Characteristics and Treatment Strategies of Different Clinical Types in Patients with Corona Virus Disease 2019

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Abstract

Objective To describe the epidemiological and clinical characteristics of patients with Corona Virus Disease 2019 (COVID19) in Beijing. To analyze the treatment strategies especially the application of corticosteroids in patients with severe pneumonia.

Methods We collected information on demographic characteristics, exposure history, clinical characteristics, treatment and outcomes of the 65 confirmed cases of COVID19 at the 5th Medical Center of PLA General Hospital from Jan 20 to Feb 23, 2020. The final follow-up date observed was Feb 29, 2020.

Results The number of patients with mild, general, severe, and critical type were 10 (15.38%), 32 (49.23%), 8 (12.31%), and 15 (23.08%), respectively. The median incubation period was 6 days. Notable outliers were 1 patient at 16 days and 1 patient at 21 days. In lymphocyte subgroup analysis, decreases in total, T, CD4, and CD8 lymphocytes were more common as the disease worsened (All P<0.05). Methylprednisolone was applied to 31 (47.69%) patients with pneumonia, including 10 (31.25%) general, 8 (100%) severe, and 13 (86.67%) critical patients, respectively. Corticosteroids inhibited Interleukin-6(IL-6) production (P=0.0215) but did not affect T lymphocyte (P=0.0796). There was no significant difference between patients using lower dose (≤2mg/kg.d) and higher dose (>2mg/kg.d) methylprednisolone in inhibiting IL-6 production (P=0.5856). Thirty of 31 patients (96.77%) had stopped methylprednisolone due to improvement of pneumonia. Virus RNA clearance time lengthened with disease progression (P=0.0001). In general type, there was no significant difference in virus clearance time between patients with (15, 12-19 days) and without (14.5, 11-18 days) (P=0.7372) methylprednisolone use.

Conclusions Lymphocyte, especially T lymphocyte, in severe and critical patients showed a dramatic decrease. Application of lower dose corticosteroids (≤2mg/kg.d) could inhibit IL-6 production (a representative of cytokines) as effectively as a higher dose. Proper use corticosteroids in general type patients did not delay virus clearance.

Authors Fangfang Liu and Chengcheng Ji contributed equally to this work.

Introduction

In December 2019, cases of acute respiratory disease (ARD), now known as a Corona Virus Disease 2019 (COVID19) occurred in Wuhan, Hubei Province, China[1–3]. Recent evidence has shown that person-to-person transmission in China is increasing[4–8]. The virus has spread to different parts of China and other countries[9]. Presently, the laboratory-confirmed cases and recorded deaths in the world, especially in China, are still increasing at an alarming rate[9,10].

COVID19 clinical types were defined according to the Diagnosis and Treatment of Pneumonia caused by Novel Coronavirus (Version 6 Trial) published on the website of the Central Government of the People's Republic of China[11]. There are four distinct clinical types based on the severity of the disease. However,

the differences in clinical characteristics, treatment, and outcomes among different clinical types have not been reported.

Acute respiratory distress syndrome (ARDS) is partly caused by host immune responses. In severe ARDS patients, the overwhelming inflammation and cytokine-related lung injury might cause rapidly progressive pneumonia. Theoretically, corticosteroid treatment can suppress lung inflammation. Corticosteroids were widely used during the outbreaks of severe acute respiratory syndrome (SARS)-CoV and Middle East respiratory syndrome (MERS)-CoV, and are being used in patients with COVID19[1,12,13]. In light of the urgent clinical demand, physicians from the Chinese Thoracic Society who participated in treating patients with 2019-nCoV pneumonia have developed an expert consensus statement on the use of corticosteroids in COVID19 [14]. The outcomes of patients with different COVID19 clinical types treated by corticosteroids have not been reported.

The aim of the study is to compare clinical characteristics, treatment strategies, and outcomes among different clinical types of COVID19 patients treated in a tertiary hospital in Beijing, and to analyze the treatment strategies especially the application of corticosteroids in patients with severe pneumonia.

Methods

Data collection

All laboratory-confirmed patients admitted to the 5th Medical Center of PLA General Hospital from January 20 to February 23, 2020, were enrolled. Cases were diagnosed based on the Diagnosis and Treatment of Pneumonia caused by Novel Coronavirus (Version 6 Trial) published on the website of the Central Government of the People's Republic of China[11]. A confirmed case of COVID19 was defined as a positive result from real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay of respiratory tract specimens[15,16]. Medical records of all confirmed cases with COVID19 were obtained from electronic medical records. The clinical outcomes, including discharges, mechanical ventilation, intensive care unit (ICU) admission, and death, were recorded up to February 29, 2020, the final follow-up date for this study.

All medical records were reviewed by a trained team of physicians. Information included demographics, exposure history, concurrent diseases, symptoms, laboratory results, chest X-ray and/or computed tomographic (CT) images, treatment (ie, antiviral therapy, corticosteroids use, respiratory support and continuous renal replacement therapy [CRRT]). Laboratory data included blood routine, biochemistry (ie. liver, kidney and cardiac function, electrolyte, creatine kinase [CK]), coagulation function, infection related biomarkers (ie. C-reactive protein [CRP], procalcitonin [PCT], Interleukin–6 [IL–6], erythrocyte sedimentation rate [ESR], serum ferritin) and lymphocyte subgroup. ARDS was defined according to the Berlin definition[17]. Acute kidney injury (AKI) was identified according to the Kidney Disease: Improving Global Outcomes definition[18].

Clinical types of COVID19 included mild, general, severe, and critical types. Mild type was diagnosed as patients with mild clinical symptoms and no pneumonia on radiological imaging. General type was diagnosed as patients with fever, respiratory symptoms, and pneumonia on imaging. Severe type was diagnosed as patients with any one of the following: 1. Respiratory distress, RR (Respiratory rates) ≥30bpm; 2. Peripheral capillary oxygen saturation (SpO_2) at rest ≤93%. 3. Arterial oxygen partial pressure (PaO_2)/ fraction of inspiration O2 (FiO_2) ≤300mmHg. (1mmHg = 0.133kPa). Critical type was diagnosed as patients with any one of the following: 1. Respiratory failure and mechanical ventilation required. 2. Shock. 3. Combined with other organ failures and ICU monitoring and treatment needed[11].

All methods in this study were performed in accordance with the Diagnosis and Treatment of Pneumonia caused by Novel Coronavirus (Version 6 Trial) published on the website of the Central Government of the People's Republic of China[11]. This study was approved by the ethics committee of the 5th Medical Center of PLA General Hospital. Written informed consent was waived by the ethics committee of the 5th Medical Center of PLA General Hospital in light of the urgent need to collect clinical data.

Statistical analysis

Continuous variables were described as mean ± standard deviation (SD) or medians (interquartile range (IQR) values) as appropriate. Categorical variables were summarized as the counts and percentages in each category. Comparisons between different clinical types were conducted using ANOVA for continuous variables when homogeneity of variance is valid, or else using Wilcoxon rank-sum test. Chi-square test was used for categorical variables when homogeneity of variance is valid, or else using Fisher's exact test. IL–6 values and T lymphocyte counts were tested every 2–3 days. A linear mixed model was built to describe the relationship between clinical type or corticosteroids used and these dynamic IL–6 values or T lymphocyte counts throughout the course of the disease. All analysis used a two-sided *P*-value of 0.05 for statistical significance. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc. Cary. NC. USA).

Results

Demographic and Clinical Characteristics

Details of demographic and clinical characteristics are shown in table 1. A total of 65 patients were included in our study with 10 (15.38%) mild, 32 (49.23%) general, 8 (12.31%) severe, and 15 (23.08%) critical type. The mean (SD) age was 48.4 (18.46) years and 55.38% of them were males. Three patients (4.62%) were under 15 years old (the youngest one was 3 years), and 15 patients (23.08%) were over 65 years old. All 3 younger patients (all with mild type) had a quick recovery to discharge with median virus RNA clearance time of 4 days. Patients with critical type tended to be older than those with mild type (P<0.0001). There was no significant difference by gender among different clinical types (P = 1.000).

A history of recent travel to or living in Wuhan, contact with people confirmed with COVID19, and contact with people from Wuhan was documented in 55.38%, 26.15% and 7.69% of patients, respectively. Not all patients could provide their exact exposure time. There were 49 patients with complete exposure time information. The range of time from exposure to onset of symptoms (incubation period) was 0 to 21 days, with median (IQR) of 6 (4–10) days. Notably, 2 patients presented at 14 days, 1 patient at 16 days and 1 patient at 21 days.

Twenty-two patients (33.85%) had at least one concurrent disease (i.e. hypertension, diabetes, malignancy, endocrine disease, and tumor). Patients with any concurrent disease were significantly more likely to be diagnosed as critical cases (60% with any concurrent disease) as compared to other patients (mild 10%, general 25%, and severe 50%) (P = 0.0264).

Fever (86.15%) and dry cough (56.92%) were the most common symptoms. The mean (SD) maximum temperature was 38.04 (0.86)℃. There was no significant difference in fever and dry cough among patients with different clinical types (all P>0.05). The median (IQR) times of onset of symptom to laboratory confirmation and pneumonia were 5 (3–7) and 6 (3–8) days, respectively. The median (IQR) time of onset of symptom to virus RNA clearance was 15 (11–20) days. Virus RNA clearance time lengthened with disease progression (P = 0.0001). The most common pattern on chest X-ray and CT in patients with pneumonia was bilateral patchy shadowing and bilateral ground-glass opacity, respectively.

Laboratory Parameters of patients in different clinical types

Details of laboratory results are shown in table 2 and supplemental table 1. Laboratory abnormalities, including aspartate amino transferase (ALT), CK, potassium, creatine kinase-MB (CKMB), myocardial troponin I (cTnI), myoglobin, N-terminal pro-brain natriuretic peptide (NT-pro BNP), and lactate (LAC), were more common as disease worsened (All P<0.05). Nineteen (29.23%) patients had lymphopenia (lymphocyte count <1.0×10⁹/L). No mild type patients had lymphopenia, however, 73.33% of critical type did (P<0.0001). In lymphocyte subgroup analysis, 20(30.77%), 29(44.62%), 35(53.85%), and 18(27.69%) patients had decreased total, T, CD4, and CD8 lymphocyte, respectively. Decreases in all four indicators above were more common as the disease worsened (All P<0.05). Meanwhile, lymphocyte counts increased gradually as patients recovered. T lymphocyte count trends in different clinical types throughout the course of the disease are shown in figure 1a.

Forty-four (67.69%), 34 (52.31%), 33 (50.77%), and 35 (53.85%) patients had increased IL–6, ESR, serum ferritin, and CRP, respectively. Increases in all four infection-related biomarkers above were observed more often in critical patients (80%, 80%, 73.33%, and 73.33%, respectively) than in mild patients (10%, 10%, 10%, and 20%, respectively) (All P<0.05). During treatment, the IL–6 levels fluctuated and then decreased to normal as patients recovered. The fluctuation was probably influenced by corticosteroids use. IL–6 trends in different clinical types throughout the course of the disease are shown in figure 1b.

Treatment and clinical outcomes in different clinical types

Details of treatment and clinical outcomes are shown in table 1. Interferon-α (IFN-α) (59, 90.77%) and lopinavir/ritonavir (50, 76.92%) were the main antivirus medicines used in these patients. Oxygen therapy, high-flow nasal cannula (HFNC), non-invasive positive pressure ventilation (NIPPV), and invasive positive pressure ventilation (IPPV) were applied to 14 (21.54%), 8 (12.31%), 12(18.46%), and 3 (4.62%) patients, respectively. The median (IQR) time of onset of symptom to HFNC use and mechanical ventilation was 13 (11–19) days and 14.5 (11.5–17) days, respectively. CRRT was applied to 3 critical patients in AKI stage 2.

Methylprednisolone was applied to 31 (47.69%) patients with pneumonia, including 10 (31.25%) general, 8 (100%) severe, and 13 (86.67%) critical patients, respectively. The dosage and duration of methylprednisolone were prescribed individually according to the severity of pneumonia and/or PaO_2/FiO_2. Thirty of the 31 patients (96.77%) had stopped methylprednisolone due to improvement of pneumonia on chest X-ray/CT or PaO_2/FiO_2. One patient died of severe ARDS during methylprednisolone use. Another patient died of septic shock after methylprednisolone use had been stopped 11 days. The median (IQR) time of methylprednisolone use was 7 (5–9) days. The side effects of using methylprednisolone in these 31 patients were hypertension (8, 25.81%), hyperglycemia (11, 35.48%), hypokalemia (11, 35.48%), arrhythmia (4, 12.9%), neuropsychiatric symptoms (2, 6.45%), and gastrointestinal bleeding (1, 3.23%). All above side effects were relived after symptomatic treatment.

The median (IQR) of virus clearance time in patients without methylprednisolone (12.5, 6–17 days) was shorter than in patients with methylprednisolone (19, 14–22 days) (P = 0.0003). But in general type, there was no significant difference in virus clearance time between patients with (15, 12–19 days) and without methylprednisolone use (14.5, 11–18 days) (P = 0.7372).

A linear mixed model showed the relationship between clinical type or corticosteroids used and dynamic IL–6 values or T lymphocyte counts throughout the course of the disease (Table 3 and 4). The confounding variables included age, gender, and concurrent disease. IL–6 increase and T lymphocyte decrease were more common as the disease worsened (All P<0.05). Corticosteroids did not affect T lymphocyte counts (P = 0.0796) but inhibited IL–6 levels (P = 0.0215). In patients using corticosteroids, there was no significant difference in dynamic IL–6 values or T lymphocyte counts between patients using lower dose (≤2mg/kg.d) and higher dose(>2mg/kg.d) methylprednisolone throughout the course of the disease (All P>0.05). The IL–6 levels in patients using corticosteroids decreased quickly after using corticosteroids. Whereas in patients without corticosteroids use, the decrease of IL–6 levels was later and more gradual as patients recovered (Figure 1c). The T lymphocyte count trends had a similar pattern throughout the course of disease in patients with and without corticosteroids use (Figure 1d).

The number of patients discharged, admitted to the ICU, and deceased were 45 (69.23%), 4 (6.15%), and 2(3.08%), respectively. All 45 patients were discharged with full recovery. In these patients, the median (IQR) time from the symptom time to discharge was 19(14–30) days, including 13 (9–18) days for mild,

19 (15–27) days for general, 31(23.5–32) days for severe, and 31 (27–34) days for critical patients (P = 0.0003).

Discussion

Our study included 65 COVID19 patients representing the full spectrum of clinical types. All patients, except for 16 who had no identified exposure history, were infected through human-to-human transmission. Human-to-human transmission was the major way spreading COVID19 in our study, which is consistent with recent reports[4–6,8]. The median incubation period was 6 days, including 2 patients at 14 days, 1 patient at 16 days and 1 patient at 21 days. Therefore, the incubation period of COVID19 is likely to be greater than 14 days. 14 days may not be long enough to rule out infection after coming in contact with infected patients. The incubation period needs to be verified with a larger population.

Fever, dry cough and bilateral patchy shadowing on chest X-ray were the most common clinical features, whereas other symptoms (ie. myalgia, fatigue, dyspnea, anorexia, diarrhea, nausea and vomiting) were observed in less than 35% of cases. Chest CT feature was more typical with bilateral ground-glass opacity. The duration of time from onset of symptoms to pneumonia was similar in different clinical types. However, the onset of symptom to virus RNA clearance time lengthened dramatically as clinical type worsened.

The laboratory abnormalities observed in this study were leucopenia, lymphopenia, elevated D-dimer, ESR, IL–6, serum ferritin, CRP, and LAC, which were related to sustained inflammatory response. All the observed abnormalities were more pronounced in critical patients than in mild ones. We also observed that COVID19 is more severe in older people as well as patients with concurrent diseases as these patients generally had weaker immune functions[19,20]. Decreased T, CD4, and CD8 lymphocytes were much more common in critical patients than in mild ones in our study. A substantial decrease in total number of lymphocytes indicates that coronavirus consumes many immune cells and inhibits the body's cellular immune function. Damage to T lymphocytes might be an important factor leading to exacerbations of patients[21]. All the evidence indicates that COVID19 might mainly act on lymphocytes, especially T lymphocytes. In this study, decreased lymphocytes, including total, T, CD4, and CD8 lymphocytes, were more common as the disease worsened.

The virus could induce a cytokine storm in the body, generating a series of immune responses. In view of the high amount of cytokines induced by SARS-CoV[22,23], MERS-CoV[24,25], and 2019-nCoV infections[1], corticosteroids were commonly used to treat patients with severe illness, for a potential benefit of reducing inflammatory-induced lung injury. Some reports did not support corticosteroid treatment, because it could inhibit immune responses and virus clearance[26–28]. However, some studies supported the use of corticosteroids in patients with coronavirus infection, because it could reduce mortality and the need for mechanical ventilation, and shorten the length of stay in hospital[29–31]. In this study, methylprednisolone was applied to 47.69% of patients with COVID19, including 31.25% general, 100% severe, and 86.67% critical patients, respectively. Thirty of the 31 patients (96.77%) with

methylprednisolone using had stopped methylprednisolone due to improvement of pneumonia. However, one patient died of septic shock on the 11th day after corticosteroids were stopped. We can't exclude the correlation between septic shock and higher dose (mean dose, 4mg/kg.d, 9 days) methylprednisolone. We found that corticosteroids inhibited IL−6 production throughout the course of the disease. Meanwhile, there was no significant difference between patients using lower dose (≤2mg/kg.d) and higher dose (>2mg/kg.d) methylprednisolone. Therefore, application of lower dose corticosteroids (≤2mg/kg.d) could inhibit IL−6 production (a representative of cytokines) as effectively as a higher dose.

Some studies reported that methylprednisolone may delay virus clearance time[13,32]. In our study, all severe and most critical patients used methylprednisolone. We could not distinguish whether the lengthened virus RNA clearance time was completely due to disease progression or if it was impacted by methylprednisolone use. We could not compare the virus clearance time of using versus not using methylprednisolone in severe and critical groups due to almost all of these patients being treated with methylprednisolone. In general type, 31.25% of patients used methylprednisolone and 68.75% of patients didn't use, and the virus clearance time was similar between users and non-users. Therefore, more study is necessary to elucidate whether properly using corticosteroids delays virus clearance time among patients with COVID19.

Timely use of mechanical ventilation is a more effective treatment for patients with moderate or severe ARDS[33]. NIPPV or IPPV could open alveoli and reduce exudation, improving the PaO_2/FiO_2, which is the signal to stop using methylprednisolone. At the same time, preventing fluid overload and early application (AKI stage 2) of CRRT also guarantee a better prognosis.

Proper use of corticosteroids could have led to the improvement observed in this study. The following rules should be considered when using corticosteroids: 1, When to start and stop using corticosteroids should be carefully weighed. 2, Dosage should be personalized, and the duration should be short, especially in critical patients. 3. Side effects should be seriously monitored and promptly addressed.

This study has several limitations. First, only 65 patients with confirmed COVID19 in Beijing were included, thus certain subgroup analyses had limited statistical power. Second, because most patients were still hospitalized, final clinical outcomes were not available for analysis at the time of manuscript submission. We will continue to follow-up these patients in order to have a more comprehensive understanding of COVID19.

Conclusion

The incubation period of COVID19 in a few patients is likely to be greater than 14 days. Lymphocyte, especially T lymphocyte, in severe and critical patients showed a dramatic decrease. Application of lower dose corticosteroids (≤2mg/kg.d) could inhibit IL−6 production (a representative of cytokines) as effectively as a higher dose. Proper use of corticosteroids in general type patients did not delay virus

clearance. For patients with moderate to severe ARDS, timely use of mechanical ventilation and CRRT guarantee a better prognosis.

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Declarations

Conflict of Interest: None to declare.

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Ethical approval: This study was approved by the ethics committee of the 5th Medical Center of PLA General Hospital. Written informed consent was waived in light of the urgent need to collect clinical data.

Tables

Due to technical limitations, Tables 1-4 are provided in the Supplementary Files section.

Figures

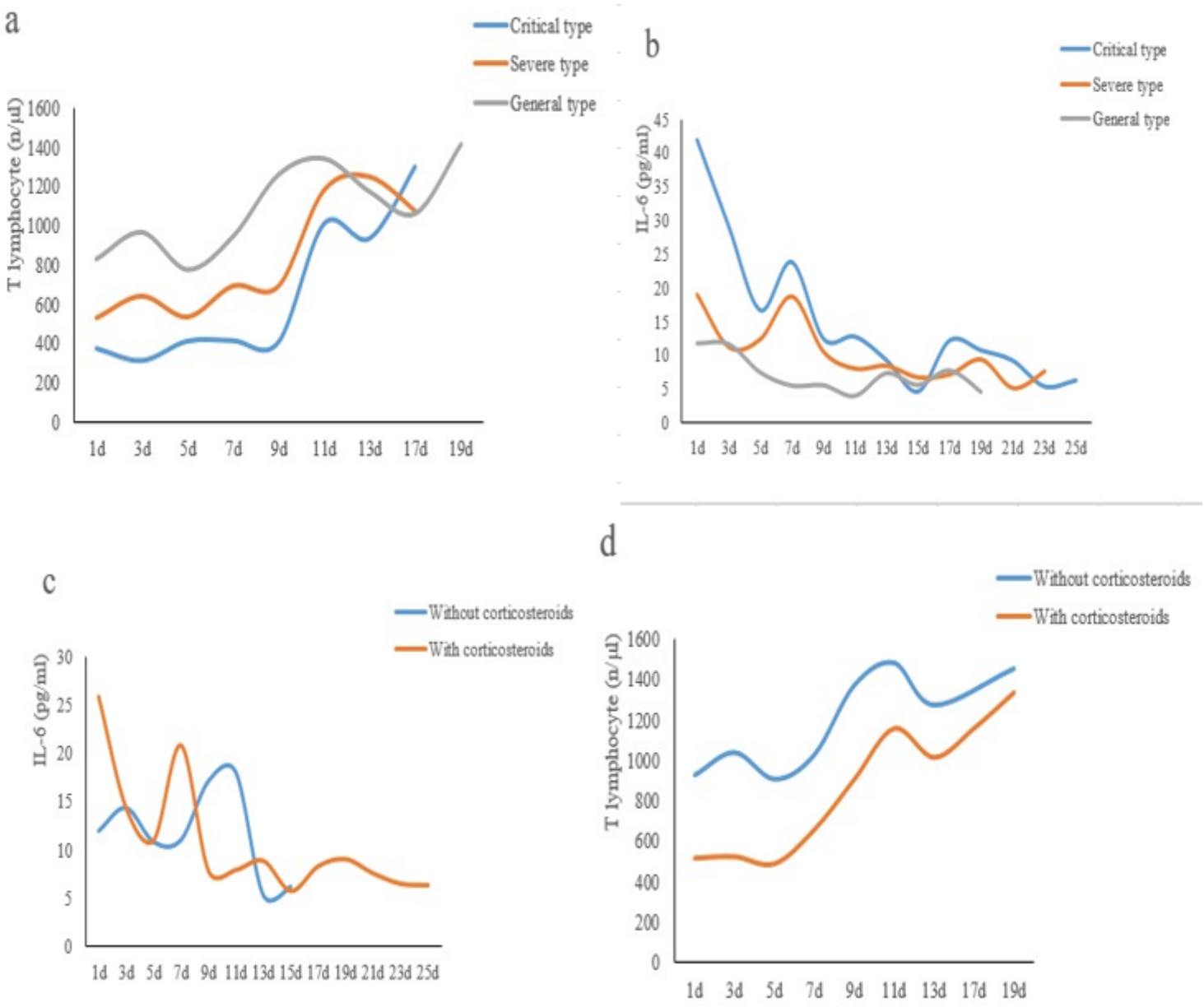

Figure 1

Dynamic IL-6 levels and T lymphocyte counts trends of patients with COVID19 in different group throughout the course of the COVID19. Abbreviations: COVID19, Corona Virus Disease 2019.IL-6, Interleukin-6.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1a.xlsx
- Table1.xlsx
- Table2.xlsx

- Table4.xlsx
- Table3.xlsx
- SupplementaryTable1b.xlsx