanced patients and that they are positively associated with patient prognosis. Therefore, administration of the ELR-negative CXC chemokines for immune activation along with pharmacological inhibition of CXCR3A might represent a promising approach to prevent metastasis in patients with lower levels of plasma CXCL9 and CXCL10.

Recent studies also focused on the roles of IFN- $\gamma$ -inducible chemokines in cancer therapy. For example, one study showed that a combination of plasmid-borne CXCL9 plus cisplatin facilitated colon cancer and lung cancer reduction [41]. Another study found that CXCL10 augmented the effectiveness of PD-1 blockade by promoting the migration of T-cells to tumors [42]. In addition, *in vitro* studies revealed that chemoresistance to gemcitabine can be induced in PDAC cells after treatment with CXCL10 [43]. In our study, we found that plasma CXCL9 and CXCL10 are correlated with the effectiveness of gemcitabine-based chemotherapy: enhanced levels of CXCL9 and CXCL10 predict improved therapeutic efficacy. Hence, further efforts are required to investigate the exact function

of CXCL9 and CXCL10 in PDAC patients who receive palliative chemotherapy.

We realized that there are limitations to this study. Due to the retrospective nature of this study, the gemcitabine-based chemotherapy regimens in our study were not uniform. The treatment may have constituted gemcitabine monotherapy or couplets such as gemcitabine with cisplatin/oxaliplatin. It is difficult to determine whether the observed chemoresistance was specific to gemcitabine alone or related to the couplets. There are new standard of care (SOC) regimens in PDAC that are not included in this study. FOLFIRINOX has been considered a standard treatment option for patients with metastatic PDAC [44]. However, patients treated with FOLFIRINOX may experience more severe side effects than those treated with gemcitabine alone, so this combination is usually reserved for patients who are healthy enough to tolerate the potential side effects. Therefore, FOLFIRINOX is not widely used for advanced PDAC treatment in China. This is also the case in our institution, and very few patients in the cohort received FOLFIRINOX. Furthermore, albumin-bound paclitaxel (ABRAXANE) was approved for use in combination with gemcitabine as first-line treatment for metastatic PDAC [17]. Whether IFN- $\gamma$ -inducible chemokines could be used for predicting survival in this situation remains unclear because of limited clinical data. However, we agree that this remains a valuable question that can be addressed by future study. Second, we did not test the levels of CXCL11, another ELR-negative CXC chemokine in the IFN- $\gamma$ /CXCL9, 10, 11/CXCR3 axis, in patients with advanced PDAC because of the retrospective nature of this study and blood sample availability. All of these limitations merit mention.

Taken together, our study not only confirmed the prognostic

prediction value of CXCL9 and CXCL10 in advanced PDAC but also suggested that administering ELR-negative CXC chemokines along with inhibiting CXCR3A may be an ideal pharmacological therapeutic method for advanced patients. Further studies are necessitated to determine whether this is a valid strategy for treating PDAC.

### Conflict of interest disclosures

None declared.

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