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ORIGINAL ARTICLE

Clinical Characteristics of Coronavirus Disease 2019 in China

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Abstract

BACKGROUND

Since December 2019, when coronavirus disease 2019 (Covid-19) emerged in Wuhan city and rapidly spread throughout China, data have been needed on the clinical characteristics of the affected patients.

METHODS

We extracted data regarding 1099 patients with laboratory-confirmed Covid-19 from 552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China through January 29, 2020. The primary composite end point was admission to an intensive care unit (ICU), the use of mechanical ventilation, or death.

RESULTS

The median age of the patients was 47 years; 41.9% of the patients were female. The primary composite end point occurred in 67 patients (6.1%), including 5.0% who were admitted to the ICU, 2.3% who underwent invasive mechanical ventilation, and 1.4% who died. Only 1.9% of the patients had a history of direct contact with wildlife. Among nonresidents of Wuhan, 72.3% had contact with residents of Wuhan, including 31.3% who had visited the city. The most common symptoms were fever (43.8% on admission and 88.7% during hospitalization) and cough (67.8%). Diarrhea was uncommon (3.8%). The median incubation period was 4 days (interquartile range, 2 to 7). On admission, ground-glass opacity was the most common radiologic finding on chest computed tomography (CT) (56.4%). No radiographic or CT abnormality was found in 157 of 877 patients (17.9%) with nonsevere disease and in 5 of 173 patients (2.9%) with severe disease. Lymphocytopenia was present in 83.2% of the patients on admission.

CONCLUSIONS

During the first 2 months of the current outbreak, Covid-19 spread rapidly throughout China and caused varying degrees of illness. Patients often presented without fever, and many did not have abnormal radiologic findings. (Funded by the National Health Commission of China and others.)

Introduction

In early December 2019, the first pneumonia cases of unknown origin were identified in Wuhan, the capital city of Hubei province.[1] The pathogen has been identified as a novel enveloped RNA betacoronavirus[2] that has currently been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has a phylogenetic similarity to SARS-CoV.[3] Patients with the infection have been documented both in hospitals and in family settings.[4-8]

The World Health Organization (WHO) has recently declared coronavirus disease 2019 (Covid-19) a public health emergency of international concern.[9] As of February 25, 2020, a total of 81,109 laboratory-

confirmed cases had been documented globally.[5,6,9-11] In recent studies, the severity of some cases of Covid-19 mimicked that of SARS-CoV.[1,12,13] Given the rapid spread of Covid-19, we determined that an updated analysis of cases throughout mainland China might help identify the defining clinical characteristics and severity of the disease. Here, we describe the results of our analysis of the clinical characteristics of Covid-19 in a selected cohort of patients throughout China.

Methods

STUDY OVERSIGHT

The study was supported by National Health Commission of China and designed by the investigators. The study was approved by the institutional review board of the National Health Commission. Written informed consent was waived in light of the urgent need to collect data. Data were analyzed and interpreted by the authors. All the authors reviewed the manuscript and vouch for the accuracy and completeness of the data and for the adherence of the study to the protocol, available with the full text of this article at NEJM.org.

DATA SOURCES

We obtained the medical records and compiled data for hospitalized patients and outpatients with laboratory-confirmed Covid-19, as reported to the National Health Commission between December 11, 2019, and January 29, 2020; the data cutoff for the study was January 31, 2020. Covid-19 was diagnosed on the basis of the WHO interim guidance.[14] A confirmed case of Covid-19 was defined as a positive result on high-throughput sequencing or real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens.[1] Only laboratory-confirmed cases were included in the analysis.

We obtained data regarding cases outside Hubei province from the National Health Commission. Because of the high workload of clinicians, three outside experts from Guangzhou performed raw data extraction at Wuhan Jinyintan Hospital, where many of the patients with Covid-19 in Wuhan were being treated.

We extracted the recent exposure history, clinical symptoms or signs, and laboratory findings on admission from electronic medical records. Radiologic assessments included chest radiography or computed tomography (CT), and all laboratory testing was performed according to the clinical care needs of the patient. We determined the presence of a radiologic abnormality on the basis of the

documentation or description in medical charts; if imaging scans were available, they were reviewed by attending physicians in respiratory medicine who extracted the data. Major disagreement between two reviewers was resolved by consultation with a third reviewer. Laboratory assessments consisted of a complete blood count, blood chemical analysis, coagulation testing, assessment of liver and renal function, and measures of electrolytes, C-reactive protein, procalcitonin, lactate dehydrogenase, and creatine kinase. We defined the degree of severity of Covid-19 (severe vs. nonsevere) at the time of admission using the American Thoracic Society guidelines for community-acquired pneumonia.[15]

All medical records were copied and sent to the data-processing center in Guangzhou, under the coordination of the National Health Commission. A team of experienced respiratory clinicians reviewed and abstracted the data. Data were entered into a computerized database and cross-checked. If the core data were missing, requests for clarification were sent to the coordinators, who subsequently contacted the attending clinicians.

STUDY OUTCOMES

The primary composite end point was admission to an intensive care unit (ICU), the use of mechanical ventilation, or death. These outcomes were used in a previous study to assess the severity of other serious infectious diseases, such as H7N9 infection.[16] Secondary end points were the rate of death and the time from symptom onset until the composite end point and until each component of the composite end point.

STUDY DEFINITIONS

The incubation period was defined as the interval between the potential earliest date of contact of the transmission source (wildlife or person with suspected or confirmed case) and the potential earliest date of symptom onset (i.e., cough, fever, fatigue, or myalgia). We excluded incubation periods of less than 1 day because some patients had continuous exposure to contamination sources; in these cases, the latest date of exposure was recorded. The summary statistics of incubation periods were calculated on the basis of 291 patients who had clear information regarding the specific date of exposure.

Fever was defined as an axillary temperature of 37.5°C or higher. Lymphocytopenia was defined as a lymphocyte count of less than 1500 cells per cubic millimeter. Thrombocytopenia was defined as a platelet count of less than 150,000 per cubic millimeter. Additional definitions — including exposure to wildlife, acute respiratory distress syndrome (ARDS), pneumonia, acute kidney failure, acute heart failure, and rhabdomyolysis — are provided in the Supplementary Appendix, available at NEJM.org.

LABORATORY CONFIRMATION

Laboratory confirmation of SARS-CoV-2 was performed at the Chinese Center for Disease Prevention and Control before January 23, 2020, and subsequently in certified tertiary care hospitals. RT-PCR assays were performed in accordance with the protocol established by the WHO.[17] Details regarding laboratory confirmation processes are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Continuous variables were expressed as medians and interquartile ranges or simple ranges, as appropriate. Categorical variables were summarized as counts and percentages. No imputation was made for missing data. Because the cohort of patients in our study was not derived from random selection, all statistics are deemed to be descriptive only. We used ArcGIS, version 10.2.2, to plot the numbers of patients with reportedly confirmed cases on a map. All the analyses were performed with the use of R software, version 3.6.2 (R Foundation for Statistical Computing).

Results

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

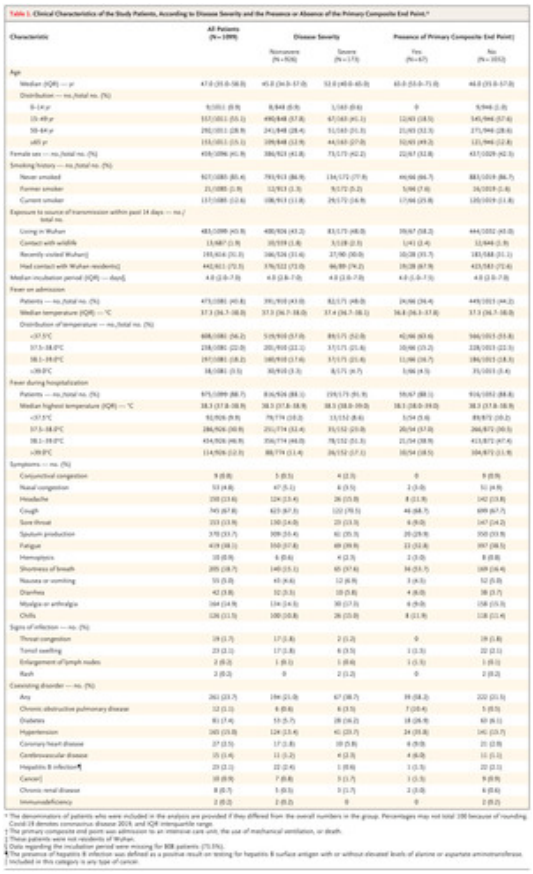
Figure 1.

Distribution of Patients with Covid-19 across Mainland China.

Of the 7736 patients with Covid-19 who had been hospitalized at 552 sites as of January 29, 2020, we obtained data regarding clinical symptoms and outcomes for 1099 patients (14.2%). The largest number of patients (132) had been admitted to Wuhan Jinyintan Hospital. The hospitals that were included in this study accounted for 29.7% of the 1856 designated hospitals where patients with Covid-19 could be

admitted in 30 provinces, autonomous regions, or municipalities across China (Figure 1).

Table 1.



Clinical Characteristics of the Study Patients, According to Disease Severity and the Presence or Absence of the Primary Composite End Point.

The demographic and clinical characteristics of the patients are shown in Table 1. A total of 3.5% were health care workers, and a history of contact with wildlife was documented in 1.9%; 483 patients (43.9%) were residents of Wuhan. Among the patients who lived outside Wuhan, 72.3% had contact with residents of Wuhan, including 31.3% who had visited the city; 25.9% of nonresidents had neither visited the city nor had contact with Wuhan residents.

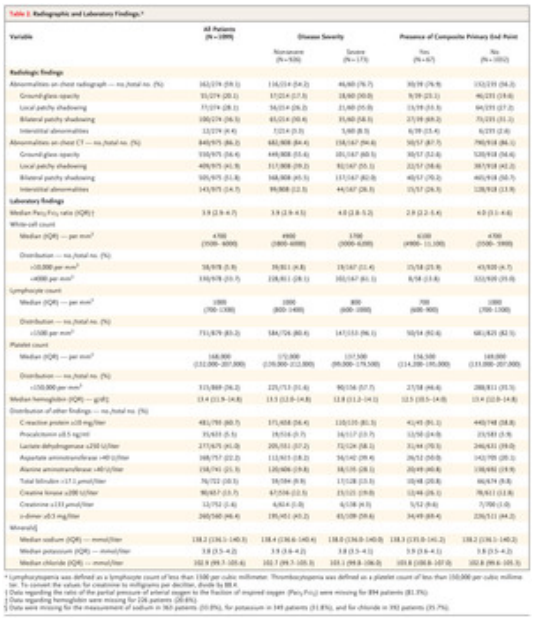
The median incubation period was 4 days (interquartile range, 2 to 7). The median age of the patients was 47 years (interquartile range, 35 to 58); 0.9% of the patients were younger than 15 years of age. A total of 41.9% were female. Fever was present in 43.8% of the patients on admission but developed in 88.7% during hospitalization. The second most common symptom was cough (67.8%); nausea or vomiting (5.0%) and diarrhea (3.8%) were uncommon. Among the overall population, 23.7% had at

least one coexisting illness (e.g., hypertension and chronic obstructive pulmonary disease).

On admission, the degree of severity of Covid-19 was categorized as nonsevere in 926 patients and severe in 173 patients. Patients with severe disease were older than those with nonsevere disease by a median of 7 years. Moreover, the presence of any coexisting illness was more common among patients with severe disease than among those with nonsevere disease (38.7% vs. 21.0%). However, the exposure history between the two groups of disease severity was similar.

RADIOLOGIC AND LABORATORY FINDINGS

Table 2.



Radiographic and Laboratory Findings.

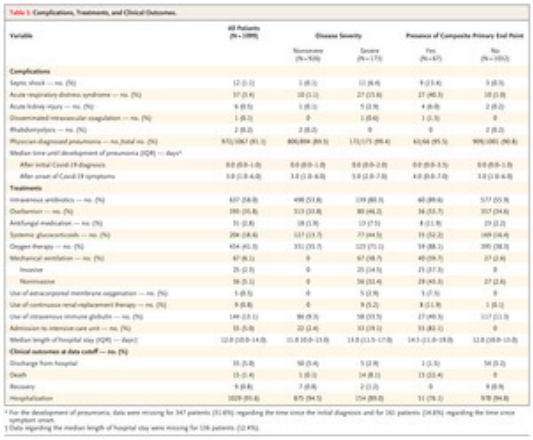
Table 2 shows the radiologic and laboratory findings on admission. Of 975 CT scans that were performed at the time of admission, 86.2% revealed abnormal results. The most common patterns on chest CT were ground-glass opacity (56.4%) and bilateral patchy shadowing (51.8%). Representative radiologic findings in two patients with nonsevere Covid-19 and in another two patients with severe Covid-19 are provided in Figure S1 in the Supplementary Appendix. No radiographic or CT abnormality was found in 157 of 877 patients (17.9%) with nonsevere disease and in 5 of 173 patients (2.9%) with severe disease.

On admission, lymphocytopenia was present in 83.2% of the patients, thrombocytopenia in 36.2%, and leukopenia in 33.7%. Most of the patients had elevated levels of C-reactive protein; less common were elevated levels of alanine aminotransferase, aspartate aminotransferase, creatine kinase, and D-dimer.

Patients with severe disease had more prominent laboratory abnormalities (including lymphocytopenia and leukopenia) than those with nonsevere disease.

CLINICAL OUTCOMES

Table 3.



Complications, Treatments, and Clinical Outcomes.

None of the 1099 patients were lost to follow-up during the study. A primary composite end-point event occurred in 67 patients (6.1%), including 5.0% who were admitted to the ICU, 2.3% who underwent invasive mechanical ventilation, and 1.4% who died (Table 3). Among the 173 patients with severe disease, a primary composite end-point event occurred in 43 patients (24.9%). Among all the patients, the cumulative risk of the composite end point was 3.6%; among those with severe disease, the cumulative risk was 20.6%.

TREATMENT AND COMPLICATIONS

A majority of the patients (58.0%) received intravenous antibiotic therapy, and 35.8% received oseltamivir therapy; oxygen therapy was administered in 41.3% and mechanical ventilation in 6.1%; higher percentages of patients with severe disease received these therapies (Table 3). Mechanical ventilation was initiated in more patients with severe disease than in those with nonsevere disease (noninvasive ventilation, 32.4% vs. 0%; invasive ventilation, 14.5% vs. 0%). Systemic glucocorticoids were given to 204 patients (18.6%), with a higher percentage among those with severe disease than nonsevere disease (44.5% vs. 13.7%). Of these 204 patients, 33 (16.2%) were admitted to the ICU, 17 (8.3%) underwent invasive ventilation, and 5 (2.5%) died. Extracorporeal membrane oxygenation was performed in 5 patients (0.5%) with severe disease.

The median duration of hospitalization was 12.0 days (mean, 12.8). During hospital admission, most of the patients received a diagnosis of pneumonia from a physician (91.1%), followed by ARDS (3.4%) and shock (1.1%). Patients with severe disease had a higher incidence of physician-diagnosed pneumonia than those with nonsevere disease (99.4% vs. 89.5%).

Discussion

During the initial phase of the Covid-19 outbreak, the diagnosis of the disease was complicated by the diversity in symptoms and imaging findings and in the severity of disease at the time of presentation. Fever was identified in 43.8% of the patients on presentation but developed in 88.7% after hospitalization. Severe illness occurred in 15.7% of the patients after admission to a hospital. No radiologic abnormalities were noted on initial presentation in 2.9% of the patients with severe disease and in 17.9% of those with nonsevere disease. Despite the number of deaths associated with Covid-19, SARS-CoV-2 appears to have a lower case fatality rate than either SARS-CoV or Middle East respiratory syndrome–related coronavirus (MERS-CoV). Compromised respiratory status on admission (the primary driver of disease severity) was associated with worse outcomes.

Approximately 2% of the patients had a history of direct contact with wildlife, whereas more than three quarters were either residents of Wuhan, had visited the city, or had contact with city residents. These findings echo the latest reports, including the outbreak of a family cluster,[4] transmission from an asymptomatic patient,[6] and the three-phase outbreak patterns.[8] Our study cannot preclude the presence of patients who have been termed “super-spreaders.”

Conventional routes of transmission of SARS-CoV, MERS-CoV, and highly pathogenic influenza consist of respiratory droplets and direct contact,[18-20] mechanisms that probably occur with SARS-CoV-2 as well. Because SARS-CoV-2 can be detected in the gastrointestinal tract, saliva, and urine, these routes of potential transmission need to be investigated[21] (Tables S1 and S2).

The term Covid-19 has been applied to patients who have laboratory-confirmed symptomatic cases without apparent radiologic manifestations. A better understanding of the spectrum of the disease is needed, since in 8.9% of the patients, SARS-CoV-2 infection was detected before the development of viral pneumonia or viral pneumonia did not develop.

In concert with recent studies,[1,8,12] we found that the clinical characteristics of Covid-19 mimic those of

SARS-CoV. Fever and cough were the dominant symptoms and gastrointestinal symptoms were uncommon, which suggests a difference in viral tropism as compared with SARS-CoV, MERS-CoV, and seasonal influenza.[22,23] The absence of fever in Covid-19 is more frequent than in SARS-CoV (1%) and MERS-CoV infection (2%),[20] so afebrile patients may be missed if the surveillance case definition focuses on fever detection.[14] Lymphocytopenia was common and, in some cases, severe, a finding that was consistent with the results of two recent reports.[1,12] We found a lower case fatality rate (1.4%) than the rate that was recently reportedly,[1,12] probably because of the difference in sample sizes and case inclusion criteria. Our findings were more similar to the national official statistics, which showed a rate of death of 3.2% among 51,857 cases of Covid-19 as of February 16, 2020.[11,24] Since patients who were mildly ill and who did not seek medical attention were not included in our study, the case fatality rate in a real-world scenario might be even lower. Early isolation, early diagnosis, and early management might have collectively contributed to the reduction in mortality in Guangdong.

Despite the phylogenetic homogeneity between SARS-CoV-2 and SARS-CoV, there are some clinical characteristics that differentiate Covid-19 from SARS-CoV, MERS-CoV, and seasonal influenza infections. (For example, seasonal influenza has been more common in respiratory outpatient clinics and wards.) Some additional characteristics that are unique to Covid-19 are detailed in Table S3.

Our study has some notable limitations. First, some cases had incomplete documentation of the exposure history and laboratory testing, given the variation in the structure of electronic databases among different participating sites and the urgent timeline for data extraction. Some cases were diagnosed in outpatient settings where medical information was briefly documented and incomplete laboratory testing was performed, along with a shortage of infrastructure and training of medical staff in nonspecialty hospitals. Second, we could estimate the incubation period in only 291 of the study patients who had documented information. The uncertainty of the exact dates (recall bias) might have inevitably affected our assessment. Third, because many patients remained in the hospital and the outcomes were unknown at the time of data cutoff, we censored the data regarding their clinical outcomes as of the time of our analysis. Fourth, we no doubt missed patients who were asymptomatic or had mild cases and who were treated at home, so our study cohort may represent the more severe end of Covid-19. Fifth, many patients did not undergo sputum bacteriologic or fungal assessment on admission because, in some hospitals, medical resources were overwhelmed. Sixth, data generation was clinically driven and not systematic.

Covid-19 has spread rapidly since it was first identified in Wuhan and has been shown to have a wide spectrum of severity. Some patients with Covid-19 do not have fever or radiologic abnormalities on initial

presentation, which has complicated the diagnosis.

Funding and Disclosures

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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A list of investigators in the China Medical Treatment Expert Group for Covid-19 study is provided in the Supplementary Appendix, available at NEJM.org.

Supplementary Material

Protocol	PDF	257KB
Supplementary Appendix	PDF	513KB
Disclosure Forms	PDF	534KB

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