Potential of C-X-C motif chemokine ligand 1/8/10/12 as diagnostic and prognostic biomarkers in idiopathic pulmonary arterial hypertension

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Abstract

Objective: This study aimed to evaluate the clinical role of C-X-C motif chemokine ligand (CXCL) family members in idiopathic pulmonary arterial hypertension (IPAH) patients.

Methods: CXCL1, CXCL8, CXCL10 and CXCL12 expressions in the serum samples of IPAH patients (N = 39) and age-/gender-matched controls (N = 40) were detected by enzyme-linked immunosorbent assay. In IPAH patients, clinical features were collected, and survival information was documented.

Results: CXCL1 (P < 0.001), CXCL8 (P = 0.001), CXCL10 (P < 0.001) and CXCL12 (P < 0.001) were increased in IPAH patients compared with controls, and receiver’s operating characteristic curves showed that their combination was highly correlated with IPAH risk (area under curve: 0.881, 95% confidence interval: 0.805–0.958). Meanwhile, CXCL1 was positively correlated with mean pulmonary artery pressure (mPAP) (P = 0.029) and high-sensitive C-reactive protein (HsCRP) (P = 0.015); CXCL8 was positively correlated with mPAP (P = 0.044) and HsCRP (P = 0.018) but negatively correlated with 6-minute walk test (6MWT) distance (P = 0.029); CXCL10 was positively correlated with mean right artery pressure (P = 0.002); and CXCL12 was positively correlated with World Health Organization functional class (P = 0.047), mPAP (P = 0.009), pulmonary vascular resistance (P = 0.004) and HsCRP (P = 0.003) but negatively correlated with 6MWT distance (P = 0.003) in IPAH patients. Moreover, CXCL12 was negatively correlated with overall survival (OS) (P = 0.025), whereas CXCL1, CXCL8 and CXCL10 only showed minor tendencies to be negatively correlated with OS in IPAH patients without statistical significance (all P > 0.05).
Conclusion: CXCL1, CXCL8, CXCL10 and CXCL12 associate with increased IPAH risk, unfavourable clinical features; besides, CXCL12 correlates with worse OS in IPAH patients.

KEYWORDS
clinical features, C-X-C motif chemokine ligand, idiopathic pulmonary arterial hypertension, overall survival, predictive value

1 | INTRODUCTION

Idiopathic pulmonary arterial hypertension (IPAH) is a subtype of PAH characterized by the progressive increase of pulmonary vascular resistance (PVR), which could lead to right heart failure and even mortality.\(^1\,^2\) Generally, IPAH is a quite rare disease affecting approximately 5.9 patients per million population.\(^3\) However, the untimely diagnosis is common among IPAH patients. Within these patients, a large proportion of patients are of the World Health Organization functional class (WHO-FC) III or IV at diagnosis (which might result in poor prognosis), and their median survival is only 2.8 years.\(^4\,^5\) Therefore, early diagnosis is critical for improving the prognosis of IPAH patients.\(^4\,^6\) One solution to solve this issue could be searching for novel biomarkers to predict the risk of IPAH.

C-X-C motif chemokine ligand (CXCL) family is a group of small proteins found initially to be highly associated with the process of inflammation, which participates in vascular endothelial dysfunction.\(^7\,^8\) Given that inflammation and vascular endothelial dysfunction play important roles in the pathobiology of IPAH,\(^9\) it is not surprising that CXCLs are dysregulated in IPAH patients. Indeed, several previous studies reveal that some CXCL family members including CXCL10, CXCL12 and CXCL13 are increased in IPAH patients compared with controls.\(^10\,^11\) However, the correlation of CXCL family members with the clinical features or prognosis in IPAH patients is rarely reported.

This study aimed to investigate the association of CXCL1, CXCL8, CXCL10 and CXCL12 with IPAH risk, clinical characteristics and prognosis in IPAH patients.

2 | MATERIALS AND METHODS

2.1 | Participants

In this prospective study, 39 IPAH patients were consecutively recruited in our hospital between January 2015 and December 2018. All IPAH patients were older than 18 years and diagnosed as IPAH confirmed by right heart catheterization (RHC) after comprehensive clinical examinations and excluding pulmonary hypertension caused by other causes (left heart disease, pulmonary disease, thromboembolism, etc.). The diagnosis was in accordance with guidelines for the diagnosis and treatment of pulmonary hypertension.\(^12\) At the same time, IPAH patients with other lung diseases, cardiovascular and cerebrovascular diseases, inflammatory diseases, autoimmune diseases, infection or malignancies were excluded from the study. Besides, this study also recruited 40 healthy volunteers as controls. All controls were enrolled when they underwent healthy examinations in our hospital from July 2018 to December 2018. The controls were enrolled in an age limit of 30–50 years and a sex ratio of 3:1 (female/male) to ensure that the age and gender of controls were matched with enrolled IPAH patients. The healthy status of controls was confirmed by medical examination, which was ineligible for recruitment if the patients had a history of pulmonary arterial hypertension, other lung diseases, cardiovascular and cerebrovascular diseases, inflammatory diseases, autoimmune diseases, infection or malignancies.

2.2 | Ethics statement

The written informed consent was collected from each recruited participant, and the approval for the current study was obtained from the Institutional Review Board of our hospital. The study procedure was conducted according to the principles expressed in the Declaration of Helsinki.

2.3 | Data collection of IPAH patients

The age and gender of enrolled IPAH patients were recorded after recruitment. The performance of the physical activity of IPAH patients was assessed according to WHO-FC. The 6-minute walk test (6MWT) was performed for all IPAH patients after hospitalization. The mean pulmonary artery pressure (mPAP), mean right atrial pressure (mRAP) and pulmonary
capillary wedge pressure (PCWP) were documented after the RHC examination, and the PVR was calculated as the following equation: $PVR = (mPAP-PCWP)/pulmonary blood flow$. The high-sensitive C-reactive protein (HsCRP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were obtained after routine laboratory tests.

### 2.4 Blood sample collection and detection

After recruitment, peripheral venous blood samples from IPAH patients and controls were collected using a covered test tube. After clotting for 30 min at room temperature, the samples were centrifuged at 2000×g for 10 min in a refrigerated centrifuge, then the serum samples were obtained and transferred into a clean polypropylene tube. Subsequently, the concentrations of CXCL1, CXCL8, CXCL10 and CXCL12 in serum samples were measured using enzyme-linked immunosorbent assay (ELISA) kits ((R&D Systems, Minneapolis, MN, USA). All ELISA procedures were performed according to the standard protocol provided by the manufacturer. The standard curve was generated with each assay by curve fitting, and the concentrations for unknown samples and controls were read from the standard curves. All samples were measured in triplicates.

### 2.5 Follow-up

After discharge, follow-up was conducted for IPAH patients through phone calls or visits, which ended in December 2019. Survival information was documented in follow-up records, which was used to evaluate the overall survival (OS). The OS was defined as the duration from study enrolment to the IPAH patients’ death.

### 2.6 Statistical analysis

Shapiro–Wilk test was performed to check the normality of quantitative data. For the normally distributed data, they were described as mean with standard deviation (SD). As for skewed distributed data, they were described as median with interquartile range (IQR). The qualitative data were described as numbers with percentages (No. [%]). Comparison of CXCL1, CXCL8, CXCL10 and CXCL12 between IPAH patients and controls was determined by the Wilcoxon rank-sum test. Correlation of CXCL1, CXCL8, CXCL10 and CXCL12 with clinical features of IPAH patients was analysed by Spearman’s rank correlation test. Receiver operating characteristic (ROC) curve analysis was performed to assess the value of CXCL1, CXCL8, CXCL10 and CXCL12 level in distinguishing IPAH patients from controls. OS was displayed using the Kaplan–Meier curve and the correlation of OS with CXCL1, CXCL8, CXCL10 and CXCL12 level was determined by the log-rank test. $P$ value $< 0.05$ was considered as statistically significant. SPSS 22.0 statistical software (IBM, Chicago, Illinois, USA) was used for statistical data processing. GraphPad Prism 7.02 (GraphPad Software Inc., San Diego, California, USA) was used for figure making.

### 3 RESULTS

#### 3.1 Clinical characteristics of IPAH patients

In IPAH patients, the mean age was $39.3 \pm 9.2$ years, and there were 28 (71.8%) females. Meanwhile, in controls, the mean age was $39.4 \pm 5.5$ years, and there were 30 (75.0%) females. Further comparison analysis showed that no difference was found in age and gender between IPAH patients and controls (both $P > 0.05$), while HsCRP level was higher in IPAH patients compared with controls ($5.5 \; [3.3–8.8]$ mg/L vs. $3.3 \; [2.1–5.6]$ mg/L) ($P = 0.002$). In IPAH patients, as to patients’ WHO-FC, 21 (53.8%) patients were of grade II, 16 (41.0%) patients were of grade III, and two (5.2%) patients were of grade IV. Additionally, the mean value of 6MWT distance was $411.7 \pm 81.4$ m. Meanwhile, the median values of mPAP, mRAP and PCWP were 52.0 (48.0–60.0), 7.0 (5.0–8.0) and 10.0 (8.0–12.0) mmHg, respectively. Besides, the mean PVR value was $948.5 \pm 274.2$ dyn·s/cm$^5$. Moreover, the mean value of NT-proBNP was $1378.6 \pm 588.7$ fmol/ml (Table 1).

#### 3.2 CXCL1, CXCL8, CXCL10 and CXCL12 expressions in IPAH patients and controls

The median values of CXCL1 (2158.0 [1617.0–2554.0] vs. 1375.0 [1008.0–1902.0]) ($P < 0.001$) (Figure 1A), CXCL8 (159.8 [120.3–286.3] vs. 109.6 [86.2–164.0]) ($P = 0.001$) (Figure 1B), CXCL10 (236.8 [157.0–311.6] vs. 144.5 [110.9–191.8]) ($P < 0.001$) (Figure 1C) and CXCL12 (2436.0 [1483.0–3074.0] vs. 1236.0 [947.7–1580.0]) ($P < 0.001$) (Figure 1D) were all increased in
IPAH patients \((N = 39)\) compared with controls \((N = 40)\). Meanwhile, ROC curves revealed that CXCL1 (AUC: 0.807, 95% CI: 0.712–0.902), CXCL8 (AUC: 0.715, 95% CI: 0.603–0.828), CXCL10 (AUC: 0.745, 95% CI: 0.635–0.855) and CXCL12 (AUC: 0.839, 95% CI: 0.754–0.924) all possessed certain abilities in discriminating IPAH patients from controls. Moreover, their combination (AUC: 0.881, 95% CI: 0.805–0.958) had good ability in discriminating IPAH patients from controls (Figure 2).

### 3.3 Correlation of CXCL1, CXCL8, CXCL10 and CXCL12 with clinical characteristics in IPAH patients

CXCL1 was positively correlated with mPAP \((P = 0.029, r = 0.350)\) and HsCRP \((P = 0.015, r = 0.386)\). Meanwhile, CXCL8 was positively correlated with mPAP \((P = 0.044, r = 0.324)\) and HsCRP \((P = 0.018, r = 0.367)\), but negatively correlated with 6MWT distance \((P = 0.029, r = -0.349)\). Besides, CXCL10 was only positively

### Table 1  Clinical characteristics of IPAH patients and controls

| Characteristics | Controls \((N = 40)\) | IPAH patients \((N = 39)\) | \(P\) value |
|-----------------|-----------------------|-----------------------------|------------|
| Age (years), mean ± SD | 39.4 ± 5.5 | 39.3 ± 9.2 | 0.968 |
| Female, No. (%) | 30 (75.0) | 28 (71.8) | 0.747 |
| WHO-FC, No. (%) | | | |
| II | - | 21 (53.8) | - |
| III | - | 16 (41.0) | - |
| IV | - | 2 (5.2) | - |
| 6MWT distance (m), mean ± SD | - | 411.7 ± 81.4 | - |
| mPAP (mmHg), median (IQR) | - | 52.0 (48.0–60.0) | - |
| mRAP (mmHg), median (IQR) | - | 7.0 (5.0–8.0) | - |
| PCWP (mmHg), median (IQR) | - | 10.0 (8.0–12.0) | - |
| PVR (dyn*s/cm⁵), mean ± SD | - | 948.5 ± 274.2 | - |
| HsCRP (mg/L), median (IQR) | 3.3 (2.1–5.6) | 5.5 (3.3–8.8) | 0.002 |
| NT-proBNP (fmol/ml), mean ± SD | - | 1378.6 ± 588.7 | - |

Abbreviations: 6MWT, 6-minute walk test; HsCRP, high-sensitive C-reactive protein; IPAH, idiopathic pulmonary arterial hypertension; IQR, interquartile range; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SD, standard deviation; WHO-FC, World Health Organization functional class.
correlated with mRAP ($P = 0.002, r = 0.473$). In addition, CXCL12 was positively associated with WHO-FC ($P = 0.047, r = 0.319$), mPAP ($P = 0.009, r = 0.413$), PVR ($P = 0.004, r = 0.451$) and HsCRP ($P = 0.003, r = 0.459$), whereas it was negatively associated with 6MWT distance ($P = 0.003, r = -0.459$) (Table 2). These data showed that CXCL1, CXCL8 and CXCL10 were associated with unfavourable clinical characteristics, and CXCL12 possessed a stronger association with unfavourable clinical features of IPAH patients.

### 3.4 Correlation of CXCL1, CXCL8, CXCL10 and CXCL12 with OS in IPAH patients

According to the median value of CXCL1, CXCL8, CXCL10 or CXCL12 in IPAH patients, the expression of the above CXCLs were divided into CXCL1 high/low expression, CXCL8 high/low expression, CXCL10 high/low expression or CXCL12 high/low expression, respectively. CXCL12 high expression was correlated with decreased OS ($P = 0.025$) (Figure 3D); however, CXCL1 ($P = 0.120$) (Figure 3A), CXCL8 ($P = 0.149$) (Figure 3B) or CXCL10 ($P = 0.053$) (Figure 3C) high expressions only showed minor tendencies to correlate with reduced OS, but no statistical significance was observed.

### 4 DISCUSSION

The CXCL family members are highly associated with the pathobiology of inflammation and vascular endothelial dysfunction. For example, CXCL1 and CXCL12 could regulate the early stage of neutrophil recruitment during tissue inflammation; meanwhile, CXCL8 induces rapid and transient phosphorylation of the extracellular signal-related kinase 1/2 (ERK1/2) and phosphatidylinositide 3-kinase/protein kinase B (PI3K/Akt) pathways in neutrophils to regulate inflammation; besides, CXCL10 upregulation promotes macrophage filtration in arteries...
from patients with giant cell arteritis. As to their role in vascular endothelial dysfunction, previous studies suggest that CXCL8 promotes proliferation but inhibits apoptosis in vascular endothelial cells and acts as a key regulator of hypertension; in addition, CXCL10 regulates the migration of vascular smooth muscle cells and permeability of the endothelial cell layer, thus participating in hypertension; moreover, CXCL12 downregulation could inhibit the proliferation of vascular smooth muscle cells and further reducing right ventricular hypertrophy and pulmonary vascular remodelling in pulmonary hypertension mouse models. Therefore, the CXCL family members are key regulators in inflammation and vascular endothelial dysfunction, and the later ones participate in the pathogenesis of IPAH.

Recognizing biomarkers to predict the incidence of IPAH could help to improve the prognosis of IPAH patients. Thus, in this study, we investigated the levels of CXCL1, CXCL8, CXCL10 and CXCL12 in IPAH patients and age/gender-matched controls. The data showed that all these CXCL family members were elevated in IPAH patients compared with controls, which was in line with several previous studies. Meanwhile, further ROC curve analyses showed that all these CXCL family members could predict IPAH risk to some extent, and their combination had good value in predicting IPAH risk. These data could be explained by that: (1) increased CXCL1, CXCL8 and CXCL12 might promote inflammation level through enhancing the recruitment of neutrophils, phosphorylation of the ERK1/2 and PI3K/Akt pathways and the infiltration of macrophages in pulmonary artery, thus increasing the possibility of IPAH incidence. However, other studies suggest that CXCLs could be induced by inflammatory cytokines. The regulation between CXCLs and inflammation could be further investigated. (2) Elevated CXCL8, CXCL10 and CXCL12 may promote the proliferation and migration of vascular smooth muscle cell proliferation to enhance pulmonary vascular remodelling, which might also increase IPAH risk. Besides, a previous study also reports that CXCLs are dysregulated in chronic thromboembolic pulmonary hypertension endothelial cells.

Regarding the correlation of CXCL family members with IPAH patients’ clinical characteristics, one previous study shows that CXCL10 and CXCL12 are correlated with NT-proBNP, tricuspid annulus plane systolic excursion and right ventricular ejection fraction; and another study reveals that CXCL13 is associated with CRP in IPAH patients. In the present study, we found that CXCL1 was positively correlated with mPAP and HsCRP, CXCL8 was positively correlated with mPAP and HsCRP, but negatively correlated with 6MWT distance, CXCL10 was positively correlated with mRAP, and CXCL12 was positively correlated with WHO-FC, mPAP, PVR and HsCRP but negatively correlated with 6MWT distance. Possible explanations for our data could be that: (1) increased CXCL1, CXCL8 and CXCL12 might promote inflammation level (as mentioned above); thus, they were positively correlated with HsCRP in IPAH patients; (2) elevated CXCL1, CXCL8, CXCL10 and CXCL12 might enhance pulmonary vascular remodelling (as mentioned above) to induce PAH. Therefore, CXCL1 and CXCL8 were positively correlated with mPAP, CXCL10 was positively correlated with mRAP, and CXCL12 was positively correlated with mPAP and PVR; (3) enhanced CXCL8 and CXCL12 might increase the inflammation level and pulmonary vascular...
remodelling to elevate pulmonary artery pressure, which could result in patients’ reduced exercise capacity. Therefore, they were negatively correlated with 6MWT distance, and CXCL12 was positively correlated with WHO-FC. Notably, CXCL12 seemed to possess a more predominant association with unfavourable clinical features of IPAH patients, implying it might be a stronger biomarker in IPAH patients; meanwhile, CXCL12 might be highly associated with the progression of IPAH, and further studies were encouraged to explore that.

As to the prognostic effect of the CXCL family members in IPAH patients, previous studies report that CXCL13 is negatively associated with survival in IPAH patients, and CXCL12α is an independent predictive factor for worse survival in IPAH patients.\textsuperscript{11,22} In this study, it was revealed that among CXCL1, CXCL8, CXCL10 and CXCL12, only CXCL12 was negatively associated with OS in IPAH patients; while CXCL1, CXCL8 or CXCL10 high patients tended to have worse OS, but no statistical significance was observed. Our data could be explained by that: (1) generally, increased CXCL1, CXCL8, CXCL10 and CXCL12 were associated with unfavourable clinical features (mentioned above), which might indirectly cause worse OS in IPAH patients; (2) CXCL12 showed a stronger correlation with worse clinical features than other CXCLs (CXCL1, CXCL8 and CXCL10); thus, it might have more influence on OS in IPAH patients; consequently, we only observed the correlation of CXCL12 (but not CXCL1, CXCL8 or CXCL10) with OS in IPAH patients; (3) the relatively small sample size might cause low statistical power; therefore, no correlation was found in CXCL1, CXCL8 or CXCL10 with OS in IPAH patients.

There were several limitations in this study. First of all, because IPAH is a relatively rare disease, the sample size of this study was small, which may cause low statistical power. Thus, further studies with larger sample sizes could be conducted to validate the role of CXCL family members in IPAH patients. Next, partly due to the relatively small sample size and late diagnosis, this study did not contain IPAH patients with WHO-FC I; therefore, further studies were encouraged to explore the clinical role of CXCL family members in those patients. Besides, the clinical role of CXCL family members in hereditary PAH patients was not investigated, for it was not the main objective of this study, which could be explored further. Additionally, the regulation of CXCL family members in the pathogenesis and progression of IPAH at the molecular level was not investigated, which might be explored in further studies.

To be conclusive, CXCL1, CXCL8, CXCL10 and CXCL12 are elevated and correlate with unfavourable clinical features in IPAH patients; meanwhile, CXCL12 correlates with worse OS in IPAH patients. This study sheds light on the potential of CXCL family members as diagnostic and prognostic biomarkers for IPAH.

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CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

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None.

AUTHOR CONTRIBUTIONS
Zhenhua Li and Jie Jiang made substantial contributions to the design of the present study. Data acquisition and interpretation were performed by Zhenhua Li, Jie Jiang and Shan Gao. Zhenhua Li, Jie Jiang and Shan Gao revised the manuscript for important intellectual content. All authors approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT
The data that supports the findings of this study are available in this article.

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