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BRIEF REVIEW

Severe COVID-19

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Abstract

Introduction: There are substantial variabilities of the clinical characteristics and outcomes of severe coronavirus disease (COVID-19) creating difficulty to do an optimal assessment of this condition. We reviewed the current English literature to quantify the findings of baselines characteristics and health outcomes of patients with severe COVID-19 primarily with acute respiratory distress syndrome (ARDS).

Methods: We examined only studies that assessed patients with proven COVID-19 by RT-PCR by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with at least one of the following severity criteria: severe COVID-19, treated in the ICUs, ARDS and/or invasive mechanical ventilation (IMV) treatment. We assessed the quality of the studies according to the National Heart, Lung and Blood Institute, Study Quality Assessment Tools.

Results: Seven of 39 studies fulfilled the inclusion criteria. These seven studies included a total 1,863 patients, the median age was 63.5 years (49-70). A total 370 (19.8%) were females. Four studies were from the USA, two from China and one from Italy. Comorbidities were reported in six studies. Fever was reported in five studies and it was present in 159 out of 272 patients. Cough and shortness of breath (SOB) were reported in four studies, they were present in 111 out of 142 and 100 out of 142 of patients respectively. The median of total lymphocytes was reported in five studies with a range of 400 – 889/ul. IMV ranged from 15% to 100% and mortality ranged from 14.6% to 88%. In a subgroup analysis by countries, patients from the US showed more comorbidities, higher percent of IMV and mortality. The assessment quality score of the seven studies was (5), for a total score of (8).

Conclusions: Severe COVID-19 was predominantly seen in male patients who were 60 years and older associated with comorbidities. Most of the patients were admitted at the ICU, needed IMV support due to ARDS and had a mortality range of 14.6-88%.

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Introduction

The new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the cause of the coronavirus disease-19 (COVID-19) and it was originally reported in Wuhan, China in December 2019. Today this unprecedented COVID-19 pandemic spread to the whole globe resulting in about 7,500,000 infected people and the loss of about 430,000 humans lives. [1] In relation to the severity of illness, COVID-19 has a spectrum of clinical presentations. Severe COVID-19 has been reported in about 14 % of patients with a fatality rate of 49%. [2] In the time of severe COVID-19 leading to an unexpectedly high number of deaths, it is important to examine history to reassure our best approaches to a new problem. Though severe COVID-19 is new for us, similar epidemics happened over time. In this regard, the historical quote the "Captain of the Men of Death" which was originally coined by John Bunyan for tuberculosis is very timely and wise to relate to severe COVID-19. [3] It is tempting to conceive that COVID-19 is the current Captain of Death.

It is important to highlight the exponential health care burden, morbidity, and mortality of severe COVID-19. The American Hospital Association estimates a total four-month financial impact of $202.6 billion in losses for America's hospitals and health systems, or an average of $50.7 billion per month. [4] The UN's Trade and Development Agency says

the slowdown in the global economy caused by the coronavirus outbreak is likely to cost at least $1 trillion. [5]

There are substantial variabilities of the clinical characteristics and outcomes of severe COVID-19, which creates difficulty in doing an optimal assessment of this condition. Though severe COVID-19 has been reported to present as septic shock, acute cardiac complication, stroke and involving many other organs; there is increasing evidence that the lung involvement resulting in ARDS is the most common and fatal complication. [6] The objective of the study is to review the current English literature to quantify the findings of clinical presentation and health outcomes of patients with severe COVID-19 primarily with acute respiratory distress syndrome (ARDS).

Methods

Database Search Strategies

We did a search in PubMed and Google Scholar using the queries "COVID-19", "Severe COVID-19", "Clinical Characteristics" and "Clinical Outcomes".

Inclusion Criteria

Studies that assessed patients with proven COVID-19 by RT-PCR for SARS-CoV-2. These studies examined and provided data of patients with severe COVID-19, patients treated in the ICUs, patients with the diagnosis of ARDS and patients who were receiving treatment with invasive mechanical ventilation.

Exclusion Criteria

Studies that did not include cases according to the inclusion criteria. Studies that claimed including cases according to our inclusion criteria, but they did not provide baseline clinical characteristics and outcomes.

Quality Assessment: We assessed the quality of the studies according to the National Heart, Lung and Blood Institute, Study Quality Assessment Tools. [7]

Results

Selected publications

Our search in the databases PubMed and Google Scholar revealed 39 publications. A total 32 publications were excluded according to the exclusion criteria and we selected eight publications for our review. Subsequently, a publication that reported assessing severe COVID-19 was eliminated because the reported findings were not consistent with severe COVID-19. This study reported A-a gradient for the non-severe and severe COVID-19 of 3.9 vs. 4.0 respectively. These reported severe cases showed a rate of ARDS of 15.6%, intensive care unit (ICU) admission of 19.1% and a mortality of 8.1%. This clearly indicates that most of these cases were not severe COVID-19. [8] Therefore, there were seven publications for our review. [2,9-14]

Total severe COVID-19 cases included by gender and age

Our study included a total 1,863 patients, the median age was 63.5 years and range was 49- 70 years. A total 370 (19.8%) were females. Four studies were from the USA, two from China and one from Italy. [2,9-14]

Reported comorbidities

The comorbidities reported in six studies were as follows: diabetes mellitus 254 (13.6%), arterial hypertension 604/1818 (33.2%), chronic obstructive pulmonary disease (COPD) 58/1779 (3.3%), chronic kidney disease (CKD) 51/1636 (3.1%).

Clinical symptoms

Fever was reported in five studies and it was reported to be present in 159 out of 272 patients included in the five studies. Cough and shortness of breath (SOB) were reported in four studies. In these four studies, cough was present in 111 out of 142 patients and SOB in 100 out of 142. None of the study reported vomiting and diarrhea.

Laboratory studies

The median of total lymphocytes was reported in five studies with a range of 400 – 889/ul. The arterial partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2) ratio was reported in three studies with a range of 69-492 (median 160).

Imaging studies

Imaging studies were reported only in four studies. Bilateral lung infiltrates in chest X-ray were reported in 161 out of 188 (85.6%) patients and ground-glass opacities (GGO) on computerized tomography (CT) in 15 out of 45 patients (33.3%).

Table 1. Baseline Characteristics and Outcomes of Patients with Severe COVID

Studies	Clinical Characteristics	Outcomes
Grasselli et al.[10] Journal. JAMA Number of patients. 1,591 Severity Criteria. ICU admission Country. Italy	Median age 63 years Female 18% DM 17%, HTN 49%, COPD 4%, CKD 3% PaO2/FiO2 median 160	Mortality 26% IMV 88%
Arentz et al.[11] Journal. JAMA Number of patients. 21 Severity Criteria. ICU admission Country. USA	Median age 70 years Female 48% DM 33.3%, COPD 33.3%, CHF 42.9%, CKD 47.6% Fever 52%, SOB 76% Total lymphocyte 889/ul PaO2/FiO2 ratio 169 CXR lung infiltrates 52%, b/l GGO 48%	Mortality 52.4% IMV 71%
Bhatraju et al.[12] Journal. NEJM Number of patients. 24 Severity Criteria. ICU admission Country. USA	Mean age 64 +/- 18 (23-97) years Female 38% DM 58%, CKD 21%, COPD 4% Fever 50%, SOB 88% Total lymphocytes 720/ul CXR lung infiltrates 100%, CT GGO 80%	Mortality 50% IMV 75%
Huang et al.[13] Journal. Lancet Number of patients. 13 Severity Criteria. ICU admission Country. China	Median age 49 years Female 15% DM 8%, HTN 15%, COPD 8%, CVD 23% Fever 100%, SOB 92% Total lymphocytes 400/ul D-dimer 2.4 mg/L CXR lung infiltrates 100%	Mortality 38% ARDS 85% IMV 15% NIMV 62% Septic shock 23% Cardiac injury 31% AKI 23%
Wu et al.[2] Journal. JAMA IM Number of patients. 84 Severity Criteria. ARDS Country. China	Median age 58.5 years Female 28.6% DM 19%, HTN 27.4% Fever 92.9%, SOB 59.5%, cough 81% Total lymphocytes 670/ul CRP 83 D-dimer 1.16 mg/L	Mortality 47.6% ICU 26.6% ARDS 41.8% IMV 21.3%
Goyal et al.[14] Journal. NEJM Number of patients. 130 Severity Criteria. IMV Country. USA	Median age 64.5 years Female 29.2% DM 27.7%, HTN 70 53.8%, COPD 5.4% Fever 34.6% CXR lung infiltrates 87.7%	Mortality 14.6%
Richardson et al.[9] Journal. JAMA Number of patients. 373 Severity Criteria. ICU admission Country. USA	Total lymphocytes 800/ul	*Mortality 88% IMV 320/373, 85.7%

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, computerized tomography; CVD, cardiovascular disease; CXR, chest x-ray; DM, diabetes mellitus; GGO, ground-glass opacities; HTN, hypertension; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIMV, noninvasive mechanical ventilation; PaO2/FIO2, arterial partial pressure of oxygen/fraction of inspired oxygen; SOB, shortness of breath. *Mortality in IMV 282/320, 88%

Outcomes

Baseline outcomes are depicted in **Table 1**.

Comparison of baseline clinical characteristics and outcomes in patients from USA and China.

To find out whether the type of medical practice and patient population by country could have influenced the clinical characteristics and outcomes, we compared the cases of severe COVID-19 by country. In this comparison, patients reported in the US showed more comorbidities more often, higher percent of IMV and mortality than those from China (**Table 2a and Table 2b**).

Table 2a. Baseline Characteristics and Outcomes of Patients with Severe COVID-19 from Studies from USA.

Studies	Clinical Characteristics	Outcomes
Arentz et al.[11] Journal. JAMA Number of patients. 21 Severity Criteria. ICU admission Country. USA	Median age 70 years Female 48% DM 33.3%, COPD 33.3%, CHF 42.9%, CKD 47.6% Fever 52%, SOB 76% Total lymphocyte 889/ul PaO2/FiO2 ratio 169 CXR lung infiltrates 52%, b/l GGO 48%	Mortality 52.4% IMV 71%
Bhatraju et al.[12] Journal. NEJM Number of patients. 24 Severity Criteria. ICU admission Country. USA	Mean age 64 +/- 18 (23-97) years Female 38% DM 58%, CKD 21%, COPD 4% Fever 50%, SOB 88% Total lymphocytes 720/ul CXR lung infiltrates 100%, CT GGO 80%	Mortality 50% IMV 75%
Goyal et al.[14] Journal. NEJM Number of patients. 130 Severity Criteria. IMV Country. USA	Median age 64.5 y Female 29.2% DM 27.7%, HTN 70 53.8%, COPD 5.4% Fever 34.6% CXR lung infiltrates 87.7%	Mortality 14.6%
Richardson et al.[9] Journal. JAMA Number of patients. 373 Severity Criteria. ICU admission Country. USA	Total lymphocytes 800/ul	*Mortality 88% IMV 320/373, 85.7%

Abbreviations: CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CT, computerized tomography; CXR, chest x-ray; DM, diabetes mellitus; GGO, ground-glass opacities; HTN, hypertension; ICU, intensive care unit; IMV, invasive mechanical ventilation; PaO2/FIO2, arterial partial pressure of oxygen/fraction of inspired oxygen; SOB, shortness of breath.

Table 2b. Baseline Characteristics and Outcomes of Patients with Severe COVID-19 from Studies from China.

Studies	Clinical Characteristics	Outcomes
Huang et al.[13] Journal. Lancet Number of patients. 13 Severity Criteria. ICU admission Country. China	Median age 49 years Female 15% DM 8%, HTN 15%, COPD 8%, CVD 23% Fever 100%, SOB 92% Total lymphocytes 400/ul D-dimer 2.4 mg/L CXR lung infiltrates 100%	Mortality 38% ARDS 85% IMV 15% NIMV 62% Septic shock 23% Cardiac injury 31% AKI 23%
Wu et al. [2] Journal. JAMA IM Number of patients. 84 Severity Criteria. ARDS Country. China	Median age 58.5 years Female 28.6% DM 19%, HTN 27.4% Fever 92.9%, SOB 59.5%, cough 81% Total lymphocytes 670/ul CRP 83 D-dimer 1.16 mg/L	Mortality 47.6% ICU 26.6% ARDS 41.8% IMV 21.3%

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; CXR, chest x-ray; DM, diabetes mellitus; HTN, hypertension; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIMV, noninvasive mechanical ventilation; SOB, shortness of breath.

Table 3. Quality Assessment of Studies of Severe COVID-19

Criteria	Grasselli, et al.[10] JAMA	Arentz et al.[11] JAMA	Bhatraju et al.[12] NEJM	Huang et al.[13] Lancet	Wu et al.[2] JAMA IM	Goyal, et al.[14] NEJM	Richards on et al.[9] JAMA
1. Was the study question or objective clearly stated?	1	1	1	1	1	1	1
2. Was the study population clearly and fully described, including a case definition?	1	1	1	1	1	1	1
3. Were the cases consecutive?	CD	CD	CD	CD	CD	CD	CD
4. Were the subjects comparable?	NR	NR	NR	NR	NR	NR	NR
5. Was the intervention clearly described?	NA	NA	NA	I	NA	NA	NA
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	1	1	1	1	1	0	1
7. Was the length of follow-up adequate?	1	0	1	0	1	1	1
8. Were the statistical methods well- described?	1	0	1	1	0	0	1
9. Were the results well-described?	1	1	1	1	1	0	1
Yes=1 No =0 Other (CD, NR, NA)* Score: / 8	6	4	6	5	5	3	6

Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Assessment of data quality

The assessment of data quality score for the seven studies was five for a total score of eight (**Table 3**).

Discussion

Our study examined seven studies addressing severe COVID-19 with an average quality score of 5 out of 8 points. These seven studies showed a substantial variability of the clinical characteristics and outcomes of patients with severe COVID-19. Severe COVID 19 was seen predominantly in males; six of the studies showed a range of 15% - 48% of females and an average of 29.5% female. [2,10-14] It means; less than 1 out of 5 patients with severe COVID-19 will be a woman. At the best interpretation of 4 out of 6 studies that provided the patients ages, the patients median age was 64 years and older. [10-12,14] Six of the studies revealed multiple comorbidities. [2,10-14] Diabetes mellitus, arterial hypertension and COPD were the most reported comorbidities.

The angiotensin converting enzyme (ACE)-2 has been established to play an essential role in preventing the development of the toxic inflammatory response in COVID-19. [15] Furthermore, ACE-2 was reported to decrease with aging and to have a lower expression in males. [16] The latter is related to the fact that the ACE-2 genes map to the X chromosome. [17] Similarly, ACE-2 is expressed less in patients with comorbidities. [15] In line with these specific distributions of the expression of the ACE-2, elderly male patients with comorbidities are expected to be the main patients with severe COVID-19 as reported by the studies in our review.

An important finding of our review is that fever was not very common among patients with severe COVID-19. Fever was common in studies reported in China and these studies have a lower mortality. [2,13] This observation is in line with the statement that fever is a marker of optimal host response to an injury. Interestingly, some studies showed that fever was present in only about 50% of patients and the same studies revealed a mortality of about 50%. [2,13] It could be speculated that patients without fever were severely ill and had a poor host response resulting in death.

Lymphopenia is a common laboratory marker of severe COVID-19 and it is being considered a major factor in the pathogenesis and mechanisms of the severity of COVID-19. [18] Severe COVID-19 has been associated with a cytokine release storm largely related to the ACE-2. The ACE-2 is found in many cells of different organs. ACE converts angiotensin-I into angiotensin-II, which through the angiotensin type-1 receptor (AT-1R), triggers vasoconstriction, inflammation, and thrombosis. [15] On the other hand, ACE-2 converts angiotensin II into angiotensin 1-7, which binds to angiotensin type 2 receptor (AT-2R) triggering vasodilation, less fibrosis and less thrombosis. Thus, ACE-2 is a master regulator of the renin-angiotensin system (RAS) by converting angiotensin I and angiotensin II to 1-9 and 1-7 respectively. Because ACE-2 is the receptor of SARS-CoV-2, upon the virus binds to ACE-2, the counter regulation activity of ACE-2 over renin-angiotensin system (RAS) is lost.

Our study has some weaknesses and strengths. Some of the weaknesses are related to the few numbers of studies, the quality of the studies, lack of standardization of baseline characteristics, and outcomes. All these factors resulted in an important variability of the characteristics and outcomes of patients with severe COVID-19. Many of the weaknesses are acceptable in view of the urgent need to report data of severe COVID-19. The strength of our review study is that according to our knowledge this is the first review study on severe COVID-19.

In conclusion, severe COVID-19 was predominantly seen in male patients aged 60 years and older associated mostly with diabetes mellitus, arterial hypertension, and COPD. Fever seems to be present in a half of the patients and more often SOB. Most of the patients were admitted at the ICU, needed IMV support due to ARDS and had a mortality range of 14.6-88%.

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