

Pathogenesis clue from early clinical presentation of 300 hospitalized COVID-19 patients

Feng Yu

Shanghai Putuo District People's Hospital

Xuemei Deng

WuHan Third Hospital

Li Ni

Shanghai Putuo District People's Hospital

Wei Li

WuHan Third Hospital

Ping Yan

Shanghai University of Traditional Chinese Medicine

Mian Huang

Wuhan Third Hospital

Xiongbiao Wang (✉ xiongbiao6@hotmail.com)

Shanghai University of Traditional Chinese Medicine

Research Article

Keywords: COVID-19; clinical characters; lymphocytes; early symptom; pathogenesis.

Posted Date: July 20th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-44006/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

The global spread of COVID-19 has been lasted more than half a year. Except for the gene sequence and virus structure of SARS-CoV-2, its clinical characteristics, pathological mechanism and corresponding measures have not been fully revealed.

Objective: To speculate the possible pathological mechanism from the early clinical manifestations of the patients with COVID-19.

Methods: The onset symptoms, laboratory examination and CT findings on admission of 300 cases in two wards of Wuhan Third Hospital from January 28 to March 15 were analyzed retrospectively.

Results: There was no difference in incidence between men and women, but women were hospitalized later after onset. Upper respiratory symptoms and sputum were seldom. The incidence of fever was 71%. Blood lymphocytes count decreased significantly on admission, which was related to the severity of the disease. In the moderate type of patients, who without hypoxia, thrombocytopenia occurred in 12.37%, CRP rose in 64.43 %, BUN elevated in 20.62 %, creatinine rose in 17.53 %, D-dimer elevated in 74.74%, creatine kinase and α -hydroxybutyrate dehydrogenase elevated in 45.36% and 54.12% patients respectively. The early CT showed a small amount of infiltration in the subpleural, the lateral zone of the lung and thickening of the interlobular septum. About 5 days later, infiltration had been worse in a part of the patients, and the affected lung was negatively correlated with the lymphocyte count.

Conclusion: There was no gender difference in patients with SARS-CoV-2 invasion. Alveolar cells and T lymphocytes maybe main targets of the virus and apoptosis maybe primary pathogenesis. The virus entering the lung maybe transmitted through lymph or blood channels, rather than direct diffused in the respiratory tract. Early damage of multiple organs maybe caused by immune response.

Introduction

After badly affecting China for more than three months, COVID-19 outbreaks have abated in China; however, the threat from COVID-19 is not over, and COVID-19 is now prevalent all over the world. As of July 6, there were more than 11.7 million cases of infection and 539554 deaths worldwide. Before a vaccine for COVID-19 is available, quarantine is a passive defensive measure that has to be taken. However, long-term quarantine is also associated with many problems, such as social and economic problems. The standardization of epidemic prevention measures is currently the main problem. How can infected individuals be identified and quarantine measures be implemented as soon as possible? Although laboratory tests (nucleic acid tests and antibody tests) have been greatly improved, the clinical recognition and judgment by doctors is still very important, especially when influenza and the common cold can occur in the same period and complicate the diagnosis.

The history of COVID-19 is quite short; it was found and identified in early January 2020. The virus 2019-nCoV causes a lower respiratory tract disease that was initially called novel coronavirus pneumonia

(NCP) by the Chinese government. The disease is now officially named COVID-19 by the World Health Organization. Moreover, 2019-nCoV was renamed SARS-CoV-2 by the International Committee on Taxonomy of Viruses. On 11 March 2020, the WHO characterized COVID-19 as a pandemic. To minimize the spread of SARS-CoV-2, China locked down Wuhan and nearby cities beginning January 23, 2020. The strong measures, including suspension of all urban transportation, was apparently successful in preventing further spreading of SARS-CoV-2 to other cities. The peak of infection occurred at the end of January 2020, and the morbidity decreased dramatically after mid-February[1]. Until March, only sporadic cases were reported. However, COVID-19 is very severe worldwide, and the WHO declared recently that COVID-19 may be present in the human population forever, which means that the fight against SARS-CoV-2 will last. Two major problems still trouble us: there is no vaccine to prevent and no drug to cure COVID-19. The present treatments are symptomatic treatments based on previous experience, but identification of additional measures should be of great importance, as COVID-19 is unique and the pathogenesis is quite different from SARS-CoV, MERS-CoV or others.

The recognition of disease first comes from clinical manifestations, especially early clinical manifestations, which can better reflect the characteristics of diseases and lay a foundation for understanding the pathological mechanism and for making treatment plans. Studies on the natural history of SARS-CoV-2 infection in humans are urgently needed. The WHO and ISARIC designed a case report form (CRF) specific for COVID-19 that can provide clinical data anonymously and in a standardized manner to obtain accurate clinical manifestations and natural history data for this purpose. The features of the clinical manifestations of COVID-19 have been described in many reports, most of which are based on early data from January 2020[2-4]. However, these reports are only the beginning of a comprehensive and systematic study. Here, we report clinical data from a cohort of COVID-19 patients and propose suggestions based on these clinical manifestations.

Materials And Methods

This study only retrospectively reviewed a cohort of patients who were admitted to the Wuhan Third Hospital in the Guanggu District, which was a referral center for local COVID-19 patients diagnosed in the public health center in Wuhan, China. All patients were confirmed to have SARS-CoV-2 by testing before admission. The test was performed on samples from nasopharyngeal swabs using real-time reverse transcriptase PCR as described previously. Due to the sudden outbreak of COVID-19 in late January, the medical system in Wuhan was caught off guard, there were not enough infectious wards, and a large number of patients remained outside of the hospital. Our hospital was temporarily restructured as a designated COVID-19 hospital. On the day of opening (Jan 28), all beds were filled immediately. A total of 332 patients in two adult wards of the hospital from January 28 to March 15 were enrolled in this study. Due to incomplete data from 32 patients, 300 patients were included in this study. The data collected included demographic, clinical symptom, and laboratory and chest CT findings. The severity of pneumonia in these patients was assessed according to the Guidelines for Diagnosis and Management of COVID-19 (6th edition, in Chinese) issued by the National Health Commission of China[5]. The study

was approved by the Ethics Committee of Wuhan Third Hospital, and written informed consent was waived because of the retrospective nature of the study.

CT image acquisition

All CT scans were obtained using one of the following scanners: SOMATOM Perspective, SOMATOM Spirit, or SOMATOM Definition AS+ (Siemens Healthineers, Forchheim, Germany) with patients in the supine position. Scans were performed from the level of the upper thoracic inlet to the inferior level of the costophrenic angle, and the following parameters were used: detector collimation widths 64×0.6 mm, 128×0.6 mm, 64×0.6 mm, and 64×0.6 mm; and tube voltage 120 kV. The tube current was regulated by an automatic exposure control system (CARE Dose 4D; Siemens Healthineers). Images were reconstructed with a slice thickness of 1.5 mm or 1 mm and an interval of 1.5 mm or 1 mm, respectively. The reconstructed images were transmitted to a workstation, and a picture archiving and communication system (PACS) was used for multiplanar reconstruction post processing.

Image interpretation

Images from patients seen at Wuhan Third Hospital were analyzed by two respiratory doctors (FY with 25 years of experience and XW with 34 years of experience). All Digital Imaging and Communications in Medicine (DICOM) images from the CT studies were analyzed without access to clinical or laboratory findings. The evaluators independently and freely assessed the CT features using both axial CT images and multiplanar reconstruction images. After separate evaluations, any disagreements in the results were resolved by discussion and consensus.

Statistics

Statistical analysis was performed using SPSS Software version 25.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive analyses were conducted for demographic, clinical, and laboratory data.

Results

Characteristics of sex, age and the days from onset of symptoms to first hospital admission

We did not find a difference in morbidity between men and women, as in previous reports[6-8], which is also different from that in MERS-CoV[9]. However, our result is consistent with 50466 case analyses from the CDC, China[2]. The average age of the patients was approximately 60 years old in both men and women. The variation of the days from onset to first admission was quite large, usually an early onset of symptoms with a delay in hospital admission, which represented the shortage of medical resources during late January and early February. The shortage was relieved very quickly as many referral hospitals were established, and the incidence of disease also decreased. Noticeably, the median time from onset of symptoms to hospital admission was significantly longer for women (Table 1). An analysis of 36 families with cluster-related infection revealed that the time of onset was essentially the same for all patients (data not shown). Members of one family were often admitted to several hospitals. The main reasons for

male patients being hospitalized earlier may be that women's resilience to symptoms was higher than in men, and men had more severe disease and more comorbidities[10].

Table 1 The characteristics of sex, age and the days from onset of symptoms to first hospital admission

N	Sex	Age [S±SD]	Days from onset to admission [d±SD]
151	Male	62.4189±12.56061	10.4189±5.2112
149	Female	60.87077±11.2789	14.1044±5.3645

Most of the patients with severe and critical disease were elderly—over 60 years old.

Because patients with mild disease were admitted to the shelter hospital, the patients in this group all had moderate, severe and critical disease based on the guidelines. Similar to previous reports, the patients with severe and critical illness were mainly elderly patients over 60 years old, and there was no difference in the sex distribution of patients (Table 2). The clinical manifestations of COVID-19 in older patients were systemic symptoms and more severe radiological abnormalities (data not shown).

Table 2 Disease severity was directly related to patient age

Age	Male(N)			Female(N)		
	Moderate	Severe	Critical	Moderate	Severe	Critical
<60	29	17	3	43	14	2
≥60,<70	35	21	1	24	11	4
≥70	42	13	3	21	14	3
	106	51	7	88	39	9

Early symptoms included fewer upper respiratory symptoms and less sputum

Most patients in this group had been treated in the outpatient department several times, and their symptoms at the time of onset were recorded. As shown in Fig.1, fever, cough and fatigue were the three main symptoms at onset, while the incidence of upper respiratory symptoms (nasal obstruction 1.34%, runny nose 2.34%, and sore throat 7.67%) was lower than the incidence of diarrhea 15.67%. In all 300 cases, more than 71% of the patients had fever, 58.3% of the patients had asthenia, and many patients had chills, but headache, dizziness, muscle pain, chills and other symptoms were rare. The fever type was classified as uncertain, low, medium and high. Most of the patients had dry cough symptoms in the early stage, occasionally accompanied by expectoration. Hemoptysis was rare.

Abnormalities in laboratory data occurred in some non-hypoxemic patients

The laboratory data of the patients at admission, including routine blood examination, CRP, liver and kidney function, coagulation and other indicators, are presented in Table 3. We also found that the lymphocyte count in patients was related to the severity of the disease. A lymphocyte count less than $0.8 \times 10^9/L$ was more likely to cause critical illness (Fig.2). Moreover, thrombocytopenia, reduced renal function, hypoalbuminemia, elevated D-dimer and elevated CRP, creatine kinase and α -hydroxybutyrate dehydrogenase were also found in COVID-19 patients and were linked to progressive infection (Table 3). It

is very interesting to note that there were abnormal myocardial enzyme spectra, liver enzyme spectra and coagulation markers in moderately ill patients who did not have hypoxemia.

Table 3 Laboratory findings on admission

	ordinary (194)	severe (90)	critical (16)
	N (%)		
HB↓	52 (26.8)	48 (53.33)	14 (87.5)
WBC↑	147 (75.77)	70 (77.78)	14 (87.5)
Lymphocytes account↓	85 (43.81)	73 (81.11)	13 (81.25)
Platelet↓	24 (12.37)	43 (47.78)	9 (56.25)
CRP↑	125 (64.43)	82 (91.11)	13 (81.25)
Procalcitonin↑	19 (9.79)	20 (22.22)	10 (62.5)
D-Dimer↑	145 (74.74)	73 (81.11)	16 (100)
ALT↑	51 (26.29)	34 (37.78)	3 (18.75)
AST↑	55 (28.35)	40 (44.44)	3 (18.75)
BSA↓	190 (97.94)	90 (100)	16 (100)
BUN↑	40 (20.62)	27 (30)	2 (12.5)
creatinine↑	34 (17.53)	25 (27.78)	2 (12.5)
lactic acid	96 (49.48)	43 (47.78)	11 (68.75)
creatine kinase↑	88 (45.36)	44 (48.89)	12 (75)
α-Hydroxybutyrate Dehydrogenase↑	105 (54.12)	68 (75.56)	13 (81.25)

Subpleural lesions were typical manifestations on lung CT in the early stage of disease

According to the analysis of the patients' first lung CT examinations, most were performed within 5 days after onset, and the images were characterized by single or multiple subpleural ground-glass opacities, consolidation, and involvement of less than 50% of the lung. After admission, the lung CT findings showed that most of the patients had reticulation, and a few patients had significantly increased infiltrative shadows, even involving the whole lung (data not shown). Moreover, we observed a relationship between lymphocyte counts and lung CT imaging findings, as shown in Fig.3. The lymphocyte count was negatively correlated with lung injury($R=0.426$).

Discussion

In this study, we retrospectively analyzed the early clinical manifestations of 300 hospitalized COVID-19 patients. The main impressions of the early clinical manifestations are that there is no sex bias in the incidence; that rare upper respiratory symptoms, age and the lymphocyte counts relate to disease severity, peripheral pulmonary involvement and lymphopenia; and that multisystem damage occurs in some moderately ill patients without hypoxia. Although many papers have been published recently, the concrete pathogenesis of COVID-19 has not yet been identified. What could we learn from the early clinical features of COVID-19? Clinical features provide many clues for pathogenesis.

The mode of transmission of the virus is thought to be largely by inhalation of respiratory droplets. Did the virus in the affected lung lesion come from airway spread? Although the nasopharynx mucosa was believed as first infected with SARS-CoV-2, the symptoms involving the upper respiratory tract occur less often, which is consistent with previous reports[7, 11-13] and indicates that the upper respiratory tract inflammation was mild. Moreover, the distribution of lung lesions was characterized by subpleural and lateral zones in the early stage, which suggested that the infection did not spread along the airway. Transmission of SARS-CoV-2 through contaminated surfaces might be possible[14], while aerosols are currently not considered the primary mode of transmission[15]. The above points suggested that the lung lesion may be infected as a result of SARS-CoV-2 moving along lymphatics or blood vessels, as well as invading other target tissues. We propose that the virus might pass through the mucous membranes of the nasal passages, larynx or skin and then enter the blood, causing viremia. The virus attacks the targets, including the lungs and T lymphocytes. It is very interesting to find that the virus could be detected in the upper respiratory tract with no symptoms and mild inflammation within the bronchi and bronchioles, along with prominent mucosal edema within the bronchial mucosa[16]. It seems that the upper respiratory tract, trachea, bronchi and bronchioles were not the targets of the virus, although their mucous membrane expressed ACE2.

The early pathogenesis of COVID-19 is still unclear. The primary cells affected by SARS-CoV-2 may be both alveolar cells and T lymphocytes. Apoptosis could be the main early event. The first evidence comes from clinical studies. The lymphocyte count is negatively related to disease severity and is commonly considered a marker of prognosis[2, 17, 18]. This phenomenon also suggests that alveolar cells and T lymphocytes are both targets of SARS-CoV-2, and the T lymphocytes count could reflect the alveolar cell counts. The main evidence should be derived from the histopathologic features: diffuse alveolar damage(DAD)[19] and T-lymphocyte apoptosis in lymphoid organs, especially the spleen[20, 21]. This is similar to MERS-CoV that can efficiently infect T cells from the peripheral blood and from human lymphoid organs and induce apoptosis in T cells, which involves the activation of both the extrinsic and intrinsic apoptosis pathways[22]. The number of CD4-positive T cells and CD8-positive T cells in the spleen and lymph nodes decreased, they were degenerated and necrotic, and macrophages proliferated in the spleen.

The immune response may explain the early clinical manifestations. The initial symptoms are mainly fever, cough, and lymphopenia. Increased values of liver enzymes, LDH, muscle enzymes, coagulation factors and C-reactive protein can be found in some mildly ill patients without hypoxia in the early stage, which means that these abnormal changes were not secondary damage from hypoxia or secondary infection. The possible pathogenesis may be damage from the virus directly or by immune response. The possibility of an immune response should be greater than the direct invasion of the virus. The most direct evidence is the result of autopsy. No SARS-CoV-2 was detected in the heart, liver, kidney, spleen, pancreas, or gastrointestinal tract by immunohistochemistry and PCR[23]. Transcriptome sequencing of RNA isolated from bronchoalveolar lavage fluid (BALF) and peripheral blood mononuclear cell (PBMC) specimens of COVID-19 patients revealed distinct host inflammatory cytokine profiles to SARS-CoV-2

infection in patients and highlighted the association between COVID-19 pathogenesis and excessive cytokine release, such as that of CCL2/MCP-1, CXCL10/IP-10, CCL3/MIP-1A, and CCL4/MIP1B[24].

It has also been hypothesized that the virus might use angiotensin converting enzyme 2(ACE2) as a receptor, similar to SARS-CoV[25]. ACE2 is also expressed on many different cell types, including cardiac, renal, intestinal, endothelial, and gut cells[26, 27]. As no virus was found in these tissues[21], the receptor for SARS-CoV-2 has not been fully elucidated. SARS-CoV-2 may use ACE2 for entry and the serine protease TMPRSS2 for S protein priming[28].

Our study has several limitations inherent to its design. First, this was a retrospective study with the potential of incomplete and possible variation of data recording from the primary care providers. Second, patients with mild disease were not included. Third, much larger cohorts are needed.

COVID-19 is a new disease, our knowledge is gradually updated based on the ongoing research findings and clinical practice experience. The current study is a start to our understanding of the clinical presentation and spectrum of the disease for greater precision of estimates and an initial step to performing prognostic and risk factor analyses. It was expected that the human-to-human transmission toxicity of COVID-19 would be reduced[29] because a genetic bottleneck of RNA viruses often occurs in the process of respiratory droplet transmission; however, the real world scenario is still serious. The spread of COVID-19 could not be stopped.

Conclusion

There was no sex difference in patients with SARS-CoV-2 infection. Alveolar cells and T lymphocytes may be the main targets of the virus, and apoptosis may be the primary mechanism of pathogenesis. The virus entering the lung may be transmitted through lymph or blood vessels rather than directly dispersing through the respiratory tract. Early damage to multiple organs may be caused by the immune response.

Declarations

The study was approved by the Ethics Committee of Wuhan Third Hospital, and written informed consent was waived because of the retrospective nature of the study.

Competing Interest:

The authors declare no competing interest

Funding:

There was no funding source for this study.

References

1. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Vital Surveillances: The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) –China, 2020. *China CDC Weekly*. 2020; 2(8):113-22.
2. Sun P, Qie S., Liu Z., Ren J., Li K., Xi J. Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: A single arm meta-analysis. *J Med Virol*. 2020; 92(6):612-17.
3. Liu Y., Yang Y., Zhang C., Huang F., Wang F., Yuan J., Wang Z., Li J., Li J., Feng C. *et al*. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Science China Life sciences*. 2020; 63(3):364-74.
4. Meo S. A., Alhowikan A. M., Al-Khlaiwi T., Meo I. M., Halepoto D. M., Iqbal M., Usmani A. M., Hajjar W., Ahmed N. Novel coronavirus 2019-nCoV: prevalence, biological and clinical characteristics comparison with SARS-CoV and MERS-CoV. *Eur Rev Med Pharmacol Sci*. 2020; 24(4):2012-19.
5. The National Health Commission of the People's Republic of China home page (<http://www.nhc.gov.cn>).
6. Shi Y., Yu X., Zhao H., Wang H., Zhao R., Sheng J. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. *Crit Care*. 2020; 24(1):108.
7. Huang C., Wang Y., Li X., Ren L., Zhao J., Hu Y., Zhang L., Fan G., Xu J., Gu X. *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395(10223):497-506.
8. Giwa A., Desai A. Novel coronavirus COVID-19: an overview for emergency clinicians. *Emerg Med Pract*. 2020; 22(2 Suppl 2):1-21.
9. Banik G. R., Alqahtani A. S., Booy R., Rashid H. Risk factors for severity and mortality in patients with MERS-CoV: Analysis of publicly available data from Saudi Arabia. *Virology*. 2016; 31(1):81-4.
10. Sharma G., Volgman A. S., Michos E. D. Sex Differences in Mortality from COVID-19 Pandemic: Are Men Vulnerable and Women Protected? *JACC Case reports*. 2020.
11. Chen N., Zhou M., Dong X., Qu J., Gong F., Han Y., Qiu Y., Wang J., Liu Y., Wei Y. *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020; 395(10223):507-13.
12. Zhu J., Ji P., Pang J., Zhong Z., Li H., He C., Zhang J., Zhao C. Clinical characteristics of 3062 COVID-19 patients: A meta-analysis. *J Med Virol*. 2020.
13. Guan W. J., Ni Z. Y., Hu Y., Liang W. H., Ou C. Q., He J. X., Liu L., Shan H., Lei C. L., Hui D. S. C. *et al*. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020; 382(18):1708-20.
14. Lu C. W., Liu X. F., Jia Z. F. 2019-nCoV transmission through the ocular surface must not be ignored. *Lancet*. 2020; 395(10224):e39.
15. Park S. E. Epidemiology, virology, and clinical features of severe acute respiratory syndrome - coronavirus-2 (SARS-CoV-2; Coronavirus Disease-19). *Clinical and experimental pediatrics*. 2020; 63(4):119-24.

16. Barton L. M., Duval E. J., Stroberg E., Ghosh S., Mukhopadhyay S. COVID-19 Autopsies, Oklahoma, USA. *Am J Clin Pathol.* 2020; 153(6):725-33.
17. Tan L., Wang Q., Zhang D., Ding J., Huang Q., Tang Y. Q., Wang Q., Miao H. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal transduction and targeted therapy.* 2020; 5(1):33.
18. Jiang M., Guo Y., Luo Q., Huang Z., Zhao R., Liu S., Le A., Li J., Wan L. T cell subset counts in peripheral blood can be used as discriminatory biomarkers for diagnosis and severity prediction of COVID-19. *J Infect Dis.* 2020.
19. Xu Z., Shi L., Wang Y., Zhang J., Huang L., Zhang C., Liu S., Zhao P., Liu H., Zhu L. *et al.* Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet Respiratory medicine.* 2020; 8(4):420-22.
20. Xu X., Chang X. N., Pan H. X., Su H., Huang B., Yang M., Luo D. J., Weng M. X., Ma L., Nie X. [Pathological changes of the spleen in ten patients with coronavirus disease 2019(COVID-19) by postmortem needle autopsy]. *Zhonghua Bing Li Xue Za Zhi.* 2020; 49(6):576-82.
21. Yao X. H., Li T. Y., He Z. C., Ping Y. F., Liu H. W., Yu S. C., Mou H. M., Wang L. H., Zhang H. R., Fu W. J. *et al.* [A pathological report of three COVID-19 cases by minimal invasive autopsies]. *Zhonghua Bing Li Xue Za Zhi.* 2020; 49(5):411-17.
22. Chu H., Zhou J., Wong B. H., Li C., Chan J. F., Cheng Z. S., Yang D., Wang D., Lee A. C., Li C. *et al.* Middle East Respiratory Syndrome Coronavirus Efficiently Infects Human Primary T Lymphocytes and Activates the Extrinsic and Intrinsic Apoptosis Pathways. *J Infect Dis.* 2016; 213(6):904-14.
23. Wu J., Lu A. D., Zhang L. P., Zuo Y. X., Jia Y. P. [Study of clinical outcome and prognosis in pediatric core binding factor-acute myeloid leukemia]. *Zhonghua xue ye xue za zhi = Zhonghua xueyexue zazhi.* 2019; 40(1):52-57.
24. Xiong Y., Liu Y., Cao L., Wang D., Guo M., Jiang A., Guo D., Hu W., Yang J., Tang Z. *et al.* Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. *Emerging microbes & infections.* 2020; 9(1):761-70.
25. Lu R., Zhao X., Li J., Niu P., Yang B., Wu H., Wang W., Song H., Huang B., Zhu N. *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* 2020; 395(10224):565-74.
26. Ding Y., He L., Zhang Q., Huang Z., Che X., Hou J., Wang H., Shen H., Qiu L., Li Z. *et al.* Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. *J Pathol.* 2004; 203(2):622-30.
27. Albin A., Di Guardo G., Noonan D. M., Lombardo M. The SARS-CoV-2 receptor, ACE-2, is expressed on many different cell types: implications for ACE-inhibitor- and angiotensin II receptor blocker-based cardiovascular therapies. *Intern Emerg Med.* 2020.
28. Hoffmann M., Kleine-Weber H., Schroeder S., Kruger N., Herrler T., Erichsen S., Schiergens T. S., Herrler G., Wu N. H., Nitsche A. *et al.* SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked

by a Clinically Proven Protease Inhibitor. Cell. 2020; 181(2):271-80 e8.

29. Cascella M., Rajnik M., Cuomo A., Dulebohn S. C., Di Napoli R. Features, Evaluation and Treatment Coronavirus (COVID-19). In: *StatPearls*. edn. Treasure Island (FL); 2020.

Figures

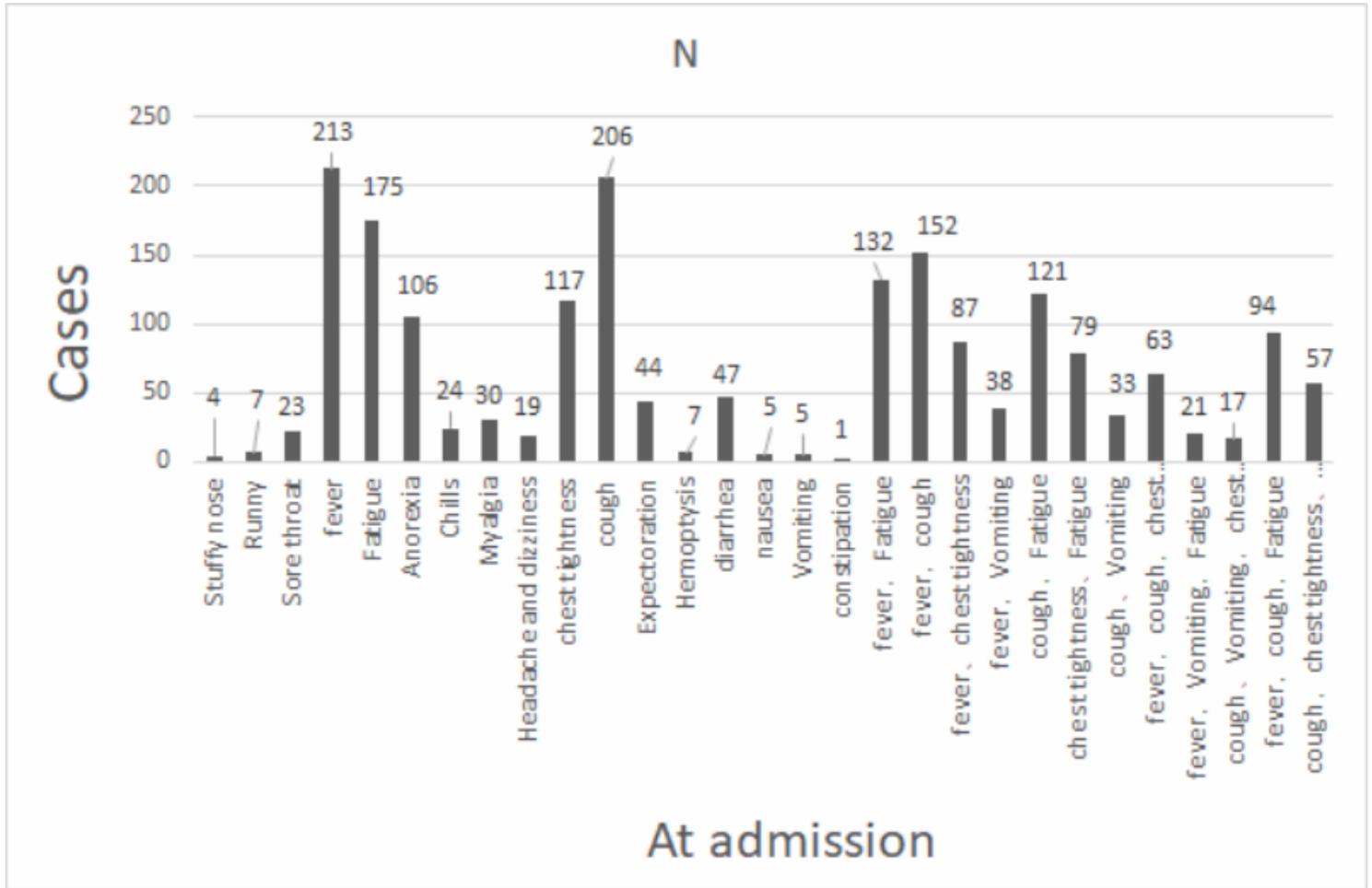


Figure 1

Clinical characters at onset (no. of cases): The symptoms were presented as numbers of cases.

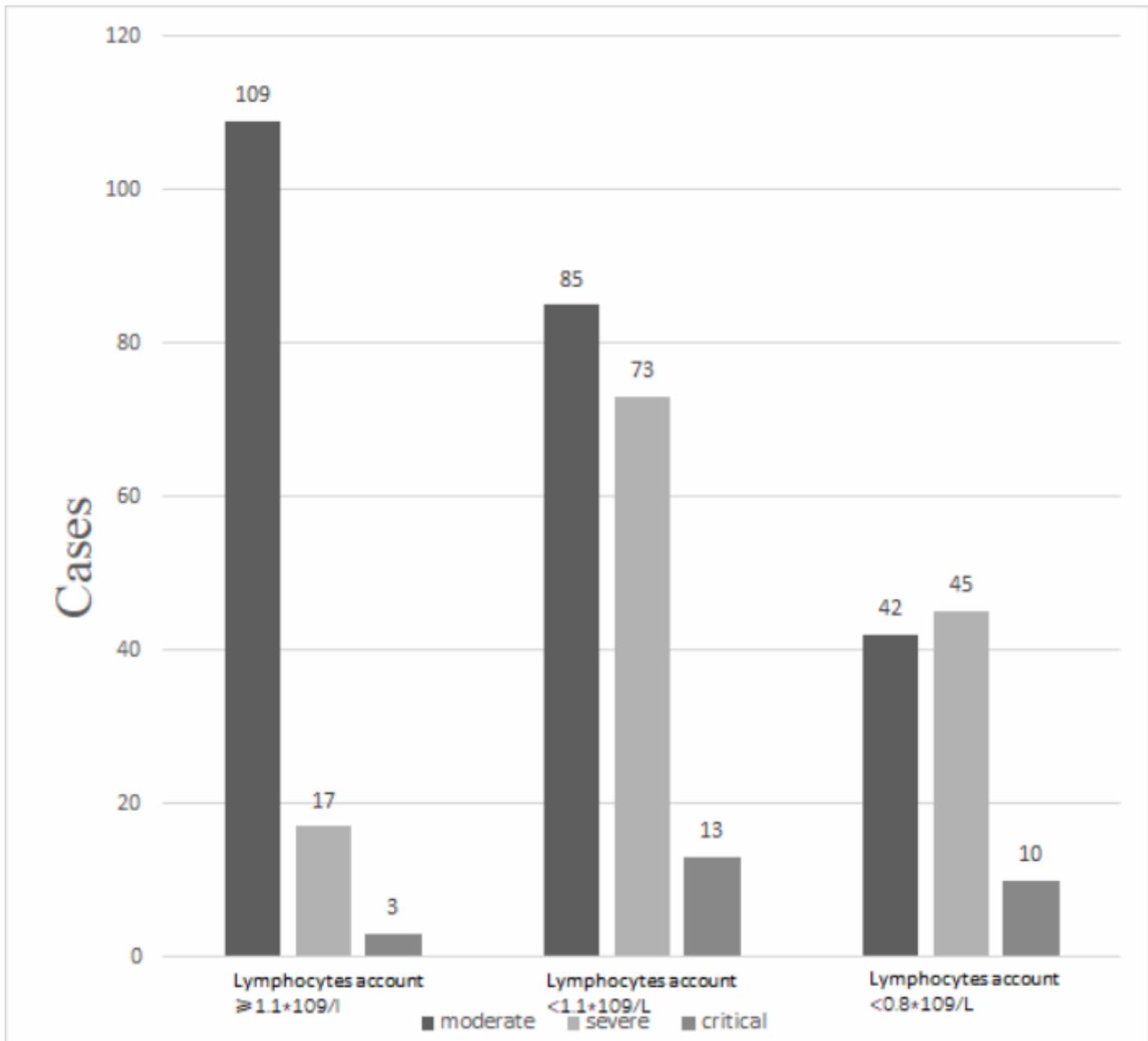


Figure 2

Lymphocyte count was associated with disease severity, which was present as lymphocytes count and disease subtypes.

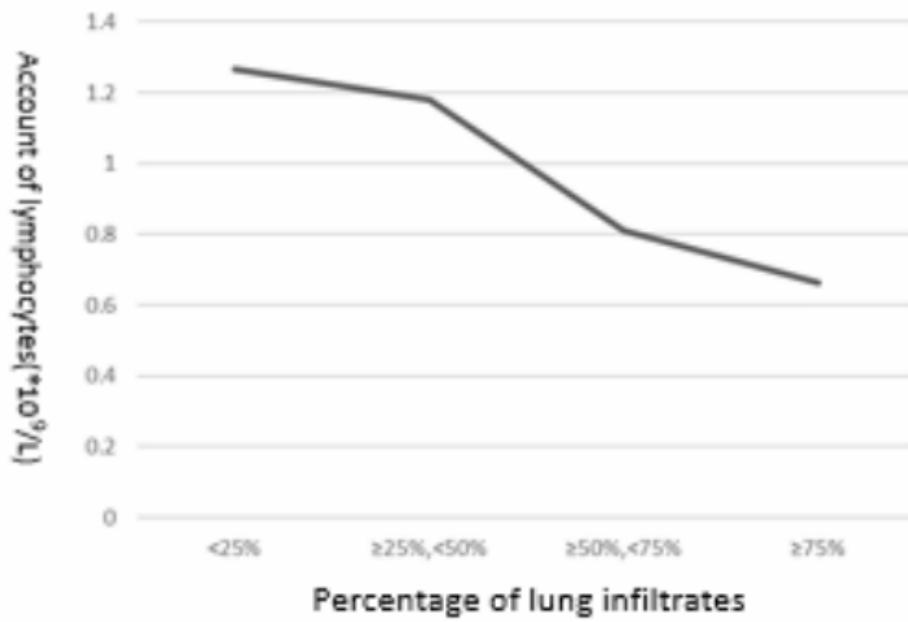


Figure 3

The relationship of involvement of lung infiltrates with lymphocytes count