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IL-6 is a predictor and potential therapeutic target for coronavirus disease 2019-related heart failure: A single-center retrospective study

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ABSTRACT

Background: Inflammation is linked to coronavirus disease 2019 (COVID-19)-related heart failure (HF), but the specific mechanisms are unclear. This study aimed to assess the relationship between specific inflammatory factors, such as interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, interferon (IFN)-α, and IFN-γ, and COVID-19-related HF.

Methods: We retrospectively identified 212 adult patients with COVID-19 who were hospitalized at Shanghai Public Health Center from March 1 to May 30, 2022 (including 80 patients with HF and 132 without HF). High-sensitivity C-reactive protein (hs-CRP), procalcitonin (PCT), and inflammatory factors, including IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, IFN-α, and IFN-γ, were compared between patients with COVID-19 with and without HF.

Results: Patients with COVID-19 having and not having HF differed with regard to sex, age, hs-CRP, PCT, and IL-6 levels ($p < 0.05$). Logistic regression analysis indicated a significant positive association between IL and 6 and HF (odds ratio = 1.055; 95 % confidence interval: 1.019–1.093, $p < 0.005$). Sex, age, and hs-CRP were also associated with HF. Women had a greater risk of HF than men. Older age, higher levels of hs-CRP, and IL-6 were associated with a greater risk of HF.

Conclusions: In patients with COVID-19, increased IL-6 levels are significantly associated with COVID-19-related HF.

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which first emerged in 2019 and has spread rapidly worldwide since, becoming one of the most significant medical and economic challenges of recent times [1,2]. As of August 14, 2022, approximately 581.68 million COVID-19 cases and 6.4 million deaths had been confirmed globally [3]. Although COVID-19 primarily affects the lungs, causing interstitial pneumonia and acute respiratory distress syndrome (ARDS), it also significantly affects the cardiovascular system because of overlapping pathophysiological processes, with the most common conditions being arrhythmia (such as atrial fibrillation, ventricular fibrillation, and other rapid ventricular arrhythmias), acute myocardial infarction, fulminant myocarditis, and heart failure (HF) [4]. A recent study on patients with COVID-19 in Wuhan, China, showed that approximately 23 % of patients experienced HF; furthermore, patients with COVID-19 were particularly prone to myocardial injury [4,5]. Another retrospective study of 191 patients with COVID-19 in Wuhan showed that HF is the fourth-most common complication associated with COVID-19 [5]. Furthermore, a study of 131 patients with COVID-19 revealed that 49 % of those who died of HF had no prior history of cardiovascular disease [6]. These studies indicate a substantial burden of COVID-19-associated HF; however, the underlying factors associated with COVID-19 and HF remain to be understood.

According to recent studies, the mechanism underlying COVID-19-induced HF could be related to inflammation, a shared pathophysiological mechanism in both diseases. After binding to the angiotensin-

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converting enzyme 2 receptor on the epithelial cell surface of the lung, heart, and other organs, SARS-CoV-2 enters the host cell and begins to replicate rapidly [7], causing inflammatory cells to infiltrate the myocardium and endocardium. Associated inflammatory cells (such as neutrophils, monocytes/macrophages, and lymphocytes) congregate around the sites of virus infiltration, resulting in the activation and release of numerous cytokines [such as interleukin (IL)-1β, IL-6, and IL-8]. These cytokines significantly upregulate matrix metalloproteinases, protease-activated receptors, and nitric oxide synthase expression, leading to severe oxidative stress and, eventually, HF [8]. Furthermore, excessive inflammatory response causes pulmonary fibrosis, which stimulates the recruitment of inflammatory cells around the myocardial cells following tissue hypoxia, creating a vicious cycle [9].

Inflammation occurs during the rapid early stage of COVID-19, causing a "cytokine storm" hypothesized to contribute to HF pathogenesis [10–12]. Inflammation triggers the onset and progression of HF in patients with COVID-19, although its precise mechanism remains unknown. Consequently, investigating anti-inflammatory treatments for patients with COVID-19-related HF has emerged as a new research area. Understanding the pathogenesis of COVID-19 and its related complications is critical for designing targeted immunotherapy. In this study, we aimed to investigate potential inflammatory biomarkers and other clinical covariates associated with COVID-19-induced HF.

2. Materials and methods

2.1. Data collection

We retrospectively identified adult patients (≥18 years of age) admitted to the Shanghai Public Health Center, Shanghai, China, between March 1 and May 30, 2022, who were diagnosed with COVID-19 after testing positive for SARS-CoV-2 on the day of admission. COVID-19 diagnosis was based on the results of reverse transcription-quantitative polymerase chain reaction and the clinical and radiological standards of SARS-CoV-2 in respiratory tract samples, according to national and international guidelines and recommendations [13–17]. Patient records were reviewed 48 h after admission for diagnosis, treatment, and laboratory test results, focusing on demographics (age and sex), levels of myocardial enzymes [troponin, myoglobin, and brain natriuretic peptide (BNP)/N-terminal (NT)-proBNP], inflammatory indicators [high-sensitivity C-reactive protein (hs-CRP), procalcitonin (PCT)], and inflammatory factors (IL-1β, IL-2, IL-4, IL-5, and IL-6). Patients were classified as either HF (n = 132) or non-HF (n = 80). Clinical and laboratory data for most patients were collected within 48 h of admission. The exclusion criteria for the patients were as follows: those with a previous history of HF, rheumatic immune system diseases, and serious liver or kidney diseases at any point in their lives, including renal and liver failure. The Ethics Committee of the Shanghai Tongji Hospital approved this study (approval number: K-W-2022–021) (2022.8.1). The requirement for obtaining informed consent was waived owing to the retrospective nature of the study.

2.2. Sample processing

Within 48 h after admission, 5 mL of blood was collected from each patient. Blood samples were centrifuged at 3,500 rpm for 10 min using a TGL16D centrifuge (Hunan Maida Instrument Co., Ltd., Hunan, China). The supernatant obtained was stored in a low-temperature refrigerator at − 70 ‘ until further testing. Enzyme-linked immunosorbent assays were used to detect serum BNP, NT-proBNP, CRP, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, and IL-17 expression levels. Cardiac troponin I and myoglobin were detected using commercially available kits according to the manufacturer's instructions. All kits were produced by Shanghai Bioengineering Co. Ltd (Shanghai, China).

2.3. Diagnostic criteria

HF was diagnosed according to the 2021 European Heart Journal guidelines; BNP ≥ 35 pg/mL or NT-proBNP ≥ 125 pg/mL indicated HF [16]. Severe, common, and mild COVID-19 cases were defined according to the guidelines for the diagnosis and treatment of COVID-19 (trial version nine) [13] as follows:

(1). Mild cases: clinical symptoms were mild, and no pneumonia was detected upon imaging.
(2). Common cases: clinical manifestations were present, and pneumonia was visible upon imaging.
(3). Severe cases: Adults who met any of the following criteria:
1. Shortness of breath, respiratory rate ≥ 30 breaths/min.
2. In the resting state, oxygen saturation during air intake was ≤ 3 %.
3. Partial pressure of arterial blood oxygen (PaO_2)/oxygen concentration (FiO_2) ≤ 300 mmHg (1 mmHg = 0.133 kPa). For areas with high altitudes (more than 1000 m above sea level), PaO_2/FiO_2 calibration was performed as follows: PaO_2/FiO_2 × [760/atmospheric pressure (mmHg)].
4. Progressive aggravation of clinical symptoms in pulmonary imaging after 24–48 h. Internal lesions progressed by more than 50 %.

2.4. Statistical analyses

All data were analyzed using IBM SPSS Statistics 26 (IBM Corp., Armonk, NY, USA). The normality of quantitative data was tested and mean ± standard deviation was used to represent data that fit the normal distribution in addition to independent sample *t*-tests. Data that did not conform to the normal distribution were represented by the median (P25 and P75 indicate the 25th and 75th percentiles, respectively) and were compared using non-parametric Mann–Whitney *U* tests. Classified data were expressed as percentages (%) and compared using the Chi-square test or Fisher's exact probability method. Multivariate logistic regression was used to develop an HF prediction model for patients with COVID-19. The receiver operating characteristic (ROC) area under the curve (AUC) was used to assess the predictive value and calculate the best cut-off value. The tests were all two-tailed, and the results were considered statistically significant at $p < 0.05$.

3. Results

3.1. Patient characteristics

The demographic and clinical characteristics of the patients with COVID-19 included in this study (n = 212) are shown in Table 1. Patients with and without HF differed significantly in sex, age, and COVID-19 severity ($p < 0.05$; Table 1). The median age of the HF group was 72 years, and 43.8 % were men, whereas that of the non-HF group was 50 years, and 59.8 % were men. Overall, 2, 55, and 144 cases of severe, common, and mild COVID-19, respectively, were identified in the study group. Common cases were the most prevalent COVID-19 diagnoses in the HF group (53.7 %), whereas mild cases were the most prevalent in the non-HF group (81.8 %). Overall, the patients in the HF group were older than those in the non-HF group ($p < 0.001$), more patients with HF were women (56.2 %, $p < 0.001$), and more patients with HF had common cases of COVID-19 ($p < 0.001$) than patients without HF. Hypertension and diabetes were more prevalent in the HF group than in the non-HF group ($p < 0.005$).

HF, heart failure; COVID-19, coronavirus disease 2019; CHD, coronary heart disease; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 1
Baseline conditions for patients with and without HF.

	HF (n = 80)	Non-HF (n = 132)	χ^2/Z	*p*-value
Sex			5.193	0.023
Male [n (%)]	35 (43.8 %)	79 (59.8 %)		
Female [n (%)]	45 (56.2 %)	53 (40.2 %)		
Age [years]	72.00 (63.50, 83.00)	50.00 (34.25, 67.00)	-6.725	<0.001
HF index			28.300	<0.001
BNP group [n (%)]	11 (13.7 %)	66 (50.0 %)		
NT-proBNP group [n (%)]	69 (86.3 %)	66 (50.0 %)		
COVID-19 severity			31.000	<0.001
Mild [n (%)]	36 (45.0 %)	108 (81.8 %)		
Common [n (%)]	43 (53.7 %)	23 (17.4 %)		
Severe [n (%)]	1 (1.3 %)	1 (0.8 %)		
High blood pressure	28 (34.1 %)	14 (10.8 %)	17.297	<0.001
Diabetes	14 (17.1 %)	9 (6.9 %)	5.450	0.020
CHD	8 (9.8 %)	7 (5.3 %)	1.500	0.221

3.2. Elevated cytokine levels in patients with COVID-19 and HF

The levels of two skeletal muscle proteins (troponin and myoglobin), 11 plasma cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, IFN-α, and IFN-γ), PCT, and hs-CRP were evaluated to assess immune response disorders in patients with COVID-19 and HF (Table 2 and Fig. 1). The levels of troponin, PCT, and hs-CRP in the HF group were significantly higher than those in the non-HF group ($p < 0.05$). Furthermore, the levels of IL-6 in the HF group were significantly higher than those in the non-HF group ($p < 0.05$).

HF, heart failure; COVID-19, coronavirus disease 2019; Tn, troponin; Mb, myoglobin; PCT, procalcitonin; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; IL, interleukin; Hs-CRP, high-sensitivity C-reactive protein; TNF, tumor necrosis factor; D-2, D-Dimer; IFN, interferon.

3.3. Factors related to patients with COVID-19 and HF

The relationship between cytokines and HF severity was also analyzed (Table 3). Statistically significant variables in the univariate analysis (sex, age, and levels of troponin, PCT, hs-CRP, and IL-6) were included in the binary logistic regression analysis. The risk of HF was higher in women than in men, and the risk increased with age (Fig. 2A and B). The higher the hs-CRP and IL-6 levels, the greater the HF risk. We used an ROC curve to assess the ability of inflammatory factors to predict HF and combined the statistically significant indicators from the single factor analysis (Table 4 and Fig. 2). The AUC was 0.882, and the best cut-off value is shown in Table 4 (the highest Youden index). The results showed that the combination of ≥ 60 years with 4.32 pg/mL hs-CRP and 2.61 pg/mL IL-6 could be used to predict HF.

Table 2
Cellular immunity and inflammatory factors in patients with COVID-19 with and without HF.

	HF (n = 80)	Non-HF (n = 132)	Baseline	t/Z	*p*-value
Tn	0.10 (0.10, 0.10)	0.05 (0.02, 0.10)	<0.03	-5.625	<0.001
Mb	27.09 (15.40, 63.43)	26.90 (13.64, 48.90)	<70	-0.875	0.381
PCT	0.10 (0.10, 0.15)	0.10 (0.04, 0.10)		-3.510	<0.001
Hs-CRP	3.64 (0.50, 17.80)	1.95 (0.50, 3.79)	<10	-2.049	0.040
D-2	0.51 (0.29, 1.03)	0.25 (0.17, 0.48)	<1	−5.479	<0.001
TNF-α	0.34 (0.30, 0.87)	0.47 (0.09, 1.06)	<16.5	-1.123	0.261
IL-1β	2.76 (1.26, 6.40)	3.19 (1.26, 6.92)	<12.4	-0.060	0.952
IL-2	0.61 (0.30, 1.39)	0.87 (0.45, 1.49)	<7.5	-1.465	0.143
IL-4	0.58 (0.50, 0.73)	0.59 (0.54, 0.75)	<8.56	-0.854	0.393
IL-5	1.34 (0.91, 2.33)	1.49 (1.04, 2.34)	<3.1	-0.977	0.329
IL-6	2.79 (1.17, 6.56)	1.64 (0.81, 3.10)	<5.4	-2.964	0.003
IL-8	0.00 (0.00, 8.94)	0.00 (0.00, 9.09)	<20.6	-0.039	0.969
IL-10	1.26 (0.98, 2.42)	1.23 (1.00, 1.71)	<12.9	-1.221	0.222
IL-12	0.95 (0.73, 1.22)	0.94 (0.78, 1.13)	<3.4	-0.072	0.943
IL-17	2.55 (1.51, 4.16)	2.73 (1.69, 3.94)	<21.4	-0.387	0.698
IFN-α	0.78 (0.33, 1.87)	0.70 (0.41, 1.51)	≤8.5	-0.138	0.891
IFN-γ	1.40 (0.78, 2.97)	1.65 (1.18, 2.63)	<5.51	-1.537	0.124

β, regression coefficient; SE, standard error; Wald, Wald statistic; Df, degrees of freedom; OR, odds ratio; LCI, lower confidence interval; UCI, upper confidence interval; HF, heart failure; COVID-19, coronavirus disease 2019; Hs-CRP, high-sensitivity C-reactive protein; IL, interleukin

CI, confidence interval; AUC, area under the curve; IL-6, interleukin-6; PCT, procalcitonin; Tn, troponin; Hs-CRP, high-sensitivity C-reactive protein

3.4. Relationship between the levels of cytokines and biochemical and hematological markers of inflammation

To investigate why inflammation increases in patients with COVID-19-related HF, we analyzed whether IL-6 was linked to other inflammatory markers. The results showed that IL-6 levels were positively correlated with hs-CRP, PCT, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, and IFN-α levels (Fig. 3).

4. Discussion

According to the latest data from the World Health Organization, more than 5,816.8 million cases of COVID-19 have been confirmed worldwide, and more than 6.4 million deaths have been reported. Additionally, approximately 20 % of patients with COVID-19 experienced moderate to severe symptoms. In the present study, we analyzed the clinical data of patients with COVID-19 diagnosed at Shanghai Public Health Center, and observed significant differences in sex, age, PCT, hs-CRP, IL-6, D-dimer, diabetes, and high blood pressure between the HF and non-HF groups. Age, PCT, hs-CRP, and IL-6 were positively correlated with HF ($p < 0.05$). In addition, a greater proportion of patients with COVID-19 presenting with HF were women. Furthermore, hypertension and diabetes were more prevalent in the HF group than in the non-HF group. HF risk increased with age, and high hs-CRP and IL-6 expression levels were associated with HF. However, there were no significant differences in IL-2, IL-4, IL-5, IL-8, IL-10, IL-12, IL-17, and IFN-α levels between the HF and non-HF groups, suggesting that specific inflammatory factors are linked to COVID-19 and the development of HF. Increased IL-6 levels were significantly associated with increased HF risk. The predictive value of IL-6 for the COVID-19-related HF incidence was further evaluated based on ROC curve analysis. The predicted AUC of the IL-6 level alone was 0.626. The combination of sex, age, PCT, hs-CRP, Tn, and IL-6 was more accurate in predicting COVID-19-related HF, with an AUC of 0.882. These results indicate that IL-6 may be a biomarker and potential therapeutic target for HF following SARS-CoV-2 infection.

Previous research has indicated that the severity of COVID-19 is related to the levels of inflammatory factors in the plasma or serum of patients [8]. IL-6 levels were significantly high in patients with HF, with an AUC of 0.626. ROC curve analysis also indicated that, compared to individual factors, the combination of sex, age, PCT, hs-CRP, troponin, and IL-6 was a more accurate predictor of the severity of COVID-19-related HF, with an AUC of 0.882. Thus, cytokine levels were considerably elevated in patients with COVID-19, and IL-6 levels were closely related to COVID-19-associated HF.

Clinical studies have highlighted that the severity of COVID-19 is positively correlated with the level of inflammatory factors in the plasma or serum of patients [14]. Through correlation analysis, we found that IL-6 and hs-CRP, PCT, IL-1β, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12, IL-17, and IFN-α were positively correlated, suggesting that many inflammatory factors were involved in the clinical manifestation of

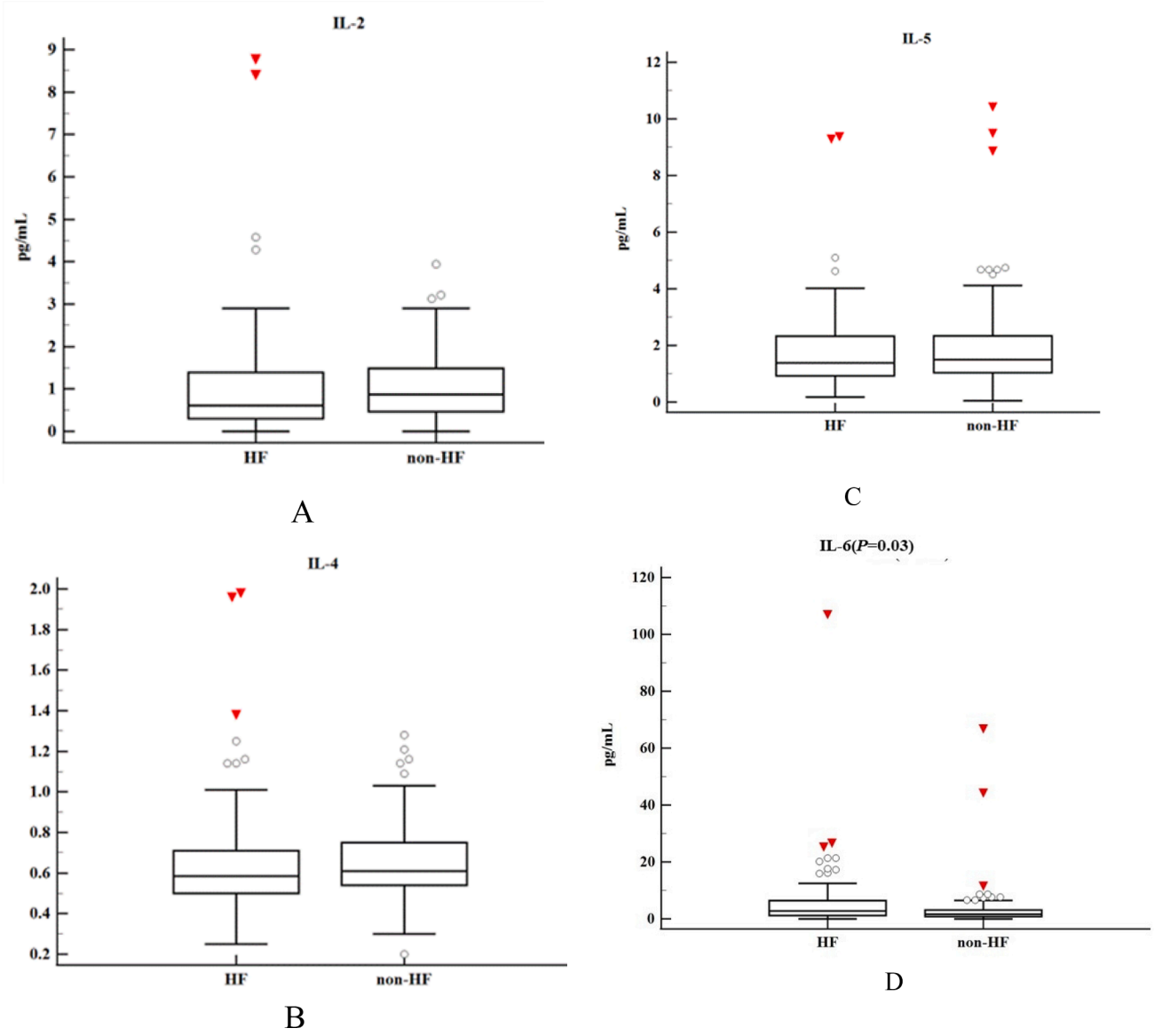
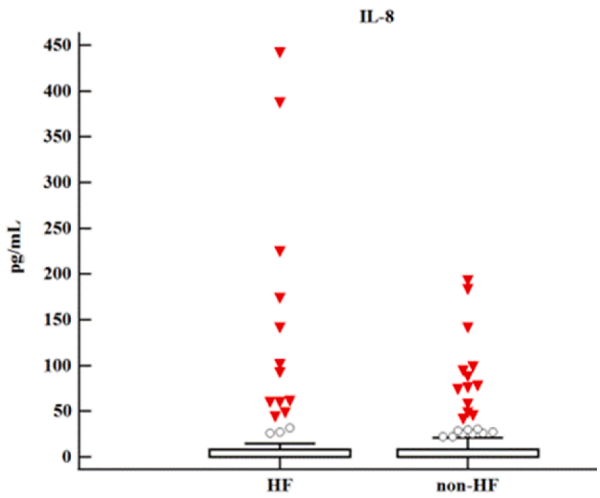


Fig. 1. Twelve cytokines, two skeletal muscle proteins, PCT, and hs-CRP were detected in patients with COVID-19 with HF upon admission. The levels of troponin, PCT, hs-CRP, and IL-6 were significantly higher in the HF group than in the non-HF group (n = 212); $p < 0.05$. HF, heart failure; BNP, brain natriuretic peptide; COVID-19, coronavirus disease 2019; IL, interleukin; Mb, myoglobin; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCT, procalcitonin; Tn, troponin; hs-CRP, high-sensitivity C-reactive protein.

COVID-19, with COVID-19-related HF being positively correlated with IL-6. A previous retrospective study indicated varying degrees of increase in the levels of inflammatory factors, such as IL-1β, IL-2, IL-6, IL-7, IL-8, and tumor necrosis factor-α in patients with COVID-19 [18]. The surge in these inflammatory factors is referred to as COVID-19 "cytokine storm," which creates a potentially fatal level of excessive inflammation mediated by the abnormal activation of natural killer cells, T cells, and macrophages, frequently leading to ARDS [18–22]. In the recently published BIOSTAT-CHF study involving 2,329 patients, increased IL-6 was an independent predictor of HF; for each 2-fold increase in IL-6 plasma concentration, the all-cause mortality of HF increased 1.16-fold [21,22]. In addition, a general population cohort showed that IL-6 is generally associated with new-onset HF [23], and a multicenter retrospective analysis of 150 patients in Wuhan revealed that the level of circulating IL-6 could be used as a clinical predictor of COVID-19 mortality [24]. The above research findings are consistent with our observations. IL-6 levels are closely associated with COVID-19-related HF.

IL-6 stimulates Th17 cells, inhibits T cells, and increases autoimmune reactions, which are characteristic of Th1 responses [25–28]. The combined effect of IL-6 on cardiomyocytes and fibroblasts may be important for the pathogenesis of HF [29]. In animal studies, infusion of IL-6 into mice caused centripetal hypertrophy and myocardial fibrosis and increased myocardial stiffness [30]. Furthermore, in vitro studies have shown that continuous IL-6 infusions can inhibit the contractility of isolated papillary muscle cells [31]. Therefore, these IL-6-related signaling pathways, including the sIL-6R and JAK-STAT pathways, may be targeted for reducing excessive inflammation and controlling "cytokine storms" in patients with COVID-19 [30].

Tocilizumab, a mIL-6R and sIL-6R inhibitor, was approved by the National Medical Products Administration of China in March 2020 for use in the treatment of severe COVID-19 in patients with elevated IL-6 levels [32–33], and its efficacy in ameliorating COVID-19 risk has been reported in several studies. For instance, a retrospective study revealed that abnormally elevated CRP levels decreased after routine



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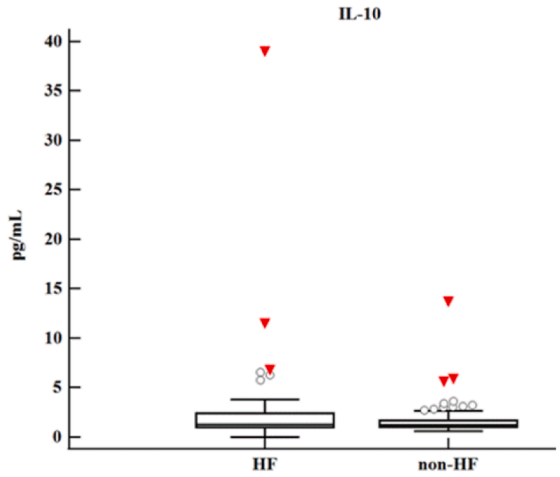

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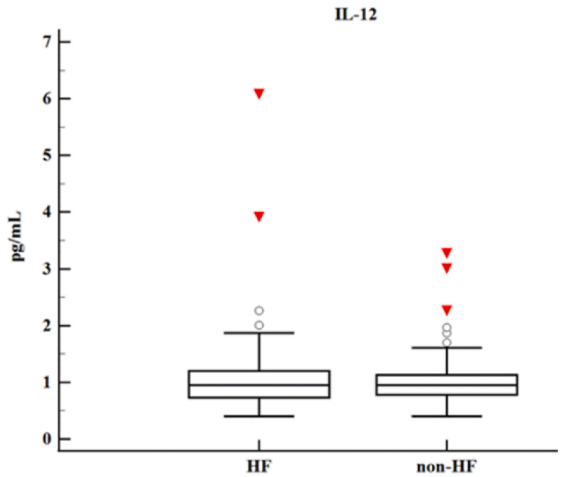

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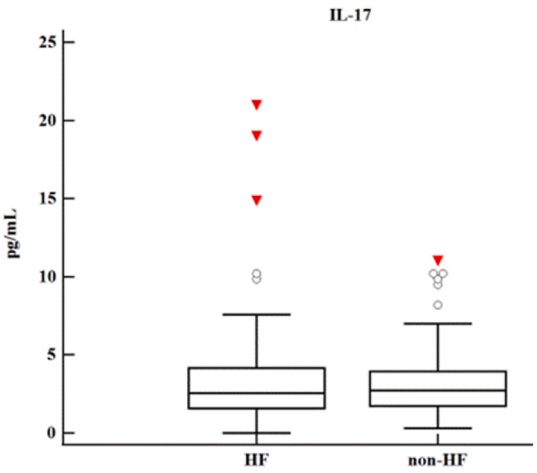

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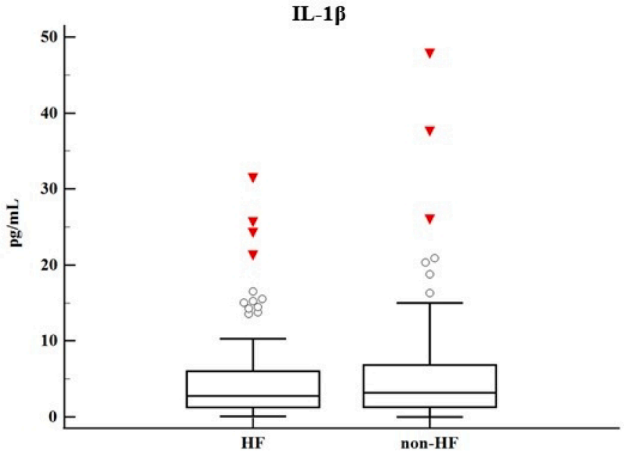

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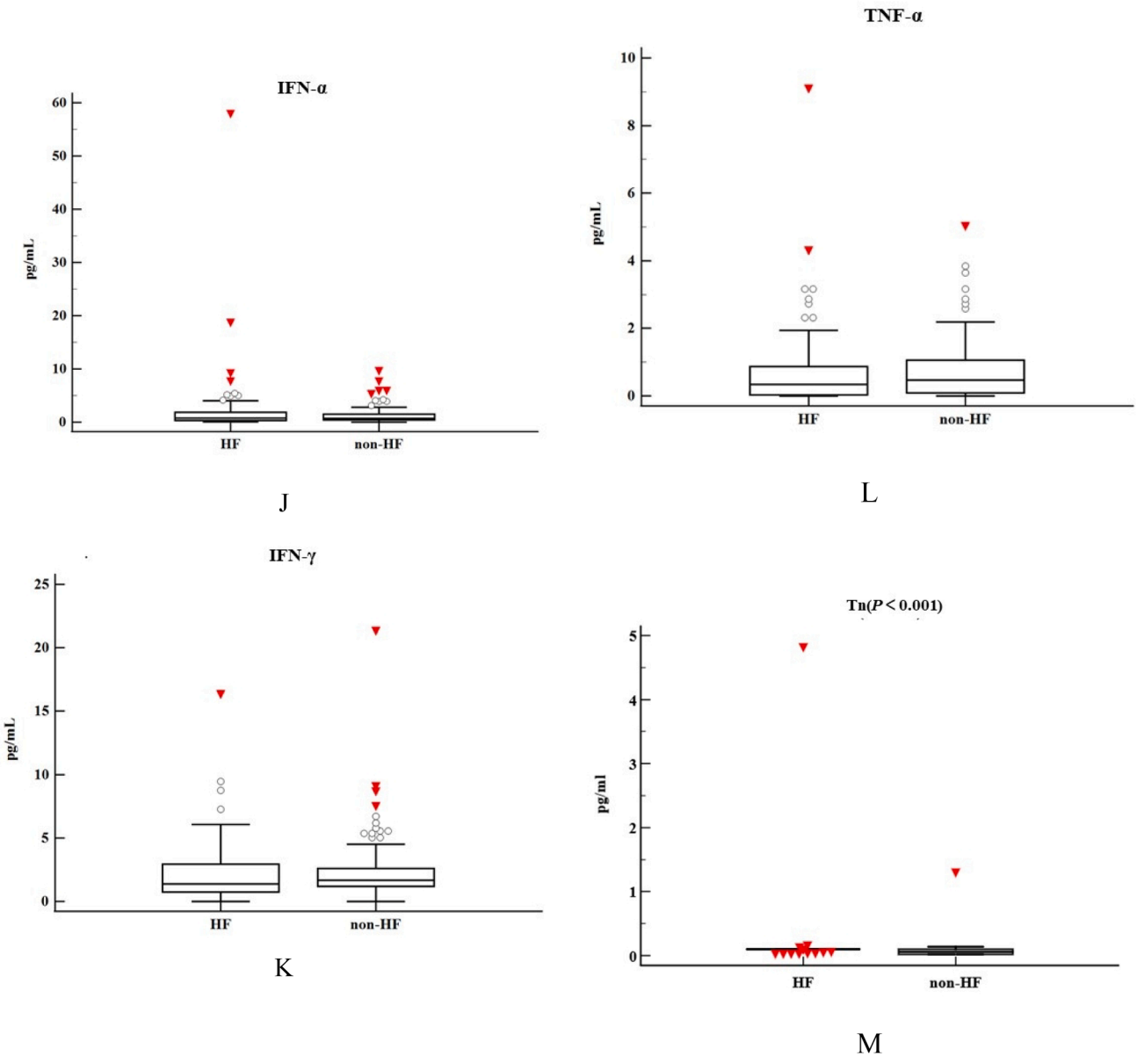
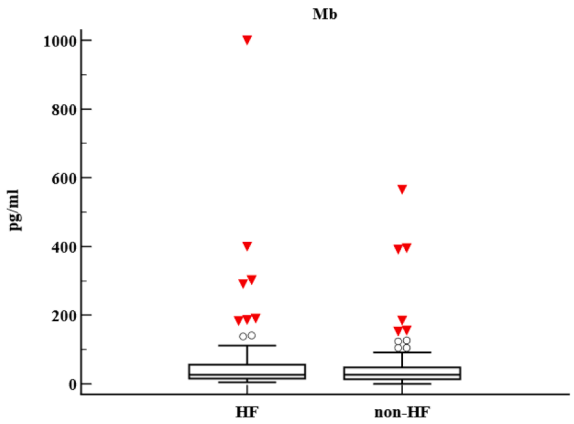


Fig. 1. (*continued*).

tocilizumab treatment [13,30,34]. Furthermore, an investigation in 2020 using data from 1,229 hospitalized patients with COVID-19 revealed that tocilizumab reduces the risk of death, intensive care unit admission rate, and mortality in patients with a CRP > 150 mg/L; however, it was ineffective in patients with CRP < 150 mg/L [10]. Moreover, the incidence of secondary infection increased in patients with severe COVID-19 treated with tocilizumab, and it was ineffective in patients with low levels of inflammation [14]. A large amount of evidence suggests that IL-6 plays a crucial role in the acute phase response of the liver after inflammation and is associated with autoimmunity [21]. Based on this evidence, IL-6 has been recognized as an attractive therapeutic target for many inflammation-related conditions. The above-mentioned IL-6 inhibitor is mainly used for the treatment of COVID-19 with high levels of inflammation. Our research results are expected to provide experimental evidence for the treatment of COVID-19-related HF with IL-6 inhibitors.

Research has found that IL-6 is one of the inflammatory factors leading to COVID-19-related HF, and some scholars have proposed that tocilizumab may also be effective in treating COVID-19-related HF. Experiments have shown that tocilizumab can reduce the expression level of NT-proBNP in patients with HF, which may reflect the cardioprotective effect of tocilizumab in addition to its anti-inflammatory effects [30]. In addition, a phase II clinical trial tested tocilizumab in patients with non-ST segment elevation myocardial infarction (non-STEMI). Preoperative administration of tocilizumab during coronary angiography reduced troponin T release and systemic inflammation [26]. However, the study showed that although IL-6 blockade reduced serum CRP, the levels of the chemokines CXCL10 and CCL4 increased, highlighting the complexity of the role of IL-6 in the inflammatory cascade response [18]. Although the targeted strategy of IL-6 inhibitors for HF has not yet been systematically and maturely studied, targeted anti-inflammatory therapy is a feasible approach for treating COVID-19. Further research on IL-6 inhibitors will help develop new treatment methods for COVID-19 to prevent HF.

Further research regarding IL-6 inhibition would facilitate the development of novel COVID-19 therapeutic strategies to prevent HF. The IL-6 inhibitors mentioned above are primarily used for treating patients with COVID-19 showing high levels of inflammation; however,



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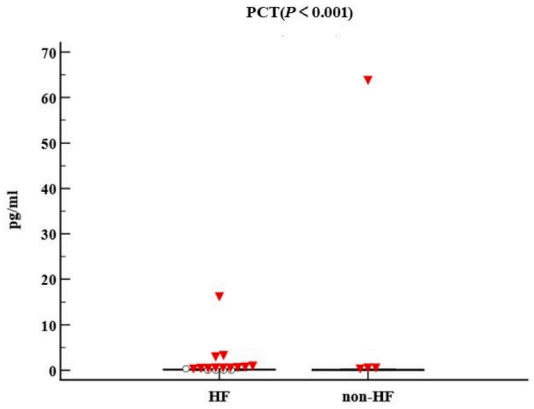

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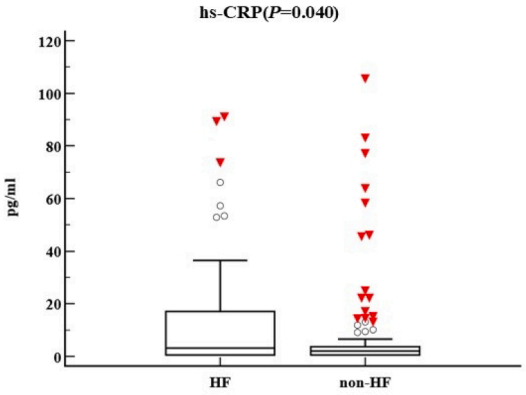

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Fig. 1. (*continued*).

the therapeutic and prognostic effects of these inhibitors on COVID-19-related HF must be investigated further [35–36]. Our findings establish a clinical foundation for using IL-6 inhibitors in the treatment of COVID-19-related HF.

Notably, we observed that female patients with COVID-19 had a higher HF incidence rate than male patients with COVID-19 in our dataset. In a recent study, we discussed sex differences in acute coronary syndrome development and subsequent HF [29,37]. The in-hospital mortality of female patients was significantly higher than that of male patients; women were more likely to develop HF after discharge. We compared the inflammatory indicators of female patients, and no sex differences in inflammatory factors were observed. Therefore, this sex difference in HF onset after COVID-19 warrants further investigation [38,39].

Table 3
Factors influencing HF in patients with COVID-19.

	β	SE	Wald	Df	*p*-value	OR	LCI	UCI
Sex (male)	1.134	0.471	5.803	1	0.016	3.109	1.235	7.825
Age	0.065	0.013	25.325	1	0.001	1.067	1.040	1.094
Hs-CRP	0.039	0.015	6.407	1	0.011	1.040	1.009	1.071
IL-6	0.054	0.018	8.851	1	0.003	1.055	1.019	1.093

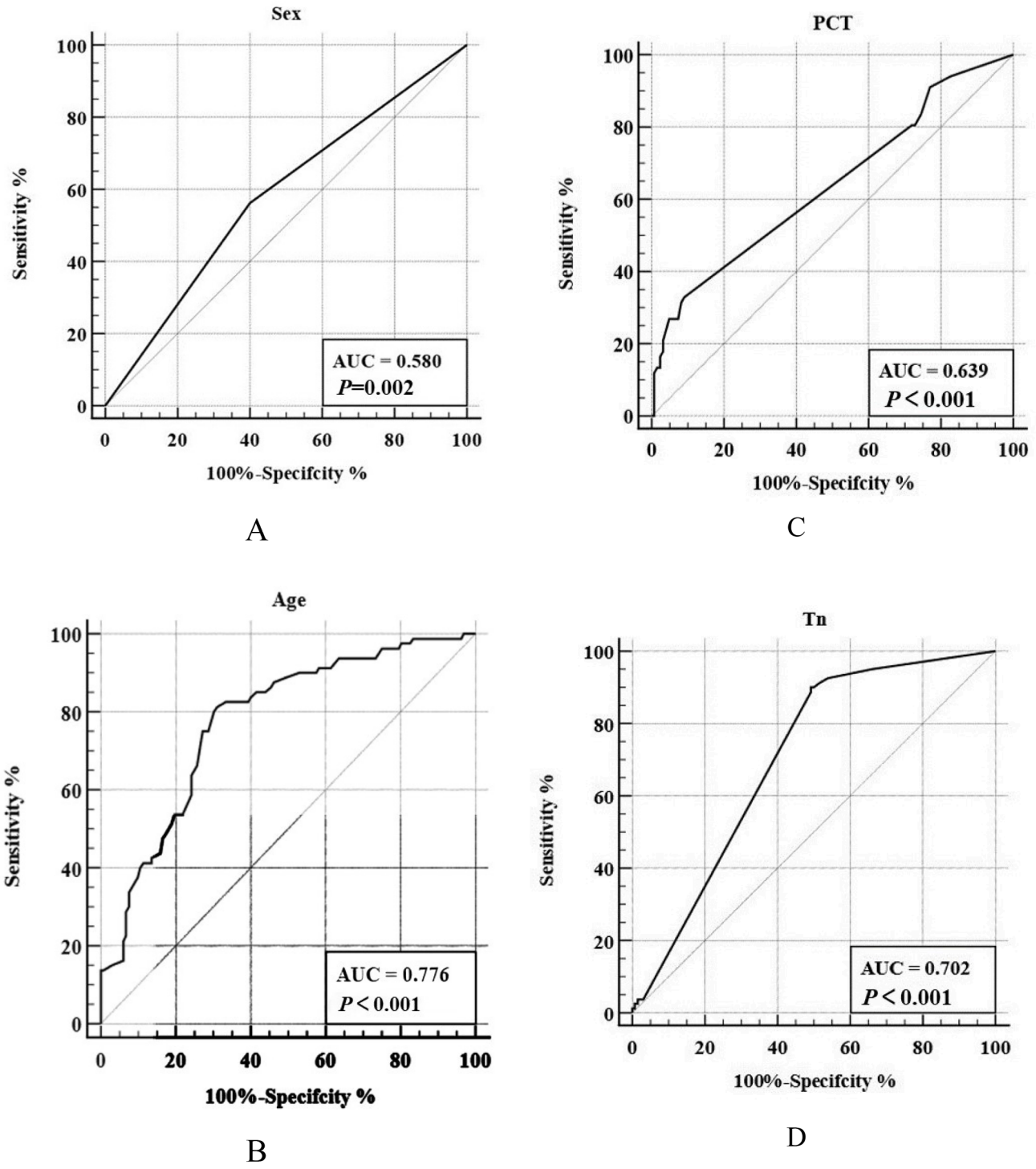
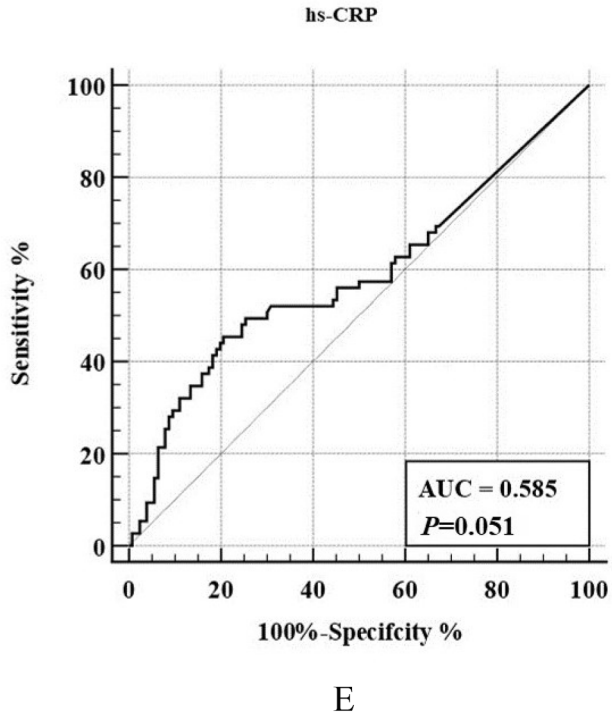


Fig. 2. ROC analysis of the cytokines in patients with HF. Cytokines, the levels of which differed significantly between patients with and without HF (Fig. 1), were selected for ROC analysis. Sensitivity, specificity, and AUC were calculated. $p < 0.05$. ROC, receiver operating characteristic; HF, heart failure; IL-6, interleukin-6; hs-CRP, high-sensitivity C-reactive protein; PCT, procalcitonin; Tn, troponin; AUC, area under the curve.



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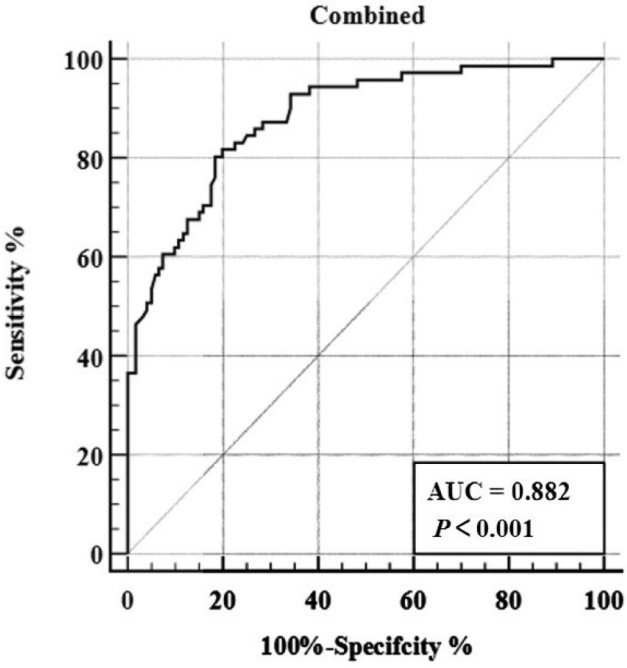

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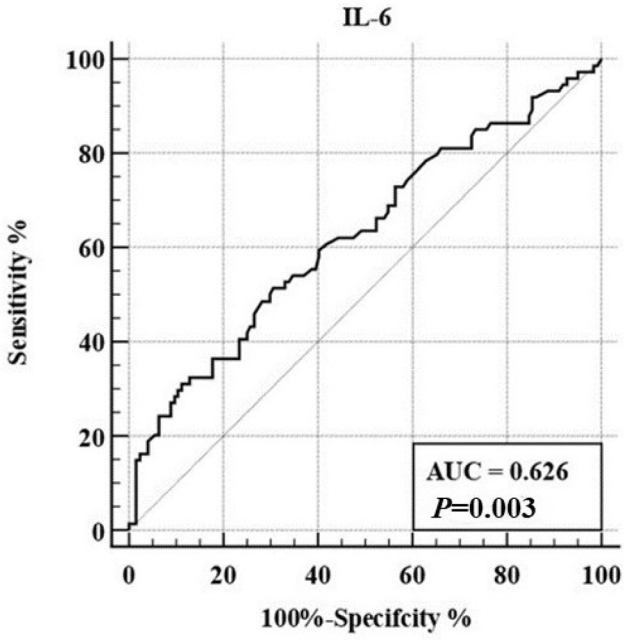
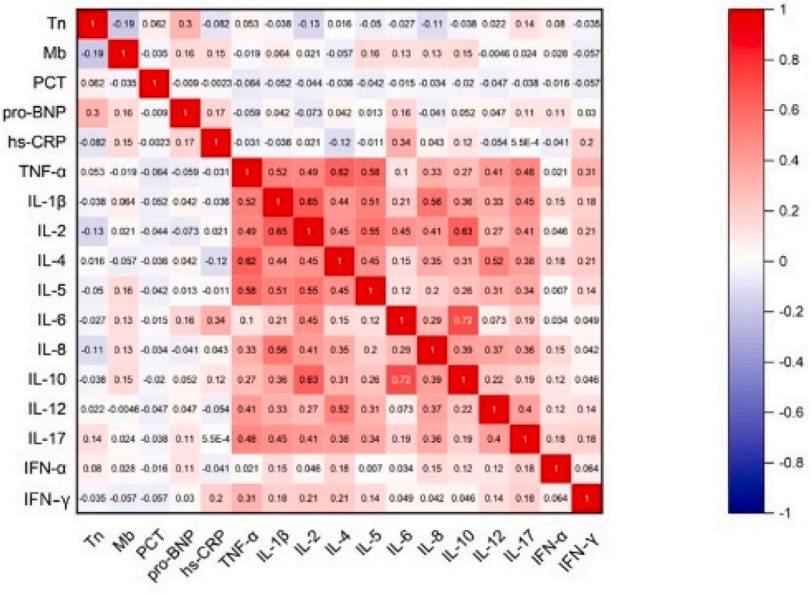


F

Fig. 2. (*continued*).

Table 4
Capacity of cellular inflammatory factors to predict HF.

	Sensitivity	95 % CI	Specificity	95 % CI	AUC	Youden index	Critical value
Sex	56.25 %	44.7 %-67.3 %	59.85 %	51.0 %-68.3 %	0.580	0.1610	1
Age	81.25 %	71.0 %–89.1 %	68.94 %	60.3 %-76.7 %	0.776	0.5019	60
Tn	90.00 %	81.2 %–95.6 %	50.77 %	41.9 %-59.6 %	0.639	0.4077	0.07
PCT	32.84 %	21.8 %–45.4 %	90.98 %	84.4 %-95.4 %	0.702	0.2382	0.1
Hs-CRP	45.33 %	33.8 %–57.3 %	79.37 %	71.2 %-86.1 %	0.585	0.2470	4.32
IL-6	51.35 %	39.4 %–63.1 %	69.35 %	60.4 %-77.3 %	0.626	0.2071	2.61
Combined	80.28 %	69.1 %–88.8 %	81.67 %	73.6 %-88.1 %	0.882	0.6195	0.69



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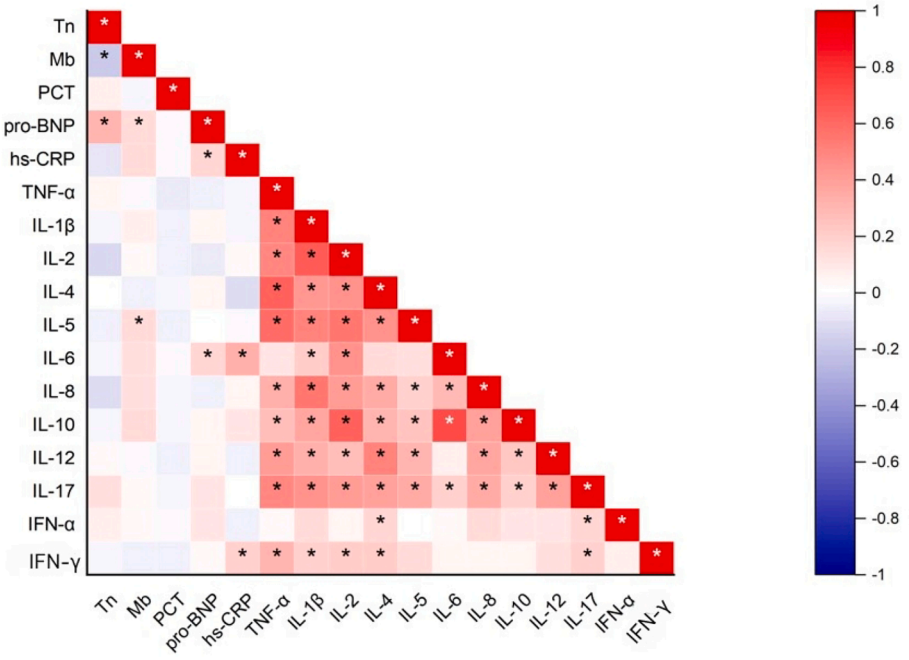

B

Fig. 3. Correlation between laboratory markers for hyperinflammation and cytokine levels. Plasma levels of IL-6 and Hs-CRP, PCT, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, and IFN-α were related, and the correlation coefficients were calculated using Spearman's correlation coefficient. Red and blue indicate positive and negative correlations, respectively. *$p < 0.05$. IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; Mb, myoglobin; PCT, procalcitonin; Tn, troponin; hs-CRP, high-sensitivity C-reactive protein. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Our study had several limitations. First, it was a single-center retrospective controlled study involving only 212 Chinese patients, with a small sample size and a single ethnicity. It is necessary to expand the sample size further and combine multiple centers and different populations to confirm our conclusion. Second, this study could not assess the causal relationship between IL and 6 expression levels and COVID-19-related HF onset; prospective cohort studies are needed to confirm any causal relationship between these two factors. Third, not all patients had complete data on inflammatory factors (including IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, and IL-17); thus, the role of these factors in predicting HF may be underestimated, and owing to differences in the testing time of the included patients, simultaneously obtaining plasma was unfeasible. Fourth, the half-life and optimal testing period of various inflammatory factors may differ, and the plasma isolated from peripheral blood may not fully reflect the immune reactions occurring in the tissue. Moreover, although we concluded that the increase in IL-6 levels was strongly correlated with COVID-19-related HF, only two patients were seriously ill, which was a significant limitation of the study's design. Fifth, the failure to investigate the differences in IL-6 levels between pre- and post-COVID-19 onset is an important limitation of the current research. Sixth, the results of ROC analysis are relative; thus, it is necessary to interpret cut-off values and cytokine predictions carefully.

5. Conclusions

The results of this study indicate that high inflammatory responses and elevated IL-6 levels were strongly correlated with COVID-19-associated HF. Therefore, IL-6 can be a specific biomarker for predicting HF occurrence in patients with COVID-19 and for developing new targeted treatments to improve disease outcomes and prognosis. Although several studies have confirmed the link between inflammatory biomarkers and COVID-19, clinically targeted anti-cytokine therapy is still in its early stages of development. Hence, further experimental evidence is required to ultimately provide appropriate treatments for patients with COVID-19.

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CRediT authorship contribution statement

Yan Xi: Writing – original draft. **Yu Mao:** Writing – original draft. **Wei Zhu:** Formal analysis. **Peng Xi:** Methodology. **Feifei Huang:** Data curation. **Hongwei Tan:** Software. **Xudong Liao:** . **Lin Zhou:** Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Acknowledgments

Not applicable

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