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ORIGINAL ARTICLE

Clinical Course and Factors Associated with Viral RNA Shedding and Radiologic Resolution in Patients with COVID-19: a Retrospective Study

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SUMMARY

Background: **The outbreak of SARS-CoV-2 lead to a worldwide pandemic which poses substantial challenges to public health.**
Methods: **We enrolled 102 consecutive recovered patients with laboratory-confirmed SARS-CoV-2 infection. Epidemiological and demographic characteristics, temporal dynamic profiles of laboratory tests and findings on chest CT radiography, and clinical outcomes were collected and analyzed.**
Results: **Independent risk factors for prolonged fever, viral RNA shedding or radiologic recovery included age of more than 44 years, female gender, having symptoms of cough and fever, a delay from the symptom onset to hospitalization of more than 3 days, a lower CD4 count of less than 500/μl on admission, and severe or critical illness in hospitalization. The estimated median time from symptom onset was 6.4 (5.5 - 7.4) days to peak viral load, 9.1 (7.9 - 10.4) days to afebrile, 8 (6.7 - 9.4) days to worst radiologic finding, 12.7 (11.2 - 14.3) days to viral RNA negativity, and 26.7 (23.8 - 29.9) days to radiologic resolution. This study included the entire cross-section of patients seen in our clinical practice and reflected the real-world situation.**
Conclusions: **These findings provide the rationale for strategies of active symptom monitoring, timing of quarantine and antiviral interventions, and duration of radiologic follow-up in patients with COVID-19.**
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Supplementary Methods

Clinical management and laboratory procedures

After admission, serial respiratory (usually nasopharyngeal and/or throat) and blood samples were collected at multiple time points (routinely one to three days interval in the first two weeks) whenever possible to determine the dynamic changes of routine blood test, cellular immunity, coagulation function, kidney and liver function, biochemical tests, myocardial injury markers, inflammation markers, and viral load as measured by cycle threshold (Ct) values, which inversely correlates with the amount of copies of the virus exponentially. Samples were assessed by RT-PCR assay to confirm the SARS-CoV-2 infection [1] and were screened for common respiratory pathogens like influenza A and B. Initial RT-PCR tests were conducted by Zhuhai Center for Disease Control and Prevention. As of February 24, tests were conducted in our clinical laboratory using the SARS-CoV-2 Kit (Shanghai ZJ Bio-Tech Co., Ltd) assayed on the ABI 7500 instrument. After collection, the nasal and throat swabs were put together into a collection tube containing 2.0 ml viral transport medium, and SARS-CoV-2 RNA from specimens was extracted within 2 hours using a nucleic acid extraction Kit (DAAN Gene Co., Ltd). The concentration of harvested RNA solution was determined by Nanodrop 2000, and the extracted products were used for real-time reverse transcription polymerase chain reaction (RT-PCR) assay of SARS-CoV-2. Three targets, including the RNA-dependent RNA polymerase (RdRP), envelope (E), and nucleocapsid (N) gene, were simultaneously amplified according to the manufacturer's protocol. Specifically,
Target 1 RdRP:
forward primer: GTGARATGGTCATGTGTGGCGG;
reverse primer:
CARATGTTAAASACACTATTAGCATA;
and the probe:
CAGGTGGAACCTCATCAGGAGATG C-BHQ1.
Target 2 E:
forward primer:
ACAGGTACGTTAATAGTTAATAGCGT;
reverse primer: ATATTGCAGCAGTACGCACACA;
and the probe:
ACACTAGCCATCCTTACTGCGCTTCG-BHQ1.
Target 3 N:
forward primer: CACATTGGCACCCGCAATC;
reverse primer: GAGGAACGAGAAGAGGCTTG;
and the probe:
ACTTCCTCAAGGAACAACATTGCCA-BHQ1.
The real-time RT-PCR assay was performed using the SARS-CoV-2 Kit according to the manufacturer's protocol (Shanghai ZJ Bio-Tech Co., Ltd). Reaction mixture contained 2 μL of reaction buffer, 1 μL of enzyme solution, 3 μL of probe primers solution, 4 μL of diethylpyrocarbonate-treated water, and 5 μL of RNA template. RT-PCR assay was performed under the following conditions: incubation at 45°C for 10 minutes and 95°C for 3 minutes, 45 cycles of denaturation at 95°C for 15 seconds, and extending and collecting fluorescence signal at 58°C for 30 seconds. Samples with cycle threshold (Ct) values less than 40 were considered as positive for SARS-CoV-2 RNA, while a Ct value of 40 or more was defined as a negative one.

Serial chest computed tomography (CT) images were obtained after initial diagnosis at varying intervals (routinely three to seven days) in the hospital and every two to four weeks after discharge until radiographic findings were consistent with radiologic resolution.

All patients hospitalized with COVID-19 were treated according to Guidelines for Diagnosis and Treatment of SARS-CoV-2 issued by the National Health Commission of the People's Republic of China (version 6.0). All patients received supportive therapy, including supplemental oxygen therapy to patients with hypoxemia or shortness of breath, sufficient calories, and maintaining homeostasis (body temperature, electrolyte, water balance, acid-base balance, etc.). Initial antimicrobial therapy for patients clinically confirmed of having community-acquired pneumonia included quinolones (levofloxacin or moxifloxacin) and/or β-lactams (piperacillin/tazobactam, ceftriaxone or cefoperazone/sulbactam) to target common pathogens causing community-acquired pneumonia. Oral oseltamivir was also given initially because of the epidemiology of seasonal or local influenza. Empirical antifungal regimen was initiated owing to the suspicion of secondary fungal infection. Once the diagnosis of COVID-19 was established, other regimens including lopinavir/ritonavir, arbidol, chloroquine, ribavirin, interferon inhalation, immunoglobulin, thymosin, fresh frozen plasma, and human albumin, either alone or in combination, were prescribed as appropriate. Corticosteroid therapy (methylprednisolone at a dose of 1 - 2 mg per kilogram of body weight per day) was given as a combined regimen if severe COVID-19 was diagnosed by treating physicians. If patients worsened, with increasing dyspnea, declining oxygen saturation, and rapid deterioration of radiographic findings, rescue use of methylprednisolone up to 500 mg intravenously daily for two or three doses was administrated at the discretion of physicians after shared decision-making and obtaining of informed consent.

The criteria for deisolation and discharge were afebrile for more than 3 days, significant remission of respiratory symptoms, radiologic improvement, and at least 2 consecutive negative PCR assay results on the testing of respiratory samples taken more than 24 hours apart. Upon discharge, they were quarantined in hospital for another 2 weeks, and the follow-up viral tests were performed on day 1, 3, 7, and 14 after discharge to confirm virus-negative status. However, the frequency of examinations and decisions regarding treatment was determined at the sole discretion by the treating physicians.

Definitions

A confirmed case was defined as a patient with a positive result for SARS-CoV-2 RNA by RT-PCR testing of respiratory specimens [1]. The date of symptom onset

was defined as the day when the symptom was noticed for symptomatic cases or the date of the first positive SARS-CoV-2 test for asymptomatic cases. The date of first radiographic abnormality was defined as the first date when the abnormal chest CT images were noticed after symptom onset. The date of peak viral RNA shedding was defined as when the lowest Ct value was observed after symptom onset. The date of worst radiographic findings was defined as the date when the most severe chest radiographic findings were observed during hospitalization. The date of afebrile was defined as the date when body temperature was less than 37.3°C for at least 12 hours and not rising after that during hospitalization without using any antipyretics. The date of negativity was defined as the date of the first negative result of persistent negative detection of respiratory specimens. The duration of viral RNA shedding was defined as the number of days from symptom onset to the first negative result of persistent negative detection of respiratory specimens. The radiologic resolution defined that the infection was controlled and the pulmonary lesion was gradually absorbed with or without minimal residual ground glass opacity (GGO) or linear opacity, with no new lesions, crazy-paving pattern, or dense consolidation being observed (Figure 1 and Supplementary Figure 1). The illness severity of COVID-19 was classified as being mild, general, severe, or critical ill according to the Guidelines. SARS-CoV-2 virus RT-PCR Ct value was grouped as low (< 30 cycles) or high (≥ 30 cycles) with low Ct value indicating high viral load. Values at nadir denote the lowest or the highest values (when appropriate) during hospitalization.

Statistical analysis

Time to events was defined as the time from symptom onset to corresponding events unless otherwise specified. To assess the risk factors for prolonged fever, viral RNA shedding, and radiologic resolution, we expressed time to corresponding events as a binary variable by a cutoff value of 10 days for fever, 14 for viral shedding, and 30 days for radiographic resolution. Furthermore, considering the sample size in our study and avoiding overfitting in the final model, 16 candidate variables were chosen for univariate analysis based on previous finding and clinical importance, including age, gender, underlying comorbidities, clinical symptoms (fever and coughing), abnormal laboratory findings (white blood cell count at nadir, lymphocyte count at nadir, CD4 count on admission, C-reactive protein at nadir, lactose dehydrogenase at nadir, RT-PCR cycle threshold value at nadir), number of lobes involved at nadir, disease severity status at nadir, and drug therapy during hospitalization (lopinavir/ritonavir and chloroquine), and duration from symptom onset to admission.

References:

1. World Health Organization. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases: interim guidance 17 January 2020. Published March 19, 2020. https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117 (accessed March 25, 2020).

Supplementary Tables and Figures

Table 1. Laboratory and radiologic findings of 102 recovered patients with COVID-19 at admission, during hospitalization, and before or after discharge.

Laboratory findings	Reference range	At admission (N = 102)			During Hospitalization (At nadir [b], N = 102)			Before or after discharge (N = 102)		
		N/n (%) [a]	Median (IQR)	Symptom Onset to Median (IQR) days	N/n (%)	Median (IQR)	Symptom Onset to Median (IQR) days	N/n (%)	Median (IQR)	Symptom Onset to Median (IQR) days
White blood cell count × 10^9 per L	3.5 - 9.5	102	4.8 (3.9 - 6.5)	3.5 (2.0 - 6.0)	100	4.2 (3.3 - 5.0)	8.5 (5.0 - 15.0)	100	5.3 (4.6 - 6.5)	20.0 (15.0 - 24.0)
< 3.5		14 (13.7)	3.1 (2.8 - 3.2)	4.0 (3.3 - 6.0)	33 (33.0)	2.9 (2.4 - 3.3)	8.0 (6.0 - 15.0)	8	3.3 (3.0 - 3.5)	21.0 (20.3 - 25.5)
Neutrophil count × 10^9 per L	1.8 - 6.3	102	2.8 (2.1 - 3.5)	4.0 (2.0 - 6.0)	100	2.1 (1.5 - 2.6)	9.0 (4.8 - 16.0)	100	2.9 (2.3 - 3.8)	20.0 (15.0 - 24.0)
< 1.8		18 (17.6)	1.5 (1.2 - 1.8)	5.5 (4.0 - 6.8)	41 (41.0)	1.4 (1.2 - 1.6)	8.0 (6.0 - 15.0)	15	1.6 (1.4 - 1.7)	18.0 (15.5 - 21.0)
Lymphocyte count × 10^9 per L	1.1 - 3.2	102	1.6 (1.1 - 2.1)	4.0 (2.0 - 6.0)	100	1.1 (0.8 - 1.5)	8.0 (5.8 - 12.0)	100	1.7 (1.4 - 2.0)	20.0 (15.0 - 24.0)
< 1.1		24 (23.5)	1.0 (0.8 - 1.0)	4.0 (2.8 - 6.0)	45 (45.0)	0.7 (0.5 - 0.9)	8.0 (6.0 - 12.0)	13	0.9 (0.8 - 1.0)	21.0 (19.0 - 21.0)
Haemoglobin g/dL	115 - 175	102	139.0 (126.3 - 151.8)	4.0 (2.0 - 6.0)	100	120.5 (107.5 - 132.3)	15.5 (10.0 - 21.0)	100	125.0 (111.0 - 138.3)	20.0 (15.8 - 24.0)
< 110		6 (5.9)	104.5 (94.3 - 107.3)	5.0 (2.5 - 6.0)	29 (29.0)	99.0 (94.0 - 105.0)	20.0 (15.0 - 22.0)	22	10.5 (94.5 - 105.0)	21.0 (20.3 - 24.5)
Platelet count × 10^9 per L	125 - 350	102	192.0 (164.3 - 245.8)	4.0 (2.0 - 6.0)	100	169.0 (137.0 - 199.5)	7.0 (5.0 - 12.3)	100	242.0 (208.8 - 297.3)	20.0 (15.0 - 24.0)
< 125		8 (7.8)	103.5 (85.5 - 116.5)	3.5 (2.5 - 4.0)	20 (20.0)	112.0 (76.8 - 119.0)	5.5 (4.0 - 7.3)	2	98.5 (90.3 - 106.8)	22.0 (21.5 - 22.5)
CD3 count/µL	955 - 2,860	94	1,087.5 (730.0 - 1,397.8)	5.0 (3.0 - 11.0)	66	826.5 (579.0 - 1059.0)	10.0 (6.0 - 14.0)	66	1,096.0 (832.8 - 1,266.8)	15.0 (11.3 - 19.8)
CD4 count/µL	550 - 1,440	94	570.5 (419.5 - 807.5)	5.0 (3.0 - 11.0)	66	439.0 (348.0 - 545.5)	10.0 (6.0 - 14.0)	66	571.0 (454.5 - 695.0)	15.0 (11.3 - 19.8)
< 500		36 (38.3)	358.5 (255.0 - 433.0)	6.0 (3.8 - 10.3)	41 (62.1)	374.0 (258.0 - 434.0)	9.0 (6.0 - 14.0)	22	411.0 (330.8 - 451.0)	15.5 (13.0 - 19.8)
CD8 count/µL	320 - 1,250	94	373.5 (236.5 - 498.8)	5.0 (3.0 - 11.0)	66	288.5 (191.8 - 369.5)	9.5 (6.0 - 13.8)	66	377.5 (293.0 - 465.8)	15.0 (11.3 - 19.8)
Prothrombin time, s	9.4 - 12.5	101	11.9 (11.3 - 12.6)	3.0 (2.0 - 6.0)	99	12.7 (12.1 - 13.1)	8.0 (4.0 - 11.5)	99	11.7 (11.0 - 12.1)	18.0 (15.0 - 24.0)
> 13		15 (14.9)	13.3 (13.2 - 13.6)	2.0 (2.0 - 4.5)	30 (30.3)	13.6 (13.3 - 14.2)	9.0 (3.3 - 11.8)	3	13.6 (13.5 - 13.7)	15.0 (13.5 - 18.0)
Activated partialthrom-boplastin time, s	25.1 - 36.5	101	31.4 (28.9 - 33.2)	3.0 (2.0 - 6.0)	99	32.0 (29.9 - 34.0)	6.0 (3.0 - 10.5)	99	29.0 (27.0 - 31.5)	18.0 (15.0 - 24.0)
Fibrinogen, g/L	2.38 - 4.98	101	3.1 (2.6 - 3.7)	3.0 (2.0 - 6.0)	99	2.3 (1.9 - 2.7)	12.0 (6.0 - 18.0)	99	2.7 (2.3 - 3.3)	18.0 (15.0 - 24.0)
D-dimer, ng/L	0 - 243	101	94.0 (52.0 - 134.0)	3.0 (2.0 - 6.0)	99	214.0 (115.0 - 499.5)	12.0 (8.0 - 15.5)	99	119.0 (71.0 - 253.5)	17.0 (14.0 - 23.0)
> 500		2 (2.0)	995.5 (813.8 - 1,177.3)	3.5 (3.3 - 3.8)	25 (25.3)	1,041.0 (615.0 - 2061.0)	14.0 (12.0 - 17.0)	12	1,065.5 (860.5 - 2,112.5)	19.5 (14.5 - 21.5)
Alanine aminotransferase U/L	9 - 50	102	15.8 (11.0 - 27.8)	4.0 (2.0 - 6.0)	100	29.2 (18.6 - 47.6)	12.0 (7.0 - 18.0)	100	19.6 (12.2 - 32.6)	18.0 (15.0 - 24.0)
> 50		8 (7.8)	60.1 (54.1 - 69.6)	2.5 (1.8 - 4.5)	23 (23.0)	66.7 (59.2 - 81.9)	15.0 (8.5 - 18.0)	5	58.5 (56.2 - 76.1)	24.0 (19.0 - 28.0)
Aspartate aminotransferase U/L	15 - 40	102	20.8 (15.1 - 29.0)	3.5 (2.0 - 6.0)	100	29.0 (20.1 - 37.1)	11.0 (5.8 - 16.0)	100	18.8 (14.9 - 26.2)	18.0 (15.0 - 24.0)

Table 1. Laboratory and radiologic findings of 102 recovered patients with COVID-19 at admission, during hospitalization, and before or after discharge (continued).

Laboratory findings	Reference range	At admission (N = 102)			During Hospitalization (At nadir [b], N = 102)			Before or after discharge (N = 102)		
		N/n (%) [a]	Median (IQR)	Symptom Onset to Median (IQR) days	N/n (%)	Median (IQR)	Symptom Onset to Median (IQR) days	N/n (%)	Median (IQR)	Symptom Onset to Median (IQR) days
> 40		4 (3.9)	44.1 (43.5 - 48.1)	4.0 (3.5 - 4.0)	22 (22.0)	54.2 (43.5 - 70.3)	14.5 (12.0 - 16.8)	3	59.2 (41.3 - 78.3)	21.0 (15.0 - 24.0)
Total bilirubin µmol/L	3 - 24	102	7.4 (5.2 - 9.9)	4.0 (2.0 - 6.0)	100	16.4 (11.7 - 26.3)	9.0 (6.0 - 13.0)	100	8.6 (6.6 - 10.9)	18.5 (15.0 - 24.3)
> 24		1 (1.0)	29.3	4.0 (4.0 - 4.0)	29 (29.0)	29.2 (26.9 - 36.2)	9.0 (5.0 - 12.0)	0	-	-
Albumin, g/L	40 - 55	102	39.5 (37.3 - 42.3)	4.0 (2.0 - 6.0)	100	36.9 (35.3 - 38.3)	9.0 (5.0 - 13.0)	100	41.1 (39.1 - 42.6)	18.0 (15.0 - 24.0)
< 40		55 (53.9)	37.4 (36.1 - 38.8)	4.0 (2.0 - 6.0)	90 (90.0)	36.6 (35.2 - 37.9)	9.0 (5.0 - 12.0)	39	38.4 (37.4 - 39.5)	18.0 (14.0 - 23.5)
Urea nitrogen mmol/L	3.1 - 8	102	3.7 (2.9 - 4.2)	4.0 (2.0 - 6.0)	100	4.6 (4.0 - 5.6)	13.0 (7.0 - 17.0)	100	4.0 (3.5 - 4.6)	18.0 (15.0 - 24.0)
> 8		2 (2.0)	16.7 (13.2 - 20.2)	1.5 (1.3 - 1.8)	5 (5.0)	14.3 (9.7 - 17.4)	14.0 (7.0 - 17.0)	2	17.2 (13.0 - 21.4)	22.0 (21.5 - 22.5)
Creatinine µmol/L	57 - 111	102	57.6 (48.4 - 71.7)	4.0 (2.0 - 6.0)	100	73.4 (61.4 - 86.3)	9.0 (6.0 - 13.0)	100	61.9 (53.8 - 73.6)	18.0 (15.0 - 24.0)
Lactate dehydrogenase U/L	120 - 250	102	168.0 (142.3 - 202.0)	4.0 (2.0 - 6.0)	100	201.5 (170.8 - 267.3)	10.0 (7.0 - 15.0)	100	152.0 (131.8 - 187.0)	18.0 (15.0 - 23.3)
> 250		10 (9.8)	273.5 (260.0 - 280.0)	6.0 (4.0 - 7.8)	33 (33.0)	302.0 (274.0 - 327.0)	11.0 (9.0 - 14.0)	5	266.0 (265.0 - 274.0)	17.0 (17.0 - 31.0)
Creatine kinase U/L	39 - 308	102	68.0 (51.3 - 97.3)	4.0 (2.0 - 6.0)	100	89.5 (63.0 - 124.5)	7.0 (3.8 - 11.0)	100	49.0 (35.0 - 67.8)	17.0 (15.0 - 23.0)
Creatine kinase-MB, U/L	0 - 25	102	13.0 (10.7 - 15.7)	4.0 (2.0 - 6.0)	100	17.8 (15.2 - 21.8)	8.0 (5.8 - 14.0)	100	11.8 (8.9 - 15.0)	17.5 (15.0 - 23.0)
> 25		6 (5.9)	36.1 (29.6 - 46.8)	4.5 (2.3 - 6.8)	17 (17.0)	34.9 (30.7 - 51.1)	9.0 (7.0 - 16.0)	6	39.0 (34.7 - 49.6)	27.5 (23.3 - 33.3)
Potassium mmol/L	3.5 - 5.3	102	3.7 (3.5 - 3.9)	4.0 (2.0 - 6.0)	100	3.4 (3.2 - 3.6)	8.0 (5.0 - 11.3)	100	4.1 (3.9 - 4.3)	18.0 (15.0 - 24.0)
< 3.5		26 (25.5)	3.3 (3.2 - 3.4)	4.0 (1.3 - 6.0)	69 (69.0)	3.3 (3.2 - 3.4)	8.0 (5.0 - 10.0)	4	3.4 (3.3 - 3.4)	18.0 (11.3 - 26.0)
Sodium mmol/L	137 - 147	102	140.0 (137.3 - 142.0)	4.0 (2.0 - 6.0)	100	137.0 (135.0 - 138.3)	8.0 (5.8 - 13.3)	100	140.0 (138.0 - 141.0)	18.0 (15.0 - 24.0)
< 137		16 (15.7)	135.5 (134.5 - 136.0)	5.0 (3.5 - 7.3)	38 (38.0)	134.5 (132.0 - 136.0)	8.0 (6.0 - 11.0)	7	135.0 (132.5 - 136.0)	18.0 (18.0 - 25.5)
Chloride mmol/L	99 - 110	102	101.0 (99.1 - 103.1)	4.0 (2.0 - 6.0)	100	97.9 (95.8 - 99.0)	10.0 (7.0 - 14.0)	100	100.4 (99.0 - 102.5)	18.0 (15.0 - 24.0)
< 99		22 (21.6)	96.6 (96.1 - 98.2)	4.0 (2.0 - 6.0)	71 (71.0)	96.3 (95.0 - 98.0)	10.0 (7.0 - 14.0)	23	97.6 (96.4 - 98.5)	16.0 (15.0 - 24.0)
NT-proBNP pg/mL	0 - 125	92	39.0 (25.8 - 84.5)	4.0 (2.0 - 7.0)	85	130.0 (54.0 - 433.0)	11.0 (6.0 - 13.0)	84	50.0 (23.8 - 93.5)	17.0 (12.8 - 23.0)
> 125		16 (16.7)	197.0 (155.3 - 287.0)	4.5 (1.8 - 7.3)	43 (50.6)	433.0 (236.0 - 1,360.0)	11.0 (9.0 - 13.5)	18	290.5 (198.5 - 770.0)	18.5 (13.5 - 22.5)
Hypersensitive cardiac troponin I, ug/L	0 - 0.0229	97	0.0 (0.0 - 0.0)	4.0 (2.0 - 8.0)	84	0.0 (0.0 - 0.0)	4.0 (2.0 - 8.0)	84	0.0 (0.0 - 0.0)	17.0 (12.8 - 23.0)
> 0.0229		1 (1.0)	0.06	4.0 (4.0 - 4.0)	11 (13.1)	0.04 (0.01 - 0.07)	8.0 (3.5 - 12.0)	1	0.03	19.0 (19.0 - 19.0)
C-reactive protein, mg/L	0 - 5	102	4.1 (0.6 - 11.0)	4.0 (2.0 - 6.0)	100	11.6 (3.4 - 39.8)	9.0 (6.0 - 11.8)	100	1.2 (0.4 - 3.3)	17.0 (15.0 - 23.0)
> 10		29 (28.4)	29.6 (17.2 - 43.4)	4.0 (2.0 - 7.0)	55 (55.0)	33.3 (18.9 - 69.2)	9.0 (6.0 - 11.0)	11	12.9 (12.3 - 18.7)	17.0 (16.0 - 20.0)
RT-PCR cycle threshold	≥ 40	76	30.2 (26.5 - 33.9)	4.5 (2.0 - 9.0)	76	28.7 (25.8 - 32.6)	5.0 (3.0 - 9.0)	-	-	-
≤ 30		38 (50)	26.4 (23.6 - 28.5)	3.5 (2.0 - 6.0)	47 (61.8)	26.5 (23.7 - 28.3)	4.0 (2.0 - 7.0)	-	-	-

Table 1. Laboratory and radiologic findings of 102 recovered patients with COVID-19 at admission, during hospitalization, and before or after discharge (continued).

Laboratory findings	Reference range	At admission (N = 102)			During Hospitalization (At nadir [b], N = 102)			Before or after discharge (N = 102)		
		N/n (%) [a]	Median (IQR)	Symptom Onset to Median (IQR) days	N/n (%)	Median (IQR)	Symptom Onset to Median (IQR) days	N/n (%)	Median (IQR)	Symptom Onset to Median (IQR) days
Radiologic findings										
Lateral pulmonary infiltrate distribution		101	-	3.0 (1.0 - 6.0)	101	-	9.0 (5.0 - 12.0)	97	-	25.0 (16.0 - 36.0)
Normal		26 (25.7)	-	2.0 (1.0 - 3.3)	18 (17.8)	-	6.5 (4.8 - 10.3)	27 (27.8)	-	16.0 (10.0 - 28.0)
Unilateral		19 (18.8)	-	4.0 (2.0 - 9.0)	16 (15.8)	-	6.5 (2.0 - 11.5)	19 (19.6)	-	25.0 (19.0 - 35.0)
Bilateral		56 (55.4)	-	4.0 (1.0 - 6.0)	67 (66.3)	-	9.0 (7.0 - 12.0)	51 (52.6)	-	34.0 (20.0 - 39.0)
Number of lobes involved		101	-	3.0 (1.0 - 6.0)	101	-	9.0 (5.0 - 12.0)	97	-	25.0 (16.0 - 36.0)
0		26 (25.7)	-	2.0 (1.0 - 3.3)	18 (17.8)	-	6.5 (4.8 - 10.3)	27 (27.8)	-	16.0 (10.0 - 28.0)
1		15 (14.9)	-	4.0 (2.0 - 9.0)	14 (13.9)	-	9.0 (3.5 - 13.5)	15 (15.5)	-	19.0 (15.0 - 33.0)
2		15 (14.9)	-	1.0 (0.0 - 5.0)	12 (11.9)	-	7.0 (0.3 - 9.0)	17 (17.5)	-	25.0 (17.5 - 36.0)
3		9 (8.9)	-	2.0 (1.0 - 7.0)	14 (13.9)	-	9.5 (4.3 - 16.8)	11 (11.3)	-	35.0 (30.0 - 39.0)
4		13 (12.9)	-	4.0 (1.0 - 6.0)	13 (12.9)	-	9.0 (6.5 - 12.0)	9 (9.3)	-	23.0 (18.5 - 34.5)
5		23 (22.8)	-	5.0 (3.0 - 7.0)	30 (29.7)	-	10.0 (8.5 - 13.0)	18 (18.6)	-	37.5 (29.8 - 48.3)
Right upper lobe involved		42 (41.6)	-	4.0 (1.0 - 7.0)	49 (48.5)	-	9.0 (7.0 - 12.5)	34 (35.1)	-	34.5 (19.8 - 40.3)
Right middle lobe involved		33 (32.7)	-	4.0 (3.0 - 7.0)	40 (39.6)	-	9.5 (6.3 - 12.8)	23 (23.7)	-	36.0 (20.0 - 44.0)
Right lower lobe involved		58 (57.4)	-	4.0 (2.0 - 6.0)	66 (65.3)	-	9.0 (6.0 - 12.0)	52 (53.6)	-	33.5 (20.8 - 38.0)
Left upper lobe involved		46 (45.5)	-	4.0 (2.0 - 7.0)	57 (56.4)	-	9.0 (7.0 - 12.0)	43 (44.3)	-	35.0 (23.0 - 40.0)
Left lower lobe involved		59 (58.4)	-	4.0 (2.0 - 7.0)	70 (69.3)	-	9.0 (6.0 - 12.0)	58 (59.8)	-	33.5 (19.8 - 38.0)

Data are n (%) or median (IQR), unless otherwise specified. [a] N denotes number of data available, whereas n denotes number of data meeting certain criterion. [b] Values at nadir denotes the lowest or the highest values (when appropriate) during hospitalization. Abbreviations: CD, cluster of differentiation; COVID-19, coronavirus disease 2019; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RT-PCR, reverse-transcription polymerase chain reaction.

Table 2. Univariate analysis of risk factors associated with prolonged duration of fever, viral RNA shedding and radiographic resolution.

Risk factors	Prolonged duration of fever (> 10 days)		Prolonged duration of viral RNA shedding (> 14 days)		Prolonged duration of radiographic resolution (> 30 days)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
< 44	Ref		Ref		Ref	
≥ 44	1.05 (0.47 - 2.37)	0.903	2.69 (1.20 - 6.03)	0.016	2.28 (1.01 - 5.18)	0.049
Man	Ref		Ref		Ref	
Female	0.74 (0.33 - 1.67)	0.463	0.82 (0.37 - 1.79)	0.616	2.34 (1.02 - 5.33)	0.044
Yes	0.56 (0.25 - 1.27)	0.167	1.09 (0.50 - 2.38)	0.827	1.34 (0.60 - 3.00)	0.470
No	Ref		Ref		Ref	
Fever						
Yes			4.83 (1.85 - 12.62)	0.001	9.63 (3.02 - 30.73)	< 0.001
No			Ref		Ref	
Yes	2.45 (1.02 - 5.87)	0.045	3.95 (1.67 - 9.31)	0.002	2.06 (0.90 - 4.74)	0.088
No	Ref		Ref		Ref	
< 3.5	2.21 (0.94 - 5.23)	0.070	1.39 (0.60 - 3.21)	0.438	3.73 (1.53 - 9.08)	0.004
≥ 3.5	Ref		Ref		Ref	
< 1.1	5.00 (2.06 - 12.11)	< 0.001	1.05 (0.48 - 2.31)	0.904	6.43 (2.63 - 15.69)	< 0.001
≥ 1.1	Ref		Ref		Ref	
< 500	7.54 (2.90 - 19.61)	< 0.001	1.65 (0.71 - 3.81)	0.241	11.65 (4.21 - 32.25)	< 0.001
≥ 500	Ref		Ref		Ref	
< 10	Ref		Ref		Ref	
≥ 10	3.86 (1.57 - 9.50)	0.003	1.56 (0.70 - 3.45)	0.277	5.21 (2.15 - 12.63)	< 0.001
< 250	Ref		Ref		Ref	
≥ 250	2.68 (1.13 - 6.37)	0.025	1.16 (0.50 - 2.68)	0.726	3.40 (1.40 - 8.29)	0.007
> 30 or undectable in our hospictal	Ref		Ref		Ref	
≤ 30	1.07 (0.48 - 2.42)	0.864	2.17 (0.98 - 4.80)	0.057	1.21 (0.54 - 2.69)	0.643
Number of lobes involved at nadir						
0 or 1	Ref		Ref		Ref	
2 or 3	4.37 (1.18 - 16.25)	0.027	1.22 (0.42 - 3.52)	0.710	6.38 (1.83 - 22.20)	0.004
4 or 5	7.33 (2.19 - 24.50)	0.001	1.92 (0.75 - 4.87)	0.172	9.36 (2.97 - 29.45)	< 0.001
Disease severity status at nadir						
Mild or general	Ref		Ref		Ref	
Severe or critical	6.49 (2.42 - 17.41)	< 0.001	2.23 (0.89 - 5.59)	0.089	4.55 (1.68 - 12.33)	0.003
Lopinavir/ritonavir						
No	Ref		Ref		Ref	
Started on day ≤ 5 of symptom onset	1.89 (0.57 - 6.19)	0.296	1.39 (0.50 - 3.84)	0.527	2.43 (0.83 - 7.13)	0.106
Started on day > 5 of symptom onset	6.86 (2.10 - 22.34)	0.001	4.07 (1.42 - 11.70)	0.009	4.40 (1.45 - 13.32)	0.009
Chloroquine						
No	Ref		Ref		Ref	
Started on day ≤ 5 of symptom onset	0.14 (0.04 - 0.52)	0.003	1.10 (0.41 - 2.97)	0.846	0.16 (0.05 - 0.49)	0.002
Started on day > 5 of symptom onset	0.67 (0.26 - 1.72)	0.402	4.17 (1.54 - 11.25)	0.005	0.57 (0.22 - 1.48)	0.247
Duration from symptom onset to admission, days						
≤ 3	Ref		Ref		Ref	
> 3	8.44 (3.36 - 21.24)	< 0.001	4.30 (1.84 - 10.07)	0.001	4.94 (2.05 - 11.90)	< 0.001

Abbreviations: CD, cluster of differentiation; CI, confidence interval; OR, odds ratio; RNA, ribonucleic acid; RT-PCR, reverse-transcription polymerase chain reaction.

Table 3. Multivariate analysis of risk factors associated with prolonged duration of fever and radiographic resolution in the main analysis and in sensitivity analysis.

Risk factors	Prolonged duration of fever				Prolonged duration of radiographic resolution			
	Overall (N = 102)		Sensitivity analysis (N = 69)		Overall (N = 97)		Sensitivity analysis (N = 79)	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Gender								
Man					Ref		Ref	
Female					7.43 (1.79 - 30.84)	0.006	6.75 (1.66 - 27.38)	0.008
CD4 on admission/μL								
< 500	6.87 (2.07 - 22.79)	0.002	4.10 (1.17 - 14.38)	0.027	10.14 (2.99 - 34.35)	< 0.001	7.05 (2.05 - 24.18)	0.002
≥ 500	Ref		Ref		Ref		Ref	
Disease severity status								
Mild or general	Ref		Ref		Ref		Ref	
Severe or critical	7.22 (1.92 - 27.13)	0.003	4.44 (1.14 - 17.29)	0.032	7.83 (1.80 - 34.02)	0.006	5.20 (1.21 - 22.30)	0.026
Duration from symptom onset to admission, days								
≤ 3	Ref		Ref		Ref		Ref	
> 3	12.18 (3.42 - 43.42)	< 0.001	7.52 (2.02 - 27.98)	0.003	5.19 (1.53 - 17.62)	0.008	3.89 (1.11 - 13.61)	0.033

Abbreviations: aOR, adjusted odds ratio; CD, cluster of differentiation; CI, confidence interval.

Table 4 Estimated durations between symptom onset and outcomes.

Percentiles	Estimated days (95% CI) since symptom to					
	First radiographic abnormality N =	Peak viral RNA shedding N =	Worst radiographic findings N =	Afebrile N =	Negativity N =	Radiographic resolution N =
5th	1.7 (1.4 - 2.0)	2.1 (1.7 - 2.6)	2.1 (1.5 - 3.2)	3.5 (2.7 - 4.7)	4.6 (3.6 - 6.0)	11.3 (9.0 - 14.7)
25th	3.2 (2.8 - 3.7)	4.0 (3.4 - 4.8)	4.6 (3.6 - 6.0)	6.1 (5.1 - 7.4)	8.4 (7.1 - 9.9)	18.8 (16.1 - 22.2)
50th	5.0 (4.3 - 5.7)	6.4 (5.5 - 7.4)	8.0 (6.7 - 9.4)	9.1 (7.9 - 10.4)	12.7 (11.2 - 14.3)	26.7 (23.8 - 29.9)
75th	7.7 (6.6 - 9.0)	10.1 (8.5 - 11.9)	13.7 (12.1 - 15.2)	13.5 (11.9 - 15.1)	19.2 (17.2 - 21.2)	38.0 (34.6 - 41.1)
95th	14.6 (11.8 - 17.5)	19.8 (15.8 - 24.1)	29.8 (25.1 - 34.3)	23.8 (20.2 - 27.5)	35.0 (29.7 - 40.3)	63.0 (56.0 - 69.3)

Abbreviations: CI, confidence interval. RNA, ribonucleic acid.

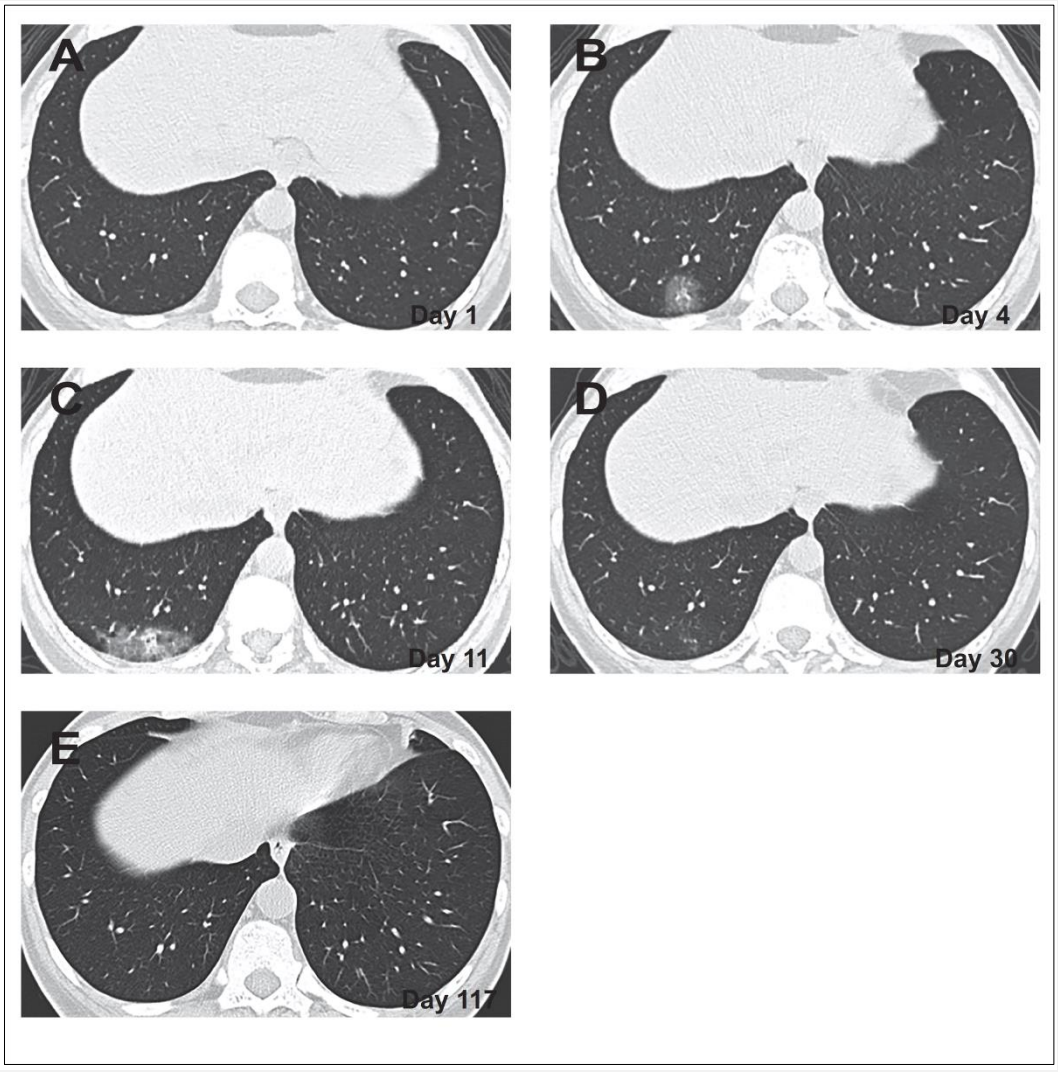

Figure 1. Typical evolution of transverse non-contrast enhanced chest CT findings of COVID-19 in a 48-year-old female presented with fever for 1 day.

(a) Admission CT images on day 1 from symptom onset showed normal baseline appearance.
(b) First abnormal radiologic images on day 4 demonstrated a new area of subpleural GGO with partial consolidation in the right lower lobe.
(c) Worst radiologic findings on day 11 showed an enlarged region of the initial GGO and consolidation.
(d) Radiologic recovery images on day 30 showed that the initial GGO and consolidation were mostly absorbed with minimal residual GGO and linear opacity, no new lesions, crazy-paving patterns, or dense consolidation being observed.
(e) **Chest images on day 117 returned to the baseline appearance and showed that the initial GGO and consolidation were absorbed entirely without residual lesions being observed.**