Pirfenidone As Potential Therapeutic Intervention for Coronavirus Disease-19 (COVID-19)

Bei Wang[1], Jing Chen[1], Chenze Li[1], Lingli Dong[1], Dao Wen Wang[1], Enrico Ammirati[2], and Jiangang Jiang[1]

[1]Huazhong University of Science and Technology
[2]ASST Grande Ospedale Metropolitano Niguarda

March 07, 2024

Abstract

Background: Coronavirus disease 2019 (COVID-19) is a pandemic with no specific drugs and high fatality. The most urgent need is to find effective treatments. We sought to determine whether pirfenidone treatment might reduce the death risk of COVID-19 patients. Methods: Clinically confirmed COVID-19 cases at Tongji Hospital, Wuhan, China from January 29, 2020 and April 27, 2020 were identified from electronic medical records. Information on their demographics, history of coexisting diseases, and therapies during hospitalization were extracted. Based on whether taking pirfenidone during hospitalization, patients were categorized into non-pirfenidone group and pirfenidone group. The patients were further matched using propensity score analysis. Results: In this retrospective study, about 59 patients were treated by pirfenidone during hospitalization and 59 patients with non-pirfenidone were matched. Compared with patients without pirfenidone therapy, patients with pirfenidone therapy showed a better clinical outcome and a decreased mortality (1.7% [1/59] vs. 32.2% [19/59]; p<0.001). In terms of chest computed tomography (CT) images, the ground-glass opacity (GGO)/consolidation signs were obviously absorbed in the pirfenidone treated patients before discharge compared with patients on admission. Moreover, the level of interleukin (IL)-6 and IL-2 receptor were reduced on day 3 after pirfenidone treatment. Moreover, there was a trend that patients with pirfenidone therapy had lower levels of IL-1β, combined with lower hs-CRP, lymphocytes, LDH and NT-proBNP on day 3 after pirfenidone administration. In addition, patients with pirfenidone therapy had higher serum albumin level on day 3 after pirfenidone administration.Conclusion: COVID-19 patients could benefit from the pirfenidone therapy during hospitalization.

1. Introduction

In December 2019, a new betacoronavirus causing acute respiratory syndrome outbreak in Wuhan, China[1]. Since then, gene sequencing of samples taken from the lower respiratory tract of infected patients has made it possible to characterize this new virus[2], called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The disease was given the abridged name COVID-19 by the World Health Organization (WHO) in February 2020. On March 12, 2020, the WHO declared COVID-19 as a pandemic. To data, this epidemic had spread to 206 countries and territories around the world and 2 international conveyances with 58 million confirmed cases, including 1.4 million deaths.

The symptoms associated with COVID-19 are different, ranging from mild upper respiratory tract symptoms to severe acute respiratory distress syndrome (ARDS). Cytokine storm[3], multiorgan failure, and ARDS are the leading cause of mortality and morbidity in patients with COVID-19[4]. Zhou, Fei et al. found that the levels of interleukin (IL)-6, serum ferritin, lactate dehydrogenase, and high-sensitivity cardiac troponin I were clearly elevated in non-survivors compared with survivors throughout the clinical course, and was associated with higher mortality in COVID-19 patients[4]. Because cytokine storm could accelerate multiorgan failure and ARDS, recent clinical observation suggests that blockage of IL-6, a major proinflammatory cytokine,

to calm down the cytokine storm caused by SARS-CoV-2 infection, in turn lead to therapeutic effects in a portion of patients[5, 6]. Although there are as yet no data reporting the incidence or mortality of SARS-CoV-2 infection in patients with Idiopathic Pulmonary Fibrosis (IPF), however, some of the COVID-19 patients were complicated with postinflammatory pulmonary fibrosis (PPF) on the follow-up CT scan when discharged, and complaining about exertional dyspnea of different levels, presenting with an UIP (usual interstitial pneumonia) pattern or NSIP (non-specific interstitial pneumonia) pattern on the CT scans[7, 8].

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone), a novel anti-fibrotic agent, has been approved for the treatment of IPF for patients with mild to moderate disease[9]. In terms of mechanism, pirfenidone was shown to modulates airway responsiveness and inflammation[10] by regulate the activity of transforming growth factor (TGF) β[11] and tumor necrosis factor (TNF) α[12] in vitro; and inhibit fibroblast proliferation and collagen synthesis and reduce cellular and histological markers of fibrosis in animal models of lung fibrosis[13-16]. Recently, through its anti-inflammatory and anti-oxidant effects[17], namely by inhibiting IL-1β and IL-4, PFD has been included in a clinical trial for the treatment of coronavirus disease (COVID-19) (NCT04282902). But, it remains unknown whether pirfenidone could protect pneumocytes and other cells from COVID-19 invasion and cytokine storm.

This study demonstrates that pirfenidone, as its anti-inflammatory and anti-oxidant effects, has dramatically decreased the mortality of patients with COVID-19 by attenuating the inflammatory cytokine storm.

2. Method

Study Design and Data Source

This was a retrospective study and conducted in Tongji hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. The study protocol was reviewed and approved by the Tongji hospital institutional ethics committee (IRBID: TJ-IRB20200229). The informed consent was waived by the review board because of a retrospective design.

From January 29, 2020 to April 1, 2020, a total of 3272 patients, admitted to hospital and diagnosed as COVID-19 based on the 5th guideline published by the National Health Commission of China, were retrospectively reviewed. In this analysis, the enrolled patients have to meet the following criterion: 1) patients were 18 years old or older; 2) the diagnosis of COVID-19 was laboratory- and clinically- confirmed during hospitalization. However, patients who were in hospital for less than 24 hours, or had gastrointestinal (GI)- and skin-related AEs for the pirfenidone therapy, or cannot obtain clinical information were excluded from the analysis. All patients were categorized into pirfenidone group and non- pirfenidone group based on whether were administrated with pirfenidone during hospitalization or not. The final date of follow-up was due to April 4, 2020.

Data Collection

We extracted the demographic information, coexisting diseases, laboratory findings, CT scans, and treatments during hospitalization of patients from the electronic medical charts using a code system. Two experienced physicians independently checked the accuracy of the data. The demographic characteristics only include age and gender because other personal information were all concealed. The clinical symptoms (fever, cough, fatigue and dyspnea) were self-reported by patients on admission. For the comorbidities, the adjudications of hypertension, diabetes mellitus, coronary heart disease, malignant tumor, and stroke were performed according to the diagnosis prior to admission. To further evaluate the disease status, we also collected the biomarkers for organ injuries, such as routine blood test, liver, renal and heart function, cytokine factors, inflammation index, and coagulation, and the administrations of drug and mechanical support throughout the hospitalization.

Statistical Analysis

Continuous data are expressed as median and interquartile range (IQR), categorical data as percentage. The comparisons for continuous and categorical data between groups were applied by Mann-Whitney U test and

chi-square test, respectively. Survival curves were depicted by Kaplan-Meier method and their differences were evaluated by the log-rank test. The univariate and multivariable Cox regression models were used to calculate the hazard ratios and 95% confidence interval (CI). In multivariable Cox regressions, we adjusted for age, sex, symptoms at admission (fever, cough, fatigue and dyspnea), vital signs (temperature, heart rate, respiratory rate, and oxygen saturation), the histories of hypertension, coronary heart disease, diabetes mellitus, chronic obstructive pulmonary disease (COPD), malignant tumor, renal disease and stroke, the levels of representative biomarkers for organ injuries (lymphocytes, NT-proBNP, albumin, LDH and hs-CRP), and the treatments (antiviral, immunoglobulin, antibiotics, steroid, tocilizumab, hydroxychloroquine, oxygen, NIV, IMV, ECMO, IABP, CRRT) before the administration of pirfenidone. To account for the retrospective and nonrandom design, we also applied propensity score matching score. The incorporated variables were the factors mentioned in the multivariable adjustment, except for vital signs, the level of d-dimer, and the administration of oxygen, ECMO, IABP and CRRT. The treated and untreated group were matched based on propensity score, and the value of caliper was set equal to 0.05. The absolute standardized difference of a variable less than 10%, indicating a small imbalance between groups, and we further adjusted for the variables that the absolute standardized difference between groups higher than 10%. Furthermore, due to a complete dataset is need for performing multivariable Cox adjustments and propensity score matching, we performed missing laboratory values imputation with mice package (version 3.1.4, Vienna, Austria) by multiple imputation method before analysis, to keep as more cases as possible. In all analysis, $p<0.05$ was considered as statistically significant, and all comparisons were two-sided. R packages (version 3.5.2, Vienna, Austria) were used to perform all statistical analyses.

3. Results

3.1 Study population: Baseline characteristics

From January 29, 2020 to April 1, 2020, there were 3272 patients with COVID-19 in our database. Of them, there were 60 patients with COVID-19 subjected to pirfenidone therapy during hospitalization. In the 60 patients with pirfenidone therapy, there was one patient with incomplete clinical information that was excluded from the analysis. Finally, 59 patients receiving pirfenidone and 3212 patients without were included in the final analysis. Of note, there were no patients found to combine with gastrointestinal (GI)- and skin-related AEs after pirfenidone therapy. In the overall study population, the median age was 61 (IQR: 49-69) years, and 50.3% of the patients were female (**Table 1**). Compared with the patients in the non-pirfenidone group, patients in the pirfenidone group were more likely to have the histories of hypertension and diabetes mellitus, present with dyspnea on admission, and were more frequently administrated with antiviral agents, immunoglobulin, steroid, antibiotics, tocilizumab, oxygen, NIV, IMV, ECMO, and CRRT before pirfenidone treatment (**Table 3**). In propensity score-match groups, there was no significant difference on their clinical characteristics. For the laboratory findings and treatments before pirfenidone administration, they were also comparable between pirfenidone group and non-pirfenidone group. We summarized the baseline clinical characteristics of study patients in **Table 1** .

3.2 Pirfenidone and clinical outcome

In the all population, we found that compared with non-pirfenidone group, patients with pirfenidone had a lower incidence of death during hospitalization (1.7% [1/60] vs. 9.4% [302/3212]; p=0.041) (Dose: From 100 to 600mg, p.o., tid.). In the propensity score matched population, it was a similar on the aspect of combination therapy (including antiviral agent, immunoglobulin, corticosteroids, antibiotic therapy, antifungal therapy, tocilizumab and chloroquine) between pirfenidone group and non-pirfenidone group (**Figure 1** and**Table 3**). After propensity score matching, we still found that compared with non-pirfenidone group, patients with pirfenidone had a lower incidence of death during hospitalization (1.7% [1/59] vs. 32.2% [19/59]; p<0.001) (**Figure 2** and**Table 4**). The administration of pirfenidone indicated a 0.15-fold hazard ratio to develop into in-hospital death. Moreover, the inflammatory cytokines were tended to be lower in pirfenidone group than that in non-pirfenidone group after propensity score matching.

3.3 The levels of biomarkers after pirfenidone administration

In the propensity-matched patients, for the laboratory testing, patients in the pirfenidone group had a lower level of inflammatory cytokines (including interleukin (IL)-1β, IL-2R, IL-6, IL-8, IL-10 and TNFα). Compared with the day on admission, the level of IL-6 was reduced on day 3 after pirfenidone therapy (6.0pg/mL [2.6, 22.5pg/mL] vs. 30.8pg/mL [7.5, 50.7pg/mL]; p=0.003). Before hospital discharge, patients in pirfenidone group still had a lower level of IL-6 (9.1pg/mL [4.9, 37.4 pg/mL] vs. 5.8 pg/mL [2.6, 12.0 pg/mL]; p=0.054) (**Figure 3**). Similarly, the level of IL-2R was also decreased on day 3 after pirfenidone therapy. At the same time, before patients discharge, the level of IL-1L was tended to decrease from 13.7pg/mL [7.9, 23.0pg/mL] to 7.5pg/mL [5.7, 12.8pg/mL], p=0.065 (**Supplementary Figure 1**).

On the aspect of hemogram, patients in the pirfenidone group also had a higher level of the lymphocyte count (1.4×10^9/L [1.1, 1.8×10^9/L] vs. 0.8×10^9/L [0.5, 1.2×10^9/L]; p<0.001) on day 3 after treatment. Meanwhile, before patient discharge, patients in pirfenidone group still had a higher lymphocyte count (1.6×10^9/L [1.2, 2.0×10^9/L] vs. 1.2×10^9/L [0.6, 1.5×10^9/L]; p<0.001) (**Figure 3**). However, there was no difference in the white blood cell, neutrophil, monocyte, haemoglobin and platelet count between pirfenidone and non-pirfenidone group.

After propensity score matching, patients in pirfenidone group had a lower level of high sensitivity C-reactive protein (hs-CRP) (2.6mg/mL [1.0, 11.1mg/mL] vs. 35.5mg/mL [12.6, 91.4mg/mL]; p<0.001) (**Figure 3**), N-terminal pro-B-type natriuretic peptide (NT-proBNP) (104.0pg/mL [35.8, 330.2pg/mL] vs. 272.5pg/mL [112.2, 766.2pg/mL]; p=0.041), lactic dehydrogenase (LDH) (215.0pg/mL [178.5, 251.0pg/mL] vs. 278.0pg/mL [215.8, 402.5pg/mL]; p<0.001) on day 3 after pirfenidone treatment (**Figure 4**). Meanwhile, patients in pirfenidone group had a higher level of albumin (39.0g/L [37.1, 41.0g/L] vs. 32.0g/L [29.8, 36.0g/L]; p<0.001) on day 3 after pirfenidone treatment (**Figure 4**).

3.4 The CT scans after pirfenidone administration

Chest CT of patients with COVID-19 should also be carefully evaluated. In our studies, we noticed a presence of massive ground-glass opacity (GGO), consolidation, fibrous stripes and crazy-paving signs on CT images of patients with COVID-19. More importantly, the signs of GGO/consolidation were obviously absorbed in pirfenidone administration group before hospital discharge compared with admission (**Figure 5**). However, in non-pirfenidone group, it still remains some ground-glass opacity (GGO), consolidation and fibrous stripes in both lungs after a combined treatment in hospital. Additionally, pirfenidone treatment also increased the finger pulse oxygen saturation (SpO_2) on day 3 (**Supplementary Figure 2**).

4. Discussion

In this retrospective analysis, 59 patients treated with pirfenidone during hospitalization were taken a propensity score matching with the non-pirfenidone treated patients. Compared with patients without pirfenidone therapy, patients with pirfenidone therapy showed a better clinical outcome, and the association of pirfenidone therapy with a decreased mortality is still significant after propensity score matching. We found that patients with pirfenidone therapy had lower IL-6, IL-2R, hs-CRP, LDH and NT-proBNP on day 3 after pirfenidone administration. Moreover, patients with pirfenidone therapy had higher lymphocyte count and albumin on day 3 after pirfenidone administration.

The mechanism of Pirfenidone in improving clinical outcome

The administration of pirfenidone indicated a 0.15-fold hazard ratio to develop into in-hospital death. Moreover, the inflammatory cytokines tended to be lower in pirfenidone group than that in non-pirfenidone group after propensity score matching. However, the mechanism of pirfenidone in improving the clinical outcome is still unclear.

With the collation and publication of more and more clinical data, a large number of data suggest that there are mild or severe cytokine storms in severe patients, which is also an important cause of death[5]. Therefore, the treatment of cytokine storm has become an important part of rescuing COVID-19 patients[5]. In terms of mechanism, pirfenidone was shown to modulates airway responsiveness and inflammation[10] by regulate the activity of transforming growth factor (TGF) β[11] and tumor necrosis factor (TNF) α[12] in vitro, and

pirfenidone was used as an anti-fibrotic agent in clinic. Recently, pirfenidone has been proved possess anti-inflammatory and anti-oxidant effects[17], mainly by inhibiting IL-1β and IL-4. In our report, we also observed the anti-inflammatory effect of pirfenidone in patients with COVID-19 and the level of IL-6 was tended to decrease on day 3 after treatment. In a retrospective cohort study with COVID-19 in Wuhan, it was shown that IL-6 were clearly elevated in non-survivors compared with survivors throughout the clinical course, and increased with illness deterioration[4]. IL-6 can be produced by almost all stromal cells and immune system cells, such as B lymphocytes, T lymphocytes, macrophages, monocytes, dendritic cells, mast cells and other non-lymphocytes, such as fibroblasts, endothelial cells, keratinocytes, glomerular Mesangial cells and tumor cells[21]. The main activators of IL-6 expression are IL-1β and tumor necrosis factor (TNF- α)[22]. Of course, there are other ways to promote the synthesis of IL-6, such as Toll-like receptors, prostaglandins, adipokines, stress response and other cytokines. We speculate that the protective effects of pirfenidone in COVID-19 may be partially by inhibition of cytokine storms (such as inhibition IL-6 and IL-1β).

In addition, cardiac complications, including new or worsening heart failure, new or worsening arrhythmia, or myocardial infarction are common in patients with pneumonia. In this retrospective study, patients in the pirfenidone group also had a lower level of hs-CRP and NT-proBNP on day 3 after pirfenidone treatment, indicating that pirfenidone had a trend to decrease the risk of cardiac complications. Therefore, taking pirfenidone may decrease the rate of myocardial injury and prevent the incident cardiovascular events after affecting with COVID-19. Nonetheless, future studies are required to investigate pathophysiological links between the association of pirfenidone therapy and decreased in-hospital mortality.

The influence of pirfenidone on biomarkers and CT scans

The changes in the levels of biomarkers were unanticipated. First, in the propensity score matched population, patients in the pirfenidone group had a better performance on the levels of biomarkers than that in the non-pirfenidone group. Although we did not observe a significant change in the levels of inflammatory cytokines and coagulation index after four days of pirfenidone administration, however, patients with pirfenidone therapy had a lower trend of those inflammatory cytokines and coagulation index. Moreover, patients with pirfenidone therapy had lower hs-CRP and LDH on day 3 after pirfenidone administration. In addition, patients with pirfenidone therapy had higher lymphocyte count and albumin on day 3 after pirfenidone administration.

Importantly, patients in pirfenidone administration had attenuated signs of GGO/consolidation on CT images before hospital discharge compared with admission, indicating that pirfenidone contributed to the recovery of lungs after infection with COVID-19.

In this context, these findings require further investigations were required to explore the possible reasons why the changes of biomarkers were contrary to the improvement of clinical outcome.

Clinical implications

Our findings have several clinical implications. First, COVID-19 infection is a devastating condition, with about 8% mortality as well as a substantial impact on medical expenditure. If a patient had the indication for the pirfenidone treatment, it is favorable for physician to prescribe it. Secondly, patients could benefit from the pirfenidone treatment, suggesting the underlying activated cytokine storm maybe one of the important contributor to the poor clinical outcome of COVID-19 patients that we should pay attention it.

Limitations

Our findings should be considered in light of several limitations. First and foremost, due to the retrospective study design, not all laboratory tests were done in all patients (such as serum ferritin), including inflammatory cytokines and main biomarkers. Therefore, their role might be underestimated in predicting in-hospital death. Secondary, although propensity scores were widely used to balance the clinical data collected in an observational study, we were nonetheless unable to address for unobservable confounding variables related to likelihood of treatment, severity of illness, and mortality. Another limitation is that the long-term clinical outcomes after hospital discharge in patients with pirfenidone therapy during hospitalization are not yet

available. Moreover, the samples of pirfenidone group and non-pirfenidone group was relative few, thus, there was only a trend of some biomarkers after pirfenidone therapy, but not occurred a statistical significance.

5. Conclusions

We found that COVID-19 patients could benefit from the pirfenidone therapy during hospitalization. The protective role of pirfenidone is partially through the reduced inflammatory biomarkers and increased lymphocyte count.

Acknowledgments

Bei Wang designed and wrote the manuscript draft, Chenze Li analyzed the data; Jing Chen, Lingli Dong and Dao Wen Wang helped collect data and references. Jiangang Jiang and Enrico Ammirati are co-corresponding authors who designed the study, and completed the writing of the manuscript. This work was supported in part by National Nature Science Foundation of China (Nos. 81900363).

Disclosures

The authors declare that they have no competing interests.

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Figure 1

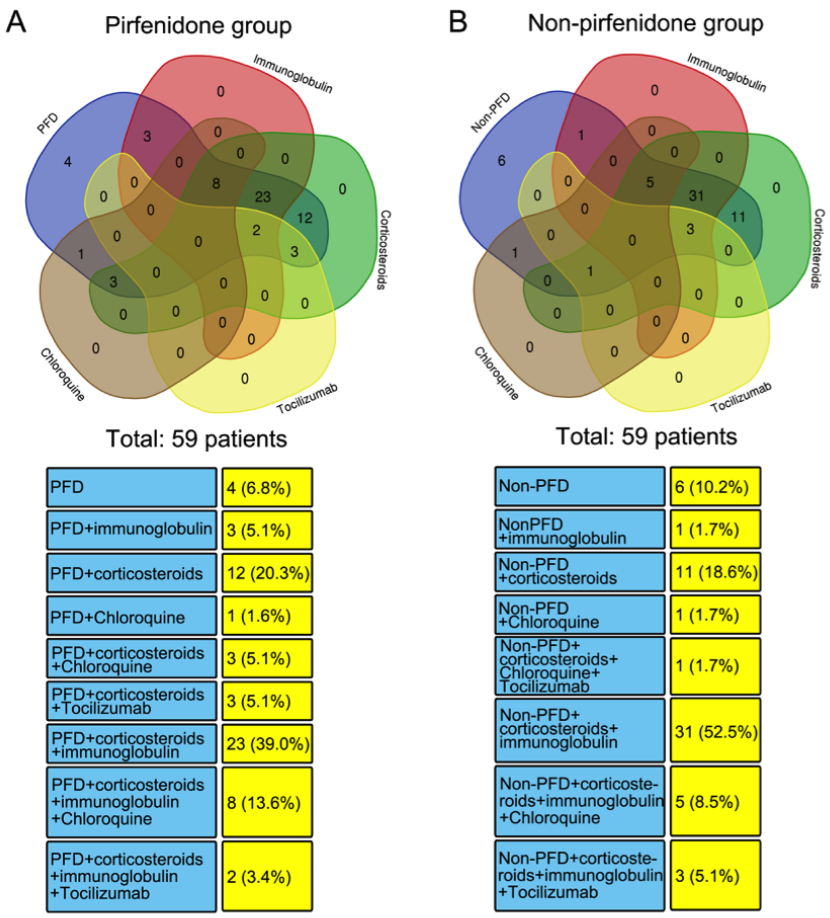

Figure 1. The combination therapies in the propensity score matched population . (A) The combination therapies included PFD, immunoglobulin, corticosteroids, tocilizumab and chloroquine in pirfenidone group; (B) The combination therapies included immunoglobulin, corticosteroids, tocilizumab and chloroquine in non-pirfenidone group. PFD=pirfenidone.

Figure 2

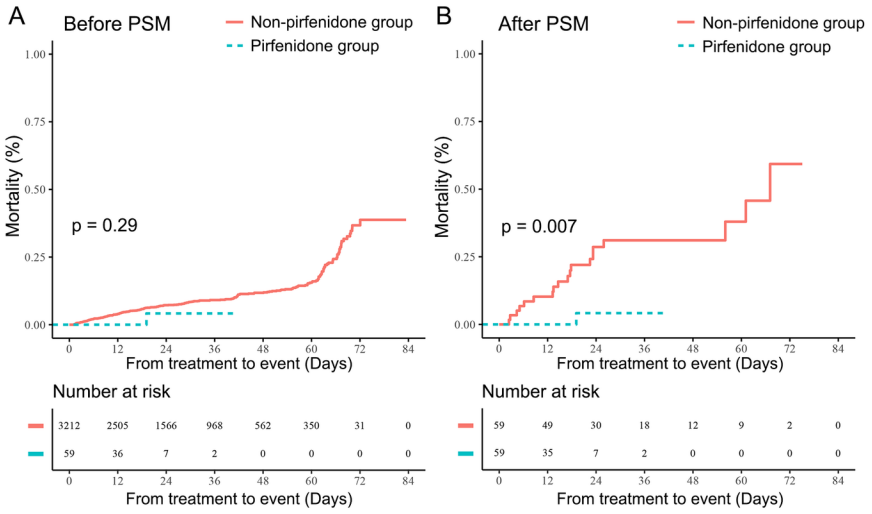

Figure 2. The Kaplan-Meier (KM) estimate of survival rate with 95% confidence interval of pirfenidone group in patients hospitalised with COVID-19 up to 40 days after pirfenidone therapy, and non-pirfenidone group up to 84 days. (A) In overall populations, before propensity score matching (PSM); (B) After propensity score matching (PSM). COVID-19=coronavirus disease 2019. PFD=Pirfenidone.

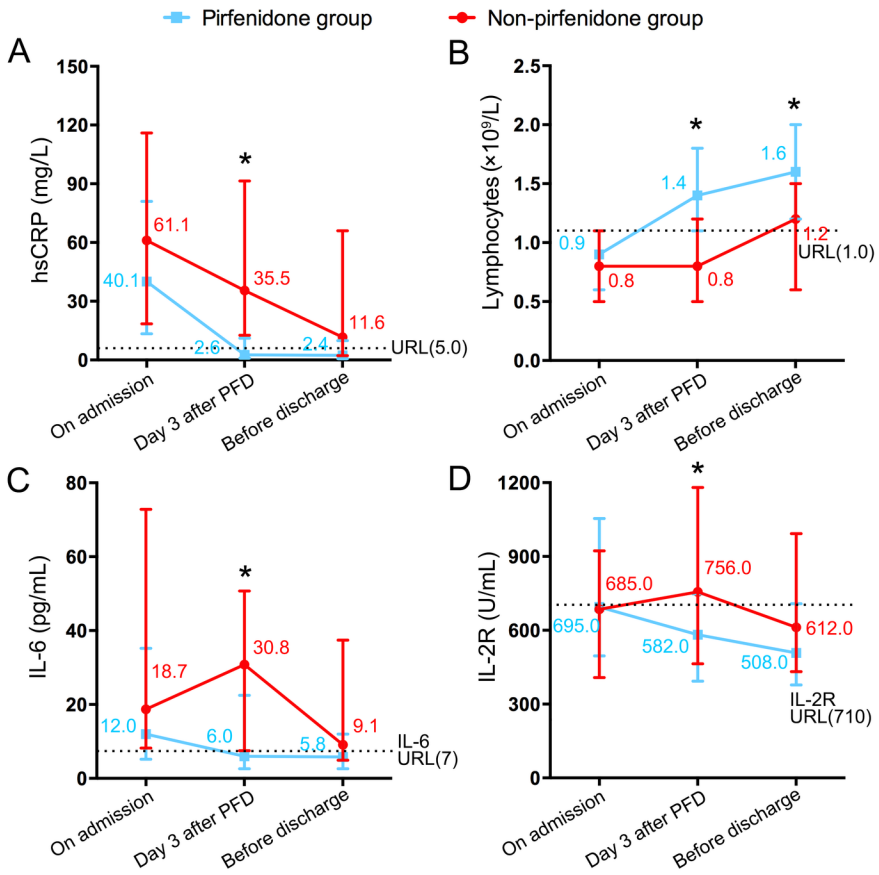

Figure 3. Temporal changes of inflammatory markers on admission, day 3 after pirfenidone therapy and before hospital discharge in patients hospitalised with COVID-19. Figure shows temporal changes in hs-CRP (A), lymphocyte count (B), IL-6 (C), and IL-2R (D). *P<0.05 vs values in non-PFD group. Differences between pirfenidone group and non-pirfenidone group were significant for all timepoints shown. COVID-19=coronavirus disease 2019. hs-CRP=high sensitivity C-reactive protein; IL=interleukin; IL-2R= interleukin 2 receptor; TNFα= tumor necrosis factor α· PFD=Pirfenidone; URL=upper range limit.

Figure 4

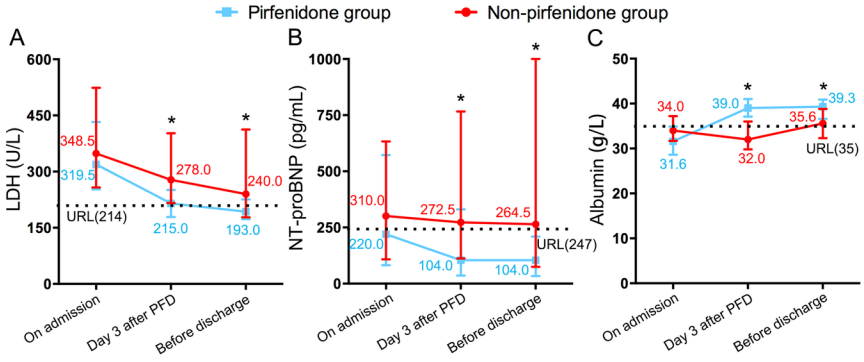

Figure 4. Temporal changes of biochemical indexes on admission, day 3 after pirfenidone therapy and before hospital discharge in patients hospitalised with COVID-19. Figure shows temporal changes in, LDH (A), NT-proBNP (B) and albumin (C). *P<0.05 vs values in non-PFD group. Differences between pirfenidone group and non-pirfenidone group were significant for all timepoints shown. LDH=lactic dehydrogenase; NT-proBNP=N-terminal pro-B-type natriuretic peptide; COVID-19=coronavirus disease 2019; PFD=Pirfenidone; URL=upper range limit.

Figure 5

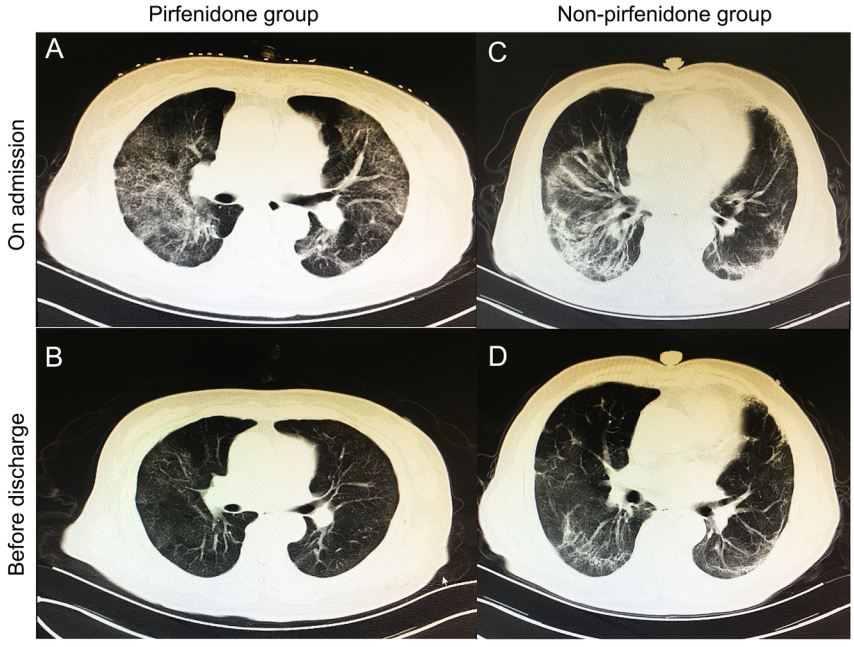

Figure 5. Chest CT of patients with COVID-19 after pirfenidone therapy. (A) CT scan image on admission in a patient with pirfenidone treatment. (B) 30 days later before discharge, the CT scan in patient (A), the GGO was obviously absorbed; (C) CT scan image on admission in a patient with non-pirfenidone treatment; (D) 30 days later before discharge, the CT scan in patient (C), the GGO was partially absorbed and the fibrous stripes/crazy-paving sign had no significant changes. GGO=ground-glass opacity; COVID-19=coronavirus disease 2019; URL=upper range limit.

Table 1. Baseline characteristics of study subjects.

	Before PSM	Before PSM	Before PSM	Before PSM	Before PSM	After PSM	After PSM	After PSM	Af PS
Characteristics	Overall (n=3272)	Non-pirfenidone (n=3212)	Pirfenidone (n=60)	p	SMD	Non-pirfenidone (n=59)	Pirfenidone (n=59)	p	SM
Age (years)	61.0 [49.0, 69.0]	61.0 [49.0, 69.0]	63.0 [53.5, 69.0]	0.295	0.201	65.0 [53.0, 73.0]	63.0 [53.0, 69.0]	0.530	0.0
Female n.(%)	1645 (50.3)	1623 (50.5)	22 (36.7)	0.033	0.282	20 (33.9)	22 (37.3)	0.701	0.0
BMI (kg/m2)	23.4 [21.5, 25.4]	23.4 [21.5, 25.4]	24.3 [21.5, 25.4]	0.712	0.002	23.7 [21.3, 25.4]	24.4 [21.6, 25.6]	0.662	0.1
Length of stay (days)	29.7 [13.1, 41.4]	27.3 [13.0, 41.1]	41.4 [31.9, 46.9]	<0.001	0.757	28.0 [17.0, 43.7]	41.1 [31.7, 46.9]	<0.001	0.5
Time from admission to pirfenidone treatment (days)	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	27.2 [13.9, 34.9]	<0.001	2.525	0.0 [0.0, 0.0]	26.8 [13.7, 36.2]	<0.001	2.4
Co-existing conditions									
History of hypertension n.(%)	973 (29.7)	947 (29.5)	26 (43.3)	0.020	0.291	20 (33.9)	25 (42.4)	0.343	0.1
History of coronary heart disease n.(%)	233 (7.1)	231 (7.2)	2 (3.3)	0.250	0.173	3 (5.1)	2 (3.4)	0.648	0.0
History of diabetes mellitus n.(%)	450 (13.8)	436 (13.6)	14 (23.3)	0.030	0.254	16 (27.1)	13 (22.0)	0.521	0.1

	Before PSM	Before PSM	Before PSM	Before PSM	Before PSM	After PSM	After PSM	After PSM	Af PS
History of COPD n.(%)	42 (1.3)	40 (1.2)	2 (3.3)	0.155	0.140	1 (1.7)	2 (3.4)	0.559	0.1
History of cancer n.(%)	88 (2.7)	87 (2.7)	1 (1.7)	0.621	0.071	1 (1.7)	1 (1.7)	1.000	<0
History of renal disease n.(%)	18 (0.6)	18 (0.6)	0 (0.0)	0.561	0.106	59 (100.0)	59 (100.0)	NA	<0
History of stroke n.(%)	113 (3.5)	111 (3.5)	2 (3.3)	0.959	0.007	3 (5.1)	2 (3.4)	0.648	0.0
Signs and symptoms on admission									
Fever n.(%)	315 (9.6)	308 (9.6)	7 (11.7)	0.589	0.067	7 (11.9)	7 (11.9)	1.000	<0
Cough n.(%)	1817 (55.5)	1784 (55.5)	33 (55.0)	0.933	0.011	36 (61.0)	33 (55.9)	0.575	0.1
Fatigue n.(%)	541 (16.5)	528 (16.4)	13 (21.7)	0.280	0.133	12 (20.3)	12 (20.3)	1.000	<0
Dyspnea n.(%)	1046 (32.0)	1015 (31.6)	31 (51.7)	0.001	0.416	27 (45.8)	30 (50.8)	0.580	0.1
Temperature(℃)	36.6 [36.3, 37.0]	36.6 [36.3, 37.0]	36.5 [36.2, 36.8]	0.219	0.094	36.7 [36.4, 37.2]	36.5 [36.2, 36.8]	0.097	0.2
Respiratory rate (counts/min)	20.0 [20.0, 22.0]	20.0 [20.0, 22.0]	20.0 [20.0, 22.5]	0.617	0.040	20.0 [20.0, 22.0]	20.0 [20.0, 22.0]	0.925	0.0
Heart rate (beats/min)	90.0 [80.0, 102.0]	90.0 [80.0, 102.0]	93.0 [85.5, 104.5]	0.082	0.129	89.0 [80.0, 102.8]	92.5 [85.2, 104.0]	0.285	0.1
Systolic pressure on admission (mm/Hg)	80.0 [72.0, 89.0]	80.0 [72.0, 89.0]	80.0 [69.5, 85.5]	0.157	0.121	80.0 [73.5, 87.0]	79.0 [69.2, 85.0]	0.254	0.1
Systolic pressure on admission (mm/Hg)	130.0 [119.0, 143.0]	130.0 [119.0, 143.0]	132.0 [115.5, 139.5]	0.580	0.026	126.5 [117.5, 143.2]	131.5 [115.2, 139.5]	0.914	0.0

PSM, propensity score matching.

Table 2. Laboratory findings ofstudy subjects.

	Before PSM	Before PSM	Before PSM	Before PSM	Before PSM	After PSM	After PSM	After PSM	Af PS
Parameters	Overall (n=3272)	Non-pirfenidone (n=3212)	Pirfenidone (n=60)	p	SMD	Non-pirfenidone (n=59)	Pirfenidone (n=59)	p	SM
Routine blood test									
White blood cells ($\times 10^9$/L)	5.9 [4.6, 7.7]	5.9 [4.6, 7.7]	7.4 [5.0, 9.6]	0.004	0.312	5.8 [4.7, 7.6]	7.4 [4.9, 9.6]	0.045	0.4
Red blood cells ($\times 10^{12}$/L)	4.2 [3.7, 4.5]	4.2 [3.8, 4.5]	4.0 [3.6, 4.4]	0.087	0.224	4.2 [3.7, 4.7]	4.0 [3.6, 4.4]	0.096	0.2
Lymphocytes ($\times 10^9$/L)	1.2 [0.8, 1.7]	1.2 [0.8, 1.7]	0.9 [0.5, 1.1]	<0.001	0.473	0.8 [0.5, 1.1]	0.9 [0.6, 1.1]	0.277	0.1
Monocytes ($\times 10^9$/L)	0.5 [0.4, 0.6]	0.5 [0.4, 0.6]	0.6 [0.4, 0.7]	0.281	0.001	0.4 [0.3, 0.6]	0.6 [0.4, 0.7]	0.069	0.3
Neutrophils ($\times 10^9$/L)	3.8 [2.7, 5.5]	3.8 [2.7, 5.5]	5.8 [3.6, 7.6]	<0.001	0.466	4.5 [3.4, 5.9]	5.8 [3.6, 7.6]	0.071	0.3
Eosinophils ($\times 10^9$/L)	0.0 [0.0, 0.1]	0.0 [0.0, 0.1]	0.0 [0.0, 0.2]	0.825	0.131	0.0 [0.0, 0.1]	0.0 [0.0, 0.2]	0.030	0.4
Basophils ($\times 10^9$/L)	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.831	0.046	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.015	0.4
Hemoglobin(g/L)	127.0 [115.5, 139.0]	127.0 [116.0, 139.0]	125.0 [108.5, 133.0]	0.104	0.256	127.0 [114.2, 143.0]	125.0 [108.2, 132.8]	0.325	0.0
Platelets ($\times 10^9$/L)	221.0 [168.0, 284.0]	220.0 [168.0, 283.0]	237.0 [156.0, 312.5]	0.259	0.239	182.0 [152.0, 261.0]	243.0 [155.5, 314.2]	0.014	0.5
Liver function									
Alanine aminotransferase (U/L)	22.0 [14.0, 37.0]	22.0 [14.0, 37.0]	28.0 [18.5, 44.5]	0.022	0.034	25.0 [15.0, 36.8]	28.0 [18.2, 44.8]	0.312	0.0
Aspartate aminotransferase (U/L)	25.0 [18.0, 36.0]	25.0 [18.0, 36.0]	29.0 [20.5, 44.5]	0.040	0.024	31.5 [24.0, 49.2]	29.5 [21.0, 45.2]	0.409	0.2
Total bilirubin (μmol/L)	9.0 [6.6, 12.5]	9.0 [6.6, 12.5]	9.2 [7.3, 12.3]	0.425	0.077	10.1 [7.3, 14.2]	9.1 [7.3, 12.1]	0.486	0.2
Direct bilirubin (μmol/L)	3.8 [2.9, 5.4]	3.8 [2.8, 5.4]	4.5 [3.4, 6.3]	0.007	0.023	4.8 [3.7, 7.0]	4.5 [3.4, 6.3]	0.671	0.2

	Before PSM	Before PSM	Before PSM	Before PSM	Before PSM	After PSM	After PSM	After PSM	Af PS
Indirect bilirubin (μmol/L)	5.1 [3.6, 7.2]	5.1 [3.6, 7.2]	4.7 [3.7, 5.9]	0.194	0.155	5.3 [3.5, 7.6]	4.7 [3.6, 6.0]	0.323	0.2
Albumin (g/L)	36.5 [32.4, 40.7]	36.6 [32.5, 40.7]	31.7 [28.6, 34.8]	<0.001	0.845	34.0 [31.7, 37.2]	31.6 [28.6, 34.9]	0.008	0.4
Globulin (g/L)	31.8 [28.2, 35.7]	31.6 [28.2, 35.7]	34.9 [32.5, 38.5]	<0.001	0.630	33.0 [29.5, 36.4]	34.8 [32.4, 38.0]	0.033	0.4
Total protein (g/L)	68.7 [65.0, 72.4]	68.7 [65.0, 72.4]	66.5 [64.5, 72.3]	0.332	0.079	67.7 [62.7, 71.5]	66.5 [64.4, 72.2]	0.758	0.0
Albumin/Globulin	1.1 [0.9, 1.4]	1.2 [0.9, 1.4]	0.9 [0.8, 1.0]	<0.001	0.894	1.0 [0.9, 1.2]	0.9 [0.8, 1.0]	0.004	0.5
Prealbumin (g/L)	224.5 [160.0, 274.2]	226.0 [161.5, 275.0]	204.0 [128.0, 256.0]	0.108	0.219	204.0 [143.0, 275.0]	205.5 [137.8, 256.8]	0.857	0.0
Total bile acids (μmol/L)	3.7 [2.2, 6.2]	3.7 [2.2, 6.1]	4.1 [1.8, 6.8]	0.728	0.082	3.9 [3.0, 5.4]	4.0 [1.8, 6.8]	0.794	0.2
Total cholesterol (mmol/L)	3.8 [3.2, 4.5]	3.8 [3.2, 4.5]	3.5 [3.2, 4.2]	0.076	0.252	3.4 [3.0, 4.1]	3.5 [3.2, 4.2]	0.666	0.0
Triglyceride (mmol/L)	1.3 [1.0, 1.8]	1.3 [1.0, 1.8]	1.6 [1.1, 2.0]	0.062	0.175	1.4 [1.1, 1.7]	1.6 [1.1, 2.0]	0.370	0.3
High density lipoprotein (mmol/L)	1.0 [0.8, 1.2]	1.0 [0.8, 1.2]	0.9 [0.7, 1.0]	0.016	0.442	0.9 [0.7, 1.0]	0.9 [0.7, 1.0]	0.983	0.0
Low density lipoprotein (mmol/L)	2.4 [1.9, 3.0]	2.4 [1.9, 3.0]	2.4 [2.0, 3.0]	0.880	0.038	2.2 [1.8, 2.5]	2.4 [2.0, 3.1]	0.080	0.5
Blood glucose (mmol/L)	5.9 [5.1, 7.5]	5.9 [5.1, 7.4]	6.9 [5.9, 10.4]	<0.001	0.466	7.1 [5.7, 9.6]	6.9 [5.9, 10.2]	0.780	0.0
Lactic dehydrogenase (U/L)	246.0 [194.0, 333.0]	245.0 [194.0, 331.0]	321.0 [254.0, 430.0]	<0.001	0.439	348.5 [257.8, 523.8]	319.5 [252.5, 432.5]	0.456	0.3
Alkaline phosphatase (U/L)	67.0 [55.0, 83.0]	67.0 [55.0, 83.0]	71.0 [61.0, 89.0]	0.081	0.141	69.5 [59.0, 100.2]	70.0 [61.0, 88.5]	0.936	0.0
Amylase (U/L)	59.0 [44.0, 77.0]	59.0 [44.0, 76.5]	65.5 [47.8, 82.2]	0.227	0.080	48.0 [39.0, 86.5]	65.5 [47.8, 82.2]	0.426	0.1
Kidney function									

	Before PSM	Before PSM	Before PSM	Before PSM	Before PSM	After PSM	After PSM	After PSM	Af PS
Creatinine (μmol/L)	68.0 [56.0, 84.0]	68.0 [56.0, 84.0]	70.0 [55.5, 85.0]	0.979	0.044	72.0 [58.0, 92.5]	69.5 [55.2, 82.8]	0.315	0.0
Urea nitrogen (mmol/L)	4.6 [3.5, 6.0]	4.6 [3.5, 6.0]	5.0 [3.8, 6.8]	0.198	0.081	5.2 [3.8, 7.3]	5.0 [3.8, 6.7]	0.350	0.1
Uric acid (μmol/L)	266.0 [206.1, 338.0]	266.7 [207.0, 338.0]	260.0 [175.7, 318.6]	0.269	0.038	257.0 [191.0, 329.1]	257.8 [174.8, 318.9]	0.988	0.1
Electrolyte									
Serum potassium (mmol/L)	4.2 [3.9, 4.5]	4.2 [3.9, 4.5]	4.2 [3.8, 4.6]	0.713	0.062	4.1 [3.7, 4.5]	4.2 [3.8, 4.6]	0.370	0.1
Serum sodium (mmol/L)	139.8 [137.4, 141.6]	139.8 [137.5, 141.7]	137.1 [134.1, 140.2]	<0.001	0.449	137.6 [134.1, 140.6]	137.2 [134.1, 140.2]	0.865	0.0
Serum chloride (mmol/L)	101.4 [98.7, 103.4]	101.4 [98.8, 103.4]	99.8 [96.3, 102.5]	0.009	0.291	99.0 [96.0, 102.0]	99.8 [96.2, 102.5]	0.530	0.0
Serum calcium (mmol/L)	2.2 [2.1, 2.2]	2.2 [2.1, 2.2]	2.1 [2.0, 2.2]	<0.001	0.626	2.1 [2.0, 2.2]	2.1 [2.0, 2.2]	0.114	0.2
Serum phospho-rus (mmol/L)	1.1 [0.9, 1.2]	1.1 [0.9, 1.3]	1.0 [0.8, 1.2]	0.012	0.364	0.9 [0.8, 1.0]	1.0 [0.8, 1.1]	0.018	0.7
Serum magne-sium (mmol/L)	0.8 [0.8, 0.9]	0.8 [0.8, 0.9]	0.8 [0.8, 0.9]	0.270	0.121	0.8 [0.7, 0.9]	0.8 [0.8, 0.9]	0.281	0.1
Coagulation func-tion									
Thrombin time (s)	16.4 [15.6, 17.3]	16.4 [15.6, 17.3]	16.6 [15.6, 17.5]	0.435	0.094	16.4 [15.5, 18.0]	16.6 [15.6, 17.5]	0.598	0.0
Prothrombin time (s)	13.7 [13.2, 14.4]	13.7 [13.2, 14.4]	14.0 [13.4, 14.6]	0.180	0.025	13.9 [13.4, 14.6]	13.9 [13.3, 14.5]	0.695	0.0
Activated partial thrombo-plastin time (s)	38.7 [35.8, 42.4]	38.7 [35.9, 42.4]	38.6 [35.2, 42.2]	0.526	0.082	42.5 [36.9, 46.1]	38.5 [35.2, 42.2]	0.022	0.4
Antithrombin activity (%)	94.0 [84.0, 102.0]	94.0 [84.0, 102.0]	91.0 [81.0, 96.0]	0.074	0.253	86.0 [71.8, 97.0]	91.0 [80.5, 96.8]	0.260	0.1
PT-INR	1.1 [1.0, 1.1]	1.1 [1.0, 1.1]	1.1 [1.0, 1.1]	0.115	0.021	1.1 [1.0, 1.1]	1.1 [1.0, 1.1]	0.846	
D-Dimer (μg/mL FEU)	0.7 [0.3, 1.6]	0.7 [0.3, 1.6]	1.9 [1.0, 4.7]	<0.001	0.627	1.1 [0.5, 1.7]	1.9 [1.0, 4.7]	0.008	0.5

	Before PSM	Before PSM	Before PSM	Before PSM	Before PSM	After PSM	After PSM	After PSM	Af PS
Fibrinogen (g/L)	4.4 [3.4, 5.6]	4.3 [3.4, 5.6]	5.0 [4.6, 6.0]	<0.001	0.416	4.8 [3.9, 5.9]	5.0 [4.6, 6.0]	0.268	0.2
Cardiac function									
NT-ProBNP (pg/mL)	119.5 [44.0, 379.5]	118.0 [43.0, 377.0]	208.0 [74.5, 570.5]	0.023	0.025	301.0 [108.0, 633.0]	220.0 [82.0, 572.0]	0.428	0.0
Myoglobin (ng/mL)	40.5 [28.5, 72.2]	40.4 [28.6, 72.0]	43.9 [26.7, 74.4]	0.947	0.167	81.9 [35.8, 147.1]	43.5 [26.6, 72.5]	0.034	0.6
Creatine kinase (U/L)	70.0 [47.0, 121.8]	71.0 [48.0, 122.0]	47.0 [31.8, 81.5]	0.002	0.113	112.0 [55.0, 195.0]	51.0 [32.0, 82.0]	0.012	0.2
CK-MB (ng/mL)	0.8 [0.5, 1.3]	0.8 [0.5, 1.3]	0.9 [0.5, 1.3]	0.663	0.173	1.0 [0.6, 1.6]	0.8 [0.5, 1.3]	0.328	0.3
hs-cTnI (pg/mL)	6.9 [3.6, 15.8]	6.9 [3.6, 15.8]	6.2 [3.9, 16.1]	0.986	0.128	10.3 [4.7, 19.2]	6.7 [4.2, 16.6]	0.178	0.2
Inflammation									
Interleukin 6 (pg/mL)	8.7 [3.2, 31.3]	8.3 [3.2, 31.1]	11.9 [4.7, 34.1]	0.091	0.026	18.7 [8.2, 72.8]	12.0 [5.2, 35.2]	0.183	0.0
Interleukin 10 (pg/mL)	8.3 [6.2, 12.1]	8.3 [6.2, 12.1]	8.5 [6.3, 12.3]	0.889	0.108	9.2 [6.7, 21.2]	8.7 [6.4, 12.5]	0.640	0.5
Interleukin 8 (pg/mL)	12.5 [8.2, 22.2]	12.4 [8.1, 21.9]	17.2 [9.7, 25.5]	0.117	0.041	17.9 [9.4, 35.5]	17.6 [9.9, 25.7]	0.560	0.0
Tumor necrosis factor-α (pg/mL)	8.3 [6.7, 10.6]	8.3 [6.6, 10.6]	9.3 [7.6, 11.5]	0.040	0.072	7.5 [7.2, 9.1]	9.3 [7.6, 11.6]	0.051	0.0
Interleukin 1β (pg/mL)	8.4 [6.3, 13.3]	8.5 [6.3, 13.6]	7.0 [5.7, 12.7]	0.316	0.204	6.7 [6.1, 28.9]	7.0 [5.7, 12.7]	0.930	0.5
Interleukin 2 receptor (U/L)	467.0 [303.0, 779.5]	457.5 [297.0, 761.8]	715.0 [496.0, 1053.0]	<0.001	0.336	685.5 [407.8, 923.0]	695.0 [496.0, 1054.2]	0.533	0.0
High sensitivity C-reactive protein (mg/L)	11.5 [1.9, 56.8]	11.1 [1.8, 55.5]	41.9 [13.4, 84.8]	<0.001	0.397	61.1 [18.5, 115.9]	40.1 [13.4, 81.0]	0.204	0.2

The levels of biomarkers in Non-pirfenidone group were collected on admission; the levels of biomarkers in pirfenidone group were collected before pirfenidone administration; PSM, propensity score matching.

Table 3. Pharmacological and mechanical therapy of study subjects before pirfenidone administration.

	Before PSM	Before PSM	Before PSM	Before PSM	Before PSM	After PSM	After PSM	After PSM	Af PS
Administration	Overall (n=3272)	Non-pirfenidone (n=3212)	Pirfenidone (n=60)	p	SMD	Non-pirfenidone (n=59)	Pirfenidone (n=59)	p	SM
Pharmacological therapy									
Antiviral agent n. (%)	1415 (43.2)	1381 (43.0)	34 (56.7)	0.034	0.276	33 (55.9)	34 (57.6)	0.853	0.0
Immunoglobulin n. (%)	819 (25.0)	782 (24.3)	37 (61.7)	<0.001	0.814	40 (67.8)	36 (61.0)	0.442	0.1
Corticosteroids n. (%)	1175 (35.9)	1128 (35.1)	47 (78.3)	<0.001	0.969	51 (86.4)	46 (78.0)	0.229	0.2
Antibiotic therapy n. (%)	2254 (68.9)	2204 (68.6)	50 (83.3)	0.015	0.350	54 (91.5)	49 (83.1)	0.167	0.2
Antifungal therapy n. (%)	123 (3.8)	117 (3.6)	6 (10.0)	0.010	0.254	9 (15.3)	6 (10.2)	0.407	0.1
Tocilizumab n. (%)	56 (1.7)	50 (1.6)	6 (10.0)	<0.001	0.368	4 (6.8)	5 (8.5)	0.729	0.1
Chloroquine n. (%)	393 (12.0)	383 (11.9)	10 (16.7)	0.263	0.136	7 (11.9)	9 (15.3)	0.591	0.0
Mechanical therapy									
Oxygen n. (%)	2663 (81.4)	2604 (81.1)	59 (98.3)	0.001	0.592	54 (91.5)	58 (98.3)	0.094	0.3
NIV n. (%)	449 (13.7)	429 (13.4)	20 (33.3)	<0.001	0.486	23 (39.0)	19 (32.2)	0.442	0.1
IMV n. (%)	300 (9.2)	289 (9.0)	11 (18.3)	0.013	0.274	14 (23.7)	10 (16.9)	0.360	0.1
IABP n. (%)	5 (0.2)	5 (0.2)	0 (0.0)	0.760	0.056	1 (1.7)	0 (0.0)	0.315	0.1
ECMO n. (%)	25 (0.8)	21 (0.7)	4 (6.7)	<0.001	0.324	1 (1.7)	4 (6.8)	0.170	0.2
CRRT n. (%)	104 (3.2)	95 (3.0)	9 (15.0)	<0.001	0.431	6 (10.2)	8 (13.6)	0.569	0.1

The usages of therapy in Non-pirfenidone group were collected throughout hospitalization; the usages of therapy in pirfenidone group were collected before pirfenidone administration; PSM, propensity score matching.

Table 4. The clinical outcome in patients with pirfenidone treatment and without.

	Before PSM				
	Overall	Non-pirfenidone group	Pirfenidone group	p	Non-
All patients					
Mortality n (%)	303/3272 (9.3)	302/3212 (9.4)	1/60 (1.7)	0.041	19/5

		Before PSM			
Hospital stay (days)	23.7 [13.1, 41.4]	23.3 [13.0, 41.1]	41.4 [31.9, 46.9]	<0.001	25.0
Oxygen n. (%)	2663 (81.4)	2605/3212 (81.1)	58/60 (96.7)	0.002	54 (9
Duration of oxygen (median days [IQR])	18.0 [9.0, 28.0]	18.0 [9.0, 28.0]	38.0 [28.0, 42.0]	<0.001	22.5
NIV n. (%)	449/3272 (13.7)	429/3212 (13.4)	20/60 (33.3)	<0.001	23 (3
Duration of NIV (median days [IQR])	4.0 [1.0, 10.0]	4.0 [1.0, 10.0]	7.5 [1.0, 13.8]	0.419	3.0 [2
IMV n. (%)	300/3272 (9.2)	289/3212 (9.0)	11/60 (18.3)	0.013	14 (2
Duration of IMV (median days [IQR])	5.0 [1.0, 12.0]	5.0 [1.0, 11.0]	13.0 [9.0, 18.0]	0.004	6.5 [4
Patients with hospital stay > 28 day					
Mortality n (%)	105/1374 (7.6)	105/1326 (7.9)	0/48 (0.0)	0.042	3/26
Hospital stay (days)	44.2 [35.5, 60.4]	44.2 [35.4, 60.4]	45.5 [39.7, 51.7]	0.761	45.3
Oxygen n. (%)	1234 (89.8)	1188/1326 (89.6)	46/48 (95.8)	0.160	25 (9
Duration of oxygen (median days [IQR])	29.0 [17.2, 38.0]	29.0 [17.0, 37.0]	40.5 [33.8, 44.0]	<0.001	37.0
NIV n. (%)	253/1374 (18.4)	237/1326 (17.9)	16/48 (33.3)	0.007	7 (26
Duration of NIV (median days [IQR])	5.0 [1.0, 13.0]	5.0 [1.0, 13.0]	6.0 [1.0, 11.5]	0.969	14.0
IMV n. (%)	150/1374 (10.9)	140/1326 (10.6)	10/48 (20.8)	0.025	5 (19
Duration of IMV (median days [IQR])	6.0 [1.0, 17.0]	5.0 [1.0, 17.0]	13.0 [8.5, 18.0]	0.042	7.0 [5

NIV, non-invasive ventilation; IMV, invasive mechanical ventilation; PSM, propensity score matching. The usages of therapy were collected throughout hospitalization.

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