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Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States

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Data on the detailed clinical progression of COVID-19 in conjunction with epidemiological and virological characteristics are limited. In this case series, we describe the first 12 US patients confirmed to have COVID-19 from 20 January to 5 February 2020, including 4 patients described previously[1–3]. Respiratory, stool, serum and urine specimens were submitted for SARS-CoV-2 real-time reverse-transcription polymerase chain reaction (rRT-PCR) testing, viral culture and whole genome sequencing. Median age was 53 years (range: 21–68); 8 patients were male. Common symptoms at illness onset were cough ($n=8$) and fever ($n=7$). Patients had mild to moderately severe illness; seven were hospitalized and demonstrated clinical or laboratory signs of worsening during the second week of illness. No patients required mechanical ventilation and all recovered. All had SARS-CoV-2 RNA detected in respiratory specimens, typically for 2–3 weeks after illness onset. Lowest real-time PCR with reverse transcription cycle threshold values in the upper respiratory tract were often detected in the first week and SARS-CoV-2 was cultured from early respiratory specimens. These data provide insight into the natural history of SARS-CoV-2. Although infectiousness is unclear, highest viral RNA levels were identified in the first week of illness. Clinicians should anticipate that some patients may worsen in the second week of illness.

Twelve patients with confirmed COVID-19 were identified in six states. Five did not require hospitalization and were isolated at home (patients 1–5) and seven were hospitalized for clinical and public health reasons (patients 6–12) (Fig. 1). Median age was 53 years (range: 21–68); eight patients were male (Table 1). Four of five patients with underlying medical conditions were hospitalized (Table 1,2).

Dates of illness onset ranged from 14 to 29 January 2020. Ten patients traveled to mainland China in the 2 weeks before illness onset, including nine to Wuhan City. Two patients were contacts of US COVID-19 patients in this series[2]. Among all patients, the duration of potential exposure ranged from 5 d to over 1 month; time between last date of possible exposure and illness onset ranged 0–5 d.

The most commonly reported initial signs or symptoms were cough ($n=8$) and fever ($n=7$) (Table 1). Two patients reported neither fever nor cough initially, though they developed them subsequently: one reported sore throat as their initial symptom and the other reported diarrhea (one day before fever and cough); the patient with diarrhea had recently traveled outside the United States before illness onset and later tested positive for *Giardia* and *Clostridiodes difficile*.

Over the course of illness, patients reported cough ($n=12$), subjective or measured fever ($n=9$), diarrhea ($n=3$) and vomiting ($n=2$). Three patients who never reported fever were never hospitalized and remained on home isolation. Of these, one patient reported only cough and rhinorrhea; one reported only cough, which began before travel to China and did not change from the initial onset until resolution; and one reported cough, chills, fatigue, headache and nausea.

The clinical course for each hospitalized patient is described in the Supplementary Information and Extended Data (Extended Data Figs. 1–7). All hospitalized patients were managed using standard, contact and airborne precautions, including eye protection. Median duration of fever was 9 d (range: 2–11). Peak body temperature during hospitalization (range: 99.1–102.9 °F) occurred at a median of illness day 9 (range: 4–10) (Fig. 2). All hospitalized patients had oxygen saturation <94% on room air at some point during their illness, with oxygen saturation nadir (range: 86–93%) occurring at a median of illness day 12 (range: 4–23) (Fig. 2). Five patients reported difficulty in breathing and four received supplemental oxygen (Table 2 and Fig. 1). Patient 9 required high-flow nasal cannula oxygen supplementation and intensive care monitoring. No patients required mechanical ventilation.

Two patients received a short course (≤3 d) of corticosteroids. Three, including one who received corticosteroids, received the investigational antiviral remdesivir (Gilead Sciences) under expanded access (compassionate use) for a duration of 4–10 d. Following remdesivir initiation, all had transient gastrointestinal symptoms, including nausea, vomiting, gastroparesis or rectal bleeding. No other post-remdesivir symptoms were observed. Patient 9 reported loose stool and rectal bleeding; as noted above, this patient had recently traveled outside the United States before illness onset and their stool later tested positive for *Giardia* and *Clostridiodes difficile*. Remdesivir was discontinued after improvement in each patient's respiratory symptoms.

Blood cultures were negative in all six hospitalized patients tested, including those obtained from four patients treated empirically for bacterial pneumonia. Molecular testing for influenza A and B on respiratory specimens was negative and multipathogen respiratory PCR panels were negative for all targets in all hospitalized patients (Table 2).

Six of seven hospitalized patients had leukopenia (<4,000 cells per μl) and the white blood cell count nadir occurred at a median of illness day 9 (range: 4–15) (Fig. 2). Procalcitonin levels were <0.25 ng ml^{-1} in all six patients tested. Aminotransferase levels were elevated in all hospitalized patients: aspartate aminotransferase (AST) levels peaked (median peak value 129 U l^{-1}, range 46–190 U l^{-1}) at a median of illness day 13 (range 7–19) and alanine aminotransferase (ALT) levels peaked (median peak value 136 U l^{-1},

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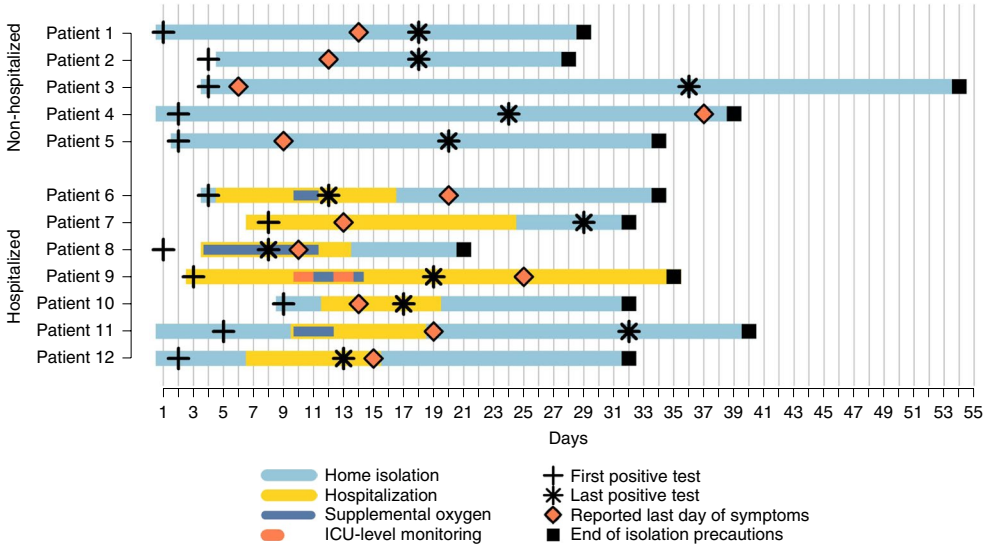

Fig. 1 | Timeline of illness onset, SARS-CoV-2 RNA detection, hospitalization, oxygen requirement and reported symptom resolution among the first 12 patients with COVID-19 in the United States, January to February 2020. Patients 1–5 were not hospitalized and patients 6–12 were hospitalized. Days are sequential from day of symptom onset (day 1). Light blue bars indicate time patients were under home isolation. Yellow bars indicate duration of hospitalization. Dark blue bars indicate duration of supplemental oxygen administration in hospital. The orange dashed bar indicates duration of intensive care unit (ICU)-level monitoring for patient 9. The black '+' indicates collection date of the earliest sample that tested positive for SARS-CoV-2 by rRT-PCR. The black asterisk indicates collection date of the latest sample tested by CDC with a positive result for SARS-CoV-2 by rRT-PCR. The orange diamond indicates date of last report of symptoms. The black square indicates the last day of isolation precautions. Patient 9 was isolated in a healthcare facility for the full time period; they were discharged from the first healthcare facility on day 27 and subsequently transferred to a second healthcare facility for public health purposes. Patient 1 reported a cough with initial onset in mid-December before the patient traveled to China. The patient reported no change in the cough from the initial onset until reported resolution on day 14. Because onset date was difficult to determine for this patient, we have used date of detection as day 1 to assess viral RNA detection.

range 66–389 U l^{-1}) at a median of illness day 14 (range: 6–23). Three of seven hospitalized patients had mildly elevated alkaline phosphatase levels >115 U l^{-1} (maximum value 163 U l^{-1}). Elevated lactate dehydrogenase levels >600 U l^{-1}, coinciding with clinical deterioration, were observed in two patients tested. No major elevations in serum total bilirubin (seven patients tested) or prolongations in prothrombin time (four patients tested) were identified. Among the three remdesivir recipients, aminotransferase elevation developed in patient 6, 1 d after starting remdesivir and in patient 8, 4 d after starting remdesivir. Patient 9 had an aminotransferase peak before starting remdesivir and a second peak 5 d after starting remdesivir.

Unilateral or bilateral opacities were seen on chest imaging for all hospitalized patients (Table 2). Four hospitalized patients had normal initial chest radiographs (illness day range: 4–9). One had an abnormal chest computed tomography scan on the day of the normal chest radiograph.

All 12 patients had initial respiratory specimens collected between illness days 1–9 (median, day 4) and all but one tested positive in ≥2 respiratory specimen types (Fig. 3). Viral culture was attempted on initial respiratory specimens from nine patients and was successful for all nine, including two patients who were not hospitalized (Fig. 3); viable SARS-CoV-2 was cultured at day 9 of illness (patient 10), but was not attempted on later specimens. SARS-CoV-2 real-time PCR with reverse transcription (rRT–PCR) cycle threshold (Ct) values of virus isolated from the first tissue culture passage were 12.3–35.7 and for one patient, virus isolated from tissue culture passage 3 had a titer of 7.75×10^6 median tissue culture infectious dose per ml (Supplementary Table 1); these data were likely more reflective of growth in tissue culture than patient viral load.

Overall, 448 specimens were collected from the 12 patients throughout the course of illness and tested at the US Centers for Disease Control and Prevention (CDC). All 12 patients had SARS-CoV-2 RNA detected in at least one nasopharyngeal (NP) swab, 11 of 12 in an oropharyngeal (OP) swab, 6 of 6 in sputum, 1 of 11 in serum, 7 of 10 in stool and 0 of 10 in urine (Fig. 3). Among 117 pairs of simultaneous NP and OP specimens, 45 (38%) had discordant results. Among 32 discordant pairs with one positive specimen, the NP specimen was positive in 21 (66%). Thirteen additional discordant pairs had one negative and one inconclusive specimen. SARS-CoV-2 RNA was detected at a maximum of day 32 in NP specimens, day 36 in OP specimens, day 29 in sputum and day 25 in stool (Fig. 3). Two patients provided sputum specimens after NP and/or OP specimens tested negative and sputum continued to be positive in both patients. In patient 7, viral RNA was detected in sputum 17 d after the last positive OP specimen and ≥2 weeks after reported symptom resolution. In seven patients who had SARS-CoV-2 RNA detected in stool, most detections occurred when viral RNA was still detectable in the respiratory tract. Among three patients who reported diarrhea, all had viral RNA detected in stool.

Mean Ct values in positive specimens were 17.0–39.0 for NP, 22.3–39.7 for OP and 24.1–39.4 for stool. Ct values of upper respiratory tract specimens were lower in the first week of illness than the second in most patients (Extended Data Fig. 8); in some patients, low Ct values continued into the second and third week of illness. SARS-CoV-2 rRT–PCR results turned positive in serum of patient 9 in the second week of illness at the time of rapid clinical deterioration.

Ct values and duration of RNA detection in the upper respiratory tract did not seem to differ by hospitalization status or oxygen requirement.

All patients reported symptom resolution (Fig. 1). Eleven patients reported cough (often intermittent) as the last symptom. Median symptom duration was 14 d (range: 6–37). SARS-CoV-2 RNA was detected after reported symptom resolution in 7 of 12 patients, including in NP ($n=6$), OP ($n=3$), sputum ($n=1$) and

Table 1 | Demographic characteristics, exposure history and clinical characteristics of the first 12 patients with COVID-19 in the United States, January to February 2020

	Values ($N=12$)	
Median age (range) – years	53	(21–68)
	n/N	%
Male sex – no.	8/12	67
State – no.		
California	6/12	50
Illinois	2/12	17
Arizona	1/12	8
Massachusetts	1/12	8
Washington	1/12	8
Wisconsin	1/12	8
Initial source of case identification – no.		
Outpatient clinic/urgent care	4/12	33
Emergency department	4/12	33
Health department[a]	2/12	17
Port of entry	1/12	8
Close contact active monitoring	1/12	8
Exposure history (≤14 d before illness onset)		
Travel to mainland China – no.	10/12	83
Travel to Wuhan, Hubei Province, China – no.	9/12	75
Exposure to a confirmed US COVID-19 patient – no.	2/12	17
Underlying medical conditions – no.	5/12	42
Cardiac disease[b] – no.	2/12	17
Hypertension – no.	2/12	17
Diabetes mellitus – no.	1/12	8
Chronic lung disease – no.	1/12	8
High cholesterol – no.	2/12	17
Fatty liver disease – no.	1/12	8
Hepatitis B – no.	1/12	8
Current tobacco use – no.	1/12	8
Symptoms reported at illness onset[c] – no.		
Fever	7/12	58
Subjective	5/7	71
Measured (≥100.4 °F or 38 °C)	2/7	29
Cough[d]	8/12	67
Fatigue	5/12	42
Shortness of breath (dyspnea)	1/12	8
Sore throat	1/12	8
Headache	3/12	25
Runny nose (rhinorrhea)	1/12	8
Chills	1/12	8
Diarrhea	1/12	8
Nausea	1/12	8
Days of first sample collection, median (range) ($n=12$)	4	(1–9)
Highest level of healthcare utilization – no.		
Outpatient clinic or urgent care	2/12	17
Emergency department	3/12	25
Hospitalized	7/12	58
Abnormal chest radiograph – no.	7/9	78

[a]Includes one person who was a contact of a confirmed COVID-19 patient. [b]Includes coronary artery disease and pacemaker for bradycardia. Reports of hypertension were not included. [c]Initial symptoms were obtained through patient interview and may have differed from symptoms at the time of identification. [d]One patient reported a cough with initial onset in mid-December before the patient traveled to China. The patient reported no change in the cough from the initial onset until resolution 2 weeks after SARS-CoV-2 was first detected.

stool ($n=3$) specimens. Home isolation or Transmission-Based Precautions were discontinued for all patients per CDC criteria[4]; the last respiratory specimens tested at CDC with a positive test result were collected from these patients on days 8–36 (median = day 19).

Complete genome sequences were generated from respiratory specimens from all 12 patients. The sequences had >99% nucleotide identity to 85 reference sequences of SARS-CoV-2 genomes; phylogenetic tree analysis identified a few distinct subgroups (Extended Data Fig. 9) that were not divergent from each other, suggesting that these patients were identified during an early stage of the outbreak.

We describe the first 12 patients with confirmed COVID-19 in the United States, including clinical course of the first 7 hospitalized patients. Ten patients had traveled to China, including nine to Wuhan City and two had close contact with a US COVID-19 patient. Illness ranged from mild to moderately severe and hospitalized patients showed signs of clinical worsening in the second week. All patients recovered and three patients tolerated treatment with the investigational antiviral remdesivir. SARS-CoV-2 RNA was detected in upper and lower respiratory specimens, stool and serum. The highest viral RNA levels in the upper respiratory tract were typically detected in the first week of illness, and viable SARS-CoV-2 was cultured from early respiratory specimens. Viral RNA was detected after reported symptom resolution for seven patients, although the implications for infectiousness and transmission later in illness are unclear. SARS-CoV-2 genome sequencing and phylogenetic analysis from these 12 patients' respiratory tract specimens support a recent zoonotic transmission event and subsequent human-to-human transmission.

The clinical manifestations described here reflect the milder end of the full disease spectrum. Severe illness and death has since been reported in the United States[5–7]. Among hospitalized patients in this report, the second week of illness was characterized by clinical or laboratory signs of worsening including hypoxemia or elevation of aminotransferases. Although some patients received empiric antibiotics for possible secondary bacterial pneumonia, we found definitive evidence of bacterial co-infection. Worsening in the second week of illness is consistent with previous reports[8,9] and highlights the importance of close monitoring beyond the first week, even in patients with mild illness or no initial radiographic abnormalities.

Patient 9, the most severely ill among this series, experienced clinical deterioration late in the second week of illness. This was the only patient with SARS-CoV-2 RNA detected in serum and detection in serum was temporally related to clinical deterioration. Similar observations have been described previously[10,11]. Increased proinflammatory cytokines have been observed in patients with COVID-19[8] and it is possible that cytokine dysregulation and endothelial dysfunction contribute to both clinical worsening and SARS-CoV-2 RNA detection in serum.

We detected viral RNA and cultured virus from upper respiratory specimens, even from patients with predominantly lower respiratory tract illness. Ct values in upper respiratory tract specimens typically were lowest during the first week of illness (suggesting high RNA levels), consistent with previous reports[11–14]. SARS-CoV-2 RNA was detected in upper respiratory tract specimens for 2–3 weeks in most patients and for as long as 36 d. Sputum specimens were less frequently available; in two patients with a productive cough and available sputum, viral RNA was detected in sputum longer than in NP or OP specimens. We detected SARS-CoV-2 RNA in stool of multiple patients and in the serum of one hospitalized patient.

SARS-CoV-2 RNA levels and duration of RNA detection in the upper respiratory tract did not seem to vary by illness severity and viral RNA was detected after reported symptom resolution in several patients. More data are needed to better understand how duration of RNA detection, RNA levels and presence of viable virus are related to symptom progression, illness severity and infectiousness.

Table 2 | Clinical characteristics of the first seven patients hospitalized with COVID-19 in the United States, January to February 2020[a]

Characteristic	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Age group (years)	30–39	60–69	60–69	30–39	50–59	50–59	50–59
Sex	Male	Female	Male	Male	Male	Male	Female
Underlying medical conditions	Hypertriglyceridemia	Hypertension, hyperlipidemia, pacemaker for bradycardia	Tobacco use, hypertension, coronary artery disease, COPD, history of lung cancer status post partial lobectomy	Type 2 diabetes mellitus, fatty liver	None	None	None
Reported symptoms on illness day 1	Cough, subjective fever	Fatigue, subjective fever	Productive cough, worsening shortness of breath, fatigue, subjective fever	Diarrhea[b]	Dizziness, cough, nasal congestion, subjective fever	Fever, fatigue, cough	Fever, headache
rRT-PCR positive extrapulmonary sites	Stool	Stool	None	Serum, stool	None	Stool	Stool
Initial normal CXR (d)	Yes (4, 7)	Yes (7)	No	Yes (4)	Yes (9)	No	No
First abnormal chest imaging findings (d)	Left basilar opacity (9)	Multifocal infiltrates, mediastinal and hilar lymphadenopathy[c] (7)	Right lower lobe infiltrate (4)	Patchy and linear opacities in the bilateral mid and lower lung fields (7)	Bilateral mid and lower lung consolidations (12)	Bilateral patchy lower lung opacities (10)	Opacification of the left lower lung (7)
T_{max}, °F (d)	102.9 (7, 9, 11)	100.8 (10)	99.2 (4, 5)	102.7 (9)	99.1 (9)	102.6 (10)	102.4 (9)
Lowest SpO_2, % (d)	90 (10, 12)	93 (23, 24)	88 (4)	87 (12)	93 (13, 14)	86 (12)	92 (11)
Maximum O_2 support received, l min^{-1}	2	None	4	20, HFNC	None	3	None
Peak AST, U l^{-1} (d)	129 (13)	46 (19)	47 (11)	99 (7)	190 (13)	167 (12)	163 (14)
Peak ALT, U l^{-1} (d)	219 (13)	66 (23)	75 (12)	136 (6)	389 (15)	248 (14)	127 (14)
Lowest WBC count, cells per μl (d)	3,300 (9)	3,000 (8, 12, 19)	3,400 (4)	3,900 (5)	3,900 (13)	5,700 (15)	2,400 (10)
Highest procalcitonin, ng ml^{-1} (d)	<0.05 (9, 11)	<0.10 (8)	Not tested	0.21 (10)	0.13 (13)	0.13 (10, 11)	0.07 (14)
Molecular test results for other viral pathogens (d)	PCR negative for adenovirus; coronavirus 229E/HKU1/NL63/OC43; HMPV; influenza A & B; parainfluenza 1–4; RSV; rhino/enterovirus; (4)	PCR negative for adenovirus; coronavirus 229E/HKU1/NL63/OC43; HMPV; influenza A & B; parainfluenza 1–4; RSV; rhino/enterovirus; (7)	PCR negative for adenovirus; coronavirus 229E/HKU1/NL63/OC43; HMPV; influenza A & B; parainfluenza 1–4; RSV; rhino/enterovirus; (4)	PCR negative for adenovirus; coronavirus 229E/HKU1/NL63/OC43; HMPV; influenza A & B; parainfluenza 1–4; RSV; rhino/enterovirus; (3)	PCR negative for adenovirus; coronavirus 229E/HKU1/NL63/OC43; HMPV; influenza A & B; parainfluenza 1–4; RSV; rhino/enterovirus; (9)	PCR negative for adenovirus; HMPV; influenza A & B; RSV; parainfluenza 1–3; rhinovirus; (10)	PCR negative for adenovirus; HMPV; influenza A & B; RSV; parainfluenza 1–3; rhinovirus (7)
Blood cultures (collection day)	Negative (7, 8, 9)	Negative (7)	Negative (4)	Negative (10)	Not collected	Negative (10)	Negative (7)
Antibiotics (d)	Vancomycin (10–11) Cefepime (10–12)	Levofloxacin (8–14)	Ceftriaxone (4– 11) Azithromycin (4– 8)	Metronidazole (33–42)	None	Ceftriaxone (9) Azithromycin (9)	None
Indication for antibiotics	Hospital-acquired pneumonia	Community-acquired pneumonia	Community-acquired pneumonia	*Giardia lamblia* *Clostridioides difficile*	n/a	Community-acquired pneumonia	n/a
Received remdesivir[d] (d)	Yes (11–15)	No	Yes (7–10)	Yes (11–20)	No	No	No
Symptoms and signs following remdesivir	Nausea; gastroparesis; elevated aminotransferase levels	n/a	Mild nausea and abdominal discomfort at start of infusion; elevated aminotransferase levels	Loose stools; one episode of bloody stool; elevated aminotransferase levels	n/a	n/a	n/a
Other medications received (day(s); indication)	Benzonatate capsules Acetaminophen Ibuprofen Dextromethorphan Guaifenesin Ondansetron Lorazepam	Methylprednisolone 40 mg i.v. Q8H (day 8–9) Prednisone 40 mg orally daily (day 9–10); nystatin (day 15–24; oral thrush)	Methylprednisolone (40 mg i.v. × 1) Prednisone 40 mg (orally × 1) (day 5–6; COPD exacerbation) Furosemide (day 5–13); nystatin (day 10–13; oral thrush)	Oseltamivir (day 3–5; empiric treatment while COVID-19 test pending); furosemide (day 10–11; worsening hypoxia)	Acetaminophen PRN Ibuprofen PRN Melatonin PRN	Acetaminophen PRN	Acetaminophen PRN

n/a, not applicable; COPD, chronic obstructive pulmonary disease; CXR, chest radiograph; HFNC, high-flow nasal cannula; HMPV, human metapneumovirus; i.v., intravenously; PRN, as needed; Q8H, every 8 h; RSV, respiratory syncytial virus. [a]All reported days are illness day. [b]Patient 9 reported diarrhea 1 d before development of fever and cough. [c]Chest computed tomography scan; findings for other patients are reported from chest radiographs. [d]Remdesivir dose: 200 mg i.v. once on day 1, then 100 mg i.v. daily.

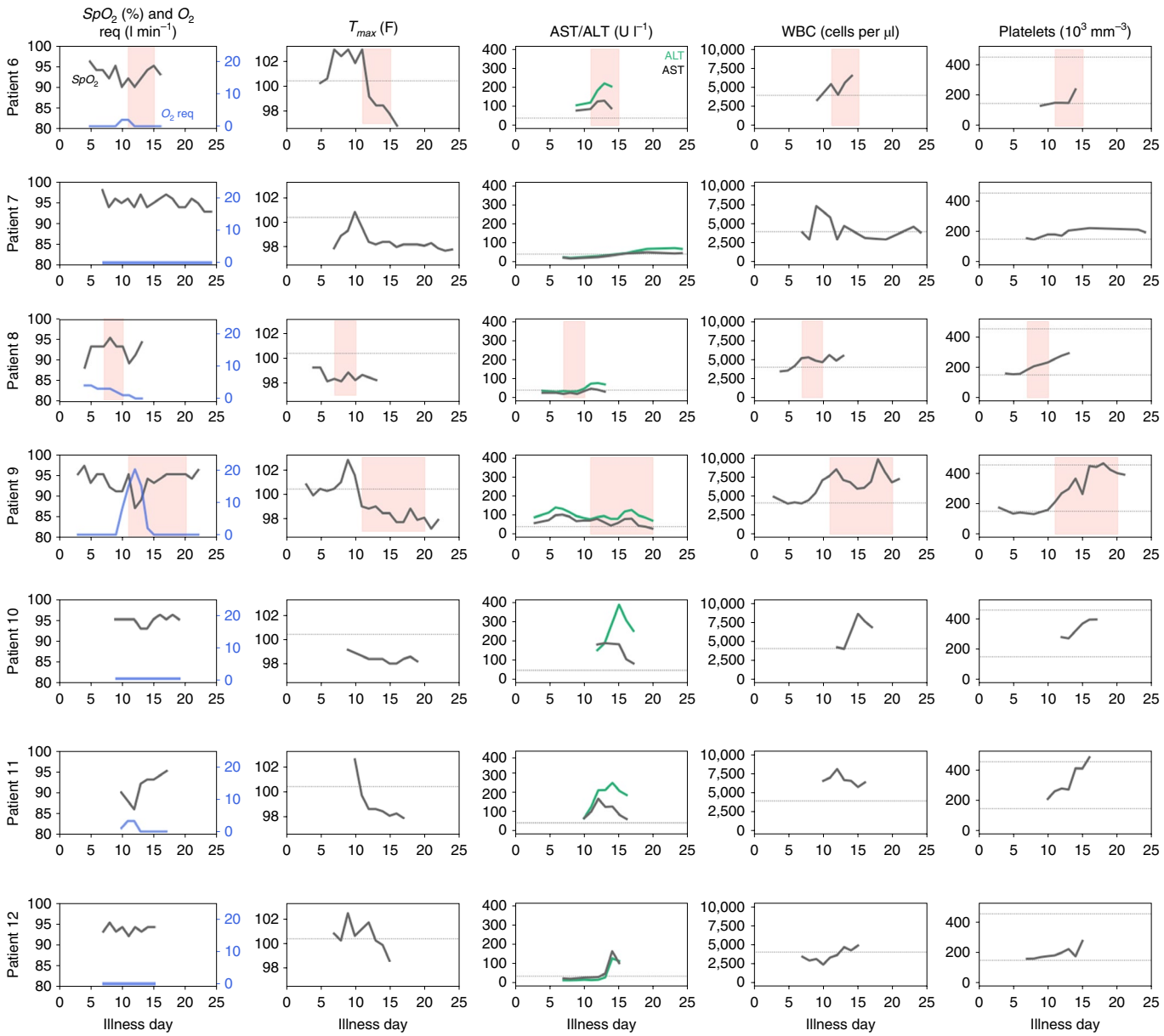

Fig. 2 | Clinical and laboratory values by illness day for the first seven patients hospitalized with COVID-19 in the United States, January to February 2020. Clinical and laboratory values collected during hospitalization are shown for seven hospitalized patients by illness day. Values include oxygen saturation (SpO_2), supplemental oxygen requirement (O_2 req), maximum body temperature (T_{max}), AST, ALT and white blood cell (WBC) count. Pink shading indicates days of remdesivir administration for three patients. Dotted lines show fever threshold of 100.4 °F (T_{max}), 40 U l^{-1} for AST and ALT, 4,000 cells per μl for WBC and 150 and 250 10^3 mm^{-3} for platelets.

Three hospitalized patients received the investigational antiviral remdesivir under expanded access (compassionate use) at the time of clinical worsening based upon a decision by each patient's clinician. Remdesivir inhibits viral replication through premature termination of RNA transcription[15,16]. In vitro studies have demonstrated that remdesivir inhibits SARS-CoV-2 replication in nonhuman cells[17]. Because remdesivir use was not given as part of a randomized controlled trial, we are unable to assess effectiveness or safety. Randomized controlled trials of remdesivir are underway[18–20]. Two hospitalized patients received corticosteroids. The World Health Organization and CDC advise against use of corticosteroids unless indicated for another reason[21].

Our investigation has several limitations. Our patient sample is small, and results may not be generalizable. Information from patient interviews may have been subject to response bias. The threshold for hospitalization in these early cases was likely low because of uncertainty about COVID-19 clinical course. Illness resolution dates may be imprecise due to nonspecific lingering symptoms or symptoms from chronic or unrelated conditions. Clinical laboratory tests and radiographic studies were ordered as a part of routine patient care and were not collected systematically. SARS-CoV-2 RNA detection does not necessarily reflect the presence of infectious virus and rRT–PCR Ct values may have varied due to specimen collection or handling.

Characterization of the first 12 COVID-19 patients identified in the United States provides insight into the epidemiology, clinical characteristics and natural history of SARS-CoV-2 infection. Although duration of infectiousness is unclear, these early data

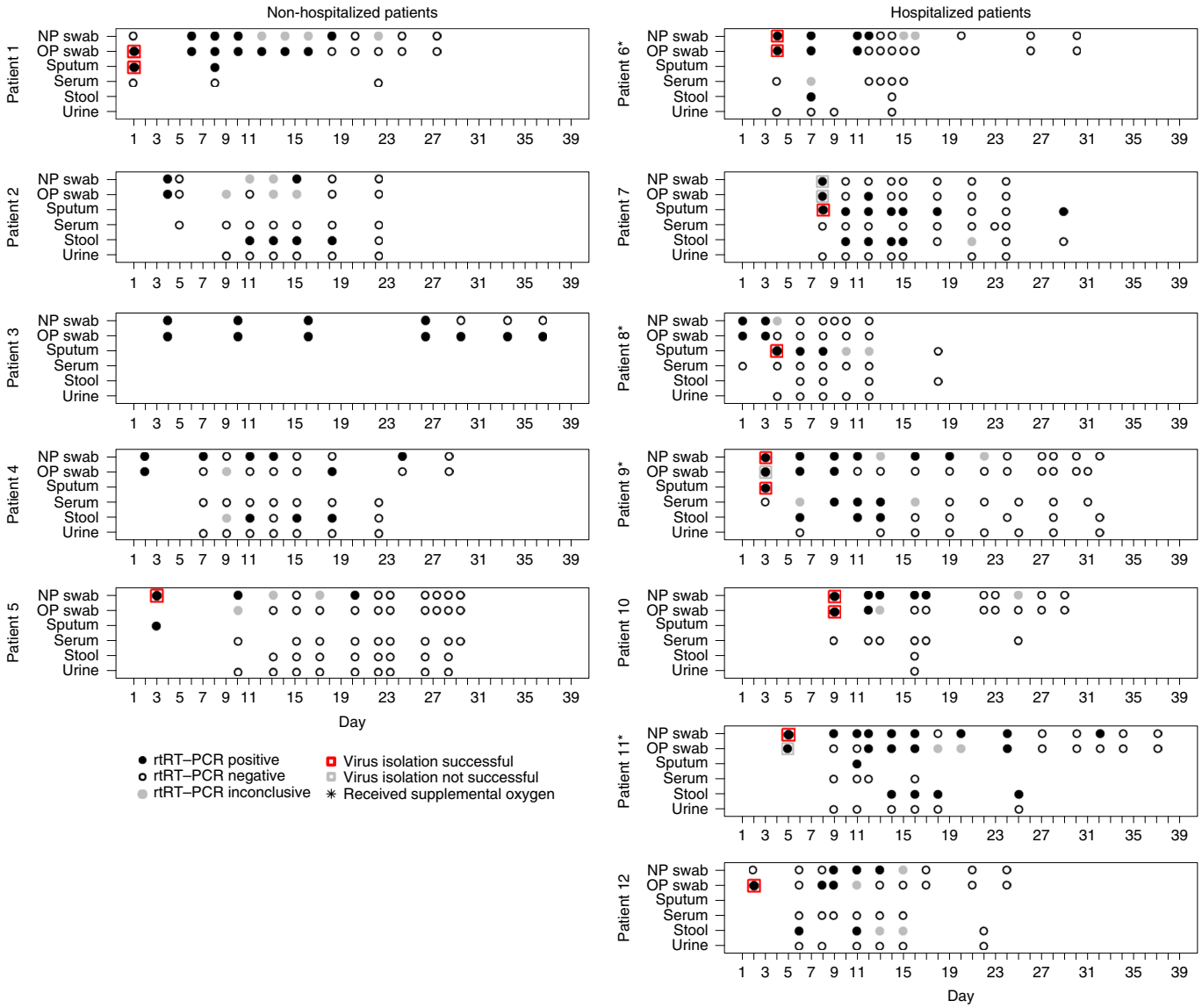

Fig. 3 | SARS-CoV-2 rRT-PCR results by specimen type and day among the first 12 patients with COVID-19 in the United States, January to February 2020. Specimen types tested include NP swab, OP swab, sputum, serum, stool and urine. Days are sequential from day of symptom onset (day 1). Viral culture was attempted on selected respiratory specimens collected early in the course of illness. rRT-PCR results were reported as positive (all three targets positive), negative (all three targets negative) or inconclusive (only one or two positive targets). Black-filled circles indicate rRT-PCR-positive specimens. Black-outlined circles indicate rRT-PCR-negative specimens. Gray-filled circles indicate specimens with inconclusive rRT-PCR results. Red squares surrounding black-filled circles indicate rRT-PCR-positive specimens from which viral culture was successful. Gray squares surrounding black-filled circles indicate rRT-PCR-positive specimens from which viral culture was unsuccessful. An asterisk indicates patients who required supplemental oxygen.

show viable virus can be cultured readily from upper respiratory tract specimens soon after illness onset; further studies on infectious period and risk factors for transmission are needed. Clinicians should anticipate that some patients may worsen in the second week of illness, but appropriate monitoring of these patients will present challenges as healthcare systems work to meet the increasing demands. Studies are urgently needed to better characterize risk factors for and early indicators of severe disease. Randomized controlled trials of therapeutic options and their effects on clinical outcomes and infectiousness are critical to guide clinical and public health management. Additional investigations to understand clinical course, immunological response, SARS-CoV-2 RNA detection, viral culture and transmission, will inform clinical management and public health strategies to prevent the spread of disease.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-020-0877-5.

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Methods

CDC's Human Research Protection Office determined that this work was exempt from human participants' research regulations as it involved identification, control or prevention of disease in response to an immediate public health threat. Patient consent was waived. Forms were approved under Office of Management and Budget, number 0920-1011.

Local health departments, in consultation with clinicians, identified patients under investigation (PUIs) for COVID-19 beginning 17 January 2020. PUI testing criteria changed during this period but included the presence of fever and/or lower respiratory symptoms (for example, cough or shortness of breath) and at least one epidemiological risk factor in the 2 weeks before symptom onset. Between 17 and 31 January 2020, epidemiological risk factors were travel from Wuhan City, close contact with a patient with laboratory-confirmed COVID-19 or currently under investigation for COVID-19 (refs. [22,23]). Beginning 1 February 2020, epidemiological risk factors changed to close contact with a patient with confirmed COVID-19 or history of travel from mainland China[24]. During both time periods, close contact was defined as being within 6 feet for a prolonged period of time[25] or contact with respiratory secretions[26]. Close contacts of patients with confirmed COVID-19 were identified by local and state health departments and monitored for illness. Specimens from PUIs, including symptomatic close contacts, were tested for SARS-CoV-2 at CDC[27].

Upper respiratory tract (NP and OP) and available lower respiratory tract (sputum) specimens were collected and tested for SARS-CoV-2 RNA by rRT–PCR[28]. A case of COVID-19 was defined as identification of laboratory-confirmed SARS-CoV-2 in ≥1 specimen from a patient. We included COVID-19 patients confirmed by CDC between 20 January 2020 and 5 February 2020; the size of this convenience sample was not predetermined and we aimed to describe the first cases as soon as possible. Patients sought outpatient or inpatient care at local facilities; some were transferred or referred to facilities that had specifically prepared to receive patients with COVID-19.

Patients were interviewed by public health officials about demographics, exposures, travel history and symptoms, including signs or symptoms before presentation. For all patients, available medical records were reviewed. For hospitalized patients, clinicians systematically abstracted data from the medical record.

Illness day 1 was defined as the first day of reported COVID-19 signs and symptoms; collection date of the first SARS-CoV-2-positive specimen was used for one patient with no clear symptom onset date. When prehospital symptoms or onset dates in the medical record differed from those reported from the public health interview, the latter were used. Results for virological tests were reported relative to illness day 1. Duration of potential exposure to SARS-CoV-2 was defined as dates of travel to China or dates of first to last exposure to a US patient with COVID-19. Fever was defined as feeling feverish or measuring body temperature ≥100.4 °F. We requested collection of NP swabs, OP swabs, sputum (if available), serum, urine and stool every 2–3 d throughout infection.

Multiple clinical and laboratory observations were included from each of the 12 patients. No associations between clinical or laboratory data and outcomes were tested statistically. Data were analyzed and visualized using Excel in Microsoft Office 365, SAS v.9.4, R v.3.6.2 and Python v.3.7.3 (refs. [29–32]).

CDC evaluated specimens using SARS-CoV-2 RNA detection, viral culture, whole genome sequencing and phylogenetic analysis.

All patient specimens were tested for the presence of SARS-CoV-2 RNA by rRT–PCR targeting three regions of the gene encoding the nucleocapsid protein[28]. The rRT–PCR results were reported as positive (all targets positive), negative (all targets negative) or inconclusive (only one or two positive targets). If an initial result was inconclusive, the specimen was re-tested; if both tests were inconclusive, the final result was reported as inconclusive. For inconclusive results, a positive detection of SARS-CoV-2 could not be definitively ruled out. If available, Ct values, which are approximately inversely related to the RNA levels in each specimen[33], were reported as the mean of three reported Ct values. Results from serial rRT–PCR testing were not immediately available to inform clinical management.

Viral culture was attempted from early SARS-CoV-2-positive respiratory specimens (NP, OP or sputum) with Ct values <33. Specifically, 100 µl of clinical specimens were diluted twofold across a 96-well plate in serum-free DMEM supplemented with 2× penicillin–streptomycin and 2× amphotericin B (Sigma). Vero CCL-81 cells were trypsinized and resuspended in DMEM + 10% FBS + 2× penicillin–streptomycin + 2× amphotericin B at 2.5 × 105 cells per ml. A 100-µl cell suspension was added directly to the clinical specimen dilutions and mixed gently by pipetting. The inoculated cultures were grown in a humidified 37 °C incubator with 5% CO_2 and observed for cytopathic effect daily. When cytopathic effect was observed, presence of SARS-CoV-2 was confirmed by rRT–PCR.

Nucleic acid was extracted from respiratory specimens (NP, OP or sputum) positive for SARS-CoV-2 rRT–PCR and used for whole genome sequencing on both Sanger and Oxford Nanopore MinION sequencing platforms. For Sanger sequencing, 37 sets of individual nested PCR assays spanning the entire 2019-nCoV genome were designed based on the reference sequence, GenBank accession number NC045512. PCR amplicons were sequenced in both directions using Big Dye 3.1 cycle sequencing kits (Thermo Fisher Scientific) on an ABI 3730 Automated Capillary Sequencer (Thermo Fisher Scientific) with PCR primers and additional internal primers. The consensus sequences were generated from both sequencing directions using Sequencher 5.4.6 (Gene Codes Corporation). For Nanopore sequencing, individual PCR amplicons were pooled and barcoded by sample, which were used for library preparation using the Ligation Sequencing kit (Oxford Nanopore Technologies). Libraries were run on a MinION sequencer and consensus sequences were generated using minimap v.2.17 and samtools v.1.9 (refs. [34,35]).

Full genome sequences from the 12 confirmed cases in this report and 85 full genome sequences (as of 11 February 2020) available from GenBank and the Global Initiative on Sharing All Influenza Data database were aligned using MAFFT v.7.450 (ref. [36]). Sequences with obvious early stop codons were excluded. Phylogenetic trees were then inferred with the maximum likelihood method using the Hasegawa Kishino Yano nucleotide substitution model with γ-distributed rate variation among sites (HKY + G) and 1,000 bootstrap replicates implemented in Geneious Prime (Biomatters) and MEGA X[37,38].

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Viral sequences generated during the current study are available in the GENBANK repository (GenBank accession numbers: MN997409 (Pt 1), MT044258 (Pt 2), MT039888 (Pt 3), MT027064 (Pt 4), MT039887 (Pt 5), MT020880 (Pt 6), MN988713 (Pt 7), MT044257 (Pt 8), MN994467 (Pt 9), MN994468 (Pt 10), MT027062 (Pt 11), MT027063 (Pt 12); GISAID numbers: 406223 (Pt 1), 410044 (Pt 2), 409067 (Pt 3), 408010 (Pt 4), 408670 (Pt 5), 407214 (Pt 6), 404253 (Pt 7), 410045 (Pt 8), 406034 (Pt 9), 406036 (Pt 10), 408008 (Pt 11) and 408009 (Pt 12)). GISAID sequences can be accessed at www.gisaid.org. Other datasets of clinical and laboratory data presented in the current study may be available from the corresponding author on request.

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Author contributions

All authors meet authorship criteria and approve of publication. C.M.M. and K.K.W. had full access to all data in the study and take responsibility for the integrity of data and accuracy of data analysis. C.M.M., S.A.K., A.J.H., A.F., S.I.G., J.T.W., S.T., N.J.T. and S.L. contributed to the concept and design of the investigation and follow-up of all patients to describe epidemiological, clinical and virological characteristics; K.K.W., J.P.C., L.E., R.R.G and T.M.U. contributed to the concept and design of the in-depth clinical investigation of hospitalized patients. All authors contributed to the acquisition, analysis or interpretation of data. S.A.K., K.K.W, J.P.C, L.E., M.E.K. and C.M.M. drafted the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content. S.A.K., K.K.W., M.E.K., G.R.A, A.U. and C.M.M. contributed to statistical analysis and data visualization. C.M.M., A.F., A.J.H., M.A.R., S.T., N.J.T. and S.L. contributed to the supervision of the investigation and follow-up of all patients to describe epidemiological, clinical and virological characteristics; T.M.U. supervised the in-depth clinical investigation of hospitalized patients.

Competing interests

The authors declare no competing interests.

Additional information

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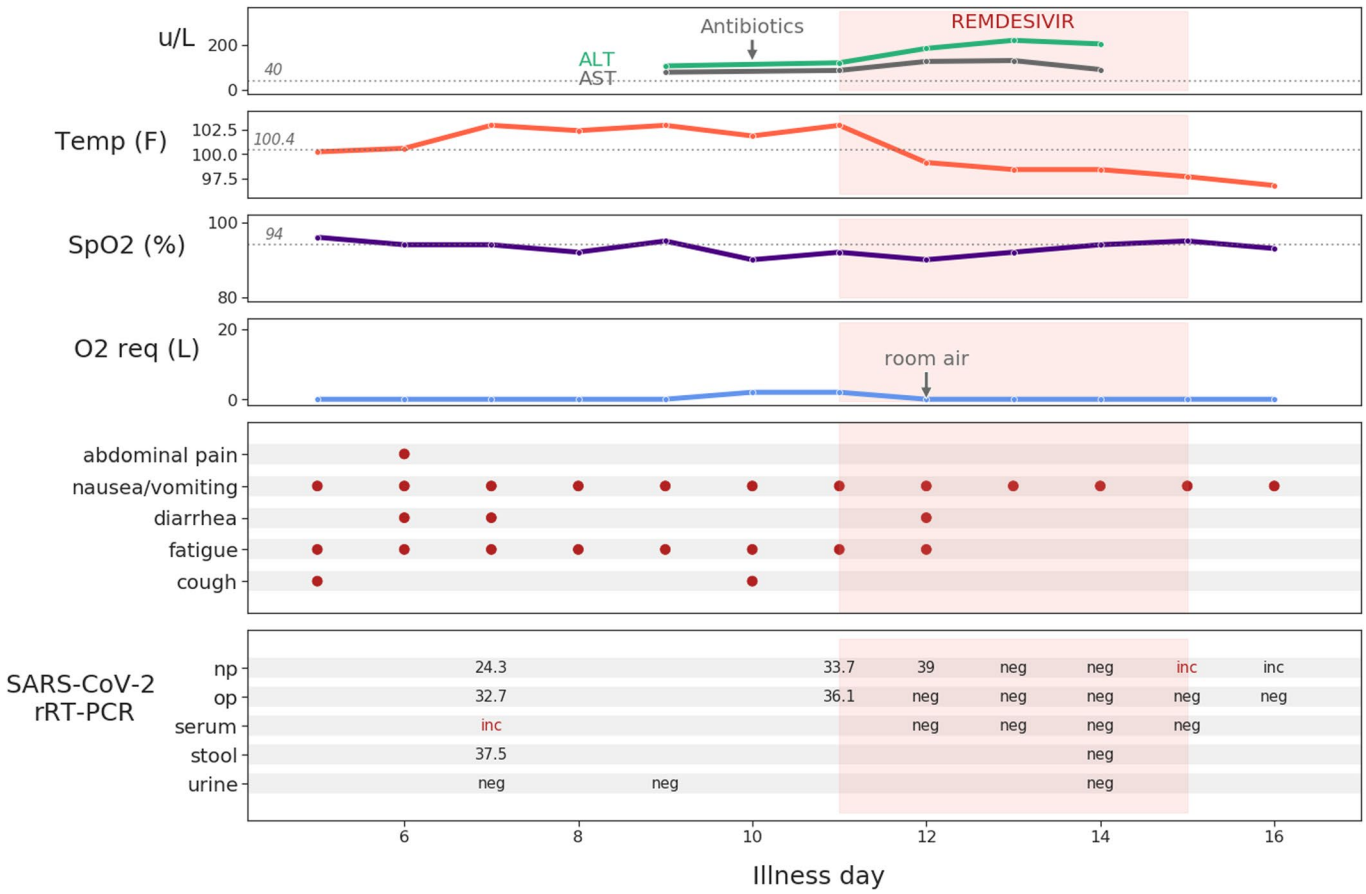
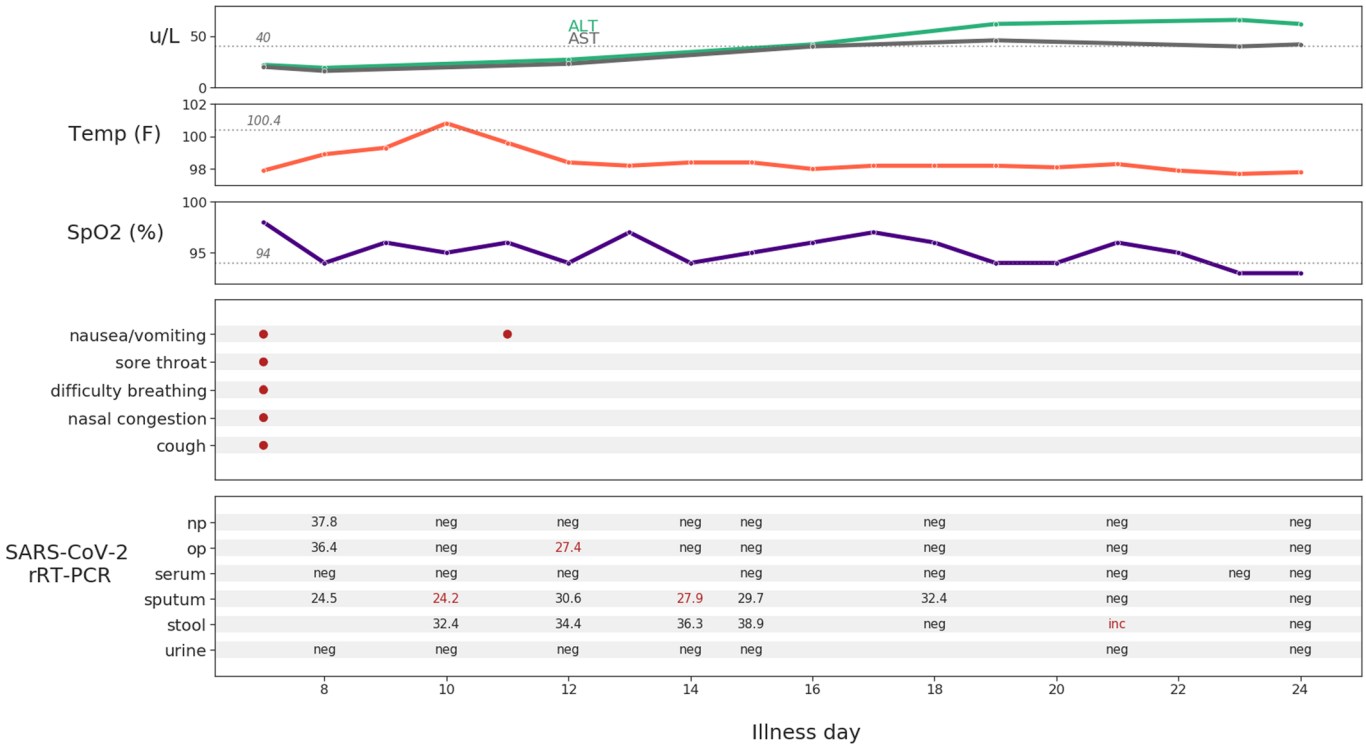
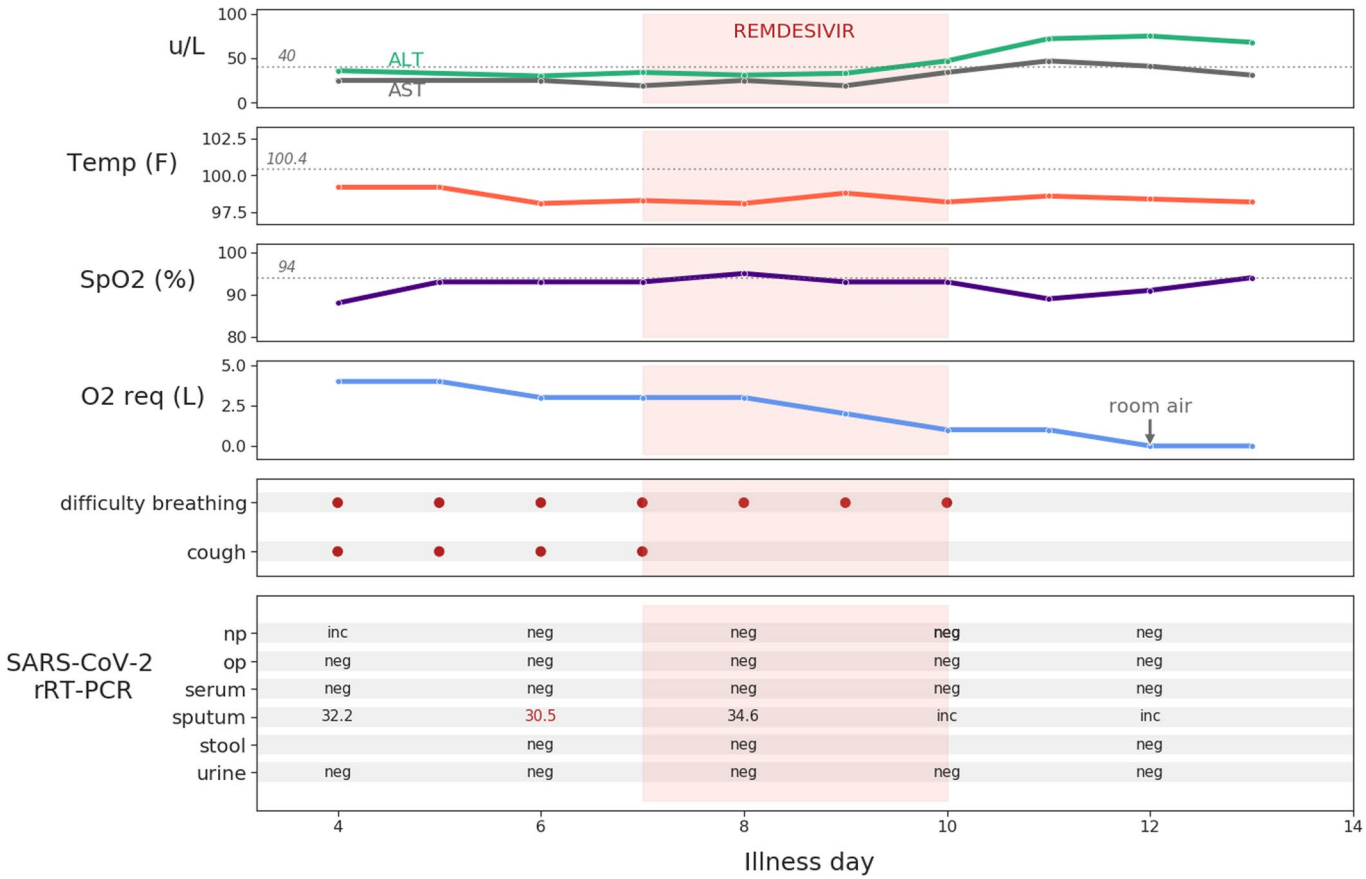


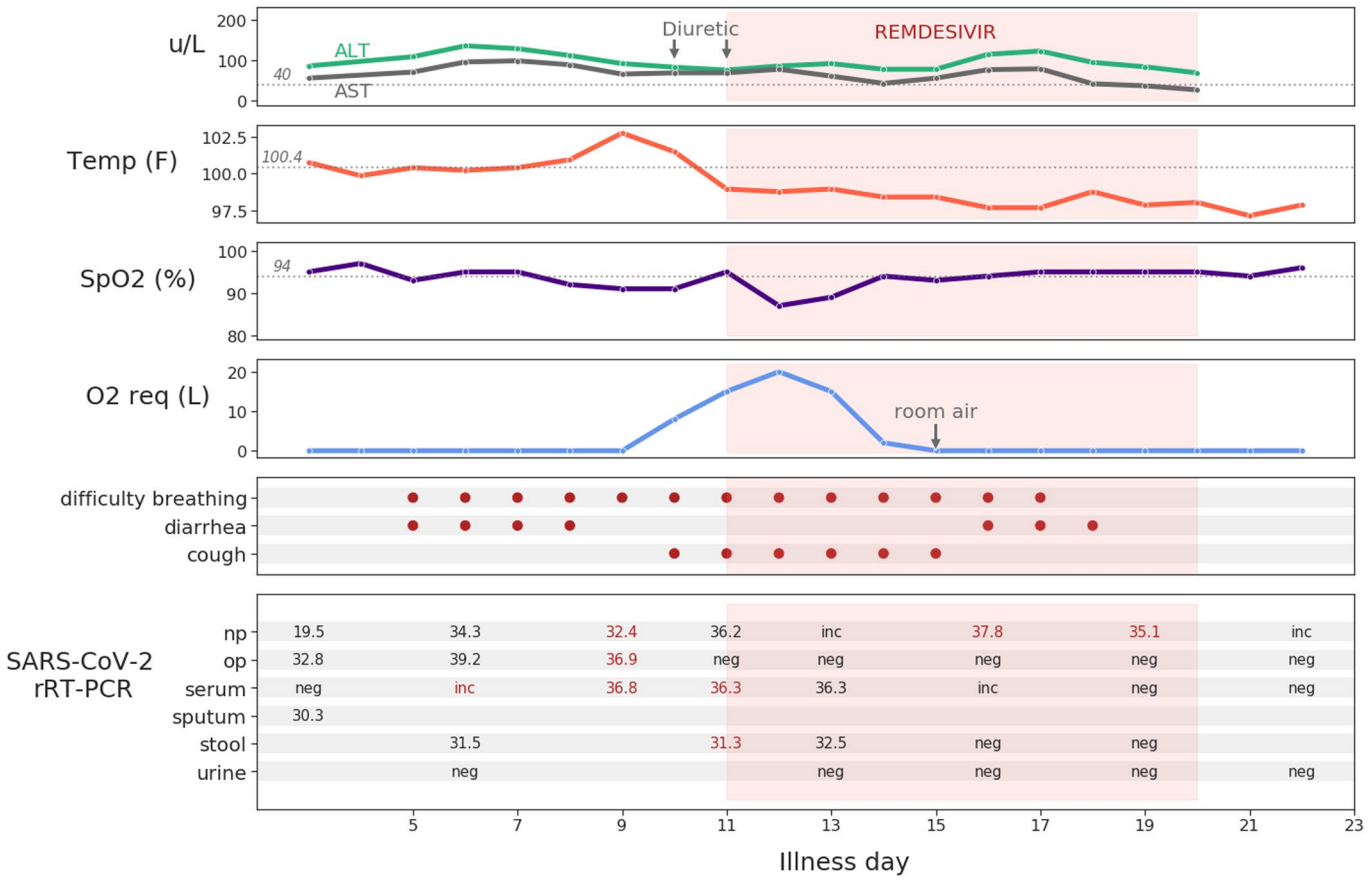
Extended Data Fig. 1 | Patient 6 laboratory and clinical values, symptoms, and SARS-CoV-2 rRT-PCR results during hospitalization. Aminotransferase levels, maximum daily body temperature, minimum daily oxygen saturation, maximum daily oxygen requirement, symptoms, and rRT-PCR results are shown for hospitalization. Pink shading indicates remdesivir administration. Cycle threshold (Ct) values are shown for positive rRT-PCR tests. Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; SpO2, oxygen saturation; op, oropharyngeal; np, nasopharyngeal; neg, negative; inc, inconclusive.



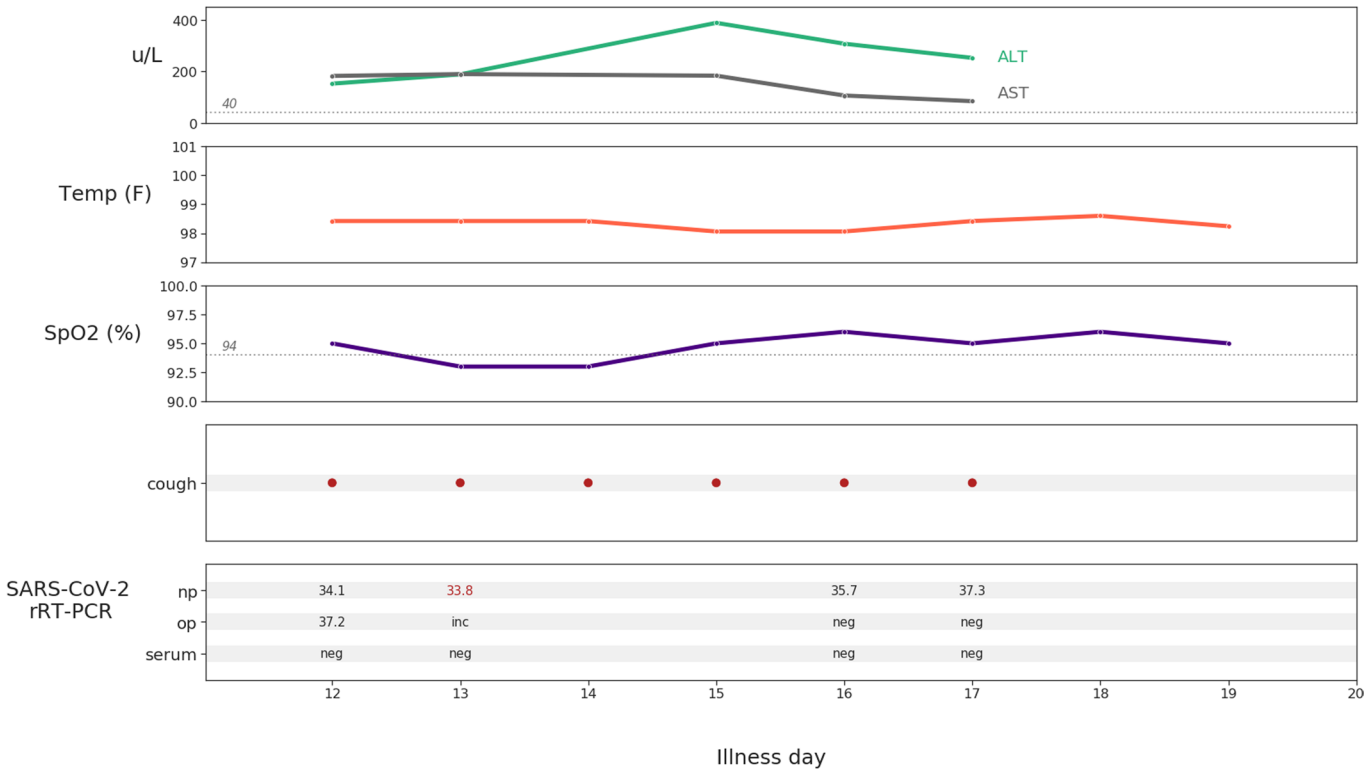
Extended Data Fig. 2 | Patient 7 laboratory and clinical values, symptoms, and SARS-CoV-2 rRT-PCR results during hospitalization. Aminotransferase levels, maximum daily body temperature, minimum daily oxygen saturation, symptoms, and rRT-PCR results are shown for hospitalization. Cycle threshold (Ct) values are shown for positive rRT-PCR tests. Red text indicates decreasing Ct values. Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; SpO2, oxygen saturation; op, oropharyngeal; np, nasopharyngeal; neg, negative; inc, inconclusive.



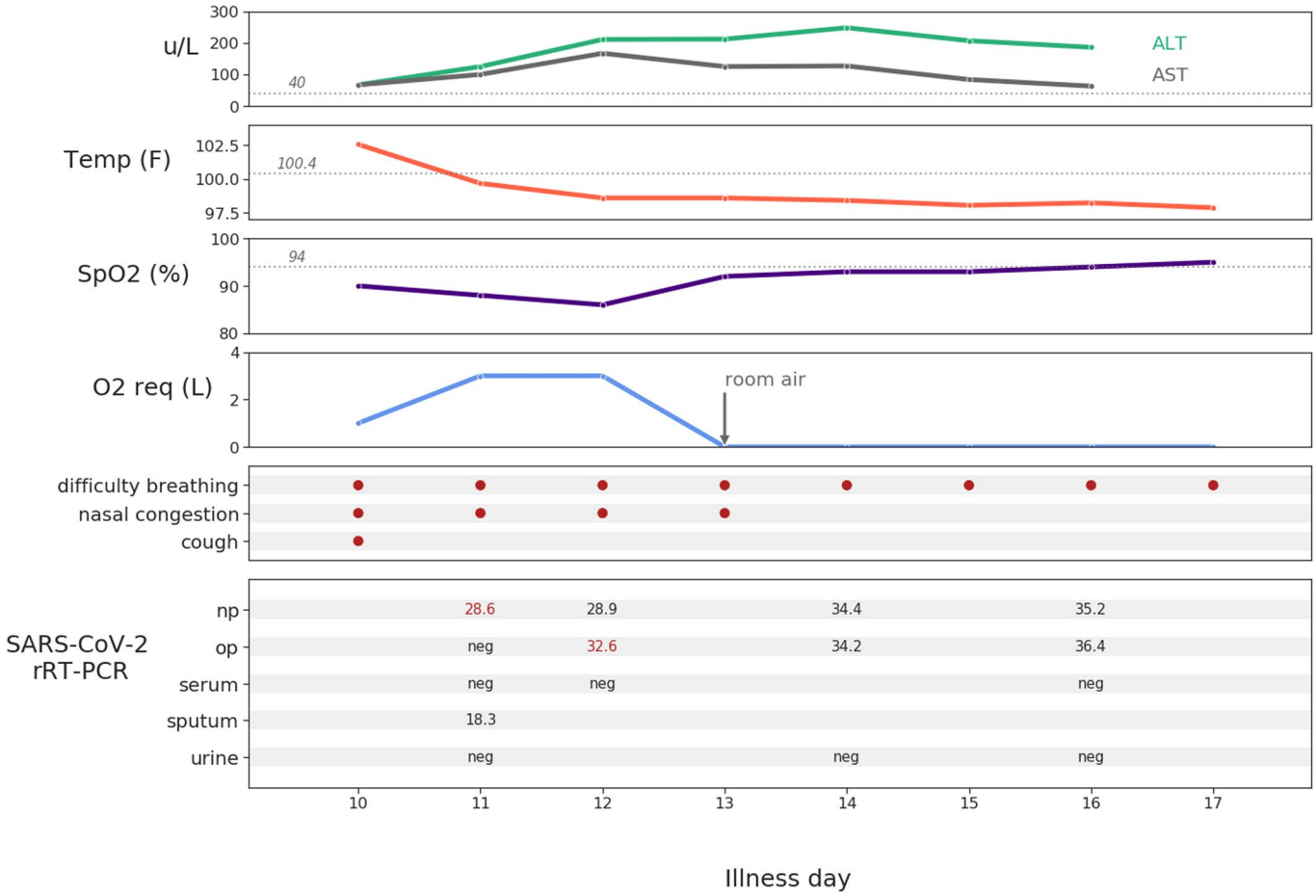
Extended Data Fig. 3 | Patient 8 laboratory and clinical values, symptoms, and SARS-CoV-2 rRT-PCR results during hospitalization. Aminotransferase levels, maximum daily body temperature, minimum daily oxygen saturation, maximum daily oxygen requirement, symptoms, and rRT-PCR results are shown for hospitalization. Pink shading indicates remdesivir administration. Cycle threshold (Ct) values are shown for positive rRT-PCR tests. Red text indicates decreasing Ct values. Patient has a chronic cough that had returned to baseline starting day 11. Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; SpO2, oxygen saturation; op, oropharyngeal; np, nasopharyngeal; neg, negative; inc, inconclusive.



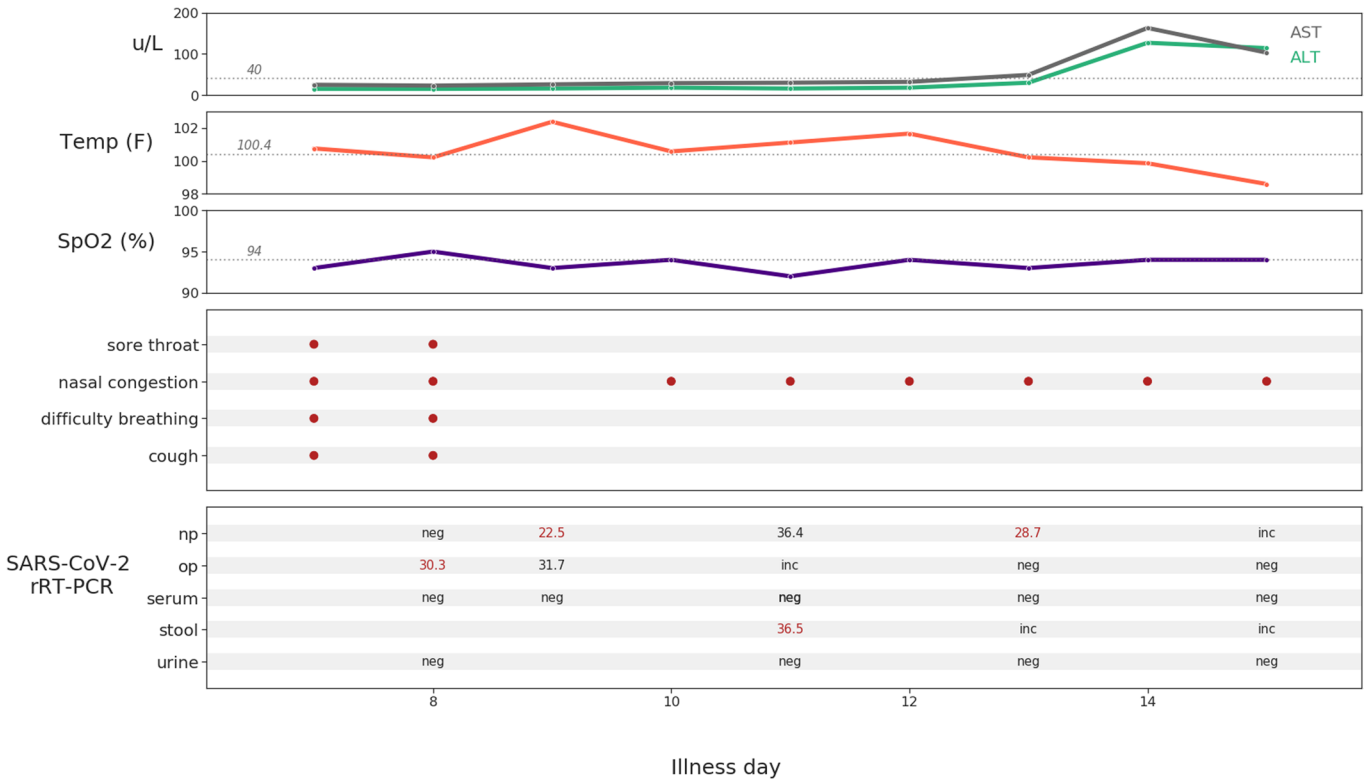
Extended Data Fig. 4 | Patient 9 laboratory and clinical values, symptoms, and SARS-CoV-2 rRT-PCR results during hospitalization. Aminotransferase levels, maximum daily body temperature, minimum daily oxygen saturation, maximum daily oxygen requirement, symptoms, and rRT-PCR results are shown for hospitalization. Pink shading indicates remdesivir administration. Cycle threshold (Ct) values are shown for positive rRT-PCR tests. Red text indicates decreasing Ct values. Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; SpO2, oxygen saturation; op, oropharyngeal; np, nasopharyngeal; neg, negative; inc, inconclusive.



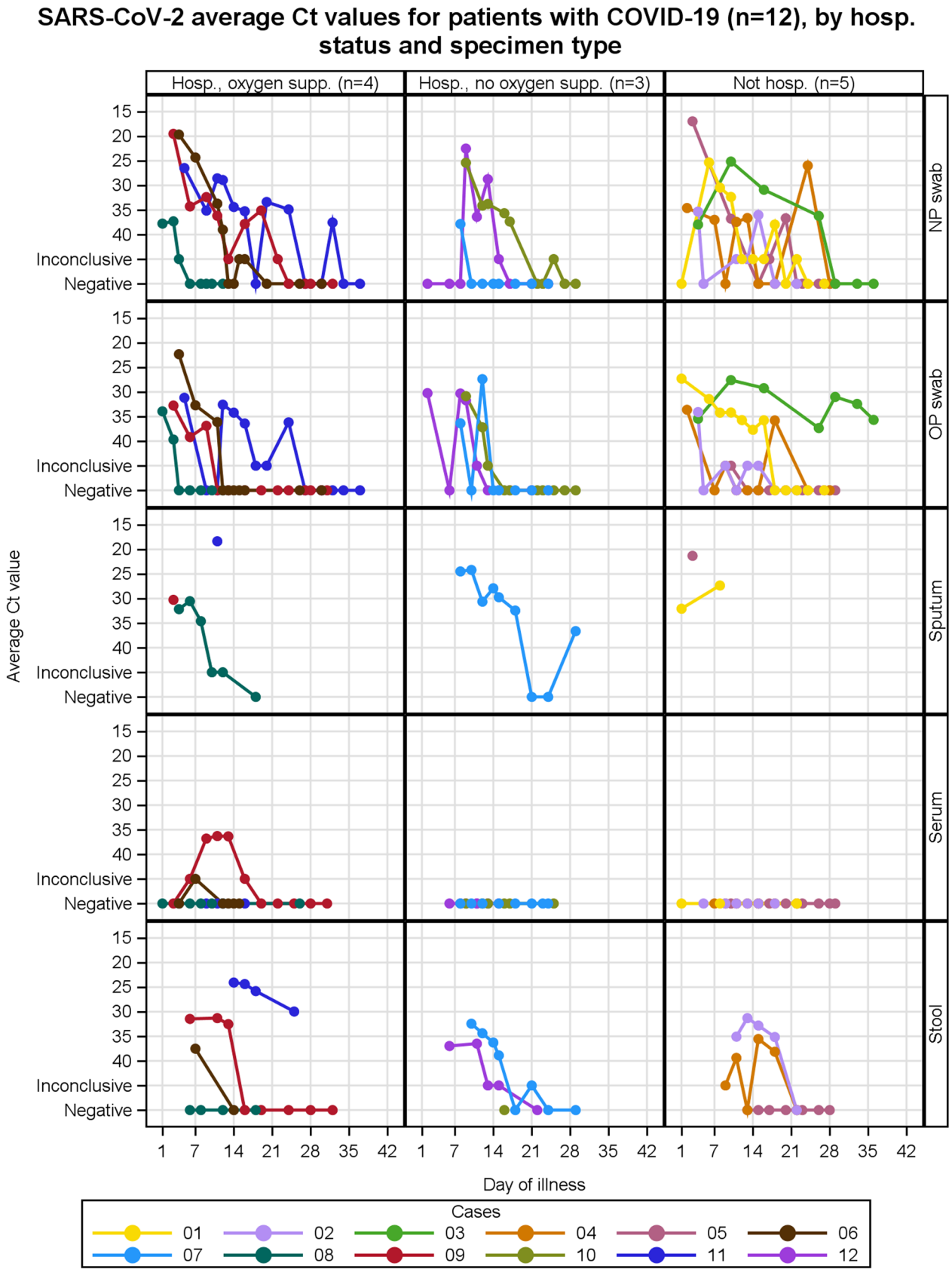
Extended Data Fig. 5 | Patient 10 laboratory and clinical values, symptoms, and SARS-CoV-2 rRT-PCR results during hospitalization. Aminotransferase levels, maximum daily body temperature, minimum daily oxygen saturation, maximum daily oxygen requirement, symptoms, and rRT-PCR results are shown for hospitalization. Cycle threshold (Ct) values are shown for positive rRT-PCR tests. Red text indicates decreasing Ct values. Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; SpO2, oxygen saturation; op, oropharyngeal; np, nasopharyngeal; neg, negative; inc, inconclusive.



Extended Data Fig. 6 | Patient 11 laboratory and clinical values, symptoms, and SARS-CoV-2 rRT-PCR results during hospitalization. Aminotransferase levels, maximum daily body temperature, minimum daily oxygen saturation, maximum daily oxygen requirement, symptoms, and rRT-PCR results are shown for hospitalization. Cycle threshold (Ct) values are shown for positive rRT-PCR tests. Red text indicates decreasing Ct values. The patient had a positive nasopharyngeal swab on day 9 with Ct value of 35.1 (not shown). Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; SpO2, oxygen saturation; op, oropharyngeal; np, nasopharyngeal; neg, negative; inc, inconclusive.

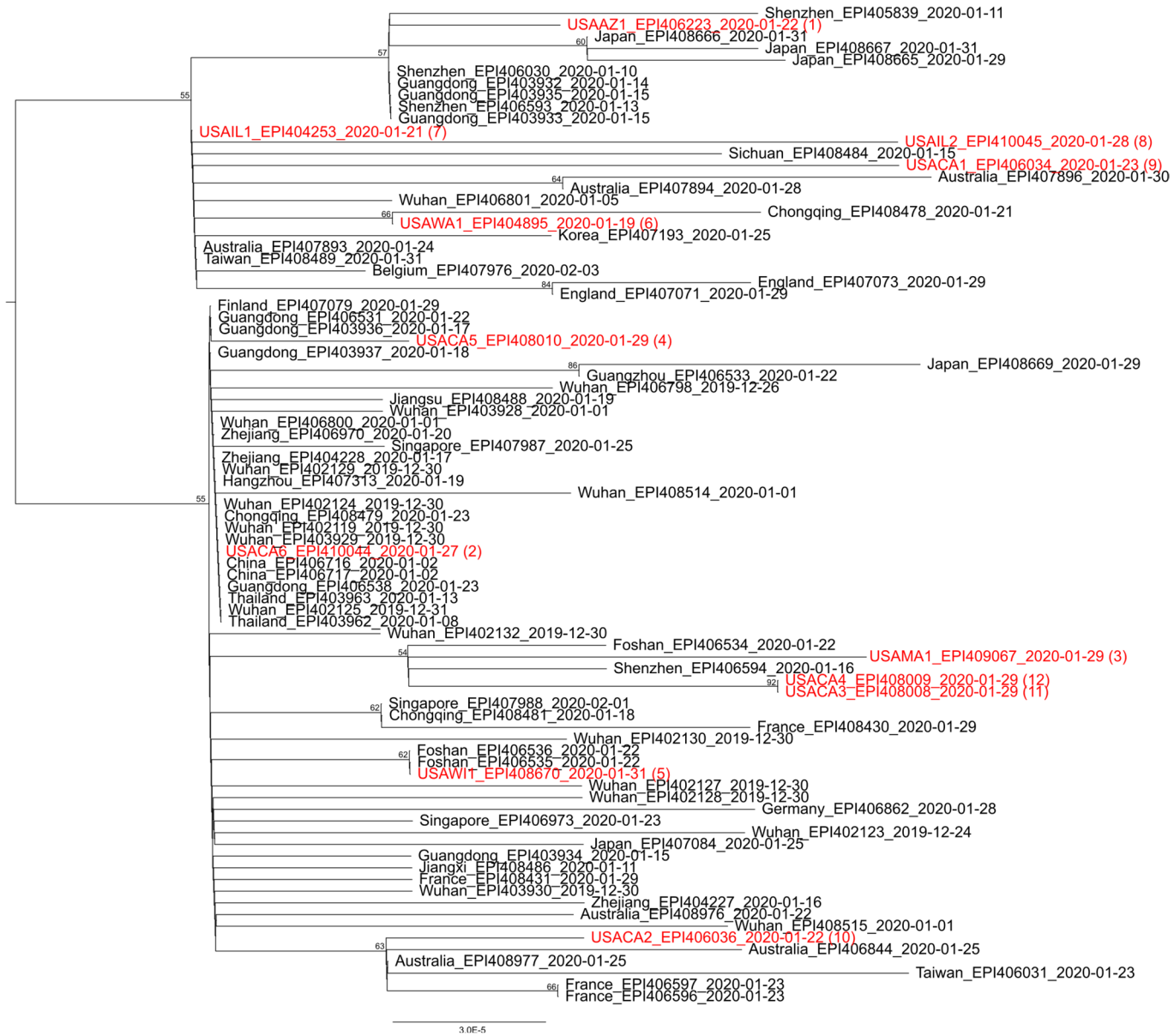


Extended Data Fig. 7 | Patient 12 laboratory and clinical values, symptoms, and SARS-CoV-2 rRT-PCR results during hospitalization. Aminotransferase levels, maximum daily body temperature, minimum daily oxygen saturation, maximum daily oxygen requirement, symptoms, and rRT-PCR results are shown for hospitalization. Cycle threshold (Ct) values are shown for positive rRT-PCR tests. Red text indicates decreasing Ct values. Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; SpO2, oxygen saturation; op, oropharyngeal; np, nasopharyngeal; neg, negative; inc, inconclusive.



Extended Data Fig. 8 | See next page for caption.

Extended Data Fig. 8 | SARS-CoV-2 average Ct values for patients with COVID-19, by hospitalization status and specimen type. For rRT-PCR-positive specimens, the average cycle threshold (Ct) value was calculated from the Ct values of three targets on the gene encoding the N protein. 'Not detected' indicated rRT-PCR-negative specimens. Inconclusive specimens were depicted as such; average Ct values were not calculated for these specimens. Categories for illness severity included **a**, not hospitalized, **b**, hospitalized with no supplemental oxygen, and **c**, hospitalized with supplemental oxygen. Specimen types depicted included nasopharyngeal (NP) swab, oropharyngeal (OP) swab, sputum, serum, and stool. Urine was not depicted because no specimens tested positive by rRT-PCR. Days are sequential from day of symptom onset (Day 1).



Extended Data Fig. 9 | Phylogenetic tree. A maximum-likelihood tree of SARS-CoV2 using selected full genome sequences from GISAID as of February 12, 2020. Strains are denoted by country (city for China when available), GISAID accession ID, date of collection and Patient ID in parentheses. Tips in red denote sequences from US cases. Bootstrap values of statistical support (50%) are shown as percentage equivalents.

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☒	☐ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐ A description of all covariates tested
☒	☐ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☒	☐ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	MinION data collected using MinKNOW 3.1.0.30. Raw data was basecalled with Guppy 3.2.8. Reads were size-filtered using seqtk 1.3 and mapped to reference (Genbank MN908947.3) using minimap2 v2.17. Primer sequences were removed using BAMClipper 1.0.0. Variants were called with bcftools 1.9 and applied using vcf_mask_lowcoverage.pl (https://github.com/CDCgov/SARS-CoV-2_Sequencing/tree/master/protocols/CDC-Comprehensive/scripts).
Data analysis	For phylogenetic analyses, sequencing data were analyzed with: Geneious Prime (BioMatters Inc., San Diego, CA) and Mega X (Kumar S, Strecher G, Li M, Knyaz C, and Tamura K (2018); MEGA X: Molecular Evolutionary Genetics Analysis across computing platforms, https://doi.org/10.1093/molbev/msy096); and Fig Tree v1.4.3 (http://tree.bio.ed.ac.uk/software/figtree/, Andrew Rambaut). Other data were analyzed and visualized using Excel in Office 365, SAS 9.4, R 3.6.2, and Python 3.7.3

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Virus sequences generated during the current study are available in the GENBANK repository (GenBank accession numbers: MN997409 (Pt 1), MT044258 (Pt 2), MT039888 (Pt 3), MT027064 (Pt 4), MT039887 (Pt 5), MT020880 (Pt 6), MN988713 (Pt 7), MT044257 (Pt 8), MN994467 (Pt 9), MN994468 (Pt 10), MT027062 (Pt 11), MT027063 (Pt 12); GISAID numbers: 406223 (Pt 1), 410044 (Pt 2), 409067 (Pt 3), 408010 (Pt 4), 408670 (Pt 5), 407214 (Pt 6), 404253 (Pt 7), 410045 (Pt 8),

406034 (Pt 9), 406036 (Pt 10), 408008 (Pt 11), 408009 (Pt 12)). Other datasets of clinical and laboratory data presented in the current study may be available from the corresponding author on request.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We have characterized the first 12 cases that were identified in the United States during a public health response; we included COVID-19 patients confirmed by CDC during January 20–February 5, 2020; the size of this convenience sample was not predetermined, and we aimed to describe the first cases as soon as possible.
Data exclusions	No cases or data were excluded from this analysis.
Replication	Data were verified by multiple authors, but this descriptive analysis on 12 cases was not replicated.
Randomization	This is not relevant to our descriptive investigation performed during a public health response.
Blinding	This was not relevant to our descriptive investigation performed during a public health response.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Vero CCL-81 cells from ATCC
Authentication	ATCC uses morphology, karyotyping, and PCR based approaches to confirm the identity of human cell lines and to rule out both intra- and interspecies contamination. These include an assay to detect species specific variants of the cytochrome C oxidase I gene (COI analysis) to rule out inter-species contamination and short tandem repeat (STR) profiling to distinguish between individual human cell lines and rule out intra-species contamination
Mycoplasma contamination	We test our cells for mycoplasma with Lookout PCR detection kit. Cell lines tested negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Human research participants

Policy information about studies involving human research participants

Population characteristics	Median age was 53 years (range: 21–68); eight patients were male.
Recruitment	Patients were identified as part of a public health response. The sample size was small, and results are not generalizable.

Ethics oversight	CDC collaborated with state and local health departments in the public health response to COVID-19 cases. This activity involved identification, control, or prevention of disease in response to an immediate public health threat; it was determined not to be public health research. Therefore, this activity did not require human subject/IRB review.

Note that full information on the approval of the study protocol must also be provided in the manuscript.