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NOVEL CORONA VIRUS (COVID-19) IN ENVIRONMENTAL ENGINEERING PERSPECTIVE

Increased Levels of serum Pentraxin 3 in Critical Coronavirus Disease-2019 Patients

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Abstract

Pentraxin 3 (PTX3) and ficolin are the plasma phase of pattern recognition receptors (PRRs) and can activate complement through classical and lectin pathways, respectively, which may contribute to disease severity. This study aimed to investigate the association between PTX3 and ficolin with disease severity in patients with coronavirus disease-2019 (COVID-19). Seventy-three COVID-19 patients and 25 healthy controls were enrolled in this study. The participants were divided into three groups as follows: 14 patients as the intensive care unit (ICU) group, 59 patients as the non-ICU group, and 25 subjects as the healthy control group. The serum levels of PTX3 and ficolin were measured by enzyme-linked immunosorbent assay (ELISA) kits. Patients in ICU and non-ICU groups had significantly higher levels of PTX3 compared to the healthy control group ($p = 0.0002$ and $p = 0.0072$, respectively). Patients in the ICU group also had an increased amount of PTX3 (1957 ± 1769 pg/ml) compared to non-ICU patients (1220 ± 1784 pg/ml). However, this difference was not significant. On the other hand, serum levels of ficolin were not different among the three groups. PTX3, as an acute phase protein, may contribute to disease severity. Its probable inflammatory role could result from the high activation of the complement system. On the other hand, it could be suggested that ficolin has no crucial role in the disease severity of COVID-19 patients.

Keywords Pentraxin 3 · Ficolin · COVID-19 · Pattern recognition receptors · Coronavirus

Introduction

New coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is associated with respiratory illnesses varying from mild to life-threatening acute respiratory distress syndrome (ARDS). Several common symptoms, including dry cough, fever, fatigue, dyspnea, myalgia, and shortness of breath, are observed in the COVID-19 patients. Innate immunity, as the first line of defense, protects the body from the pathogens and activates the adaptive immune system through cytokines' production (Gholipour et al. 2020; Merad and Martin 2020; Taefehshokr et al. 2020; Yousefi et al. 2021).

Innate immunity through pattern recognition receptors (PRRs) recognizes the conserved pattern of microorganisms, such as lipid A portion of lipopolysaccharide (LPS), known as pathogen-associated molecular patterns (PAMPs) (Taefehshokr et al. 2020). Pentraxins belong to the soluble components of PRRs. Pentraxin family consists of short and long pentraxins, which activates the classical pathway of complement. C-reactive protein (CRP) and serum amyloid P (SAP) are short pentraxin subfamily, while pentraxin 3 (PTX3) is a long one (Staubli et al. 2019; Vilahur and Badimon 2015). Ficolin is another family of soluble components of PRRs, which binds to the pathogens and activates the lectin pathway of complement (Garred et al. 2016). Myeloid cells, particularly dendritic cells (DCs), are the main sources of PTX3 among immune cells (Balhara et al. 2013). However, the neutrophils appear to be a main source and reservoir of ficolin, especially ficolin-1 (Garred et al. 2010).

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CRP and SAP are produced by liver cells in response to inflammatory mediators, such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), while PTX3 is released from different innate immune cells and endothelial cells in response to TNF-α or toll-like receptors (TLRs) ligand (Staubli et al. 2019, Vilahur and Badimon 2015). Complement activation via PTX3 and ficolin could result in a high inflammatory condition, activation, and chemotaxis of leukocytes into inflammatory tissue (Vilahur and Badimon 2015). Previous research on the prognostic importance of PTX3 and ficolin in systemic inflammatory diseases, vascular pathology, and also COVID-19 (Brunetta et al. 2021; Latini et al. 2004b; Polycarpou et al. 2020) led the current study, which aimed to learn more about the significance of PTX3 and ficolin in critically ill COVID-19 patients.

Materials and methods

Study populations

A total of 98 participants were enrolled in this study as follows: A number of 14 patients were admitted to intensive care unit (ICU) (mean age ± SD = 53 ± 18, 8 males, 6 females); 59 patients were in the non-ICU group (mean age ± SD = 59 ± 19, 38 males, 21 females); and 25 subjects were in the healthy control group (mean age ± SD = 46 ± 6.5, 16 males, 9 females). All patients (n = 73) with COVID-19 enrolled in this study were confirmed with positive SARS-CoV-2 real-time reverse transcription-polymerase chain reaction (RT-PCR) tests of respiratory secretions and admitted to Ayatollah Rouhani, Shahid Yahya Nezhad, and Shahid Beheshti Hospitals of Babol Medical University (Babol, Iran). The control group consisted of healthy persons with no known history of COVID-19 infection or other infection symptoms, negative RT-PCR, and normal laboratory findings. The study was approved by the Ethics Committee of Babol University of Medical Sciences (Code: IR.MUBABOL.HRI.REC.1399.090).

Sample collection, ficolin, and pentraxin measurements

Five milliliters of peripheral blood was obtained from all participants, and then their sera were considered for the measurement of ficolin and PTX3. The concentrations of ficolin and PTX3 were measured by enzyme-linked immunosorbent assay (ELISA) kits (Boster Bio, Pleasanton, CA, USA). All assays were performed in duplicate according to the manufacturer's instructions.

Statistical analysis

Data were analyzed via GraphPad Prism 8.0 for Windows (GraphPad Software, Inc., San Diego, USA). The one-way analysis of variance (ANOVA) or the Kruskal–Wallis test was used, and the p value of < 0.05 was considered significant in all statistical tests.

Results

Demographic and clinical characteristics of study subjects

The demographic and clinical features of COVID-19 patients and healthy control subjects are shown in Table 1 (age- and sex-matched). The main clinical and laboratory findings were significantly different between ICU and non-ICU patients. ICU patients had significantly lower O^2 saturation ($p < 0.0001$) and higher respiratory rate ($p < 0.0001$) compared with non-ICU patients. On the other hand, in ICU patients, lymphocytes were significantly reduced, and neutrophils were significantly increased compared to the non-ICU group (Table 1).

Increased amount of PTX3 in COVID-19 patients

PTX3, as the main component of the pentraxin family, was measured in COVID-19 patients and compared with healthy controls. Both ICU and non-ICU groups had remarkably increased levels of PTX3 compared with healthy controls ($p = 0.0002$ and $p = 0.0072$, respectively [Table 2, Fig. 1]). Although the difference between ICU and non-ICU patients was not significant, ICU patients (1957 ± 1769 pg/ml) had higher levels of PTX3 than non-ICU patients (1220 ± 1784 pg/ml [Fig. 1]).

Same level of ficolin in all study subjects

Ficolin was measured using ELISA between study subjects. Kruskal–Wallis analysis did not show any significant difference between the three groups (Table 2, Fig. 1).

Discussion

Several cell types, such as lung epithelial cells, produce PTX3; it was shown that PTX3 gene expression is induced in respiratory tract epithelial cells in response to SARS-CoV-2 (Brunetta et al. 2021). In the inflammatory condition and in response to the microbial recognition, PTX3 is rapidly increased, which could indicate fungal or viral infection (Cunha et al. 2014; Mairuhu et al. 2005). Moreover, in other

Table 1 Demographic and clinical characteristics of study subjects

Variables	Healthy (25)	Non-ICU (59)	ICU (14)	P value
Age (years)	46±6.5	59±19	53±18	
Gender				
Female	9	21	6	
Male	16	38	8	
Temperature	36.5±0.1	37.4±1	37.4±0.4	0.0001
O^2 saturation	-	90±5	79±7	<0.0001
Respiratory rate	-	20.5±3	27.5±6	<0.0001
LDH	-	519±192	1241±1029	<0.0001
CRP	1.7±1.5	87±69	176±85	<0.0001
ESR	-	56±33	62±27	0.5407
Ferritin	103±52	638±834	507±342	0.0227
BUN	15±3.6	22±17	34±21	0.0040
AST	21±4	51±35	81±73	0.0059
ALT	18±7	45±28	56±48	0.0093
WBC	7489±1931	8256±3228	9171±2491	0.31
Lymphocytes (% in differential)	32±5	24±12	12±5	<0.0001
Neutrophil (%in differential)	67±10	71±10	83±9	<0.0001
PLT	269214 ±107329	252485 ±138840	219643 ±135754	0.5129
NLR	2.06±0.53	4.18±2.18	7.17±2.86	<0.0001
PLR	114±41	155±77	190±95	0.0507
Hb	-	11±1	10±1	0.1283

inflammatory conditions, such as cardiovascular disease (Latini et al. 2004a) and sepsis (Lee et al. 2018), PTX3 is increased and associated with disease severity and mortality (Brunetta et al. 2021). In support, in the setting of sepsis, Song et al. showed that a highly increased amount of PTX3 (> 26 ng/ml) was associated with mortality (Song et al. 2020).

In terms of COVID-19 patients, Brunetta et al. showed that an increased amount of PTX3 could independently predict 28 days mortality. They finally reported that PTX3 is a better prognostic marker compared with CRP, IL-6, ferritin, and D-dimer (Brunetta et al. 2021). In another study, it was found that PTX3 had higher levels in severe COVID-19 patients than in asymptomatic patients and was positively correlated with D-dimer and body math index (BMI) (Krishnamachary et al. 2020). In the current study, our results confirmed the results of previous studies. We showed that both non-ICU and ICU groups had an increased amount of PTX3 compared with healthy controls. Although the difference was not significant between ICU and non-ICU patients, ICU patients showed higher levels of PTX3 with mean rank = 17.04. Moreover, PTX3 is associated with the severity of other lung injuries. In pulmonary contusion patients, PTX3 is remarkably increased and plays the main role in the pathophysiology of pulmonary contusion (Tatli et al. 2017).

Inflammatory factors, such as cytokines (IL-17, IL-1β, and IL-6), acute phase proteins, and neutrophils, are associated with disease severity, and some of these factors may be reduced after the current treatment protocol (Kataržytė et al. 2020). PTX3 is the major acute phase protein, which remarkably increases in COVID-19 patients and may contribute to disease severity. One of the possible functions of PTX3 may result from the increased activation of the complement cascade, which therefore increases the inflammation. Although it was reported that PTX3 could also reduce inflammation (Slusher et al. 2016; Vilahur and Badimon 2015), in terms of COVID-19 patients, it may not regulate uncontrolled inflammation.

Table 2 Levels of PTX3 and ficolin in the subjects

	Healthy (25)	Non-ICU (59)	ICU (14)	P value
Pentraxin (pg/ml)	275±167	1220±1784	1957±1769	0.0002
Ficolin (pg/ml)	21±4	23±6.6	19±9	0.0523

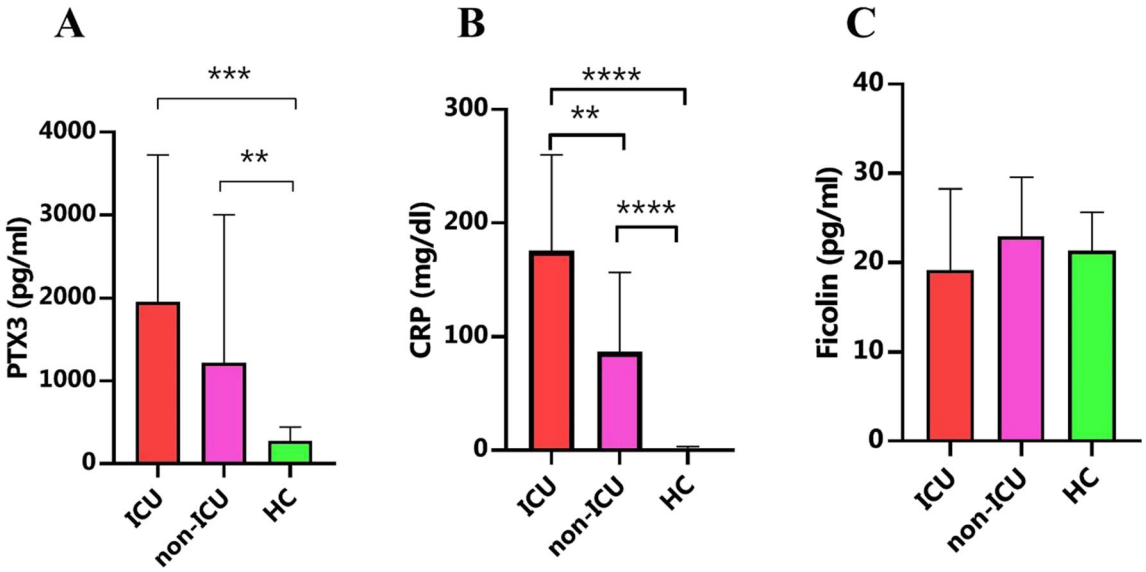

Fig. 1 Increased level of PTX3 in COVID-19 patients. Serum samples were considered for the measurement of ficolin and PTX3 by enzyme-linked immunosorbent assay (ELISA) kits. Both ICU and non-ICU groups had remarkably increased levels of PTX3 compared with healthy controls (**A**). These differences were also significant for CRP levels between groups (**B**). However, ficolin levels did not show any significant difference between the three groups (**C**). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$

Conclusion

In summary, PTX3 in addition to CRP could be considered as an important factor, which contributes to disease severity. Furthermore, the early assessment of PTX3 along with CRP could be used as a prognostic factor for severe COVID-19 patients, which could be controlled by a modified therapeutic strategy.

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Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate This project has been registered in Babol University of Medical Sciences with the code of ethics of MUBABOL.HRI.REC.1399.09

Consent for publication Not applicable

Competing interests The authors declare no competing interests.

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