Clinical and epidemiological characteristics of severe Covid-19 Intensivecare units-admitted patients in the University Hospital of Blida- Algeria.

Caractéristiques cliniques et épidémiologiques des patients admis dansles unités de soins intensifs de l'hôpital universitaire de Blida- Algérie

A. Bouamra[1], A. Elkeboub[1], A. Ammimer[1], S. Dahnene[1], k. Sahraoui[2], A.R. Bouhamed[3], Z. Boukara[4], Y. Saada[5], Bezzaoucha[1]

1 : Epidemiology department - UH Blida - Faculty of medicine Blida-1 University (Algeria)
2 : Neurosurgery Department - UH Blida - Faculty of medicine Blida-1 –(Algeria)
3 : Infectious diseases Department - UH Blida – Faculty of medicine Blida-1 - (Algeria)
4 : Department of internal medicine and cardiology, UH Blida – Faculty of medicine Blida-1 (Algeria)
5 : Physical medicine and rehabilitation- - UH Blida – Faculty of medicine Blida-1 –(Algeria)
6 : Maxillo-facial Surgery Department– UH Douera- Saad- Dahleb University of Blida 1 (Algeria).

RESUME

OBJECTIVE

The aim of this study is to describe the clinical characteristics of the severe Covid-19 Intensive care units-admitted cases in the university hospital of Blida.

METHODS

The World Health Organization criteria, according to the local instructions, have been used to define a SARS-CoV-2 case. RT-PCR test or chest CT-Scan was required to classify the cases. Suspected or confirmed Covid-19 patients admitted in Intensive care units constituted the target-population of the study. The data were analyzed by SPSS software (20 versions).

RESULTS

In total, 560 patients were admitted in university hospital of Blida, 62.7% were admitted in Intensive care units. Most of the patients (62%) were male, median age was 65 YO [IQR 52.7-74.2]. More than a half presented co morbidity (55.4%). The most reported clinical characteristics were; Dyspnea (78.8%), cough (78.0%) and fever (77.9%). 262 deaths have been registered, 46.8% including 70.4% in ICU. Median age of deceased patients was 69 YO; more than half dead patients had at least one comorbidity (58%).

CONCLUSION

Clinical data of Covid-19 patients admitted in ICU of university hospital Blida contribute objectively to measure the degree of seriousness of the disease, and to get a better orientation and management of patients.

KEY WORDS: SARS-CoV-2, clinical characteristics, Intensive Care Unit, University hospital Blida (Algeria).

1 .INTRODUCTION

In December 2019, a series of acute pneumonia cases was identified in Wuhan- China, a virus-like pneumonia, recalling SARS-Cov.After the sequencing of samples collected in the lower respiratory tract, theChinese Center For Disease Control and Prevention (CCDC) isolated on January, 07, 2020 a novel Coronavirus: SARS-Cov-2[1,2], baptized on January12, 2020as 2019-CoVn [3] by the World Health Organization (WHO), then renamed Covid-19 three weeks later [4].In the latest three months, the Covid-19 epidemic spread all over the world[1]; on march 11, 2020, the WHO declared the SARS-Cov-2 pandemic [5],reaching at April 7 2020, 211 countries, with 1 214 466 confirmed cases and 67 767 deaths. In Algeria, at May 9, 2020, 494 deaths were reported among 5558 confirmed cases including 913 in the province of Blida [6].

The coronavirus, such as SARS and MERS,are responsible of respiratory tract infections in human[7]. The disease features in both infections and SARS-Cov-2 are similar, ranging from mild forms with good prognosis to serious forms with acute respiratory distress syndrome (ARDS) leading to hospitalization in Intensive care units (ICU) and sometimes to death, with a high mortality ratio (around 70%) [8,9]. This severe respiratory disease is named Covid-19 by the WHO [8].

The definitive diagnosis relies on the identification of the virus by the reverse transcription polymerization chain reaction (RT-PCR) in the respiratory collected samples[10,11]. However, facing the limited access to this technique, the diagnosis is made on the association of clinical evocative symptoms and radiological characteristic images, namely peripheral distribution (80%), ground-glass opacities (91%) and vascular thickening (58%)[12].

Due to the lack of PCR-kits in the university Hospital of Blida, only a part of suspected cases of SARS-Cov 2 were diagnosed by PCR technique and the CT-scan imaging was used as an orientation mean for diagnosis. Being non-specific, the CT-scanwas reserved to high probability cases (hospitalized patients with severe evocative clinical signs).

Furthermore, the physiopathologyof SARS-Cov-2 remains to this day, unclear. And without a vaccine, capable of decreasing the frequency and seriousness of this disease, it is particularly paramountto analyze the clinical characteristics, in order to identify, isolate and take over the potential cases, with the purpose of restraining the spread of the epidemic[13].

In this context, we aim, through this study to describe the clinical features reported in seriouspatients admitted in Intensive care unit of hospital of Blida (UH) of Blida, in comparison to patients hospitalized in two other units of the UH of Blida, dedicated to the management of moderate and severe Covid-19 cases.

2. METHODS

It is a descriptive cohortstudy about patients admitted in the intensive care unit of UH of Blida, and two other wards dedicated to Covid-19 management in the same hospital, during the period from March12, 2020 to May 09, 2020.

According to the official instructions, Covid-19 is suspected in three clinical situations: ***a) possible case:*** each individual showing clinical symptoms of acute respiratory infection with temperature or febrile sensation. ***b) Probable case:*** a/each individual with clinical symptoms of acute respiratory infection-having appeared within the 14 days following a close contact with a confirmed Covid-19 patient; or: b/each individual with clinical symptoms of acute respiratory infection and evocative thoracic CT-Scan Covid-19 images. ***c) Confirmed case:*** each symptomatic or non-symptomatic individual with confirmed SARS-CoV-2 infection byRT-PCRon a collected sample [14].

Are included in the study, all patients admitted in both wards of the hospital dedicated for suspected and confirmed Covid-19 cases, and all those hospitalized in the ICU, whether referred from Pulmonology ward and Infectious diseases ward, or directly admitted in ICU.

Data collection was performed by the medical crew of the department of Epidemiology and Preventive Medicine (SEMEP), with the collaboration of medical and paramedical staffs of the three concerned wards. The ICU was provided by 62 hospitalization beds and 52 respirators, supervised by a sufficient number of reanimation doctors and paramedics. With the objective, to take care of all serious cases referred from the 6 hospitals of the province of Blida. The two other Covid-19 wards were overseen by Infectious Diseases specialists and their staffs, disposing of respectively 48 and 56 beds and 2 respirators.

Standardized survey questionnaires provided by the National Health Ministry were used to collect data, after adjustement by the SEMEPto match the objective of the study.

For each survey questionnaire, we registered personal characteristics: municipality of residence, sex and age of the patient. Besides clinical characteristics: Clinical signs at the moment of admission, comorbidity, radiological features (CT scan imaging), virologic status (RT-PCR results on nasopharyngeal samples) and the hospital discharge modality (recovery, death).

The data were gathered from the medical file of each patient, the interrogatory of the doctor in charge of the patient, and theadministrative register of admissions department. The whole completed by the confirmation tests performed in the Virologic Laboratoryof Pasteur Institute of Algiers (IPA).

The patients involved in this study were Covid-19 confirmed cases by RT-PCR test, or patients presenting obvious evocative CT-scan images of SARS-CoV-2 pneumonia.

A major Epidemiologist Resident was in charge of compiling, controlling and capturing the data from the questionnaires.

The ARDS, mild and severe pneumopathy were defined according to the latest temporary WHO directives for the clinical management of severe acute respiratory infection [15]. Kidney lesion according to KADIGO world classification[16]. Cardiacimpairments: in case of new abnormalities on Electrocardiograma (ECG), Echocardiography and Troponin superior to the referenced limit[17] .Hypoxia: was defined as a PaO2/FIO2 ratio inferior to 300 mmHG[18].

The typical aspects of CT-scan images in SARS-CoV-2 pneumonia were identified as: posterior and sub-pleural distribution of ground-glass opacities associated to alveolar condensation homes, linear opacities, thickening of the bronchial walls and rarely pleurisy and pericardial effusion [19,20].

Hence, the clinical signs of SARS-CoV-2 infection comprised: temperature superior to 37,5°C, cough, sputum, dyspnea, breathlessness, myalgia, digestive symptoms such as diarrhea, nausea/vomit, neurological signs as headaches, anosmia, agueusia, mental confusion and stroke, but alsorenal disorders, myocardial lesions and ophthalmologic signs as conjunctivitis[21].

Comorbidity included: Hypertension, diabetes, nephropathies, pneumopathies, cardiovascular, neurological and neuromuscular diseases, cancer as well as some conditions like pregnancy, post-partum, Immunodeficiency, overweight, smoking...etc.

2.1 STATISTICAL ANALYSIS

The results were expressed through: Median, inter-quartile interval, and averagesupported by the standard deviation for quantitative variables and percentages for the qualitative variables. The admission and mortality rates were determined by the ratio of the numberof Covid-19 cases and the number of deaths, to the sum ofhospitalizations all diseases included, registered in the UH of Blida during the period of study.

The denominator used originates from the data of admission register. Box plots weredrawn up to illustrate the distribution of the quantitative variables. To meet the major objective, a descriptive analysis of the population wasperformed on the demographic, epidemiologic, radiologic, virologic, clinical and medical history data.

To meet the secondary objective, statistical tests (Pearson's chi-square test for qualitative variable and Student's t-test for quantitative variables) were used for comparison based on the medical and clinical characteristics of patientsin search of prognostic factors.

The data were analyzed by SPSS software (20th version) and Open Epi Calculator (Open Source Epidemiologic Statistics for Public Heath, www.OpenEpi.com). Significance level was agreed at 0, 05 and all the tests were bilateral.

3. RESULTS

Overall, 560 mildly to critically Covid-19- suffering patients of the province of Blida, were admitted in the UH of Blida from March 12, 2020 to May 09, 2020, corresponding to an admission rate of Covid-19 of 9,2%. Among whom, 348 cases were hospitalized in ICU, 62.1% of the whole cohort and 212 patients, 37.9% were admitted in the two other Covid-19 wards. The median Age of patients was 65 YO [IQR 52.7-74.2]. 65 YO and more was the more affected group age, with 56.2% in ICU versus 46.1% in the other wards **(p=0.027)**. It seemed also that patients under 18 YO represented 0.6% of the ICU-hospitalized cohort. Whatever was the hospitalization ward (ICU or the two others); male gender was predominant (62.0% of the cohort). In ICU, male gender represented 67.8%, while it was 52.4% in the other wards (p<0.001) *(Table 1)*. Concerning the clinical characteristics: dyspnea, cough, fever, asthenia, breathlessness were the most common signs, respectively (78.8%, 78.0%, 77.9%, 64.6% and 52.3%). The difference between ICU and the two other wards was only significant for dyspnea and breathlessness (p<0.001). Neurological signs were rare: mental confusion, irritability and seizures, respectively: 3.6%, 2.7% and 0.9% *(Table 2)*. The number of probable admitted cases (88.2%) was substantially more significant than PCR-confirmed cases (11.8%), (p<0.001). The Covid-19 characteristic CT-scan image was encountered without significant difference, in ICU patients (83.6%), and those who were admitted in the other wards (95.8%). The number of confirmed cases was significantly higher in ICU (16.4%) than in the other wards (4.2%). The average duration of hospitalization in ICU was shorter (3.25 ± 3.66 days), with a 2 days median, than in the other wards (5.31 ± 4.56 days), with a 5 days median (p=0.03) (Figure1). However, the median length of stay in the ICU for intubated patients was 1.5 days.

The exposition to a confirmed Covid-19 case in the 14 days preceding the first symptoms was found in 29 cases, 5.2% of the whole cohort with no significant difference between ICU and the other Covid-19 wards (p =0.24). Concerning

comorbidity: Arterial hypertension, was on the top with 33.9%, followed by diabetes (25.4%), Cardiovascular diseases (12.0%), chronic pneumopathies (6.3%), and renaldiseases(4.5%), without any significant difference between the three wards. ARDS was strongly related to age (54.1%, p= 0.01), but also to cough (80.0% p=0.02), fever (76.9%), hypertension (34%), diabetes (25.9%) and cardiovascular diseases (13.4%), however without any significant difference, with the exception of diabetes (p=0.03). *(Table3)*

Till the date of May 9, 2020, 262 deaths were registered, 46.8% of the whole cohort, representing a hospital mortality by Covid-19 of 4.3%. The ICU was involved in ¾ of deaths, (70.4%). while, the other two Covid-19 wards were involved in only 8.0 % of the total of Covid-19 deceased patients. The median time between symptoms appearance and admission at the hospital of all the cohort was 07 days (IIQ=4 – 9) and in deceased patient, the median time between the appearance of first symptoms and hospitalization was 09 days (IIQ 6- 14.5). The median age of deceased patients was 69 YO (IIQ: 59 – 77) which was significantly older than the undeceased patients, 59 years of age (IIQ: 46 – 72) Figure 2. Male gender was predominant in dead cases (71.8%; p<0.001). More than one in two, showed at least one comorbidity (58%). The most common associated diseases in dead cases was hypertension, diabetes, cardiovascular diseases, chronic pneumopathies, renal diseases and immunodeficiency, thyroid diseases respectively 33.6%,28.6%, 13.0%, 6.9%, 4.6%, 4.2%, and 1,9 %without any significant difference with non-deceased patients (34.2%,22.5%,11.1%, 6.0 %, 4.4 %, 3.4 % and 5.7 %), with the exception of thyroid disease, where the difference was significant (p=0.02).

Only few dead patients had history of cancer, smoking or overweight (1.5%, 0.4% and 1.1%). ARDS was far more frequent in deceased patients (n=235, 98.7%) versus undeceased patients (n=206; 69.1%): p<0.001a (Table 4). in ICU, acute respiratory distress syndrome was the most common complication in deceased patients (n=223; 91%) versus undeceased patients (n=81; 78%): p=0.002. Among the 348 ICU-admitted patients, 125 were intubated (35.9%), among whom 123 deceased: 98.4% of patients who had undergone invasive mechanical ventilation. In the two other Covid-19 wards, 06 patients have been intubated (2.8%), 02 of which had deceased (33.3%).

4. DISCUSSION
4.1 PRINCIPAL RESULTS

Our study described the main differences of clinical characteristics between Covid-19 patients admitted in ICU (recovered or deceased) and those with less serious condition, admitted in two other wards dedicated to Covid-19 management (recovered or deceased).

In ICU, the age of the admitted patients was substantially higher than the other individuals of the cohort. Male gender was predominant, ARDS was more common, and neurological disorders were greatly more encountered in ICU-admitted patients than in those hospitalized in the other Covid-19 wards. The average stay duration was shorter in ICU-admitted patients. The same clinical signs were found in cases admitted in the three wards, with dominance of cough and dyspnea in ICU. Digestive signs were far less common. ARDS was strongly related to age and commonly encountered in patients with hypertension and diabetes. The majority of the cohort cases presented Covid-19 characteristic radiological images (CT-scan). The median age in deceased patients was higher than in recovered ones. Male gender was predominant in deceased patients who had, at least, one comorbidity and ARDS was far more common in dead cases than in recovered ones. The ICU fatality was very high, and almost all individuals having undergone invasive mechanical ventilation deceased. The knowledge of clinical characteristics during this period, particularly marked by a lack of RT-PCR kits in the province of Blida, as well as all over the country, represented a huge contribution to the practitioners in charge of Covid-19 management wards.

4.2 EXPLANATION OF THE OBTAINED RESULTS

The opening of an Intensive Care Unit in the UHC of Blida, the sole in the province of Blida, was undoubtedly decisive in data collecting. In fact, it allowed gathering all the critical Covid-19 cases occurring in the province population, that completed the mass of information obtained in the two other wards dedicated to the management of mild and severe Covid-19 cases. Not to mention, the efficient collaboration of the medical and paramedical personnel of the concerned wards, as well as, the teamwork of the medical crew of the department of Epidemiology (SEMEP) who permitted achieving this study.

4.3 COMPARISON WITH OTHER STUDIES

The clinical characteristics of Covid-19 vary hugely depending on the degree of disease seriousness. Ranging from an asymptomatic illness[22,23]to a severe pneumopathy with high lethal risk. In accordance with the latest studies on the characteristics of Covid-19 patients requiring an ICU management[13,24]: Age superior to 65 YO, male gender, comorbidities, notably cardiovascular

diseases and hypertension, would be considered as aggravating factors of Covid-19 infection. Female patients seem to be less sensitive to SARS-CoV-2 particularly and viral respiratory infection in general (SARS-Cov-1 and MERS-Cov)[25-27]. This might be due to the protective role of chromosome X and sexual hormones, either through innate or adaptative immunity. Furthermore, over half the cases presented comorbidity, which would suggest the necessity of an early and special care of patients with risk factors. The median time between the appearance of symptoms and hospitalization was 07 days; this underlines the necessity to raise the population's awareness about the importance of early consultation and management, especially in persons with risk factors.

In line with the results of the latest studies on the characteristics of Covid-19 patients, the cardinal physical signswere: fever, cough, dyspnea and sputum[27,28],and there was no significant difference between ICU-patients and those admitted in the two other Covid-19 wards, except for dyspnea, breathlessness and neurological signs, which indicatea severe form of the illness, previously noticed during SARS-CoV-1 epidemic, where patients showed mental confusion, seizures and strokes[29,30].

The acute respiratory distress syndrome (ARDS), seemed to be strongly associated to the ICU fatality rate, but the frequency of ARDS observed, was far higher than reported in other studies [29]. Besides, the median time of stay in ICU was 1.5 days, lower than reported in the other studies [31,32], with a fatality rate of (70.4%), far higher than observed in the recent reports ranging from:16% to 26% ,38% and 62%[13,31–34].

The number of patients who required invasive mechanical ventilation represented 35.9%, less than in the recent studies (71%) (Whashinghton State, US)[32], 47% (Wuhan, China)[31], 42% (Wuhan, China)[8]. This could be explained by the management of most of the cases requiring non-invasive mechanical ventilation in the other Covid-19 wards. The mortality was almost total in the intubated patients of our series, higher than observed in other studies (81%)[8]; this might be due to multiple reasons,the serious condition of our patients who were referred in extremis to ICU after a time delay, in the other hand, being a new department created hastily, around a qualified but heterogeneous team, not used to work together under the authority of a new chief, it got hardly overwhelmed by the flood of ARDS in the early weeks of epidemic, lacking in this critical context of efficient pre-existing processes and therapeutic protocols, ever-changing, capable of adaptation to the patients specifics (elderly and/or with comorbidity).

4.4 STRENGTHS AND WEAKNESSES OF THE STUDY:

The serious shortage of RT-PCR collecting kits, in our country during the sanitary crisis of Covid-19, has made paramount the knowledge of the clinical and radiological of Covid-19 patients, to facilitate their diagnosis and anticipate their management. In this regard, our study was valuable by providing early descriptions of the clinical characteristics observed in moderate and severe patients admitted in the only intensive care unit dedicated to Covid-19, in the whole province of Blida, epicenter of the epidemic in Algeria. The active compilation of data by the physicians of the department of Epidemiology by extracting directly the information at source has chased away the spectre of failure of the procedure.

Nevertheless, our study has a few limits. Firstly, for most cases of the cohort, the diagnosis was, based on radiology (CT-scan), and not on RT-PCR; secondly, the follow-up was short compared to the evolution of the disease, and the becoming of the patientswho remain in hospital is unknown. Therefore, the stay and mortality rates might evolve. The third point is that there is certainly some loss of data, considering the fact that information was mainly collected from the medical files and an exhaustive interrogatory was hardly possible giventhe critical condition of patients at admissionwith impaired consciousness, which lead automatically to a loss of valuable information about medical history, comorbidity and subjective clinical signs. Thereby, a deeper study seems indicated for a better comprehension of risks factors, and the improvement of the medical management of patients.

Patients likely to be admitted in Intensive Care Unit are elderly men with comorbidity, and high risk of mortality, which emphasizes on the necessity of limiting the exposition of this vulnerable category of persons, providing them early medical care, and a closemonitoring during the hospitalization. The clinical data of the ICU patients of HUC of Blida, contribute, objectively to appreciate the degree of seriousness of the Covid-19 disease and the better management of each case.

BIBLIOGRAPHIE

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. New England Journal of Medicine 2020.

[2] Wu Y, Ho W, Huang Y, Jin D-Y, Li S, Liu S-L, et al. SARS-CoV-2 is an appropriate name for the new coronavirus. The Lancet 2020; 395:949–950.

[3] 3/-WHO.Clinical management of severe acute respiratory infection when Novel coronavirus (nCoV) infection is suspected: interim guidance: (accessed June 7, 2020).

[4] WHO.WHO Director-General's remarks at the media briefing on 2019-nCoV on 11February 2020.

[5] WHO Director-General's opening remarks at the media briefing on COVID-19 - 18 March 2020 - World.

[6] Suivi quotidien du Coronavirus COVID-19 Samedi 09 mai 2020 n.d.

[7] Yin Y, Wunderink RG. MERS, SARS and other coronaviruses as causes of pneumonia. Respirology 2018;23:130–137.

[8] Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine 2020.

[9] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Medicine 2020:1–3.

[10] Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Eurosurveillance 2020;25:2000045.

[11] Li Y, Yao L, Li J, Chen L, Song Y, Cai Z, et al. Stability issues of RT-PCR testing of SARS-CoV-2 for hospitalized patients clinically diagnosed with COVID-19. Journal of Medical Virology 2020.

[12] Bai HX, Hsieh B, Xiong Z, Halsey K, Choi JW, Tran TML, et al. Performance of radiologists in differentiating COVID-19 from viral pneumonia on chest CT. Radiology 2020:200823.

[13] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020;395:497–506.

[14] COVID-19_definition_cas_20200313.pdf n.d.

[15] Mondiale de la Santé O. Prise en charge clinique de l'infection respiratoire aiguë sévère (IRAS) en cas de suspicion de maladie à coronavirus 2019 (COVID-19): lignes directrices provisoires, 13 mars 2020. WHO/2019-nCoV/Clinical/2020.4; 2020.

[16] Maladie rénale: amélioration des résultats mondiaux (KDIGO) groupe de travail sur les lésions rénales aiguës Lignes directrices de pratique clinique du KDIGO pour les lésions rénales aiguës. Mars 2012.

[17] Gao C, Wang Y, Gu X, Shen X, Zhou D, Zhou S, et al. Association Between Cardiac Injury and Mortality in Hospitalized Patients Infected With Avian Influenza A (H7N9) Virus. Crit Care Med 2020;48:451–8.

[18] Sanz F, Gimeno C, Lloret T, Tormo N, Briones M, Fernández E, et al. Relationship between the presence of hypoxemia and the inflammatory response measured by C-reactive protein in bacteremic pneumococcal pneumonia. European Respiratory Journal 2011;38.

[19] Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, et al. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Investigative Radiology 2020;55:327–331.

[20] Zu ZY, Jiang MD, Xu PP, Chen W, Ni QQ, Lu GM, et al. Coronavirus disease 2019 (COVID-19): a perspective from China. Radiology 2020:200490.

[21] Plaçais L, Richier Q. COVID-19 : caractéristiques cliniques, biologiques et radiologiques chez l'adulte, la femme enceinte et l'enfant. Une mise au point au cœur de la pandémie. La Revue de Médecine Interne 2020;41:308–18.

[22] Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Eurosurveillance 2020;25:2000180.

[23] Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Science China Life Sciences 2020:1–6.

[24] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708–20. https://doi.org/10.1056/NEJMoa2002032.

[25] Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. International Journal of Infectious Diseases 2016; 49:129–33.

[26] Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, Perlman S. Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. J Immunol 2017;198:4046–53.

[27] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020.

[28] Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Internal Medicine 2020.

[29] Li Y-C, Bai W-Z, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. Journal of Medical Virology 2020;92:552–555.

[30] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurology 2020.

[31] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA 2020;323:1061–9. https://doi.org/10.1001/jama.2020.1585.

[32] Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. Jama 2020;323:1612–1614.

[33] Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. for the COVID-19 Lombardy ICU Network. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. Published online April 06, 2020. JAMA Doi 2020;10.

[34] Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. Jama 2020; 323:1612–1614.