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COVID-19: initial clinical presentation and its correlation with the severity of the disease

COVID-19: presentación clínica inicial y su correlación con la gravedad de la enfermedad

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ABSTRACT

Patients with COVID-19 have a broad spectrum of clinical presentations, and mortality rates are relatively high in severe cases. Early identification of risk factors that are related to the severity of the disease is of vital importance.

In order to correlate the initial symptoms of COVID-19 with disease severity, the present retrospective, cross-sectional, observational cohort study was conducted, including 413 patients diagnosed with COVID-19 between January and March, 2021. Of all the initial symptoms that were studied, dyspnea (p < 001), fever (p 0.001), cough (p 0.002), odynophagia (p 0.01), headache (p 0.01), and gastrointestinal symptoms (p 0.03) were associated with the development of severe illness. The comorbidities that were associated with the worst prognoses were: arterial hypertension (p < 0.001), obesity (p < 0.001), COPD (chronic obstructive pulmonary disease) (p < 0.001), former smoking (p < 0.001), diabetes (p 0.01), previous cardiovascular disease (p 0.03), and active oncological disease (p 0.04).

In conclusion, patients diagnosed with COVID-19 whose initial manifestations include dyspnea, fever, cough, odynophagia, headache, and gastrointestinal symptoms should be closely monitored to prevent disease deterioration.

Key words: SARS-CoV-2 Infection; COVID-19; Clinical Presentation; Severity

RESUMEN

Los pacientes con COVID-19 tienen un amplio espectro de presentación clínica y las tasas de mortalidad en los casos graves son relativamente altas. La identificación temprana de los factores de riesgo que se relacionan con la gravedad de la enfermedad es de vital importancia.

Con el objetivo de correlacionar los síntomas iniciales de COVID-19 con la gravedad de la enfermedad, se realizó el presente estudio de cohorte transversal retrospectivo y observacional de 413 pacientes con diagnóstico de COVID-19 entre enero y marzo 2021. De todos los síntomas iniciales estudiados, la disnea (p < 001), fiebre (p 0.001), tos (p 0.002), odinofagia (p 0.01), cefalea (p 0.01) y síntomas gastrointestinales (p 0.03), se asociaron con el desarrollo de una enfermedad grave. Las comorbilidades que

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se asociaron con peor pronóstico fueron: hipertensión arterial (p < 0.001), obesidad (p <0.001), EPOC (p < 0.001), ex tabaquismo (p < 0.001), diabetes (p 0.01), enfermedad cardiovascular previa (p 0.03), y enfermedad oncológica activa (p 0.04).
En conclusión, los pacientes con diagnóstico de COVID-19, cuya manifestación inicial es disnea, fiebre, tos, odinofagia, cefalea y síntomas gastrointestinales, deben ser monitoreados de cerca para prevenir el deterioro de la enfermedad.

Palabras clave: Infección por SARS-CoV-2; COVID-19; Presentación Clínica; Gravedad

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a strain of coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The first cases were seen in Wuhan, China, in late December 2019, and from there it has spread practically all over the world. It was officially recognized as a pandemic by the World Health Organization (WHO) on March 11, 2020.[1-3]

According to PAHO (Pan American Health Organization) as of April 1, 2021, the number of confirmed cases worldwide reached 128 million, and more than 2 million deaths. In Argentina, the data available up to now indicated 2,348,821 cases and 55,858 deaths associated with COVID-19.

The disease mainly affects tissues that express high levels of ACE2 (angiotensin converting enzyme 2 receptor), including the lungs, heart, and gastrointestinal tract.[2] The presence of underlying comorbidities is associated with a higher risk of progressing to severe COVID-19. Advanced age, cardiovascular disease, diabetes mellitus, arterial hypertension, chronic obstructive pulmonary disease (COPD), cancer (especially hematologic neoplasms, lung cancer, and metastatic disease), chronic kidney disease, obesity, and smoking have been mentioned as the main risk factors for developing severe disease.[1, 2, 4, 5]

Numerous studies have highlighted the clinical characteristics of the disease, showing that 80% of patients with COVID-19 present mild disease with an overall mortality rate of 2-5%.[1, 5, 6, 7, 8, 9] However, a subset of approximately 15% of patients showed moderate lung involvement and required hospitalization, and 5% had severe respiratory failure, resulting in death in half of these cases.[1, 6, 7, 9, 10]

The analytical alterations that have been associated with the worst prognoses include: lymphopenia, elevation of liver enzymes, of LDH (lactate dehydrogenase), of inflammatory markers such as PCR and ferritin, D-dimer, troponin, and CPK (creatine phosphate kinase), prolonged prothrombin time, and acute kidney injury. Coagulation test alterations have also been observed, with a state of hypercoagulability that conditions a tendency to thrombosis.[1, 6, 11]

Mortality rates of severe forms of the disease are relatively high (half of the cases)[1, 6, 7, 9, 10], so early identification of risk factors related to the severity of the disease could facilitate the implementation of timely interventions and probably help reduce the fatality rate.

In this context, the present research was conducted with the purpose of correlating the initial symptoms of COVID-19 with the severity of the disease. Also, to determine the main comorbidities associated with a poor prognosis and describe the main elevated biomarkers in COVID-19.

MATERIALS AND METHODS

A retrospective, cross-sectional, observational cohort study was conducted in patients diagnosed with COVID-19 who attended the Emergency Department of the Sanatorio Güemes between January 1st and March 31st, 2021, whose diagnosis had been confirmed by reverse transcription polymerase chain reaction (RT-PCR).

Sanatorio Güemes is a high-complexity private healthcare institution located in the Autonomous City of Buenos Aires, with a unique information repository for each patient, which is centralized through an Electronic Health Record (EHR). All patients, upon admission to the institution, have voluntarily and officially signed informed consent for the use of their data for research purposes. The information of this study was obtained from the EHR database and was entered into an electronic form designed specifically for this purpose, which was accessible only to the authors of the study, thus preserving the anonymity of all participants.

Inclusion criteria: the study included individuals over 18 years of age with a diagnosis of COVID-19 confirmed by RT-PCR in throat and nasopharyngeal swab.

Exclusion criteria: individuals with suspected COVID-19 without confirmation at the time of the analysis and those with positive COVID-19 antibodies (but without RT-PCR or with negative RT-PCR) were excluded. Additionally, patients whose medical records didn't include demographic data, comorbidities, and initial symptoms of the disease, and those who hadn't been followed up by the Sanatorio Güemes until the time of medical discharge were excluded.

Clinical information, laboratory data, and assessment of disease severity correspond to data obtained upon hospital admission. Initial symptoms were defined as the first symptoms to appear at the onset of the illness. Lymphopenia was defined as a lymphocyte count < 1000/μL or a percentage of less than 20%. Thrombocytopenia was defined as a platelet count < 100,000/mm^3 ; and thrombocytosis, as a count > 450,000/mm^3. A PCR value of ≥ 10 mg/l was considered elevated; D-dimer was considered elevated with a value of ≥ 0.5 mg/l; LDH was considered elevated with values of > 250 U/L, and for ferritin, it was defined as elevated with values of > 300 ng/mL in men and > 150 ng/mL in women.

Based on the National Institutes of Health (NIH) guidelines, individuals who test positive for SARS-CoV-2 but don't have symptoms compatible with COVID-19 are considered to have an asymptomatic infection. Mild disease: individuals who have any of the various signs and symptoms of COVID-19 but do not show breathing difficulty, dyspnea, or abnormal chest imaging. Moderate disease: individuals who show evidence of lower airways illness during clinical evaluation or imaging and have an oxygen saturation (SpO_2) ≥ 94% on room air at sea level. Severe disease: individuals who have SpO_2 < 94%, arterial oxygen partial pressure/fraction of inspired oxygen (PaO_2/FiO_2) ratio of < 300 mmHg, respiratory rate > 30 breaths/min, or pulmonary infiltrates > 50%. Critical disease: people who have respiratory failure, septic shock, and/or multi-organ dysfunction.[4] In order to perform statistical analysis with practical relevance for the study's objectives, the population was divided into three groups: mild disease (asymptomatic and mild cases), moderate disease, and severe disease (severe and critical cases).

Descriptive statistics were used to analyze the median (interquartile range [IQR]), frequencies, and proportions. Categorical variables were compared using the Chi-square test and Fisher's exact test when the expected frequencies were less than 5. Odds ratio (OR) and 95% confidence interval (CI) were used to estimate the association between initial symptoms, comorbidities, and severe COVID-19 ($p < 0.05$ was considered statistically significant). Statistical analyses were performed using SPSS software (version 26.0).

RESULTS

A total of 413 patients with diagnosis of COVID-19 confirmed by RT-PCR were included. The median age was 37 years ([IQR] 28-48), 228 cases (55.2%) were female, and 185 (44.8%) were male. A total of 154 cases (37.3%) presented with one or more comorbidities at the time of diagnosis (Table 1).

Among the main comorbidities, 9.9% were hypertensive, 8.2% former smokers, 6.3% current smokers, 4.6% asthmatic, and 4.6% obese. The remaining characteristics are detailed in Table 1.

The initial clinical presentation was characterized by the presence of fever and headache, each in 43.6% of cases; 39.5% had odynophagia, 34.9% cough, 29.1% myalgia, 20.8% anosmia, 13.1% dysgeusia, 8.5% rhinitis/nasal congestion, 7.7% gastrointestinal symptoms, and only 1% dyspnea.

Regarding laboratory findings, these were requested according to the treating physician's criteria, so we do not have data on all patients. LDH was requested in 73 cases, of which 91.8% had elevated LDH; the PCR was elevated in 85.7% of 77 patients; elevated ferritin was found in 85.1% of 47 cases; D-dimer was elevated in 42.3% of 26 patients; lymphopenia was found in 31.1% of 90 cases; thrombocytopenia was present in 3.4% of 89 patients, and no evidence of thrombocytosis was found in any of the studies.

Of the 413 patients, 82.6% (341) were indicated home medical care and daily telephone follow-up; 16.9% required hospitalization in a general ward, and 0.5% had to be hospitalized at the intensive care unit (ICU) upon their admission to the institution. The median time from symptom onset to medical consultation was 3 days (IQR 2-4).

81.1% developed mild disease, 12.8% moderate disease, and 6.1% severe disease. When correlating initial symptoms with severe COVID-19, the severity of the disease was significantly associated with dyspnea (OR = 1.19, CI: 1.003-1.41, p < 0.001), fever (OR = 4.46, CI: 1.74-11.43, p 0.001), cough (OR = 3.61, CI: 1.55-8.39, p 0.002), odynophagia (OR =3.42, CI: 1.19-9.79, p 0.01), headache (OR = 3.09, CI: 1.18-8.07), and gastrointestinal symptoms (OR = 3.34, CI: 1.16-9.60, p 0.03) (Table 2).

As for comorbidities, those significantly associated with severe disease were arterial hypertension (OR = 11.42, CI: 4.78 - 27.30, p < 0.001), obesity (OR = 21.26, CI: 7.59 - 59.56, p < 0.001), COPD (OR = 60.95, CI: 11.53 - 322.2, p < 0.001), former smoking (OR = 12.46, CI: 5.09 - 30.51, p < 0.001), diabetes (OR = 5.96, CI: 1.77-0.09, p 0.01), previous cardiovascular disease (OR = 5.74, CI: 1.45-22.72, p 0.03), and active oncological disease (OR = 8.34, CI: 1.45 - 47.97, p 0.04) (Table 2).

All patients who received home hospitalization completed their telephone follow-up without any reported deaths or need for hospitalization. Among the patients who required hospitalization (72 cases), the median length of hospital stay was 6

TABLE 1. General characteristics of patients, comorbidities and initial clinical presentation (n = 413)

Characteristics	Frequency, % (n)
Age in years, median (IQR 25-75%)	37 (28-48)
Sex	
Female	55.2 (228)
Male	44.8 (185)
Comorbidities (n = 154)	
Arterial hypertension	9.9 (41)
Former smokers	8.2 (34)
Smokers	6.3 (26)
Obesity	4.6 (19)
Asthma	4.6 (19)
Hypothyroidism	4.4 (18)
Diabetes	3.9 (16)
Previous cardiovascular disease*	2.9 (12)
COPD	1.9 (8)
Active oncological disease	1.5 (6)
HIV infection**	1 (4)
Chronic renal disease***	0.7 (3)
Initial clinical presentation	
Fever	43.6 (180)
Headache	43.6 (180)
Odynophagia	39.5 (163)
Cough	34.9 (144)
Myalgia	29.1 (120)
Anosmia	20.8 (86)
Dysgeusia	13.1 (54)
Rhinitis/nasal congestion	8.5 (35)
Gastrointestinal symptoms	7.7 (32)
Dyspnea	1 (4)

IQR: interquartile range; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus.
*History of acute myocardial infarction, coronary artery disease requiring revascularization, heart failure, or atrial fibrillation.
** On antiretroviral therapy, CD4 value was unknown.
*** No dialysis required.

days (IQR 3.25-9.75). Of those initially hospitalized in a general ward (70 cases), 11.4% subsequently required ICU care. Mortality among hospitalized patients was 8.3% (6 cases). All 6 deceased patients required ICU stay and mechanical ventilation, and they all showed symptoms and comorbidities associated with greater severity. The overall mortality rate was 1.5% (6/413 patients).

DISCUSSION

Our work describes the main clinical characteristics, comorbidities, and commonly requested laboratory tests in cases of COVID-19 and the association between initial symptoms and comorbidities that are related to the severity of the disease. As relevant data, 37.3% showed comorbidities at

TABLE 2. Initial clinical presentation and comorbidities associated with severe

Symptoms	OR (95% CI)	*p-value*
Fever	4.46 (1.74-11.43)	0.001
Headache	3.09 (1.18-8.07)	0.01
Odynophagia	3.42 (1.19-9.79)	0.01
Cough	3.61 (1.55-8.39)	0.002
Myalgia	1.16 (0.48-2.76)	0.44
Anosmia	0.31 (0.07-1.36)	0.09
Dysgeusia	0.26 (0.03-1.98)	0.16
Rhinitis/nasal congestion	0.93 (0.90-0.95)	0.10
Gastrointestinal symptoms	3.34 (1.16-9.60)	0.03
Dyspnea	1.19 (1.003-1.41)	< 0.001
Comorbidities		
Arterial hypertension	11.42 (4.78-27.30)	< 0.001
Former smokers	12.46 (5.09-30.51)	< 0.001
Smokers	0.27 (0.01-4.70)	0.67
Obesity	21.26 (7.59-59.56)	< 0.001
Asthma	1.89 (0.41-8.71)	0.42
Hypothyroidism	2.02 (0.43-9.32)	0.35
Diabetes	5.96 (1.77-20.09)	0.01
Previous cardiovascular disease	5.74 (1.45-22.72)	0.03
COPD	60.95 (11.53-322.2)	< 0.001
Active oncological disease	8.34 (1.45-47.97)	0.04
HIV infection	1.92 (0.09-37.33)	0.27
Chronic renal disease	0.93 (0.91-0.96)	0.82

OR: odds ratio; CI: confidence interval

the time of diagnosis, with arterial hypertension being the main one, followed by a history of past smoking, current smoking, and obesity; similar to what has been observed in national studies such as that of Pulido et al.[12] The first symptoms to appear were fever and headache in 43.6% of cases, followed by odynophagia and cough. These data are consistent with several studies published in the literature.[3, 5-7, 13, 14]

Out of our entire population, 81.1% developed a mild disease, 12.8% moderate, and 6.1% had severe disease. These data are related to several studies that showed that 80% of patients with COVID-19 show mild disease.[1, 5-8] 15% of patients had moderate lung involvement, which required hospitalization, and 5% had severe respiratory failure, which resulted in death in half of these cases.[1, 6,7, 9, 10]

As a relevant finding of our study, we found that the initial symptoms of COVID-19 that are associated with the development of severe disease are: dyspnea ($p < 0.001$), fever (p 0.001), cough (p 0.002), odynophagia (p 0.01), headache (p 0.01), and gastrointestinal symptoms (p 0.03). Likewise, comorbidities associated with the worst prognoses were: arterial hypertension ($p < 0.001$), obesity ($p < 0.001$), COPD ($p < 0.001$), former smoking ($p < 0.001$), diabetes (p 0.01), previous cardiovascular disease (p 0.03), and active oncological disease (p 0.04).

As of the writing of this study, there are no national publications that assess the initial symptoms and their relationship with the severity of the disease. When comparing our results with the international literature, we saw that He et al[3] found in a population of 3,326 patients (selected from 20 articles, all based on the Chinese population), that from the initial symptoms, cough ($p < 0.001$), fever ($p < 0.001$), dyspnea (< 0.001), diarrhea ($p < 0.001$), fatigue ($p < 0.01$), expectoration ($p < 0.01$), myalgia ($p < 0.001$), hemoptysis

($p < 0.001$), abdominal pain ($p < 0.001$), and anorexia ($p < 0.001$) were associated with the risk of progressing to severe disease.

Rubio et al[7] conducted a cluster analysis of the Spanish SEMI-COVID-19 registry including 11 phenotypic variables in a cohort of 12,066 hospitalized patients. The study identified 4 phenotypic groups that predicted hospital prognosis. The groups associated with poor prognosis were C1 (cases that showed the isolated triad of fever, cough, and dyspnea) and C4 (diarrhea, vomiting, and/or abdominal pain). On the other hand, patients who belonged to group C2 (dysgeusia and/or anosmia) showed the best prognosis, along with group C3 (arthromyalgia, headache, and odynophagia).

Regarding comorbidities, several studies on different population groups have described that the presence of these comorbidities is associated with a higher risk of progressing to severe COVID-19. Advanced age, cardiovascular disease, diabetes mellitus, arterial hypertension, COPD, cancer, chronic kidney disease, obesity, and smoking are the main risk factors associated with severe COVID-19.[1, 2, 4, 5] Our findings mostly agree with published data, however; in contrast, former smoking ($p < 0.001$) was associated with a risk of severe disease. This result is consistent with what was published by Zhang et al[15] in a meta-analysis of 25 articles, which suggested that there was a significant relationship between former smokers and the risk of severe COVID-19, compared to current smokers (combined OR: 1.85, 95% CI: 1.33-2.55, $I^2 = 67.7\%$, $p < 0.001$).

Different studies have identified the main biomarkers that are associated with a higher risk of developing a worse course of the disease. In this regard, Tjendra et al[5] conducted a review of 43 cohort studies and 11 systematic reviews (including the meta-analysis) where they found that upon admission, most patients showed lymphopenia, neutrophilia, thrombocytopenia, prolonged PT, elevated D-dimer, high lactate levels, lower oxygen saturation, high neutrophil-to-lymphocyte ratio (> 5.0), and high systemic immune inflammation index (> 500). All patients had high initial levels of PCR and IL-6 (> 10 pg/ml), and a large subset of patients had elevated levels of LDH, D-dimer, procalcitonin, and ferritin. The presence of these abnormalities was associated with critical illness. Similarly, Zhou et al[14] conducted a retrospective cohort study including 191 patients with COVID-19. In comparison to survivors, non-survivors more frequently showed high LDH ($p < 0.001$), high procalcitonin ($p < 0.001$), increased levels of serum ferritin ($p < 0.001$), and elevated IL-6 ($p < 0.001$). When comparing these results with those obtained in our study, all patients who developed severe disease had mainly elevated levels of LDH, PCR, ferritin, and D-dimer.

The overall mortality rate was 1.5%, similar to what has been reported in different publications that mention a fatality rate between 1.4% and 4.3%.[16,17]

Our study has some limitations. As a retrospective study, collected data comes from electronic medical records, which are subject to biases that are inherent in data collection. The results only correspond to the experience of a single hospital center rather than multiple centers. In addition, several records were excluded because they did not have the minimum data necessary for the study or medical follow-up until final discharge. Biomarkers were requested according to the treating physician's criteria, so we do not have that particular data on all patients. Although we found significant associations with disease severity, more multicenter studies are necessary, with a larger number of participants, to replicate our findings in a large percentage of the national population.

In conclusion, patients diagnosed with COVID-19 whose initial manifestations include dyspnea, fever, cough, odynophagia, headache, and gastrointestinal symptoms have higher risk of developing a severe course of the disease. High blood pressure, obesity, COPD, former smoking, diabetes, previous cardiovascular disease, and active oncological disease are associated with a poor prognosis.

In order to prevent disease deterioration, it is vital to identify initial symptoms and comorbidities related to poor outcomes as soon as possible.

Conflict of interest
Authors have no conflict of interest to declare.

REFERENCES

1. Martínez E, Díez A, Ibáñez L, Ossaba S, Borruel S. Diagnóstico radiológico del paciente con COVID-19. Radiología 63. 2021;56-73. https://doi.org/10.1016/j.rx.2020.11.001

2. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol. 2020;1–14.
3. He X, Cheng X, Feng X, Wan H, Chen S, Xiong M. Clinical Symptom Differences Between Mild and Severe COVID-19 Patients in China: A Meta-Analysis. Front Public Health. 2021;8:561264. https://doi.org/10.3389/fpubh.2020.561264
4. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed [5/12/2021].
5. Tjendra Y, Al Mana AF, Espejo AP, et al. Predicting Disease Severity and Outcome in COVID-19 Patients: A Review of Multiple Biomarkers. Arch Pathol Lab Med. 2020;144:1465-74. https://doi.org/10.5858/arpa.2020-0471-SA
6. Wang D, Li1 R, Wang J, et al. Correlation analysis between disease severity and clinical and biochemical characteristics of 143 cases of COVID-19 in Wuhan, China: a descriptive study. BMC Infectious Diseases. 2020;20:519. https://doi.org/10.1186/s12879-020-05242-w
7. Rubio M, Corbella X, Mora JM, et al. Predicting Clinical Outcome with Phenotypic Clusters in COVID-19 Pneumonia: An Analysis of 12,066 Hospitalized Patients from the Spanish Registry SEMI-COVID-19. J. Clin. Med. 2020;9:3488. https://doi.org/10.3390/jcm9113488
8. Ministerio de Salud de la Nación. Recomendaciones para equipos de salud. Nuevo Coronavirus COVID-19. Actualizado al 14/04/2021. Disponible en: https://www.argentina.gob.ar/coronavirus/equipos-salud.
9. Geng MJ, Wang LP, Ren X, et al. Risk factors for developing severe COVID-19 in China: an analysis of disease surveillance data. Geng et al. Infect Dis Poverty. 2021;10:48 https://doi.org/10.1186/s40249-021-00820-9
10. Bats ML, Rucheton B, Fleur T, et al. Covichem: A biochemical severity risk score of COVID-19 upon hospital admission. PLoS One. 2021;16:e0250956. https://doi.org/10.1371/journal.pone.0250956
11. Coté A, Ternacle J, Pibarot P. Early prediction of the risk of severe coronavirus disease 2019: A key step in therapeutic decision making. EBioMedicine. 2020;59:102948. https://doi.org/10.1016/j.ebiom.2020.102948
12. Pulido L, Solís M, Ibarrola M, et al. Experiencia inicial en la atención de pacientes con COVID-19 en un hospital privado de alta complejidad de la Ciudad de Buenos Aires. Medicina (B Aires). 2020;80:433-38.
13. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382:1708-20. https://doi.org/10.1056/NEJMoa2002032
14. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054-62. https://doi.org/10.1016/S0140-6736(20)30566-3
14. Zhang H, Ma S, Han T, et al. Association of smoking history with severe and critical outcomes in COVID-19 patients: A systemic review and meta-analysis. Eur J Integr Med. 2021;43:101313. https://doi.org/10.1016/j.eujim.2021.101313
16. Du Y, Tu L, Zhu P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan. A retrospective observational study. Am J Respir Crit Care Med. 2020;201:1372-9. https://doi.org/10.1164/rccm.202003-0543OC
17. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-20. https://doi.org/10.1056/NEJMoa2002032