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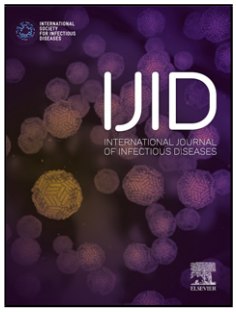

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Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings

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Highlight

- COVID-19 has be a great threat to world health.
- We aim to investigate clinical features of patients with abnormal imaging findings.
- Those with abnormal images have more obvious clinical and laboratory features.
- Combing clinical data with imaging score can predict severe/critical type.

Abstract

Purpose: To investigate the epidemiological, clinical characteristics of COVID-19 patients with abnormal imaging findings.

Methods: Patients confirmed with SARS-CoV-2 infection of Zhejiang province from Jan 17 to Feb 8 underwent CT or x-ray were enrolled. Epidemiological, clinical data were analyzed between those with abnormal or normal imaging findings.

Results: Excluding 72 patients with normal images, 230 of 573 patients affected more than two lobes. The median radiograph score was 2.0 and there's negative correlation between the score and oxygenation index (ρ=-0.657, *P<0.001*). Patients with abnormal images were older (46.65±13.82), with higher rate of coexisting condition(28.8%), lower rate of exposure history and longer time between onset and confirmation(5d) than non-pneumonia patients(all *P<0.05*). Higher rate of fever, cough, expectoration, and headache, lower lymphocytes, albumin, serum sodium levels and higher total bilirubin, creatine kinase, lactate dehydrogenase and C-reactive

protein levels and lower oxygenation index were observed in pneumonia patients (all *P<0.05*). Muscle ache, shortness of breath, nausea and vomiting, lower lymphocytes levels and higher serum creatinine and radiograph score at admission were predictive factors for severe/critical subtype.

Conclusion: Patients with abnormal images have more obvious clinical manifestations and laboratory changes. Combing clinical features and radiograph score can effectively predict severe/critical type.

Keywords: SRAS-CoV-2; imaging findings; epidemiological; clinical; predictive factors

Introduction

At the end of 2019, several cases of atypical pneumonia, caused by unknown aetiology, was initially detected and reported in Wuhan, Hubei province, China. Shortly afterwards, the novel coronavirus was identified by the Chinese Center for Disease Control and Prevention(CDC) from the throat swab sample of a patient as the causative agent and officially announced on 7 January 2020.[Tan WJ, 2020, WorldHealthOrganization, 2020a] and renamed the previously provisionally named 2019-nCoV as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2 by International Committee on Taxonomy of Viruses[Alexander E. Gorbalenya, 2020]. Though it was one month since the first novel coronavirus infected disease (COVID-19) was diagnosed. As of Feb 9(18:00 GMT), 2020, there have been 34598 confirmed cases in China, including

723 deaths related to the illness, and 288 cases have been cumulatively reported from other countries, which has caused worldwide concern[(WorldHealthOrganization, 2020b)].

Coronavirus is a kind of enveloped positive-sense RNA virus, which was named for the crown-like spikes on the surface. It is a complex pathogen due to the ability to infect multiple hosts and cause different diseases in spite of common association with acute respiratory infections in humans[(Fung and Liu, 2019)]. Frequent interactions of human beings and wild animals make them a common source of zoonotic infections. SRAS-CoV-2 was the another identified coronavirus with human infection ability apart from Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV)[(Kickbusch and Leung, 2020)]. And it's Genomic sequences showed close relation to bat-SL-CoVZC45 and bat-SL-CoVZXC21 and homology modelling revealed a similar receptor-binding domain structure to SARS-CoV[(Lu et al., 2020)].

Viral diagnostics is an important role in this battle to SARS-CoV-2. However, due to the conduction of diagnostic testing for SARS-CoV-2 only at CDC and the strain of spectrum of the available diagnostic tools for this newly discovered virus at this time[(Phan, 2020)], imaging examination is one of the quick and convenient methods to diagnosis and monitor disease progress during treatment. Nevertheless, imaging findings of pneumonia caused by viruses can be completely different, sometimes overlapping with other infectious and inflammatory diseases. It is mentioned in a recent study includes 21 symptomatic patients at the time of initial presentation that CT findings are variable, ranging from normal to multiple lobes involvement and

patients show different radiologic progression (Chung et al., 2020). Up to now, there's limited information about clinical features of patients of COVID-19 with abnormal imaging findings. In view of the crucial role of imaging for the diagnostic workup for suspected cases and care of patients, we retrospectively evaluate the epidemiological, clinical features and laboratory data of 573 cases of COVID-19 presented with abnormal images.

Materials and Methods

1.Subjects and Data

For this retrospective study, 645 patients confirmed with SARS-CoV-2 infection between Jan 17 to Feb 8, 2020 underwent CT examination or X-ray, in Zhejiang, China. All patients were admitted in different designated hospitals according to the government emergency rule of Zhejiang province.

Data including epidemiological, clinical characteristics, laboratory results and imaging findings were uniformly collected by the Health Commission of Zhejiang. All data of included cases have been shared with WHO and the primary analytic results were reported to the authority of Zhejiang. The cases collection and analysis were determined by the Health Commission of Zhejiang under national authorization, and our study was approved by the medical ethics committee of the First Affiliated Hospital, College of Medicine, Zhejiang University, which conformed to the ethical guidelines of the Helsinki Declaration.

During analysis, patients were divided into two groups according to imaging findings (pneumonia group *vs* non-pneumonia group).

2.Diagnostic criteria

The diagnosis of novel coronavirus disease (COVID-19) was based on WHO interim guidance(WorldHealthOrganization, 2020c). And subtype definition of COVID-19 was according to the diagnosis and treatment scheme for SARS-CoV-2 of China (5th edition)(Medicine, 2020). For mild type: slight clinical symptoms without no pneumonia presentation in imaging. For common type: manifestations such as fever and/or respiratory presentation with pneumonia under radiography. For severe type (meeting any of the followings): (1) dyspnea, RR≥ 30 times / minute; (2) finger oxygen saturation under resting≤93%；(3) arterial PaO_2/FiO_2≤300mmHg(1mmHg=0.133kpa). For critical type (meeting any of the followings): (1) respiratory failure and need mechanical ventilation; (2) shock; (3) combined with other organ failure and an intensive care unit is needed.

3.Radiograph and pulmonary injury evaluation

The location of the lesion was analyzed by the lobes of the lung. To quantitatively evaluate the pulmonary involvement of all these abnormalities, a semi-quantitative scoring system was proposed according to the chest X-ray scoring standard in the Murray score. Each of the 5 lung lobes (the upper, lower lobe of left lung and upper, middle, lower lobe of right lung) was used as a scoring unit and was visually scored from 0 to 1 as: 0, no involvement; 1, involvement. The total score was the sum of the individual lobar score and range from 0 to 5. Radiographs were scored by consensus of two physician reviewers.

Lung injury and hypoxemia can be caused by SARS-CoV-2 infection. To

evaluate hypoxemia, arterial blood gas analysis is always adopted. Among the parameters, due to the fact that most patients were supplied oxygen before blood gas analysis was performed, arterial partial pressure of oxygen (PaO_2) was not suitable. Since Horovitz proposed that oxygenation index was measured by the arterial partial pressure of oxygen to fraction of inspired oxygen, it has been used as criterion for acute respiratory distress syndrome and lung injury[Horovitz et al., 1974, Ranieri et al., 2012]. Thus, we used oxygenation index to evaluate pulmonary function.

4. Statistical analysis

Statistical analyses were performed using SPSS software (Version 23.0). Continuous variables with a normal distribution were represented by mean± standard deviation (SD), and median (interquartile range, IQR) were used for abnormally distributed data, and the comparison between groups was performed by *t* test or non-parametric test when appropriate. Categorical variables were expressed as number (%), and chi-square test were used for comparison between groups. To assess the association of radiograph score and oxygenation index, spearman correlation analysis was used. Binary logistic regression analysis was used for predictive factors associated with severe/critical type pneumonia. All *p*-values were based on a two-tailed test of significance. Statistical significance was always defined as a *p*-value <0.05.

Result

Imaging findings

645 patients infected with SARS-CoV-2 underwent CT scan or chest radiography

at admission were included in this study, 72 patients of whom had entirely normal examinations. Excluding those with a normal initial imaging finding, the remaining 573 of 645 patients by definition had ground-glass opacities, consolidation, or both affecting at least one lobe. 139(21.5%) patients of the total 645 patients affected one lobe, 204(31.6%) patients had two affected lobes, 136(21.1%) patients had three lobes affected, 66(10.2%) had four affected lobes and 28(4.4%) patients had affected five lobes. Of the 645 patients, 432(67.0%) patients had bilateral lung disease. The right upper lobe was involved in 172(26.7%) patients, the right middle lobe was involved in 118(18.3%) patients and the right lower lobe was involved in 433(67.1%) patients. 219(34.0%) patients had left upper lobe affected and left lower lobe was involved in 417(64.7%) patients (shown in Table1).

The median of total radiograph score was 2.0 and the radiograph score was significantly correlated with oxygenation index (ρ=-0.657, $P<0.001$) (Figure 1).

Demographic, epidemiologic Characteristics

The demographic and epidemiologic characteristics of patients were shown in Table2. 295(51.5%) of 573 patients were man and only 37(6.5%) patients were current smokers. The average age of those with pneumonia was 46.65±13.82y, which was significantly older than that of those with normal imaging findings ($P<0.001$). Accompanied with at least one coexisting underlying conditions and hypertension were observed in 28.8% and 16.8% patients, respectively, which was significantly higher than the non-pneumonia patients (all $P<0.05$). Intriguingly, among the patients with abnormal imaging findings, the proportion of clear exposure to Wuhan and/or

confirmed patients was 81.0%, significantly lower than that of 91.7% among those with normal imaging findings（*P<0.05*）. More importantly, the time from onset to SARS-CoV-2 infection confirmation was 5.0(2.5-7.0) days among patients with abnormal imaging, which was significantly longer when comparing with that of non-pneumonia patients(*P<0.05*).

Clinical symptoms and Laboratory results

The clinical features and characteristics with imaging abnormalities were shown in Table3. Generally, the symptoms of fever, cough and expectoration, sore throat, headache were initiated in 85.9%, 68.4%, 36.3%, 14.0%, 11.3% of patients with novel coronavirus pneumonia, respectively, significantly higher than their respective counterparts with normal imaging findings (all *P<0.05*). However, concerning other symptoms of COVID-19, including fatigue, shortness of breath and diarrhea, there were no significant difference when comparing with those with normal images.

In addition, the levels of lymphocytes, albumin and serum sodium was significantly lower as compared with non-pneumonia patients (1.23±0.52 vs 1.39±0.61; 41.02±4.47 vs 42.53±4.70; 137.93±3.76 vs 138.99±2.79, respectively, all *P<0.05*). Significantly higher levels of total bilirubin, creatine kinase and lactate dehydrogenase were observed in those with abnormal imaging findings (11.26±8.04 vs 9.11±4.86; 73.0 vs 62.5; 213.0 vs 174.5, respectively, all *P<0.05*). As for infection-related biomarkers, it was shown that C-reactive protein level of patients with imaging abnormalities was significantly higher than its counterparts (8.8 vs 2.3, *P<0.05*). Significantly lower oxygenation index was observed in patient with

pneumonia appearance than that in those with normal imaging findings (381.46 *vs* 478.79, *P<0.001*) (shown in Table3).

Complications and Treatment

All patients were treated in isolation with supportive and empiric medication in designated hospital. As shown in Table4, 488(85.2%) patients in pneumonia group and 56(77.8%) patients with non-pneumonia were administrated with antiviral treatment. If oxygenation index (PaO_2/FiO_2) <300 mmHg, glucocorticoid therapy is considered and is not recommended for mild patients. A significantly high rate of corticosteroid therapy was observed when comparing with non-pneumonia group (13.4% *vs* 0.0%, *P=0.001*).

Besides, a significantly higher rate of oxygen therapy was observed in patients with abnormal imaging findings than that in patients with normal imaging (43.6% *vs* 11.1%, *P<0.001*). 9 of 573 patients received mechanical ventilation. Till Feb 8, only 4 patients were admitted into intensive unit. no patients were administrated with continuous blood purification and extracorporeal membrane oxygenation (EMCO).

Liver injury was the most common complication (in 75 patients), followed by acute respiratory distress (in 14 patients) in pneumonia patients. By the end of Feb 8, all patients were survived.

Clinical predictive factors for severe/critical novel coronavirus pneumonia

According to the diagnosis and treatment scheme for SARS-CoV-2 of China (5^{th} edition), a total of 64 patients were confirmed with severe/critical novel coronavirus pneumonia among those with abnormal images. Our univariate analysis showed that

30 risk factors(age, man, time from onset to be confirmed, et al, shown in Table 5) associated with severe/critical novel coronavirus pneumonia when comparing with mild and common subtypes ($P<0.05$). However, further multivariate analysis was performed based on these variables and showed that with the symptoms of muscle ache(P=0.002), shortness of breath($P=0.002$), nausea and vomiting($P=0.001$), combined with higher serum creatinine level ($P=0.004$) and lower lymphocytes levels ($P=0.008$) and accompanied with higher total radiograph score were the possible predictive factors for severe/critical subtype(shown in Table 5)

Discussion

The recent emergence of SARS-CoV-2 has caused an outbreak of unusual viral pneumonia in patients in Wuhan. In a short period, national spreading and global dispersal of the causative agent have become a big threat to global health[(Biscayart et al., 2020, WorldHealthOrganization, 2020a)]. The symptoms of COVID-19 are similar to other respiratory viruses, including fever, cough and fatigue, diarrhea and vomiting, with radiographs showing invasive lesions in the lung. And some of patients may be presented with serious complications such as acute respiratory distress syndrome or shock[(Chen et al., 2020, Huang et al., 2020, Zhu et al., 2020)]. With the continuous improvement of modern imaging technology, imaging examination is more conducive to the objective assessment and early detection of lung abnormality. In view of the current situation that images conform to features of SARS-CoV-2 pneumonia while the etiology test is negative at initial until the subsequent repeated tests are positive[(Xie et al., 2020)], combing images with clinical features is necessary to diagnosis. Therefore, in our retrospective

study, we evaluated the epidemiological, clinical features, laboratory data of those with abnormal imaging findings.

The imaging findings of SARS-CoV-2 pneumonia are similar to acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which is characterized as pulmonary ground-glass opacities and consolidation[Das et al., 2016, Kanne, 2020, Wong et al., 2003]. On the basis of our results, we found a total of 72 patients infected with SARS-CoV-2 were absent of both ground-glass opacities and consolidation. And more than two lobes affecting with appearance of ground-glass or consolidation in 230(35.7%) patients were observed, suggesting COVID-19 is prone to multifocal involvement, which is consistent with former report[Chung et al., 2020]. There are some certain characteristics in chest imaging of this novel coronavirus pneumonia. However, there is limited information about difference between cases of COVID-19 presented with or without abnormal imaging findings.

Therefore, we evaluated the basic and clinical characteristics of SARS-CoV-2 pneumonia. Among those with abnormal images, fever and cough are the most common symptoms, followed by sputum production, which was consistent with former report[Chen et al., 2020]. Different from former report, which tended to infect older (median 55.5y), man (68%) with underlying medical condition (50%), the average age of novel coronavirus pneumonia was 46.65±13.82y, the gender ratio was close to 1:1 and the rate of patients with coexisting condition was 28.8% in our study [Chen et al., 2020]. One possibility was that the number of cases of our study was larger than that of 99 cases. Another was that our results were based on Zhejiang province, far away from

Wuhan and SARS-CoV-2 itself may has virulence changes during human-to-human dissemination, including epidemiological features. Our results may suggest general susceptibility.

Compared with patients with normal imaging findings, the average age of patient with pneumonia appearance was older and the rate of at least one coexisting medical condition was higher. This may suggest that relatively older patients and accompanying with chronic diseases are prone to have lung injury. Interestingly, the rate of exposure history from Wuhan and/or contact with confirmed patients was higher and the time from onset to SARS-CoV-2 infection confirmation was shorter in non-pneumonia patients. A possible explanation for these results were that those patients were in the state of medical observation. Once they were presented with any discomfort, they were requested to test whether the SARS-CoV-2 was positive and even some patients were initiative to ask for testing.

Besides, we identified significantly higher rate of symptoms of fever, cough, sputum production and headache. The rate of sore throat of patients with abnormal images was significantly lower than that of the counterpart. Since former report indicated that the initial and early-progress radiograph can be normal(Holshue et al., 2020), the clinical symptoms were not typical and obvious. The imaging of non-pneumonia patients at the initial of admission may gradually progress. As there was no obvious abnormality in CT examination of patients with positive nucleic acid test, which suggested that there might be some lag between X-ray and CT examination, those patients should be monitored closely in case of timely treatment. However, different

from patients infected with H1N1 that diarrhea is associated with chest X-ray abnormalities[Cao et al., 2009], the difference of gastrointestinal symptoms of two groups in our study were not significant. One possible explanation is that SARS-CoV-2 can bind to ACE2 of intestinal tract[Hao Zhang ZK, Wan et al., 2020] while H1N1 binds to Saα2, 3Gal receptor[Riquelme et al., 2009], but the specific mechanism is not clear at present.

Laboratory results were also monitored, as we found that the patients with imaging abnormalities had lower lymphocytes, albumin, serum sodium levels and higher lactate dehydrogenase and C-reactive protein levels. This finding may suggest that that having pneumonia may be associated with severe disease, and patients tended to have more severe clinical features, which was in accordance with lower oxygenation index, an index to evaluate respiratory function and the severity of the disease. For further study, radiograph score which may be helpful for rough estimation lung lesions was proposed. Then we found a significant negative correlation (ρ=-0.657, $P<0.001$) between radiograph score and oxygenation index. Therefore, we guess the more involvement of lobes, the worse pulmonary functions.

Currently, no effective antiviral therapy for COVID-19 was confirmed[Zhang and Liu, 2020]. Interferon-α, Lopinavir/Ritonavir and Arbidol were used according to previous experience, however, there's a lack of evidence of unified treatment plan. A significant higher rate of glucocorticoid application in patients with abnormal imaging than that the counterpart. A former study showed proper use of corticosteroid in critical SARS reduced the mortality[Chen et al., 2006]. Thus, patients with multiple lobes involvement may be considered for corticosteroid to control the progression. Oxygen

therapy plays a key role in supportive care of patients. Generally, patients with hypoxemia (PaO_2 <60mmHg or SaO_2<90% under the condition of air) or with symptom of dyspnea may be considered for it by nasal cannula or mask. When the symptom or hypoxemia is improved (SaO_2>90% or the level of PaO_2 reach to 60-70mmHg), the flow of oxygen can be gradually reduced and even stopped. Otherwise, high flow oxygen inhalation or noninvasive ventilation is considered and invasive ventilation can be adopted if the disease still progress(Medicine, 2020). However, some patients may be administrated with low flow oxygen therapy on admission in order to reduce the burden of lung. In our study, we also found the rate of oxygen therapy in patients with abnormal imaging was significantly higher, which may be related to lower oxygenation index. In view of the current stage to explore a standard treatment regimen, we are not sure early use of oxygen therapy is helpful for prognosis, which can be further discussed.

We also in depth analyzed the predictive factors of severe/critical novel coronavirus pneumonia. Patients with the symptoms of shortness of breath and nausea and vomiting tended to be severe, and the similar results related to H1N1 pneumonia had been revealed in previous report, showing that the symptoms mentioned above were risk factors(Kanchana et al., 2013, Na et al., 2011). Lower lymphocytes level at initial of admission was also the significantly predictive factors, which were also described as prognostic indicators for ARDS and death in H5N1 and H1N1 infections(Chotpitayasunondh et al., 2005, Reyes et al., 2011). Besides, we found higher serum creatinine was one of predictors, as former study revealed acute kidney injury was the common

complication of severe H1N1 infection and related to higher mortality[Trimarchi et al., 2010]. Higher radiograph score was related to severity of disease, in accordance with former report which used another CT score[Xu et al., 2020]. These clinical features may be a useful tool for predicting of severe/critical type as it is convenient to tested in hospitals.

There are several limitations of our study. Firstly, at the time of this writing, only preliminary data have been collected and many patients still remained in the hospital, and it's better to obtain the progress of imaging and the outcomes of patients. Second, the description of imaging should be more detailed, which may be helpful for the judgment of the disease and the treatment in the later stage. Thirdly, our study was limited by the observational nature of the investigation. Finally, according to the data in admission, risk factors for severe/critical type of COVID-19 were identified, however, it is still lack prediction model for disease progression.

In conclusion, there are some certain characteristics in chest imaging of COVID-19. And we reported the difference of specific epidemiological and clinical features of between patients with abnormal or normal imaging, including fever, cough and sputum production and relatively poor laboratory results. Symptoms of muscle ache, shortness of breath and nausea and vomiting, lower lymphocytes and higher serum creatinine and radiograph score were predictive factors for severe/critical subtype.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Alexander E. Gorbalenya SCB, Ralph S. Baric, Raoul J. de Groot, Christian Drosten, Anastasia A. Gulyaeva, Bart L. Haagmans, Chris Lauber, Andrey M Leontovich, Benjamin W. Neuman, Dmitry Penzar, Stanley Perlman, Leo L.M. Poon, Dmitry Samborskiy, Igor A. Sidorov, Isabel Sola, John Ziebuhr. Severe acute respiratory syndrome-related coronavirus: the species and its viruses—a statement of the Coronavirus Study Group. bioRxiv. https://doiorg/101101/20200207937862[Accessed 11 Mar. 2020]

Biscayart C, Angeleri P, Lloveras S, Chaves TdSS, Schlagenhauf P, Rodriguez-Morales AJ. The next big threat to global health? 2019 novel coronavirus (2019-nCoV): What advice can we give to travellers? - Interim recommendations January 2020, from the Latin-American society for Travel Medicine (SLAMVI). Travel medicine and infectious disease 2020:101567.

Cao B, Li XW, Mao Y, Wang J, Lu HZ, Chen YS, et al. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. N Engl J Med 2009;361(26):2507-17.

Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet (London, England) 2020.

Chen RC, Tang XP, Tan SY, Liang BL, Wan ZY, Fang JQ, et al. Treatment of severe acute respiratory syndrome with glucosteroids: the Guangzhou experience. Chest 2006;129(6):1441-52.

Chotpitayasunondh T, Ungchusak K, Hanshaoworakul W, Chunsuthiwat S, Sawanpanyalert P, Kijphati R, et al. Human disease from influenza A (H5N1), Thailand, 2004. Emerg Infect Dis 2005;11(2):201-9.

Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). Radiology 2020:200230.

Das KM, Lee EY, Langer RD, Larsson SG. Middle East Respiratory Syndrome

Coronavirus: What Does a Radiologist Need to Know? American Journal of Roentgenology 2016;206(6):1193-201.
Fung TS, Liu DX. Human Coronavirus: Host-Pathogen Interaction. Annual review of microbiology 2019;73:529-57.
Hao Zhang ZK HG, Da Xu, Jing Wang, Zifu Li. the digestive system is a potentila route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. bioRxiv 2020.
Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First Case of 2019 Novel Coronavirus in the United States. The New England journal of medicine 2020.
Horovitz JH, Carrico CJ, Shires GT. Pulmonary response to major injury. Arch Surg 1974;108(3):349-55.
Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England) 2020.
Kanchana S, Kanchana S, Vijitsopa T, Thammakumpee K, Yamwong S, Sawanyawisuth K. Clinical factors predictive of pneumonia caused by pandemic 2009 H1N1 influenza virus. Am J Trop Med Hyg 2013;88(3):461-3.
Kanne JP. Chest CT Findings in 2019 Novel Coronavirus (2019-nCoV) Infections from Wuhan, China: Key Points for the Radiologist. Radiology 2020:200241-.
Kickbusch I, Leung G. Response to the emerging novel coronavirus outbreak. BMJ (Clinical research ed) 2020;368:m406.
Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet (London, England) 2020.
National Administration of Traditional Chinese Medicine. Diagnosis and treatment of novel coronavirus infected pneumonia (The fifth edition). Available from: http://www.satcm.gov.cn[Accessed 9 Feb. 2020]
Na S, Kim MN, Kim WY, Kim W, Hong SB, Lim CM, et al. Prevalence and clinical features of pneumonia in patients with laboratory-confirmed pandemic influenza A H1N1 2009 infection in South Korea. Scand J Infect Dis 2011;43(1):19-26.
Phan T. Novel coronavirus: From discovery to clinical diagnostics. Infect Genet Evol 2020;79:104211.
Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. Jama 2012;307(23):2526-33.
Reyes S, Montull B, Martinez R, Cordoba J, Molina JM, Marti V, et al. Risk factors of A/H1N1 etiology in pneumonia and its impact on mortality. Respir Med 2011;105(9):1404-11.
Riquelme A, Alvarez-Lobos M, Pavez C, Hasbun P, Dabanch J, Cofre C, et al. Gastrointestinal manifestations among Chilean patients infected with novel influenza A (H1N1) 2009 virus. Gut 2009;58(11):1567-8.
Tan WJ ZX, Ma XJ. A novel coronavirus genome identified in a cluster of pneumonia cases—Wuhan, China 2019-2020. China CDC Weekly 2020:2020;2:61-2.

Trimarchi H, Greloni G, Campolo-Girard V, Giannasi S, Pomeranz V, San-Roman E, et al. H1N1 infection and the kidney in critically ill patients. J Nephrol 2010;23(6):725-31.
Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. J Virol 2020.
Wong KT, Antonio GE, Hui DSC, Lee N, Yuen EHY, Wu A, et al. Severe acute respiratory syndrome: Radiographic appearances and pattern of progression in 138 patients. Radiology 2003;228(2):401-6.
World Health Organization. Novel coronavirus-China. Jan 12, 2020.http://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/[Accessed Feb 9,2020]
World Health Organization. Novel coronavirus(2019-nCoV) situation report.https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200208-sitrep-19-ncov.pdf?sfvrsn=6e091ce6_2[Accessed Feb 9,2020]
World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidence. Jan 11, 2020.https://wwwwhoint/internal-publications-detail/clinical-management-of-severe-acute respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected [accessed Jan 30,2020]
Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical 2019-nCoV Pneumonia: Relationship to Negative RT-PCR Testing. Radiology 2020:200343.
Xu X, Yu C, Qu J, Zhang L, Jiang S, Huang D, et al. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. Eur J Nucl Med Mol Imaging 2020.
Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. J Med Virol 2020.
Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. The New England journal of medicine 2020.

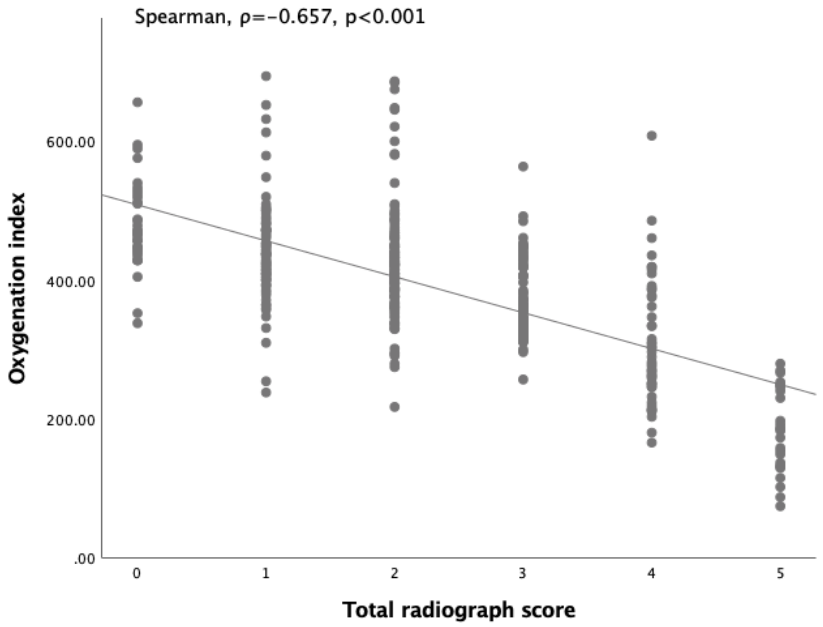

Figure1: The total radiograph score was significantly correlated with oxygenation index.

Table1. Findings on initial imaging in 645 patients

Characteristics	Patients(n=645)
Ground-glass opacities and consolidation	
Absence of both ground-glass opacities and consolidation	72(11.2%)
Presence of either ground-glass opacities or consolidation or both	573(88.8%)
Number of lobes affected	
1	139(21.5%)
2	204(31.6%)
3	136(21.1%)
4	66(10.2%)
5	28(4.4%)
More than 2 lobes affected	230(35.7%)
Bilateral Lung Disease	432(67.0%)
Frequency of lobe involvement	
Right upper lobe	172(26.7%)
Right middle lobe	118(18.3%)
Right lower lobe	433(67.1%)
Left upper lobe	219(34.0%)
Left lower lobe	417(64.7%)
Total radiograph score	2.0(1.0-3.0)

Table2. Demographic and epidemiologic characteristics of patients infected with 2019-nCoV with normal or abnormal imaging findings

Characteristics	Normal imaging findings （n=72）	Abnormal imaging findings （n=573）	P value
age	34.90±14.20	46.65±13.82	<0.001
Sex (Male/Female)	33(45.8%)/39(54.2%)	295(51.5%)/278(48.5%)	0.366
Current smoker (Yes/No)	4(5.6%)/68(94.4%)	37(6.5%)/536(93.5%)	0.969
Exposure history: from Wuhan and/or contact with confirmed patients (Yes/No)	66(91.7%)/6(8.3%)	464(81.0%)/109(19.0%)	0.026
Coexisting Condition (Yes/No)			
Any (Yes/No)	12(16.7%)/60(83.3%)	165(28.8%)/408(71.2%)	0.03
Hypertension (Yes/No)	4(5.6%)/68(94.4%)	96(16.8%)/477(83.2%)	0.013
Diabetes (Yes/No)	4(5.6%)/68(94.4%)	44(7.7%)/529(92.3%)	0.518
Heart disease (Yes/No)	0(0.0%)/72(100.0%)	5(1.0%)/568(99.0%)	1.000
COPD (Yes/No)	0(0.0%)/72(100.0%)	1(0.0%)/572(100.0%)	1.000
Chronic liver disease (Yes/No)	2(2.8%)/70(97.2%)	23(4.0%)/550(96.0%)	0.851
Chronic renal disease (Yes/No)	0(0.0%)/72(100.0%)	6(1.0%)/567(99.0%)	0.825
Cancer (Yes/No)	0(0.0%)/72(100.0%)	6(1.0%)/567(99.0%)	0.825
Others (Yes/No)	3(4.2%)/69(95.8%)	37(6.5%)/536(93.5%)	0.617
Time from onset to be confirmed (days)	2(1-4)	5(2.5-7)	<0.001

Table3. clinical characteristics and laboratory results of patients infected with 2019-nCoV with normal or abnormal imaging findings

Characteristics	Normal imaging findings （n=72）	Abnormal imaging findings （n=573）	P value
Fever (Yes/No)	48(66.7%)/24(33.3%)	492(85.9%)/81(14.1%)	<0.001
Cough (Yes/No)	33(45.8%)/39(54.2%)	392(68.4%)/181(31.6%)	0.016
Expectoration (Yes/No)	17(23.6%)/55(76.4%)	208(36.3%)/365(63.7%)	0.033
Hemoptysis (Yes/No)	0(0.0%)/72(100.0%)	11(2.0%)/562(98.0%)	0.482
Sore throat (Yes/No)	17(23.6%)/55(76.4%)	80(14.0%)/493(86.0%)	0.031
Nasal obstruction (Yes/No)	7(9.7%)/65(90.3%)	29(5.1%)/544(94.9%)	0.177
Muscle ache (Yes/No)	5(7.0%)/67(93.0%)	66(11.5%)/507(88.5%)	0.243
Fatigue (Yes/No)	9(12.5%)/63(87.5%)	109(19.0%)/464(81.0%)	0.177
Shortness of breath (Yes/No)	0(0.0%)/72(100.0%)	26(4.5%)/547(95.5%)	0.127
Diarrhea (Yes/No)	8(11.1%)/64(88.9%)	45(7.9%)/528(92.1%)	0.343
Nausea and vomiting (Yes/No)	0(0.0%)/72(100.0%)	22(3.8%)/551(96.2%)	0.178
Headache (Yes/No)	2(2.8%)/70(97.2%)	65(11.3%)/508(88.7%)	0.025
Blood routine			
Leucocytes (× 10^9 per L; normal range 4–10)	5.42±2.00	5.01±1.87	0.079
Neutrophils (× 10^9 per L; normal range 2–7)	3.48±1.88	3.29±1.68	0.397
Lymphocytes (× 10^9 per L; normal range 0.8–4)	1.39±0.61	1.23±0.52	0.021
Haemoglobin (g/L; normal range：male 131–172, female 113-151)	141.04±15.62	138.09±16.47	0.15
Platelets (× 10^9 per L; normal range: male 83–303, female 101-320)	198.44±58.44	185.22±62.42	0.088
International normalized ration (normal range 0.85-1.15)	1.03±0.09	1.04±0.10	0.384
Blood biochemistry			
Albumin (g/L; normal range 40–55)	42.53±4.70	41.02±4.47	0.007
Alanine aminotransferase (U/L; male normal range 9–50, female 7-40)	25.53±19.96	29.37±25.71	0.222
Aspartate aminotransferase (U/L; male normal range 15–40, female 13-35)	25.67±15.52	30.08±20.37	0.077
Total bilirubin (μmol/L; normal range 0–26)	9.11±4.86	11.26±8.04	0.027
Serum potassium (mmol/L; normal range 3.5-5.3)	3.88±0.42	3.85±0.44	0.632
Serum sodium (mmol/L; normal range 137-147)	138.99±2.79	137.93±3.76	0.021
Blood urea nitrogen (mmol/L; normal range 3·1–8)	3.90±1.13	4.04±1.69	0.505
Serum creatinine (μmol/L; normal range: male 57–97, female 41-73)	65.54±13.16	69.17±24.52	0.053
Creatine kinase (U/L; normal range 50–310)	62.5(47-83.75)	73.0(48.0-111.0)	0.01
Lactate dehydrogenase (U/L; normal range 120–250)	174.5(148-235.5)	213.0(173.0-268.0)	<0.001
Glucose (mmol/L; normal range 3·9–6·1)	6.57±3.24	6.62±2.91	0.891
Infection-related biomarkers			
Procalcitonin (ng/mL; normal range 0·0–0.5)	0.05(0.04-0.07)	0.05(0.04-0.08)	0.415
C-reactive protein (mg/L; normal range 0·0–5·0)	2.3(0.9-9.5)	8.8(3.1-22.0)	<0.001
Oxygenation index (PO_2/FiO_2)	478.79(468.93-478.79)	381.46(354.73-419.05)	<0.001

Table4. Complications and treatments of patients infected with 2019-nCoV with normal or abnormal imaging findings

	Normal imaging findings （n=72）	Abnormal imaging findings （n=573）	P value
Complications			
Acute respiratory distress syndrome (Yes/No)	0(0.00)/72(100.0%)	14(2.4%)/559(97.6%)	0.362
Shock (Yes/No)	0(0.00)/72(100.0%)	2(0.3%)/571(99.7%)	1.000
Liver function abnormality (Yes/No)	6(8.3%)/66(91.7%)	75(13.1%)/498(86.9%)	0.251
Acute kidney injury (Yes/No)	0(0.00)/72(100.0%)	2(0.3%)/571(99.7%)	1.000
Treatments			
Anti-coronavirus treatment (Yes/No)	56(77.8%)/16(22.2%)	488(85.2%)/85(14.8%)	0.104
Glucocorticoids (Yes/No)	0(0.00)/72(100.0%)	77(13.4%)/496(86.6%)	0.001
Oxygen therapy (Yes/No)	8(11.1%)/64(88.9%)	250(43.6%)/323(56.4%)	<0.001
Mechanical ventilation (including non-invasive and invasive)	0(0.0%)/72(100.0%)	9(1.6%%)/564(98.4%)	0.591
CRRT (Yes/No)	0(0.0%)/72(100.0%)	0(0.0%)/573(100.0%)	
ECMO (Yes/No)	0(0.0%)/72(100.0%)	0(0.0%)/573(100.0%)	
Admission to intensive unit (Yes/No)	0(0.0%)/72(100.0%)	4(0.7%)/569(99.3%)	0.622

Table5. Univariate and multivariate logistic regression analysis of predictors for severe/critical pneumonia

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.04	1.02-1.06	<0.001			
Sex (Male/Female)	2.09	1.21-3.62	0.009			
Time from onset to be confirmed	1.11	1.04-1.18	0.001			
Coexisting Condition (Yes/No)						
Any	4.08	2.39-6.96	<0.001			
Hypertension	3.95	2.26-6.93	<0.001			
Diabetes	2.22	1.01-4.84	0.047			
cancer	8.30	1.64-42.01	0.011			
Symptoms (Yes/No)						
Fever	3.68	1.13-12.02	0.031			
Cough	2.73	1.36-5.50	0.005			
Expectoration	2.03	1.20-3.43	0.008			
Hemoptysis	7.11	2.10-23.99	0.002			
Muscle ache	2.74	1.44-5.25	0.002	4.67	1.75-12.46	0.002
Fatigue	1.97	1.10-3.52	0.023			
Shortness of breath	38.11	14.55-99.82	<0.001	9.02	2.20-37.01	0.002
Diarrhea	3.80	1.88-7.70	<0.001			
Nausea and vomiting	5.05	2.03-12.57	<0.001	15.55	2.86-84.50	0.001
Headache	1.99	1.00-3.96	0.051			
Laboratory results						
Leucocytes	1.19	1.05-1.33	0.005			
Neutrophils	1.33	1.17-1.51	<0.001			
Lymphocytes	0.12	0.054-0.25	<0.001	0.26	0.09-0.70	0.008
International normalized ration	10.98	1.20-100.69	0.034			
Albumin	0.83	0.77-0.88	<0.001			
Aspartate aminotransferase	1.01	1.00-1.02	0.043			
Serum sodium	0.93	0.87-0.99	0.023			
Blood urea nitrogen	1.18	1.04-1.33	0.012			
Serum creatinine	1.02	1.01-1.03	0.004	1.03	1.00-1.05	0.004
Creatine kinase	1.001	1.000-1.002	0.007			
Lactate dehydrogenase	1.003	1.001-1.004	0.004			
Glucose	1.10	1.03-1.18	0.004			
C-reactive protein	1.03	1.02-1.04	<0.001			
Total radiograph score	6.43	4.35-9.49	<0.001	6.28	3.90-10.10	<0.001