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Clinical characteristics and outcomes of patients with COVID-19 infection undergoing orthopaedic surgeries

Journal:	*Journal of Orthopaedic Surgery*
Manuscript ID	OSJ-20-0611
Manuscript Type:	Original Article
Keywords:	COVID-19, SARS-CoV-2, Orthopaedic, Surgery, Lymphocyte
Abstract:	Background: Coronavirus disease 2019 (COVID-19) is an acute infectious disease caused by a novel coronavirus. Data on the clinical characteristics and outcomes of COVID-19 patients who had undergone orthopaedic surgeries were very limited. The goal of this study was to report the clinical characteristics, complications and outcomes of COVID-19 patients affected by bone fractures and soft tissue injuries. Methods: We retrospectively analyzed the clinical data of eight patients with COVID-19 pneumonia and orthopaedic conditions at our hospital from February 9 to March 20, 2020. Results: The age range of the eight patients was 35 to 87 years. Their common symptoms included fever (50%), cough (100%) and fatigue (37.5%). Two of the eight patients had lymphopenia. Five patients had elevated concentrations of C-reactive protein. All of them had high levels of D-dimer. Five patients had either hip or spinal compression fractures. The CD4+/CD8+ ratio in two patients was less than one. Of the four patients who required orthopaedic surgery, two of them developed fever (range 37.8–38.5°C), while all had reduced lymphocyte counts and elevated concentrations of C-reactive protein after the operation. One patient died of COVID-19 associated complications on postoperative day 9. Conclusions: Stress arising from orthopaedic surgery may accelerate and aggravate the progression of COVID-19, especially for elderly patients. Clinicians should assess the immunological status of the COVID-19 patients at pre-operation, and track both lymphocyte counts and IL-6 levels before and after any operation to monitor patient status and prognosis.

Clinical characteristics and outcomes of patients with COVID-19 infection undergoing orthopaedic surgeries

Abstract

Background: Coronavirus disease 2019 (COVID-19) is an acute infectious disease caused by a novel coronavirus. Data on the clinical characteristics and outcomes of COVID-19 patients who had undergone orthopaedic surgeries were very limited. The goal of this study was to report the clinical characteristics, complications and outcomes of COVID-19 patients affected by bone fractures and soft tissue injuries.

Methods: We retrospectively analyzed the clinical data of eight patients with COVID-19 pneumonia and orthopaedic conditions at our hospital from February 9 to March 20, 2020.

Results: The age range of the eight patients was 35 to 87 years. Their common symptoms included fever (50%), cough (100%) and fatigue (37.5%). Two of the eight patients had lymphopenia. Five patients had elevated concentrations of C-reactive protein. All of them had high levels of D-dimer. Five patients had either hip or spinal compression fractures. The $CD4^+/CD8^+$ ratio in two patients was less than one. Of the four patients who required orthopaedic surgery, two of them developed fever (range 37.8–38.5°C), while all had reduced lymphocyte counts and elevated concentrations of C-reactive protein after the operation. One patient died of COVID-19 associated complications on postoperative day 9.

Conclusions: Stress arising from orthopaedic surgery may accelerate and aggravate the

progression of COVID-19, especially for elderly patients. Clinicians should assess the immunological status of the COVID-19 patients at pre-operation, and track both lymphocyte counts and IL-6 levels before and after any operation to monitor patient status and prognosis.

Keywords: COVID-19, SARS-CoV-2, Orthopaedic, Surgery, Lymphocyte

Introduction

In December 2019, an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was first reported in Wuhan, Hubei Province, China [1]. It has subsequently been reported in other areas of China and around the world. On February 12, 2020, the World Health Organization officially named the disease caused by the SARS-CoV-2 as Coronavirus Disease 2019 (COVID-19) and declared it as a Public Health Emergency of International Concern. By April 28, 2020, there were 7,553,182 confirmed cases with 423,349 related deaths from 216 countries [2].

Across the globe, many cities have implemented extraordinary measures to restrict the spread of the virus and were in “lockdown”. In order to utilize the limited resources for managing the COVID-19 pandemic, “elective” surgery has been largely postponed and stopped [3,4]. However, some patients affected by bone fractures or soft tissue injury still needed surgery. Previous studies have reported the clinical characteristics

and early prognosis of ten COVID-19 patients with fracture [5]. The surgeries performed on those patients were unintentional and were not planned, and the conditions of those patients with facture were more severe than those without facture. At the present, the clinical characteristics, surgical risk and outcomes of the COVID-19 patients undergoing planned orthopaedic surgery operations remained unknown. Herein, we retrospectively collected and analyzed detailed clinical data from eight orthopaedic patients with COVID-19 infection admitted to our hospital. The objective of this study was mainly to describe treatment outcomes among patients undergoing planned orthopaedic surgery at the time of SARS-CoV-2 infection. Findings of the SARS-CoV-2 associated postoperative morbidity and mortality from this study can inform and benefit the global community in the battle against COVID-19.

Methods

Study design and patients

We conducted a retrospective review of medical records on eight patients with COVID-19 pneumonia and orthopaedic conditions admitted to our hospital from February 9 to March 20, 2020. Diagnosis of COVID-19 pneumonia was based on the New Coronavirus Pneumonia Prevention and Control Program (6th edition) published by the National Health Commission of China [6]. Six patients with COVID-19 pneumonia tested positive for SARS-CoV-2 by using quantitative RT-PCR (qRT-PCR)

from throat swab samples. The other two COVID-19 patients were laboratory confirmed by the presence of positive IgM/IgG anti-SARS-CoV-2 antibody. All patients presented with ground-glass opacities on chest computed tomography (CT) scans.

Data collection

We reviewed clinical records, laboratory test results, chest CT scans, treatment and clinical outcomes for all eight patients. All information was organized and recorded on a customized data collection form. The throat swab samples were collected and tested for SARS-CoV-2 using the Chinese Center for Disease Control and Prevention recommended Kit (BioGerm, Shanghai, China), following the WHO guidelines for qRT-PCR [7,8]. All samples were processed at the Department of Clinical Laboratory of our hospital. Primers were designed based on the sequence of Wuhan-Hu-1 (MN908947). Partial S segment sequences (nt 21730-22458) were amplified with primers: 5′-CTCAGGACTTGTTCTTACCTT-3′ and 5′-CAAGTGCACAGTCTACAGC-3′.

Statistical analyses

Data were analyzed using standard descriptive statistics as appropriate. Continuous variables were directly expressed as a range. Categorical variables were

reported as count and proportion. All statistical analyses were conducted using the SPSS software version 23.0 (Chicago, IL., USA). Diagrams were drawn using the Prism software version 8.0 (San Diego, CA., USA).

Results

All patients were residents of Wuhan City in China and had a history of exposure to COVID-19. Among them, six confirmed of COVID-19 via positive SARS-CoV-2 nucleic acid test, and two diagnosed with COVID-19 by positive IgM/IgG anti-SARS-CoV-2 antibody. Additionally, five patients tested positive on the anti-SARS-CoV-2 antibody IgG test. However, none of the eight patients was negative for both the COVID-19 antibody and SARS-CoV-2 nucleic acid tests.

The age range of the patients was 35 to 87 years. Seven patients had bone fractures, and one patient was referred to our hospital for surgical treatment of lower extremity ischemia and necrosis. Five of the seven patients with hip fracture or spinal compression fracture demonstrated that osteoporosis was the main cause of fracture. All elderly patients had underlying diseases such as chronic obstructive pulmonary disease, chronic hypertension, malignancy, cerebrovascular disease and rheumatoid arthritis.

Four of the eight patients were presented with a fever without chills, but none of them had high fever (body temperature >39°C). Eight patients (100%) had a cough, three patients (37.5%) reported myalgia and fatigue, and two (25%) reported a sore throat.

Additionally, one (12.5%) patient showed dyspnea and chest pain. None of them had diarrhea.

Results from laboratory tests showed that two of the eight patients had a white cell count below the normal range and had lymphopenia. Five patients had elevated concentrations of C-reactive protein (CRP). Four patients had increased concentrations of alanine aminotransferase and aspartate aminotransferase. Additionally, due to restriction of activities, all of the patients had high level of D-dimer (table 1). All eight patients had a chest CT scan, and showed multiple patchy ground-glass shadows in their lungs (figure 1).

To evaluate the immune function of the patients, we examined the lymphocyte subsets. We found the the $CD4^+/CD8^+$ ratio in patient 3 and 7 was 0.45 and 0.95 respectively (table 2).

Four patients underwent orthopaedic surgery (figure 2). Before surgery, all four patients were in a stable condition with no fever and dyspnea. One patient had cough, but this patient's phlegm culture was negative. Two patients received general anesthesia, and the other two received spinal anesthesia. After surgery, all patients were given oxygen support, antiviral therapy and empirical antibiotic treatment (table 3). Two patients later developed fever (range 37.8–38.5°C) during the postoperative period. The lymphocyte count was further reduced and the concentrations of CRP were significantly elevated for all patients after the operation (figure 3). However, patient 3 showed increasing levels of inflammatory cytokine progressively, and he was presented with acute myocardial infarction, which progressed rapidly to multisystem organ failure.

Unfortunately, he died nine days after the operation. The remaining three surgical patients were discharged at 11, 15, 17 days after surgery, respectively.

There were four non-surgical patients. Their age ranged from 80 to 87 years old. They each received conservative treatment and by the end of April 3, 2020, two patients had been discharged but two were still in the hospital.

Higher than normal levels of serum cytokine (IL-6) were detected in all eight patients, particularly in patient 3 who died after surgery. The plasma concentration of IL-6 in patient 3 was 336.2 pg/mL (normal value ≤7 pg/mL) (table 2). Patient 3's leukopenia persisted and inflammation intensified (CRP 189.95 mg/l) (figure 3).

Discussion

In the midst of the COVID-19 pandemic, healthcare providers are struggling to understand how to properly respond and treat COVID-19 patients with orthopaedic conditions. To shed light on the treatment options of COVID-19, we present clinical findings from eight patients with COVID-19 pneumonia who were hospitalized in an orthopaedic unit in China. The clinical characteristics of these patients were similar to those of non-fracture patients with COVID-19 infection, as previously reported in the literature [9]. Four of the eight patients underwent surgical treatment, and all of the four patients showed elevated inflammatory markers and decreased lymphocytes after surgery, with one patient died of multiple organ failure. The remaining four non-surgical patients had advanced age and severe underlying diseases, thus they were

treated conservatively. None of the four non-surgical patients developed severe pneumonia nor died, as of April 4, 2020. Notably, based on the findings of these eight patients, there was evidence to suggest that surgical stress could lead to occurrence of severe adverse outcomes in the COVID-19 patients, especially in the elderly.

People are generally susceptible to COVID-19. The elderly patients and those with underlying diseases can be affected even more seriously [10]. Since the elderly patients are particularly susceptible to osteoporosis, they are more likely to develop fragility fracture [11]. In this study, we treated seven patients who had bone fractures, with three of them having hip fracture and two having vertebral compression fracture. Five elderly patients developed fractures during the treatment for COVID-19 pneumonia, which could be explained by the fact that the COVID-19 patients were more prone to falls due to a weak physical health state, and their long-term bedridden treatment could lead to more severe osteoporosis. Therefore, it is necessary to take adequate measures to prevent fracture in elderly patients with COVID-19 pneumonia [12].

Elderly patients with hip fractures are at risk for cardiovascular, pulmonary, thrombotic, infectious, and bleeding complications [13]. These complications can result in death. Therefore, performing timely surgery for these patients remains the mainstay of treatment. However, surgical procedures can also pose risks to the COVID-19 pneumonia patients, especially for the elderly. During the outbreak of SARS, a geriatric patient with a hip fracture was reported dead seven days after surgery [14]. A recent study showed that 7 out 34 surgical patients (20.6%) died from COVID-19 related complications [15]. These findings suggest that stress arising from surgery may

accelerate and aggravate the progression of COVID-19. In addition, the Centers for Disease Control and Prevention in the United States reported that 80% of COVID-19 deaths were observed in adults 65 years or older [16] and that the patients were still required to stay in hospitals after the surgery to treat pneumonia. As such, comprehensive strategies that take into account of conservative treatment measures for elderly patients are needed. After the COVID-19 is cured, a second stage of operation could be further considered. On the other hand, for younger patients who have no serious underlying disease, a joint consultation with anesthesiologist, respiratory doctors and intensive care unit doctors is recommended to ensure patient safety before and after surgery.

Research has shown that SARS-CoV-2 mainly acts on lymphocytes to induce a cytokine storm in the body and generate a series of immune responses, resulting in leukopenia. Thus, a patient's immune function plays an important role in fighting off the SARS-CoV-2 infection [10]. Lymphocyte count and lymphocyte subset are of great value to ensure immune system functionality. Studies have demonstrated that the $CD4^+/CD8^+$ ratio of less than 1 is linked to immune senescence and all-cause mortality [17,18]. Moreover, in HIV patients, having a low $CD4^+$ percentage and a low $CD4^+/CD8^+$ ratio prior to the initiation of antiretroviral therapy is predictive of the risk of adverse clinical progression [19]. Of note, $CD4^+$ and $CD8^+$ counts reflect the severity of infection and may predict the clinical outcomes in patients with COVID-19 [20-22]. In the present study, patient 3 had a low $CD4^+$ percentage and his $CD4^+/CD8^+$ ratio was 0.45 preoperatively, which were indicative of his low immune function before surgery.

Having low immune system function likely explains why he developed rapid disease progression of COVID-19 after surgery. Thus, the $CD4^+/CD8^+$ ratio may be used as a biomarker to identify patients with the worst prognosis, and the immunological status of the COVID-19 patients should be considered when selecting treatment options for them.

Surgery not only can damage the immune system [23], but also can induce the body to produce an inflammatory response [24]. The high levels of circulating inflammatory cytokines and the progressively decline of lymphocytes have been reported to correlate with the severity of COVID-19 [6,9]. Recent research has shown that the increased amounts of proinflammatory cytokines in serum, in particular IL-6, may drive the deleterious consequences of the infection [25]. Consistent with these findings, all of the four patients who underwent surgical treatment in this study had experienced further lymphocytic decline and increased levels of inflammatory cytokines after surgery. One (25%) patient died of multiple organ failure nine days after operation. Of importance, this patient's leukopenia and inflammatory marker elevation persisted (lymphocyte 0.45×10^9 /L, CRP 151.4 mg/L, IL-6 336.2 pg/mL) postoperatively. His condition progressed rapidly with acute respiratory distress syndrome and acute myocardial infarction which eventually followed by multiple organ failure. Therefore, evaluation of the immune system function of the COVID-19 patients is critical and can help physicians to identify patients with potential poor prognosis. Additionally, early identification and timely treatment of lymphopenia are important in the postoperative care of the COVID-19 patients.

In summary, we described the clinical characteristics and outcomes of patients with COVID-19 infection who underwent orthopaedic surgery. Although our conclusions are limited by the small sample size, we believe that the findings reported here are important for management of orthopaedic patients. Clinicians should consider tracking both the lymphocyte count and IL-6 during the postoperative period to monitor patient status and prognosis. Risk factors for the poor prognosis of orthopaedic operative patients with COVID-19 need to be further studied.

Abbreviations

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus Disease 2019; CRP: C-reactive protein; COPD: chronic obstructive pulmonary disease; ALT: alanine aminotransferase; AST: Aspartate aminotransferase.

Acknowledgments

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Authors' contributions

YL and YL-L conceived and conceptualized the study. YL-L drafted the manuscript with help from LF, WT, and MH. YL-C and YL-L helped in the statistical analyses. Statistical analysis was discussed with YL-L, ZW-S, WT and YL. YL, MH, and LF contributed to the revision. All authors were involved in the editing the article, and

agree on the final version.

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Availability of data and materials

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the Ethics Commission of the Wuhan Union Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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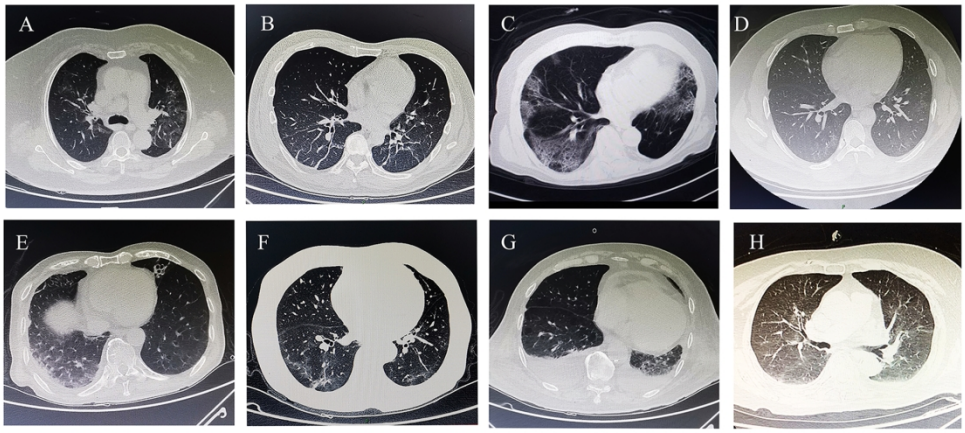
Figure legends

Figure 1 Computed tomography of the chest of eight patients with COVID-19. All patients had bilateral ground-glass opacity and subsegmental areas of consolidation. Fig. 1-A patient 1, Fig. 1-B patient 2, Fig. 1-C patient 3, Fig. 1-D patient 4, Fig. 1-E

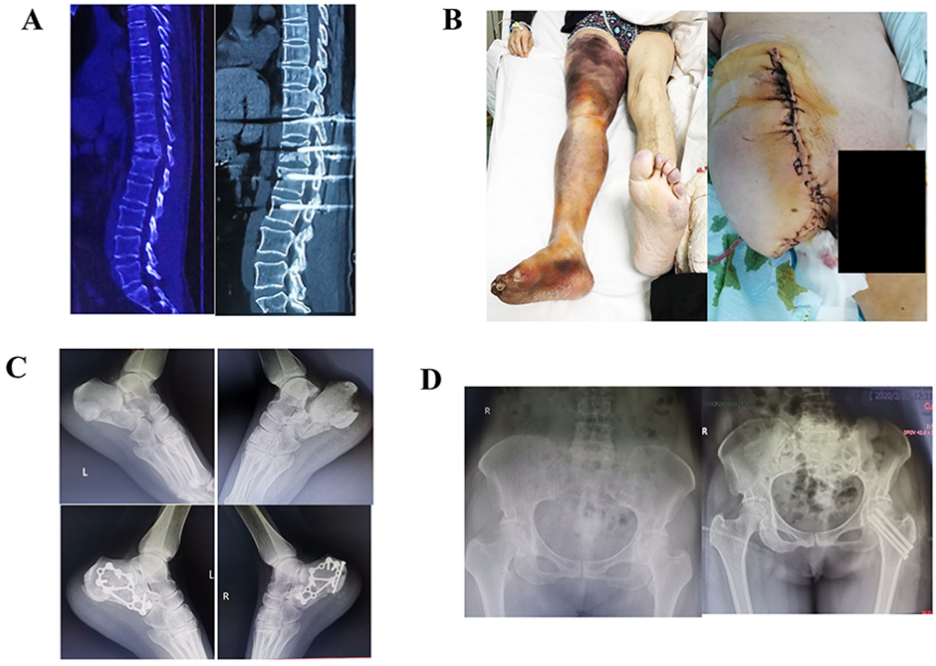
patient 5, Fig. 1-F patient 6, Fig. 1-G patient 7, Fig. 1-H patient 8.

Figure 2 Radiographic images and photographs of the four patients underwent surgery. Fig. 2-A patient 2. Preoperative and postoperative CT scans showing T12、L1 vertebral fracture, Fig. 2-B patient 3. Preoperative and postoperative photographs showing right lower limb ischemic necrosis, Fig. 2-C patient 4. Preoperative and postoperative radiographs of the patient with bilateral calcaneal fracture. Fig. 2-D patient 6. Preoperative and postoperative radiographs of the patient with a femoral neck fracture.

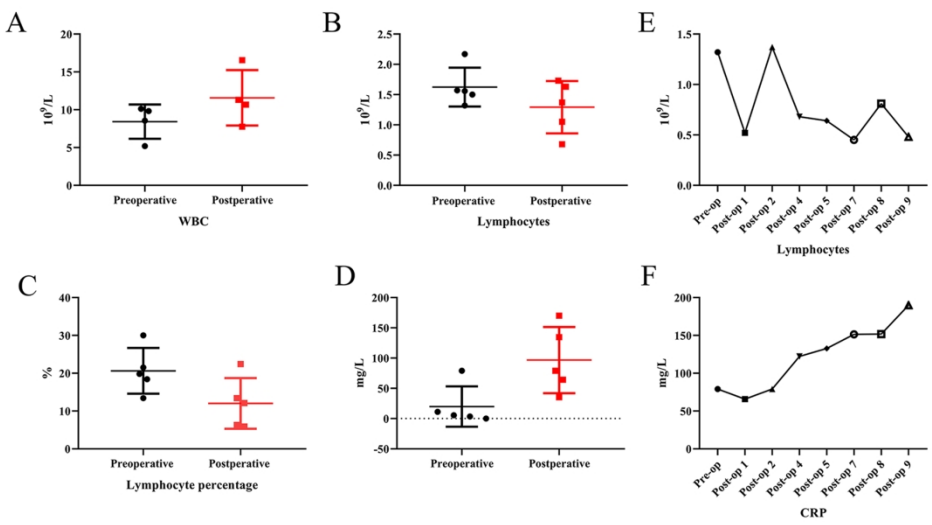
Figure 3 Laboratory characteristics of the four operative patients before and after surgery. (A) The change of postoperative white blood cells. The white blood cell count increased significantly after the operation. (B) The change of postoperative lymphocyte percentage. The percentage of lymphocytes decreased after surgery. (C) The change of lymphocyte count at post-operation. The lymphocyte count decreased after operation. (D) The change of C- reactive protein at post-operation. The C- reactive protein increased significantly after the operation. (E) The change of lymphocyte count in patient 3 after operation. His lymphocyte count continued to decline at post-operation. (F) The change of C- reactive protein in patient 3 after operation. The values of C-reactive protein continued to increase at post-operation.



Computed tomography of the chest of eight patients with COVID-19



Radiographic images and photographs of the four patients underwent surgery.



Laboratory characteristics of the four operative patients before and after surgery.

Table 1. Clinical presentation and pertinent laboratory findings of the patients with COVID-19.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	n (%)
Date of admission	Feb.9	Feb.18	Feb.20	Feb.21	Feb.21	Feb.27	Feb.29	Mar.3	
Age (years)	81	41	70	35	80	63	87	82	
Gender	Female	Male	Male	Male	Male	Female	Male	Female	
Epidemiological history	exposure to relevant environment	exposure to relevant environment	exposure to relevant environment	exposure to relevant environment	contact with infected person	contact with infected person	exposure to relevant environment	exposure to relevant environment	8(100%)
orthopaedic diagnosis	L2 vertebral compression fracture	T12, L1 vertebral fracture	Right lower limb ischemic necrosis	Bilateral calcaneal fracture	Left femoral neck fracture	Left femoral neck fracture	Right femoral neck fracture	T12 vertebral compression fracture	
Complications	chronic bronchitis	No	Postoperative lung cancer	No	Diabetes, Cerebrovascular disease	rheumatoid arthritis	COPD, hypertension	Cerebrovascular disease	
operation	No	Yes	Yes	Yes	No	Yes	No	No	4(50%)
Signs and symptoms									
Fever	No	No	Yes	Yes	No	Yes	No	Yes	4(50%)
Myalgia	Yes	Yes	Yes	No	No	No	No	No	3(37.5%)
Fatigue	Yes	No	Yes	No	No	Yes	No	No	3(37.5%)
Rigor	No	No	No	No	No	No	No	No	0(0%)
Cough	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8(100%)
Dyspnoea	No	No	No	No	No	No	No	Yes	1(12.5%)
Sore throat	No	Yes	No	Yes	No	No	No	No	2(25%)
Diarrhoea	No	No	No	No	No	No	No	No	0(0%)
Chest pain	No	No	No	No	No	No	No	Yes	1(12.5%)
Laboratory characteristics									
White blood cell count ($\times 10^9$ cells per L)	4.51	11.89	9.83	11.4	11.5	7.47	11.57	8.24	
Low or normal leukocyte count (<9·5 $\times 10^9$ cells	Yes	No	No	No	No	Yes	No	No	2(25%)

per L)									
Lymphocyte count (× 10^9 cells per L)	1.13	1.69	1.32	3.02	0.57	1.01	0.49	1.58	
Lymphopenia (<10^9 cells per L)	No	No	No	No	Yes	No	Yes	No	2(25%)
C-reactive protein concentration (mg/L)	8.47	0.47	79.08	61.42	105.04	68.7	109.97	3.25	
Elevated C-reactive protein (>10 mg/L)	No	No	Yes	Yes	Yes	Yes	Yes	No	5(62.5%)
ALT (U/L)	36	24	68	62	19	86	17	18	
AST (U/L)	24	17	65	51	39	48	18	28	
Elevated ALT (>45 U/L) or AST (>35 U/L)	No	No	Yes	Yes	No	Yes	No	No	4(50%)
D-dimer concentration	3.6	1.26	6.55	3.5	1.49	6.35	8.5	0.66	
Elevated D-dimer (> 0.5 mg/L)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8(100%)
COVID-19 Ig G	Positive	Negative	Positive	Positive	Negative	Positive	Positive	Negative	5(62.5%)
COVID-19 Ig M	Positive	Negative	Positive	Negative	Negative	Negative	Positive	Negative	3(37.5%)
Confirmatory test done (SARS-CoV-2 quantitative RT-PCR)	Positive	Positive	Positive	Negative	Positive	Positive	Negative	Positive	6(75%)
CT evidence of pneumonia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8(100%)

COPD, chronic obstructive pulmonary disease; ALT, alanine aminotransferase; AST, Aspartate aminotransferase.

Table 2. Lymphocyte subset percentage and IL-6 of the eight patients with COVID-19.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
IL-6(pg/mL)	7.46	9.93	336.2	7.89	28.32	19.82	23.37	132.81
T lymphocytes (%)	75.78	76.14	78.01	80.36	84.5	70.24	76.97	71.09
$CD4^+$T (%)	50.74	41.1	26.45	45.28	47.72	49.21	36.02	42.9
$CD8^+$T (%)	20.97	30.12	48.7	26.24	35.08	19.53	37.9	24.21
$CD4^+/CD8^+$	2.42	1.36	0.54	1.73	1.36	2.52	0.95	1.77

Table 3. Characteristics of the operative patients with COVID-19 infection.

	Patient2	Patient3	Patient4	Patient6	n (%)
Onset to operation (days)	5	1	18	8	
Preoperative symptoms and signs					
Fever	No	No	No	No	0(0%)
Cough	No	Yes	No	No	1(25%)
Dyspnea	No	No	No	No	0(0%)
Orthopaedic surgery	Open reduction and internal fixation via posterior approach	hip disarticulation	Open reduction and internal fixation	Closed reduction and internal fixation	
anesthesia method	general anesthesia	general anesthesia	spinal anesthesia	spinal anesthesia	
Post-operative symptoms and signs					
Fever	No	Yes	No	Yes	2(50%)
Cough	No	Yes	No	No	1(25%)
Dyspnea	No	Yes	No	No	1(25%)
Treatment after operation					
Oxygen support	Yes	Yes	Yes	Yes	8(100%)
Antiviral therapy	Yes	Yes	Yes	Yes	8(100%)
Antibiotic therapy	Yes	Yes	Yes	Yes	8(100%)
Use of corticosteroid	No	No	No	No	0(0%)
outcome	Getting better and discharged	Death	Getting better and discharged	Getting better and discharged	