Clinical findings of second-generation patients with 2019 novel coronavirus: a multicenter, retrospective, observational study

Journal:	*BMJ*
Manuscript ID	BMJ-2020-054741
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	31-Jan-2020
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Keywords:	2019-novel coronavirus, clinical characteristics, human transmission, second-generation patients

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Abstract:

Objective: To study the clinical characteristics of the imported 2019-novel coronavirus patients in Zhejiang Province.

Design: Multicenter, retrospective, observational study

Setting: The study covering eight hospitals which located in the different part of Zhejiang province.

Participants: Since January 2020, we collected data of 62 patients with laboratory-confirmed 2019-nCoV in designated hospitals of Zhejiang province.

Main outcome measures: We used a standardized case-report form to collect clinical data. If information was not clear, the working group in Hangzhou contacted the physician responsible for the treatment of the patient for clarification.

Results: Of the 62 patients studied, only one patient was admitted to the intensive care unit (ICU), no patient died until the submission time. According to our research, none of the infection cases in Zhejiang had ever been exposed to the Huanan seafood marker, all the patients were infected by human transmission. The most common symptoms at onset of illness were fever (48 [77.4 %]), cough (50 [80.6%]), expectoration (35 [56.5%]), headache (21 [33.9%]), myalgia or fatigue (32 [51.6%]), diarrhoea (3 [8.1%]), and hemoptysis (2 [3.2%]). Rare of patients (2 [3.2%]) developed shortness of breath. The median time from exposure to infections to illness onset was 4 days (IQR: 3-5 days), from onset of symptoms to first hospital admission was 2 days (IQR: 1-4.3 days).

Conclusions: The 2019-nCoV could be easily transmitted from human to human. At present, the symptoms of secondary infection patients are relatively mild.

68   **Introduction**

69   In December, 2019, a group of patients with pneumonia of unknown reason were confirmed

70   to be infected with 2019 novel coronavirus (2019-nCoV) in Wuhan, Hubei, China, which had

71   not been detected in humans and animals before.[1] Epidemiological evidence suggested that

72   most of those patients had been presented in a local seafood market in Wuhan[2] and the virus

73   gene sequence of patients was highly similar to that of bats and snakes.[3,4] The viral

74   2019-nCoV was a kind of coronavirus that was very similar to the severe acute respiratory

75   syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus

76   (MERS-CoV) which had caused more than 10000 cases and 1632 deaths across the globe.[5-7]

77   Some researchers found that the 2019-nCoV has good affinity to human respiratory receptor,[8]

78   which indicated that 2019-nCoV may have the potential to pose a global public health threat.

79   At the beginning, nearly all of the patients were related to the Huanan seafood market

80   and the cases were concentrated in Wuhan.[9] Global attention was soon attracted on the

81   situation because of the increasing number of new cases.[2] The new type of coronavirus

82   infection is mainly transmitted from animals to humans, and by January 2020, the main

83   infection cases was suspected to be transmitted from human to human.[10] Since January 2020,

84   the spread of 2019-nCoV starts to escalate at an alarming rate and the virus quickly expand to

85   most parts of China and even other countries. Up to 25 January 2020, there were a total of

86   1320 confirmed cases, including 1297 cases from China and 23 oversea cases from 9

87   countries.[11] These figures update every day and are expected to increase in the further.

88   Despite the increasing number of confirmed cases, the clinical investigation of patients

89   was still limited in the literature. A previous study has reported the clinical characteristics of

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90   initial 41 patients in Wuhan area, which contributes to our epidemiological, clinical,

91   laboratory, and radiological characteristics and treatment and clinical outcomes of those

92   initial patients.[9] Another study conducted by Chan et al. revealed a familial cluster of

93   2019-nCoV and clearly suggested person-to-person transmission in family homes or hospital,

94   and intercity spread of this novel coronavirus are possible.[10] At present, as large number of

95   people were returning home from Wuhan during the Chinese Lunar New Year travel rush,

96   more second-generation or later-generations cases are expected to emerge all over the country

97   and even all over the world. We found that the characteristics of the imported patients were

98   different from those initial patients in Wuhan reported by Bin Cao.[10] It is very important to

99   study the clinical characteristics of the imported patients in Zhejiang Province.

100   Through the analysis of the characteristics of these people, we aim to provide the

101   experiences for prevention and treatment of new coronavirus infection all over the country

102   and abroad. In this article, we described clinical characteristics and laboratory abnormalities

103   in 62 cases of second generation patients infected with 2019 novel coronavirus in Zhejiang,

104   China.

105

106   **Method**

107   **Data sources**

108   We conducted a retrospective study focusing on the clinical characteristics of confirmed

109   cases of the 2019-nCoV infection in Zhejiang Province. All suspected cases with fever and

110   dry cough, especial those with travel history to Wuhan or history of exposure to infected

111   person within 2 weeks before the onset of illness, were transferred to designated hospitals

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112   since January, 2020. The case definitions of confirmed human infection with the 2019-nCoV

113   have been described by Zhu et al.[1] Only patients with laboratory-confirmed infection were

114   enrolled in this study.

115   The medical records of patients were extracted and sent to the data-collection center in

116   Hangzhou. A team of physicians who had been taking care of patients with 2019-nCoV

117   infection collected and reviewed the data. This study was approved by the Ethics Committee

118   of the First Affiliated Hospital, Zhejiang University School of Medicine. Because of the

119   urgent need to collect data on this emerging pathogen, the requirement for informed consent

120   was waived. We used a standardized case-report form to collect clinical data. If information

121   was not clear, the working group in Hangzhou contacted the physician responsible for the

122   treatment of the patient for clarification.

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124   **Laboratory confirmation and treatment**

125   Laboratory confirmation of the 2019-nCoV was performed with real-time PCR described by

126   Huang et al.[9] The virus detection was repeated for two times with 24 hours apart.

127   .   Basic tests were conducted including complete blood count, serum biochemical test and

128   so on. Most of patients received anti-virus treatment including interferon beta-1b inhalation

129   (5MU/bid) or Lopina veletonavir (400mg/100mg bid). When the resting respiratory rate of

130   patient is more than 30 times per minute at rest, or the oxygen saturation of the patient is

131   below 93% without oxygen, or the multiple pulmonary lobes of patients were involved with

132   more than 50% progress in 48 hours, the corticosteroid therapy and gamma globulin therapy

133   were given to the patients. The probiotics therapy was performed in most cases. Antibiotics

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134   (oral and intravenous) were administered if the fever lasted longer than 7 days or CRP ≥ 30.

135   Suspected patients have no access to hospital discharge or discontinuation of isolation until

136   2019-nCoV clearance.

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Statistical analysis

139   Since Huang et al.[9] have shown that patients would get worse on the 10th day after onset, we

140   compared the whole cohort with the ones with the course of longer than 10 days. Continuous

141   variables were summarized as either means and standard deviations or medians with

142   interquartile ranges. For categorical variables, the percentages of patients in each category

143   were calculated. All analyses were done with SPSS software, version 22.0

144

Results

Epidemiologic characteristics

147   By Jan 23, 2020, the clinical data of 62 patients identified as laboratory-confirmed

148   2019-nCoV infection were collected in Zhejiang. Twenty-five (40.3%) of the

149   2019-nCoV-infected patients were aged 19-40 years, and 33 (53.2%) were aged 41-65 years,

150   2 (3.2%) were children and 2 (3.2%) were elderly. The median age of the patients was 41

151   years (IQR 32–52; table 1). In our cohort of the 62 patients as of January 23, more than half

152   of the infected patients were men (36 [58.1%]); no patients had a history of Huanan seafood

153   market exposure, all patients (62/62) had exposure to confirmed 2019-nCoV infected patients.

154   Among 62 patients, 23(37.1%) patients had long term residence in Wuhan. Other 39(62.9%)

155   patients had short term trip to Wuhan before onset. These patients who had short term trip to

156 Wuhan were concluded to calculate the incubation period. At the same time, we selected the

157 patients (n=33) with course longer than 10 days. Among these patients, 10 (30.3%) of the

158 2019-nCoV-infected patients were aged 19-40 years, and 22 (66.7%) were aged 41-65 years,

159 and 1 (3%) were elderly. The median age of the patients was 45 years (IQR 37–54.5; table 1).

160

Clinical features

162 Among the group of 62 patients, one third of patients had underlying diseases (20 [32.3%]),

163 including liver disease (7 [11.3%]), hypertension (5 [8.1%]), chronic obstructive pulmonary

164 disease diabetes (1 [1.6%]), renal diseases (1 [1.6%]) and cardiovascular disease (1 [1.6%]).

165 More than one third were found to be associated with familial clusters (21 [33.9%]). At the

166 same time, we selected the patients (n=33) with course longer than 10 days. More than one

167 third patients had underlying diseases (13 [39.4%]), including liver disease (4 [12.1%]),

168 hypertension (4 [12.1%]), chronic obstructive pulmonary disease diabetes (1 [3%]), and

169 cardiovascular disease (1 [1.6%]). Less than one third were found to be associated with

170 familial clusters (21 [33.9%]).

171   Among the group of 62 patients, we found that the median time of incubation period

172 from exposure was 4 days (IQR 3-5). The median time from onset of symptoms to first

173 hospital admission was 2 days (IQR 1-4.3). The most common symptoms at onset of illness

174 were fever (48 [77.4 %]), cough (50 [80.6%]), expectoration (35 [56.5%]), headache (21

175 [33.9%]),   myalgia or fatigue (32 [51.6%]), diarrhoea (3 [8.1%]), and hemoptysis (2 [3.2%]).

176 Only 2 patients (2 [3.2%]) developed shortness of breath. Among those patients who have

177 disease course over 10 days. We found that the median time of incubation period from

178 exposure was 3 days (IQR 3-4). The median time from onset of symptoms to first hospital

179 admission was 6.5 days (IQR 5.0-9.0). The most common symptoms at onset of illness were

180 cough (27 [81.8 %]), fever (26 [78.8%]), expectoration (19 [57.6%]), myalgia or fatigue (19

181 [57.6%]) , headache (15 [45.5%]), diarrhea (3 [9.1%]), and hemoptysis (2 [6.1%]). Only 1

182 patient (1 [3.0%]) developed shortness of breath.

183 On admission, among the group of 62 patients, the blood counts of patients showed

184 leucopenia (white blood cell count less than 4×10^9/L; 19 [30.6%]) and lymphopenia

185 (lymphocyte count $<1.0 \times 10^9$/L; 26 [41.9%]; table 2). The D-dimer level were higher

186 (median D-dimer level 0.2 mg/L [IQR 0.2-0.5]). Levels of aspartate aminotransferase

187 increased in 10 patients (16.1%). Most patients had normal serum levels of procalcitonin

188 (procalcitonin <0.1 ng/mL; 55 [88.7%] patients). Abnormalities in chest CT images or X ray

189 were detected among all patients. Of the 62 patients, 52 (83.9%) had bilateral involvement

190 (table 2). The typical findings of chest CT images of infection patients on admission were

191 bilateral or multiple lobular or subsegmental areas of consolidation or bilateral ground-glass

192 opacity (Figure 1). Only 1 patient didn't have pneumonia. Among the 62 patients, only 1

193 patient transferred to intensive care unit for acute respiratory distress syndrome and received

194 mechanical ventilation (Table 3). Of all the patients, 88.7% (55/62) received antiviral therapy,

195 45.2% (28/62) were administered with empirical antibiotic treatment. Besides, 25.8% (16/62)

196 patients were given systematic corticosteroids and gamma globulin therapy. One (1.6%)

197 patients have been discharged and no patients died up to now. Fitness for discharge was

198 based on abatement of fever for at least 3 days, with improvement of chest radiographic

199 evidence and viral clearance in respiratory samples from lower respiratory tract.

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Discussion

As of January 27, 2020, more than 2000 laboratory-confirmed 2019-nCoV infections were

reported in China.[12] The number of infections is increasing quickly. It is possible that a larger

number of patients with infections were not diagnosed because their symptoms were less

severe and the infection has a period of incubation. Thousands of suspected patients might be

diagnosed in the next few days. The clinical features of 2019-nCoV cases in Wuhan were not

same as that in other areas in China. According to our data, none of the infection cases in

Zhejiang had ever been exposed to the Huanan seafood marker, all the patients were infected

by human transmission. In addition, there are a large part of family clusters in Zhejiang

infected cases, which is consistent with Professor Yuan's article and more effectively proves

the view of human to human transmission.[10] This would stress on the importance of air

prevention.

The large part of Zhejiang patients were male patients, but the age range is larger, as

the 2019-nCoV also infected children and the elderly.[9] There is not much difference between

the initial clinical symptoms of the Zhejiang cases and those in Wuhan. But most of the

patients in Zhejiang Province are of mild to moderate symptoms, and only a small part of

them have dyspnea. Only one patient developed to acute respiratory distress syndrome and

admitted to the ICU. From the laboratory test indicators, the illness of the second-generation

of patients are also mild. In particular, there were less patients with abnormal renal function,

lactate dehydrogenase and procalcitonin. Through media and national advocacy, the patients

with fever, cough, expectoration and other upper respiratory symptoms were asked to go to

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222 hospital at an earlier stage. Even those with the contact with other patients or suspected

223 patients were asked to go to hospital. We selected some patients with a course of more than

224 10 days for analysis. However, after comparing the clinical features of our patient (with

225 course longer than 10 days) with Wuhan patients, we found that the secondary-generation

226 cases in Zhejiang Province are less severe than the primary cases in Wuhan[9] (Table 4). This

227 phenomenon had also appeared in during the transmission of MERS-CoV. The global case

228 mortality of MERS-CoV was about 40%, while the mortality of second generation of

229 MERS-CoV was about 20%.[13,14]

230   There was not much differences in the antivirus therapy between Zhejiang and Wuhan.

231 However, the antibiotic treatment usage rate and corticosteroid usage rate were different.

232 Less than half patients received antibiotic therapy in Zhejiang Province. Whether the use of

233 antibiotics and steroids affects the prognosis of patients remains unknown. Till now, we have

234 no death patient in Zhejiang province and one patient has recovered after 7 days of treatment

235 in hospital.

236   Given that most infections in Zhejiang were secondary-generation infections, our

237 finding will provide valuable information to understand the clinical features of the

238 increasingly second-generation and later-generation patients. The clinical characteristics of

239 our study population can represent most of the patient's infection since January 2020. Many

240 proposals should be administrated by the government, such as sealing off the city from all

241 outside contact of Wuhan; forbidding gathering of more than 100 persons; efficient daily

242 public education of 2019-nCoV precaution; encouraging people to cancel the traditional

243 family gathering during Chinese Lunar New Year and extending the New Year holiday to

244   prevent large-scale spreading.

245   Our study has several limitations. Firstly, there are only 62 cases were included in our

246   study. During the period of data collection, a large number of patients showed up So we just

247   collected most but not all of the patients with laboratory confirmed illness in Zhejiang

248   Province in that time. Secondly, the patients were only from Zhejiang province which may

249   not be able to fully reveal the clinical features of secondary infection patients. Thirdly, at the

250   time of submission of the manuscript, most patients were still not discharged, so we were

251   unable to estimate either the case fatality rate or predictors of fatality. Moreover, the course

252   of some of our patients may be shorter than 10 days of observation period, which may cause

253   the bias of clinical observation characteristics.

254   In conclusion, 2019-nCoV was easily transmitted from human to human At present, the

255   symptoms of secondary-generation patients are relatively mild. At present, there is no

256   effective drug treatment and vaccine. It is still necessary to strengthen virus monitoring in

257   time and to develop drugs and vaccines for 2019-nCoV as soon as possible.

258

259   **Acknowledgments.** We thank Dr. Song-Jia Tang for the help of English polishing.

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261   **Footnotes**

262   **Contributors:** XW Xu and LJ Li conceptualized the paper. XX Wu analyzed the data with

263   input from JF Sheng, KJ Xu, XG Jiang, LJ Ying, CL Ma, SB Li, HY Wang, S Zhang, HN

264   Gao, HL Cai and YQ Qiu. XW Xu and XX Wu wrote the initial draft with all authors

265   providing critical feedback and edits to subsequent revisions. All authors approved the final

266   draft of the manuscript. The corresponding author attests that all listed authors meet

267 authorship criteria and that no others meeting the criteria have been omitted.

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333   Table 1. Demographic and Epidemiologic Characteristics of 62 Patients Infected with 2019-nCoV   in

334   Zhejiang, China.

Characteristics	All patients (n= 62)	Patients with course longer than 10 days (n= 33)
Age yr	41 (32-52)	45 (37-54.5)
18 and younger	2 (3.2)	0 (0)
19-40	25 (40.3)	10 (30.3)
41-65	33 (53.2)	22 (66.7)
66 and above	2 (3.2)	1 (3.0)
Sex		
Men	36 (58.1)	19 (57.6)
Women	27 (43.5)	14 (42.4)
Coexisting condition		
Any	20 (32.3)	13 (39.4)
Hypertension	5 (8.1)	4 (12.1)
Diabetes	1 (1.6)	1 (3.0)
Chronic obstructive pulmonary disease	1 (1.6)	1 (3.0)
Cerebrovascular disease	1 (1.6)	1 (3.0)
Renal diseases	1 (1.6)	0 (0)
Liver disease	7 (11.3)	4 (12.1)

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Familial cluster	21 (33.9)	9 (27.3)
signs and symptoms		
Fever	48 (77.4)	26 (78.8)
Highest temperature (℃)		
< 37.3	14 (22.6)	9 (27.3)
37.3-38.0	22 (35.5）	10 (30.3)
38.01-39.0	18 (29.0)	9 (27.3)
> 39.0	8 (12.9)	5 (15.2)
Cough	50 (80.6)	27 (81.8)
Myalgia or fatigue	32 (51.6)	19 (57.6)
Expectoration	35 (56.5)	19 (57.6)
Hemoptysis	32 (3.2)	2 (6.1)
Headache	21 (33.9)	15 (45.5)
Diarrhoea	3 (8.1)	3 (9.1)
Incubation period	4 (3-5)	3.0 (3.0-4.0)
Respiratory rate >24 breaths per min	2 (3.2)	1(3.0)
Duration from illness onset to first admission	2 (1-4.3)	6.5 (5.0-9.0)

335 Data are median (IQR) or n/N (%), where N is the total number of patients with available data.

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339 Table 2: Laboratory findings and chest radiographs of patients infected with 2019-nCoV on admission to

340 hospital

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	All patients (n= 62)	Patients with course longer than 10 days (n= 33)
White blood cell count, x109/L	4.7 (3.5-5.8)	4.5 (3.1-6.1)
<4	19 (30.6)	13 (39.4)
4-10	42 (67.7)	20 (60.6)
>10	1 (1.6)	0 (0)
Neutrophil count	2.9 (2.0-3.7)	2.8 (1.7-3.9)
Lymphocyte count	1.0 (0.8-1.5)	1.0 (0.7-1.4)
<1.0	26 (41.9)	15 (45.5)
≧1.0	36 (58.1)	18 (54.5)
Haemoglobin, g/L	137.0 (128.8-152.3)	137.5 (129.0-149.5)
Platelet count,	176.0 (135.8-215.5)	172.5 (128.8-202.8)
<100	3 (4.8)	3 (9.1)
≧100	59 (95.2)	30 (90.9)
D-dimer, mg/L	0.2 (0.2-0.5)	0.2 (0.2-0.6)
Alanine aminotansferase, U/L	22 (14-34)	22.5 (13.6-35.1)
Aspartate aminotansferase, U/L	26 (20-32)	27.5 (18.5-34.7)
<40	52 (83.9)	28 (84.8)
≧40	10 (16.1)	5 (15.2)

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Potassium, mmol/L	3.7 (3.5-3.9)	3.6 (3.5-3.9)
Sodium, mmol/L	139 (127-141)	138.6 (136.9-140.6)
Creatine, umol/L	72.0 (61.0-84.0)	71.5 (61.0-82.2)
$\leqq$133	59 (95.2)	33 (100)
>133	3 (4.8)	0 (0)
Creatine kinase, U/L	69.0 (40.5-101.0)	60.0 (40.0-106.8)
$\leqq$185	57 (91.9)	31 (93.9)
>185	5 (8.1)	2 (6.1)
Lactate dehydrogenase, U/L	205.0 (184.0-260.5)	233.5 (198.0-312.3)
$\leqq$245	45 (72.6)	19 (57.6)
>245	17 (27.4)	14 (42.4)
Procalcitonin, ng/mL	0.04 (0.03-0.06)	0.4 (0.035-0.06)
<0.1	55 (88.7)	31 (93.9)
$\geqq$0.1	7 (11.3)	2 (6.1)
Bilateral involvement of chest radiographs	52 (83.9)	32 (97.0)
Pneumonia	61 (98.4)	33 (100)

342   Data are median (IQR) or n/N (%), where N is the total number of patients with available data.

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347   Table 3. Treatments and outcomes of patients infected with 2019-nCoV

	All patients (n= 62)	Patients with course longer than 10 days (n= 33)
Admission to Intensive Care Unit	1 (1.6)	1 (3.0)
Acute respiratory distress syndrome	1 (1.6)	1 (3.0)
Treatment		
Antiviral therapy	55 (88.7)	31 (93.9)
Antibiotic therapy	28 (45.2)	16 (48.5)
Corticosteroid and gamma globulin therapy	16 (25.8)	11 (33.3)
Prognosis		
Hospitalization	61 (98.4)	32 (97.0)
Discharge	1 (1.6)	1 (3.0)
Death	0	0

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349   Data are median (IQR) or n/N (%), where N is the total number of patients with available data.

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356   Table 4   The compare of the clinical features between our with NO ICU care patients reported by Bin Cao

| Characteristics	NO ICU care patients (n=28)	All patients (n= 62)	Patients with course longer than 10 days (n= 33)
Fever	27(96%)	48 (77.4)	26 (78.8)
Highest temperature			
< 37.3	1(4.0)	14 (22.6)	9 (27.3)
37.3-38.0	5(18.0)	22 (35.5）	10 (30.3)
38.01-39.0	11(39.0)	18 (29.0)	9 (27.3)
> 39.0	11(39.0)	8 (12.9)	5 (15.2)
Respiratory rate >24 breaths per min	4(14.0)	2 (3.2)	1(3.0)
Bilateral involvement of chest radiographs	27(96%)	52 (83.9)	32 (97.0)

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365 **Figure 1:** Transverse chest CT images of the patient. Transverse chest CT images from a

366 32-year-old man showing ground-glass opacity and consolidation of lower lobe of right lung

367 near the pleura on day 1 after symptom onset (A), and bilateral ground-glass opacity and

368 consolidation on day 7 after symptom onset (B).

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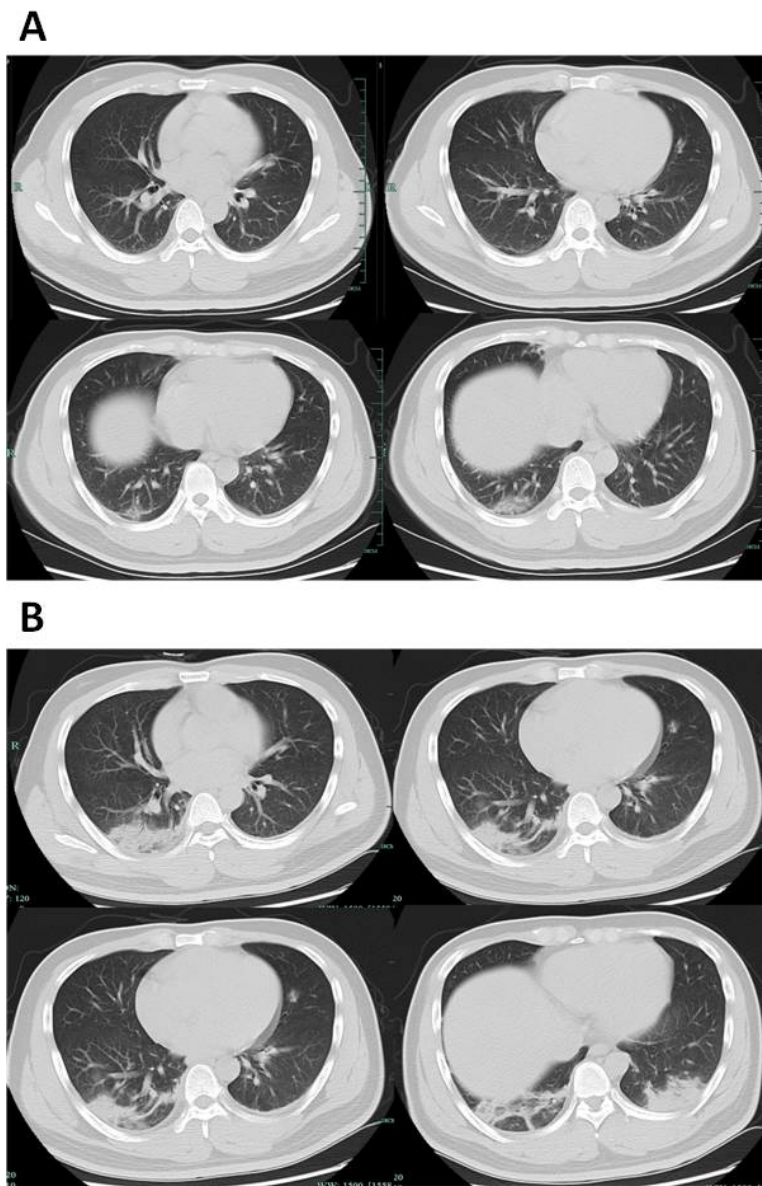
Transverse chest CT images of the patient. Transverse chest CT images from a 32-year-old man showing ground-glass opacity and consolidation of lower lobe of right lung near the pleura on day 1 after symptom onset (A), and bilateral ground-glass opacity and consolidation on day 7 after symptom onset (B).

159x250mm (96 x 96 DPI)