Confirmed or Unconfirmed Cases of 2019 Novel Coronavirus Pneumonia in Italian Patients: A Retrospective Analysis of Clinical Features

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Research article

Keywords: Pneumonia, COVID-19, Clinical and laboratory findings, Outcomes

Posted Date: June 29th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-35575/v1

Version of Record: A version of this preprint was published on October 19th, 2020. See the published version at https://doi.org/10.1186/s12879-020-05504-7.

Abstract

This study was aimed to compare clinical features of 165 Italian patients with laboratory confirmed or unconfirmed 2019-nCoV (also termed SARS-CoV-2) pneumonia. On March 31 2020, hospitalized patients who presented with fever and/or respiratory symptoms, exposures, and presence of lung imaging features consistent with 2019-nCoV pneumonia, were included. Before admission to a hospital ward, patients underwent RT-PCR based SARS-CoV-2 RNA detection in their nasopharyngeal swab samples. Of 165 patients studied, 119 had positive RT-PCR results and 46 were RT-PCR negative for two days or longer (i.e., when the last swab sample was obtained). The median age was 70 years (IQR, 58–78), and 123 (74.6%) of 165 patients had at least one comorbidity. The majority of patients (101/165, 61.2%) had a mild pneumonia, and the remaining patients (64/165, 38.8%) a severe/critical pneumonia. We did not find any substantial difference in symptoms, incubation periods, and radiographic/CT abnormalities as well as in many of the biological abnormalities recorded. However, at multivariable analysis, higher concentrations of hemoglobin (OR, 1.34; 95% CI, 1.11—1.65; *P* = 0.003) and lactate dehydrogenase (OR, 1.00; 95% CI, 0.99—1.01; *P* = 0.05), and lower counts of leukocytes (OR, 0.81; 95% CI, 0.72—0.90; *P* <0.001) were independently associated with confirmed COVID-19 diagnosis. While mortality rates were similar, patients with confirmed diagnosis were more likely to receive antivirals (95% vs 19.6%, *P* <0.001) and to develop ARDS (63% vs 37%, *P* = 0.003) than those with unconfirmed COVID-19 diagnosis. In conclusion, our findings suggest that unconfirmed 2019-nCoV pneumonia cases may be actually COVID-19 cases and that clinicians should be cautious when managing patients with presentations compatible with COVID-19.

Introduction

The 2019 novel coronavirus (2019-nCoV), named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), became notorious since December 2019 as a new etiologic agent of viral pneumonia [1]. In early illness stages, patients with coronavirus disease 2019 (COVID-19) present with symptoms of acute respiratory infection, which can progress to acute respiratory distress syndrome (ARDS) and other serious complications [2]. Because of substantial pneumonia-related morbidity and mortality [3], testing for SARS-CoV-2 infection of patients who meet the suspected-case definition for COVID-19 [4] is central for their management. Accordingly, provision of supportive care (e.g., oxygenation, ventilation, and fluid therapy) and/or administration of antiviral/antimalarial agents may be decisive [5].

Real-time reverse-transcriptase—polymerase-chain-reaction (RT-PCR) based SARS-CoV-2 RNA detection in respiratory samples (e.g., nasopharyngeal swabs) is the reference diagnostic method to confirm COVID-19 patients [6]. However, one or more negative results do not exclude the likelihood of SARS-CoV-2 infection [4]. Currently published studies suggest lung imaging, biomarkers, and other non-microbiological tests as ancillary diagnostic methods [6], encouraging further investigation to understand the value of radiological or laboratory findings to diagnose COVID-19. We comparatively explored the clinical features of 165 patients with laboratory confirmed or unconfirmed 2019-nCoV pneumonia admitted to COVID-19 wards of the Fondazione Policlinico A. Gemelli (FPG) IRCCS, which is a tertiary care

university hospital in Rome, Italy. Thus, we investigated the prospect that cases with a negative RT-PCR test result are actually cases of 2019-nCoV pneumonia or, in other words, are not to distinguish from those without confirmation test performed.

Methods

This retrospective, single-center observational study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the FPG (approval number 17057/20), and informed consent was obtained from each enrolled patient. All patients who were hospitalized for suspected 2019-nCoV pneumonia [7] on March 31 2020 were considered for recruitment. Inclusion criteria were: fever and/or respiratory symptoms, exposures, and presence of lung imaging features consistent with 2019-nCoV pneumonia [8]. All patients with other viral or bacterial respiratory infections were excluded.

At the emergency room (before admission to a hospital ward), all eligible patients underwent nasal and oropharyngeal swabs, which were tested for one or more SARS-CoV-2 specific nucleic acid targets [9]. If samples resulted negative, swabs were repeated after 48–72 hours. Then, samples were subjected to RNA extraction followed by RT-PCR for target detection using the Korean Ministry of Food and Drug Safety approved Allplex 2019-nCoV assay (Arrow Diagnostics S.r.l., Genova, Italy).

We retrieved demographic, clinical, laboratory, imaging, treatment, and outcome data from medical chart records of all enrolled patients, and we followed up clinical outcomes up to 23 April 2020. We classified cases as mild (see above specification), severe (i.e., dyspnea, respiratory rate $\geq$ 30 breaths/min, blood oxygen saturation $\leq$ 93%, and partial pressure of arterial oxygen [PaO_2]/fraction of inspired oxygen [FiO_2] $\leq$ 300 mm Hg), or critical (i.e., respiratory failure, septic shock, and/or multiple organ failure) pneumonia. We recorded chest X-ray or computed tomography (CT) features using the Fleischner Society terminology [10], as well as we defined ARDS based on timing, lung imaging, origin of edema, and oxygenation as specified in the Berlin definition [11], and liver injury as two- to three-times elevation of transaminases (e.g., alanine aminotransferase). According to the Italian Society of Infectious Diseases guidelines for COVID-19 treatment [12], we administered antiviral agents (e.g., lopinavir/ritonavir alone or in combination with chloroquine phosphate) to all patients with severe/critical disease and to > 70-year aged and/or comorbidity-presenting patients with mild disease.

Categorical variables were expressed as number with percentage and compared using the χ^2 test, and continuous variables were expressed as median with interquartile range (IQR) and compared using the Mann-Whitney *U*-test. All significant variables at univariate analysis were included in a multivariable logistic regression model to identify independent predictors of confirmed diagnosis. Odds ratio (OR) values with 95% confidence intervals (CIs) were calculated. A two-sided *P* value of < 0.05 was considered statistically significant. All analyses were performed with Stata software version 11.1 (StataCorp, College Station, TX, USA).

Results

On March 31 2020, 176 patients were hospitalized to our center with a suspicion of 2019-nCoV pneumonia. Of them, 11 were diagnosed with other viral or bacterial respiratory pathogens. Of the 165 remaining patients, 119 were confirmed COVID-19 cases based on positive RT-PCR results on nasopharyngeal swabs [4], and 46 were RT-PCR negative for two days or longer (i.e., when the last swab sample was obtained).

Table 1 shows demographic and clinical characteristics of 165 patients at baseline. The median age was 70 years (IQR, 58–78), and 113 patients were males. One hundred and twenty-three (74.6%) patients had at least one comorbidity. The median time to the onset of symptoms was 7 days (IQR, 3–10). The most common symptoms at admission were fever (n = 155, 93.9%), dyspnea (n = 92, 55.8%) and cough (n = 77, 46.7%). Overall, lactate dehydrogenase levels (median value, 289 U/L; IQR, 230–415) and C-reactive protein levels (median, 74.0 mg/L; IQR, 32.2–139.4) were elevated. One hundred and twenty-seven patients (77%) presented with X-ray signs of ground-glass opacity, and 106 (64.2%) with signs of consolidation. At admission, 101 (61.2%) presented with a mild pneumonia, and the remaining 64 patients (38.8%) with a severe/critical pneumonia.

Table 1
Demographics, baseline characteristics, and outcomes of patients diagnosed with 2019-nCoV pneumonia

Variable	Total (n = 165)	Confirmed Diagnosis[a] (n = 119)	Unconfirmed Diagnosis[a] (n = 46)	*P* Value
Age (years), median (IQR)	70 (58–78)	68 (58–77)	73.5 (58–85)	0.09
Male sex	113 (68.5)	85 (71.4)	28 (60.9)	0.19
Pre-existing conditions				
Any	123 (74.6)	86 (72.3)	37 (80.4)	0.28
Cardiovascular disease	77 (46.7)	59 (49.6)	18 (39.1)	0.23
Connective tissue disease	30 (18.2)	23 (19.3)	7 (15.2)	0.54
Nervous system disease	29 (17.6)	18 (15.1)	11 (23.9)	0.18
Diabetes	22 (13.3)	15 (12.6)	7 (15.2)	0.66
Malignancy	21 (12.7)	12 (10.1)	9 (19.6)	0.10
Respiratory system disease	18 (10.9)	12 (10.1)	6 (13.0)	0.59
Chronic kidney disease	15 (9.1)	8 (6.7)	7 (15.2)	0.09
Immunodeficiency	7 (4.2)	3 (2.5)	4 (8.7)	0.08
Chronic liver disease	3 (1.8)	3 (2.5)	0 (0.0)	0.28
Other[b]	29 (17.6)	17 (14.3)	12 (26.1)	0.07
Symptoms at admission				
Fever	155 (93.9)	115 (96.6)	40 (87.0)	0.02
Shortness of breath (or dyspnea)	92 (55.8)	63 (52.9)	29 (63.0)	0.24

Data are no. (%) unless specified otherwise. Denominators indicate data lacking for 53 patients. Abbreviations: IQR, interquartile range; qSOFA, quick sepsis-related organ failure assessment; CT, computed tomography.

[a] Laboratory-based confirmation of 2019-nCoV pneumonia was done by SARS-CoV-2 RNA detection using a well-established RT-PCR assay [9].

[b] Includes anemia, endocrine disorders, inflammatory bowel disease, and obesity.

[c] CT findings in all 112 patients were assessed according to imaging features described elsewhere [10].

[d] Patients were admitted between 3/6/2020 and 3/31/2020, with follow-up through 4/23/2020.

Variable	Total (n = 165)	Confirmed Diagnosis[a] (n = 119)	Unconfirmed Diagnosis[a] (n = 46)	*P* Value
Cough	77 (46.7)	60 (50.4)	17 (37.0)	0.12
Diarrhea/Nausea/Vomiting	6 (3.6)	3 (2.5)	3 (6.5)	0.22
Duration of symptoms, median (IQR)	7 (3–10)	7 (3–10)	7 (3–10)	0.41
Signs at admission, median (IQR)				
Heart rate (beats/min)	89 (80–101)	89 (80–102)	92 (80–100)	0.99
Respiration rate (breaths/min)	14 (12–15)	14 (12–16)	13 (12–15)	0.24
Blood oxygen saturation (%)	94 (90–96)	94 (90–96)	93 (90–97)	0.74
Systolic blood pressure (mmHg)	130 (120–140)	130 (120–140)	130 (118–140)	0.97
Diastolic blood pressure (mmHg)	80 (70–86)	80 (70–86)	75 (66–88)	0.56
qSOFA score (≥ 2)	25 (15.2)	17 (14.3)	8 (17.4)	0.62
Chest X-ray/CT findings				
Ground-glass opacity (GGO)	127 (77.0)	96 (80.7)	31 (67.4)	0.07
Consolidation	106 (64.2)	79 (66.4)	27 (58.7)	0.35
Pleural effusion	40 (24.2)	24 (20.2)	16 (34.8)	0.19
CT findings only[c]				
GGO and reticular	29/112 (17.6)	21/76 (17.6)	8/36 (17.4)	0.54
Pleural thickening/retraction	6/112 (3.6)	3/76 (2.5)	3/36 (6.5)	0.34

Data are no. (%) unless specified otherwise. Denominators indicate data lacking for 53 patients. Abbreviations: IQR, interquartile range; qSOFA, quick sepsis-related organ failure assessment; CT, computed tomography.

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[d] Patients were admitted between 3/6/2020 and 3/31/2020, with follow-up through 4/23/2020.

Variable	Total (n = 165)	Confirmed Diagnosis[a] (n = 119)	Unconfirmed Diagnosis[a] (n = 46)	*P* Value
Fibrotic steaks	5/112 (3.0)	3/76 (2.5)	2/36 (4.3)	0.70
Air bronchogram	3/112 (1.8)	2/76 (1.7)	1/36 (2.2)	0.96
Bronchus distortion	2/112 (1.2)	2/76 (1.7)	0/36 (0.0)	0.33
Spectrum of disease				
Mild	101 (61.2)	72 (60.5)	29 (63.0)	0.76
Severe	53 (32.1)	39 (32.8)	14 (30.4)	0.77
Critical	11 (6.7)	8 (6.7)	3 (6.5)	0.96
Blood parameters, median (IQR)				
Leucocytes (× 10^9/L; normal range 4.0–10.0)	6.4 (4.8–9.7)	6.0 (4.7–8.1)	10.1 (6.1–15.4)	< 0.001
Neutrophils (× 10^9/L; normal range 2.0–7.0)	4.9 (3.5–7.7)	4.6 (3.3–6.3)	7.7 (4.6–11.7)	< 0.001
Lymphocytes (× 10^9/L; normal range 1.0–3.0)	1.1 (0.8–1.4)	1.1 (0.8–1.4)	1.2 (0.7–1.6)	0.78
Neutrophils (%)	77.1 (69.5–82.8)	76.3 (67.6–82.4)	80.1 (71.9–87.3)	0.03
Lymphocytes (%)	15.8 (10.5–23.4)	17.6 (12.5–24.3)	12.1 (7.6–20.4)	0.003
Platelets (× 10^9/L; normal range 150–450)	210 (169–264)	203 (165–252)	250 (189–301)	0.01
Hemoglobin (g/dL; normal range: 13–17)	13.8 (12.1–14.9)	14.1 (13.0–15.1)	12.1 (10.6–14.1)	< 0.001

Data are no. (%) unless specified otherwise. Denominators indicate data lacking for 53 patients. Abbreviations: IQR, interquartile range; qSOFA, quick sepsis-related organ failure assessment; CT, computed tomography.

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Variable	Total (n = 165)	Confirmed Diagnosis[a] (n = 119)	Unconfirmed Diagnosis[a] (n = 46)	*P* Value
Serum parameters, median (IQR)				
Alanine aminotransferase (U/L; normal range 7–45)	24 (16–39)	26 (17–40)	19 (13–33)	0.02
Lactate dehydrogenase (U/L; normal range 120–250)	289 (230–415)	316 (254–433)	245 (195–336)	< 0.001
Creatinine (mg/dL; normal range: 0.7–1.1)	0.9 (0.8–1.3)	0.9 (0.8–1.3)	1.0 (0.8–1.3)	0.59
Creatine kinase (U/L; normal range 30–170)	120 (66–219)	122 (72–218)	107 (51–219)	0.36
Urea (mg/dL; normal range 10–23)	17 (14–26)	17 (13–25)	19 (15–32)	0.32
Infection-related biomarkers, median (IQR)				
Procalcitonin (ng/mL; normal range 0–0.5)	0.09 (0.04–0.18)	0.08 (0.04–0.15)	0.15 (0.07–0.63)	0.006
C-reactive protein (mg/L; normal range 0–5.0)	74.0 (32.2–139.4)	66.9 (33.6–130.5)	93.6 (22.1–163.9)	0.59
Complications				
Acute respiratory distress syndrome	92 (55.8)	75 (63.0)	17 (37.0)	0.003
Liver injury	47 (28.5)	38 (31.9)	9 (19.6)	0.11
Septic shock	14 (8.5)	7 (5.9)	7 (15.2)	0.06
Admission to intensive care unit	14 (8.5)	12 (10.1)	2 (4.4)	0.23
Treatment				

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[b] Includes anemia, endocrine disorders, inflammatory bowel disease, and obesity.

[c] CT findings in all 112 patients were assessed according to imaging features described elsewhere [10].

[d] Patients were admitted between 3/6/2020 and 3/31/2020, with follow-up through 4/23/2020.

Variable	Total (n = 165)	Confirmed Diagnosis[a] (n = 119)	Unconfirmed Diagnosis[a] (n = 46)	*P* Value
Oxygen support (nasal cannula)	128 (77.6)	98 (82.4)	30 (65.2)	0.02
Antiviral therapy	122 (73.9)	113 (95.0)	9 (19.6)	< 0.001
Antibiotic therapy	133 (80.6)	93 (78.2)	40 (87.0)	0.20
Interleukin-6 receptor inhibitor therapy	46 (27.9)	45 (37.8)	1 (2.2)	< 0.001
Outcome				
Discharged	125 (75.8)	88 (74.0)	37 (80.4)	0.38
Still in hospital as of 4/23/2020[d]	24 (14.6)	20 (16.8)	4 (8.7)	0.18
Died	16 (9.7)	11 (9.2)	5 (10.9)	0.75

Data are no. (%) unless specified otherwise. Denominators indicate data lacking for 53 patients. Abbreviations: IQR, interquartile range; qSOFA, quick sepsis-related organ failure assessment; CT, computed tomography.

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[b] Includes anemia, endocrine disorders, inflammatory bowel disease, and obesity.

[c] CT findings in all 112 patients were assessed according to imaging features described elsewhere [10].

[d] Patients were admitted between 3/6/2020 and 3/31/2020, with follow-up through 4/23/2020.

Treatments and outcomes of 165 patients are detailed in Table 1. Overall, 92 patients (55.8%) developed ARDS, and 14 of them (8.5%) septic shock, which needed transfer to ICU. Most patients (n = 128, 77.6%) were treated with oxygen support, antivirals (n = 122, 73.9%), and antibiotics (n = 133, 80.6%). Forty-six patients (27.9%) received therapy with interleukin-6 receptor inhibitors. Overall, 16 patients died at the follow-up end (n = 13 because ARDS, n = 2 because of septic shock, n = 1 because of multiple comorbidities).

At univariate analysis, fever was significantly more frequent in patients with confirmed diagnosis (96.6% vs 87%, $P = 0.02$). This group presented also with significantly lower levels of leucocytes (median value, 6.0×10^9/L vs 10.1×10^9/L; $P < 0.001$), neutrophils (median value, 4.6×10^9/L vs 7.7×10^9/L; $P < 0.001$), platelets (median value, 203×10^9/L vs 250×10^9/L; $P = 0.01$), lactate dehydrogenase (median value, 316 U/L vs 245 U/L; $P < 0.001$), and procalcitonin (median value, 0.08 ng/mL vs 0.15 ng/mL, $P = 0.006$), and higher levels of hemoglobin (median value, 14.1 g/dL vs 12.1 g/dL; $P < 0.001$) and alanine

aminotransferase (median value, 26 U/L vs 19 U/L, $P = 0.02$), Patients with confirmed diagnosis were also more likely to receive antivirals (95% vs 19.6%, $P < 0.001$) and to develop ARDS (63% vs 37%, $P = 0.003$) than those without confirmed diagnosis. There were no other significant differences between the two groups.

At multivariable analysis, higher concentrations of hemoglobin (OR, 1.34; 95% CI, 1.11—1.65; $P = 0.003$) and lactate dehydrogenase (OR, 1.00; 95% CI, 0.99—1.01; $P = 0.05$), and lower counts of leukocytes (OR, 0.81; 95% CI, 0.72—0.90; $P < 0.001$) were found to be independently associated with confirmed diagnosis in the overall cohort.

Discussion

We tested the hypothesis that negative patients did not differ from SARS-CoV-2 RNA positive patients by comparing features of 165 cases with clinically diagnosed 2019-nCoV pneumonia in our hospital. We did not find any substantial difference in symptoms, incubation periods, and radiographic/CT abnormalities as well as in many of the biological abnormalities recorded. However, blood/serum test results showed that patients with laboratory-confirmed diagnosis of 2019-nCoV pneumonia were more likely to have abnormal levels of lactate dehydrogenase and normal levels of hemoglobin and leukocytes. Additionally, the proportion of ARDS in the group of COVID-19 confirmed patients was significantly higher than in the group of COVID-19 unconfirmed patients.

Large or small descriptive studies published in 2020 mainly focused on patients with laboratory-confirmed 2019-nCoV pneumonia [2, 13, 14]. Nonetheless, among 72,314 cases (as of February 11, 2020) from the COVID-19 outbreak in China, 16,186 (22%) cases and 10,567 (15%) were classified as suspected or diagnosed cases, respectively, because of insufficient laboratory testing capacity according to the needs at that time [8]. Although testing for SARS-CoV-2 in our laboratory was not restricted [15], 46 (27.8%) of 165 patients with 2019-nCoV pneumonia did not have a laboratory-confirmed diagnosis in our study. Despite a well-documented active virus replication in the upper respiratory tract [16], swab samples may have a limited sensitivity to identify cases. Sampling or testing related factors may be responsible for false-negative RT-PCR results so as samples from the lower respiratory tract (e.g., sputum samples) should be collected and tested [4].

It is plausible that our SARS-CoV-2 negative patients were beyond their shedding peak in the upper respiratory tract samples or did not have symptoms highly suggestive for upper respiratory tract infection [16]. Consistently, eight of 119 patients with positive RT-PCR results became positive only with swabs taken on subsequent days after the first (negative) sampled swab. Furthermore, using the Allplex 2019-nCoV assay, which is a triplex assay, might have led to false negativity of samples due to their probably low virus concentrations that, in turn, might have resulted in late threshold cycles in one or two viral genes targeted by the assay. In our study, all 46 patients had a radiological evidence of pneumonia not attributed to any typical respiratory viral infection agents, including the human coronaviruses HKU1, OC43, NL63, 229E, the influenza virus A and B, and others (data not shown). It is worthy to note that the

finding of typical ground glass opacities in chest CTs of clinically diagnosed patients [17] prompted the Chinese authorities, at one point in early February 2020, to count these patients as confirmed cases [18]. This allowed identifying and quarantining patients as early as possible.

In conclusion, using the clinical diagnosis as the reference standard, the RT-PCR testing allowed to correctly identify two thirds of our patients as COVID-19 while one third was not correctly identified. However, as undocumented SARS-CoV-2 infections may be a relevant source of transmission among hospitalized patients [19], we believe that clinicians should exceed on the side of caution when managing patients with presentations compatible with COVID-19.

Abbreviations

2019-nCoV
2019 novel coronavirus; SARS-CoV-2:Severe acute respiratory syndrome coronavirus 2; COVID-19:Coronavirus disease 2019; ARDS:Acute respiratory distress syndrome; RT-PCR:Reverse-transcriptase–polymerase-chain-reaction; PaO_2:Partial pressure of arterial oxygen; FiO_2:Fraction of inspired oxygen; CT:Computed tomography; IQR:Interquartile range; OR:Odds ratio; CI:Confidence interval; ICU:Intensive care unit

Declarations

Acknowledgments

The authors are grateful to Franziska Lohmeyer PhD for her English language assistance and to clinical staff members for collection of samples.

Authors' contributions

GDA, BP, MS, and AG conceived and designed the study. GDA, FB, GI, LZDV acquired, analyzed, and interpreted the data. GDA and FB performed statistical analyses. BP, MS, and AG supervised the work. BP was the major contributor in writing the manuscript. PC and FF critically revised the manuscript for important intellectual concept. All authors read and approved the final manuscript.

Funding

The Reale Group and the Fondazione Valentino Garavani & Giancarlo Giammetti, to support the COVID-19 Research in our Institution, financed this work. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available as the data also forms part of an ongoing study but are available from the corresponding author on reasonable request.

Ethical approval and consent to participate

This retrospective, single-center observational study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the FPG (approval number 17057/20), and informed consent was obtained from each patient.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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