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Clinical presentation and course of COVID-19

ABSTRACT

Information about the clinical presentation and course of COVID-19 is evolving rapidly. On presentation, cough and fever predominate, but extrapulmonary symptoms are also common; in some patients, loss of sense of smell may be an early but favorable sign. The mortality rate varies widely in different reports but should become clearer as more data are collected. Risk factors for severe disease and death include comorbid conditions such as hypertension, cardiovascular disease, diabetes mellitus, and chronic obstructive pulmonary disease. Other implicated factors include older age, obesity, end-stage renal disease, and a higher neutrophil-lymphocyte ratio.

KEY POINTS

Patients with COVID-19 who have ground-glass opacities, consolidative opacities, increased inflammatory markers, older age, and comorbid conditions have been shown to have increased risk of ventilation and death.

Anosmia may be a sign of favorable infection outcome.

Those with obesity, hypertension, or underlying lung or heart disease tended to do worse in studies of mortality and severity.

For predictive markers, the neutrophil-lymphocyte ratio, Sequential Organ Failure Assessment score, and CURB-65 score may correlate with worse disease.

doi:10.3949/ccjm.87a.ccc013

Relatively few studies are available that show the symptoms, course, and prognostic factors of COVID-19 disease, but the data are evolving rapidly. The disease affects not only the lungs, but also other organ systems. Patients with comorbidities are most vulnerable. Novel symptoms and markers of risk continue to be identified.

FEVER AND COUGH PREDOMINATE BUT OTHER SYMPTOMS ARE COMMON

Zhou et al[1] reported the characteristics and outcomes of 191 patients hospitalized for COVID-19 in 2 hospitals in Wuhan, China. Fever was present in 94%, cough in 79%, sputum production in 23%, myalgia in 15%, and diarrhea in 5%; 54 patients died.

Others (reviewed by Lai et al[2]) cite similar numbers, with some variation in less-specific symptoms, such as myalgia in up to 43.9% of patients and diarrhea in up to 10.1%.

Arentz et al[3] described 21 patients admitted to the intensive care unit with COVID-19 in Evergreen Hospital in Kirkland, WA. Symptoms included cough in 11, shortness of breath in 17, and fever in 11. In the intensive care unit, 15 patients required mechanical ventilation, 8 developed severe acute respiratory distress syndrome (ARDS), and 11 died.

Jin et al[4] reported that 74 (11%) of 651 COVID-19 patients in Zhejiang province in China had at least 1 gastrointestinal symptom (nausea, vomiting, or diarrhea). Other symptoms included sore throat in 99 (15%) fatigue in 119 (18%), shortness of breath in 27 (4%), headache in 67 (10%), cough in 435 (67%), and fever in 130 (20%).

Rodriguez-Morales et al[5] performed a systematic review and meta-analysis that includ-

ed 656 patients. The most common symptoms were fever (reported in 88.7% of cases), cough (57.6%), dyspnea (45.6%), myalgia or fatigue (29.4%), sore throat (11.0%), headache (8.0%), and diarrhea (6.1%).

On radiography, 25% of patients had unilateral chest opacities, and 72.9% had bilateral opacities; 68.5% had ground-glass opacities on computed tomography.

On laboratory testing, 43.1% had lymphopenia, 58.3% had high C-reactive protein levels, and 57% had high lactate dehydrogenase levels.

Outcomes included death in 15.9%, discharge in 38.1%, acute respiratory distress syndrome (ARDS) in 7.1%, and secondary infection in only 1.6%.

Kim et al[6] reported on the first 28 cases of COVID-19 in Korea. The median age was 40 years, 15 patients were male, 28.6% had cough, 28.6% had sore throat, 25% had fever, and 10.7% had diarrhea, but 2 patients had no symptoms. Nearly half (46.4%) of the patients had infiltrates on chest radiography, and 88.9% had infiltrates on computed tomography. Six patients (21%) were hypoxic, but none required mechanical ventilation.

In general, the majority of patients present with fever, cough, dyspnea, and elevated C-reactive protein, with or without elevated lactate dehydrogenase. Less-common symptoms include diarrhea, nausea, vomiting, sore throat, headache, and fatigue.

Loss of smell an early but favorable sign

Anosmia, or olfactory loss, has been reported as an early sign of COVID-19.

Yan et al,[7] at the University of California San Diego, reviewed the cases of 169 patients with laboratory-confirmed COVID-19 infections, of whom 128 had olfactory and gustatory data available; 26 were hospitalized. The investigators performed univariate and multivariate logistic regressions to identify risk factors for hospital admission and anosmia.

Hospital admission was strongly associated with intact smell and taste, older age, diabetes, and parameters associated with respiratory failure. Anosmia was independently associated with outpatient care (adjusted odds ratio [OR] 0.09, 95% confidence interval [CI] 0.01–0.74). The finding of pulmonary infiltrates or pleural effusion on chest radiography was independently associated with admission (adjusted OR 8.01, 95% CI 1.12–57.49).

This implicates anosmia as a sign of mild clinical course and reinforces radiographic abnormalities as a predictor for a worse clinical course.

WHO SURVIVES COVID-19?

Wang et al[8] reviewed the cases of 1,012 patients who were admitted to the hospital in China because they had positive results on polymerase chain reaction testing but were not critically ill. Only 4.5% had hypertension, 2.7% had diabetes mellitus, 1.5% had cardiovascular disease, and 2.0% had respiratory disease at baseline. Their median age was 50 (interquartile range 39–58, total range 16–89). Three percent of the patients had no symptoms, 75.2% had fever, 18% had chills, 5.6% had rhinorrhea, 52.4% had cough, 15% had headache, and 15% had diarrhea. Median admission length of stay was 10 days (interquartile range 7–14).

Computed tomography of the chest showed large ground-glass opacities in 508 patients and large consolidated opacity in 54 patients. None of the patients died.

In essence, fewer comorbid conditions indicates better prognosis, but more research needs to be done to show the true prognostic factors for those who do well.

Novel symptoms and markers of risk continue to be identified

WHO DIES OF COVID-19?

Deaths in COVID-19 have been attributed to multiple organ failure with ARDS, cardiac injury, acute kidney injury, and shock.[5]

The mortality rate may be variable when patient admission criteria are not standardized: ie, if the threshold for admission is lower, then the mortality rate will be lower. This may also reflect testing bias, as the cause of death may not be attributed to SARS-CoV-2 if the patient went untested or died at home without a clear diagnosis after discharge.

Pooled analysis of 278 patients in Wuhan, China,[2] showed that 72 (26%) required intensive care unit admission, 56 (20%) developed ARDS, 23 (8%) required invasive mechanical ventilation, and 9 (3%) required extracorporeal membrane oxygenation for refractory hypoxemia. Hemodynamic shock was seen in

6.8% of patients, and the mortality rate was 4% to 15%. The median time of death from first symptoms was 14 days.[2]

Zhou et al[1] compared survivors of COVID-19 and those who died of it with univariate and multivariate logistic regression models used to determine significant differences. Compared with survivors, patients who died were statistically significantly more likely to have:

- Older age (median age 69 vs 52)
- Comorbidities such as hypertension, diabetes, coronary heart disease, and chronic obstructive lung disease (67% vs 40%)
- Tachypnea (63% vs 16%)
- A higher Sequential Organ Failure Assessment (SOFA) score[9] (4.5 vs 1.0)
- A higher CURB-65 score (**c**onfusion, **u**rea, **r**espiratory rate, **b**lood pressure, age ≥ **65**)[10] (2.0 vs 0.0)
- A higher white blood cell count (9.8 vs 5.2 × 10^9/L)
- A lower lymphocyte count (0.6 vs 1.1 × 10^9/L)
- A lower platelet count (165 vs 220 × 10^9/L)
- Lower serum albumin (29.1 vs 33.6 g/L)
- Higher alanine aminotransferase (ALT) (40.0 vs 27.0 U/L)
- Serum creatinine > 133 µmol/L (1.5 mg/dL) (9% vs 2%)
- Higher creatine kinase (39.0 vs 18.0 U/L)
- Elevated high-sensitivity cardiac troponin I (22.2 vs 3.0 pg/mL)
- Longer prothrombin time (12.1 vs 11.4 seconds)
- Higher D-dimer levels (5.2 vs 0.6 µg/mL)
- Higher serum ferritin levels (1,435.3 vs 503.2 µg/L)
- Higher interleukin 1 (11.0 vs 6.3 pg/mL)
- Procalcitonin ≥ 0.6 ng/mL (25% vs 1%)
- Radiographic consolidation (74% vs 53%)
- Ground-glass opacity (81% vs 67%)
- Bilateral pulmonary infiltrates (83% vs 72%).

Deaths are due to multiple organ failure with ARDS, cardiac injury, acute kidney injury, and shock

Li et al[11] examined the records of 25 patients who died. Their ages ranged from 55 to 100 years. Initial laboratory testing showed the following median values:

- ALT 24 U/L
- Aspartate aminotransferase 37 U/L
- Albumin 3.2 mg/dL
- Blood urea nitrogen 9.29 mmol/L (26 mg/dL)
- Creatinine 66 µmol/L (0.75 mg/dL)
- Hypersensitive troponin I 316 ng/mL
- White blood cell count 11.01 × 10^9/L
- Neutrophil count 10.41 × 10^9/L
- Lymphocyte count 0.52 × 10^9/L
- Procalcitonin 0.36 (ng/mL)
- C-reactive protein 91.1 mg/L
- Lactate 3.35 mmol/L.

The median course of disease was 9 days (range 4–20 days). Mechanical ventilation was needed in 23 patients, 16 patients had hypertension, 10 patients had diabetes, and 8 patients had heart disease.

Cummings et al[12] performed a prospective cohort study of 257 critically ill patients with laboratory-confirmed COVID-19 in New York City. The most common comorbidity was hypertension (63%), followed by obesity (46%) and diabetes (36%). Of the 257 patients, 203 received mechanical ventilation for a median of 18 days (interquartile range 9–28 days), 170 required vasopressors, and 79 needed renal replacement therapy. The median time to in-hospital deterioration was 3 days (interquartile range 1–6).

In total, 101 patients died. A multivariable Cox model identified the following as independently associated with in-hospital mortality:

- Older age (adjusted hazard ratio [aHR] 1.31 per 10-year increase [95% CI 1.09–1.57])
- Chronic cardiac disease (aHR 1.76 [1.08–2.86])
- Chronic pulmonary disease (aHR 2.94 [1.48–5.84])
- Higher interleukin 6 levels (aHR 1.11 per decile increase [1.02–1.20])
- Higher D-dimer levels (aHR 1.10 per decile increase [1.01–1.19]).

Overall, patients with older age, baseline lung or heart disease, and radiographic opacities are more likely to develop progressive COVID-19 infection and to die. Data indicate that those who present with higher CURB-65 and SOFA scores tend to do worse as well.

CAN WE PREDICT SEVERE DISEASE?

Comorbid conditions

Wang et al[13] performed a meta-analysis of 34 reports, many of which are included in this

review. The following comorbid diseases were associated with severe COVID-19:

- Hypertension (odds ratio [OR] 2.92, 95% CI 2.35–3.64, I^2 45.2% [indicating moderate heterogeneity])
- Cardiovascular disease (OR 3.84, 95% CI 2.90–5.07, I^2 3.5%)
- Chronic kidney disease (OR 2.22, 95% CI 1.14–4.31, I^2 38.1%)
- Chronic liver disease (OR 0.86, 95% CI 0.42–1.75, I^2 0%)
- Diabetes (OR 2.61, 95% CI 2.05–3.33, I^2 39.2%).

Radiographic progression

Liu et al[14] performed a retrospective cohort study of computed tomography of pneumonia lesions in early hospitalization to predict progression to severe illness. The researchers used artificial intelligence algorithms to measure ground-glass opacity volume, semiconsolidation volume, and consolidation volume of both lungs in 134 patients with confirmed COVID-19 in Shanghai, China, of whom 19 (14.2%) were severely ill.

Changes on computed tomography from day 0 to day 4 had the best predictive value for developing severe illness, with a hazard ratio of 1.39 (95% CI 1.05–1.84) for ground-glass opacity volume and 1.67 (95% CI 1.17–2.38) for consolidative volume.

Neutrophil-lymphocyte ratio

Pereira et al,[15] in Spain, evaluated the characteristics of 60 pregnant women with SARS-CoV-2 infection, of whom 75.5% presented with fever and cough, 37.8% reported dyspnea, and 68.6% required hospital admission; however, more than half of the admissions were for delivery. The most common laboratory findings were lymphopenia, thrombocytopenia, and elevated C-reactive protein. A neutrophil-lymphocyte ratio less than 3 appeared to be the most sensitive marker of disease improvement, with relative risk of 6.6.

Liu et al[16] investigated laboratory markers as predictors of critical illness, finding that patients with a neutrophil-lymphocyte ratio of 3.13 or higher and age 50 or older had a higher tendency to progress into critical illness (P = .0004). However, they did not report a hazard ratio associated with their Cox proportion hazards regression analysis. They do report that area under the receiver operator curve was 0.867 for the neutrophil-lymphocyte ratio. This study involved 61 patients in their derivation cohort and 54 patients in a validation cohort.

Obesity

Hajifathalian et al[17] performed a retrospective chart review of 770 COVID-19 patients in New York City. Their mean body mass index was 29 kg/m^2, and 277 patients had a body mass index greater than 30. The obese patients were more likely to present with fever, cough, and shortness of breath, and they had a significantly higher rate of intensive care unit admission or death (relative risk 1.58, P = .002).

Acute liver injury

Phipps et al[18] performed a retrospective cohort study of acute liver injury in patients undergoing testing for SARS-CoV-2 in New York City. Of 3,381 patients tested, 2,273 had positive results and 1,108 had negative results. Those who tested positive had higher median initial and peak ALT levels than those who tested negative. Of those who tested positive, those with the highest peak ALT levels were most likely to need intensive care, intubation, or renal replacement therapy and to die in the hospital.

An artificial intelligence program measured pneumonia volume

Hemodialysis

Goicoechea et al[19] reported the outcomes of 36 patients on hemodialysis in Spain who were hospitalized for COVID-19. Over the course of 1 month, 11 patients (31%) died, and 18 (including the 11 who died) had a worsening of their clinical status, defined as an increase in oxygen requirement of more than 4 liters and radiographic worsening.

Nonsurvivors had significantly longer time on dialysis than survivors, higher lactate dehydrogenase levels (490 vs 281 U/L), higher C-reactive protein levels (18.3 vs 8.1 mg/dL), and lower lymphocyte counts (0.38 vs 0.76 × 10^9/L). The median time on dialysis for both groups was 29 months; 19 patients had arteriovenous fistulas and 17 patients had permanent central venous catheters.

6.5 MILLION CASES AND COUNTING

At the time of this writing, the US Centers for

Disease Control and Prevention is reporting 1,842,101 US cases and 107,029 deaths, resulting in a 5.8% mortality rate.[20] The World Health Organization has listed 6,515,796 confirmed cases with 387,298 deaths, which results in a mortality rate of 2.6%.[21] As testing improves and becomes more widely available, these numbers should settle on the true mortality rate; however, they continue to fluctuate.

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