Original Article

The Diagnostic and Predictive Value of Biomarkers for Pulmonary Fibrosis in Patients with Coronavirus Disease 2019

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Abstract

Introduction: In coronavirus disease 2019 (COVID-19), particularly in older people, dysregulated immune response and aberrant repair can result in varied severity secondary pulmonary fibrosis (PF). By detecting some indicators, the occurrence and prognosis of fibrosis can be measured, providing directions for COVID-19 treatment. **Methods:** The research study lasted for 3 months and involved 88 COVID-19 patients. According to the chest radiological examination, 47 (53.41%) individuals were found to have no PF, while 41 (46.59%) showed PF. Clinical data such as inflammation markers, imaging findings, blood gas analysis, and hospital stay length were collected. **Results:** With area under the curve values of 0.7413, 0.7741, and 0.7048, respectively, and the study of the receiver operating characteristic curve demonstrated that mucin 1 (MUC1), carcinoembryonic antigen (CEA), and CXC chemokine receptor 10 (CXCL10) could diagnose the presence of COVID-19 PF. To evaluate the possibility of PF following severe acute respiratory syndrome coronavirus-2 infection, we established particular values for MUC1, CEA, and CXCL10 (1.296 ng/ml, 4.315 ng/ml, and 32.77 ng/ml, respectively). The survival curve for hospital days indicated that the length of hospital stays positively correlated with these three factors ($P < 0.01$). Transforming growth factor-beta did not correlate significantly with the severity of COVID-19 or PF. **Conclusion:** The results of this study suggested that the MUC1, CEA, and CXCL10 can be employed to explore the severity of secondary PF in COVID-19.

Keywords: Carcinoembryonic antigen, coronavirus disease 2019, CXC chemokine receptor 10, mucin 1, pulmonary fibrosis, transforming growth factor-beta

Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-caused disease, commonly referred to as coronavirus disease 2019 (COVID-19), has spread quickly worldwide and resulted in a pandemic.[1] The Omicron variant is the main epidemic and the most severe novel coronavirus variant worldwide.[2,3] However, there is still a chance that persons of all ages might acquire a severe disease from the Omicron variant, with older ages being associated with more comorbid conditions and poorer outcomes. A crucial aspect of "severe COVID-19 pulmonary fibrosis (PF)" is a pathological outcome of chronic and acute interstitial lung diseases connected to defective wound healing. Patients with PF may have poor prognoses. In the near partial of those with moderate–to-severe COVID-19 pneumonia, decreased lung diffusion may occur.[4] The disease's key histological characteristics include affected alveolar epithelium rebuilding, fibroblast persistence, abnormal extracellular matrix (ECM) component deposition, including collagen deposition, and the breakdown of normal lung architecture.[5] Therefore, predicting PF is extremely important for clinicians to identify the severity of the disease and adjust treatment in time to avoid continued deterioration. No standard for assessing lung PF risk using COVID-19 is available yet. Unluckily, there is insufficient research on the processes that lie behind post-COVID-19 PF. As a result, we aim to develop preliminary criteria for evaluating the risk of fibrosis in COVID-19 patients. To determine the risk of secondary PF in COVID-19 patients, this study uses the markers mucin 1 (MUC1), CXC chemokine

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receptor 10 (CXCL10), carcinoembryonic antigen (CEA), and transforming growth factor-beta (TGF-β). It also investigates whether these markers can predict severe pneumonia to determine the prognosis.

Human type II alveolar epithelial cells (AECs) usually express the MUC1 on their surface. Recent research shows that the degree of MUC1 which correlated with COVID-19 severity can be utilized as a diagnostic estimation signal.[6,7] In both innate and adaptive immune responses, TGF-β is essential. When defending against infection, many immune cell types can generate and secrete TGF-β, albeit excessive amounts can prevent effective immune responses. This has been noticed in many respiratory viral infections.[8] The differentiation of fibroblasts into myofibroblasts is another process aided by TGF-β. According to Colarusso *et al*., who identified greater IL-1a, CXCL10, and TGF-β plasma levels in post-COVID-19 people who displayed ground-glass opacities in the chest CT scan, TGF-β may have a role in the mechanisms behind the post-COVID-19 sequelae of ECM remodeling.[9] CXCL10 promotes the Th1-type CD4+ and CD8+ effector T cells recruitment to infected or inflamed tissues[10] and involved in regulating the progression and intensity of inflammation brought on by SARS-CoV-2.[11-13] In COVID-19 patients, Ravindran *et al*. assessed the immune response's dynamics. They identified that several chemokines and cytokines (SCGF-β, MCP-1, IL-2Rα, CCL5, Gro-α, G-CSF, eotaxin, and CXCL10) were substantially higher upon hospital admission. Noteworthy, only CXCL10 levels decreased after their health improved.[13] The glycoprotein CEA was used as a tumor marker to track tumor progression.[14] Cancers of the respiratory system or digestive system, gonorrhea, and chronic inflammatory diseases such as PF have been associated with CEA.[15] High CEA expression has been observed in the metaplastic bronchiolar and type II alveolar epithelia of lung tissues from PF patients after immunohistochemical staining.[16] Numerous investigations of COVID-19 autopsy and biopsies have identified extensive interstitial fibrosis and type II AEC hyperplasia, which are identical to the pathological alterations observed with PF.[17] Therefore, it has been hypothesized that CEA may play a role in the development of fibrosis in COVID-19 pneumonia.

MUC1, CXCL10, and CEA were examined in the current investigation as prospective PF indicators following infection with SARS-CoV-2. Their correlation with the severity of COVID-19 and the length of hospital stays and their potential utility for patient classification were also examined.

Methods

Study enrollment criteria

The ethics committee authorized the research presented here. Between December 18, 2022, and January 16, 2023, 88 COVID-19 cases and 50 healthy people were recruited for this study at our hospital. Oropharyngeal swab specimens were used for reverse transcriptase polymerase chain reaction and were confirmed positive when Ct ≤ 35.0. According to the severity of the disease using the Infection Disease Society of America[18] complemented with the WHO criteria,[19] patients were evaluated by specialist pulmonologists using clinical and laboratory criteria to stratify them in the following groups: moderate patients should have a persistent high fever for more than 3 days, along with coughing, feeling short of breath, etc., but a respiratory rate of <30 beats/min and an oxygen saturation of more than 94% on room air. Chest radiography revealed pneumonia or fibrosis symptoms typical with new coronavirus infections. Patients who were severe should breathe ≥30 times/min; the oxygen saturation was ≤94% on room air. Moreover, the critical patients who presented acute respiratory distress syndrome (ARDS) and required invasive mechanical ventilation were also included in this group. All patients were classified into two groups based on the results of a CT scan: PF (n = 37) and nonpulmonary fibrosis (NPF; n = 51). The patients' previous physical examination data were checked to confirm that there was no PF change, and the patients with PF disease were excluded Supplement Table 1. Healthy people came from physical examination center of our hospital and rule out underlying medical conditions.

ELISA

Serum from patients was drawn (3000 rpm, 5 min, room temperature) and kept at − 20°C. The enzyme-linked immunosorbent assay was used to measure MUC1 (E-EL-H0616c, detection range: 0.16–10 ng/mL, Elabscience, China), TGF-β (E-EL-H1587c, detection range: 31.25–2000 pg/mL, Elabscience, China), and CXCL10 (E-EL-H10050c, detection range: 7.81–500 pg/mL, Elabscience, China). Each serum sample was done in triplicate. Standard curve detected 8 concentrations, repeated 2 times, $R^2 \geq 0.99$.

Carcinoembryonic antigen determination

The detection method of CEA was Access Immunoassay Systems (BECKMAN COULTER 33200, Reagent lot#395012, USA) in our hospital's clinical laboratory, and the detection ranges of CEA were 0.1–1000 ng/ml; each batch was corrected according to the standard products (n = 4).

Data collection

All information on demographic characteristics, underlying medical issues, diagnostic tests, length of hospital stay, choices for treatment, and prognosis were extracted from electronic medical records. Venous blood samples were collected after fasting for 12 h in the morning, 1 day after admission, and were analyzed within 2 h. All data were checked by two doctors.

Statistical analysis

The nonnormal distribution measures were reported as median (quartile), while categorical and continuous variables were represented as n (%) and median (interquartile range). All data were statistically examined using the GraphPad 8.0 program. The count data were presented as samples and

percentages, the sample rate comparison was carried out using the Fisher's exact or Chi-square test to compare categorical and continuous variables, and the between-group comparisons were made using the Mann–Whitney *U*-test. The Kruskal–Wallis rank sum test evaluated the difference between the group of severe pneumonia and moderate pneumonia, and the diagnostic value of IL-6, CRP, PCT, SF, WBC/LYM, and CEA was assessed by logistic regression and receiver operating characteristic (ROC) curve, and the difference in $P < 0.05$ was statistically significant.

Results

Patient characteristics

This study comprised 88 patients with COVID-19 pneumonia who satisfied the criteria, including 49 males and 39 females. Among them, there were 41 (46.6%) patients in the secondary PF group and 47 (53.4%) patients in the NPF group, and the relevant population baseline data are detailed in Supplementary Table 1. In patients with COVID-19 pneumonia, man had a higher proportion in PF ($P < 0.05$). Analysis of baseline data found that SARS-CoV-2 infection with PF had a higher proportion of severe patients and a worse oxygenation index [Table 1].

Changes in inflammatory makers in coronavirus pulmonary fibrosis

A variety of inflammatory indexes were collected from the two groups, including leukocytes, lymphocytes, ferritin, procalcitonin, and IL-6, and statistical analysis showed that most of the inflammatory indexes were not related to whether the infection with SARS-CoV-2 had interstitial changes, except for ferritin in the PF group than NPF [Table 2]. Through this result, we found that inflammatory indexes cannot be used to predict secondary PF after SARS-CoV-2 infection.

Heterogeneity of fibrosis markers in patients with coronavirus disease 2019

We acquired CEA data from these COVID-19 patients and tested their remaining clinical serum samples for MUC1, TGF-β, and CXCL10 by ELISA methods. CEA levels were considerably elevated among individuals with PF compared to those without [$P < 0.01$, Figure 1a]. MUC1 and CXCL10 were also significantly elevated ($P < 0.01$) [Figure 1b and c]. However, the TGF-β was not statistically significant between these tow groups [Figure 1d].

Mucin 1, transforming growth factor-beta, carcinoembryonic antigen, and CXC chemokine receptor 10 diagnostic effectiveness analysis for fibrosis in coronavirus disease 2019 patients

According to the ROC curve, the CEA, CXCL10, and MUC1 test values after admission can predict the incidence of fibrosis with area under the curves of 0.7413 (0.6075–0.8751), 0.7741 (0.6670–0.8813), and 0.7048 (0.5943–0.8153). The optimal threshold that distinguishes COVID-19 patients without fibrosis and with fibrosis of CEA was 4.315 ng/ml, with a sensitivity of 69.23% and specificity of 80.65% [$P < 0.01$, Figure 2a]. In comparison, the optimal threshold of CXCL10 was 32.77 ng/mL, with a sensitivity of 65.71% and a specificity of 83.78% [$P < 0.001$, Figure 2b]. The optimum threshold for differentiating COVID-19 individuals with and without MUC1 fibrosis was 1.296 ng/mL, with a sensitivity of 60.87% and a specificity of 71.79% [$P < 0.01$, Figure 2d]. However, the TGF-β had no significant difference between COVID-19 patients with or without PF [Figure 2c].

Correlation of fibrosis markers with coronavirus disease 2019 patient severity

There were 51 serums of healthy individuals (male = 25, female = 26; without underlying medical conditions)

Table 1: The individual's clinical features according to their level of pulmonary fibrosis

	PF (*n*=41), *n* (%)	NPF (*n*=47), *n* (%)	*P*
Sex			
Male	27 (65.85)	22 (46.81)	0.0313*
Female	14 (34.15)	25 (53.19)	
Age			
≤60	5 (12.19)	4 (8.51)	0.5473
61–80	24 (58.53)	27 (57.45)	
≥81	12 (29.27)	16 (34.04)	
Underlying medical conditions	36 (87.80)	40 (85.11)	0.8389
Hypertension	26 (63.41)	31 (65.96)	0.7677
Type 2 diabetes	15 (36.59)	13 (27.66)	0.2232
Cancer	14 (34.15)	15 (31.91)	0.7628
Chronic lung disease	7 (17.07)	8 (17.02)	>0.9999
Oxygenation index	235.0392857 (140.0–404.0)	328.0554976 (169.0–531.0)	0.0077**
Hierarchical			
Moderate	16 (39.02)	29 (61.70)	0.0029**
Severe	25 (60.97)	18 (38.29)	

*P<0.05, **P<0.01. PF: Pulmonary fibrosis, NPF: None pulmonary fibrosis

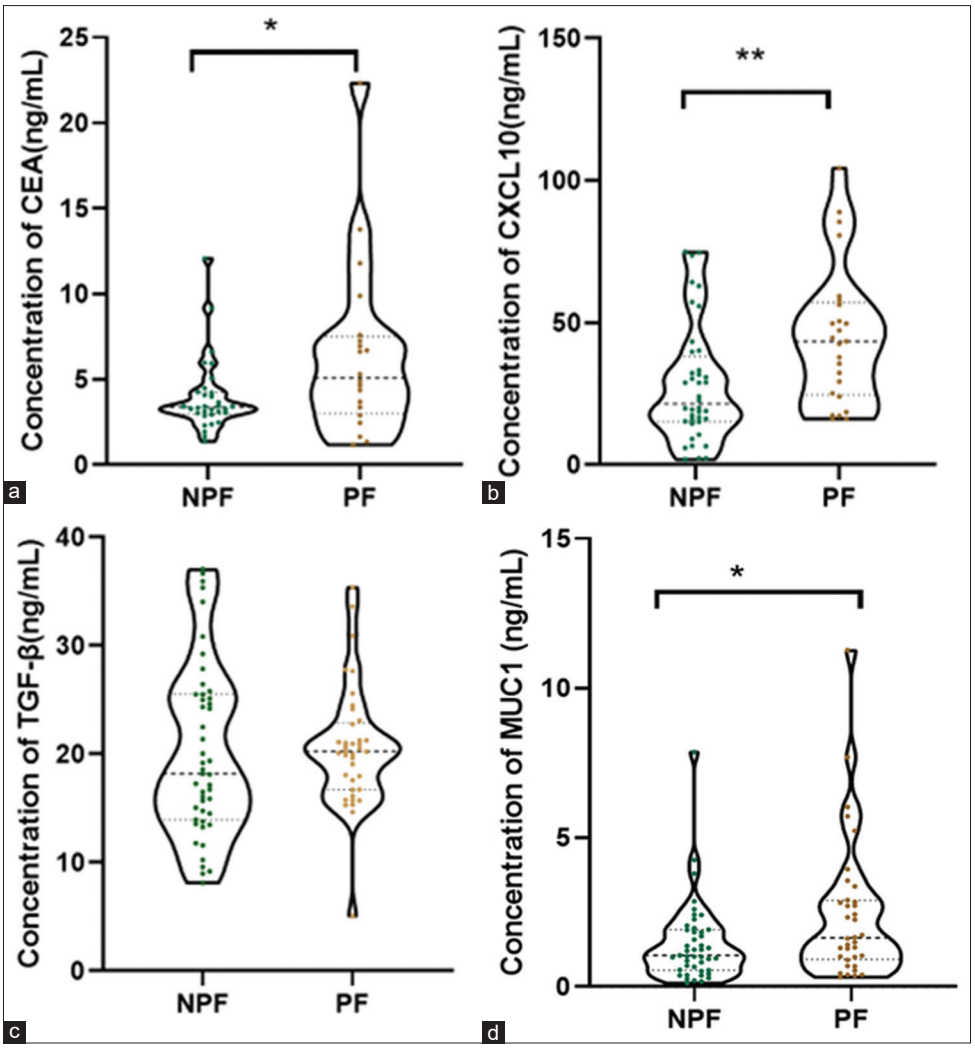

Figure 1: The level of fibrosis biomarkers in coronavirus disease 2019 (COVID-19) patients (a) The difference of carcinoembryonic antigen levels in COVID-19 patients with and without fibrosis; (b) The difference of CXC chemokine receptor 10 levels in COVID-19 patients with and without fibrosis; (c) The difference of Transforming growth factor-beta levels in COVID-19 patients with and without fibrosis; (d) The difference of Mucin 1 levels in COVID-19 patients with and without fibrosis. *P<0.05, **P<0.01

Table 2: Inflammatory indexes between pulmonary fibrosis and none pulmonary fibrosis

	PF	Non-PF	*P*
Leukocyte (10^9/L)	8.72 (3.9–18.4)	8.06 (1.9–16.9)	0.9407
Lymphocyte (10^9/L)	1.04 (0.17–2.07)	1.29 (0.17–2.7)	0.8943
CRP (mg/mL)	33.53 (1.01–98.7)	47.56 (1.3–109)	0.3966
PCT (ng/mL)	0.33 (0.02–1.45)	0.48 (0.04–0.75)	0.7259
SF (ng/mL)	802.51 (154–1873)	509.51 (103.9 1080)	0.0385*
IL-6 (pg/mL)	173.51 (2–1158)	72.73 (2–236)	0.2711

*P<0.05. IL-6: Interleukin 6, CRP: C-reactive protein, SF: Serum ferritin, PCT: Procalcitonin, PF: Pulmonary fibrosis

collected for detecting MUC1, CXCL10, and TGF-β and its CEA by ELISA Supplementary Table 2. We found that CEA and MUC1 were substantially upregulated in the COVID-19 group than the control group and had higher levels of disease exacerbation (P < 0.001) [Figure 3a and d]. However, compared with the control group, CXCL10 was not statistically significant in patients with moderate COVID-19 pneumonia, but it was increased considerably in the severe COVID-19 group (P < 0.01) [Figure 3b]. In addition, COVID-19 patients had greater TGF-β, unrelated to the disease development [Figure 3c].

The association between fibrosis indicators and hospital stay length

Seventy-four patients showed improvement and were released after 60 days, whereas 14 died. We illustrate the COVID-19 patient survival curves based on days spent in the hospital [Figure 4]. The fibrosis markers' test results showed that the patients were split into two groups. According to the results of the log-rank test, there was a significant difference in the number of days spent in the hospital between the two groups; the longer the days spent in the hospital, along with CXCL10 (P < 0.05) and MUC1, the higher the CEA (P < 0.05).

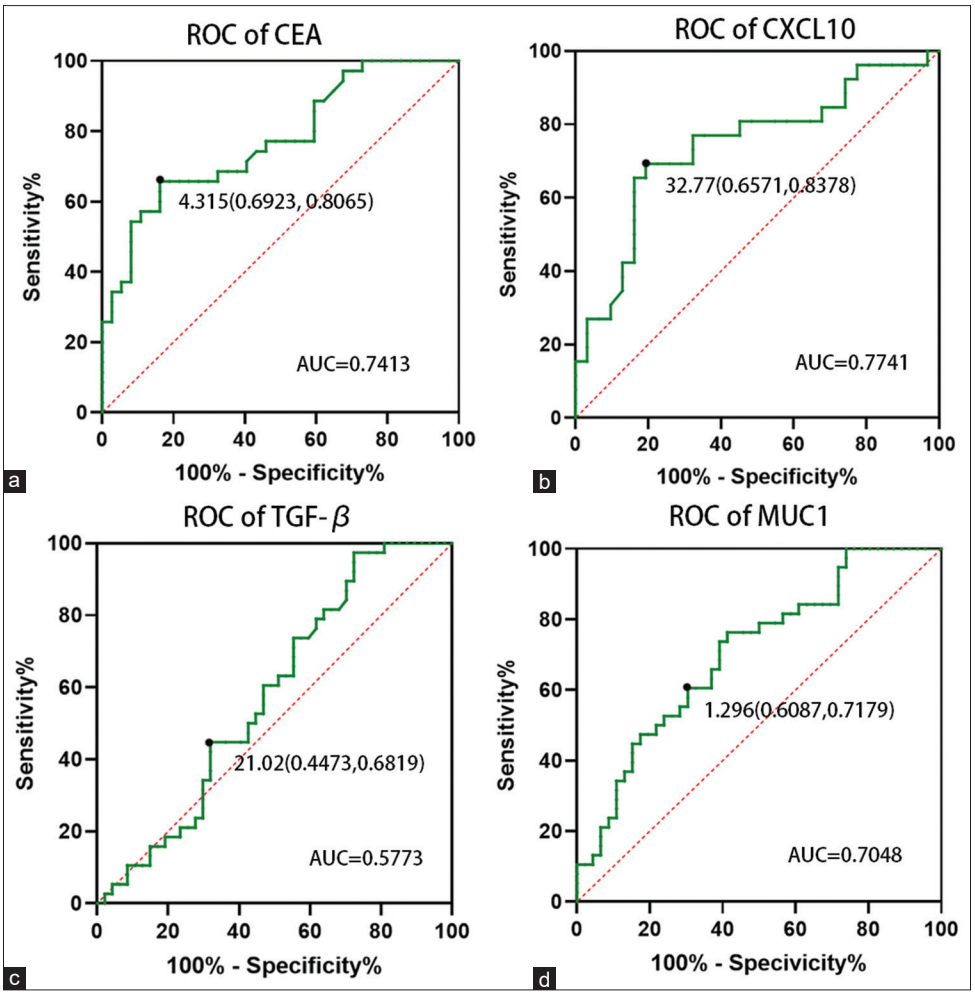

Figure 2: The diagnostic efficiency of biomarkers (a) The receiver operating characteristic (ROC) curve illustrating performance of carcinoembryonic antigen to distinguish coronavirus disease 2019 (COVID-19) patients with and without fibrosis. (b) The ROC curve illustrating performance of CXC chemokine receptor 10 to distinguish COVID-19 patients with and without fibrosis. (c) The ROC curve illustrating performance of transforming growth factor-beta to distinguish COVID-19 patients with and without fibrosis. (d) The ROC curve illustrating performance of Mucin 1 to distinguish COVID-19 patients with and without fibrosis. The green line means AUC (Area Under the Curve); The red line means random classifier. ROC: Receiver operating characteristic, CEA: Carcinoembryonic antigen, TGF-β: Transforming growth factor-beta, CXCL10: CXC chemokine receptor 10, MUC1: Mucin 1

However, the level of TGF-β value did not significantly affect the length of hospital stay of patients.

Discussion

As is well known, PF is a severe side effect of COVID-19, and deteriorated lung health may necessitate lung transplantation or hasten death. When aberrant collagen accumulates in the ECM, it results in lung stiffness and a lack of compliance required for normal breathing, which leads to PF. Following assessing the medical records of 88 COVID-19 patients hospitalized at the Affiliated People's Hospital of Ningbo University for this COVID-19 study, we discovered that as many as 46% showed fibrotic stripe shadows in the early stages. In patients with COVID-19, there was a considerably increased expression of MUC1, CEA, TGF-β, and CXCL10. Among these, MUC1, CEA, and CXCL10 are capable of being employed to predict the likelihood of PF in COVID-19 patients. These three markers indicate an increased level of expression, particularly in the severe patient group, and they have correlations with the course and relapse of the disease.

In addition to nonneoplastic lung disorders, CEA is a biomarker that can detect adenocarcinoma, which can occur in tumors of the respiratory or digestive systems.[20,21] After ruling out these conditions, we discovered that patients with COVID-19 had considerably higher serum CEA levels than healthy individuals, which is consistent with the research of Abdelhakam *et al*.[22] Furthermore, in COVID-19, both prognosis and elevated serum CEA levels were linked to PF. The primary targets of SARS-CoV-2 in the lungs are type II AECs and bronchiolar cells. Along with the production of CEA, SARS-CoV-2 infection causes significant type II AEC death and abnormal type II pneumocyte regeneration, similar to what is seen in the unregulated development of lung adenocarcinoma. In addition, abnormal epithelial and fibroblast growth may exacerbate lung consolidation and bronchiole blockage, leading to refractory hypoxemia.[23,24] Drugs, including nintedanib, which target

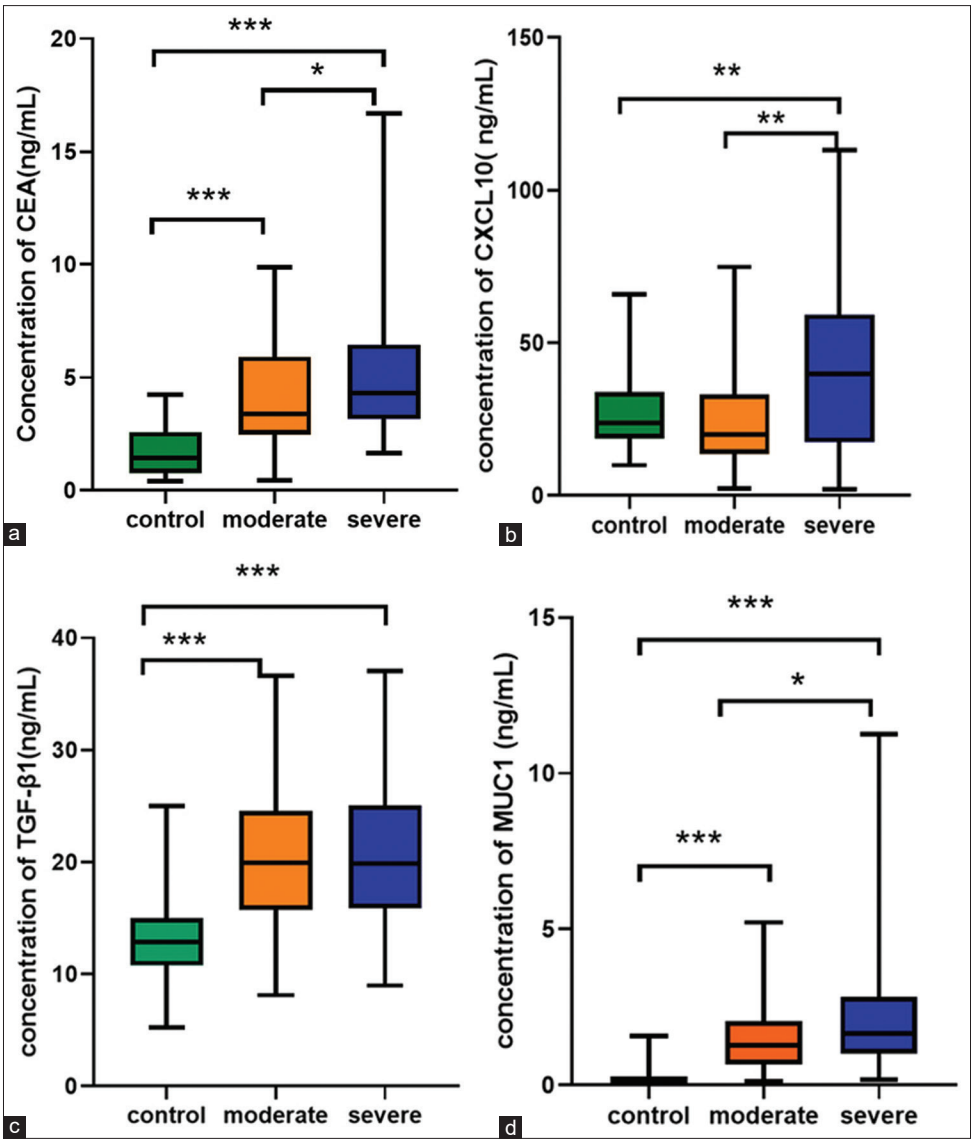

Figure 3: Concentrations of biomarkers in patients with different severity of coronavirus disease 2019 (COVID-19) (a) Concentrations of carcinoembryonic antigen in different severity of COVID-19; (b) Concentrations of CXC chemokine receptor 10 in different severity of COVID-19; (c) Concentrations of Transforming growth factor-beta in different severity of COVID-19; (d) Concentrations of Mucin 1 in different severity of COVID-19. *$P < 0.05$, **<0.01, ***$P < 0.001$. CEA: Carcinoembryonic antigen, TGF-β: Transforming growth factor-beta, CXCL10: CXC chemokine receptor 10, MUC1: Mucin 1

fibrotic proliferation and atypical epithelial, may be a possible treatment approach to lower mortality in COVID-19 patients based on the correlation between lung fibrosis and type II pneumocyte hyperplasia and CEA.[25]

We hypothesized that MUC1 concentrations might also accurately predict the severity of COVID-19 interstitial pneumonia following earlier studies showing a correlation between these two variables.[26,27] In our sample, MUC1 correlated with the size of the PF lesions at the CT scan and was considerably more prominent in individuals with severe disease than with mild and healthy individuals. Taking 1.296 ng/ml as the cutoff value, when the serum MUC1 concentration was higher than this concentration, the length of hospital days of COVID-19 patients increased significantly. Undoubtedly, compared to patients with intermediate disease, patients with severe disease often have greater levels of MUC1 and an elevated possibility of subsequent PF.

AECs-II and bronchiolar epithelial cells generate MUC1, a mucin-like, high molecular weight glycoprotein on their surface membranes. It is a solubilized component of the pulmonary epithelial lining fluid produced mainly by type II alveolar pneumocytes that are injured or regenerating.[28] MUC1 levels in the serum of individuals with PF have been reported to be raised due to generalized hyperplasia of AECs and enhanced spillover into the systemic circulation due to leakage of the structural integrity of the alveoli-capillary membrane.[29,30] According to a recent study, patients with PF had MUC1 levels that were considerably greater than those without the condition. Patients with irreversible fibrosis also had MUC1 levels that were substantially higher than those

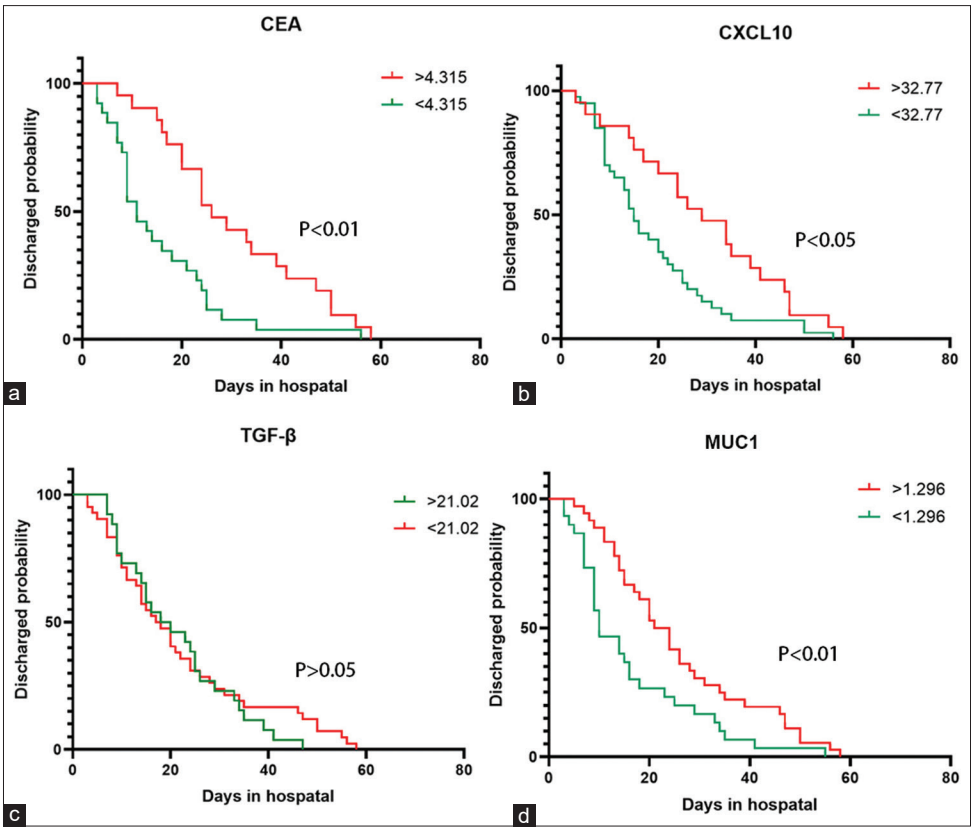

Figure 4: The survival curve for coronavirus disease 2019 patients' hospital days. The patients were grouped according to the detection results of relevant indexes in serum at admission. (a) The red line: carcinoembryonic antigen (CEA) >4.315 ng/ml, the green line: CEA < 4.315 ng/ml; (b) The red line: CXC chemokine receptor 10 (CXCL10) >32.77 ng/ml, the green line: CXCL10 < 32.77 ng/ml; (c) The red line: Transforming growth factor-beta (TGF-β) >21.02 ng/ml, the green line: TGF-β <21.02 ng/ml; (d) The red line: Mucin 1 (MUC1) >1.296 ng/ml, the green line: MUC1 < 1.296 ng/ml. CEA: Carcinoembryonic antigen, TGF-β: Transforming growth factor-beta, CXCL10: CXC chemokine receptor 10, MUC1: Mucin 1

of patients with reversible fibrosis, and high MUC1 levels are linked to prolonged hospital stays.[26] This study has also shown that MUC1 is elevated before imaging lesions manifest, which may indicate that apparent organic damage manifests after MUC1.[26] Therefore, it is feasible that the radiological image remains unchanged when we find high MUC1 levels. This shows that it might function as a predictor of lung injury in COVID-19.

According to various studies in severe COVID-19 patients, the host's initial viral elimination breakdown is triggered by a premature TGF-β synthesis associated with the degradation of immune cells such as B cells and NK cells.[29,30] It also coincides with this study. However, we did not observe the difference in TGF-β between NPF and NPF. This may be due to insufficient sample size in this study. In recent times, it was believed that TGF-β was involved in the ifferentiation of fibroblasts into myofibroblasts and that myofibroblasts had undergone differentiation and expressed - SMA was responsible for producing integrins, MMP, protease inhibitors, small GTPase regulators, and components of the ECM.

In addition, TGF-β1 suppresses the proliferation and repair of epithelial cells and the synthesis of antifibrotic chemicals such as prostaglandin E2.[31,32] However, there is also confirmation that early epithelial TGF-β production during viral lung infection negatively regulates the host's local immune system.[33] As a result, more research into TGF-β as a biomarker of COVID-19 is warranted.

COVID-19 and CXCL10 have both been associated with inflammatory disorders. Inflammation causes CXCL10 to activate its receptor, primarily found in B cells, natural killer cells, dendritic cells, T lymphocytes, and macrophages. Increased white blood cell activation causes systemic inflammation, which can cause tissue damage.[34] Furthermore, it has been discovered that CXCL10 is a crucial immunological event that triggers cytokine storms in COVID-19 patients and may be a predictor for therapeutic prognosis.[35,36] According to recent studies, CXCL10 may help distinguish between lung lesions linked to COVID-19 and other diseases of a similar nature. CXCL10 was discovered to be significantly upregulated in the epithelial endometrial fluid and plasma of the COVID-19 ARDS group compared to the non-COVID-19 ARDS group in plasma and bronchoalveolar lavage fluid of 1 control, 7 non-COVID-19 ARDS, and 14 COVID-19 ARDS patients.[37] CXCL10 levels are also distinct between COVID-19-associated and non-COVID-19-associated lower respiratory tract infections.[38] This is because the SUD (SARS-CoV-2 unique domain) considerably upregulates

the expression of CXCL10 in human lung epithelial cells,[39] which controls lung inflammation caused by CXCL10 in a way that depends on the NLRP3 inflammasome.

Early high-inflammatory injury is equally likely to result in long-term PF and immediate harm to lung tissue, as the patient will require more mechanical breathing as the inflammation builds up. Even though mechanical ventilation frequently saves lives, the risk of ventilator-induced lung damage (VILI) drastically increases. According to Bocchino *et al*., PF was substantially connected with the amount of time ARDS patients spent on pressure-controlled mechanical ventilation, and 85% of patients still had it 6 months after being extubated.[39] In addition, we discovered that patients with COVID-19 PF have serum CXCL10 levels that are considerably greater than those with NPF and that are linked to a bad prognosis. Therefore, early management of elevated inflammation is even more crucial to lessen the long-term fibrosis effects of COVID-19.

There are a few limitations regarding the current research. Despite being confirmed patients in our institution, the 88 COVID-19 instances are uncommon. These individuals do not adequately represent all of China, the world, or even secondary infections. Furthermore, we found a higher proportion of men with PF patients, which we speculate may be related to higher smoking rates among men. However, this is just speculation. The data may also be biased due to insufficient statistical sample size. In the future, we will expand the sample size and include smoking as an indicator to further test this question.

Conclusion

In this regard, recent research shows that MUC1, CEA, and CXCL10 are related to tissue damage and inflammation and may serve as novel diagnostic and prognostic indicators for COVID-19. Furthermore, the risk of subsequent PF was predicted using one particular value of these targets. These numbers serve as a reliable predictor of the prognosis.

Data availability statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to institutional policies.

Research quality and ethics statement

This study was approved by the Institutional Ethics Committee (The People's Hospital affiliated to Ningbo University's Ethics Committee, No. 2023-073). The authors followed applicable EQUATOR Network guidelines during the conduct of this research project.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Information of coronavirus disease-2019 patients

Number	NPF: 1, PF: 2	Man: 1, female: 2	Grade moderate: 1, sever: 2	Length of hospital (days)	Weight (kg)	Height (m)	Age ≤60: 1; 60–80: 2; >80: 3	Oxygenation index	Underlying medical (hypertension: 1; type 2 diabetes: 2; tumor: 3; chronic lung disease: 4)	Leukocyte ($\times 10^9$/L)
1	1	1	1	18	50	1.65	3	306	1	12.2
2	2	1	2	18	70	1.7	2	255.1	1, 3	16.7
3	2	2	1	11	40	1.58	2	314	1, 3, 4	6.7
4	2	2	1	10	50	1.6	3	\	1	6.8
5	2	2	2	15	55	1.55	3	186.2	1, 2	12.7
6	2	1	2	15	70	1.71	2	180	1, 4	12.5
7	1	2	1	10	56	1.5	3	486	1, 4	9.8
8	1	2	2	20	75	1.6	3	264.5	1, 2	5.4
9	1	1	2	5	61	1.68	3	272	1	4.1
10	2	1	2	9	94	1.7	2	114	1, 2	7.4
11	2	1	2	24	70	1.75	2	290	1	14.4
12	1	2	2	44	75	1.63	2	169	1	2.7
13	1	1	2	20	50	1.76	2	224	\	13.1
14	2	1	2	66	75	1.8	2	148	\	11.4
15	2	1	2	34	75	1.8	2	148	\	11.4
16	1	1	2	24	79	1.74	2	207	1, 4	11
17	1	2	2	39	80	1.75	2	202	1	7.4
18	1	2	2	41	55	1.5	2	262	1, 2	1.7
19	1	2	1	23	45	1.5	3	376	1, 4	9
20	2	1	1	16	61	1.71	3	\	4	7.9
21	1	2	1	7	54	1.63	3		1, 2	4.5
22	1	2	1	29	45	1.6	2	531	1, 3	21.6
23	2	2	2	26	40	1.5	2	448.2	2	12.2
24	1	2	1	33	90	1.73	2	355	1, 2, 4	5
25	1	1	2	7	75	1.7	2	289	1, 2	7
26	2	1	2	20	76	1.72	3	150	1, 2	13.3
27	1	2	1	8	65	1.54	2	\	1	8.8
28	1	1	1	9	54	1.61	2	\	2	7.7
29	1	2	1	9	38	1.54	2	\	3	12.1
30	1	2	1	25	65	1.6	3	333	1	10.1
31	1	1	2	11	58	1.75	2	274	3, 4	12.8
32	2	1	2	29	70	1.75	2	256.6	1, 2	29
33	1	1	1	14	60	1.6	3	\	1, 3	16.2
34	1	2	1	9	50	1.5	3	463	1, 3	6.9
35	2	1	2	39	85	1.7	2	215	1	13.1
36	2	1	2	28	52	1.7	3	173	1, 4	4.1
37	2	1	2	22	60	1.75	3	175	1	4.3

Contd...

Supplementary Table 1: Contd...

Number	NPF: 1, PF: 2	Man: 1, female: 2	Grade moderate: 1, sever: 2	Length of hospital (days)	Weight (kg)	Height (m)	Age ≤60: 1; 60–80: 2; >80: 3	Oxygenation index	Underlying medical (hypertension: 1; type 2 diabetes: 2; tumor: 3; chronic lung disease: 4)	Leukocyte ($\times 10^9$/L)
38	1	1	2	50	60	1.6	1	254	1, 2	10.7
39	2	2	2	47	63	1.63	2	254	1, 2, 3	6.3
40	2	1	2	33	70	1.7	3	212.5	1, 2, 4	4.2
41	1	1	2	50	70	1.75	3	231.0345	1.2	16.9
42	2	1	2	41	65	1.65	2	140	1, 2, 3	8.9
43	1	1	2	24	75	1.72	2	262	1, 2	6.4
44	1	2	1	9	77	1.6	2	900	1, 3	4.4
45	1	1	1	24	70	1.68	3	641	1, 3	5.2
46	2	1	2	58	70	1.78	1	210	1	13.5
47	2	2	1	26	48	1.55	2	\	1, 3	4
48	2	2	1	17	53	1.6	2	\	1, 3	3.4
49	2	2	1	16	50	1.5	3	\	1, 2, 3	4.3
50	1	1	1	11	67.3	1.6	2	468	\	12.1
51	2	1	1	24	65	1.75	2	\	1	3.9
52	1	2	1	23	55	1.57	2	\	3	10.6
53	2	1	2	18	72	1.7	2	286	1, 3	9.1
54	1	2	1	13	52	1.5	3	310	1	8.4
55	2	2	1	65	72	1.58	2	\	1, 2, 3	18.4
56	1	1	1	13	80	1.62	2	\	1, 2, 4	7.5
57	2	1	1	7	55	1.69	2	\	1, 4	5.8
58	2	2	1	15	69	1.63	2	\	2	6.7
59	2	1	2	55	50	1.52	3	113	\	11
60	1	2	2	3	85	1.7	1	258	1, 3, 4	5.2
61	1	1	2	22	50	1.74	2	165	1, 3	6.6
62	1	2	1	56	61	1.63	2	\	3	1.2
63	2	2	1	29	65	1.7	3		1, 3	5.2
64	2	2	2	46	65	1.6	2	226.2	1, 2, 3	4
65	2	1	1	26	48	1.55	1	\	3	2.2
66	1	1	1	14	70	1.68	2	\	3	1.9
67	1	1	2	22	60	1.7	2	186	\	3.6
68	1	2	2	41	/	/	3	116	1, 2, 4	6.3
69	2	1	2	35	58	1.7	3	163	1, 4	20.1
70	2	1	2	35	70	1.74	2	313.3	1, 2	4.5
71	2	2	1	34	40	1.55	3	431	\	4.5
72	1	2	1	5	49	1.6	2	\	3	7
73	1	2	1	25	65	1.6	3	527	1	5.6
74	1	1	1	31	43	1.5	3	\	\	16.9

Contd...

Supplementary Table 1: Contd...

Number	NPF: 1, PF: 2	Man: 1, female: 2	Grade moderate: 1, sever: 2	Length of hospital (days)	Weight (kg)	Height (m)	Age ≤60: 1; 60–80: 2; >80: 3	Oxygenation index	Underlying medical (hypertension: 1; type 2 diabetes: 2; tumor: 3; chronic lung disease: 4)	Leukocyte ($\times 10^9$/L)
75	2	1	1	20	75	1.7	2	344	3	4.5
76	1	2	1	14	60	1.62	2	\	1, 3	2.2
77	2	1	2	50	60	1.6	1	228	1, 2	7.5
78	1	2	1	10	50	1.5	2	\	3	5.2
79	2	1	1	21	80	1.74	1	404	1	5.3
80	1	1	1	4	75	1.69	2		2	7.6
81	1	1	1	9	80	1.8	2	\	1	8.3
82	1	1	2	9	73	1.68	2	227	\	10.7
83	1	2	1	7	84	1.63	3	\	1, 2	8.5
84	2	1	1	14	52	1.74	1	\	\	4.6
85	1	2	1	7	68	1.73	1	\	\	4.4
86	2	2	2	47	63	1.63	2	\	1, 2, 3	4.8
87	2	1	2	20	70	1.7	2	203	1	6.9
88	1	1	2	3	70	1.74	1	283.1304	\	6.4

Number	Lymphocyte ($\times 10^9$/L)	CRP (mg/mL)	PCT (ng/mL)	SF (ng/mL)	IL-6 (pg/mL)	CEA (ng/mL)	MUC1 (ng/mL)	CXCL10 (ng/mL)	TGF-β (ng/mL)	Discharge (improved: 1; other: 2)
1	\	15.1	0.06	\	182.5	\	1.24311	\	20.0427	1
2	1.02	1.5	0.03	940.1	2	4.89	1.65518	42.59231	27.6768	2
3	0.34	8.9	0.02	72.8	22	\	\	\	\	1
4	0.34	7.6	0.19	795.2	2	\	0.70063	\	36.6406	1
5	1.31	22.8	0.1	562.5	3.89	\	2.40045	22.59822	24.1999	1
6	1.94	2	0.02	509.5	3	\	1.0123	49.65106	20.4883	1
7	0.79	0.7	0.06	144.1	1.94	6.94	0.37282	\	20.6732	1
8	0.66	64.8	0.32	599.5	7	4.48	1.96197	\	27.8619	1
9	0.49	20.4	0.14	\	20.75	\	0.86479	\	\	1
10	0.27	25.1	0.06	1249	2449.6	\	2.84345	\	19.6277	2
11	0.52	21.7	1.45	803.9	2	16.69	\	\	\	1
12	0.8	43.1	0.16	1057	2	\	\	\	\	1
13	0.17	61.8	11.04	253	4	\	\	16.55792	13.2543	1
14	1.33	98.7	0.33	1873	1158	\	0.99063	\	30.9176	2
15	1.33	98.7	0.33	1873	1158	\	2.32571	47.26776	22.761	1
16	0.77	22.69	0.19	358.2	8	\	1.572			1
17	0.29	164.79	0.12	459.6	236	\	0.55698	32.231	18.5832	2
18	0.26	33.67	0.18	396.4	25	\	1.82849	64.172	25.0094	2
19	1.4	68.81	0.24	165.2	22	3.11	3.78857	28.88702	16.7419	2
20	1.38	1.1		2355		3.37	1.28128	16.10659	21.2595	1

Contd...

Supplementary Table 1: Contd...

Number	Lymphocyte ($\times 10^9$/L)	CRP (mg/mL)	PCT (ng/mL)	SF (ng/mL)	IL-6 (pg/mL)	CEA (ng/mL)	MUC1 (ng/mL)	CXCL10 (ng/mL)	TGF-β (ng/mL)	Discharge (improved: 1; other: 2)
21	1.82	1.3	0.04	150.6	2	\	1.00009	9.13068	35.3501	1
22	1.51	99.16	0.38	624		6.78	0.9532	30.29724	16.0535	1
23	6.5	53.78	0.17	416.5	16	13.77	3.93197	57.75703	35.3856	1
24	17.8	23.41	0.52	165.8	\	5.93	0.2911	10.57391	24.3722	1
25	1.39	21.74	0.49	\	20.23	\	1.19875	15.04992	29.2403	1
26	0.56	52.7	4.05	355.3	30.85	1.65	5.70702	104.284	21.0988	2
27	0.94	3.2	\	315	\	2.47	2.25788	55.80999	22.4842	1
28	1.32	13.3	\	223.6	\	4.07	1.37604	2.32947	35.9202	1
29	0.54	49.5	\	834.3	\	3.29	1.24311	20.03698	25.8033	1
30	1.57	17.56	0.1	907.8	787	3.42	1.02457	31.68864	34.0528	1
31	0.31	8.76	\	354.3	62	3.03	2.8578	\	17.1515	1
32	0.55	1.42	0.21	557.5	548	3.65	2.858	16.23618	25.1262	2
33	0.36	16.3	0.09	867.9	5	3.29	0.37763	18.97135	24.6318	1
34	0.94	<0.5	<0.04	126.3	\	3.42	0.25148	16.10659	25.5077	1
35	1.47	2.8	\	1104.3	7.29	7.58	1.39962	37.82914	27.7693	1
36	0.29	0.61	0.1	524.1	\	2.9	2.81488	23.96927	16.7419	1
37	0.1	4.34	0.35	\	9.5	\	2.71179	88.85919	17.5901	2
38	0.83	97.27	0.14	573.5	4.48	6.62	1.90384	23.96927	15.8893	1
39	0.54	31.52	0.08	\	65.18	\	1.31872	44.60492	15.2859	1
40	0.91	50.8	0.21	1226.5	3.45	3.13	1.36823	74.68511	18.1331	2
41	0.22	98	0.75	588	34	3.25	2.41115	43.24819	11.7748	2
42	0.23	77.77	0.6	1166	19.19	5.3	0.544	59.28551	25.5962	1
43	0.33	96.48	0.12	602.4	18.17	2.38		40.10122	37.0406	1
44	0.46	3.3	0.04	\	4.39	3.27	0.202	2.32947	11.5897	1
45	0.58	26.3	\	23.6	31.08	9.15	2.5955	\	8.1312	1
46	0.96	143	0.33	154	6.6	4.37	11.262	80.61461	16.694	1
47	0.46	\	\	557.5	\	2.45	0.69475	56.23639	33.6038	2
48	0.19	13.6	0.05	155.3	28	5.87	1.91129	74.84091	13.9546	1
49	0.77	1.5	0.03	385.3	2	7.25	0.44478	29.29203	15.7258	1
50	0.91	7.4	0.1	724.4	2	4	1.82123	28.83627	19.3704	1
51	0.34	71.14	0.18	626.8	41.66	5.34	1.61245	50.44655	16.1477	1
52	0.31	34.09	0.54	1136.9	27	2.3	1.29581	19.8612	25.5077	1
53	2.19	0.9	0.03	354	2	3.68	1.2965	14.36966	24.4874	1
54	2.92	2.46	0.04	255.2	2	\	4.24452	6.50225	17.2728	1
55	1.12	92.7	1.46	397.9	\	9.88	1.03553	49.65106	19.9126	2
56	1.95	2.9	\	103.9	\	1.67	1.68804	18.67043	26.4299	1

Contd...

Supplementary Table 1: Contd...

Number	Lymphocyte ($\times 10^9$/L)	CRP (mg/mL)	PCT (ng/mL)	SF (ng/mL)	IL-6 (pg/mL)	CEA (ng/mL)	MUC1 (ng/mL)	CXCL10 (ng/mL)	TGF-β (ng/mL)	Discharge (improved: 1; other: 2)
57	0.93	62.77	0.08	297	67.78	4.65	1.72668	17.44278	19.9906	1
58	1.92	7.8	\	\	43.9	6.7	2.7141	25.15072	24.1426	1
59	2.07	32.5	0.15	\	54	11.79	0.6854	43.34183	15.7725	1
60	1.01	6.74	0.05	134.6	27.62	3.43	0.99468	39.77099	14.5123	1
61	0.15	504.4	0.15	396.7	706	\	\	6.61029	8.9714	1
62	0.09	109	0.16	2632	111	3.26	5.21569	3.48811	20.8832	1
63	0.26	86.32	0.15	1209.4	42.46	\	2.24721	113.1213	23.0755	1
64	0.17	5.14		\	9	\	2.41971	70.535	20.095	1
65	0.12	98.89	0.11	4399	131.37	\	3.35618	9.56811	19.0733	1
66	0.73	90.17	0.32	858	98.41	\	1.49203	6.187	20.943	1
67	0.4	2.8	0.03	498.5	2	\	\	\	\	1
68	1.75	38.9	0.25	283.1	30	3.42	1.05345	30.84594	16.5269	2
69	0.54	27.7	0.13	390.8	34	\	3.54736	85.39876	15.7491	1
70	0.69	56.1	0.25	396.7	14	2.94	0.55481	17.44278	21.367	1
71	1.22	29.7	0.23	1145.9	\	6.05	0.6622	73.65041	15.0566	1
72	0.99	44.4	0.29	117.2	23	3.33	2.04234	57.13838	15.7725	1
73	1.06	3.7	0.04	745.2	2	1.94	\	30.846	30.846	1
74	1.23	70.6	0.16	834.2	2	\	2.90118	32.32901	20.2256	1
75	2.12	1.5	0.03	459.6	53	\	2.32429	35.53487	15.3089	1
76	0.26	0.5	0.05	1080		\	0.11516	23.57534	14.7663	1
77	1.06	17	0.17	337.4	7	6.62	6.01393	17.19226	20.278	1
78	1.4	2.18	\	\	\	\	0.89172	16.23618	14.6476	1
79	1.36	7.6	0.03	487.9	2	1.18	1.68358	18.54943	18.0586	1
80	2.7	5.89	\	\	\	1.37	0.82314	19.44827	15.7025	1
81	0.78	38.1	\	323	\	4.22	0.38246	14.50704	13.4933	1
82	0.87	77.6	0.18	\	\	\	1.01502	28.98843	13.5588	1
83	1.02	55.6	0.04	254.9	28	1.95	0.39119	\	18.1829	1
84	1.99	1.01	0.02	246.7	2	\	1.85751	62.9039	9.1955	1
85	0.83	1.69	0.02	41.9	2	0.45	0.52046	5.94469	19.1913	1
86	0.59	5.9	0.15	149.2	\	5.08	3.39607	33.2104	21.2595	1
87	0.69	14.7	0.07	355.8	32	5.96	1.39998	15.31757	17.9595	1
88	1.41	17.6	0.21	170.7	5	4.26	0.174	1.89172	13.7781	1

"\" means the indicator has not been detected clinically, or the experimental sample does not meet the standard. IL-6: Interleukin 6, CRP: C-reactive protein, SF: Serum ferritin, PCT: Procalcitonin, PF: Pulmonary fibrosis, NPF: None pulmonary fibrosis, CEA: Carcinoembryonic antigen, MUC1: Mucin 1, CXCL10: CXC chemokine receptor 10, TGF-β: Transforming growth factor-beta

Supplement Table 2: Information of healthy people

Number	Man: 1 famale: 2	Age	Weight (kg)	Height (m)	Leukocyte (×10~9/L)	Lymphocyte (×10~9/L)	SF (ng/mL)	CEA (ng/mL)	MUC1 (ng/mL)	CXCL10 (ng/mL)	TGF-β (ng/mL)
1	1	26	55	1.6	5.39	2.04		0.95	0.09792	19.44827	15.9303
2	1	54	76	1.71	6.95	1.93	172.5	2.51	0.017	39.34589	10.8791
3	2	37	54	1.62	3,39	2.22	41.7	3.35	0.1278	30.44459	16.1634
4	2	37	52	158	7.33	3.03	45.6	1.59	0.23201	43.65393	13.2434
5	2	27	48	1.63	5.43	2.38	\	\	0.10137	19.55498	12.8694
6	1	24	65	1.75	6.94	1.92	\	\	0.0761	22.26617	13.2199
7	2	27	46	1.6	5.14	2.69	46	2.02	0.11746	65.86397	14.1037
8	1	57	70	1.76	6.04	1.95	\	\	0.12205	33.57201	8.1186
9	1	61	68	1.72	5.9	1.97	\	1.21	0.08529	104.12026	13.9102
10	2	32	45	1.59	6.88	2.83	29.2	1.21	0.34899	14.81093	6.1538
11	2	25	48	1.63	6.12	2.05	\	2.03	0.15314	38.1388	15.0155
12	2	41	58	1.57	5.47	1.88	\	0.56	0.23785	32.32285	17.845
13	2	34	47	1.64	8.46	2.29	128.5	0.99	0.10711	35.56059	15.2921
14	1	56	66	1.68			\	2.01	0.27775	35.84987	5.2275
15	1	53	67	1.73	3.39	1.12	3.6	3.22	1.57527	53.27843	10.0954
16	2	38	56	1.66	3.39	1.12	3.6	0.49	0.07035	17.52041	16.1114
17	2	35	45	1.62	4.5	1.78	176.2	0.51	0.76992	24.81636	14.7414
18	2	30	42	1.66	7.2	1.74	\	0.44	0.16122	22.82956	11.2477
19	1	55	73	1.7	6.9	1.79	\	4.24	0.11056	36.88522	25.0006
20	1	59	68	1.75	7.2	2.51	\	3.1	0.1232	23.31679	12.9158
21	2	23	65	1.76	8.1	2.21	\		0.15775	33.39461	15.3933
22	1	37	70	1.7	8.7	2.62	259.8	2.57	0.22501	23.79896	14.3718
23	1	31	80	1.8	4.7	1.44	\	\	0.07954	22.61913	10.8361
24	1	21	71	1.81	11.6	3.21	\	\	0.19825	23.59291	10.0329
25	2	24	54	1.65	7.2	2.24	\	\	0.09218	21.98172	10.7717
26	2	65	60	1.57	5.3	1.9	\	2.6	0.42141	87.99923	10.8576
27	1	43	60	1.7	5.3	2	\	\	0.14392	24.54707	12.5921
28	2	21	40	1.62	5.3	2.05	34.8	2.98	0.13471	17.03184	17.0331
29	1	40	62	1.78	5.8	2	582.7	1.96	0.12435	36.48368	14.2253
30	2	24	67	1.75	4.7	1.48	29.7	0.96	0.09103	16.45139	13.2669
31	2	47	75	1.7	5.8	2.33	\	0.54	0.11401	23.10861	18.7902
32	1	41	70	1.72	5	1.95	\	0.41	0.14853	25.35077	15.4694
33	2	35	50	1.62	8.9	2.44	6.1	0.57	0.18434	19.32639	13.2905
34	1	27	55	1.63	6.3	1.83	\	0.9	0.69217	13.99497	20.8832
35	2	46	58	1.55	5.2	1.52	\	1.45	0.16468	24.61452	11.2477
36	2	38	46	1.6	4.8	1.56	4.8	1.44	0.11631	13.05288	13.0324
37	1	34	67	1.75	8.5	2.5	\	3.17	274.6	14.17874	12.5233
38	2	33	45	1.59	5.6	1.73	19.1	1.47	0.19013	18.3179	11.2914
39	2	39	45	1.6	8.2	2.31	16.1	2.83	0.20057	23.17811	9.5799
40	1	31	70	1.76	6.1	1.56	\	\	0.20987	27.24565	12.1363
41	1	31	42	1.55	6.3	1.77	\	\	0.15775	34.68807	10.4101
42	2	29	45	1.63	5.4	2.44	5.4	0.55	0.69478	27.9488	11.8889
43	1	50	65	1.73	7	2.6	\	2.41	0.16122	18.63144	12.1816
44	1	54	76	1.72	5.6	1.98	\	2.78	0.19477	36.3687	13.7421
45	1	25	70	1.79	8.5	3.23	\	\	0.14968	9.92111	17.167
46	2	35	47	1.59	5.7	2.68	\	\	0.11401	109.29828	6.3101
47	2	26	46	1.63	4.7	1.21×iao	\	2.33	0.18897	105.32891	11.6882
48	1	32	55	1.65	6.1	1.96	\	2.23	0.12665	15.42731	7.0573
49	1	33	67	1.78	6.8	1.87	\	\	0.15314	12.56583	10.158
50	1	26	65	1.77	5.3	1.56	\	\	0.11401	24.61452	8.9362
51	2	25	43	1.59	5.1	2.04	\	\	\	\	6.102

"\" means the indicator has not been detected clinically, or the experimental sample does not meet the standard. SF: Serum ferritin, CEA: Carcinoembryonic antigen, MUC1: Mucin 1, CXCL10: CXC chemokine receptor 10, TGF-β: Transforming growth factor-bet