Temporal Dynamics in Clinical and Laboratory Manifestations During COVID-19 Progression

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Research article

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Abstract

BAckground

Severe COVID-19 patients account for most of the mortality of this disease. Early detection of severe cases of the disease remains a major challenge. Here, we performed clinical and laboratory profiling of COVID-19 to explore the early warning indicators of severe cases.

Methods

An analysis of the evolution during the hospitalization of clinical and laboratory findings from 78 confirmed COVID-19 patients and the associated risk factors.

Results

Of the 78 patients who were classified as un-severe at admission, 60 patients(stable group) were stable as mild cases until discharge, and the remaining 18 patients progressed to severe cases(exacerbated group) during hospitalization. Compared with stable patients, exacerbated patients exhibited older, higher BMI values and higher proportion of smokers. In the exacerbated patients, the median time from onset to deterioration was 7.5 days. Before the time point(days 0–7 from onset), we observed higher-levels of White blood cells(WBC), neutrophil, Neutrophi-Lymphocyte-Ratio(NLR), Lactose-dehydrogenase(LDH), D-dimer, and lower-levels of albumin in the exacerbated group, compared with the stable group. In the second week after the time point, the exacerbated patients displayed lower numbers of lymphocytes, $CD3^+$, and $CD8^+$T-cells, and higher-levels of C-reactive protein(CRP), erythrocyte-sedimentation-rate(ESR), Alanine-aminotransferase(ALT),Aspartate-aminotransferase(AST), and Interleukin-6. In the third week, the highest temperature and the proportion of febrile patients declined. All of the laboratory indicators gradually improved.

Conclusions

Advanced age and smoking history could be risk factors for COVID-19 progression. In the early stage, high-levels of WBC and neutrophils, with noticeably increased LDH and D-dimer, could be early indicators of the disease's conversion from mild to severe, followed by elevated inflammatory markers, liver enzymes, and decreased T-lymphocytes in the next week.

Background

In December 2019, an outbreak of a respiratory disease in humans (COVID-19) raised an acute and severe global concern[1–3], which was rapidly proved to be caused by a virus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[1, 4]. By June 1, 2020, a total of 5,939,234 confirmed COVID-19 cases and 367,255 associated deaths were recorded all over the world[5]. The number of confirmed COVID-19 cases reported to the World Health Organization (WHO) continues to rise worldwide.

Although the majority of COVID-19 patients have an uncomplicated or mild illness (81%), some will develop a severe illness (14%), and approximately 5% will require intensive care unit treatment. Of those critically ill, the mortality is as high as 61.5%[6]. The early detection of these severe patients could decrease the mortality rate but remains a major clinical challenge. Currently, severe cases are mainly diagnosed empirically based on a set of clinical characteristics, such as respiratory rate (≥ 30 times/min), mean oxygen saturation (93% in the rest state), or arterial blood oxygen partial pressure/oxygen concentration (300 mmHg)[7]. In fact, patients exhibiting these clinical manifestations have already progressed to the clinically severe phase with a high risk of death. Therefore, it is critical to develop new approaches to predict which cases will likely become clinically severe. This would anticipate the initiation of the appropriate treatment to reduce the risk of rapid deterioration.

Previous studies have focused on the difference between non-severe and severe patients[8–11]. It was reported that severe patients have higher blood white counts (WBC), neutrophil counts, and higher levels of C-reactive protein, D-dimer, lactate dehydrogenase, and Interleukin-6[8, 10, 12, 13]. However, the kinetic changes of these abnormal indicators that occur throughout the course of COVID-19, especially during deterioration, and how they relate to the clinical features remains unknown

In this study, we retrospectively investigated and compared the dynamic changes of the clinical presentation and laboratory indicators between those stable non-severe cases and those with an initial mild illness that progressed into a severe case of COVID-19 during hospitalization. We hypothesized that the clinical and laboratory profiling of these COVID-19 patients may shed light on the early warning indicators of severe cases.

Methods

Ethics statement

Data collection and analysis of patients were approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (2020 – 0120). Written informed consent was waived as part of a public health outbreak investigation, and oral consent was obtained from each patient.

Patients

This was a retrospective single-center study that included 78 confirmed COVID-19 patients treated at the Wuhan Union Hospital from January 1, 2020, through February 30, 2020. The flow chart, from a total of 243 patients up to 78 patients of the study, is shown in Figure S1. Of the 243 patients, 158 cases were classified as severe or critically ill at admission, and seven cases lacking relevant data were excluded.

The clinical classification followed was according to the Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Trial Version 7) developed by the National Health Committee of the People's Republic of China[7]. Laboratory confirmation of SARS-CoV-2 infection was performed within bio-safety level 2 facilities at the Wuhan Union Hospital[14].

Baseline Data Collection

The epidemiological characteristics, clinical symptoms, laboratory findings, medical treatment, and outcome were obtained from electronic medical records. The laboratory tests included blood routine, biochemical indicators, lymphocyte subsets, plasma cytokines, inflammation markers, and coagulation function.

Follow-up

After admission, the patients were re-examined for laboratory indexes, and symptoms, treatments, and outcome events were recorded. The endpoint was discharge or death. The discharge criteria were based on the Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Trial Version 7)[7].

Statistical analysis

Student's t-tests or Mann-Whitney tests were applied to continuous variables, while chi-square tests were applied to categorical variables. Time-course data were aligned to date of symptom onset and aggregated over 3-4-day intervals to account for data not being available for all patients at all time points during the disease course. For each interval, the means were compared by the Sidak-Bonferroni method. Time from symptoms onset to discharge was compared using the Log-rank(Mantel-Cox) test. All analyses were performed using the SPSS 13.0(SPSS Inc). $p < 0.05$ was considered as statistically significant.

Results

Demographic and clinical characteristics of COVID-19 patients

A total of 78 patients with COVID-19 were enrolled in the study. The flow chart is displayed in Figure S1. They were all classified as non-severe patients on admission and received antiviral therapy after admission, such as Ribavirin, Arbidol, and/or IFN-α[7].

Of the 78 patients, 18 patients exacerbated even with treatment after admission and then rapidly developed to severe illness. The conditions of the remaining 60 patients were stable and gradually improved until discharge. Based on this, the 78 patients were divided into two groups, the exacerbated group (18 patients) and the stable group (60 patients).

Table 1 summarizes the patient demographics and clinical characteristics. The median age of the two groups was statistically different, at 57.5 years old for the exacerbated group and 35 years old for the stable group ($p = 0.0001$). The Body Mass Index (BMI) was also significantly different between the two groups, with 23.98 (IQR: 21.92–28.54) for the exacerbated patients and 22.77 (IQR: 21.09–24.46) for the stable patients ($p = 0.0441$). The percentage of patients with a smoking history was 22.2% and 3.3% for the exacerbated and stable groups, respectively ($p = 0.0083$).

Table 1
Clinical characteristics of 78 Patients with COVID-19

Characteristics Symptoms	All patients (n = 78)	Trend		
		Exacerbation (n = 18)	Stable (n = 60)	P value
Age, Median (range) - yrs	36(31.5–57)	57.5(44–63)	35(31–48)	**0.0001**
Age groups – No. %	-	-	-	
20–39 yrs	42/78(53.8)	2/18(11.1)	40/60(66.7)	**< 0.0001**
40–59 yrs	24/78(30.8)	9/18(50)	15/60(25.0)	**0.0438**
≥ 60 yrs	12/78(15.4	7/18(38.9)	5/60(8.3)	**0.0016**
Sex – No.%	-	-	-	-
Male	28/78(35.9)	8/18(44.4)	20/60(33.3)	0.3887
Body Mass Index, Median (range)	22.86(21.36–25.39)	23.98(21.92–28.54)	22.77(21.09–24.46)	**0.0441**
< 18.5	3/53(5.7)	0/14	3/39(7.7)	0.2583
18.5–23.9	30/53(56.6)	7/14(50.0)	23/39(59.0)	0.5611
≥ 24	20/53(37.7)	7/14(50.0)	13/39(33.3)	0.2698
Smoking history – No.%				
Current smokers	6/78(7.7)	4/18(22.2)	2/60(3.3)	**0.0083**
Symptoms – No.%	-	-	-	-
Fever	69/78(88.5)	18/18(100)	51/60(85)	0.0806
Highest temperature (range)	38.6(38–39)	38.8(38.3-39.05)	38.5(37.78-39)	0.0516
Sore throat	19/78(24.4)	3/18(16.7)	16/60(26.7)	0.3860
Nasal congestion	6/78(7.7)	2/18(11.1)	4/60(6.7)	0.5348
Cough	47/78(60.3)	12/18(66.7)	35/60(58.3)	0.5263
Sputum production	28/78(35.9)	8/18(44.4)	20/60(33.3)	0.3887
Dyspnea	30/78(38.5)	6/18(33.3)	24/60(40.0)	0.6101
Chest pain	6/78(7.7)	2/18(11.1)	4/60(6.7)	0.5348
Fatigue	45/78(57.7)	10/18(55.6)	35/60(58.3)	0.8343
Myalgia	23/78(29.5)	4/18(22.2)	19/60(31.7)	0.4409
Anorexia	24/78(30.8)	9/18(50.0)	15/60(25.0)	0.0910
Headache	23/78(29.5)	6/18(33.3)	17/60(28.3)	0.6833
Diarrhea	18/78(23.1)	2/18(11.1)	16/60(26.7)	0.1601
Vomiting	4/78(5.1)	1/18(5.6)	3/60(5.0)	0.9253
Palpitation	7/78(9.0)	1/18(5.6)	6/60(10.0)	0.5628
Night Sweats	2/78(2.6)	0/18	2/60(3.3)	0.4326

Data are presented as medians (interquartile ranges, IQR) and n/N (%).

[a] Hypertension, diabetes, thyroid disease, asthma, arteriosclerosis, cancer.

[b]All cancer cases were stable disease.

Continuous variables were compared by Student's t-tests or Mann-Whitney tests, and categorical variables were compared by the chi-square tests.

Characteristics Symptoms	All patients (n = 78)	Trend		
		Exacerbation (n = 18)	Stable (n = 60)	P value
Coexisting disorders[a] – No. %	17/78(23.1)	6/18(33.3)	11/60(18.3)	0.1764
Diabetes	7/78(9)	4/18(22.2)	3/60(5.0)	0.2606
Hypertension	6/78(7.7)	1/18(5.6)	5/60(8.3)	0.9370
Cancers[b]	3/78(3.8)	3/18(16.7)	0/60(0)	**0.0013**
Treatment – No. %				
Administration of antiviral medications	78/78(100)	18/18(100)	60/60(100)	-
Administration of intravenous antibiotics	78/78(100)	18/18(100)	60/60(100)	-
Administration of systemic corticosteroids	3/78(3.8)	3/18(16.7)	0/60	**0.0013**
Use of intravenous immunoglobin	16/78(20.5)	5/18(27.8)	11/60(19.3)	0.3841
Oxygen therapy	30/78(39.2)	15/18(83.3)	15/60(25.0)	**< 0.0001**
Onset of symptom to, median (range)	-	-	-	-
First hospital visit	4(2–7)	6(2–8)	3.5(2–7)	0.3276
Hospital admission	7(5–10)	7(2–9)	7(4.5–10)	0.8501
Discharge	20(16–24)	23(20-36.3)	19(16–23)	**0.0003**
Exacerbation	-	7.5(2-11.25)	-	**-**
Hospitalization days, median (range)	13(8–17)	17(14.75–23.25)	11.5(7–16)	**0.0006**
Outcomes– No. %				
Discharge	77/78(98.7)	17/18(100)	60/60(100)	0.0661
Death	1/78(1.3)	1/18(5.6)	0/60(0)	0.0661
Data are presented as medians (interquartile ranges, IQR) and n/N (%).				
[a] Hypertension, diabetes, thyroid disease, asthma, arteriosclerosis, cancer.				
[b]All cancer cases were stable disease.				
Continuous variables were compared by Student's t-tests or Mann-Whitney tests, and categorical variables				
were compared by the chi-square tests.				

Time To Event Analysis In Covid-19 Patients

Of the 18 exacerbated patients, 17 cases eventually recovered and were discharged. The one patient that died (on day six after symptom onset) had been admitted with gastric cancer and was confirmed as COVID-19 positive after surgery. The median time from onset to exacerbation was 7.5 days (IQR:2–11.5) for the exacerbated patients (Fig. 1).

The disease course was defined from the day of symptom onset to discharge, and the data revealed the median disease course was longer for the exacerbated group compared with the stable group patients (23 *vs.* 19 days, $p = 0.0015$, Table 1 and Fig.S2). The average hospitalization days were 11.5 (IQR:7–16) days for stable patients and 17 (IQR:14.75–23.25) days for the exacerbated patients ($p = 0.0006$). Nevertheless, the two groups did not differ in the median duration from illness onset to a first hospital visit and hospital admission (Table 1), which indicated that the deterioration of patients after admission was not due to the pre-hospitalization delay.

Dynamic Changes In Febrile Patients

Of the 78 patients, a total of 88.5% of patients exhibited fever (temperature > 37.3 °C) during COVID-19 (Table.S1). After 12 days from the onset, the highest temperatures of all febrile patients subsequently improved, and the trend and magnitude were similar between the exacerbated and stable groups (Fig. 2A). The proportion of febrile patients also significantly declined on day 12 (Fig. 2B), but there were no differences in the proportion of febrile patients between the two groups within 12 days from onset. Interestingly, at 13–17 days from symptom onset, the proportion of febrile patients in the exacerbated group was significantly higher than in the stable group (33.3% vs. 5%, $p = 0.001$, Table S1, and Fig. 2B), indicating the longer duration of abnormal temperature in the exacerbated group.

Dynamic Profiling Of Laboratory Findings

To elucidate the dynamic changes in laboratory indicators throughout the disease course, blood routine and lymphocyte subsets (Fig. 3), biochemical and coagulation indicators (Fig. 4), plasma cytokines, and inflammatory biomarkers (Fig. 5) were collected during hospitalization at 3-day or 4-day intervals.

At days 0–3 from symptom onset, the exacerbated cases exhibited higher WBC (8.1 *vs.* 4.8×10^9/L, Fig. 3A) and neutrophil counts (6.5 *vs.* 3.1×10^9/L, Fig. 3B), and higher levels of lactate dehydrogenase (LDH; 337.2 *vs.*216.5 U/L, Fig. 4D), D-dimer (4.1 *vs.* 0.6 mg/L, Fig. 5C), and lower levels of albumin (33 *vs.* 38.6 g/L, Fig. 4C), compared with stable patients (all $p < 0.05$).

At days 4–7 from symptom onset, we observed a clear distinction of the neutrophil-lymphocyte-ratio(NLR) between the exacerbated and stable cases (6.4 *vs.*2.5, $p = 0.0015$, Fig. 3C).

At days 8–12 from the onset, the WBC(Fig. 3A) and neutrophil counts (Fig. 3B), and the levels of NLR (Fig. 3C), albumin (Fig. 4C) and LDH (Fig. 4D) decreased slightly in the exacerbated group, but still with significant statistical differences between the two groups. Notably, higher levels of alanine aminotransferase (ALT; 68.3 vs.22.1 U/L, $p = 0.0007$; Fig. 4A), aspartate aminotransferase (AST; 48 *vs.* 24.2 U/L, $p = 0.0019$; Fig. 4B), C-reactive protein (CRP; 50.8 vs.18.4 mg/L, $p = 0.0003$; Fig. 5G), ESR; 38.2 *vs.*23 mm/h, $p = 0.0368$; Fig. 5H) and interleukin-6 (IL-6; 22.9 *vs.* 5.4 pg/mL, $p = 0.0002$; Fig. 5C) were observed in the exacerbated patients when compared with the stable patients at this point. The lymphocyte counts of exacerbated patients were significantly lower than in stable patients (1.0 *vs.*1.3×10^9/L, $p = 0.0023$; Fig. 3E). The level of D-dimer between the two groups showed the same trend as before. (Fig. 4I).

At days 13–17 from symptom onset, an obvious distinction of lymphocyte counts remained between the two groups (1.1 *vs.* 1.3×10^9/L, $p = 0.02$; Fig. 3E). More specifically, the lowest proportions of $CD3^+$T cells and $CD8^+$T cells were observed in exacerbated patients at this time point, which significantly differed from the stable patients (54.4% *vs.* 78.3%, $p = 0.0012$, Fig. 3F; 17.6% vs. 28.9%, $p = 0.0289$, Fig. 3H; respectively). However, the differences in $CD4^+$T cells between the two groups did not reach a statistical significance at any time point (Fig. 3G). There was a noticeable rise in the platelet count (PLT) at this time in the exacerbated patients, which was significantly higher than in the stable patients (Fig. 3D). Additionally, the WBC (Fig. 3A), neutrophil counts (Fig. 3B), and the NLR (Fig. 3C), LDH (Fig. 4D), and IL-6 (Fig. 5C) levels were greatly decreased at this duration, all of which showed the same tendency between the two groups.

At days 18–22 from the onset, only AST (Fig. 4B), albumin (Fig. 4C), PLT (Fig. 3D), and ESR (Fig. 5H) exhibited significant differences between the two groups.

At days 23–27 from the onset, except for PLT(Fig. 3D), there were no discernible differences in any of the laboratory indicators between the exacerbated and stable patients (Fig. 3–5).

High-risk Factors Associated With Progression

To explore the early warning indicators of progression, we assessed the risk factors of progression of COVID-19 patients (Fig. S3). The results showed that age ≥ 60 years, smoking history, WBC ≥ 4×10^9/L, neutrophil count ≥ 6.3×10^9/L, lymphocyte ≤ 1.0×10^9/L, NLR ≥ 2.5, LDH > 245 U/L, Album < 35 g/L and D-dimer ≥ 0.5 mg/L were high-risk factors associated with progression of the illness (Fig. S3).

Conclusions

This is the first study to describe the clinical features and consecutive laboratory characteristics of COVID-19. Of the 78 patients who were classified as non-severe patients at admission, 18 patients progressed to a severe illness (the exacerbated group) after hospitalization. In comparison, the remaining 60 patients (the stable group) were stable and gradually recovered. In our study, the exacerbated group had a higher frequency of older patients and smokers when compared with the stable group. These data show that advanced age and smoking are important risk factors for disease progression.

In this study, the median time from onset to deterioration was 7.5 days for the exacerbated patients. Before this time point (days 0–7 from onset), compared with the stable group, we observed significantly higher WBC and neutrophil counts, higher levels of NLR, LDH, and D-dimer, and lower levels of albumin in the exacerbated group. We suggest that these abnormal laboratory indexes might be the earliest warning indicators to predict the patients with a high risk of deterioration before the appearance of the clinical manifestations of severe COVID-19. In the second week (days 8–12), lower lymphocytes, $CD3^+$T cells, and $CD8^+$T cells, and higher levels of CRP, ESR, ALT, AST, IL-6 subsequently appeared in the exacerbated patients.

By evaluating the condition of patients with fever, we observed that the highest temperature and the proportion of febrile patients both declined on days 13–17 from symptom onset. Day 12 from symptom onset might be an inflection point, suggesting an improvement of the disease course. In the late third week (days 18–22), except for AST, albumin, PLT, and ESR, the rest laboratory indicators of the exacerbated patients greatly improved and did not differ from the stable patients. Notably, the median disease course of stable patients was 19 (IQR:16–23) days, suggesting that most stable patients would recover and be discharged during that week. In the fourth week (days 23–27), except for PLT, there were no different indicators between the two groups. A study reported that platelets could trigger B cells to increase their production of IgG1, IgG2, and IgG3, suggesting that the platelet content can contribute to B-cell function and alter adaptive immunity[15, 16]. Similarly, the elevated level of PLT, which was observed in the late stage of disease course, was suggested to be associated with the recovery of COVID-19 in the current data.

Only based on clinical symptoms, it is difficult to determine whether a patient is at risk of progression. There was no difference in symptoms between the exacerbated and stable groups at admission. Nonetheless, notable differences in laboratory indexes were observed during the whole course of COVID-19, indicating the importance of monitoring laboratory indexes timely, not just the clinical features. However, considering the rapidly growing number of COVID-19 cases, the inadequate responses, and insufficient medical staff, it was difficult to take care of every patient, and extra blood tests would undoubtedly have increased the burden on the nurses and on patients as well. In addition, such testing implies a higher patient-clinician interaction and laboratory personnel exposure, increasing the risk of transmission. Therefore, based on our findings, monitoring the laboratory indicators distinctively according to the timetable from symptom onset may help to efficiently diagnosis the patients with high risk to rapid deterioration, before clinical manifestations. In the early stage, the clinician should pay more attention to the WBC and neutrophil counts, as well as the levels of NLR, LDH, and D-dimer. Any increase in these levels should be an alert for disease progression, and then the focus should be on the levels of CRP, IL-6, AST, and ALT. An elevation of these indicators may be a sign that the COVID-19 patient progressed or has a high risk of progressing to severe conditions. According to these changes, clinicians may take effective measures timely to reduce the risk of deterioration and regulate the schedule and items of follow-up indexes to benefit the patient as much as possible.

This study has some limitations. First, it was a retrospective study in a single center in Wuhan, which may have resulted in unavoidable bias. Second, the sample size of exacerbated patients was smaller than that of patients without deterioration. Third, an accurate risk assessment model has not been established due to the small number of exacerbated cases enrolled in the current study.

In summary, advanced age and smoking history are risk factors for COVID-19 progression. High WBC and neutrophil counts, and high levels of LDH and D-dimer could be early indicators for patients with a high risk of progression in the first week after symptom onset. The secondary changes included elevated IL-6, CRP, ESR, AST, and ALT in the next week, and after that, the changes of lymphocyte subsets. Thus, we have shown that it is feasible to predict severe COVID-19 patients based on a panel of laboratory indexes. Our data offer an optimal laboratory detection time point, which may help to efficiently anticipate the recognition of suspected patients with a high risk of progression into severe COVID-19.

Declarations

Ethics approval and consent to participate: Data collection and analysis of patients were approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (2020-0120).

Consent for publication: Not applicable

Availability of data and material: All the clinical data can be shared if necessary.

Competing Interests: The authors declare that they have no competing interests.

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Authors' contributions: QZ conceived the idea, designed and supervised the study, had full access to all data and took responsibility for the integrity of the data. LLY and WBP contributed to collected, analyzed and interpreted the data. XSW, XRW and WBY recruited the patients. XW,

ZHW XX and XLH recorded and sorted the data. FX and YS checked and verified the integrity of the data and the accuracy of the data. All authors read, critically revised, and approved the final manuscript.

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Figures

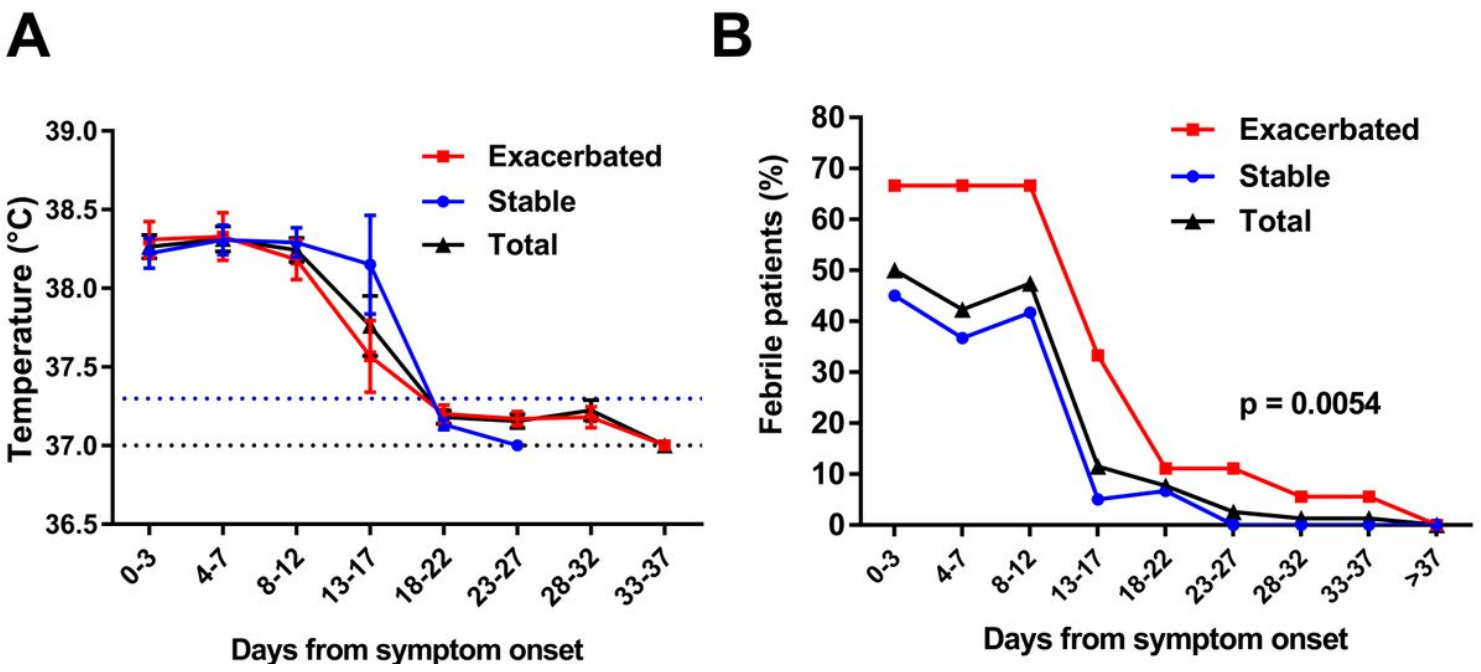

Figure 1

Timeline of 18 exacerbated patients with COVID-19 after onset of illness

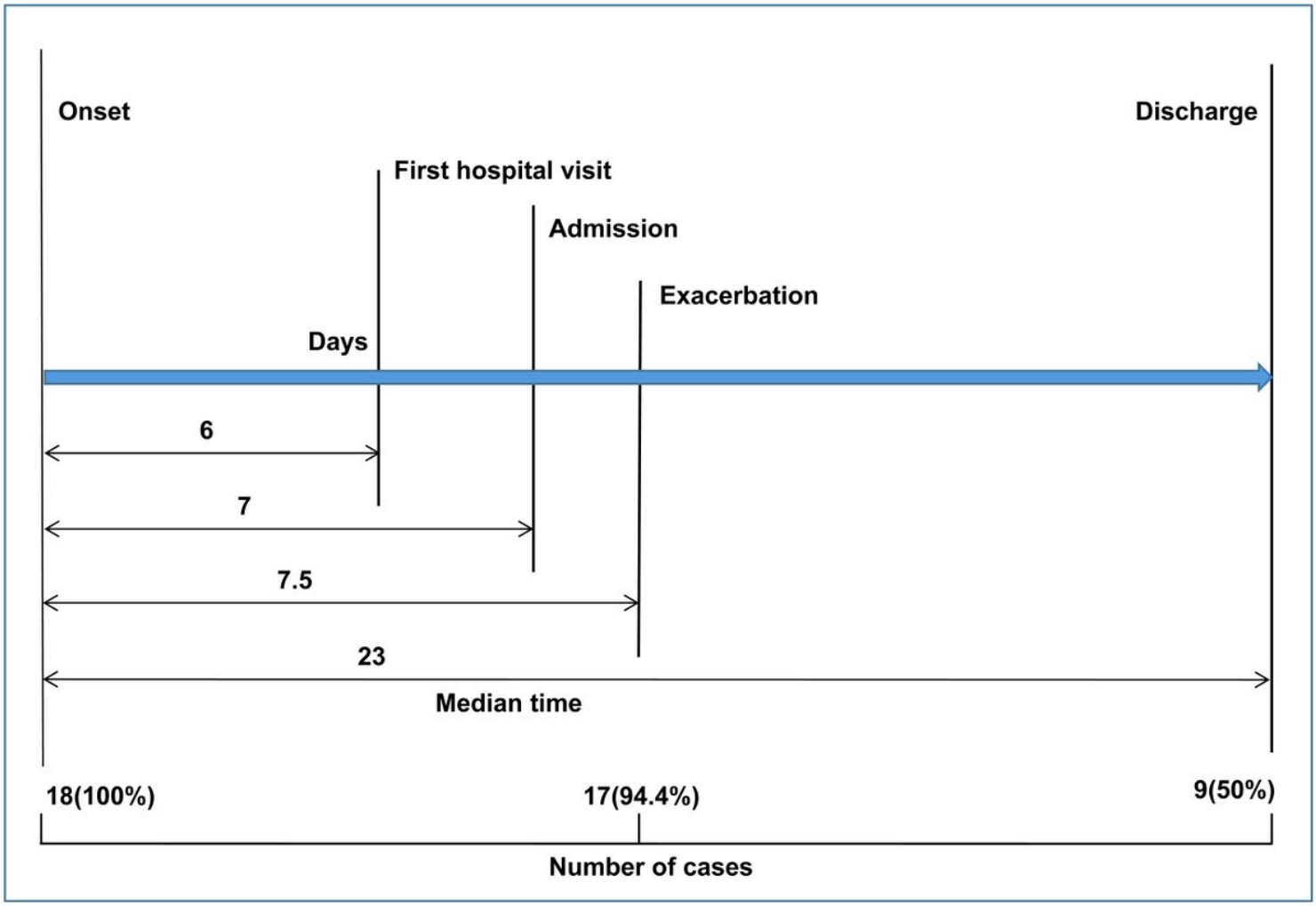

Figure 2

Kinetic analysis of febrile conditions in COVID-19 patients The highest Temperature (A) and the proportions of febrile patients were analyzed over the course of COVID-19 disease. The dotted line shows the the upper normal limit of fever. The solid line indicate the threshold of the temperature values being recorded in this study. Error bars, mean ± s.e.m.; *p <0.05 were determined by Student's t-tests.

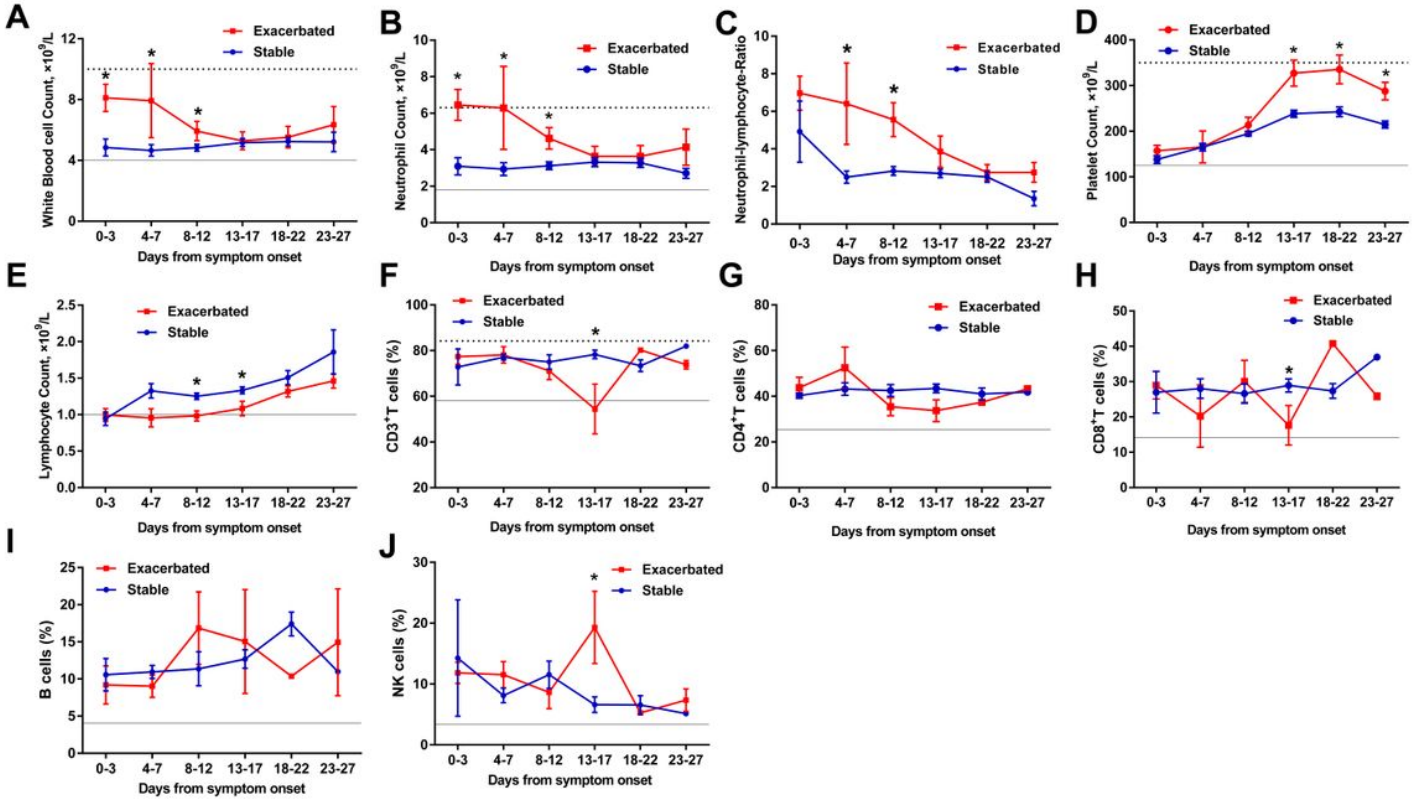

Figure 3

Kinetic analysis of blood cell parameters in COVID-19 patients The absolute numbers of White Blood Leukocyte Counts (WBC; A), neutrophils (B), Neutrophil-to-Lymphocyte Ratio (NLR;C), platelets(D) and lymphocytes(E) in the peripheral blood, and the proportions of CD3+T cells(F), CD4+T cells(G),CD8+T cells(H), B cells(I) and NK cells(J) in peripheral lymphocytes of stable (blue line) and exacerbated (red line) patients were analyzed at different time points after symptom onset. Error bars, mean ± s.e.m.; *p <0.05 were determined using Sidak-Bonferroni method. The dotted lines show the upper normal limit of each parameter, and the solid lines show the lower normal limit of each parameter.

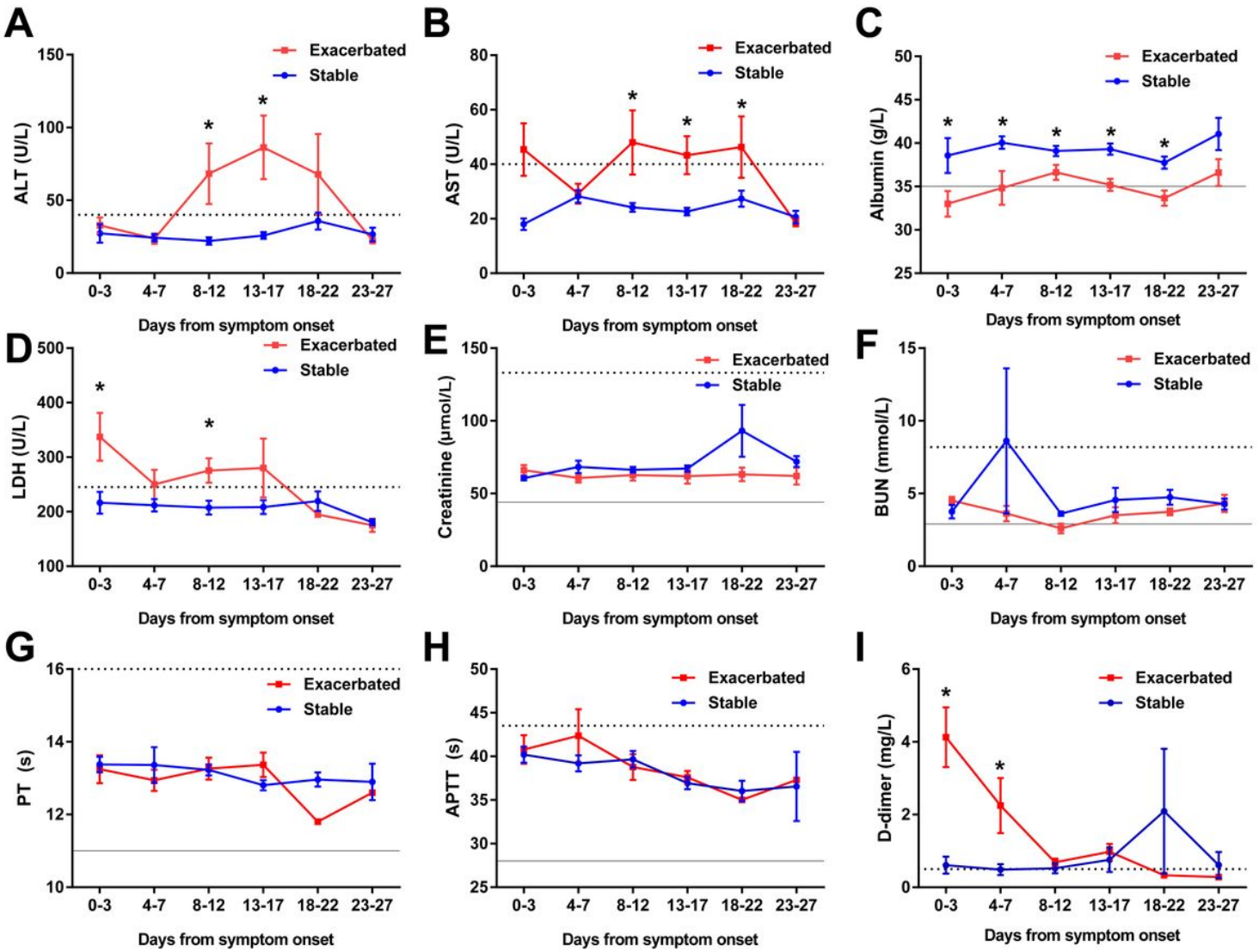

Figure 4

Kinetic analysis of blood chemistries and coagulation function parameters in COVID-19 patients The concentrations of alanine aminotransferase(ALT; A), aspartate aminotransferase (AST;B), albumin (C), lactose dehydrogenase(LDH;D), creatinine (E), blood urea nitrogen (BUN;F) and the time of prothrombin time (PT; G) and activated partialthromboplastin time(APTT;H), the concentrations of D-dimer (I) in the peripheral blood of stable (blue line) and exacerbated (red line) patients were analyzed at different time points after symptom onset. Error bars, mean ± s.e.m.; *p<0.05 were determined using Sidak-Bonferroni method . The dotted lines show the upper normal limit of each parameter, and the solid lines show the lower normal limit of each parameter.

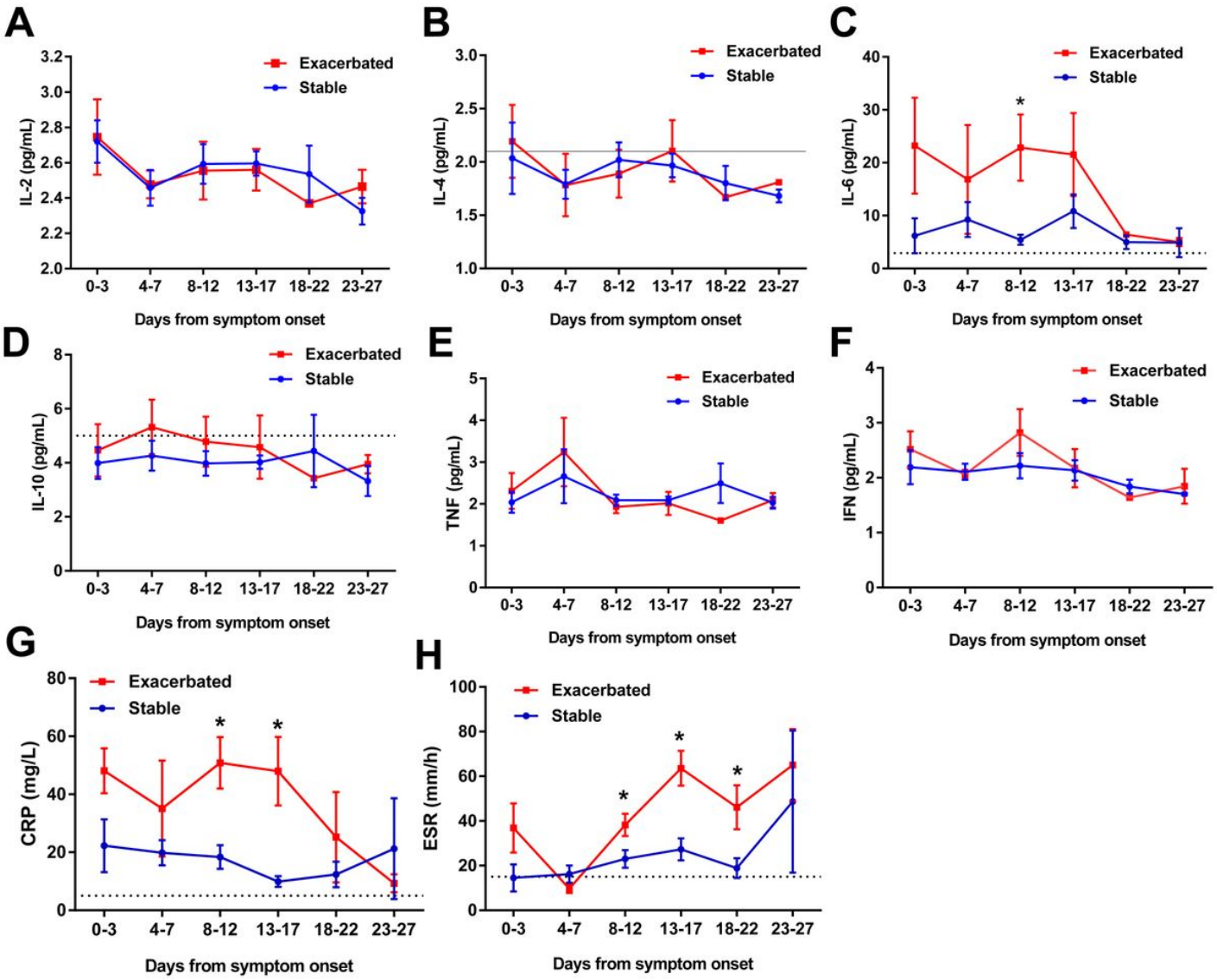

Figure 5

Kinetic analysis of plasma cytokines and inflammatory markers in COVID-19 patients The concentrations of IL-2 (A), IL-4 (B), IL-6 (C), IL-10 (D), TNF-α (E) and IFN-γ (F),C-Reactive Proteins(CRP;G), and the value of erythrocyte sedimentation rate(ESR;H) in the serum of stable (blue line) and exacerbated (red line) patients were analyzed at different time points after symptom onset. Error bars, mean ± s.e.m.; *p<0.05 were determined using Sidak-Bonferroni method. The dotted lines show the upper normal limit of each parameter.

Supplementary Files

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