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ORIGINAL ARTICLE

Clinical outcomes of COVID-19 patients with rheumatic diseases: a retrospective cohort study and synthesis analysis in Wuhan, China

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Abstract

Background The clinical outcomes of patients with rheumatic diseases infected with COVID-19 were inconsistent characteristics across regions and time periods. We need to revisit and sort out the clinical characteristics of these patients at the beginning of the global COVID-19 epidemic.

Methods We collected data from confirmed COVID-19 patients from two military-run field hospitals and classified them into the rheumatic disease group and no rheumatic disease groups, and the latter was further distinguished by ARD and non-ARD. We compared the primary outcome, which we defined as mortality, and the secondary outcome, which we defined as the ICU occupancy rate, the duration of hospitalization and the duration of viral clearance, between the patients with and without rheumatic diseases after PSM. A study-level meta-analysis of four studies was conducted on the mortality of the COVID-19 patients with and without rheumatic diseases.

Results A total of 4353 COVID-19 patients were included in our cohort study; 91 had rheumatic diseases. The mean age of the entire cohort was 59.37, and 2281 (52.40%) patients were female. The mortalities after PSM were 1.11% and 3.46% in the rheumatic diseases and no rheumatic disease groups, respectively. The ICU occupancy rates after PSM were 2.22% and 4.61% in the rheumatic diseases and no rheumatic disease groups. The duration of hospitalization and viral clearance in the rheumatic disease group were 15.97 and 43.69, respectively; moreover, the same parameters in the no rheumatic diseases after PSM were 15.48 and 45.48. No significant differences were found in either the primary or secondary outcomes. After excluding the gout cases, the results were still similar. However, there was a significant difference between the two groups upon meta-analysis ($RR = 1.70$, 95% CI 1.35–2.13).

Conclusions Rheumatic diseases seemed to aggravate the course of COVID-19 infection. However, the poor outcomes of COVID-19 seemed to be unassociated with rheumatic diseases undergoing an adequate medical intervention.

Key points

- *We compared the outcomes and prognosis of COVID-19 patients in China at the beginning of the outbreak regarding the presence or absence of rheumatic disease patients and made some meaningful conclusions for future outbreaks of similar infectious diseases.*
- *We compared similar recent studies from other countries and explored the changes and differences in patient outcomes associated with COVID-19 as it continued to spread worldwide during the year, providing clinical evidence to further explore the role rheumatic diseases play in COVID-19 patient outcomes.*
- *We provided evidence for the treatment of relevant patients and made rationalized recommendations for treatment strategy.*

Keywords COVID-19 · Meta-analysis · Mortality · Propensity score matching · Rheumatic diseases

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Introduction

COVID-19 (coronavirus disease 2019) has become the most serious public health crisis since the second world war [1]. Particularly worrying about this pandemic is that its spread does not appear to have been effectively curbed. Patients with COVID-19, along with those with pre-existing comorbidities such as hypertension, cancer, and diabetes, may have a higher risk for entering the critical phase of the COVID-19 infection as well as a higher risk of mortality [2–7].

Rheumatic diseases, most of which are autoimmune diseases, attack joints, bones, muscles, blood vessels, and related soft tissues or connective tissues. Many immune cells and factors, such as regulatory T cells (T reg cells), interleukin-6 (IL-6), and granulocyte colony-stimulating factor (GM-CSF), are considered to be involved in these diseases and contribute to disease progression [8]. Notably, in published immunological studies on COVID-19, the roles of multiple cytokine-mediated immune disorders in the progression of COVID-19 have drawn much attention from investigators [9–11]. The concept of "cytokine storm" has been deeply studied in the treatment of critical patients [12, 13]. Therefore, the possibility that patients with both COVID-19 and rheumatic diseases would experience overlapping effects had been a major concern at the beginning of the COVID-19 pandemic [14–21]. Previously, we retrieved five studies involving the progression and prognosis of patients with rheumatic diseases after SARS-CoV-2 virus infection in Spain, Italy, China, and the UK [22–26]. However, the mortality rate between COVID-19 patients with and without rheumatic diseases varied from study to study. Moreover, the sample size in two of published studies being rather small and uneven which resulted in lower statistical power [23, 24]. Therefore, further studies about the clinical outcome of COVID-19 patients with rheumatic diseases are needed.

In this study, we used patient data from two military-run field hospitals to examine the clinical prognosis of COVID-19 patients with rheumatic diseases. Furthermore, in order to improve the statistical power, we conducted a meta-analysis to synthesize the results from retrieved literature reports. With this study, we attempted to draw an accurate portrait of the brand new infectious disease in the patients with rheumatic diseases at the initial stages of its global pandemic. This study could provide some evidences or references for subsequent more in-depth studies.

Methods

Study design and patient selection

This is a retrospective observational study comparing the difference in clinical characteristics and outcomes between COVID-19 patients with and without rheumatic diseases, and the latter was further distinguished by ARD (autoimmune rheumatic diseases) and non-ARD. All patients included in the study were adults (age over 18 years) diagnosed with COVID-19 between Feb 4, 2020, and Apr 1, 2020, at HuoShenShan Hospital and Guanggu District Maternal and Child Health Hospital of Hubei Province, Wuhan, China. The diagnosis of COVID-19 was confirmed using a positive nucleic acid detection for SARS-CoV-2. The severity of COVID-19 cases was classified upon admission according to protocols for the diagnosis and treatment of COVID-19 issued by the Chinese National Health Commission [27, 28]. In addition, the therapeutic principles of COVID-19 also followed the above protocols.

Information on clinical signs and symptoms, physical examinations, laboratory tests, and the therapeutic schedule was extracted from the hospital information system. The complete course and length of the disease in the hospital were also recorded. All patients' records were retrieved, proofread, and organized by two independent investigators to form the structural dataset.

The definition and range of rheumatic diseases were all from the authoritative Chinese monographs on rheumatic diseases, Clinical rheumatism Handbook [29]. The presence of rheumatic diseases was identified from the secondary diagnosis on discharge records. Furthermore, the diagnosis upon admission was also checked to doublecheck the diagnosis of rheumatic diseases.

Statistical analysis

The primary clinical endpoint was mortality due to COVID-19. Secondary endpoints included ICU occupancy rate due to COVID-19; days of viral clearance—the interval from a mean incubation period (i.e., 2 weeks) prior to the date the patient complains of first detecting the symptom (including fever, cough, malaise) to the date of two consecutive negative nucleic acid tests; and duration of hospital stay. We compared and analyzed differences in all outcomes between patients with and without rheumatic diseases, and between patients with ARD and non-ARD. Categorical variables were expressed as frequencies and percentages. Categorical variables between groups were compared by the Chi test or the Fisher's exact method. Continuous variables with approximate normality were expressed as mean and *SD*, compared by the *T* test. Otherwise, the abnormal continuous variables were expressed as median and IQR, compared by the nonparametric test (Kruskal–Wallis *H* test).

To compare the clinical outcome between patients with and without rheumatic diseases, PSM (propensity score matching) was used to balance the baseline. Propensity score was estimated using multivariable logistic regression. According to the published studies, we matched the

following variables: age; gender; height; weight; temperature upon admission; respiratory rate upon admission; oxyhemoglobin saturation upon admission; history of chronic obstructive pulmonary disorder, diabetes, hypertension, coronary heart disease; and treatment with antivirals, glucocorticoids, tocilizumab, and hydroxychloroquine [3, 7, 30–33]. The nearest-neighbor matching was used for PSM, with a matching ratio of 1:4.

In order to synthesize and compare with the current research progress in this area in other regions of the world, we searched for reports on COVID-19 infection in patients with rheumatic diseases as of April 2021. Among these reports, we further screened for studies with similar primary or secondary outcomes to our study to be included in the meta-analysis. For the meta-analysis, if $I^2 > 50\%$, a random effect model would been used to pool the data from the retrieved published studies. The primary outcome of the meta-analysis was mortality due to COVID-19. *RR* (risk ratio) was used as the effect size.

R version 4.0.2 (R Foundation, Vienna, Austria) was used for the statistical analysis and the meta-analysis. $P < 0.05$ was considered to indicate statistical significance. All statistical tests were two-tailed.

Result

Study population

Figure 1 shows the inclusion flow chart of the patients. Data of 4804 patients were retrieved from the hospital information systems between February 4 and April 15, 2020. After excluding records of patients who were less than 18 years old and records with missing essential information, 4353 patients with COVID-19 were included. Of these 4353 patients, 91 (2.09%) patients suffered from rheumatic diseases (i.e., rheumatic disease group), 57 with gout, 20 with RA (rheumatoid arthritis), 4 with SLE (systemic lupus

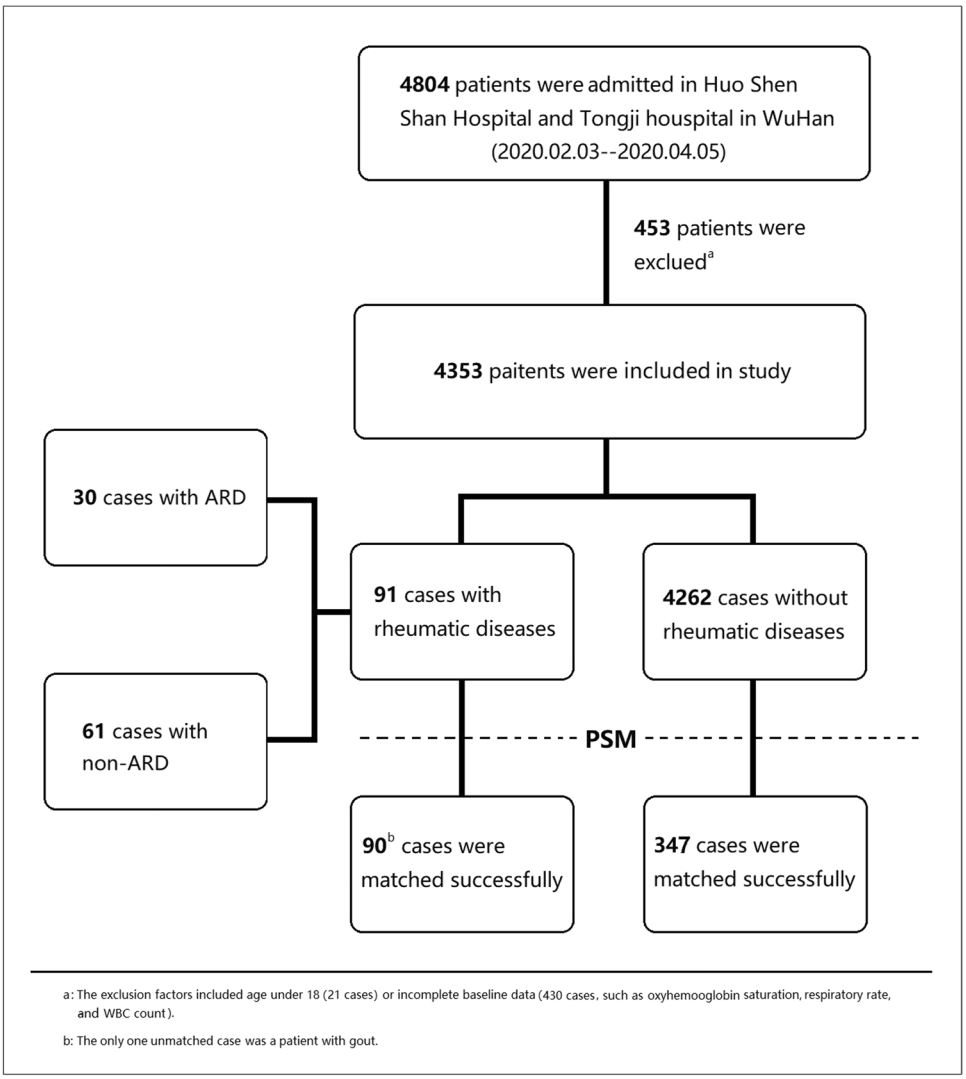

Fig. 1 Flow chart of the whole study

erythematosus), 3 with osteoarthritis, 2 with MCTD (mixed connective tissue disease), 2 with AS (ankylosing spondylitis), 1 with pSS (primary Sjogren's syndrome), 1 with Tietze syndrome, and the other 1 with DM (dermatomyositis). Based on the pathogenesis of these rheumatic diseases, RA, SLE, MCTD, AS, pSS, and DM were considered to be ARD in 30 cases, while 61 cases with other rheumatic diseases, including gout, osteoarthritis, and Tietze syndrome, were regarded as non-ARD.

The basic clinical characteristics of the included patients are shown in Table 1 and Table 2. The average age of the entire cohort of patients was 59.37 years, and 2281 (52.40%) were female, and the no rheumatic disease group had a higher percentage of female ($P=0.02$) than the rheumatic disease group, but the proportion of women in the crowd with ARD was higher than that with non-ARD ($P<0.01$). The most common recorded comorbidities were hypertension (30.21%), diabetes (13.71%), and coronary heart disease (6.11%). The most common symptoms were fever (62.60%, $P=0.04$), cough (57.41%), and fatigue (35.06%) in all cases. Finally, it is worth mentioning that patients with rheumatic diseases were more prone to receive glucocorticoid treatment (25.34% vs. 12.03%, $P<0.01$) than those without rheumatic diseases. Moreover, patients with ARD had a higher rate of glucocorticoid treatment ($P<0.01$) than patients with non-ARD.

As shown in Table 1, there was a significant difference in the severity of COVID-19 between the no rheumatic disease group and rheumatic disease group ($P=0.04$). Nearly 80% of COVID-19 cases were considered to be of moderate or mild severity, but cases of 29.67% patients with both rheumatic diseases and COVID-19 were considered severe or critical. However, this difference in severity of COVID-19 was not demonstrated between the patients with ARD and non-ARD, as shown in Table 2.

In Table 3, some of the more detailed immune-related laboratory findings were presented. Although constrained by some medical treatment norms and medical ethics, these laboratory tests could not be collected in all patients, we can find that the median level of lymphocyte count and percentage, hemoglobin, and platelet count in COVID-19 patients with SLE was higher than that without SLE or with other rheumatic diseases. Hemoglobin, lymphocyte percentage, and IL-6 levels were significantly different among the groups.

PSM analysis results

Table 4 shows the clinical characteristics of the patients before and after PSM. In PSM analysis, 90 patients in the rheumatic disease group were matched with 347 patients in the no rheumatic disease group, and the two groups struck a balance in all 15 variables. The standard mean differences have been shown in Fig. 2. The differences in the primary and secondary outcomes have been presented in Table 5 and Table 6. For the mortality due to COVID-19, there was no difference between patients with and without rheumatic diseases after PSM ($RR=0.31$, 95% CI: 0.04–2.44). There was also no significant difference between the two groups for duration of hospitalization ($P=0.64$); duration of viral clearance ($P=0.33$); and the ICU occupancy rate ($P=0.47$). Furthermore, similar results were obtained when the same analysis about the primary and secondary outcomes was performed between the patients with ARD and the patients in no rheumatic disease group.

Finally, as shown in Table 7, we also compared and analyzed the primary and secondary outcomes within patients with rheumatic diseases (i.e., between the patients with ARD and non-ARD). The results showed that all outcomes were not significantly different in both groups of patients.

Meta-analysis results

After a systematic search of studies on the clinical outcome for COVID-19 patients with and without rheumatic diseases, five studies were retrieved [22–26]. The pooled results (Fig. 3) revealed a significant difference between the two groups for the mortality due to COVID-19, the patients with rheumatic diseases at a greater risk than the others ($RR=1.70$, 95% CI 1.35–2.13, $P<0.0001$, $I^2=53\%$).

Discussion

In this study, we aimed to analyze the progression of patients with rheumatic diseases after COVID-19 infection by analyzing the inpatients' demographic, clinical, and laboratory data, their comorbidities, treatment, and clinical outcomes. Our data showed that the severity of COVID-19 in patients with rheumatic diseases would be greater than that of COVID-19 in patients without rheumatic diseases, especially which may cause systemic immune level disorders. This conclusion could also be reflected by the fact that a significantly higher proportion of patients with rheumatic diseases had fever as their first symptom. However, the prognosis of COVID-19 was independent of whether or not the patient had rheumatic diseases.

COVID-19 is caused by the SARS-CoV-2 virus, a single-stranded positive-faced RNA virus [34]. It is an acute infectious disease, with primary manifestations being severe acute respiratory syndrome and resembling viral pneumonia [35, 36]. In our study, the IL-6 levels of patients with rheumatic diseases were higher than those in patients without rheumatic diseases. Besides, the lymphocyte percentage in the plasma of COVID-19 patients with rheumatic diseases, especially SLE, was lower than that in other patients. In

Table 1 Baseline characteristics of the COVID-19 patients with rheumatic diseases or not

	Total ($n=4353$)	Rheumatic disease group ($n=91$)	No rheumatic disease group ($n=4262$)	Testing statistic	*P* value
Diagnosis of rheumatic diseases					
Gout (%)		57 (62.63)			
Rheumatoid arthritis (RA, %)		20 (21.98)			
Systemic lupus erythematosus (SLE, %)		4 (4.40)			
Others (%)		10 (10.99)			
Age, years, mean (*SD*)	59.37 (14.64)	62.15 (11.88)	59.31 (14.69)	$t=1.83$ [a]	0.07
Height, cm, mean (*SD*)	162.06 (9.22)	163.41 (8.53)	162.03 (9.23)	$t=1.41$	0..16
Weight, kg, mean (*SD*)	59.84 (6.97)	59.94 (6.65)	59.84 (6.67)	$t=0.14$	0.89
Gender					
Male (%)	2072 (47.60)	54 (59.32)	2018 (47.31)	$\chi^2=5.14$ [b]	0.02
Female (%)	2281 (52.40)	37 (40.68)	2244 (52.69)		
Severity of COVID-19					
Mild or moderate (%)	3461 (79.51)	64 (70.33)	3396 (79.68)	$\chi^2=3.96$	0.04
Severe or critical (%)	892 (20.49)	27 (29.67)	866 (20.32)		
Critical (%)					
Hypertension (%)	1315 (30.21)	39 (42.91)	1276 (29.91)	$\chi^2=7.05$	0.01
Diabetes (%)	597 (13.71)	15 (16.51)	582 (13.72)	$\chi^2=0.62$	0.43
Coronary heart disease (%)	266 (6.11)	9 (9.92)	257 (6.02)	$\chi^2=2.31$	0.12
Other chronic diseases or surgeries in bronchi and lungs (%)	163 (3.74)	4 (2.45)	159 (3.73)	$\sim\chi^2<0.01$ [c]	0.96
COPD (%)	47 (1.08)	1 (1.11)	46 (1.12)	*Exact* [d]	>0.99
Cancer (%)	40 (0.92)	0 (0.00)	40 (0.90)	*Exact*	>0.99
General physical conditions					
Temperature, degree centigrade, mean (*SD*)	36.52 (0.43)	36.46 (0.43)	36.52 (0.43)	$t=1.32$	0.19
Respiratory rate, breaths per min, mean (*SD*)	19.92 (2.22)	20.29 (2.17)	19.91 (2.23)	$t=1.61$	0.11
Heart rate, beats per min, mean (*SD*)	85.99 (13.60)	87.31 (14.12)	85.96 (13.59)	$t=0.93$	0.35
Oxyhemoglobin saturation percentage, mean (*SD*)	97.27 (2.42)	97.52 (1.96)	97.26 (2.44)	$t=1.01$	0.31
Blood pressure					
Systolic, mmHg, mean (*SD*)	130.71 (17.03)	129.68 (14.75)	130.73 (17.08)	$t=0.58$	0.56
Diastolic, mmHg, mean (*SD*)	81.41 (11.56)	81.44 (10.06)	81.41 (11.59)	$t=0.02$	0.98
Signs and symptoms					
Fever (%)	2725 (62.60)	66 (72.52)	2659 (62.42)	$\chi^2=3.91$	0.04
Cough (%)	2499 (57.41)	56 (61.52)	2443 (57.32)	$\chi^2=0.64$	0.42
Fatigue (%)	1526 (35.06)	31 (34.12)	1495 (35.10)	$\chi^2=0.04$	0.84
Gasp (%)	673 (15.46)	17 (18.73)	656 (15.40)	$\chi^2=0.73$	0.39
Chest pain (%)	555 (12.75)	17 (18.71)	538 (12.64)	$\chi^2=2.94$	0.09
Sputum (%)	217 (4.99)	3 (3.31)	214 (5.01)	$\sim\chi^2=0.99$	0.25
Headache (%)	45 (1.03)	3 (3.31)	42 (1.01)	*Exact*	0.07
Muscle ache (%)	87 (2.00)	0 (0.00)	87 (2.02)	*Exact*	0.26
Laboratory finds					
White blood cell count, $\times 10^9$/L, mean (*SD*)	6.15 (2.79)	6.62 (2.72)	6.14 (2.80)	$t=1.62$	0.11
Neutrophil count, $\times 10^9$/L, mean (*SD*)	3.98 (2.41)	4.45 (2.63)	3.97 (2.41)	$t=1.88$	0.06
Lymphocyte count, $\times 10^9$/L, mean (*SD*)	1.55 (0.61)	1.46 (0.60)	1.56 (0.61)	$t=1.55$	0.12
Monocyte count, $\times 10^9$/L, mean (*SD*)	0.44 (0.65)	0.51 (0.20)	0.44 (0.66)	$t=1.01$	0.31
Treatment					
Antiviral treatment (%)	2526 (58.03)	51 (56.04)	2475 (58.10)	$\chi^2=0.15$	0.70
Glucocorticoid (%)	534 (12.27)	23 (25.34)	511 (12.03)	$\chi^2=14.6$	<0.01
Hydroxychloroquine (HCQ, %)	180 (4.14)	5 (5.49)	175 (4.11)	$\sim\chi^2=0.15$	0.69
Tocilizumab (TCZ, %)	129 (2.96)	4 (4.40)	125 (2.93)	$\sim\chi^2=0.25$	0.62

[a] "*t*" meant using the *T* test

[b] "χ^2" meant using the Chi test

[c] "$\sim\chi^2$" meant using the Chi test with Yates continuity corrections

[d] "*Exact*" meant using the Fisher's exact method

addition, glucocorticoid usage in patients with rheumatic diseases was higher than that in patients without rheumatic diseases. Therefore, it seemed that the abnormal immune function might make the situation worse in patients with rheumatic diseases than in those without after SARS-CoV-2 virus infection.

Currently, the reason for the exacerbation of COVID-19 due to rheumatic diseases is unclear, and there are no

Table 2 Baseline characteristics of the COVID-19 patients with ARD and non-ARD

	Patients with rheumatic diseases ($n=91$)	Patients with ARD ($n=30$)	Patients with non-ARD ($n=61$)	Testing statistic	*P* value
Age, years, mean (*SD*)	62.15 (11.88)	60.23 (13.17)	63.09 (1.19)	$t=1.08$	0.28
Height, cm, mean (*SD*)	163.41 (8.53)	161.97 (8.13)	164.11 (8.69)	$t=1.13$	0.26
Weight, kg, mean (*SD*)	59.94 (6.65)	60.67 (6.75)	59.58 (6.76)	t = 0.73	0.47
Gender					
Male (%)	54 (59.32)	9 (30.00)	45 (73.77)	$\chi^2=15.97$	< 0.01
Female (%)	37 (40.68)	21 (70.00)	16 (26.23)		
Severity of COVID-19					
Mild or moderate (%)	64 (70.33)	20 (66.67)	44 (72.13)	$\chi^2=0.29$	0.59
Severe or critical (%)	27 (29.67)	10 (33.33)	17 (27.87)		
Critical (%)					
Hypertension (%)	39 (42.91)	11 (36.67)	28 (45.91)	$\chi^2=0.70$	0.40
Diabetes (%)	15 (16.51)	4 (13.33)	11 (18.03)	$\chi^2=0.32$	0.57
Coronary heart disease (%)	9 (9.92)	3 (10.00)	6 (9.84)	$\sim\chi^2=0.12$	0.72
Other chronic diseases or surgeries in bronchi and lungs (%)	4 (2.45)	1 (3.33)	3 (4.92)	$\sim\chi^2=0.04$	0.84
COPD (%)	1 (1.11)	0 (0.00)	1 (1.64)	*Exact*	0.67
General physical conditions					
Temperature, degree centigrade, mean (*SD*)	36.46 (0.43)	36.39 (0.27)	36.49 (0.49)	$t=1.09$	0.28
Respiratory rate, breaths per min, mean (*SD*)	20.29 (2.17)	20.75 (3.01)	20.06 (1.58)	$t=1.43$	0.15
Heart rate, beats per min, mean (*SD*)	87.31 (14.12)	87.47 (15.63)	87.23 (13.45)	$t=0.08$	0.94
Oxyhemoglobin saturation percentage, mean (*SD*)	97.52 (1.96)	97.80 (1.52)	97.38 (2.14)	$t=0.96$	0.34
Blood pressure					
Systolic, mmHg, mean (*SD*)	129.68 (14.75)	128.50 (14.56)	130.26 (14.92)	$t=0.53$	0.59
Diastolic, mmHg, mean (*SD*)	81.44 (10.06)	78.83 (13.34)	82.72 (13.34)	$t=1.75$	0.08
Signs and symptoms					
Fever (%)	66 (72.52)	28 (93.33)	38 (62.30)	$\chi^2=9.72$	< 0.01
Cough (%)	56 (61.52)	18 (60.00)	38 (62.30)	$\chi^2=0.04$	0.83
Fatigue (%)	31 (34.12)	10 (33.33)	21 (34.43)	$\chi^2=0.01$	0.92
Gasp (%)	17 (18.73)	6 (20.00)	11 (18.03)	$\chi^2=0.05$	0.82
Chest pain (%)	17 (18.71)	5 (16.67)	12 (19.67)	$\chi^2=0.11$	0.73
Sputum (%)	3 (3.31)	1 (3.33)	2 (3.28)	*Exact*	0.45
Headache (%)	3 (3.31)	1 (3.33)	2 (3.28)	*Exact*	0.45
Laboratory finds					
White blood cell count, $\times 10^9$/L, mean (*SD*)	6.62 (2.72)	6.31 (2.51)	6.77 (2.82)	$t=0.76$	0.45
Neutrophil count, $\times 10^9$/L, mean (*SD*)	4.45 (2.63)	4.41 (2.31)	4.47 (2.79)	$t=0.10$	0.92
Lymphocyte count, $\times 10^9$/L, mean (*SD*)	1.46 (0.60)	1.35 (0.67)	1.22 (0.56)	$t=1.00$	0.32
Monocyte count, $\times 10^9$/L, mean (*SD*)	0.51 (0.20)	0.53 (0.14)	0.50 (0.22)	$t=0.67$	0.51
Treatment					
Antiviral treatment (%)	51 (56.04)	19 (63.33)	32 (52.46)	$\chi^2=0.97$	0.33
Glucocorticoid (%)	23 (25.34)	15 (50.00)	8 (13.11)	$\chi^2=14.49$	< 0.01
Hydroxychloroquine (HCQ, %)	5 (5.49)	3 (10.00)	2 (3.28)	$\sim\chi^2=0.69$	0.40
Tocilizumab (TCZ, %)	4 (4.40)	2 (6.67)	3 (4.92)	$\sim\chi^2=0.02$	0.88

Table 3 Clinical classification of COVID-19 and some laboratory finds among the patients with different rheumatic diseases

	No rheumatic diseases	Gout	Rheumatoid arthritis (RA)	Systemic lupus erythematosus (SLE)	Others	Testing statistic	*P* value
Severity of COVID-19	***n* = 4262**	***n* = 57**	***n* = 20**	***n* = 4**	***n* = 10**		
Mild and moderate (%)	3396 (79.68)	41 (71.93)	13 (65.00)	1 (25.00)	9 (90.00)		
Severe (%)	783 (18.37)	16 (28.07)	7 (35.00)	2 (50.00)	1 (10.00)		
Critical (%)	83 (1.95)	–	–	1 (25.00)	–		
Laboratory finds	***n* = 2828**	***n* = 43**	***n* = 16**	***n* = 4**	***n* = 6**		
Hemoglobin, g/L, median (IQR)	124.00 (114.00, 134.50)	120.00 (109.88, 130.00)	115.50 (102.62, 121.75)	102.25 (91.34, 113.19)	111.92 (103.38, 117.77)	$H = 16.01$ [a]	< 0.01
Lymphocyte count, $\times 10^9$/L, median (IQR)	1.54 (1.21, 1.90)	1.60 (1.27, 1.91)	1.53 (1.34, 1.60)	1.02 (0.71, 1.26)	1.16 (1.03, 1.33)	$H = 8.02$	0.09
Lymphocyte percentage, %, median (IQR)	27.60 (21.80, 33.10)	27.85 (20.86, 31.15)	27.17 (24.07, 30.52)	13.99 (8.50, 18.56)	21.27 (17.18, 26.84)	$H = 11.34$	0.02
Platelet count, $\times 10^9$/L, median (IQR)	222.00 (184.00, 267.00)	237.00 (187.50, 273.50)	233.50 (211.88, 254.00)	188.12 (152.04, 208.44)	228.67 (191.00, 255.86)	$H = 3.99$	0.41
Interleukin-6, pg/mL, median (IQR)	***n* = 2157** 1.50 (1.50, 3.92)	***n* = 31** 2.22 (1.50, 6.04)	***n* = 12** 9.75 (1.77, 25.66)	***n* = 3** 11.53 (6.51, 27.57)	***n* = 4** 8.41 (1.50, 17.48)	$H = 12.50$	0.01
Erythrocyte sedimentation rate (ESR), mm/H, median (IQR)	*n* = **586** 27.00 (12.62, 50.00)	*n* = **7** 50.33 (38.75, 78.00)	*n* = **3** 52.00 (30.00, 64.50)	*n* = **0** –	*n* = **2** 42.50 (36.25, 48.75)	$H = 6.21$	0.10
SARS-cov-2 IgM, median (IQR)	*n* = **1842** 31.57 (10.38, 68.12)	*n* = **33** 28.31 (17.52, 84.60)	*n* = **16** 19.71 (7.25, 85.55)	*n* = **3** 13.28 (11.63, 29.78)	*n* = **5** 36.73 (7.38, 47.71)	$H = 1.24$	0.87
SARS-cov-2 IgG, median (IQR)	144.72 (95.41, 179.37)	163.23 (119.40, 180.94)	113.07 (88.95, 162.02)	108.39 (54.96, 137.18)	127.82 (82.16, 152.29)	$H = 4.47$	0.35

[a]"*H*" meant using the Kruskal–Wallis *H* test

animal models or in vitro experiments to confirm or explain the underlying molecular and immunological mechanisms. Several published studies had reported that some cytokines (such as IL-6), which had been regarded as the pathogenic factors in many rheumatic diseases, could be connected with the multiple organ injury in patients with COVID-19 [27, 28]. In contrast, some studies suggested that patients with rheumatic diseases, especially SLE and RA, were at a greater risk of developing infection due to treatment with immunosuppressants, such as glucocorticoids, tocilizumab, and hydroxychloroquine [21, 32]. Therefore, having a systemic autoimmune condition could increase the risk of hospital admission [30] and there was a higher chance that patients with rheumatic diseases would need admission under intensive care or need mechanical ventilation.

Nevertheless, our data showed that the outcomes, regardless of the primary or secondary endpoint, of COVID-19 patients seemed to be unrelated to whether or not the patients had rheumatic diseases. Similarly, even when discussing in depth the subgroups within patients with rheumatic diseases (ARD and non-ARD), all considered outcomes did not show any significant differences. This conclusion was similar to a previous study, which did not suggest that bad prognosis of patients with both COVID-19 and rheumatic diseases [37]. In addition, the prognosis of COVID-19 was ever reported to be more likely related to risk factors other than the rheumatic and musculoskeletal diseases or immunosuppressant treatment [23]. We think that we could not yet hastily overturn the conclusion that patients with co-morbid rheumatic diseases were at higher risk for COVID-19 infestation, although all disease outcomes in the current study did not show significant differences in different populations. In the complete COVID-19 evolution, it was not sufficient to judge the prognosis of patients by their co-morbidities (rheumatic diseases)

Table 4 The factors after PSM

	Rheumatic disease group ($n=90$)	No rheumatic disease group ($n=347$)	Testing statistic	*P* value
Age, years, mean (*SD*)	62.04 (11.90)	62.09 (14.09)	$t=0.03$	0.98
Gender, male (%)	53 (58.89)	198 (57.1)	$\chi^2=0.10$	0.76
Height, cm, mean (*SD*)	163.31 (8.53)	163.18 (8.39)	$t=0.13$	0.89
Weight, kg, mean (*SD*)	59.89 (6.67)	59.98 (6.75)	$t=0.10$	0.92
Temperature, degree centigrade, mean (*SD*)	36.47 (0.42)	36.48 (0.40)	$t=0.10$	0.92
Respiratory rate, breaths per min, mean (*SD*)	20.27 (2.18)	20.10 (2.32)	$t=0.683$	0.49
Oxyhemoglobin saturation, percentage, mean (*SD*)	97.47 (1.96)	97.02 (3.036)	$t=1.40$	0.165
COPD (%)	1 (1.11)	4 (1.15)	$\sim\chi^2<0.01$	>0.99
Diabetes (%)	15 (14.60)	56 (16.13)	$\chi^2=0.02$	0.90
Hypertension (%)	38 (42.22)	143 (41.21)	$\chi^2=0.03$	0.86
Coronary heart disease (%)	9 (10.00)	30 (8.64)	$\chi^2=0.16$	0.69
Antiviral treatment (%)	51 (56.67)	197 (56.77)	$\chi^2<0.01$	0.99
Glucocorticoid (%)	22 (24.44)	72 (20.75)	$\chi^2=0.58$	0.45
Tocilizumab (TCZ, %)	4 (4.44)	16 (4.61)	$\sim\chi^2<0.01$	>0.99
Hydroxychloroquine (HCQ, %)	5 (5.56)	20 (5.76)	$\chi^2=0.01$	0.94

alone, especially in the absence of relevant information on the evaluation and treatment of their co-morbidities, whereas the results of the meta-analysis were not entirely consistent with our study. After systematic search, six studies were included in the meta-analysis. The patient populations were from the UK, Spain, Italy, and China. The meta-analysis has provided some sufficient evidence to deem rheumatic diseases as a factor influencing the mortality of COVID-19 patients [22–26]. However, it was important to note that this meta-analysis had a strong heterogeneity, due to the different study populations included, unbalanced sample sizes, and different response strategies for COVID-19 in each region. In particular, considering differences in COVID-19 response strategies across regions and the surge of cases in the short-term, we could not be sure that every patient received a complete medical treatment in those studies. The study by Shintaro Akiyama et al. in 2020 suggested that a regular anti-rheumatic therapy (including glucocorticoids or conventional synthetic disease-modifying antirheumatic drugs) helped to reduce the severity of COVID-19 [38]. In our study, each patient underwent a full and complete medical cycle of COVID-19. Therefore, we preferred to think that the results of this meta-analysis represent an effect of rheumatic diseases on patients with COVID-19 at an inadequate medical intervention or semi-intervention. In addition, Shintaro Akiyama also retrieved a large number of studies about COVID-19 cases with rheumatic diseases or ARD in that study and performed a meta-analysis of them. Interestingly, in the meta-analysis of those case-controlled trial studies, there was also no significant difference in the mortality rate of COVID-19 patients with rheumatic diseases.

Of course, we needed to be alert to the potential risk from the rheumatic diseases after SARS-CoV-2 virus infection. The study by Anja et al. suggested that people with rheumatic diseases with higher disease activity would have higher odds of COVID-19-related death [39], and in the study by Ning Rosenthal et al., COVID-19 patients with rheumatic diseases had a mortality rate as high as 20.45%, much higher than the average mortality rate of 11.35% reported in his article [40]. In addition, the study by Omar et al. suggested that immunosuppression was an important predictor for COVID-19 related 30-day mortality in Mexico [41]. Patients with rheumatic diseases might experience immunosuppression due to the use of glucocorticoids or other immunomodulatory drugs.

There were some limitations in this study. Firstly, this was a single-center retrospective research with a sample size imbalance between the two groups; the sample size of rheumatic disease group was smaller than that of the no rheumatic disease group. Secondly, some laboratory tests for the detection of anti-nuclear antibody and anti-keratin antibody (ANA and AKA, which serve as markers reflecting the active status of the rheumatic diseases) were not performed, and some other laboratory tests for erythrocyte sedimentation rate and IL-6 levels were not performed for all patients because of emergency. Thus, it was difficult to evaluate the activity and severity of rheumatic diseases in patients with COVID-19 during their hospitalization. Lastly, because the cases collected were from a single-center sample at the beginning of the COVID-19 global pandemic, there were not sufficient samples to focus the study more deeply on the level of immune-mediated rheumatic diseases. However,

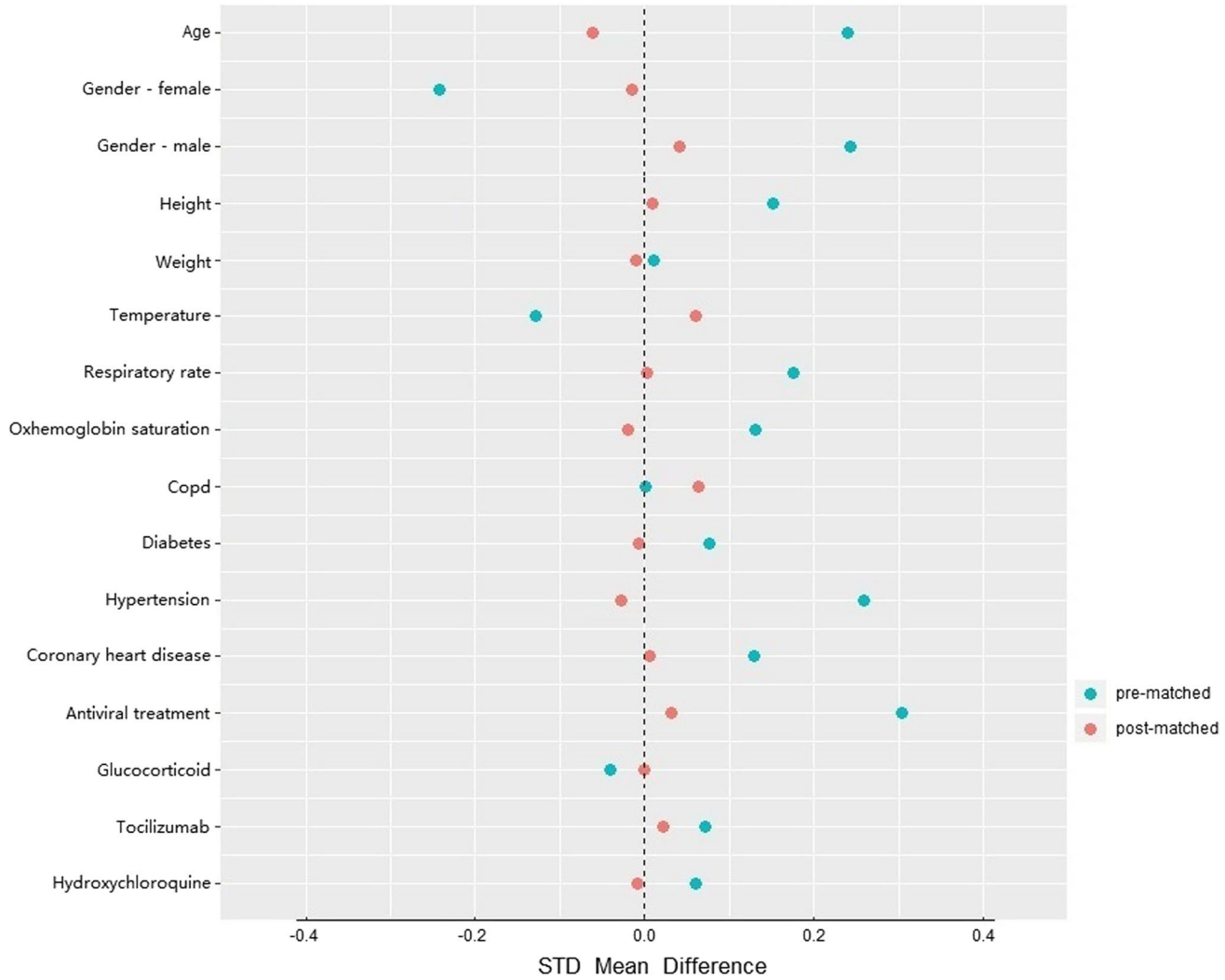

Fig. 2 The forest plot shows the change in STD mean difference before and after matching for all co-variates included in the PSM

Table 5 The PSM outcomes between two groups — rheumatic disease group and no rheumatic disease group

	Total ($n=4353$)		Rheumatic disease group	No rheumatic disease group	Testing statistic	*P* value	*RR* (95%CI)
Duration in hospital, mean (*SD*)	15.40 (8.07)	Pre-matched (91: 4262)	16.16 (8.27)	15.38 (8.07)	$t=0.92$	0.36	
		Post-matched (90: 347)	15.97 (8.08)	15.48 (9.12)	$t=0.46$	0.64	
Duration of viral clearance, mean (*SD*)	42.09 (14.91)	Pre-matched (91: 4262)	44.23 (14.97)	42.04 (14.92)	$t=1.38$	0.17	
		Post-matched (90: 347)	43.69 (14.63)	45.48 (15.60)	$t=0.98$	0.33	
ICU (%)	125 (2.87)	Pre-matched (91: 4262)	2 (2.20)	123 (2.89)	$\sim\chi^2=0.05$	0.94	0.76 (0.18, 3.11)
		Post-matched (90: 347)	2 (2.22)	16 (4.61)	$\sim\chi^2=0.52$	0.47	0.47 (0.11, 2.08)
Death (%)	95 (2.18)	Pre-matched (91: 4262)	1 (1.10)	94 (2.21)	$\sim\chi^2=0.12$	0.73	0.49 (0.07, 3.57)
		Post-matched (90: 347)	1 (1.11)	12 (3.46)	$\sim\chi^2=0.68$	0.41	0.31 (0.04, 2.44)

Table 6 The PSM outcomes between the patients with ARD and the patients in no rheumatic disease group

		Patients with ARD ($n=30$)	Patients in No rheumatic disease group ($n=4262$)	Testing statistic	*P* value	*RR* (95%CI)
Duration in hospital, mean (*SD*)	Pre-matched (30: 4262)	16.92 (8.78)	15.38 (8.07)	$t=1.04$	0.29	
	Post-matched (30: 108)	16.92 (8.78)	15.87 (9.36)	$t=0.55$	0.58	
Duration of viral clearance, mean (*SD*)	Pre-matched (30: 4262)	44.52 (15.67)	42.04 (14.92)	$t=0.90$	0.36	
	Post-matched (30: 108)	44.52 (15.67)	44.07 (15.08)	$t=0.14$	0.89	
ICU (%)	Pre-matched (30: 4262)	2 (6.67)	123 (2.89)	*Exact*	0.22	2.40 (0.57, 10.20)
	Post-matched (30: 108)	2 (6.67)	5 (4.63)	$\sim\chi^2<0.01$	0.98	1.47 (0.27, 7.99)
Death (%)	Pre-matched (30: 4262)	1 (3.33)	94 (2.21)	*Exact*	0.49	1.53 (0.21, 11.34)
	Post-matched (30: 108)	1 (3.33)	3 (2.77)	*Exact*	>0.99	1.21 (0.12, 12.04)

Table 7 The outcomes between the COVID-19 patients with ARD and non-ARD

	Patients with rheumatic diseases ($n=91$)	Patients with ARD ($n=30$)	Patients with non-ARD ($n=61$)	Testing statistic	*P* value
Duration in hospital, mean (*SD*)	16.16 (8.27)	16.92 (8.78)	15.79 (8.06)	$t=0.62$	0.54
Duration of viral clearance, mean (*SD*)	44.23 (14.97)	44.52 (15.67)	44.09 (14.75)	$t=0.13$	0.90
ICU (%)	2 (2.20)	2 (6.67)	0 (0.00)	*Exact*	0.11
Death (%)	1 (1.10)	1 (3.33)	0 (0.00)	*Exact*	0.33

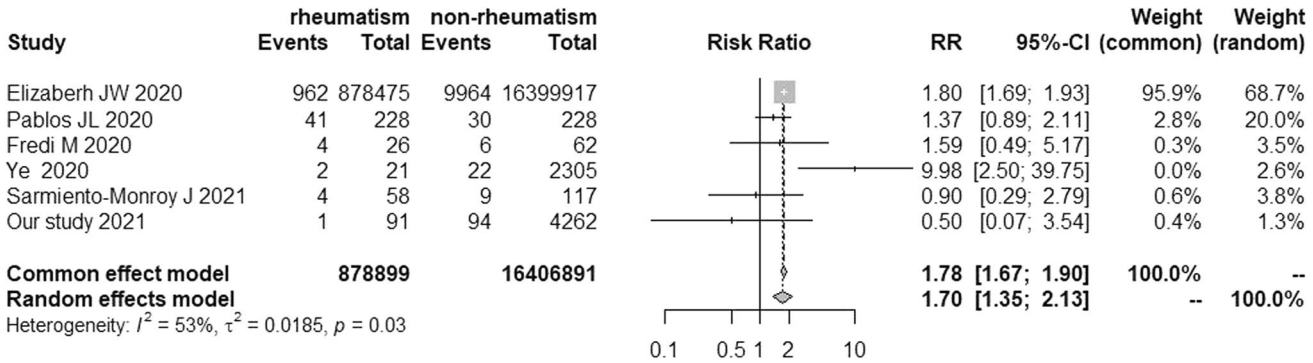

Fig. 3 The meta-analysis of COVID-19 patients with and without rheumatic diseases. The COVID-19 patients with rheumatic diseases were at a greater risk than the ones without rheumatic diseases, $P < 0.0001$

as cases are being pooled over a longer period of time and across more regions, we will conduct more in-depth studies in subsequent work.

In summary, no significant difference was observed between COVID-19 patients with and without rheumatic diseases in terms of time to progression or mortality with adequate medical intervention, and rheumatic diseases could not yet be considered an independent risk factor for COVID-19 in this study. However, caution is advocated. The immunological and pathophysiological interactions between rheumatic diseases and COVID-19 need to be explored in larger populations.

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Author contribution Conception and design: ZCJ and JH; data analysis and interpretation: GYQ, HW, and YFG; drafting the manuscript for intellectual content: GYQ, CP, and CXZ; revision of the manuscript: ZCJ, TC, and JH. The authors read and approved the final manuscript.

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Data availability The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate Ethics approval was granted by the Ethical Committee of HuoShenShan Hospital, Wuhan, China (HSSLL030), and the Committee on Ethics of Medicine, Navy Medical University, PLA. Written informed consent documents were waived by the ethical committee due to the patients' emergency condition.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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