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Elevated serum CXCL10 in patients with *Clostridium difficile* infection are associated with disease severity

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ABSTRACT

Clostridium difficile infection (CDI) is the primary cause of community- and health care-associated diarrhea. CXCL10, also known as IFN-γ-inducible protein of 10 (IP-10), is involved in various inflammatory diseases, but its role in CDI remains unknown. In this study, We determined the serum concentration of CXCL10 in 80 CDI patients and 76 sex & age-matched diarrhea patients by enzyme-linked immunosorbent assay (ELISA) and analyzed the correlation between CXCL10 levels and CDI disease severity parameters. Besides, we also measured the level of other cytokines and/or chemokines in CDI patients, such as IL-1β, IL-6, TNF-α and CXCL9. We found that serum CXCL10 in CDI patients was significantly higher compared with those in non-*C. difficile* diarrhea patients, especially in the moderate disease. Elevated serum CXCL10 correlated positively and significantly with severity score index (SSI) score in all CDI patients. CXCL10 levels were also positively correlated with WBC count, creatinine and inflammatory cytokines including, IL-1β, IL-6 and CXCL9, but negatively correlated with albumin. Furthermore, serum CXCL10 concentration could be significantly decreased after effective treatment of CDI. Therefore, the above results suggest that the up-regulated release of CXCL10 is important in the immunopathogenesis of CDI, and may be served as a potential alternative biomarker for the monitoring of CDI disease severity and therapeutic efficacy.

1. Introduction

Clostridium difficile is an obligate anaerobic, spore-bearing, Gram-positive rod bacterium that is the main causative agent of healthcare-onset diarrhea and pseudomembranous colitis [1]. It is recently reported that *C. difficile* caused an estimated half a million infections and approximately 29,300 deaths each year, and care facilities costs of about $4.8 billion in the United States [2]. Additionally, it is the leading cause of nosocomial infection of the gastrointestinal tract and nosocomial diarrhea [3].

Clostridium difficile infections (CDI) have significantly increased in incidence, severity and mortality, particularly with the emergence of highly virulent strain (BI/NAP1/027) in Canada, North America, Europe and Asia [4,5]. Clinical manifestation ranges in severity from asymptomatic colonization to fulminant colitis, Polymicrobial sepsis and death [1]. It is generally accepted that the pathogenesis of *Clostridium difficile* infection (CDI) is multifactorial, depends on the virulence factor of pathogenic bacteria, intestinal flora disorder and immune response of host [6], and yet it remains poorly understood why some people develop formidable disease. Therefore, it is critical to assess the severity of CDI at an early stage.

Current severity scores based on clinical characteristics is less sensitive and specific in assessing the severity of CDI [7]. In recent years, Molecular markers for *C. difficile* detection, such as calprotectin, procalcitonin (PCT), IL-2 and IL-15, were proposed to may be correlated with disease progression [8–10]. However, these inflammatory factors lack specificity and are less indicative of disease severity. Therefore, finding biomarkers that can rapidly and accurately assess the severity of disease is crucial to improve the management of treatment.

C-X-C motif chemokine ligand 10 (CXCL10), also known as IFN-γ-inducible protein of 10 (IP-10), was initially identified in studying the immune response to IFN-γ in 1985 by Luster AD et al. [11]. CXCL10 is produced by monocytes, dendritic cells, macrophages, T cells, fibroblasts and vascular endothelial cells, and exerts its biological effects

Abbreviations: CDI, *Clostridium difficile* infection; CDAD, *Clostridium difficile* associated diarrhea; CXCL10, C-X-C motif chemokine ligand 10; CXCL9, C-X-C motif chemokine ligand 9; SSI, severity score index; PCT, procalcitonin; CRP, C-reactive protein; ROC, Receiver Operating Characteristic curve; AUC, Area Under Curve; MCP-1/CCL2, monocyte chemoattractant protein 1/C-C chemokine ligand 2

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mainly via binding to CXCR3 receptor [12]. Earlier evidence revealed that CXCL10 correlates with the occurrence of chronic diseases such as diabetes mellitus, systemic lupus erythematosus or cancer [13–15].

Recent studies of CXCL10 expression in patients with marginal periodontitis, *Mycoplasma* pneumonia or Acquired Immune Deficiency Syndrome (AIDS) suggests that this chemokine plays an important role in the initiation and progression of bacterial infection [16–18]. However, the role of CXCL10 in CDI patients remains unknown.

In the present study, we investigated the possible correlation between the serum level of CXCL10 and clinic severity in CDI patients, and aimed was to evaluate whether CXCL10 can be used as a potential disease severity biomarker in early *Clostridium difficile* infection.

2. Materials and methods

2.1. Study population

A total of 156 diarrhea (defined as ≥3 unformed stools in 24 h) patients were recruited at The First Affiliated Hospital of Chongqing Medical University from October 2016 through September 2018. According to the 2017 Update by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) criteria, Finally diagnosis of 80 CDI patients was established as a positive toxigenic *C. difficile* culture (positive for tcdA or/and tcdB) from a hospitalized patient with acute diarrhea [19]. Moreover, the severity of disease in CDI patients were classified into mild disease(0–3 points) and moderate disease (4–6 points) on the basis of severity score index (SSI) by Iris Velazquez-Gomez et al. [20]. We excluded patients with < 18 years, repeated tests, recurrent CDI, autoimmune diseases, inflammatory bowel disease and coinfection. Meanwhile, the sex & age-matched 76 diarrhea individuals who served as controls, presented negative results for both A/B toxins detection by enzyme immuno-assay (EIA) and toxigenic culture.

Vancomycin and metronidazole are commonly used antibiotics to treat *C. difficile* associated diarrhea (CDAD), but vancomycin is superior for treating patients with more severe CDAD [21]. Among the moderate CDI patients, 16 patients who received mono-therapy of vancomycin (125 mg 4 times per day) for 10 days were cured and eligible to enroll in our study for efficacy evaluation. Cure was defined as resolution of diarrhea by day 6 of treatment and a negative result of a *C. difficile* toxin assay at days 6 and 10 of treatment [22]. Patients were not allowed to receive any antidiarrheal medications, treatment with vancomycin or metronidazole during the previous 14 days.

Each CDI patients received a standardized medical history collection and physical examination. All serum samples were immediately collected within 24–48 h after diarrhea and stored at −80 °C until analysis. The above protocol was approved by the Clinical Research Ethics Committee of The First Affiliated Hospital of Chongqing Medical University, and informed consent was obtained from all participants according to guidelines for the protection of human subjects.

2.2. Clinic data collection

All data was retrospectively retrieved from Laboratory Information System (LIS) and Clinical Electronic Medical Record, including demographic information (age, gender, hospitalization days, ward distribution, antibiotics exposure, Charlson Comorbidity Index [23]), clinical manifestations, and laboratory measures. CDI-related features included altered mental status, fever > 38 °C, abdominal pain or bloating, ascites or colitis, leukocytosis (WBC > 20,000 cells/μl), hypoalbuminemia (< 2.5 g/l), hypotension (mean arterial pressure < 65 mmHg), tachycardia (> 110 bpm), as well as admission Intensive Care Unit and were based on SSI score.

2.3. C. difficile culture and toxins detection

Alcohol-shock stools were inoculated on plates containing cycloserin cefoxitin fructose agar (CCFA) in an anaerobic environment (BBL GasPak Plus system; BD Biosciences) and colonies suspicious as *C. difficile* were subjected to mass spectrometry (Vitek MS, bioMerieux, France). Stool specimens and *C. difficile* strains were detected for toxin A and toxin B antigen by enzyme linked fluorescent assay (ELFA) (Vidas mini, bioMerieux, France).

2.4. Measurements of cytokine/chemokine

Concentration of serum CXCL10 was determined by using enzyme linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN), The levels of IL-1β, IL-6, tumor necrosis factor (TNF)-α, and C-X-C motif chemokine ligand 9 (CXCL9) were assessed by Quantikine ELISA (Neobioscience Technology Co., Ltd), according to the manufacturer's protocol.

2.5. Statistical analysis

All data in our study were analyzed by SPSS 22.0 or GraphPad Prism 5.0 software. Differences in continuous variables were evaluated using the Mann-Whitney rank sum test and analysis of variance (ANOVA), the differences in distribution of categorical was analyzed using chi-square test or Fisher's exact-test as appropriate. CXCL10 levels before or after treatment were estimated by using a paired *t*-test. The relationships of serum CXCL10 concentration with clinical parameters and inflammatory mediators were assessed using Spearman's rank correlation test. The sensitivity and specificity of serum biomarkers were illustrated by analyzing the receiver operator characteristic (ROC) curves. The cut-off value was determined when Youden's index took the max value. For all comparisons, A two-tailed p value < .05 was considered to represent statistical significance.

3. Results

3.1. Serum CXCL10 is elevated in CDI

Serum CXCL10 levels in 80 CDI patients and the controls were determined by ELISA. As shown in Fig. 1A, serum CXCL10 concentration was significantly higher in CDI patients than those in non-*C. difficile* diarrhea patients [median (interquartile range): CXCL10 levels in CDI patients 171.9 (107.8–264.8) pg/ml, non-*C.difficile* diarrhea 91.2 (66.7–162.3) pg/ml]. Moreover, the level of serum CXCL10 increased with age in CDI patients (Fig. 1B).

3.2. C. difficile infection subjects

A total of 80 CDI patients were enrolled in our study, including 33 CDI patients with mild disease and 47 CDI patients with moderate disease. Clinical and demographic characteristics of the study populations are summarized in Supplementary Table S1. Patients with moderate had a higher mortality (p = .034), mean age (66.2 vs 60.4 years; p = .027), and median comorbidity burden(4 vs 2; p = .001), but they otherwise did not differ significantly in gender, ward distribution, or defecation habits. Compared with mild disease group, the moderate disease group was treated with significantly more different length (13 vs 9; p = .031) and classes(3 vs 2; p = .025) of antibiotics before diarrhea developed. Furthermore, the median level of WBC (10,270 vs 8300; p = .019), neutrophile (8765 vs 6265; p = .041) and PCT (0.52 vs 0.23; p = .027) were significantly elevated in the moderate disease. However, albumin (ALB) concentration, lymphocyte and eosinophil counts were remarkably decreased.

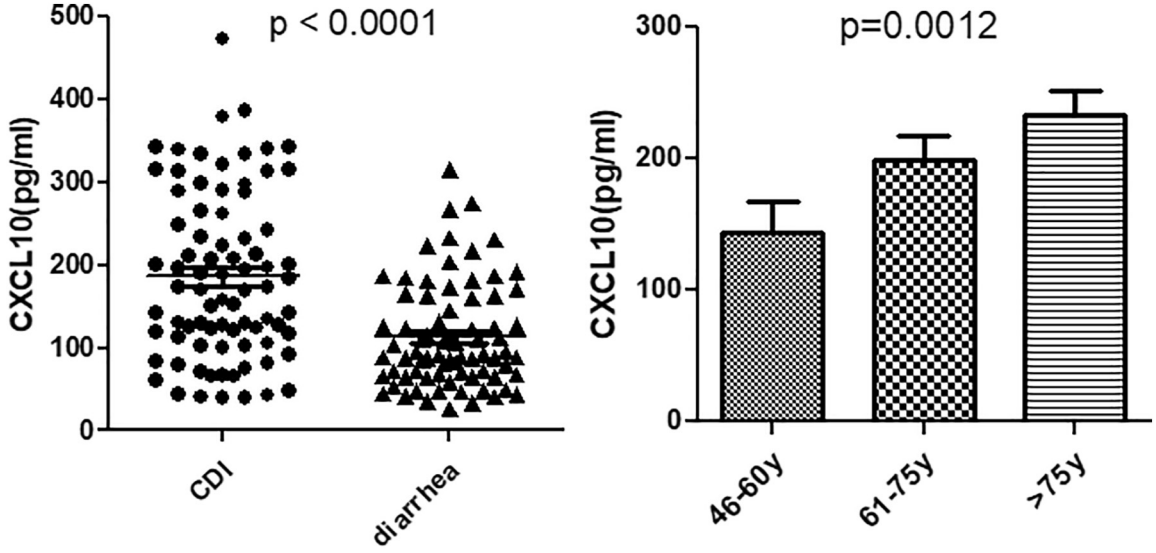

Fig. 1. Determination of CXCL10 values between CDI patients and control subjects. (A) Scatter-plots of serum CXCL10 levels in CDI patients and diarrhea individuals. The horizontal lines indicate the median concentration for each group. The differences between CDI patients and diarrhea were determined by non-parametric Mann-Whitney *U* test; (B) A histogram of serum CXCL10 concentration in CDI patients in different age groups. The differences among different age groups were evaluated by analysis of variance.

3.3. Serum concentrations of CXCL10 and CDI clinical disease severity

As shown in Fig. 2A, the CXCL10 level was significantly higher in the moderate disease 233.7 (148.5–316.4) pg/ml, than in the mild disease [123.2 (70.1–171.1) pg/ml; $p < .0001$]. Meanwhile, the difference was performed in female and male (Fig. 2B). Moreover, concentration of serum CXCL10 exhibited a positive and significant correlation with severity score index (SSI) in CDI patients ($r = 0.472$, $p < .0001$; Fig. 3A).

3.4. Correlation between serum CXCL10 and laboratory parameters in CDI patients

Serum CXCL10 levels demonstrated a significantly positive correlation with WBC ($r = 0.258$, $p = .018$; Fig. 3B) and PCT ($r = 0.227$, $p = .040$; Fig. 3C) and Cr ($r = 0.223$, $p = .038$; Fig. 3F). Contrary to the above observation, serum CXCL10 levels demonstrated a significantly negative correlation with the levels of ALB ($r = -0.224$, $p = .038$; Fig. 3E) in CDI patients.

3.5. Correlation analysis of CXCL10 level in CDI serum with mediators of inflammation

We further assessed in CDI patients for content of the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α, as well as of the C-X-C motif chemokine ligand 9 (CXCL9). Notably, as shown in Supplementary Fig. S1, CXCL10 positively and significantly correlated with IL-1β, IL-6 and CXCL9 during CDI, but not with TNF-α. Meanwhile, we also found that the expression of CXCL9 is markedly related to the severity of the disease (Supplementary Table S2), while there was no statistically significant difference in L-1β, IL-6 and TNF-α.

3.6. CXCL10 is a sensitive indicator in evaluating CDI disease severity

The indicative efficiency of serum CXCL10, WBC, CRP and PCT for identification of disease severity in CDI patients were analyzed by ROC

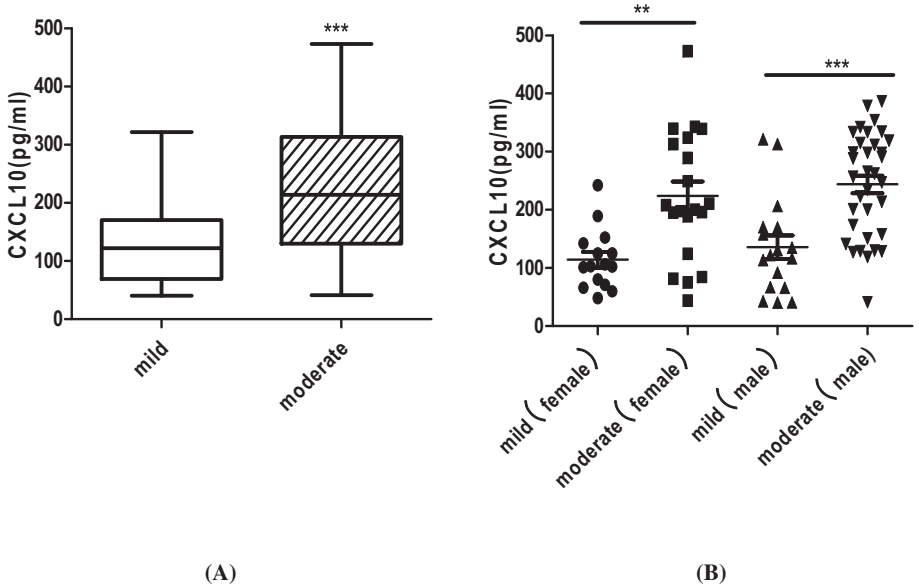

Fig. 2. The role of CXCL10 in reflecting disease severity in CDI. (A) CXCL10 levels of patients with mild CDI and moderate CDI. The box plot shows the median (bold line), the first quartile (lower border of the box) and the third quartile (upper border of the box). (B) scatter-plots of concentrations of serum CXCL10 in different sex groups. $^{***}p < .001$, $^{**}p < .01$.

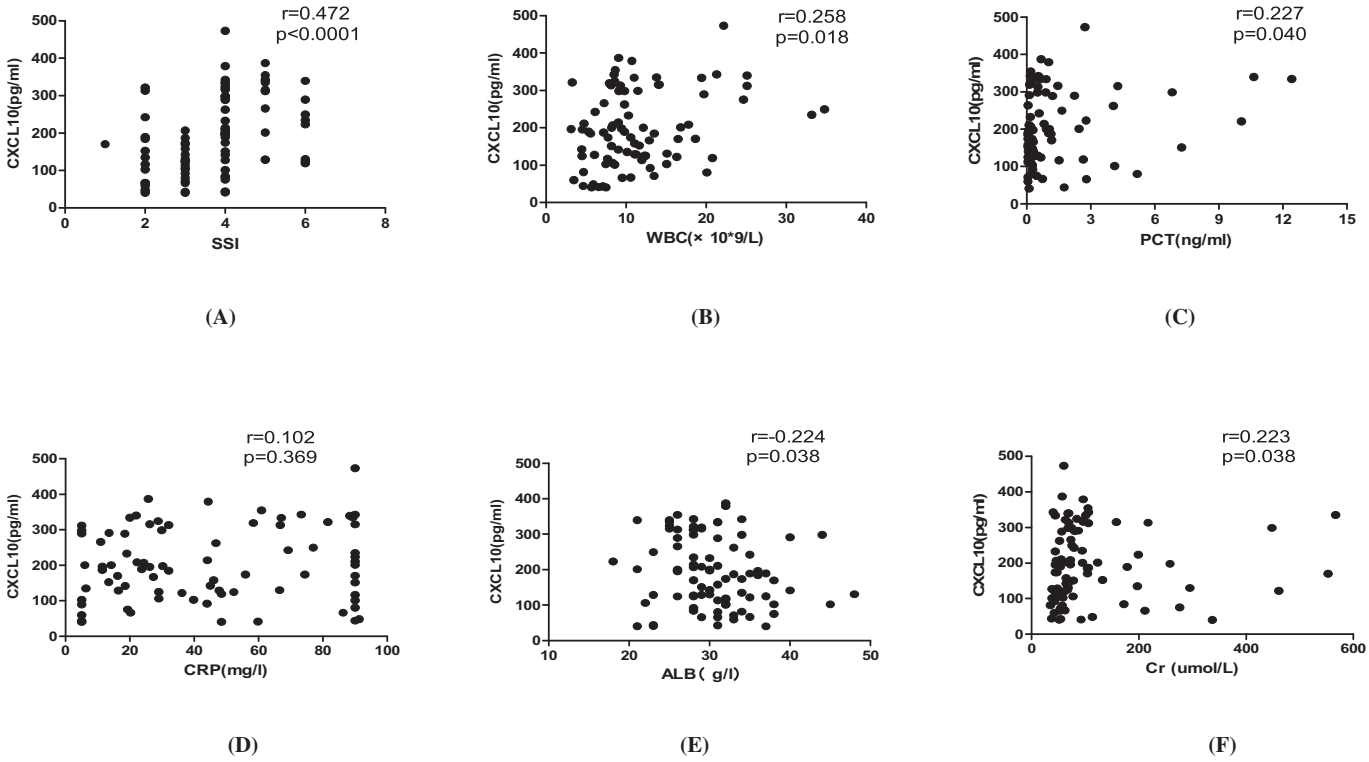

Fig. 3. Correlation of serum CXCL10 concentration with parameters related to disease severity. Data were analyzed with Spearman's rank correlation test.

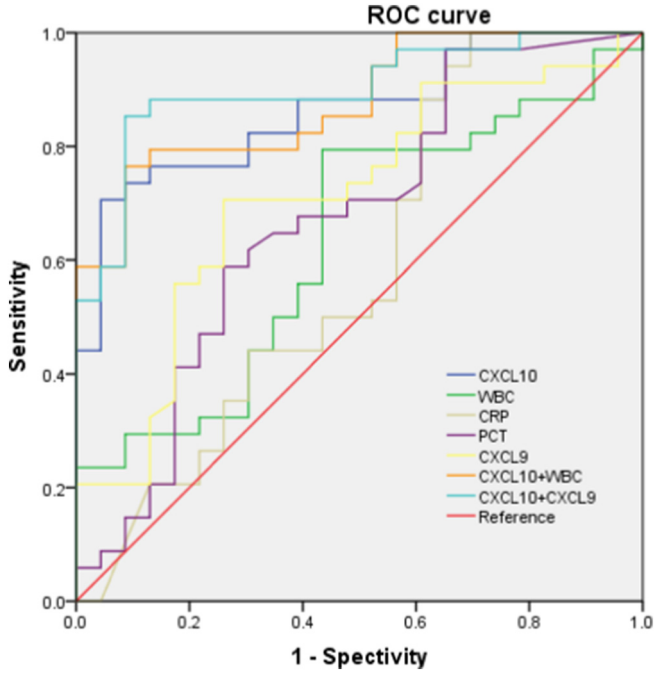

Fig. 4. ROC curves of CXCL10, WBC, CRP and PCT for identification of the higher disease activity in CDI.

curves (Fig. 4). The sensitivity and specificity of CXCL10 (Sensitivity 73.1%, Specificity 87.9%, AUC 0.854) in predicting higher disease severity was markedly higher than those of WBC (Sensitivity 82.2%, Specificity 51.6%, AUC 0.643), CRP (Sensitivity 86.8%, Specificity 35.5%, AUC 0.637), PCT (Sensitivity 68.9%, Specificity 71.0%, AUC 0.708), and CXCL9 (Sensitivity 70.6%, Specificity 73.9%, AUC 0.710, Table 1). Subsequently, combined use for CXCL10 and WBC counts/CXCL9 indicated that the area under the curve was 0.881/0.900. Its sensitivity and specificity was 77.8%/85.3% and 89%/82.6%, respectively. In consequence, the results suggested that CXCL10 may be a potential marker of disease severity, and its combined detection with WBC counts/CXCL9 was superior to a single measurement. (See Table 2.)

3.7. Effect of treatment on the production of CXCL10 in CDI patients

Sixteen CDI patients with successfully cured were recruited after an ten days treatment with vancomycin liquid (125 mg 4 times per day), and we found that serum CXCL10 level in all 16 patients were significantly decreased by ten days treatment ($p < .0001$, Fig. 5).

4. Discussion

In recent years, host inflammatory response to CDI have gained significantly interest by the scientific community. Virulence factors TcdA and TcdB of *C. difficile* directly damage the intestinal epithelium barrier and initiate the host's acute inflammatory response the via eliciting the release of pro-inflammatory cytokines and chemokines, which is a hallmark of CDI [24,25]. Recently, clinical setting suggests that persistent diarrhea in CDI patients is associated with intestinal inflammation rather than the burden of pathogens [26]. Therefore, elucidation of host inflammatory response involved in *C. difficile* infection provides a new perspective for its therapeutic targets and disease prognosis. However, the roles of CXCL10 in CDI was scarcely explored.

For the first time, we compared the levels of CXCL10 0f CDI patients with non-*C.difficile* diarrhea individuals. we demonstrated that serum CXCL10 were significantly elevated in CDI patients, especially in the moderate disease as evaluated by the SSI score. In addition, our results shown that circulating levels of CXCL10 are significantly correlated with severity score index (SSI) and blood test indicators including WBC count, PCT, ALB, as well as Cr (Fig. 3), which may indicate that mucosal inflammation and toxin damage induced by the moderate disease are more severe. These results suggested that the elevation of serum

Table 1
Diagnostic values of CXCL10, WBC, CRP, PCT and CXCL9 in moderate disease severity in CDI patients.

Index	AUC	Std	*p*-Value	95% CI for AUC		Cut-off	Sensitivity	Specificity	Youden
				Lower	Upper				
CXCL10	0.854	0.042	0.000	0.772	0.936	173.752	0.731	0.879	0.604
WBC	0.643	0.064	0.035	0.518	0.769	8.311	0.822	0.516	0.338
CRP	0.637	0.066	0.044	0.507	0.766	13.450	0.868	0.355	0.256
PCT	0.708	0.062	0.002	0.586	0.829	0.322	0.689	0.710	0.399
CXCL9	0.710	0.070	0.007	0.573	0.848	164.871	0.706	0.739	0.445
CXCL10 + WBC	0.881	0.037	0.000	0.808	0.954		0.778	0.890	0.680
CXCL10 + CXCL9	0.900	0.041	0.000	0.819	0.981		0.853	0.826	0.708

AUC, Area Under Curve.

Table 2
Correlation analysis of CXCL10 levels in CDI serum with mediators of inflammation.

Mediators of inflammation	Spearman correlation coefficient	*p*-Value
IL-1β (pg/ml)	0.264	0.047
IL-6 (pg/ml)	0.352	0.007
TNF-α (pg/ml)	0.085	0.531
CXCL9 (pg/ml)	0.512	< 0.0001

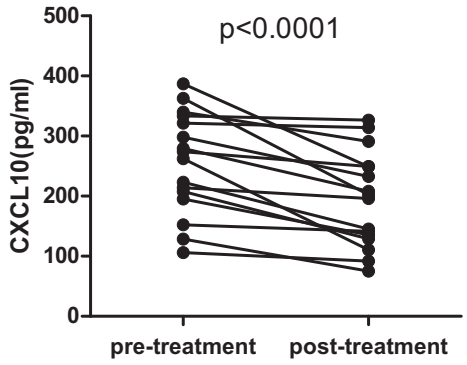

Fig. 5. Effect of vancomycin treatment on the production of CXCL10. 16 patients with the moderate disease were recruited after 6–10 days of effective treatment to investigate the concentrations of CXCL10 by ELISA.

CXCL10 is significantly correlated with severity of disease and may play a crucial role in the pathologic progression of CDI, This finding supports previous reports [9,19,20].

Recently, one study have revealed that interferon-γ (IFN-γ) and monocyte recruitment are the main driving factors of inflammatory response to CDI. IFN-γ-inducible chemokines (CXCL9, CXCL10) and Monocyte-derived cytokines including IL-1β, IL-6, TNF-α and MCP-1 are implicated in the development of inflammation and epithelial damage during colitis [27,28]. To further study the role of CXCL10 in CDI, we investigated the possible correlation between the expression of CXCL10 and these inflammatory mediators. As the results shown that CXCL10 level correlated positively and significantly with inflammatory cytokines during CDI, such as IL-1β, IL-6 and CXCL9, but not with TNF-α. Meanwhile, we also found that the expression of CXCL9 is markedly related to the severity of the disease, which can be used as a supplementary indicator of the severity of the disease. These data provided an important basis for CXCL10 participated in the initiation and progression of CDI.

More importantly, we identified CXCL10 as a relatively specific and sensitive biomarker for predicting the higher severity of CDI by further ROC analysis. Our findings suggested that CXCL10 may be served as a potential marker of CDI severity, and its combined detection with WBC counts/CXCL9 was superior to a single measurement.

Additionally, we focused on the alteration of serum CXCL10 pre- and post-treatment. The CXCL10/CXCR3 axis is a potential pharmacological target of various human diseases. Singh et al. [29] have been proved that antibody targeting to block CXCL10 or CXCR3 receptors attenuated inflammatory colitis in mice. Besides, Andrew et al. [27] found that neutralization of IFN-γ down-regulated the expression of CXCL10 in mice with acute *C.difficile* infection. Vancomycin is a clinically recommended drug for the treatment of severe CDI. Recently, it has been reported that the expression of inflammatory cytokines, such as TNF-α, IL-6, IL-10 and IL-1β [30,31], is involved in the treatment of infectious diseases by vancomycin. This clinical study indicates that serum CXCL10 levels of 16 CDI patients with the moderate disease decreased significantly after disease amelioration by effective treatment, which may implicate its involvement in the disease progression of CDI, but further studies are needed. This result strengthens CXCL10 compatibility as a sensitive indicator for evaluating CDI disease severity.

Our study has some limitations. First, as we chose a specific scoring index, it was difficult to compare our results with those of other studies using different scoring method [10,32]. Second, our study population didn't enroll patients with severe CDI. Therefore, the diagnostic and prognostic value of CXCL10 should be further verified by recruiting more CDI patients including those with severe CDI. Finally we did not detect alteration of CXCL10 circulating level in patients receiving other treatment regimens when evaluating therapeutic effect. Further studies should compare changes in CXCL10 level in different treatment regimens to guide clinical medication.

In conclusion, our results shown that CXCL10 level may be severed as a new and alternative biomarker to monitor the severity of CDI and therapeutic efficacy. Determination of this serological marker is simple and rapid. It is important to be able to identify relatively severe patients as early as possible and administer appropriate treatment administration. Therefore, this study provides new insight into the pathological role of CXCL13 in CDI.

Disclosure statement

All authors declare no conflicts of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.03.033.

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