ORIGINAL RESEARCH

Elevated Serum Levels of Progranulin and Soluble Vascular Cell Adhesion Molecule-1 in Patients with COVID-19

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Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with the angiocentric inflammation and angiogenesis, yet the molecules involved in this process remain to be determined.

Methods: We did a cross-sectional study of a cohort of patients with COVID-19 in Zunyi, China between February 1 and March 30, 2020. Serum concentrations of PGRN were determined by enzyme-linked immunosorbent assay in patients with COVID-19 at hospital admission and at discharge. In parallel, the serum levels of soluble adhesion molecules, vascular cell adhesion molecule-1 (sVCAM-1), intercellular adhesion molecule-1 (sICAM-1), P-selectin (sP-selectin), and E-selectin (sE-selectin) were assayed by a human adhesion molecule multiplex kit. The association between serum PGRN levels and other laboratory test results was analyzed by Spearman correlation analysis.

Results: At baseline, the median serum PGRN levels in patients with COVID-19 were 94.8 ng/mL [interquartile range (IQR): 66.6–119.6 ng/mL], which was significantly elevated compared with those in healthy controls (46.3 ng/mL, IQR: 41.8–55.6 ng/mL). Moreover, the median serum sVCAM-1 levels were significantly higher in COVID-19 patients (1396.0 ng/mL, IQR: 1019.1–1774.8 ng/mL) than those in healthy controls (612.4 ng/mL, IQR: 466.4–689.3 ng/mL). However, the levels of sICAM-1, sP-selectin, and sE-selectin were not significantly elevated in patients with COVID-19 when compared to healthy controls. Further analysis showed that serum PGRN levels were significantly positively associated with sVCAM-1 ($r= 0.675$, $P= 0.008$) and inversely with sICAM-1 ($r= -0.609$, $P= 0.021$) and aspartate aminotransferase levels ($r= -0.560$, $P= 0.037$) in patients with COVID-19 at hospital admission. In COVID-19 patients, serum PGRN and sVCAM-1 levels fell significantly after successful treatment.

Conclusion: The present study demonstrates elevated serum PGRN and sVCAM-1 levels in patients with COVID-19, which may provide clues as to the mechanisms underlying the pathogenesis of COVID-19. Further studies are warranted to evaluate the potential of PGRN and sVCAM-1 as biomarkers and investigate their role in the pathogenesis of COVID-19.

Keywords: COVID-19, PGRN, soluble adhesion molecules, pathogenesis, biomarker

Introduction

Coronavirus disease 2019 (COVID-19) is a well-known contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has so far killed millions of lives worldwide. According to the data released by the World Health Organization,[1] as of July 19, 2021, more than 188 million cases have been confirmed and over 4 million cases have died of SARS-CoV-2, and more alarming is that the number of the cases is still on the increase.

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Evidence has shown that COVID-19 patients, especially those severe and critical patients, commonly had histological characteristics of endotheliopathy, vascular thrombosis, and new vessel growth in lungs,[2–6] suggesting the presence of endothelial activation and recruitment of immune cells as well as angiogenesis in the lesions caused by SARS-CoV-2 infection. To understand the immunology of SARS-CoV-2 infection, efforts had been made to reveal differentially regulated markers in COVID-19 patients,[7–9] and dozens of molecules, including endothelial cell adhesion molecules and matrix metalloproteinase-1 (MMP-1), have been successively identified. Nonetheless, the pathophysiological factors that contribute to the pathogenesis of COVID-19 remain inadequately defined.

Progranulin (PGRN) is a cysteine-rich glycoprotein, which can be secreted by endothelial cells and immune cells, such as macrophage following multiple infections.[10,11] PGRN mediates a variety of biological functions, including host defense, inflammation, and tumorigenesis.[10,12,13] Cross-sectional studies have shown that serum PGRN levels were increased in patients with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infection.[12,14] Animal experiments confirmed the observation that PGRN was up-regulated in infection models and revealed that PGRN was implicated in host defense against bacterial pneumonia, influenza virus-induced lung injury, and sepsis.[10,11,15] However, whether serum PGRN levels are quantitatively elevated in COVID-19 patients remain to be determined.

Growing evidence shows that the activated endothelial cells play a pivotal role in the progression of SARS-CoV -2-induced inflammation and suggests that the levels of serum soluble endothelial adhesion makers, such as sVCAM-1, sICAM-1, sP-selectin, are associated with disease severity of COVID-19.[6,8,9] However, discrepant results regarding the levels of sVCAM-1 and sICAM-1 have been observed between two cohorts of patients with mild/moderate COVID-19.[8,9] E-selectin is another important inducible endothelial cell surface molecule, which can also be transcriptionally upregulated by proinflammatory factors, such as tumor necrosis factor-α (TNF-α) and interleukin 1 (IL-1), and hence mediates rolling of leukocytes, such as neutrophils, lymphocytes and monocytes on the endothelium.[16] No study has investigated the levels of sE-selectin in patients with COVID-19.

Therefore, the objective of this study was to quantitatively determine the serum levels of PGRN and the soluble adhesion molecules, sVCAM-1, sICAM-1, sP-selectin and sE-selectin in patients with COVID-19, as well as to evaluate whether serum PGRN levels correlate to endothelial activation markers and other laboratory test results.

Methods
Participants
In this cross-sectional study, fourteen laboratory-confirmed COVID-19 cases from the Zunyi Medical University Third Affiliated Hospital (n= 12) and the Fourth People's Hospital of Zunyi (n= 2) between 1 February and 30 March, 2020, were enrolled. The diagnosis of COVID-19 was made according to the guideline for COVID-19, which was officially issued by the National Health Commission of the People's Republic of China.[17] Mild/moderate cases were defined as patients having lesions in lungs visible on high-resolution computed tomography images and positive nucleic acid tests for SARS-CoV-2. Severe cases were patients had one or more of the following evidence, including respiratory distress with a respiratory rate more than 30 times per minute, oxygen saturation less than 93% at rest, oxygenation index less than 300 mmHg, and respiratory failure requiring ventilation. All patients received drugs of interferon α-2b, lopinavir, and Chinese medicine as suggested by the guideline. Patients were discharged when their clinical signs and symptoms were effectively improved, and especially when they had two consecutive SARS-CoV-2 nucleic acid tests (24-hours apart) negative.[17]

Patient characteristics including age, sex, disease history, laboratory test results, and treatments were retrieved from hospital information system and laboratory information system. To have reference ranges of serum PGRN and soluble adhesion molecules, we enrolled additional fourteen volunteers who went to the First People's Hospital of Zunyi for annual healthy checkup between August 25 and August 28, 2020. These healthy subjects were not previously or currently infected with SARS-CoV-2.

Sample Collection and Storage
For patients, blood samples were collected on the day of hospital admission or hospital discharge, and fasting blood samples were drawn for testing of blood glucose (Glu), urea nitrogen (BUN), PGRN and soluble adhesion molecules. For healthy donors, fasting blood samples were collected on the morning of the checkup day. The remaining serum samples were safely kept at −80°C prior to further testing.

Laboratory Testing

The China National Accreditation Service for Conformity Assessment (CNAS) has accredited the laboratory testing at the department of laboratory medicine of the First People's Hospital of Zunyi under the ISO15189 accreditation standard. Routine blood tests, including whole-blood cell counts, lymphocyte counts, neutrophil counts, monocyte counts were analyzed on the Sysmex XN-1000 Hematology Analyzer. C-reactive protein (CRP) was determined by the turbidimetry method on the Lifotronic PA900 analyzer (Shenzhen, China). Biochemical analytes including alanine aminotransferase (ALT), aspartate aminotransferase (AST), BUN, Glu, were determined on Beckman coulter AU5800 automatic biochemistry analyzer.

The presence of SARS-CoV-2 RNA on nasopharyngeal swabs was detected using two different real-time PCR kits provided by Zhongshan Daan gene Biotech. Co., Guangzhou, China, and Shanghai Zhijiang Biotech. Co., Shanghai, China, and run on the SLAN96 real-time PCR instrument (Shanghai Hongshi Biotechnology Co., Shanghai, China). Anti-HIV antibodies were detected by chemiluminescence assay on the Autobio A2000 plus analyzer (Zhengzhou, China). Influenza A virus (Flu A) IgM, influenza B virus (Flu B) IgM, *Mycoplasma pneumoniae* (*M. pneumoniae*) IgM, parainfluenza (PIV) IgM, adenovirus IgM, respiratory syncytial virus (RSV) IgM, *Legionella pneumophila* (*L. pneumophila*) IgM, *Chlamydia pneumoniae* IgM, and *Rickettsiae* IgM were detected by indirect immunofluorescence assay (Nine respiratory tract pathogens IgM detection kit; Vircell Inc., Spain).

Luminex Assay and Enzyme-Linked Immunosorbent Assay

Levels of sVCAM-1, sICAM-1, sP-selectin, and sE-selectin were determined using Magnetic Luminex High Performance Assay kits (Catalog number: LKTM007, R&D Systems, USA) and analyzed on the Magpix platform according to the manufacturer's instructions. PGRN levels were determined using commercially available ELISA kit (R&D Systems, USA) according to the manufacturer's instructions.

Statistical Analysis

Data were analyzed using IBM SPSS V.19.0 software (IBM Corp, Armonk, NY, USA) and further processed, where necessary, using GraphPad Prism 5.0 or Microsoft Excel 2007. All categorical variables were reported as frequency and percentage, and their differences among the groups were compared using the Pearson χ^2 or Fisher's exact test. Quantitative data were reported as median with interquartile range (IQR) and were compared between the groups using the Mann–Whitney test. The association between PGRN and other laboratory index data was analyzed using the Spearman's rank correlation test. Levels of PGRN and soluble adhesion molecules in patients at the onset of illness and on the day of discharge were compared by using Wilcoxon signed-rank test. P value < 0.05 was considered as statistically significant.

Results

Characteristics of Enrolled Subjects

Overall, fourteen COVID-19 patients, and fourteen healthy controls were included in this study. Their demographic data and clinical characteristics are summarized in Table 1. Briefly, both groups were equally with seven males and seven females. The median ages were 40 years (IQR: 18.3–53.0) and 36 years (IQR: 27.8–45.8) for the patients and the healthy controls, respectively. All healthy controls were negative for SARS-CoV-2 infection. Significant differences in age, gender, disease history, eg, diabetes mellitus (DM) and chronic hepatitis disease between patients and healthy controls were not found (P > 0.05). All patients and healthy controls were tested negative for anti-HIV antibodies. The median serum levels of ALT (33.3 U/L vs 13.4 U/L, P < 0.001), AST (34.9 U/L vs 18.9 U/L, P < 0.001), and fasting blood glucose (6.1 mmol/L vs 4.7 mmol/L, P < 0.001) were significantly higher in COVID-19 patients than healthy controls, respectively. Lymphocyte counts and the levels of BUN in COVID-19 patients were significantly lower than those in healthy controls, while significant differences in whole-blood cell counts, neutrophil counts, monocyte counts and levels of CRP were not found between groups. Of the twelve cases with serological test results, it was found that six (50%) were positive for other viral or atypical bacterial IgM antibodies. Specifically, three, one, two and two patients were *M. pneumoniae* IgM, *C. pneumoniae* IgM, Parainfluenza IgM, and Influenza B virus IgM positive, respectively, one was both *M. pneumoniae* and Parainfluenza IgM positive, and one was both *M. pneumoniae* and Influenza B virus IgM positive.

PGRN and Soluble Adhesion Molecules Levels in COVID-19 Patients and Health Controls

The median serum levels of PGRN in COVID-19 patients were significantly higher at 94.8 ng/mL (IQR: 66.6–119.6 ng/mL) than those in healthy controls (46.3 ng/mL, IQR:

Table 1 Demographic and Clinical Characteristics of the Enrolled Subjects

Characteristics	COVID-19 Patients (n=14)	HC (n=14)	*P* value
Age, years, median (range)	40 (18.3–53.0)	36 (27.8–45.8)	0.945
Male/female (n)	7/7	7/7	
Smoking	2/14 (14.3%)	0/14 (0%)	
Alcohol usage	2/14 (14.3%)	2/14 (14.3%)	
Diabetes mellitus	1/14 (7.1%)	0/14 (0%)	
Cardiovascular disease	1/14 (7.1%)	0/14 (0%)	
Autoimmune disease	0/14 (0%)	0/14 (0%)	
Chronic hepatitis disease	0/14 (0%)	0/14 (0%)	
ALT (U/L)	33.3 (20.5–56.9)	13.4 (10.7–15.6)	< 0.001
AST (U/L)	34.9 (28.3–39.4)	18.9 (17.6–22.3)	< 0.001
BUN (mmol/L)	3.6 (3.0–5.1)	4.4 (4.0–5.3)	0.048
Glu (mmol/L)	6.1 (5.4–6.7)	4.7 (4.3–5.1)	< 0.001
Whole blood cell count (×10^9/L)	5.4 (4.2–6.6)	6.2 (4.9–6.7)	0.421
Neutrophil count (×10^9/L)	3.4 (2.3–4.3)	3.9 (2.4–4.2)	0.765
Lymphocyte count (×10^9/L)	1.3 (1.0–1.8)	1.9 (1.7–2.1)	0.025
Monocyte count (×10^9/L)	0.5 (0.3–0.7)	0.5 (0.3–0.5)	0.214
CRP (mg/L)	0.9 (0.5–5.5)	0.9 (0.6–1.9)	0.547
Duration from symptom onset to admission, median (IQR), days	1 (0–7)	/	
Anti-HIV antibodies	0/14 (0%)	0/14 (0%)	
M. pneumoniae IgM	3/12 (25.0%)	NA	
C. pneumoniae IgM	1/12 (8.3%)	NA	
Parainfluenza IgM	2/12 (16.7%)	NA	
Influenza B virus IgM	2/12 (16.7%)	NA	
Severe case	1/14 (7.1%)	/	

Notes: Data are median (IQR) or n/N (%), where N is the number of patients with available data; /, not applicable; *P* values were determined by Mann–Whitney *U*-test. **Abbreviation:** NA, not available.

41.8–55.6 ng/mL) as shown in Figure 1. The median serum levels of sVCAM-1 in COVID-19 patients were 1396.0 ng/mL (IQR: 1019.1–1774.8 ng/mL), which was also significantly higher than those in healthy controls (612.4 ng/mL, IQR: 466.4–689.3 ng/mL). However, the median serum levels for other adhesion molecules were 80.8 ng/mL (sICAM-1), 54.3 ng/mL (sP-selectin), and 23.0 ng/mL (sE-selectin) in COVID-19 patients, which were not significantly higher than those in healthy controls at 66.4 ng/mL (sICAM-1), 57.0 ng/mL (sP-selectin), and 19.2 ng/mL (sE-selectin), respectively (Figure 1).

Association of Serum PGRN with Available Laboratory Test Results in COVID-19 Patients

The serum levels of PGRN were positively correlated with those of sVCAM-1 in COVID-19 patients at the time of admission (Figure 2). Furthermore, serum PGRN levels were inversely correlated with the levels of sICAM-1 and AST in patients (Figure 2). No correlation was noted between serum levels of PGRN and sP-

selectin as well as sE-selectin (Figure S1). Moreover, no correlation was found between serum PGRN and other routine laboratory tests, including CRP, glucose, and lactate dehydrogenase (LDH) in COVID-19 patients (Figure S2).

Reduced Levels of PGRN and sVCAM-1 Following Effective Therapy

Five patients were lost to follow-up, because they were moved to the provincial designated hospital for further treatment; thus, nine patients were recruited on the day of hospital discharge (median hospitalization days: 13, IQR: 8–20), and serum levels of PGRN and soluble adhesion molecules were determined. Both serum levels of PGRN and sVCAM-1 were significantly decreased in the patients who have recovered from COVID-19, when compared with their corresponding baseline levels (Figure 3). Significant differences were not observed for the other adhesion molecules, sICAM-1, sP-selectin, and sE-selectin.
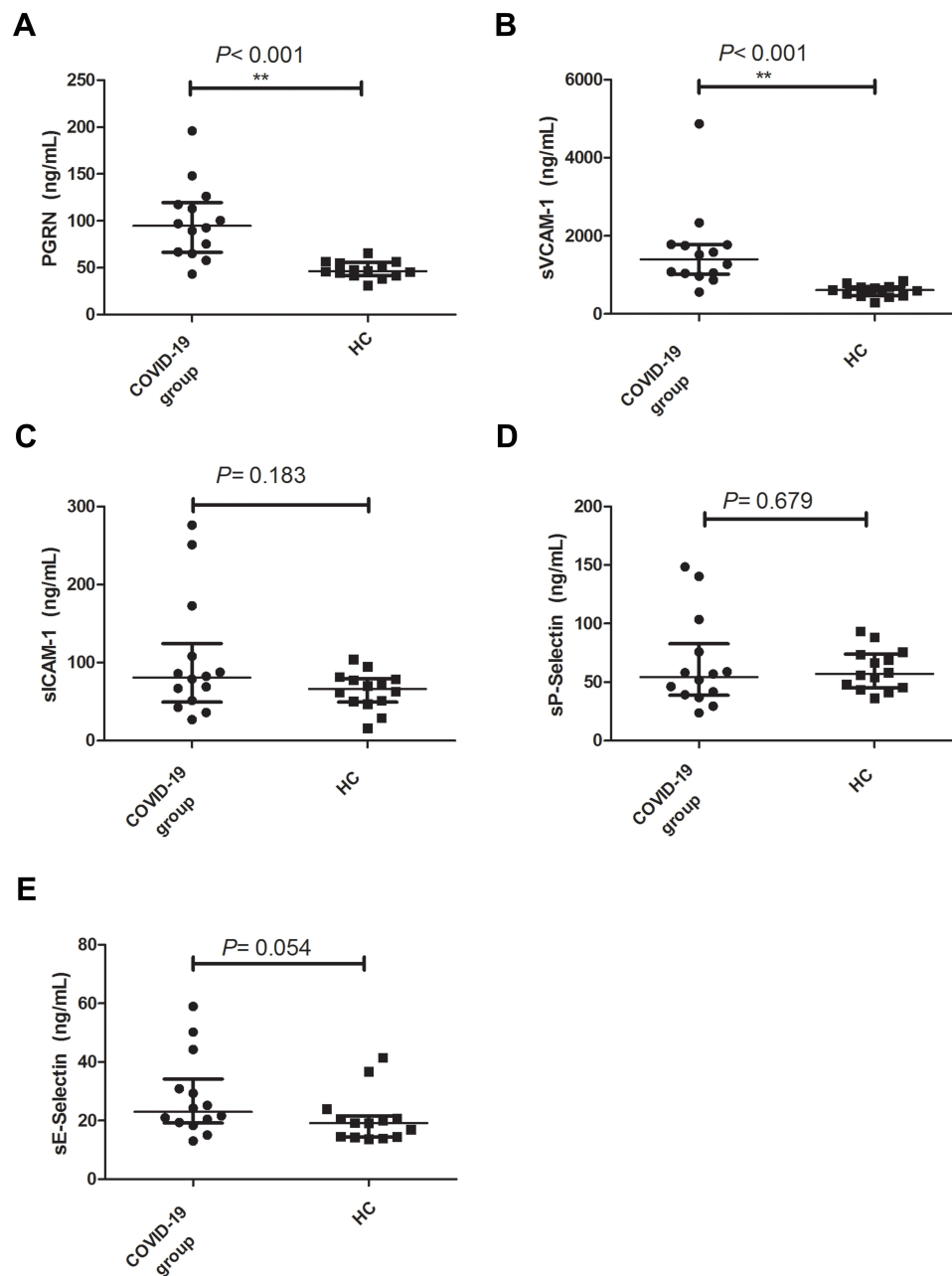
Figure 1 Scatter-plots of serum levels of PGRN, and soluble adhesion molecules in COVID-19 patients on admission and healthy controls (HC). Serum levels of PGRN (**A**) were determined using an ELISA assay kit, and serum levels of sVCAM-1 (**B**), sICAM-1 (**C**), sP-Selectin (**D**), sE-Selectin (**E**) were determined using the Luminex assay kit designed for soluble adhesion molecules. The horizontal lines represent the median concentrations of the indicated indexes in both groups. *P* values are indicated in the figures, and all comparisons were conducted using Mann Whitney *U*-test.

Discussion

Lymphocytic inflammation, microvascular injury, and new vessel growth have been recognized as hallmarks of the pathology in the lungs of patients with COVID-19.[5,6] We show here that serum levels of PGRN and sVCAM-1, but not sICAM-1, sP-selectin and sE-selectin, are significantly increased and related to response to therapy in patients with COVID-19. Moreover, we demonstrate that serum levels of PGRN positively correlate with the levels of endothelial activation marker of sVCAM-1 and inversely correlate with the levels of sICAM-1 and AST. Our data are in line with a very recent report on the levels of PGRN in COVID-19, which was based on proximity extension assay but did not quantitatively determine the levels of PGRN.[18] Moreover, our data are not completely in agreement with previous results from Tong et al[8] and Syed
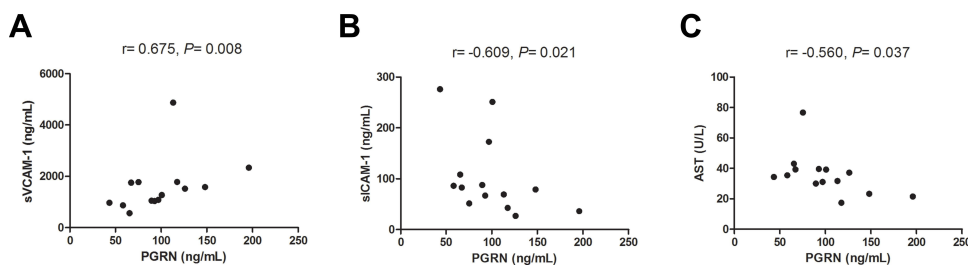
Figure 2 Correlations of serum PGRN levels with other laboratory test results in patients with COVID-19 on admission. (**A**) Spearman correlation analysis between serum levels of PGRN and sVCAM-1 in COVID-19 patients. (**B**) Spearman correlation analysis between serum levels of PGRN and sICAM-1 in COVID-19 patients. (**C**) Spearman correlation analysis between serum levels of PGRN and AST in COVID-19 patients. r and P values are indicated in the figures.

et al,[9] showing significantly increased levels of sVCAM-1 in patients with mild/moderate COVID-19, which probably results from the varied analytical performance of the assay kits used and differences in the severity of patients. Finally, for the first time, we investigated the levels of sE-selectin in patients with COVID-19.

There is evidence showing an impaired antiviral immune response in COVID-19.[19] Interferons play critical roles in the antiviral immune response as they harbor capacity to reduce viral replication; however, a repression of type I interferon signaling has been observed in patients with COVID-19.[19,20] It is known from the influenza virus infection that PGRN is involved in the attenuation of type I interferon signaling, which impairs the survival of mice from lethal infection.[10,13] The significant increase in levels of PGRN in COVID-19 patients may therefore suggest that the PGRN-mediated antiviral strategy is also functional in SARS-CoV-2 infection. Nevertheless, Thurner et al[21] have recently reported the presence of autoantibodies against PGRN in patients with critical COVID-19 and showed that plasma from PGRN-Autoantibodies-negative patients was more effective than plasma from PGRN-Autoantibodies-positive patients to neutralize the TNF-α-induced cytotoxicity. It was therefore proposed that the significantly decreased levels of PGRN are responsible for the critical COVID-19. Based on these conflicting observations, further studies are warranted to address the potential roles of PGRN in the pathogenesis of COVID-19. In addition, since convalescent plasma therapy is suggested for use in patients with critical COVID-19,[22] quantitative determination of PGRN levels is therefore required, and it seems that only plasma with PGRN in normal ranges is acceptable.

SARS-CoV-2 infection is histologically featured by angiocentric inflammation with endothelial injury and massive leukocyte infiltration, as well as thrombosis in some severe cases.[6] Since VCAM-1 is normally absent on resting endothelial cells but could be significantly induced following TNF-α and IL-1 stimulation,[23] the high levels of sVCAM-1 in patients with COVID-19 therefore indicate the presence of endothelial activation and leukocyte infiltration. It's known that VCAM-1 signaling is involved in the activation of endothelial cell-associated matrix metalloproteinases (MMPs), which digest the extracellular matrix, and is implicated in the activation of endothelial cell NADPH dual oxidase 2 (NOX2) which leads to the formation of intercellular gap, suggesting the critical role of VCAM signaling in thrombosis by exposing tissue factors. Moreover, it has been reported that sVCAM-1 have inhibitory effects on T cell activation in rheumatoid arthritis,[24] however, whether this effect occurs in the pathogenesis of COVID-19 is worthy of further investigation. Even with obvious infection lesions in lungs of patients enrolled in this cohort, the levels of CRP were not significantly higher in patients as compared to healthy controls, which is consistent with the result from a previous meta-analysis showing that CRP is only robustly elevated in severe/critical cases.[25] Additionally, it is known that PGRN could competitively bind to tumor necrosis factor receptor 1 (TNFR1)[26,27] and TNF-α/TNFR1 is implicated in activating coagulation pathways,[28] it is therefore possible that the high levels of PGRN may block TNF-α mediated inflammation and probably coagulation pathways in COVID-19. Presumably, a lack of competitive blockage of TNF-α-induced coagulatory response due to decreased levels of PGRN in patients with severe/critical COVID-19 may be one of the mechanisms connecting PGRN to the disease severity of COVID-19 as discussed above.

SARS-CoV-2 infection is associated with angiogenesis. Ackermann et al reported the formation of new blood vessels in lungs of patients infected with SARS-CoV-2 at
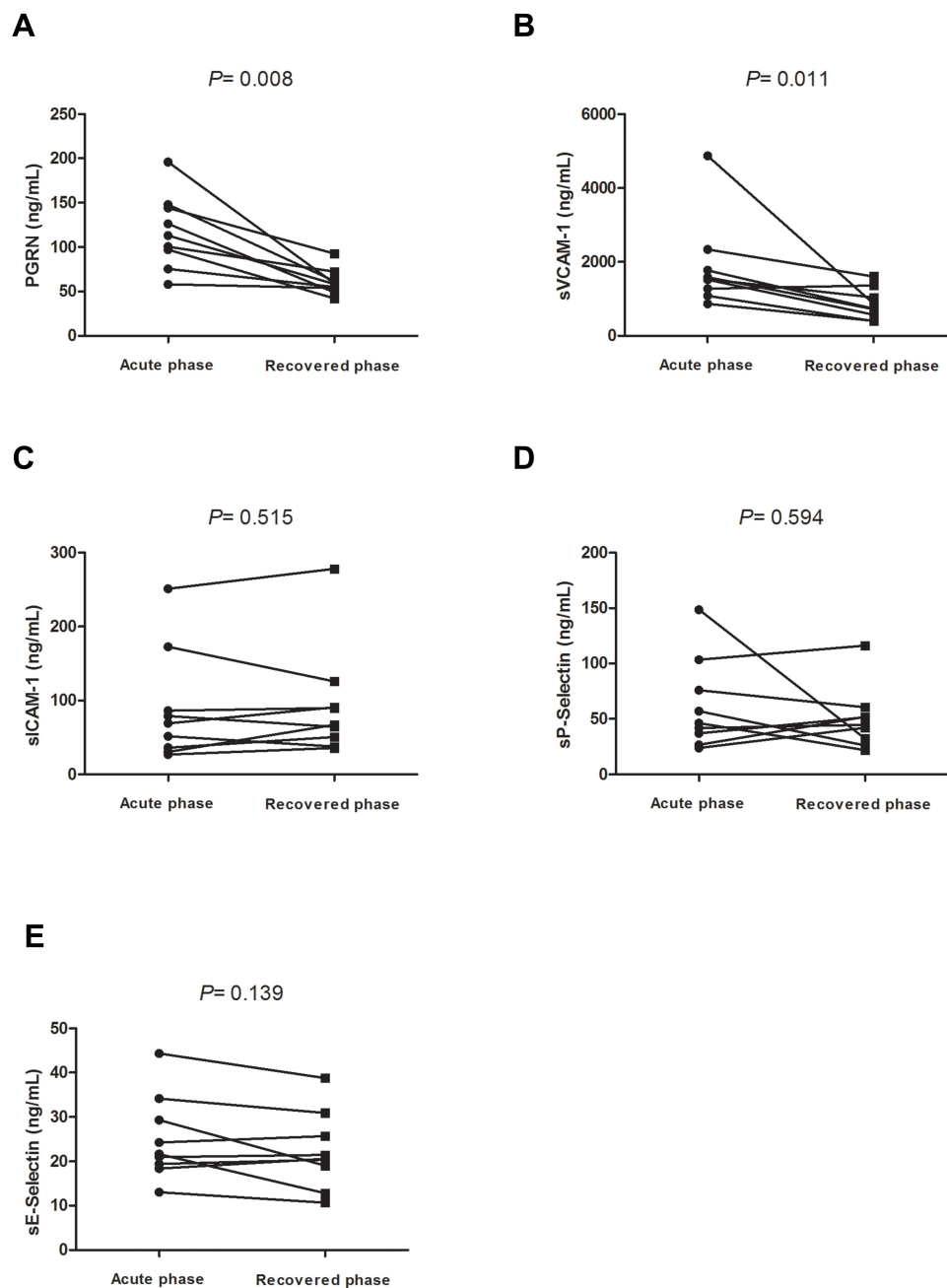
Figure 3 Serum levels of PGRN and sVCAM-1 in patients with COVID-19 were decreased following effective therapy. Serum levels of PGRN (**A**), sVCAM-1 (**B**), sICAM-1 (**C**), sP-selectin (**D**), and sE-selectin (**E**) in COVID-19 patients on hospital admission (acute phase) and discharge (recovered phase) were determined and compared. Wilcoxon signed-rank test was used to assess the differences. *P* values are indicated in the figures.

autopsy.[5] The mechanisms underlying angiogenesis in COVID-19 remain to be determined. Tan et al[29] reported on elevated angiogenic cytokines, eg, vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) in COVID-19 patients. Other factors, including PGRN, VCAM-1, and trace elements, such as copper, are also found to have a profound impact on angiogenesis.[30–32] We show here that both PGRN and sVCAM-1 are elevated in

COVID-19 patients, suggested a potential involvement of PGRN and sVCAM-1 in the formation of new vessels in COVID-19. Although the present study demonstrates that the levels of PGRN correlate positively with the levels of sVCAM-1, it remains unclear whether those factors have any direct and collaborative effect on the angiogenesis in COVID-19. Experimental studies are required to address this question.

Apart from the acute effects, SARS-CoV-2 infection has been associated with long-term damage to organs, particularly the heart.[33,34] A previous study of 100 German patients with COVID-19 showed that 60% of the cases had cardiac injuries even after recovery.[34] The underlying mechanisms remain obscure. However, considering PGRN is implicated in inhibition of NF-κB signaling-mediated inflammation, evidence from Thurner et al[21] may suggest that the long-term cardiac injuries are possibly associated with significantly decreased levels of PGRN due to the presence of PGRN autoantibodies. In addition, Pour et al[35] reported on significantly decreased levels of zinc in Iranian patients with critical COVID-19 and demonstrated that low concentrations of zinc were associated with poor outcomes of the disease. This finding may suggest an impaired role for zinc in the modulation of NF-κB signaling and redox signaling, as well as direct inhibition of viral entry and replication in COVID-19, as proposed elsewhere.[36,37] Together, these observations may suggest the importance of monitoring levels of endothelial activation markers, such as sVCAM-1, trace elements, such as zinc, and the proinflammatory factors, such as TNF-α in patients even recovered from SARS-CoV-2 infection.

It is well known that ICAM-1 also plays an important role in mediating the recruitment of leukocytes from circulation to sites of inflammation.[38] In line with previous findings,[4,8] the present work shows that serum levels of sICAM-1 are elevated in patients with COVID-19 as compared to healthy control, albeit not significantly higher due to small patient numbers. We show here that serum PGRN levels inversely correlate with the levels of ICAM-1 in patients with COVID-19. The reasons for this observation remain obscure in the current situation. One possible explanation would be that PGRN is able to inhibit the production of ICAM-1, because it has been shown that exogenous PGRN reduces the expression of ICAM-1 in human umbilical venous endothelial cells.[39] The regulatory mechanisms of ICAM-1 by PGRN and its implication in the pathogenesis of COVID-19 remain to be determined.

Evidence indicates an increase of P-selectin on the surface of platelets following SARS-CoV-2 infection.[40] Nevertheless, the present study did not show significant differences in levels of sP-selectin between the two groups, which is coincident with the finding from Goshua et al.[6] While P-selectin blockade may be helpful to alleviate the pathobiology of acute respiratory distress syndrome (ARDS) in patients with severe/critical COVID-19,[41] the present evidence does not support preventive usage of a P-selectin inhibitor in patients with mild/moderate COVID-19 to avoid thrombosis or ARDS.

The major limitation of this study is the small sample size and heterogeneity of the patients enrolled, so that some data may not be effectively analyzed, for instance, the significance of correlations between the variables. Second, the majority of the patients were mild/moderate cases that may not reflect the full picture of the patients with COVID-19. Third, the impact of co-infection with other organisms on the levels of serum PGRN and soluble adhesion molecules was not evaluated due to the small number of the cases.

In conclusion, although the sample size is relatively small, the present study shows elevated serum levels of both PGRN and sVCAM-1 in patients with COVID-19, suggesting their potential as biomarkers and roles in the pathogenesis of COVID-19. Further studies are warranted to strengthen these findings and investigate the potential roles and mechanisms of PGRN and sVCAM-1 in the pathogenesis of COVID-19.

Ethics Statement

This study was in compliance with the Helsinki Declaration and was approved by the Human Research Ethics Committee of the First People's Hospital of Zunyi (Registration number: 2020-03, Approved on 12 Mar, 2020). Since any non-medical contact with the patients or their lineal relatives is prohibited according to the institutional requirements for clinical management of COIVD-19 and the use of surplus clinical blood samples does not cause direct patient harm, a waiver of informed consent from patients was approved by the Human Research Ethics Committee of the First People's Hospital of Zunyi. Signed consents were obtained from healthy subjects before sample collection.

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Disclosure

The authors report no conflicts of interest in this work.

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