INTRODUCTION

Coronavirus Disease 2019 (COVID-19), caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has become a pandemic since its outbreak in Wuhan, China in late December, 2019. As of 14 July 2020, the World Health Organization has reported 12,964,809 infected individuals and 570,288 deaths globally.¹ Thus, the spread of COVID-19 has become a threat to global health.

Multiple studies have summarised the clinical manifestations and radiographic characteristics of COVID-19.² ⁴ Compared with that in non-COVID-19 pneumonia patients, COVID-19 patients are...
less likely to exhibit pleural effusions. However, pleural effusion has been observed in severe and critical patients with COVID-19 as compared with that in moderate cases. Moreover, pleural effusion is associated with a high rate of mortality and longer hospital stay for patients with community-acquired pneumonia. Thus, whether pleural effusion indicates the poor prognosis of COVID-19 pneumonia remains to be investigated.

In this study, we analysed the differences between the clinical manifestations, laboratory examinations, imaging features and clinical outcomes among COVID-19 patients with or without pleural effusion.

2 | METHODS

2.1 | Sources of data

We retrospectively selected confirmed COVID-19 patients admitted to the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology between the 20 January and 29 of February, 2020 for this study. Patients were confirmed based on the positive readout for SARS-CoV-2 nucleic acid in throat swabs using real-time polymerase chain reaction (RT-PCR).

We collected the medical records of the enrolled patients, including clinical features, laboratory results, imaging and clinical outcomes. The extent of pneumonia of patients were assessed using the CT scoring system as following: each of the five lung lobes was visually scored on a scale of 0-5: 0 indicating no involvement; 1, <5% involvement; 2, >5%-25% involvement; 3, 26%-49% involvement; 4, 50%-75% involvement and 5, >75% involvement. The total score of all the five lobes was each patient's CT score (range from 5 to 25). After they were discharged, 217 of these patients returned to the outpatient department of the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. We also collected the computed tomography (CT) scans of the patients from their subsequent visits. Patients were followed up to 30 May 2020.

Ethics approval was obtained from the institutional ethics board of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (approval #2020-0120). Oral consent was obtained from all the patients. The need for written informed consent was exempt as per the ethics approval (2020-0120).

2.2 | Laboratory confirmation

Throat swabs were tested for the presence of SARS-CoV-2 using RT-PCR as per the recommendation by the World Health Organization. The patient specimens from the upper respiratory tract were collected in tubes pre-filled with virus preservatives. Total RNA was extracted using the High Pure Viral RNA Kit (Roche, Basel, Switzerland). Two target genes were assayed to identify SARS-CoV-2 RNA, namely open reading frame1ab (ORF1ab) and nucleocapsid protein (N). Samples were considered positive (+) or negative (−) based on the “Novel Coronavirus Infected Pneumonia Lab Test Technical Guide Version 2,” released by the National Health Commission & State Administration of Traditional Chinese Medicine on 22 January 2020.

2.3 | Statistical analysis

Continuous variables have been represented as mean ± standard deviation or median and interquartile range (IQR). Categorical variables have been summarised as counts and percentages for each patient category. Statistical significance between groups was determined using unpaired t-test or chi-squared test as appropriate. All statistical analyses were performed using SPSS22.0 (SPSS Inc).

3 | RESULTS

3.1 | Clinical manifestations

In all, 827 patients with COVID-19 pneumonia were included in this study (Table 1). The mean age of the cohort was 51 years and 451 (54.53%) patients were males. We suspected contact exposure for 198 patients. At admission, 76 (9.19%) patients presented with pleural effusion based on their CT scans. Patients with pleural effusion were significantly older (60.72 ± 15.40 vs 49.96 ± 15.86 years P < .001), suffered dyspnoea more common (68.42% vs 27.16%, P < .001), and more likely to be severe (53.95% vs 32.05%, P < .001) or critical cases (27.63% vs 5.64%, P < .001) as compared with patients without pleural effusion. The number of days from the onset of symptoms to hospital admission was lower for patients with pleural effusion as compared with that for patients without pleural effusion (7 [IQR 3-10] vs 8 [IQR 5-12] days, P < .002).

3.2 | Laboratory and radiological findings

On admission, patients with pleural effusion had lower levels of white blood cells, lymphocytes, platelets, haemoglobin and Albumin as compared with those in patients without pleural effusion (P < .05, Table 2). Moreover, the levels of neutrophil, Aspartate aminotransferase, Lactic dehydrogenase, Creatine kinase, Prothrombin time, Activated partial thromboplastin time, D-Dimer and Erythrocyte sedimentation rate in patients with pleural effusion were much higher than those in patients without pleural effusion were (P < .05, Table 2). There was a higher proportion of patients with pleural effusion and higher levels of C-reaction protein or Procalcitonin as compared with those without pleural effusion (P < .001, Table 2). Table 3 shows that COVID-19 patients with pleural effusion showed a higher IL-6, IL-10 and TNF-α content and lower levels of CD8+ T cells (P < .01). According to CT image features, consolidation was more
common in patients with pleural effusion as compared with those without pleural effusion (47.37% vs 31.42%, \(P = .007\); Table S1). Typical CT images are shown in Figure S1.

Among the 76 COVID-19 patients with pleural effusion, 62 patients were bilateral effusion, the rest 14 patients were unilateral pleural effusion. The amount of pleural effusion was small quantity in 73 patients, medium quantity in 3 patients. The CT scores of the patients with small quantity of pleural effusion had no significant difference, to those with medium quantity of pleural effusion (12.84 ± 5.31 vs 16.67 ± 6.66, \(P = .23\)).

### 3.3 Treatments and clinical outcomes

As shown in Table 4, all patients were administered antiviral agents, including Arbidol, Alpha-interferon, Ribavirin and Lopinavir/ritonavir.
Among these, 779 (94.20%), 126 (15.24%), 206 (24.91%) and 431 (52.12%) patients were co-administered antibiotics, corticosteroids, immunoglobulin and thymopeptide, respectively, during hospitalisation. There were no differences in drug therapy between these two groups.

COVID-19 patients with pleural effusion were more likely to undergo high-flow nasal cannula oxygen therapy (13.16% vs 6.13%, \( P = .029 \)), non-invasive mechanical ventilation (10.53% vs 2.93%, \( P = .004 \)) and invasive mechanical ventilation (3.95% vs 0.67%, \( P = .030 \)).

The incidence of respiratory failure and acute respiratory distress syndrome (ARDS) in patients with pleural effusion was significantly higher than that in patients without pleural effusion (44.74% vs 14.91% and 19.74% vs 6.26%, respectively; \( P < .001 \)). Among the 827 patients, 28 died unfortunately. The rate of mortality in patients with pleural effusion was higher than that in patients without pleural effusion (7.89% vs 2.93%, \( P = .0361 \)). The remaining 799 patients were discharged as of 17 April 2020.

| TABLE 2 | Laboratory findings of 827 patients infected with SARS-CoV-2 on admission to hospital |
|-----------------------------------------------|----------------------------------|-----------------------------------------------|-----------------------------------------------|
| | Total (n = 827) | Non-pleural effusion (n = 751) | Pleural effusion (n = 76) | \( P \) value |
| White blood cell count, \( \times 10^9/L \) | 5.40 ± 2.40 | 5.24 ± 2.15 | 6.10 ± 3.24 | .002 |
| <3.5, n (%) | 162 (19.59) | 147 (19.57) | 15 (19.74) | .015 |
| 3.5–9.5, n (%) | 617 (74.61) | 566 (75.37) | 51 (67.10) | .345 |
| >9.5, n (%) | 48 (5.80) | 38 (5.06) | 10 (13.16) | .209 |
| Neutrophil count, \( \times 10^9/L \) | 3.66 ± 2.30 | 3.43 ± 1.99 | 4.69 ± 3.14 | <.001 |
| Lymphocyte count, \( \times 10^9/L \) | 1.22 ± 0.54 | 1.29 ± 0.54 | 0.93 ± 0.43 | <.001 |
| <1.1, n (%) | 372 (44.98) | 319 (42.47) | 53 (69.74) | <.001 |
| 1.1–3.2, n (%) | 453 (54.78) | 430 (57.26) | 23 (30.26) | .941 |
| >3.2, n (%) | 2 (0.24) | 2 (0.27) | 0 (0) | .941 |
| Platelet count, \( \times 10^9/L \) | 224.39 ± 94.8 | 229.53 ± 96.02 | 201.63 ± 86.15 | .015 |
| Haemoglobin, g/L | 124.57 ± 15.54 | 125.91 ± 14.89 | 118.68 ± 17.07 | <.001 |
| ALB, g/L | 36.92 ± 5.20 | 37.74 ± 4.87 | 33.30 ± 5.13 | <.001 |
| ALT, U/L | 34.85 ± 32.38 | 34.57 ± 31.86 | 36.15 ± 34.85 | .683 |
| AST, U/L | 33.63 ± 25.48 | 31.53 ± 21.63 | 42.93 ± 36.89 | <.001 |
| T-BIL, \( \mu \)mol/L | 11.66 ± 5.78 | 11.45 ± 4.81 | 12.58 ± 8.89 | .078 |
| D-BIL, \( \mu \)mol/L | 3.97 ± 2.46 | 3.98 ± 2.37 | 3.92 ± 2.86 | .829 |
| BUN, mmol/L | 4.32 ± 2.19 | 4.27 ± 2.16 | 4.57 ± 2.30 | .250 |
| CREA, \( \mu \)mol/L | 73.22 ± 29.81 | 72.6 ± 29.58 | 75.98 ± 30.84 | .345 |
| LDH, U/L | 276.51 ± 129.03 | 262.98 ± 122.34 | 336.53 ± 141.71 | <.001 |
| CK, U/L | 107.23 ± 165.92 | 100.01 ± 140.94 | 139.22 ± 246.79 | .034 |
| PT, s | 13.44 ± 1.43 | 13.25 ± 1.11 | 14.29 ± 2.20 | <.001 |
| APTT, s | 38.79 ± 4.47 | 38.39 ± 3.99 | 40.58 ± 5.87 | <.001 |
| D-Dimer, mg/L | 1.373 ± 2.52 | 1.06 ± 1.84 | 2.77 ± 4.16 | <.001 |
| CRP, \( \mu \)g/L, n (%) | \(<8.0\) | 292 (35.31) | 283 (37.68) | 9 (11.84) | <.001 |
| \(\geq8.0\) | 535 (64.69) | 468 (62.32) | 67 (88.16) | <.001 |
| PCT, \( \mu \)g/L, n (%) | \(<0.5\) | 795 (96.13) | 728 (96.94) | 67 (88.16) | <.001 |
| \(\geq0.5\) | 32 (3.87) | 23 (3.06) | 9 (11.84) | <.001 |
| ESR, mm/h | 37.68 ± 28.38 | 35.39 ± 27.66 | 47.83 ± 29.49 | <.001 |

Abbreviations: ALB, Albumin; ALT, Alanine aminotransferase; APTT, Activated partial thromboplastin time; AST, Aspartate aminotransferase; BUN, Blood urea nitrogen; CK, Creatine kinase; CREA, Creatinine; CRP, C-reaction protein; D-BIL, Direct bilirubin; ESR, Erythrocyte sedimentation rate; LDH, Lactic dehydrogenase; PCT, Procalcitonin; PT, Prothrombin time; T-BIL, Total bilirubin.
patients, the length of hospital stay and duration of viral shedding after the onset of COVID-19 was longer for patients with pleural effusion as compared with those for patients without pleural effusion (18 [IQR 13-26] vs 25 [IQR 18-31] days, \( P < .001 \); 24 [IQR 18-31] vs 26 [23-31], \( P < .05 \); respectively, Figure 1A,B). In all, 217 patients returned for follow-up CT scans at the Wuhan Union Hospital (41 and 176 patients with and without pleural effusion, respectively). CT scans showed that the mean duration for resolution of inflammation in the lung, after the onset of COVID-19, was longer in patients with pleural effusion as compared with that in patients without pleural effusion (49 [IQR 40-63] vs 66 [IQR 48-80] days, \( P < .001 \), Figure 1C).

3.4 | Risk factors associated with pleural effusion in COVID-19 patients

Using univariate analysis, we find several variables that showed significant difference between COVID-19 patients with pleural effusion and those without, including older age, had an underlying illness of respiratory disease (Table S2). All underlying illness and other variables which showed statistical significance with \( P < .05 \) between two groups, were further processed using a multivariable logistic regression. As shown in Table S3, older age, history of respiratory disease, lower level of platelet and ALB, higher level of PT, APTT, D-Dimer and TNF-\( \alpha \) were risk factors for pleural effusion in COVID-19 patients.

To evaluate the risk factors associated with pleural effusion further, patients with and without pleural effusion were matched in a 1:2 ratio (76:152 patients) based on age, gender and comorbidity (Table S4). Fourteen factors from the univariate analysis were used as part of the multivariate analysis to identify reliable prognostic factors for pleural effusion in patients with COVID-19 (Tables S5 and S6). Low platelet counts and high levels of TNF-\( \alpha \) were risk factors for pleural effusion in COVID-19 (Table S6).

4 | DISCUSSION

In this retrospective cohort study, COVID-19 patients with radiologically defined pleural effusion at admission were older, more likely to

| TABLE 3 Cytokine and lymphocyte subsets in patients infected with SARS-CoV-2 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                 | Total (n = 827) | Non-pleural effusion (n = 751) | Pleural effusion (n = 76) | P value |
| IL-2 (pg/mL; normal range 0.10-4.10) | 2.73 ± 1.51 | 2.74 ± 1.67 | 2.67 ± 0.34 | .730 |
| IL-4 (pg/mL; normal range 0.10-3.20) | 2.15 ± 1.39 | 2.17 ± 1.52 | 2.10 ± 0.56 | .728 |
| IL-6 (pg/mL; normal range 0.10-2.90) | 26.52 ± 56.55 | 23.15 ± 59.34 | 41.45 ± 38.97 | .009 |
| Increased, n (%) | 721 (87.18) | 648 (86.29) | 73 (96.05) | .011 |
| IL-10 (pg/mL; normal range 0.10-5.00) | 4.83 ± 4.17 | 4.52 ± 4.01 | 6.18 ± 4.53 | <.001 |
| Increased, n (%) | 221 (26.72) | 182 (24.23) | 39 (51.32) | <.001 |
| TNF-\( \alpha \) (pg/mL; normal range 0.10-23.00) | 4.09 ± 6.73 | 3.03 ± 3.17 | 8.48 ± 13.16 | <.001 |
| IFN-\( \gamma \) (pg/mL; normal range 58.17-84.22) | 72.13 ± 10.68 | 72.43 ± 10.67 | 70.8 ± 10.68 | .205 |
| CD8\(^+\) T cells (%; normal range 24.34-31.37) | 44.04 ± 9.96 | 43.74 ± 9.897 | 45.35 ± 10.2 | .178 |
| CD8\(^+\) T cells (%; normal range 14.23-38.95) | 24.13 ± 8.46 | 24.71 ± 8.67 | 21.55 ± 6.92 | .002 |
| B cells (%; normal range 14.20-18.31) | 14.22 ± 6.55 | 13.99 ± 6.32 | 15.27 ± 7.42 | .099 |
| NK cells (%; normal range 3.33-30.47) | 10.34 ± 6.99 | 10.26 ± 7.24 | 10.72 ± 5.79 | .608 |
| CD4\(^+\)/CD8\(^+\) ratio (normal range 0.41-2.72) | 2.12 ± 1.12 | 2.07 ± 1.14 | 2.36 ± 0.97 | .036 |

Note: Values are expressed as Mean ± SD.
be severe or critical cases, exhibited a severe inflammatory response and more likely to suffer from respiratory failure or ARDS as compared with patients without pleural effusion. Furthermore, pleural effusion was associated with poor prognosis in COVID-19 patients, including higher mortality and longer duration of SARS-CoV-2 viral shedding and resolution of inflammation in the lungs.
Previous studies have shown pleural effusion in 5.3%-10.3% of COVID-19 patients. In accordance with this, we observed pleural effusion in 9.19% of the COVID-19 patients. Patients with pleural effusion had similar symptoms (excluding dyspnoea) as those in patients without pleural effusion: dyspnoea was more common in COVID-19 patients with pleural effusion. Moreover, pleural effusion was associated with the severity of COVID-19: pleural effusion was observed in a larger percentage of severe or critical patients than that in moderate cases. Thus, pleural effusion may be an indicator of poor prognosis for SARS-CoV-2 infection.

Pleural effusion is associated with a higher 30-day rate of mortality and longer hospital stay for emergency patients with pneumonia. Previous reports have also shown pleural effusion to indicate poor prognosis of adenovirus pneumonia, H5N1 viral pneumonia and acute Middle East respiratory syndrome coronavirus infection. This study showed that COVID-19 patients with pleural effusion were associated with a greater rate of mortality, higher incidence of respiratory failure and ARDS, and longer hospital stay. This could be attributed to the exacerbated inflammatory response and progressing pneumonia.

Multiple laboratory tests showed differences between patients with and without pleural effusion. Patients with pleural effusion showed higher levels of white blood cells, neutrophils, CRP, PCT and ESR as compared with those in patients without pleural effusion. This indicated severe inflammation in patients with pleural effusion. Increased CRP and PCT are indicators of poor prognosis in COVID-19 patients. Furthermore, patients with pleural effusion had higher levels of inflammatory cytokines, including IL-6, IL-10 and TNF-α, indicating an intense cytokine storm. As a pro-inflammatory mediator, excessive IL-6 results in a severe inflammatory response. Tocilizumab, a humanised anti-IL-6 receptor antibody, has shown efficacy in COVID-19 patients. IL-10 is a potent anti-inflammatory cytokine that induces T cell exhaustion and reduces inflammation. During rhadovirus infection, TNF-α inhibits the clearance of virus particles by hindering host antiviral response. Inhibition of TNF-α signalling alleviates the pathogenic effects of SARS-CoV infection in mice. Thus, there is an urgent need for clinical trials based on cytokine and anti-cytokine therapies for the treatment of COVID-19.

Host immune cells play a pivotal role in infectious diseases. We observed low levels of lymphocytes and CD8⁺ T cells in COVID-19 patients with pleural effusion as compared with those in patients without pleural effusion. Moreover, the duration of SARS-CoV-2 particle shedding was longer among patients with pleural effusion. Previous studies have shown that increased IL-10 content and decreased CD8⁺ T cells are associated with prolonged duration of SARS-CoV-2 shedding. Further studies are warranted to explore the underlying mechanism(s) involved in dysregulated immunity and SARS-CoV-2 infection.

Pleural effusion indicates severe pneumonia. In this study, patients with pleural effusion were more likely to manifest with consolidation in CT scans at admission and required a longer time for the resolution of lung inflammation. The presence of consolidation indicated viral invasion into the respiratory epithelium, resulting in diffuse alveolar injury and inflammatory exudates. Pleural effusion results from biological processes, such as increased interstitial oedema and capillary permeability. In this study, multi-factor regression analysis showed that decreased platelet and increased TNF-α contents may be risk factors for pleural effusion. TNF-α is important for pleural inflammation and parapneumonic effusion.

However, this study has several limitations. First, this was a single-centre retrospective study. Second, most patients with pleural effusion were not subjected to thoracentesis owing to the low level of pleural effusion, thereby limiting the potential for understanding the aetiology of pleural effusion. Third, only some of the discharged patients returned for a follow-up examination. This prevented the study of resolution of lung inflammation in all the patients. Thus, multi-centre retrospective studies are needed to understand the clinical outcome of COVID-19 patients with pleural effusion in the future.

5 CONCLUSIONS

In summary, COVID-19 patients with pleural effusion had higher rates of mortality, respiratory failure and ARDS, and experienced longer hospital stay. Thus, pleural effusion may serve as an indicator of poor prognosis among COVID-19 patients.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval was obtained from the institutional ethics board of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (approval #2020-0120). Oral consent was obtained from all the patients. The need for written informed consent was exempt as per the ethics approval (2020-0120).

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHORS’ CONTRIBUTIONS

QZ and JCZ conceived the idea, designed and supervised the study, had full access to all data and took responsibility for the integrity of the data. XSW and XW, collected and analysed the clinical and laboratory data. LLY, YRN, WBP and ZHW evaluated pulmonary computed tomographic images. XSW analysed data and performed statistical analysis. All authors reviewed and approved the final version.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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