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Clinical characteristics predicting progression of COVID-19

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Abstract:	Background With the outbreak of COVID-19 from Wuhan, Hubei Province, China since January 2020, there is a tremendous pressure on medical resources. We studied predictive factors of progression to severe disease to facilitate proper allocation of patients to different level of medical facilities. Methods All COVID-19 patients admitted to our hospital from 20 Jan 2020 were enrolled and follow-up until16 Feb 2020.The patients were divided into two groups: stable non-severe and progressive to severe diseases. Clinical data was prospectively collected and compared between the two groups. Findings Forty-nine COVID-19 patients,mean age: 43·6±17·1 years, 63·3%male, were enrolled. Sixteen (32·7%)had at least one comorbidity (hypertension, diabetes mellitus, cardiovascular disease and lung disease). Thirty-four 34 (69·4%) had stable non-severe disease and 15 (30·6%) progressed to severe disease. Univariate analysis showed that comorbidity, age >50, lymphocyte counts <1500 /μL andserum ferritin >400 ng/mL at presentation were predictive of progression to severe diseases. Seventy-three percent of patients (11/15) with three or all four risk factors progressed to severe disease, requiring intubation or intensive unit care as compared with11·8% (4/34) of subjects with 0-2 risk factors (odds ratio 6·2,95 % CI: 1·7 to 22·8, p =0·006). None of the subjects with absence of all 4 risk factors progressed to more severe diseases. Interpretation Around one-fifth of patients with COVID-19 will progress to severe

	diseases.Four simple clinical parameters at presentation, namely comorbidity, age, lymphocyte counts and serum ferritin were able to identify a group of patients with low risk of progression. This will greatly facilitate optimal utilization of the very tight medical resources in places with huge patient loads. Funding Chinese PLA General Hospital and Beijing Municipal Science and Technology Commission.

Clinical characteristics predicting progression of COVID-19

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Summary (word count -286)

Background With the outbreak of COVID-19 from Wuhan, Hubei Province, China since January 2020, there is a tremendous pressure on medical resources. We studied predictive factors of progression to severe disease to facilitate proper allocation of patients to different level of medical facilities.

Methods All COVID-19 patients admitted to our hospital from 20 Jan 2020 were enrolled and follow-up until 16 Feb 2020. The patients were divided into two groups: stable non-severe and progressive to severe diseases. Clinical data was prospectively collected and compared between the two groups.

Findings Forty-nine COVID-19 patients, mean age: 43·6±17·1 years, 63·3% male, were enrolled. Sixteen (32·7%) had at least one comorbidity (hypertension, diabetes mellitus, cardiovascular disease and lung disease). Thirty-four 34 (69·4%) had stable non-severe disease and 15 (30·6%) progressed to severe disease. Univariate analysis showed that comorbidity, age >50, lymphocyte counts <1500 /μL and serum ferritin >400 ng/mL at presentation were predictive of progression to severe diseases. Seventy-three percent of patients (11/15) with three or all four risk factors progressed to severe disease, requiring intubation or intensive unit care as compared with 11·8% (4/34) of subjects with 0-2 risk factors (odds ratio 6·2, 95 % CI: 1·7 to 22·8, *p*=0·006). None of the subjects with absence of all 4 risk factors progressed to more severe diseases.

Interpretation Around one-fifth of patients with COVID-19 will progress to severe diseases. Four simple clinical parameters at presentation, namely comorbidity, age, lymphocyte counts and serum ferritin were able to identify a group of patients with low risk of progression. This will greatly facilitate optimal utilization of the very tight medical resources in places with huge patient loads.

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Keywords: COVID-19, prediction, risk factors, severity of disease

Research in context (word count-308)

Evidence before this study

We searched PubMed, google scholar and the China National Knowledge Infrastructure database for articles published up to Feb 16, 2020, using the keywords “novel coronavirus”, “2019 novel coronavirus”, “2019-nCoV”, “pneumonia”, “coronavirus”, “Wuhan”, and “COVID-19” for articles published in both Chinese and English. We found three articles: one titled Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, and another entitled “Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study”, both published recently in *The Lancet*, . There is a third article “Clinical characteristics of 2019 novel coronavirus infection in China published online in MedRxiv preprint. https://doi.org/10.1101/2020.02.06.20020974.

All three articles described clinical and epidemiological features of COVID-19 patients and made some comparisons between severe and less severe diseases. However, none of these articles specifically address predictive factors for disease progression.

Added value of this study

We prospectively reviewed clinical records, laboratory findings, and chest CT scans of 49 patients with laboratory-confirmed COVID-19 and specifically identified clinical features at presentation that may predict disease progression. We found that comorbidity, age >50, absolute lymphocyte counts <1500 /µL and serum ferritin >400 ng/mL at presentation were predictive of progression to severe diseases. Seventy three percent of subjects (11/15) with three or all four risk factors progressed to severe disease, intubation or intensive care unit (ICU) as compared with 11·8% (4/34) of subjects with 0-2 risk factors (odds ratio 6·2, 95 % CI: 1·7 to 22·8, p=0·006).

Implications of all the available evidence

Our findings will help to identify which group of patients could be safely managed in community hospitals in rural area, with less medical facilities and which group will benefit from early transfer to tertiary or specialized centers. This will allow optimal utilization of limited medical resources in places with huge patient loads.

Introduction

The outbreak of COVID-19 due to SARS-CoV-2 infection has affected all 31 provinces in China and 28 countries worldwide. By Feb 16, 2020, there were over 69000 cases, and among them, around one-fifth were severe. To date, over 1600 (2·3%) patients had died.[1] The absolute number of new cases and severe cases have been increasing rapidly daily due to enhanced transmissibility of the virus.

Patients with mild or moderate symptoms may require only proper isolation and will recover within a short period of time. These patients can be safely managed in rural and community hospitals. However, those with severe disease may require more intensive supportive care, huge human and medical resources. Therefore, identification of risks factors that predict progression to severe disease will greatly facilitate optimal utilization of limited medical resources. This will be of great value for those less affluent countries with disease outbreaks. In the present study, we explored the clinical characteristics of patients outside Wuhan, and identified that comorbidity, age, lymphocyte counts and serum ferritin at presentation were able to predict a group of patients with low risk of progression.

Methods

Study design and patients

For this prospective, single-center, non-interventional cohort study, we enrolled all the confirmed COVID-19 patients presented to the Fifth Medical Center of Chinese PLA general hospital since Jan 20, 2020. On 20 Jan 2020 our hospital was assigned as the municipal treatment center of Beijing for COVID-19, formerly called Novel coronavirus pneumonia (NCP). COVID-19 was diagnosed based on the WHO interim guidance[2] and the protocol for diagnosis and treatment of NCP (Trial version 5)[3] issued by General Office of National Health Commission of the People's Republic of China and Office of State Administration of traditional Chinese Medicine. Briefly, the suspected cases must have the following epidemiological exposure history in the 14 days before onset of illness: travel to an area with documented cases of COVID-19 or close contact with any confirmed/probable case of COVID-19 or presence in a healthcare facility where COVID-19 infections have been managed or in a laboratory handling suspected or confirmed COVID-19 samples or direct contact with animals in countries where the COVID-19 is known to be circulating in animal populations or where human infections have occurred as a result of presumed zoonotic transmission. The subject must also have one of following additional clinical criteria: body temperature > 37·3℃ with or without cough, low white cell count or lymphocyte count or X-ray findings suggestive of viral pneumonia. If the patient had no epidemiological history, he must have all the additional clinical criteria. The diagnosis of COVID-19 was confirmed with the detection of SAS-CoV-2 in the throat swab by RT-PCR. Only those subjects with confirmed COVID-19 cases were included in the study (Figure 1).

The exclusion criteria were primary infection by other pathogens, such as bacteria, fungi, other respiratory virus, mycoplasma, or chlamydia. With follow-up, the enrolled patients were divided into two groups: stable non-severe group consisting of patients with mild or moderate symptoms on presentation and remained so during the entire observation period, and progressive severe group consisting of patients whose symptoms progressed in severity during the observation period or those eventually required intubation or ICU support. The simplified IDSA/ATS criteria for severe community-acquired pneumonia[4] were used to differentiate between the stable non-severe group and the progressive severe group. Progression to severe COVID-19 was defined as new development of at least two of the followings: respiratory distress (respiratory rate ≥ 30 breaths/min), resting oxygen saturation ≤ 93%, or PaO2/FiO2 ratio ≤39.9 kPa)] or need for positive airway pressure or continuous positive airway pressure or worsening of lung CT findings with development of multi-lobar infiltrates or confusion/disorientation or systolic blood pressure <90 mmHg requiring fluid resuscitations or uremia with blood urea nitrogen level ≥20 mg/dL during the observation period. Requirement of either invasive mechanical ventilation or development of shock requiring vasopressor support would also represent severe COVID-19 progression. The clinical and laboratory characteristics of the stable non-severe group and progressive severe were compared. Those clinical or laboratory characteristics that showed a statistical difference of $p<0{\cdot}005$ on univariate analysis would be considered as potential risk factors for predicting progression to severe disease. The study was approved by the Ethics Committees of the Fifth Medical Center of Chinese PLA General Hospital, Beijing, China (2020005D). Written informed consent was waived in view of the new emerging infectious diseases in a designated hospital.

Procedures

Patients with fever, sore throat with or without cough presented to district hospitals were assessed according to the diagnostic criteria of COVID-19 and throat swab specimen was taken by nurses. If the patients met the suspected case diagnosis criteria, they would be arranged to an isolation ward to receive treatment. If the results of COVID-19 were positive by both district level and municipal center for diseases prevention and control (CDC), Beijing, China, the patients would be transferred to one of the three municipal designated hospital in Beijing, according to proximity principle by negative pressure isolation ambulance (Figure 1). The presence of SARS-CoV-2 in respiratory specimens was confirmed using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay by both Beijing district level and municipal Center for Diseases Prevention and Control (CDC), as described previously.[2]

After admission, the chief complaint, presentation history, comorbidity status, epidemiologic history, and vital signs of patients were collected. Comorbidity was defined as having at least one of the followings: hypertension, diabetes, cardiovascular disease, liver disease, asthma, chronic lung disease, HIV

infections and malignancy for at least 6 months. Blood test for routine complete blood picture, renal function test and liver function test together with serum ferritin, were measured. Clinical outcomes were monitored up to Feb 16, 2020 and the laboratory parameters, including complete blood count, coagulation profile, liver and renal function, creatine kinase (CK), ferritin, iron, lactate dehydrogenase (LDH), procalcitonin (PCT), troponin (cTn), and electrolytes were examined. Blood gas analysis was performed for patients with respiratory distress. Respiratory specimens, including nasal and pharyngeal swabs, or sputum were tested for influenza, avian influenza, respiratory syncytial virus, adenovirus, parainfluenza virus using real-time RT-PCR assays approved by the China Food and Drug Administration. All patients were also examined by chest X-ray or CT scan.

In terms of treatment, all patients received oxygen support (nasal cannula, invasive mechanical ventilation) according to the severity of hypoxemia, inhalation of interferon-α (500w IU, twice daily), and oral administration of lopinavir/ritonavir (200 mg/50 mg per capsule, 2 capsules, twice daily) . For those with severe symptoms, antibiotic (moxifloxacin, piperacillin sodium and tazobactam sodium and meropenem) and methylprednisolone (1-2 mg per kg weight per day) were also administered, orally or intravenously, according to the clinical characteristics and physicians' discretion. For those with respiratory failure, shock, or multi-organ failures, life support measures including ECMO were administered in intensive care unit (ICU).

The criteria of hospital discharge or discontinuation of isolation included all the following conditions: body temperatures remained normal over 3 days, the symptoms of respiratory improved obviously, pulmonary imaging shows remarkable absorption of inflammation, and repeated tests for SARS-CoV-2 at least 24 hours apart confirmed viral clearance.

Data collection

All the patients' information, such as epidemiological, demographic, clinical, laboratory, treatment and outcome data, were collected from medical records. The admission data was from Jan 20, 2020, the observation time was at least 5 days and clinical outcomes were followed up till Feb 16, 2020. All the data were collected with the modified novel coronavirus (nCoV) acute respiratory infection clinical characterization data tool (the nCoV Case Record Form Version 1.2, 28 Jan 2020, shared and recommended by World Health Organization and the International Severe Acute Respiratory and Emerging Infection Consortium)[5] from electronic and written medical records. The date in source documents were confirmed independently by at least two researchers (DJ, DZ, EQ).

Statistical analysis

Continuous variables of normal distribution were expressed as mean ± SD and compared using the unpaired, 2-tailed student's t test. Continuous variables of

skewed distribution were shown as median [interquartile range (IQR)] and compared with Mann-Whitney test. Categorical variables were presented as numbers (percentage) and compared by the chi-square test. A *p*-value <0·05 was considered as significant for all statistical tests. The statistical analyses were performed using SPSS version 22·0 and R software, version 3·6·1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/). The significance of clinical characteristics on admission were assessed by univariate Cox proportional regression analysis for investigating the independent risk factors of progression (multivariate analysis was not applicable due to the small sample size).

Role of the funding source
The funder had no role in the study design, collection, analysis, and interpretation of data, writing of the report and in the decision to submit the paper for publication. The corresponding authors had full access to all the data in the study and had full responsibility for the decision to submit for publication.

Results

Characteristics of enrolled patients

Totally, 49 hospitalized patients with confirmed COVID-19 were included in the present study. Overall, the average age was 43·6±17·1 years, 31 (63·3%) were male, 16 (32·7%) had at least one comorbidity. Hypertension, diabetes, cardiovascular disease, liver disease, asthma and chronic lung diseases constitute 95% of comorbidities in this cohort. Thirty-two subjects (65·3%) had been to Wuhan and 17 (34·7%) had contacted with subjects from Wuhan. Regarding to the relationship between fever and chest X-ray proven pneumonia, four (8·2%) patients had no symptoms, five (10·2%) patients had pneumonia with fever, nine (18·4%) patients had fever without pneumonia, and 31 (63·3%) patients had fever followed by pneumonia. In terms of clinical manifestations, fever (79·6%), dry cough (34·7%), and expectoration (22·4%) were the most common symptoms. Less common symptoms were fatigue (18·4%), headache (18·4%), shortness of breath (12·2%), myalgia (12·2%), pharyngalgia (8·2%) and diarrhea (8·2%). (Table 1).

There were 34 (69·4%) patients in stable non-severe group and 15 patients (30·6%) in progressive severe group respectively. There were significant differences between the two groups in terms of age, comorbidity, serum ferritin and lymphocyte counts (Table 2).

Predictive factors for progression to severe COVID-19

Age, comorbidity (Table 1), serum ferritin, lymphocyte counts, serum LDH, D-dimer, CD4 and CD8 counts at presentation were statistically significantly different between the two groups with $p<0·005$ (Table 2). We chose Comorbidity (HR: 14·8, 95% CI: 4·0–54·7, $p<0·001$), Age >50 years (HR:4·7, 95%CI: 1·6-13·7, $p=0·003$), Lymphocyte counts <1500 /μL (HR: 5·0, 95% CI:

1·1–22·0, *p*=0·01) and Ferritin > 400 ng/mL (HR: 7·1, 95% CI: 2·6–19·8, *p*=0·002) as risk factors (CALF) for progression to severe disease because these 4 factors are easily available nationwide. Seventy-three percent of subjects (11/15) with three or all four risk factors progressed to severe disease, intubation or ICU as compared with 11·8% (4/34) of subjects with 0-2 risk factors (odds ratio 6·2, 95 % CI: 1·7 to 22·8, *p*=0·006).

None of the thirteen subjects with zero risk factor progressed to severe diseases as compared with 8 out of the 9 subjects with all four risk factors had disease progression (*p*<0·0001). Twenty-six out of the 34 (76·5%) subjects in the stable non-severe group were successfully discharged by 16 Feb 2020 as compare to only 1 out of 15 (6·7%) in the severe group (*p*<0·001). Overall, 70·6% (24/34) of subjects with 0-2 risk factors were successfully discharged as compared to 20% (3/15) in patients with 3 or 4 risk factors (*p*=0·001). Among the patients with zero, one and two risk factors, 85% (11/13), 75% (6/8) and 54% (7/13) were successfully discharged respectively. Nine out of 16 (60%) subjects in the progressive severe group still required supplement oxygen, intubation or ICU care as compared with none in the non-severe group. One patient in the severe group had died, this patient had all 4 risk factors (Table 3). Four patients presented with severe diseases, one patient had 2 risk factors only, while the remaining three had all four risk factors. All 4 patients' condition worsened during the study period. Excluding these 4 subjects from the analysis did not affect the predictive values of the risk score, 67 % of subjects (8/12) with 3 or more risk factors progressed as compared to 12% (3/33) of subjects with 0-2 risk factors (odds ratio 7·3, 95 % CI: 1·7 to 32·3, *p*=0·008).

Discussion

SARS-CoV-2 infection has over 69,000 patients worldwide causing over 1600 deaths. About 19 % of cases are severe cases. While mild to moderate cases could be managed in community hospitals with adequate isolation or quarantine procedures, patients with severe disease may require more intensive supportive care, huge human and medical resources. Therefore, identification of risks factors that predict progression to severe disease will greatly facilitate optimal utilization of limited medical resources. Huang et al[6] in series of 41 COVID-19 patients showed that ICU patients were more likely to have lymphopenia <1000 /μL compared to ICU patients, 11/13 (85%) vs 15/28 (54%), *p*=0·045. Compared with non-ICU patients, ICU patients had higher plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα. However, these assays were not readily available in many community hospitals. Chen et al[7] in a descriptive study of 99 COVID-19 patients, noted that the MuLBSTA score system comprising of six indexes, namely multilobular infiltration, lymphopenia, bacterial co-infection, smoking history, hypertension, and age may be predictive of mortality in COVID-19. However, the paper did not address whether the score was predictive of progression to severe disease. Guan et al[8] described the clinical characteristics of 1,099 patients with laboratory-confirmed COVID-19

from 552 hospitals in 31 provinces or provincial municipalities through January 29th, 2020. Lymphopenia was observed in 82·1% of patients. Oxygen saturation, respiratory rate, blood leukocyte or lymphocyte count and positive chest X-ray or CT findings predicted poor clinical outcomes. Increasing age and comorbidities were associated disease. Severe cases had more prominent laboratory abnormalities (i.e., leukopenia, lymphopenia, thrombocytopenia, elevated C-reactive protein levels) as compared to non-severe cases. Serum ferritin was not mentioned in the study.

In this study of patients outside Wuhan, we showed that four simple clinical parameters, namely comorbidity, age, lymphocyte counts and serum ferritin at presentation were able to identify a group of patients with low risk of progression. We chose these four parameters because they showed high hazard ratios on univariate analysis and were easily obtainable. Age, and comorbidities had been shown to be prognostic factors in COVID-19.[6-8] Hyperferritinemia, a marker of inflammation, has been shown to be associated with complications in viral diseases such as dengue fever.[9,10] Lymphopenia is a prognostic factor in HIV infections, influenza.[11–13] We did not use CD4 and CD8 counts because these were not routinely available. None of the subjects with the absence of all four risk factors progressed to more severe disease. This group of patients could be safely managed in rural or peripheral medical centers. On the other hand, over 70% of the subjects with three or more risk factors progressed to require high flow oxygen supplement, intubation or ICU care. Early transfer of this group of patients to tertiary or specialized center will help to reduce overall mortality. This group of patients may also be candidate for early treatment with protease inhibitors, Oseltamivir or participation in clinical trials of experimental therapy such as remdesivir.[14] These four clinical parameters may facilitate optimal utilization of limited medical resources and help to stratify subjects enrolled in phase/II/III clinical trials.

Our study has several limitations. First, the sample size is rather small with only 49 patients with confirmed COVID-19. It involved only patients in a center outside Hubei and may not be applicable to the patients in Wuhan or Hubei. Secondly, all the patients were either from Hubei or has travelled to Hubei or in contact with a COVID-19 patient from Hubei. Therefore, the findings may not be applicable to those COVID-19 cases with no travel history or direct link to Hubei cases. Thirdly, the follow-up period is rather short with the average time from first symptoms to the end of the observation period being 24.6 (range 18-33) days in the stable non-severe group. There is still a possibility that some of these subjects may progress with longer follow-up. One may also argue that if a patient presented with severe or critical disease, such patient should be transferred to a tertiary center anyway and the risk scores will be meaningless. In our cohort, there were four subjects presenting with severe diseases and even excluding these four patents, the predictability of the risk factors remained unchanged.

The four predictive clinical parameters we used are readily available and could be easily validated in clinical cohorts in other provinces or countries. If confirmed in other clinical cohorts, this will provide a simple mean to identify patients with low risk of progression.

Contributors

DJ, DZ, ZC, ZX, PZ, BL, HL and EQ treated the patients. DJ, DZ and GY collected the epidemiological and clinical data. DJ, MZ, LZ, GC, YW and GL processed statistical data and drafted the manuscript. JJ, GL and EQ revised the final manuscript and are responsible for summarizing all the data.

Declaration of interests

We declare no competing interests.

Acknowledgments

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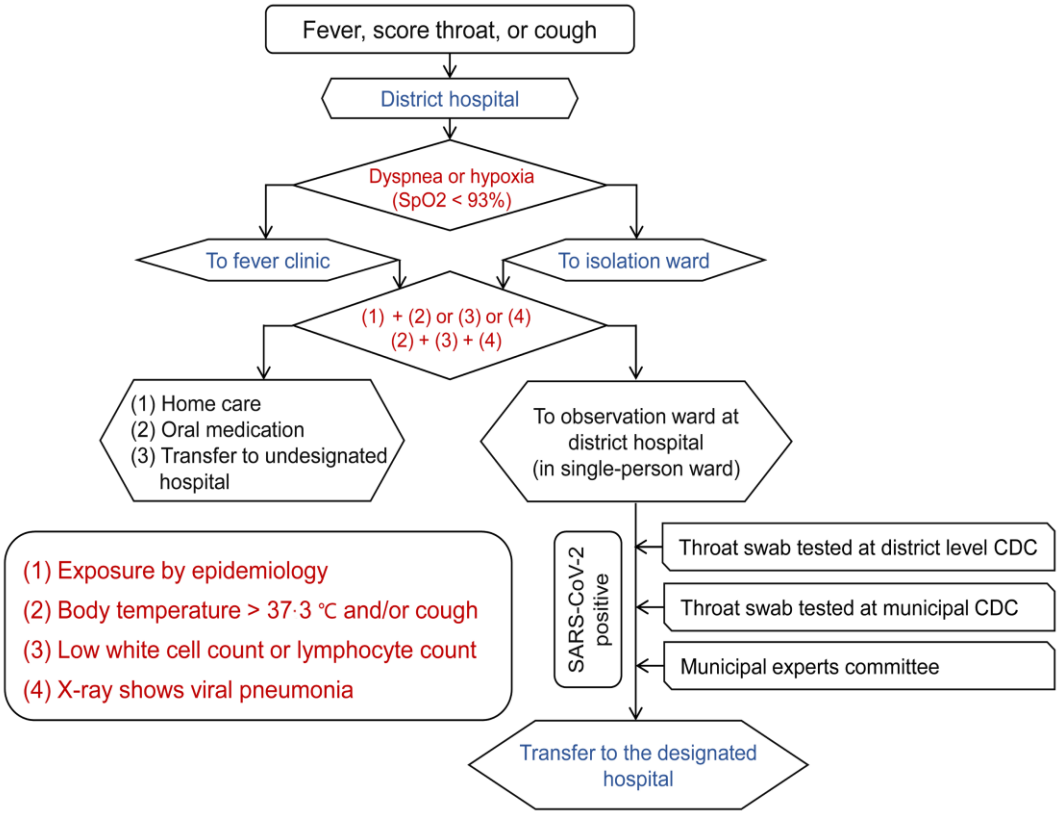

Figure 1. Flow-chart for the management of all patients presented with upper respiratory symptom, such as cough, sore throat and cough in Beijing.

Table 1. Clinical characteristics of patients with COVID-19 on admission to hospital

	All patients (n=49)	Stable Non-severe (n=34)	Progressive Severe (n=15)	*P* value
Male sex (n, %)	31 (63·3)	21 (61·8)	10 (66·7)	0·995
Age (years)	43·6 ± 17·1	37·9 (14·2)	56·5 (16·5)	<0·001
BMI (kg/m^2)	24·9 ± 3·4	24·3 (3·6)	26·4 (2·8)	0·053
Epidemiology# (n, %)	17 (34·7)	11 (32·4)	6 (40·0)	0·847
Comorbidity (n, %)	16 (32·7)	3 (8·8)	12 (80·0)	<0·001
Highest temperature (℃)	38·1 ± 0·8	38·16 (0·8)	37·90 (0·7)	0·299
Smoke (n, %)	1 (2·0)	0 (0·0)	1 (7·1)	0·643
Drink (n, %)				0·027
Never	44 (89·8)	33 (97·1)	10 (71·4)	
Ever	4 (8·2)	1 (2·9)	3 (21·4)	
Current	1 (2·0)	0 (0·0)	1 (7·1)	
Signs and symptoms (n, %)				
Fever	39 (79·6)	28 (82·4)	11 (73·3)	0·736
Dry cough	17 (34·7)	14 (41·2)	3 (20·0)	0·267
Expectoration	11 (22·4)	6 (17·6)	5 (33·3)	0·400
Fatigue	9 (18·4)	4 (11·8)	5 (33·3)	0·162
Headache	9 (18·4)	5 (14·7)	4 (26·7)	0·551
Shortness of breath	6 (12·2)	0 (0·0)	6 (40·0)	0·001
Myalgia	6 (12·2)	3 (8·8)	3 (20·0)	0·531
Pharyngalgia	4 (8·2)	2 (5·9)	2 (13·3)	0·755
Diarrhea	4 (8·2)	3 (8·8)	0 (0·0)	0·589
Abnomalities on chest CT (n, %)				
Ground-glass opacity	39 (79·6)	24 (70·6)	15 (100·0)	0·049
Local patchy shadowing	4 (8·2)	4 (11·8)	0 (0·0)	0·298
Bilateral patchy shadowing	35 (71·4)	20 (58·8)	15 (100·0)	<0·001
Observation time (first symptoms to Feb 16, 2020)	25·0 (17–38)	24·6 (18–33)	25·9 (17–38)	0·345

Continuous parameters presented as mean ± SD and compared using student's t test, categorical data as n (%) and compared using chi-square test . # never been to Wuhan and contacted with persons from Wuhan. NCP, novel coronavirus pneumonia; BMI, body mass index.

Table 2. Laboratory features of patients with COVID-19 on admission to hospital

	Normal Range	All patients (n=49)	Stable Non-severe (n=34)	Progressive Severe (n=15)	*P* value
WBC (×10^9/L)	3·7 – 9·2	4·9 ± 1·8	4·8 ± 1·2	5·5 ± 2·8	0·164
Neutrocyte (%)	50 – 70	59·5 ± 16·2	55·7 ± 10·1	68·3 ± 23·3	0·010
Lymphocyte (%)	20 – 40	29·9 ± 12·3	34·80 ± 10·03	18·91 ± 9·7	<0·001
Monocyte (%)	3 – 10	7·5 ± 3·2	7·98 ± 2·7	6·30 ± 4·1	0·095
Lymphocyte count(×10^9/L)	0·8 – 4·0	1·4 ± 0·7	1·62 ± 0·7	0·92 ± 0·5	0·001
HGB (g/L)	113 – 151	137·5 ± 16·8	140·6 ± 17·7	130·6 ± 12·5	0·054
PLT (×10^9/L)	101 – 320	179·0 ± 53·2	171·3 ± 47·5	196·4 ± 62·7	0·129
ALT (U/L)	5 – 40	26·0 (15·0 – 40·0)	26·0 (14·3 – 38·8)	31·0 (16·5 – 57·0	0·441
AST (U/L)	8 – 40	27·0 (23·0 – 39·0)	27·00 (23·0 – 37·3)	31·0 (22·0 – 57·0)	0·268
TBIL (μmol/L)	3·4 – 20·5	11·0 (8·5 – 14·7)	10·70 (8·2 – 14·7)	11·30 (8·7 – 14·7)	0·879
LDH (U/L)	109 – 245	249·1 ± 104·6	215·8 ± 67·3	324·5 ± 134·4	<0·001
PT (s)	10·2 – 14·3	11·8 ± 0·8	11·8 ± 0·8	12·0 ± 0·8	0·489
D-dimer (mg/L)	< 0·55	0·22 (0·17 – 0·43)	0·21 (0·17 – 0·31)	0·50 (0·34 – 1·08)	<0·001
INR	0·8 – 1·2	1·04 ± 0·12	1·02 ± 0·07	1·08 ± 0·19	0·101
Ferritin (ng/ml)	30 – 400	502·1 ± 444·8	318·1 ± 257·8	907·4 ± 593·7	<0·001
Fe (μmol/L)	11 – 30	11·4 ± 7·3	11·13 ± 6·76	11·99 ± 8·49	0·710
Na (mmol/L)	136 – 145	149·8 ± 86·3	137·8 ± 2·4	176·9 ± 156·1	0·145
K (mmol/L)	3·5 – 5·2	4·3 ± 0·4	4·3 ± 0·5	4·2 ± 0·4	0·737
CRE (μmol/L)	62 – 115	78·1 ± 13·5	77·2 ± 14·8	80·0 ± 10·2	0·510
cTn (ng/mL)	0 – 0·100	0·004 (0·003 – 0·006)	0·004 (0·003 – 0·005)	0·005 (0·003 – 0·008)	0·594
PCT (ng/mL)	0 – 0·500	0·052 (0·035 – 0·067)	0·045 (0·034 – 0·063)	0·059 (0·043 – 0·088)	0·108

Continuous variables of normal distribution were expressed as mean ± SD and compared using the unpaired, 2-tailed student's t test, continuous variables of skewed distribution were showed as median [interquartile range (IQR)] and compared with Mann-Whitney test, categorical variables were presented as numbers (percentage) and compared by the chi-square test.

Table 3. The distribution of CALF risk factors in patients with COVID-19

CALF Risk factors	Total patients (n=49)		Recovered discharged patients (n=27)	
	Stable Non-severe (n=34)	Progressive Severe (n=15)	Stable Non-severe(n=26)	Progressive Severe (n=1)
0 (n=13)	13	0	11	0
1 (n=8)	7	1	6	0
2 (n=13)	10	3	7	0
3 (n=6)	3	3	2	0
4 (n=9)	1	8*	0	1

CALF Risk factors: **C**omorbidity, **A**ge >50 years, **L**ymphocyte counts <1500 /µL, **F**erritin > 400 ng/mL.
*One patient with all four risk factors died of progressive disease.