

Research on pneumonia exacerbation in patients infected with SARS-CoV-2 in Wuhan, China

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Research

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Abstract

Background

SARS-CoV-2 pneumonia occasionally exacerbates to critical condition that is hard to manage. We aim to describe exacerbations of SARS-CoV-2 pneumonia among inpatients.

Methods

We included confirmed SARS-CoV-2 patients with pneumonia exacerbation admitted to Wuhan Pulmonary Hospital, Hubei Province, China between January 6 and February 17, 2020 and discharged or died before February 25. Their demographic characteristics, clinical symptoms, laboratory tests, CT manifestations, complications and clinical outcomes were collected.

Results

A total of 158 patients were collected, among them 107 patients were stable and discharged after recovery, 24 patients were already critically severe at hospital admission. 14 patients were excluded for insufficient clinical data. Eventually, 13 confirmed cases were included. The mean age was 65 (\pm 9.81) years. Ten of the 13 (76.9%) patients were female. Nine (69.2%) had underlying comorbidities. Fever and cough were the most common symptoms (12/13, 92.3%). 10/13(76.9%) patients had their exacerbation in the second week of disease course. All patients had both negative and positive nucleic acid test (NAT) results during the course. Increased range of ground-glass opacity (GGO) on CT imaging are consistent to disease exacerbation. ARDS, MODS, respiratory failure were found in 5/13(38.5%), 3/13(23.1%), 6/13(46.2%) patients respectively. Five (38.5%) patients did not survive.

Conclusions

SARS-CoV-2 pneumonia exacerbations often occurs in the second week of disease course. Negative NAT result could not exclude exacerbation. CT manifestation is consistent with disease progression. Early admissions have positive effects on reducing complications and mortality.

Background

Since December 2019, the outbreak of novel coronavirus diseases COVID-19 has exerted profound influence globally. The World Health Organization (WHO) has declared COVID-19 as a pandemic. Up to March 17,2020, a total of 571678 confirmed cases and 26494 deaths were reported¹. The highly pathogenic virus is now named as SARS-CoV-2 (initially as 2019-nCoV)². Some studies have reported the

epidemiological features, clinical characteristics and computed tomography (CT) changes of the SARS-CoV-2 pneumonia³⁻⁷. The aim of this study is to report the disease exacerbation during hospitalization.

Methods

Study design and material

This is a retrospective, single-center, observational study. Laboratory-confirmed SARS-CoV-2 patients with pneumonia exacerbation after admitted to Wuhan Pulmonary Hospital, Hubei Province, China (a COVID-19-designated hospital in the event of epidemic outbreak) between January 6 and February 17, 2020 and discharged or died before February 25 are included.

Diagnosis of SARS-CoV-2 pneumonia were confirmed by viral nucleic acid test (NAT) using high-throughput sequencing or amplification of open reading frame 1ab (ORF1ab) and nucleocapsid protein (NP) genes fragments from sputum, pharyngeal swab or lower respiratory tract samples as described in previous study³. In this study, sampling site also included urine and stool.

NAT-confirmed patients were divided into three types according to the severity grading: 1) moderate: with fever and respiratory symptoms, or with pneumonia performance on imaging. 2) severe: met one of the following criteria: respiratory distress, respiratory rate ≥ 30 times/min; pulse oxygen saturation $< 93\%$ at rest; oxygenation index (artery partial pressure of oxygen / inspired oxygen fraction (P_{aO_2}/F_{iO_2}) ≤ 300 mmHg; obvious progression of $> 50\%$ lesion within 24-48 hours as shown on CT. 3) critically severe: met one of the following criteria: respiratory failure and mechanical ventilation required; shock; multi-organ failure required intensive care unit (ICU) care. Disease exacerbation is defined as the escalation of severity grading during the course of disease.

We counted the detection results of ORF1ab and NP genes, respectively. Double-positive is defined as both ORF1ab and NP positive while double-negative is defined as both ORF1ab and NP negative.

Data collection

We extracted the age, gender, underlying comorbidities, clinical symptoms, vital signs, laboratory findings on admission and CT during hospitalization. All laboratory testing and examinations are performed according to the clinical care needs of the patient.

Definitions

The course of illness of non-survivor cases was defined as the duration from onset to death. The course of illness of survivor cases was defined as the duration from onset to the sampling date of the second negative NAT of two consecutive NATs before discharge. We adopted this new method of definition to reflect the duration of detectable SARS-CoV-2 RNA as accurate as possible.

Early Admission was defined as hospitalized within 7 days from onset. Late admission was defined as hospitalized after 7 days from onset.

Lymphopenia was defined as lymphocyte count $< 0.8 \times 10^9/L$. Thrombocytopenia is defined as platelet count $< 100 \times 10^9/L$. Anemia is defined as hemoglobin $< 110g/L$. Hyponatremia is defined as serum sodium $< 135mmol/L$. Hypokalemia is defined as serum potassium $< 3.5mmol/L$. Hypoalbuminemia is defined as plasma albumin $< 35g/L$. Elevation or reduction criteria of each laboratory value were listed on Table 1.

The survival outcome was defined as survival to hospital discharge.

Statistical analysis

All continuous variables were described as mean (standard deviation (SD), range) and categorical variables were defined as number and percentage. SPSS software (version 19) was used for the statistical analysis.

Results

Demographic data and clinical symptoms

Of the 13 patients, the average age was 65 (SD: 9.81, range: 39–80) years old. Ten (76.9%) were women and 9 (69.2%) had one or more underlying comorbidities, including hypertension, diabetes, heart disease, chronic kidney disease, hepatic disease, etc. With respect to initial symptoms, fever and cough are most common symptoms (12/13, 92.3%). 1/13 (7.7%) patient had hypodynamia, 4/13 (30.8%) patients had shortness of breath, 3/13 (23.1%) patients had chest distress, 1/13 (7.7%) patient had abdominal pain and diarrhea, 1/13 (7.7%) patient had palpitation (shown in Table 1). At admission, 7/13 (53.8%) patients were diagnosed as moderate pneumonia, 6/13 (46.2%) were diagnosed as severe pneumonia. Figure 1 shows the course of illness of all patients.

Nucleic acid tests

All NAT results and the corresponding sampling sites of 13 patients are collected and shown on Fig. 2. All cases had both double-negative result and double-positive result in different during disease course. NP gene positive with ORF1Ab negative result are shown in four cases (case 6,8,9,13). It is worth noting that two cases (case 2 and 4) tested positive post hospital discharge whereas their two consecutive NAT tests showed double-negative results before discharge.

Laboratory tests

Laboratory values are shown in Table 1. 1/13 (7.7%) had procalcitonin elevation. 7/13 (53.8%) had elevated D-Dimer. 13/13 (100%) had elevated C-reaction protein. 3/13 (23.1%) had leukopenia. 11/13 (84.6%) had lymphopenia. Increased neutrophilic granulocyte count and decreased monocyte

count are observed in 4/13(30.8%) patients separately. 1/13(7.7%) had thrombocytopenia. 3/13(23.1%) had anemia. 12/13 (92.3%) had elevated lactate dehydrogenase. Elevation of total bilirubin and direct bilirubin are not detected. 2/13(15.4%) had increased glutamic-pyruvic transaminase, 4/13(30.7%) had increased glutamic-oxaloacetic transaminase. 2/13(15.4%) had abnormal creatinine. 8/13(61.5%) decrease of plasma albumin. 5/13(38.5%) presented blood urea nitrogen increase. 3/13(23.1%) had hyponatremia. 3/13(23.1%) had hypokalemia. 2/13(15.4%) had prolonged active partial thromboplastin time. 3/13(23.1%) had cardiac troponin elevation. 6/13(46.2%) had elevated creatine kinase.

Imaging examinations

Intact CT imaging of all cases except case 7 and case 8 are available. Features of CT imaging, including location, proportion, numbers of associated lung lobes and manifestation, were shown in the table2-supplementary table. CT imaging of case2 and case10 are shown in Fig. 3. Ground-glass opacity in both lungs were characteristically observed on CT (11/11,100%). Peripheral distribution and bilateral sides involvement were observed in 11/11 (100%) and 10/11 (90.9%) patients, respectively. One patient with unilateral abnormality at onset progressed to bilateral in 3 days. As the disease progressed, the lesions became consolidated, and central zone and more lung lobes were involved. Pleural effusion and thickened pleura were detected in 2 different patients.

Treatment

Antiviral drugs and glucocorticoids were given to all patients (13/13, 100%).Antibiotics were given to 12/13 (92.3%) patients. Mechanical ventilation was given to 6/7 (85.7%) critically severe patients.

Exacerbations,complications and outcome

Seven cases (case 1,2,3,4,11,12,13) presented as moderate type at admission, among them only case11 progressed to the critically severe type. The other six cases progressed to the severe type. The cases presented as the severe type (case5,6,7,8,9,10) at admission all deteriorated to be critically severe. 10/13(76.9%) patients had their exacerbation in the second week of disease course.

Among all included cases, 5/13 (38.5%) had ARDS, 3/13 (23.1%) had MODS, 6/13 (46.2%) had respiratory failure, 8/13 (61.5%) had hypoalbuminemia. 42.8% (3/7) early admission cases and 66.6% (4/6) late admission cases developed to critically severe type.

The majority of critically severe type (case5,6,7,8,10) (5/7,71.4%) did not survive. The overall survival rate is 53.8% (7/13). Mortality rate is 28.6% (2/7) in the early group and 50.0% (3/6) in the late group. Incidence of ARDS is 28.6% (2/7) vs. 50.0% (3/6), MODS 28/6% (2/7) vs. 16.6% (1/6), respiratory failure 33.3% (2/6) vs. 66.6% (4/6), hypoalbuminemia 28.6% (2/7) vs. 100.0% (6/6) respectively.

Discussion

We analyzed 13 confirmed cases of SARS-CoV-2 pneumonia patients with disease exacerbation after admission. Exacerbation of SARS-CoV-2 pneumonia does not always but indeed happen (13/120, 10.8%) among inpatients.

Review the age distribution of 13 patients, 11(11/13 85%) had exceeded 60 years old. The majority of patients (9/13 69%) had underlying comorbidities, including but limited to hypertension, diabetes, heart disease, chronic kidney disease, hepatic disease. Two patients under 60 years of age had obesity, hyperlipidemia (case1), and coronary artery disease, hypertension (case2) separately. Aging and underlying diseases may collaborate and contribute to the decline of host immunity that is the prerequisite of virus infection and disease exacerbation.

In this study, 10/13(76.9%) cases were female. This ratio seems to be quite contradictory to previous report on COVID-19 that claimed approximately 70% infections occur in male⁸. and also inconsistent with the proportion of male patients (67%) in severe SARS-CoV-2 pneumonia reported in another study⁸. Since this study had excluded patients admitted but has not been discharged or died before February 25, the total number and proportion of male patients could be underestimated.

Disease exacerbation mostly occurred in the second week of disease course (10/13, 76.9%). Patients (case 1,4,5,10,11,12,13) admitted early (within 7days) of the disease course had a relatively better prognosis than those (case 2,3,6,7,8,9) admitted later (after the first 7days). The early group demonstrated lower probability of complications and death. These results indicate that early admission is crucial to restrain deterioration and reduce mortality.

The overall mortality rate was 38.4%(5/13), and in critically severe cases,the mortality rate was 71.4% (5/7), slightly higher than former study⁸. These results may be attributed to the fact that the inclusion criteria of this study are different from those of the above studies. These data do not apply to the entire herd of infected patients.

In our study, fever and cough were the most common symptoms at hospital admission. Initial reports of the COVID-19 virus suggested that symptoms of SAR-CoV-2 pneumonia are similar to that of SARS and MERS, since most patients presenting with fever, cough, fatigue and hypodynamia^{9,10}. However, one patient (case12) did not manifest fever during the entire course of disease. This is an 80 years old female patient presented to clinic with a complain of chest distress and palpitation. Since she was in the epidemic area, she underwent a CT scan which demonstrated pneumonia. Then nucleic acid test was administrated and this case is confirmed. Besides, patients presented diarrhea as the initial symptom of disease have been reported¹¹. These extra-pulmonary initial symptoms deserve more attention outside of fever clinic.

Elevation of C-reaction protein, D-Dimer and lactate dehydrogenase, reduction of lymphocyte count and albumin are observed in more than half of the cases. Anemia, transaminase abnormality, elevated

myocardial index and renal dysfunction are also detected as disease exacerbate. These changes are consistent with previous reports^{3,12,13}.

Ground-glass opacity and consolidation are the main changes in CT imaging. CT manifestations are indicative of the exacerbation of pneumonia. In the process of exacerbation, more lobes were involved, range of GGOs were expanded and density of consolidation was increased. Additional signs on CT imaging include vascular enlargement, interlobular septal thickening in crazy-paving pattern, air bronchogram sign and discrete pulmonary nodules, which were previously reported in some studies^{14,15}. CT imaging may serve as a standard method in the rapid diagnosis of COVID-19. Previous studies have reported that the sensitivity of chest CT is significantly greater than that of RT-PCR (98% vs 71%, respectively, $p < .001$)¹⁶. And false negative rate is very low (3.9%)¹⁶. Nevertheless, CT is still incapable of distinguish between different viruses.

Nucleic acid RT-PCR testing is a standard test for suspected cases to confirm the SARS-CoV-2 infection. Sampling site plays an important role in virus detection. Case 10 was sampled at 4 sites (pharyngeal swab, urine, venous blood, stool) on the same day, only stool sample demonstrated positive result. The patient's medical records showed severe diarrhea and significant weight loss, which suggests that stool specimen in patients presenting gastrointestinal symptoms is probably more sensitive to the virus than pharyngeal swabs. Controversial NAT results were also observed in case 8 whose sputum and urine sample were taken on the same day. Urine sampling is not of high priority in clinical routine due to lack of sufficient data to support it as a usual shedding route of coronavirus. For different sampling sites, bronchoalveolar lavage fluid exhibited the highest positive rate, followed by sputum, nasal and pharyngeal swabs showing poor positive rate in patients with fever¹⁷. Another study reported the detection rates of SARS-CoV-2 from sputum specimens are significantly higher than throat swabs¹⁸. SARS-CoV-2 has the ability to transmit through multiple routes^{19,20} and manifest diverse clinical symptoms which should be taken into account while sampling. We infer that while determine where specimens are collected, considering the location of initial symptoms may increase positive rate.

In 4 cases (case 6, 8, 9, 13), NAT showed ORF1ab negative and NP positive result. Low viral load might lead to this result since PCR kits currently used in clinical practice are generally more sensitive to the amplification of the N protein gene than ORF1ab. On the other hand, crossovers of other coronaviruses may cause the same result since ORF1ab sequence is more conservative than N protein gene. Patients presented single-positive result should be re-checked by test kits from a different manufacture or different test method.

NAT results has turned out to be controversial in 2 cases(case2,4). After discharge from hospital (20 days for case 2, 14 days for case 4), their NAT result reversed to be positive. It is not clear that whether these patients are still contagious. Virus isolation and antibody test may provide further confirmation. The shedding mode of virus might be relevant to a re-positive result of NAT. Intermittent shedding have been found in Epstein-Barr-virus infected patients²¹ and pulsed shedding of viruses in wildlives²² have been reported. This may also suggest that SARS-CoV-2 has acquired the ability of chronic infection, as HIV

integrates itself into the host's genome by reverse transcription^{23,24} and Hepatitis B virus invades into liver cells and transforms into covalently closed circular DNA²⁵. But this hypothesis is yet unfounded and requires further investigation.

All medical treatment administered in our cases suits clinical demands. The efficacy of antibiotics, antivirals, glucocorticoids is not discussed here since sample size is too small to summarize any conclusion.

This study has obvious limitations. First, only 13 cases were eventually involved. However, all included cases have intact medical records available to trace back and changes in severity grading over time is recorded in details. Second, due to the diversity of clinical needs, NAT sample site choosing changes in every case and CT examinations not administered in 2 cases. Third, the course of illness is defined as the time interval between onset and outcome event in this study. Disregarding the incubation period leads to an underestimation of the actual span of disease course. Last but not least, as a retrospective study, recall bias and selection bias inevitably affected our assessment. Further studies on aggravating factors of pneumonia, early identification and prevention methods of exacerbation are needed.

Conclusion

In conclusion, our study provides a preliminary sight into the exacerbation of SARS-CoV-2 pneumonia. Disease exacerbation mostly occurs in the second week of disease course. Negative NAT does not exclude exacerbation. CT manifestations may provide evidence of the exacerbation of pneumonia. Early admission appears to have positive effects on reducing complications and mortality.

Abbreviations

NAT
nucleic acid test
GGO
ground-glass opacity
CT
computed tomography
ARDS
acute respiratory distress syndrome
MODS
multiple organ dysfunction syndrome
COVID-19
coronavirus disease 2019
WHO
the World Health Organization
RT-PCR

real-time reverse-transcriptase–polymerase-chain-reaction
ORF1ab
open reading frame 1ab
NP
nucleocapsid protein
PaO₂/FiO₂
artery partial pressure of oxygen / inspired oxygen fraction
ICU
intensive care unit
SARS
severe acute respiratory syndrome
MERS
middle east respiratory syndrome

Declarations

Ethics approval and consent to participate

Informed consent was exempted with the approval of Medical Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China (No. XHEC-D-2020-030).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

GX Chen and X Lan collected the data, C Ji and XP Li accomplished data analysis, Y An, D Zhang and GW Zeng performed imaging processing, YP Tang and L Wang drafted the manuscript and made literature

review, L Yang, YY Cai and H Huang designed the study and reviewed the manuscript. All authors read and approved the final manuscript.

Co-first authors: YP Tang, GX Chen, L Wang, X Lan and C Ji contributed equally to this work.

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Not applicable.

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Figures

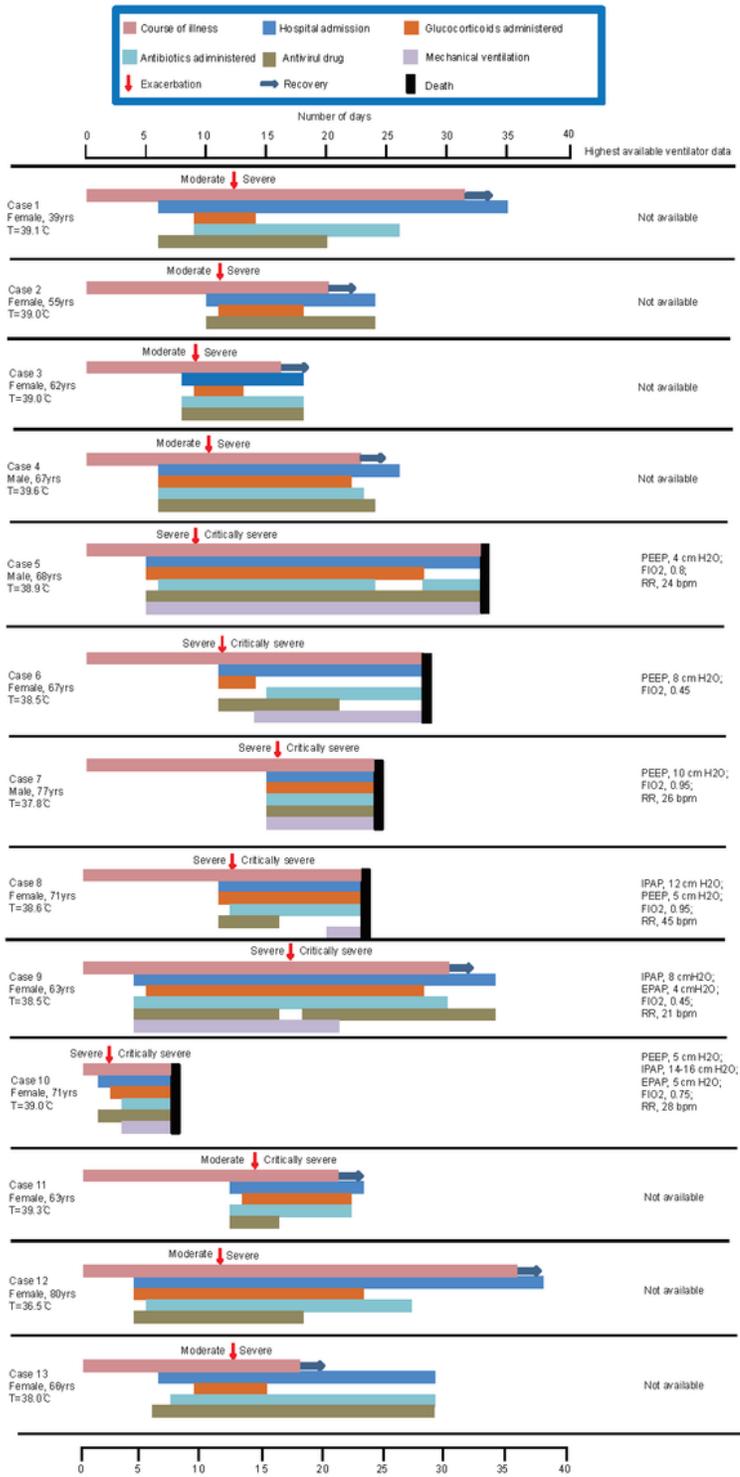


Figure 1

The course of illness of all patients.

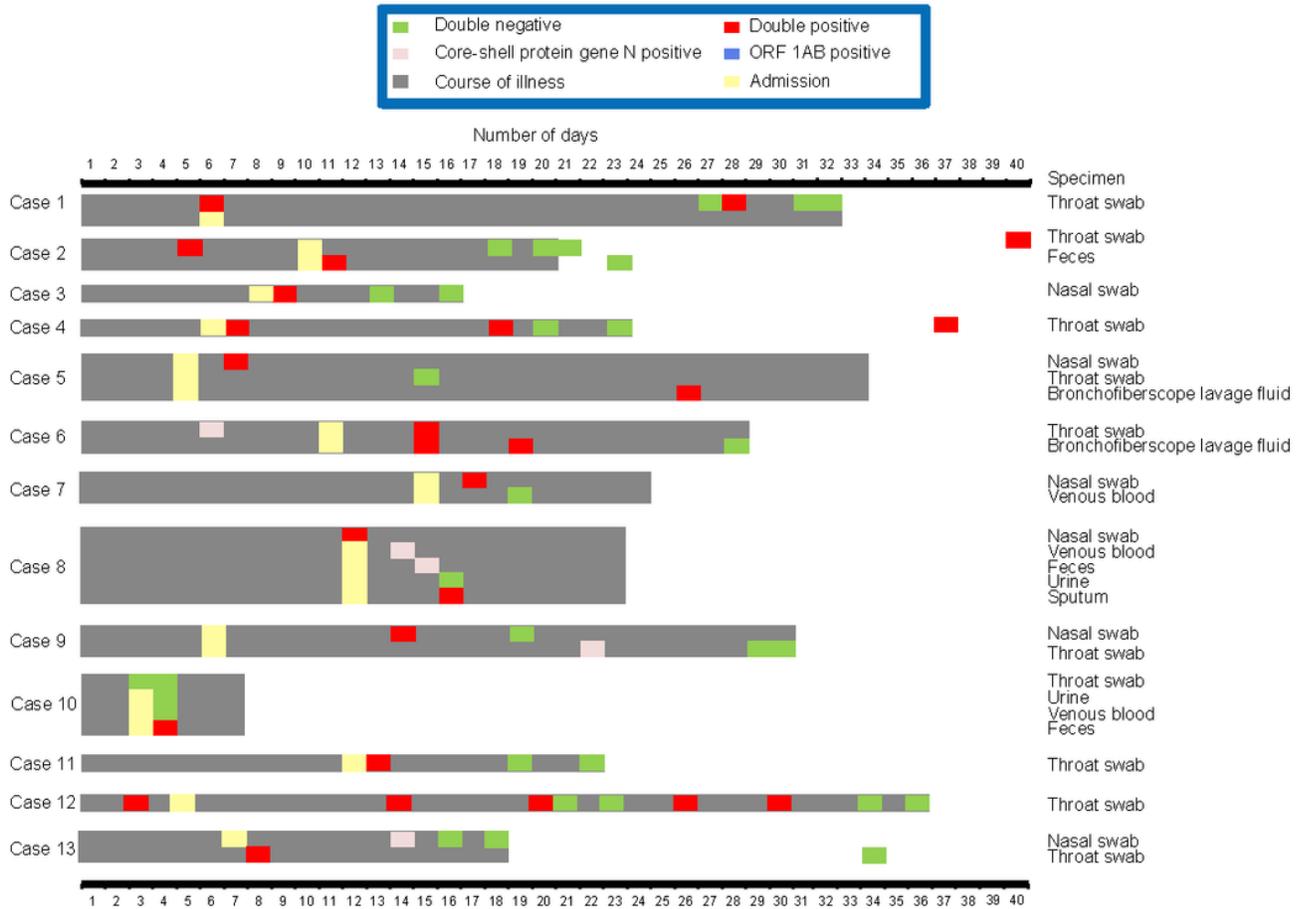


Figure 2

NAT results and the corresponding sampling sites of 13 patients.



Figure 3

High-Resolution computed tomographic imaging of case 2 and case 10. The imaging of these two cases showed us that the features of CT imaging were presented as ground glass opacity (GGO), peripheral distribution and bilateral lung involvement. As the disease progressed, the lesions became consolidated, central zone and more lung lobes are involved. Panel A1, A2 and A3 demonstrated an exacerbation process of case 10. Her condition rapidly deteriorated into critically severe type after admission and did not survive eventually. Meanwhile, CT imaging manifested increased range of GGO and consolidation. A typical “white lung” can be seen in Panel A3. CT imaging of case 2 was shown in Panel B1, B2 and B3. In Panel B1, the proportion of lesions were 35%. In the process of pneumonia exacerbation, the proportion climbed up to 90% (shown in Panel B2). The range of lesions decreased to 57.5% (shown in Panel B3) when her condition is relieved. *number of associated lung lobes ✖CT imaging was unavailable because CT examination was completed before admission in another hospital. # CT imaging of case7 and case 8 are absent because their critical condition does not permit a CT scan.

Supplementary Files

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

- [Table1.xlsx](#)
- [Table2supplementary.xlsx](#)