

Heterogeneity analysis of COVID - 19 clinical phenotype in Wuhan

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Abstract

Background

Since the outbreak of coronavirus disease 2019 (COVID-19), some studies reported the clinical characteristics of COVID-19 patients in hospital. However, these studies did not investigate the clinical symptoms heterogeneity of COVID-19 patients in the outpatient. This study aimed to describe the heterogeneity of clinical characteristics of outpatient COVID-19 patients.

Methods

COVID-19 patients visiting the respiratory outpatient department of our hospital from January 1st to February 28st 2020 were retrospectively analyzed. Based on the complaints, the patients were classified into four groups including group A (patients without symptoms), group B (patients with fever), group C (patients with respiratory symptoms but without fever), and group D (patients with extra-respiratory symptoms but without fever). The difference of clinical characteristics, basic diseases, laboratory examination of outpatient, characteristics of chest CT imaging among all the groups were analyzed and compared.

Results

A total of 309 COVID-19 patients were included with 126 men and 183 women. The common symptoms included fatigue (59.87%, 95% CI: 54.17-65.38%), loss of appetite (51.13%, 95% CI: 45.41-56.83%), fever (50.81%, 95% CI: 45.09-56.51%), muscle soreness (41.42%, 95% CI:35.88-47.14%), and dry cough (35.28%, 95% CI:29.95-40.89%). The percentages of group A to group D were 2.91%, 50.81%, 18.12%, and 28.16%, respectively. The most common symptoms in Group D included fatigue, loss of appetite, muscle soreness.

Conclusion

The heterogeneity of clinical symptoms for COVID-19 patients in the outpatient is significant. We should pay attention to patients without symptoms or those with only extra-respiratory symptoms, who are prone to missed diagnosis.

Background

In December 27th of 2019, we treated three patients with viral pneumonia from one family, and then treated four patients with similar viral pneumonia from South-China seafood market. We then firstly reported these patients with unexplained pneumonia to both Wuhan Municipal Health Commission and Hubei Municipal Health Commission¹, thus started the battle for this epidemic situation. Among the three patients from one family, the mother firstly visited the respiratory outpatient due to symptoms of fever, dry cough, and wheezing, who was admitted as “community acquired pneumonia”. In the same day, the father visited the neurology department due to headache and was transferred to respiratory department

based on the “pneumonia” findings by chest CT examination. We found similar chest CT imaging from the couple. Then we let their son without any symptoms perform chest CT scanning and found pneumonia-like change, which indicated that the clinical symptoms of this disease had significant heterogeneity. The pathogen has been named as 2019 novel coronavirus (2019-nCoV)² and this disease is named as coronavirus disease 2019 (COVID-19) by World Health Organization³.

Up to March 13th 2020, a total of 132 758 patients were diagnosed as COVID-19 worldwide and 122 counties or districts had reported cases⁴. Since the outbreak of COVID-19, some studies reported the clinical characteristics of COVID-19 patients in hospital⁵⁻⁷, but no study analyzed the clinical features of COVID-19 patients in the outpatient. We found that the clinical symptoms of outpatient COVID-19 patients had significant heterogeneity, which could have manifestations from occult infection without symptoms to acute respiratory distress syndrome. This study aimed to describe the difference of clinical features, laboratory examinations and imaging of COVID-19 patients with different syndromes at respiratory outpatient in January and February 2020 and provided early diagnosis reference of 2019-nCoV for physicians of districts with COVID-19 worldwide.

Methods

Study Design and Population

COVID-19 patients were included in the respiratory outpatient of our hospital from January 1st to February 28st 2020 based on the diagnosis criteria of Diagnosis and Treatment Protocol of Novel Coronavirus Pneumonia (edition 5) by National Municipal Health Commission⁸. The inclusion criteria included: 1) age > 18 years; 2) first visit with complete outpatient patient materials; 3) with results of blood routine, CRP, chest CT imaging and RT-PCR test positive for 2019 n-Cov; 4) patient with $SpO_2 \leq 93$ was diagnosed as severe case in resting condition. Exclusion criteria included: 1) revisit with first visit in other hospital; 2) incomplete patient materials; 3) without results of blood routine, CRP and chest CT imaging. Institutional review board approval was obtained and informed consent was waived (No. 2020011).

Based on the complaints in visit, the patients were classified into four groups including group A (patients without symptoms), group B (fever patients with respiratory or extra-respiratory symptoms), group C (patients with only respiratory symptoms but without fever), and group D (patients with extra-respiratory symptoms such as loss of appetite, muscle soreness, fatigue, and fatigue, but without fever).

Our hospital is a public Tertiary hospital, located in the center of epidemic area, which is only 1.5 miles away from South-China seafood market. Our hospital firstly found and reported the outbreak of this epidemic to the government.

Observational Indicators

The demographic data, history, comorbidities, symptoms, laboratory examinations, and chest HRCT scanning of patients were collected from the electric medical report system in the outpatient. The results of chest HRCT scanning were reviewed by two associate chief physicians. As lots of patients were still in hospital, this study did not include the final outcomes in the data analysis.

Statistical analysis

Due to all quantitative variables did not fit the normal distribution well, the statistical description of these variables was expressed as median and IQR (inter quartile range), and the comparisons among groups were performed by using Kruskal-Wallis test, then Student-Newman-Keuls test was used for pairwise comparisons based on the rank. For qualitative variables, statistical description was expressed as frequency (percentage), 95% CI (confidence interval) of proportions was estimated by using Clopper-Pearson method, Fisher exact probability method was chosen for comparisons among groups, and stepdown-Bonferroni method was selected for pairwise comparisons. Statistical software was SAS 9.4 (SAS Institute Inc, Cary, NC), and all hypothesis tests were two-sided tests with a significance level of 0.05.

Results

Common symptoms of patients

A total of 309 COVID-19 patients were included with 126 male cases and 183 female cases (median age: 54.00 years, inter quartile range: 42.00–63.00 years). The common symptoms included fatigue (59.87%, 95% CI: 54.17–65.38%), loss of appetite (51.13%, 95% CI: 45.41–56.83%), fever (50.81%, 95% CI: 45.09–56.51%), muscle soreness (41.42%, 95% CI: 35.88–47.14%), and dry cough (35.28%, 95% CI: 29.95–40.89%) (Table 1).

Table 1
Symptom distributions among all patients with COVID-19 (n = 309)

Symptom	N	Proportion (%)	95% CI (%)
Fatigue	185	59.87	(54.17, 65.38)
Loss of appetite	158	51.13	(45.41, 56.83)
Fever	157	50.81	(45.09, 56.51)
Muscle soreness	128	41.42	(35.88, 47.14)
Dry cough	109	35.28	(29.95, 40.89)
Chest congestion	55	17.80	(13.70, 22.53)
Pharyngalgia	51	16.50	(12.54, 21.12)
Runny and stuffy nose	43	13.92	(10.26, 18.28)
Dyspnea	28	9.06	(6.11, 12.83)
Sputum	24	7.77	(5.04, 11.34)
Diarrhea	24	7.77	(5.04, 11.34)
Headache	18	5.83	(3.49, 9.05)
COVID, coronavirus disease; CI, confidence interval.			

Comparisons Of Characteristics Among The Groups

The percentages of all the groups included 2.91% (95% CI: 1.34–5.46%) in group A, 50.81% (95% CI: 45.09–56.51%) in group B, 18.12% (95% CI: 13.99–22.88%) in group C, 28.16% (95% CI: 23.21–33.53%) in group D. All the patients in group D had no fever and most of them had fatigue, loss of appetite, muscle soreness and others (Table 2).

Table 2
Symptom distributions in group D (n = 87)

Symptom	N	Proportion (%)	95% CI (%)
Fatigue	83	95.40	(88.64, 98.73)
Loss of appetite	79	90.80	(82.68, 95.95)
Muscle soreness	52	59.77	(48.71, 70.15)
Diarrhea	15	17.24	(9.98, 26.84)
Headache	10	11.49	(5.65, 20.12)
CI, confidence interval.			

The ages among the groups were significantly different ($P = 0.0001$). The median age of group A was 33.00 years (IQR: 31.00–49.00 years), which was younger than the other three groups. The gender among the groups were significantly different ($P = 0.0386$). The percentage of male in group was the highest (66.67%), but no significant difference was identified between the groups after P-value adjustment. The percentage of patients with hypertension history among the groups were significantly different ($P = 0.0196$). The percentage of patients with hypertension in group D was significantly higher than that of group C, but no significant difference was found in other group comparisons. The levels of CRP among groups were significantly different ($P = 0.0167$). The level of CRP in group A was significantly lower than that of group C, but no significant difference was found in other group comparisons. The comparisons for the level of SpO₂ found that the hypoxia condition of group A was better than other three groups, but no significant difference was found between other three groups. Only one side and multiple GGO of imaging signs among the groups were significantly different ($P = 0.0381$), but it did not maintain statistically difference after further P value adjustment. The percentages of severe patients among the groups were significantly different ($P = 0.0156$). No patient in group A met with the severe criteria, but no significant difference was found in other group comparisons. Analysis of chest CT signs for all the patients in the first visit found common changes included bilateral lung multiple ground glass opacity (GGO) (71.52%, 95% CI: 66.14–76.49%), interlobular septal thickening (68.28%, 95% CI: 62.78–73.44%), and thickening of broncho-vascular tracts (22.98%, 95% CI: 18.40-28.08%), but no significant difference of other signs were found among the group comparisons (Table 3).

Table 3
Comparisons of NCP patient characteristics among four groups

Variable	Total (n = 309)	Group				P value
		A (n = 9)	B (n = 157)	C (n = 56)	D (n = 87)	
Age, median (IQR), y	54.00 (42.00, 63.00)	33.00 (31.00, 49.00)	50.00 (36.00, 62.00)	55.00 (45.50, 61.50)	58.00 (50.00, 65.00)	0.0001
Male, n (%)	126 (40.78)	6 (66.67)	73 (46.50)	19 (33.93)	28 (32.18)	0.0386
Comorbidities						
COPD or asthma, n (%)	14 (4.53)	0 (0.00)	8 (5.10)	3 (5.36)	3 (3.45)	0.8790
Chronic liver disease, n (%)	6 (1.94)	0 (0.00)	3 (1.91)	1 (1.79)	2 (2.30)	1.0000
Chronic nephrosis, n (%)	8 (2.59)	0 (0.00)	4 (2.55)	1 (1.79)	3 (3.45)	0.9170
Diabetes, n (%)	39 (12.62)	0 (0.00)	14 (8.92)	7 (12.50)	18 (20.69)	0.0511
Hypertension, n (%)	54 (17.48)	0 (0.00)	28 (17.83)	4 (7.14)	22 (25.29)	0.0196
Malignant tumor, n (%)	9 (2.91)	0 (0.00)	4 (2.55)	1 (1.79)	4 (4.60)	0.7354
Outpatient laboratory examinations						
White blood cell count, median (IQR), 10 ⁹ /L	4.92 (3.90, 5.93)	5.43 (3.86, 6.57)	4.75 (3.86, 5.87)	4.82 (3.77, 5.71)	5.07 (4.16, 6.18)	0.5498
Neutrophil count, median (IQR), 10 ⁹ /L	3.12 (2.30, 4.11)	3.87 (2.07, 4.56)	3.03 (2.26, 4.05)	2.91 (2.40, 3.68)	3.30 (2.51, 4.41)	0.2447
Lymphocyte count, median (IQR), 10 ⁹ /L	1.20 (0.95, 1.53)	1.20 (0.91, 1.44)	1.20 (0.95, 1.53)	1.35 (0.95, 1.81)	1.18 (0.95, 1.47)	0.5417
Monocyte count, median (IQR)t, 10 ⁹ /L	0.42 (0.32, 0.56)	0.49 (0.44, 0.62)	0.43 (0.32, 0.57)	0.43 (0.30, 0.53)	0.42 (0.32, 0.58)	0.4796
Platelet count, median (IQR), 10 ⁹ /L	168.00 (138.00, 202.00)	176.00 (121.00, 207.00)	167.00 (136.00, 197.00)	169.00 (143.00, 201.00)	168.00 (144.00, 205.00)	0.9012

NCP, novel coronavirus pneumonia; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; SpO₂, pulse oxygen saturation; CT, computed tomography; GGO, ground glass opacity.

Variable	Total (n = 309)	Group				P value
		A (n = 9)	B (n = 157)	C (n = 56)	D (n = 87)	
C-reactive protein, median (IQR), mg/L	13.81 (6.54, 26.54)	6.62 (5.24, 12.40)	11.67 (5.99, 22.33)	20.32 (6.74, 33.40)	18.69 (8.40, 29.96)	0.0167
SpO ₂ , median (IQR), %	96.00 (93.00, 97.00)	97 (96, 99.00)	96.00 (94.00, 97.00)	95.00 (90.50, 96.50)	95.00 (92.00, 97.00)	0.0129
Chest CT image signs						
Bronchovascular bundle thickening, n (%)	71 (22.98)	1 (11.11)	32 (20.38)	12 (21.43)	26 (29.89)	0.3324
Interlobular septal thickening, n (%)	211 (68.28)	6 (66.67)	101 (64.33)	43 (76.79)	61 (70.11)	0.3574
Paving stone sign, n (%)	29 (9.39)	0 (0.00)	17 (10.83)	3 (5.36)	9 (10.34)	0.6046
Single GGO, n (%)	46 (14.89)	0 (0.00)	30 (19.11)	4 (7.14)	12 (13.79)	0.1064
Unilateral multiple GGO, n (%)	22 (7.12)	3 (33.33)	8 (5.10)	5 (8.93)	6 (6.90)	0.0381
Bilateral multiple GGO, n (%)	221 (71.52)	7 (77.78)	110 (70.06)	43 (76.79)	61 (70.11)	0.8120
Pulmonary consolidation, n (%)	34 (11.00)	1 (11.11)	18 (11.46)	4 (7.14)	11 (12.64)	0.7367
White lung, n (%)	48 (15.53)	0 (0.00)	19 (12.10)	15 (26.79)	14 (16.09)	0.0502
Fiber cords, n (%)	38 (12.30)	0 (0.00)	22 (14.01)	4 (7.14)	12 (13.79)	0.4395
Severe patients, n (%)	84 (27.18)	0 (0.00)	36 (22.93)	23 (41.07)	25 (28.74)	0.0156
NCP, novel coronavirus pneumonia; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; SpO ₂ , pulse oxygen saturation; CT, computed tomography; GGO, ground glass opacity.						

Discussion

The results of this study indicated that the percentage of patients with occult infection in group A was 2.91% with median age of 33 years (IQR: 31.00–49.00 years), which was significantly lower than that of other three groups. All of them had no symptoms and basic diseases as well as normal blood routine, CRP and SpO₂. Only new single or multiple patch or cluster shadows were found in chest CT (Figure A & B). Occult infection is an important feature for 2019-nCoV infection. A previous news media reported that

a COVID-19 patient in a Wuhan hospital had no symptoms before surgery, who caused the infections of 14 medical staffs. This indicated that occult infection was an important infection source and added the difficulty for the prevention and control of COVID-19.

In previous published clinical studies on 2019-nCoV, the percentages of patients with fever were 83-98.6%⁵⁻⁷, but Guan et al.⁹ reported that only 43.1% of patients had fever symptom in early stage. Our study showed that the percentage of patients with complaint of fever in visit was 50.81%, which was similar to the results of the later study. As all the patients in the previous studies were in hospital, they had already progressed into moderate or advanced stage and fever symptom was more common. However, all the patients in our study were in the early stage, therefore our result was similar to the later one. The incidences of cough in relevant reports were 59.4–82%^{6,7,9}, and our study found that the percentage of dry cough was 35.28%. This difference of results may be related with the difference of included subjects. All the subject in our study were patients in the outpatients, who was less severe than patients in hospital and had less fever and respiratory symptoms in the early stage. This indicated that the percentage of pneumonia patients without fever after the 2019-nCoV infection was significantly higher than that of SARS¹⁰ and MERS (middle east respiratory syndrome)¹¹. If we use fever to screen early infected patients, it will lead to the missed diagnosis of many patients, which indicated that it was more difficult to prevent and control 2019-nCoV infection.

During this COVID-19 epidemic, many pneumonia patients visited with extra-respiratory symptoms such as fatigue, fatigue, loss of appetite, and muscle soreness, which are patients of group D in our study. The percentage of group D was 28.16% with median age of 58.00 years (IQR: 50.00–65.00 years) who was older than those of other three groups of patients without statistically significant difference. 67.82% (59/87) of them were female. All of them had no fever. The time from disease onset to visit was almost around 10 days. Their blood routines were almost normal. The scope of effusion lesions were relatively wide in chest CT (Figure G & H), which were significantly different from the clinical symptoms of severe acute respiratory syndrome coronavirus (SARS-CoV) infection¹⁰. However, above relevant clinical studies⁵⁻⁷ seldomly described the features of patients with this syndrome.

As the infection of 2019-nCoV is occult without symptom or with first symptoms beyond respiratory tract, this group of patients may visit other non-infection departments, which causes missed diagnosis, thus increases the risk of virus spread. The daily new cases of China mainland gradually decreased recently, but this numbers in other countries such as European Region are continuously increasing¹². In order to control the epidemic, we suggested that 1) physicians in epidemic areas should pay attention to patients with atypical and extra-respiratory symptoms and people with close contact history, and perform chest CT scanning to screen COVID-19 especially in areas with limited capability to detect 2019-nCoV nucleic acid; 2) it is not enough for disease prevention and control organization of epidemic area as well as control and prevention staffs in public place to just monitor body temperature to screen COVID-19, but also need to collect information of atypical symptoms such as fatigue, loss of appetite and muscle soreness.

The results of study by Wang et al from Zhong Nan Hospital of Wuhan University

indicated that decreased lymphocytes was one of the features for COVID-19 and consistent decreasing for this number indicated poor prognosis⁷. Due to the consistent inflammatory response, the apoptosis of lymphocytes increased with the dramatical decreasing for the number of lymphocytes, thus started “immune inhibition” or “immune paralysis” condition¹³. During the rescue treatment for patients with severe infection, except for pathogen, we should pay attention to immune imbalance secondary to excessive inflammatory response, which is an important feature of pathophysiological process, and main cause of the aggravation and death of patients with severe infection¹⁴. Our study showed that the percentage of patients with decreased lymphocytes was 12.94% (95% CI: 9.41–17.21%) and the median number of lymphocytes was $1.20 \times 10^9/L$ (IQR: $0.95-1.53 \times 10^9/L$), which were significantly different from the report of Wang et al⁷. This may be related with subjects with first visit to the outpatient. Most patients in this group were in the early stage and some patients probably had no decreased lymphocytes.

Although the imaging of viral pneumonia was not non-specific¹⁵, chest CT scanning had convenient and rapid advantages, especially during initial stage that it was difficult to detect viral nucleic acid. Although we found that lung imaging of each group had their own features (Figure A-H), our study did not find statistical difference of imaging signs among each group probably due to lack of digital tools to describe the imaging features and not able to describe the location and scope of signs distribution. We thought that in area with high incidence of disease, HRCT had imaging features of viral pneumonia, which could make the clinical diagnosis of COVID-19 together with epidemiological materials and clinical symptoms. However, Wáng et al.¹⁶ thought that the clinical significance of CT examination for 2019-nCoV was not defined, avoided as much as possible, and recommended chest X-ray examination to observe the progression and regression of lung lesions for patients with moderate/severe patients. We thought that if this strategy causes mild or early patients not able to be diagnosed timely, it will increase the risk to spread virus for this group of patients as infection source.

Our study had several limitations. Firstly, all the included subjects were outpatient patients. The information of outpatient medical record system is relatively simple, which may miss some important information, and the number of severe patients in the outpatient is small, which may have selection bias. Secondly, as the number of patients in group A is small, and the power of test is small when group A is compared with other groups, which may explain why the difference among the groups was statistically significant but comparisons between each group were negative. Thirdly, as lots of patients were still in hospital, we could not analyze the risk factors of adverse consequence and need to continuously follow up these patients.

In conclusion, the heterogeneity of early clinical symptoms for COVID-19 patients was significant. It was impossible to early screen these patients by only symptoms of fever and cough, which may lead to the missed diagnosis of patients without symptoms or only with extra-respiratory symptoms. In the epidemic area, it is necessary to screen COVID-19 for patients without fever, patients with symptoms such as fatigue, loss of appetite, and muscle soreness as well as people with close contact history.

Abbreviations

2019-nCoV, 2019 novel coronavirus; COVID-19, coronavirus disease 2019; HRCT, High resolution computed tomographic; IQR, inter quartile range; CI, confidence interval; GGO, ground glass opacity; CRP, C-reactive protein.

Declarations

Ethics approval and consent to participate

All participants provided written informed consent. The study received ethical approval from the Ethics Committee of Hubei Provincial Hospital of Integrated Chinese & Western Medicine(No. 2020011).

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 no competing interests.

Funding

No funding was obtained for this study.

Authors' contributions

YY and WX are responsible for the whole manuscript. QY and JX helped with data entry and manuscript writing. ZF helped with data analysis. WZ helped with CT reading and analysis. JZ helped with collection of laboratory data. All authors participated in the revision of this manuscript and approved the content.

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Not applicable.

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Figures

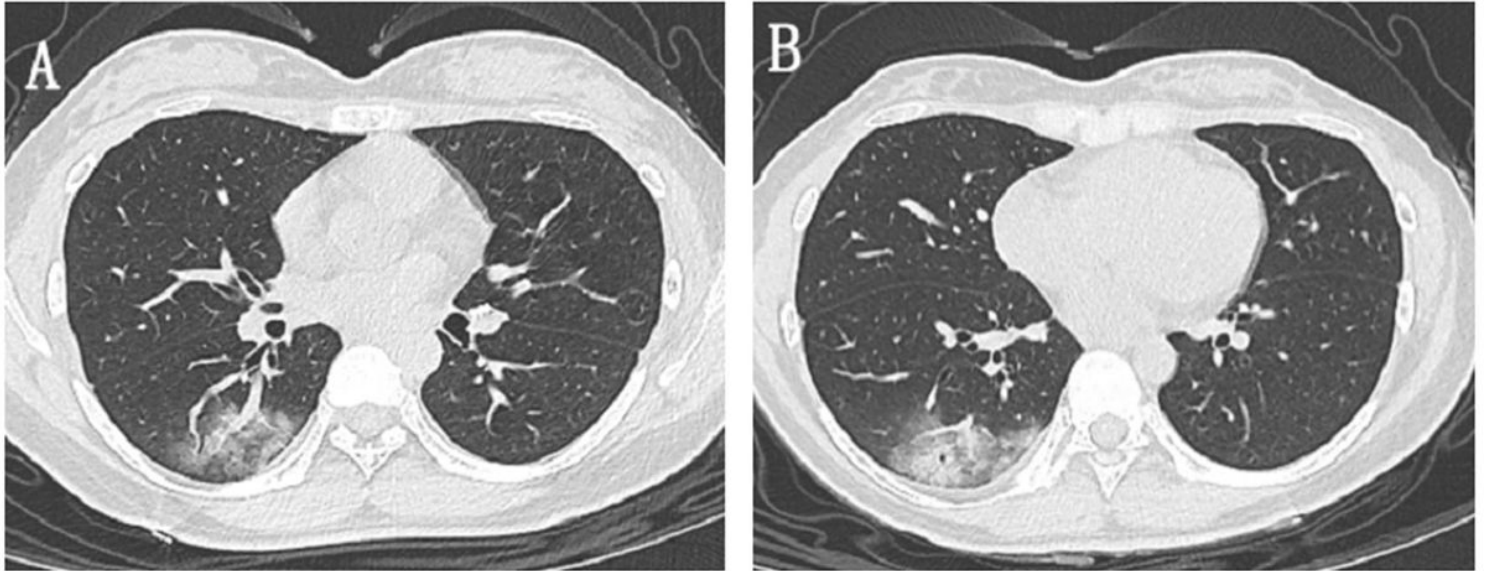


Figure 1

HRCT scan of the lung area in a young woman of who is a NCP close contact with no symptoms showing ground-glass opacities, consolidation, the blood vessel thickening.

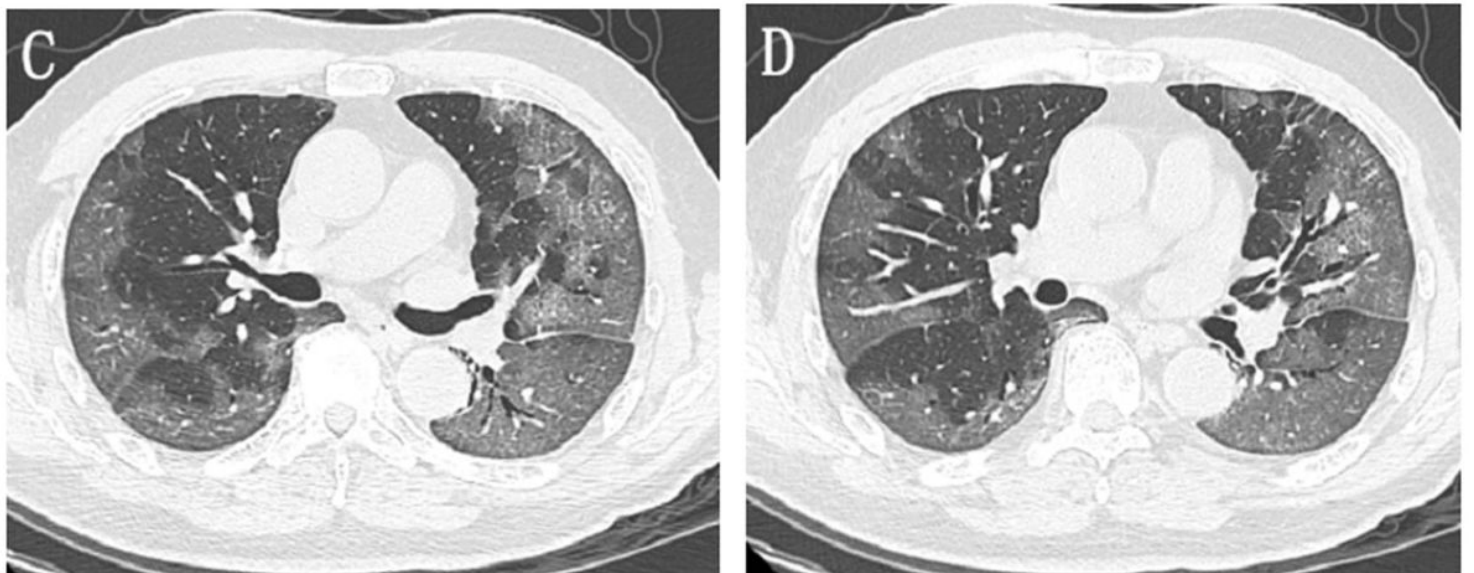


Figure 2

HRCT scan of the lung area in a old man whose chief complaint is shortness of breath and weak for a week showing multiple ground-glass opacities and diffusely thickened interlobular septa giving crazy-

paving appearance in both lung subpleural areas.

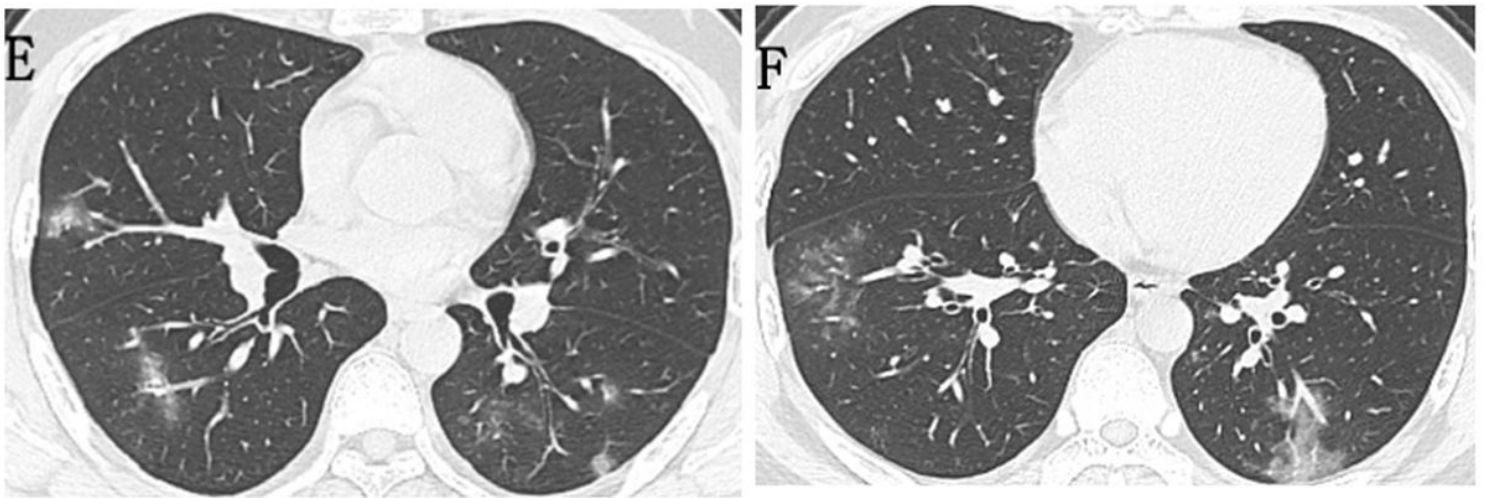


Figure 3

HRCT scan of the lung area in a young man whose chief complaint is fever and cough for a week showing multiple ground-glass opacities, and some area showing mixed ground-glass opacities with blood vessel thickening inside.

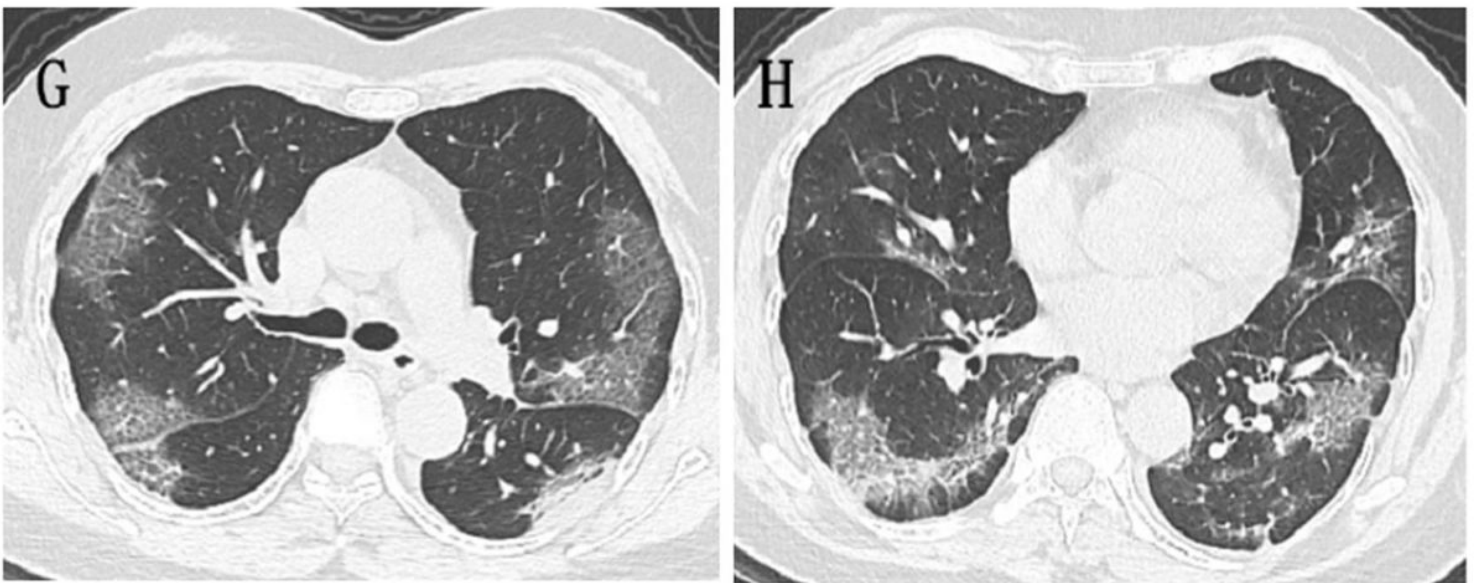


Figure 4

HRCT scan of the lung area in a old woman whose chief complaint is weak, anorexia and muscle soreness for 10 days showing multiple ground-glass opacities and diffusely thickened interlobular septa giving crazy-paving appearance in both lung subpleural areas. Some areas showing consolidation, oblique fissure thickening on the left side of pleura, traction deformation of oblique fissure on both sides, anterior displacement, and multiple tentorial adhesion of pleura.