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DETERMINANTS OF IN-HOSPITAL MORTALITY OF COVID-19 AMONG 2954 INPATIENTS IN A PRIVATE HOSPITAL NETWORK IN THE METROPOLITAN REGION OF BELO HORIZONTE

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ABSTRACT

Background: The COVID-19 pandemic brought challenges to different health systems around the world. Brazil was not spared. Information on the demographic characteristics of patients and their evolution are essential for coping with large numbers of patients. *Methods:* This retrospective cohort of 2954 patients with COVID-19 admitted to the Rede Mater Dei de Saúde Network, Belo Horizonte, Brazil, between March 21, 2020 and June 22, 2021 assessed demographic and clinical data as well as the use of therapeutic resources and mortality. Results: Our samples included 2954 patients, predominantly male (62.1%). The mean age of patients was 58.2 ± 17.5 years, it was found that increasing age was related to increased mortality. The overall mortality was 13.7%, and evaluations in a multivariate analysis, including: age (HR:1.074, CI:1.060-1.089, p=0.0001), systemic arterial hypertension (HR:1.595, CI:1.074-2.369, p=0.021), diabetes (HR:1.589, CI:1.092-2.312, p=0.016), increased respiratory rate (HR:1.053, CI:1.020-1.087, p=0.001), CRP (HR:1.012, CI:1.011-1.014, p=0.0001), TGO (HR:1.004, CI:1.001-1.007, p=0.006), lactate (HR:1.039, CI:1.007-1.072, p=0.015), total leucocytes (HR:1.356, CI:1.152-1.596, p=0.0001) and platelet count (HR:0.465, CI:0.366-0.593, p=0.0001), were able to predict the prognosis. *Conclusions:* There is a high mortality in patients hospitalized due to COVID-19, the presence of comorbidities, and age significantly increases mortality and the use of resources in the hospital.

INTRODUCTION

In late December 2019, several health units reported clusters of patients suffering from an unknown pneumonia, which were epidemiologically linked to a fish market in Wuhan City, Hubei Province in China[1,2]. On December 31, 2019, the China Center for Disease Control and Prevention (China CDC) sent a team of experts to Wuhan to investigate the etiology of the disease and its epidemiology[2]. On the same day, the Chinese authorities reported the presence of cases to the WHO China Country Office. After contacts with the Chinese health authorities, on January 5th, the WHO made the first preliminary report to the international scientific community[3]. On January 7, the Chinese CDC identified the etiological agent of the new disease outbreak, identified it as Coronavirus 2019 (2019-nCoV) and the disease called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Subsequently, on the recommendation of the WHO, it was officially named Coronavirus Disease 2019 (COVID-19)[3,4].

Less than 60 days later, WHO, on February 25, 2020, classified the disease as an International Public Health Emergency, and on March 11, its status was elevated to a pandemic[5]. Coronaviruses are RNA viruses that are widely distributed among different animal species such as cats, camels, cattle, and bats. However, on rare occasions, some anomalies occur where it can be transferred from animals to humans and subsequently, start transmissions between humans[6]. Some types of human coronaviruses can cause mild respiratory, intestinal, hepatic and neurological diseases[6,7]. Other types, including SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), can cause more serious and often fatal illnesses[8]. Both diseases started as animal diseases that were responsible for outbreaks in 2002-2003 in Guangdong, China, and in 2012 in the Middle East[9-12]respectively. Although 2019-nCoV is similar to some beta-coronaviruses seen in bats, it is demonstrably different from SARS-CoV and MERS-CoV2. SARS-CoV-2 is transmitted from person to person through respiratory particles of varying sizes, droplets (large particles) and aerosols (small particles) that are released from symptomatic individuals, or in the pre-symptomatic phase through coughing, sneezing or even speaking[13]. Like SARS-CoV, SARS-

CoV-2 enters human epithelial cells through angiotensin-converting enzyme receptors[14]. The biggest challenge in interrupting the transmission of the disease is that patients can transmit the disease 1 to 3 days before the onset of symptoms, and between 40 to 50% can be attributed to transmission in the asymptomatic or pre-symptomatic period[15-17]. Immediately before and shortly after the onset of symptoms, patients have high levels of viruses in the nasopharynx, which then drop rapidly over a period of 1 to 2 weeks. These levels are rarely maintained for a longer period, but the transmissibility in these circumstances is low[18]. Clinical manifestations are multiple and range from asymptomatic patients to pulmonary involvement leading to severe acute respiratory failure. The most common symptoms are fever (98.6%), fatigue (69.6%), dry cough (59.4%), anorexia (39.9%), muscle pain (34.8%), dyspnea (31 .2%), coughing up expectoration (26.8%), sore throat (17.4%),similartoInfluenza[19]. Manifestations outside the respiratory tract are less frequent, with diarrhea (10.1%), nausea (10.1%) and dizziness (9.4%) occurring 2 days before respiratory symptoms. Nausea is more frequently reported by less severe patients, while, in more severe cases, dyspnea is the leading symptom in patients that required ICU care[19].

Olfactory dysfunction often, but not always, was associated with ageusia, and may be an independent symptom. In a study that compiled several publications, with different research methods, reported prevalence rates were between 19.4 and 98.3%[20]. Heart rate and blood pressure on admission were similar both in more severe patients, admitted to the ICU, and less severe patients, admitted to the ward. Leukocytosis with neutrophilia, high levels of D-dimer, total CK and creatinine were higher in more severely compromised patients. Images can strongly suggest the diagnosis of coronavirus pneumonia. Typical changes can be seen in ground-glass infiltrates or alveolar consolidation. The mean time from symptom onset to ICU admission was 10 days[19]. The course of the disease varies greatly, with most cases classified as mild, and only a small number of critical cases. In a large series from China[21], 81% of caseswere mild (no pneumonia or mild pneumonia), 14% were classified as severe; where there was compromised oxygenation capacity or increased work respiratory rate, and thus required hospital admission (respiratory rate > 30, saturation < 93, when breathing room air, PaO2/FIO2 ratio < 300 or pulmonary infiltrate > 50%) and finally, 5% were critical, i.e., exhibited respiratory or circulatory failure or dysfunction of some other major physiological system. Overall mortality was 2.3%, with no deaths in mild cases, and no deaths in patients younger than 9 years of age. Mortality was measured to be at 49% among critical cases, and there was a positive association between increased mortality and increasing age and/or presence of specific comorbidities. Mortality was 8% among patients aged 70 to 80 years and 14.8% among patients with over 80 years of age. Patients with comorbidities also had a significant increase in mortality, with cardiovascular disease (10.5%), diabetes (7.3%), previous lung disease (6.3%), arterial hypertension (6%) and active neoplasia (5.3%) being the most frequent[21].

METHODS

The Mater Dei Health Network comprises of three private hospitals in the Metropolitan Region of Belo Horizonte, State of Minas Gerais. Combined, there are 536 infirmary beds, and 80 Intensive Care Unit (ICU) beds. During the peak period of the pandemic, however, there were 156 ICU beds. We performed an observational work, a retrospective cohort of all hospitalized patients, starting 03/21/2020 and ending 06/22/2021. The laboratory diagnosis was confirmed through a positive RT-PCR result for SARS-Cov-2 (Real-Time reverse transcriptase-polymerase chain reaction), according to the WHO guideline[22]. Data was automatically extracted from the patients' electronic medical records (gender, age, vital data, laboratory tests, length of stay, use of therapeutic resources and clinical outcome), and only data referring to comorbidities was obtained manually. Using this data, the variables were isolated, and indicators were calculated. The study was approved by the Research Ethics Committee of the Mater Dei Hospital, which waived the patient's informed consent, as

it was an observational, retrospective study in which no individual data could be identified.

Statistical Analyses

Data was entered in Microsoft Excel™ database for labeling and data tracking, and later analyzed using SPSS software (version 20.0, SPSS Inc., Chicago, Illinois). Comparisons between the study groups were made using bilateral hypothesis tests considering a significance level of 5% (α = 0.05). Continuous variables were evaluated by Student's t test and categorical variables by the x^2 test to compare differences between patients discharged or died. For the assessment of risk factors related to in-hospital mortality, univariate and multivariate analysis was performed using logistic regression with a 95% confidence interval as an estimate of the risk associated with a selected variable. Multivariate analysis was performed including all variables selected in univariate analysis.

RESULTS

The data refer to all adult patients (over 18 years old), admitted to the Mater Dei Health Network, with a diagnosis of acute infection by COVID-19, with the date of the first hospitalization being 03/21/2020 and the date of the last hospitalization on 06/22/2021. Patients were predominantly hospitalized from the Emergency Room of the hospital itself, with a small group of them being transferred from other institutions. During this period,the institution had 2954 hospitalizations with COVID-19 diagnosis. Those hospitalizations were used for the data in this retrospective cohort.In line with other publications, the hospitalized patients were predominantly male, with 62.1% of cases and 37.9% female (Table 1).

Table 1. Baseline characteristics of 2954 patients hospitalized with COVID-19 in a Health Network in the Metropolitan Region of Belo Horizonte

Characteristics	-
Male Gender n (%)	1835 (62.1)
Age ± DP (years)	58.2 ± 17.5
Obesity n (%)	921 (31.7)
Smoking n (%)	157 (5.3)
Hypertension n (%)	1426 (48.3)
Diabetes n (%)	683 (23.1)
COPD n (%)	111 (3.7)
Asthma n (%)	93 (3.1)
Coronary Disease n (%)	203 (6.9)
Cancer n (%)	102 (3.5)
Cerebrovascular Disease n (%)	100 (3.4)
Heart Failure n (%)	126 (4.3)
Liver Disease n (%)	20 (0.7)
Chronic kidney Disease n (%)	127 (4.3)
ICU Admission n (%)	865 (29.3)
Invasive Ventilation n (%)	570 (19.3)
Hospitalization time (days)	6.9 ± 10.8
Death n (%)	405 (13.7)

COPD: Chronic obstructive pulmonary disease

The overall mean age of the patients was 58.2 ± 17.5 years. This contrasts with the age of surviving patients (51.5±17.7), and of those who did not survive, the mean age was of 71.6 ± 15.7, which was significant, both in a univariate and multivariate analysis, with an HR of 1,065 (CI:1,057–1,077), for each year over 18 years of age. The mean hospital stay was 6.9 ± 10.8 days, with 6.01 days for those who survived, and 16.3 days for those who progressed todeath. The overall mortality of the studied population was 13.7%. Different factors, as seen below, were responsible for different fatalities rates. 865 patients required ICU admission, representing 29.3% of the sample, and 19.3% used invasive MV. The mortality of patients who required ICU admission was 36.3%, those who required invasive mechanical ventilation, mortality was measured at 62.5%. For those admitted to the ICU, the mean stay was 8.67±9 days, being 6.6±7.3 for survivors who were discharged, and significantly longer for non-survivors, being 12.4±10.5 (p=0.0001) (Table 2).

Table 2. Univariate analysis of clinical determinants of mortality in 2954 patients hospitalized with COVID-19 in a Health Network in the Metropolitan Region of Belo Horizonte

Variable	Death (405)	Discharge (2549)	Hazard ratio (CI)	p
Age (Media/DP)	71.6 ± 15.7	51.5 ± 17.7	1.065 (1.057–1.077)	0.0001
Male Gendern(%)	256 (63.8)	1579 (61.9)	1.055 (0.849–1.312)	0.626
Smoking n(%)	27 (6.7)	130 (5.1)	2.086 (0.964–4.513)	0.062
Hypertension (%)	263 (64.9)	1163 (45.6)	2.207 (1.774-2.746)	0.0001
Diabetesn(%)	153 (37.8)	530 (20.8)	3.239 (0.784 –13.387)	0.104
Obesity n(%)	105 (25.9)	816 (32)	2.971 (1.520–5.811)	0.001
COPD n(%)	37 (9.1)	74 (2.9)	1.853 (1.062-3.233)	0.000
Asthma n(%)	18 (4.4)	75 (2.9)	2.203 (1.241-3.911)	0.007
Coronary Disease n(%)	62 (15.3)	141 (5.5)	2.026 (1.140-3.600)	0.016
Cerebrovascular Disease n(%)	30 (7.4)	70 (2.7)	1.718 (1.033-2.858)	0.037
Heart Failure n(%)	33 (8.1)	93 (3.6)	2.071(1.189-3.606)	0.010
Chronic kidney Disease n(%)	45 (11.1)	82 (3.2)	1.799 (1050-3.084)	0.033
Liver Disease n(%)	6 (1.5)	14 (0.5)	1.800 (1.083-2.992)	0.023
Cancer n(%)	32 (7.9)	70 (2.7)	1.790 (1.061-3.019)	0.029
Systolic BP (mmHg)	126.4 ± 21.5	123.7 ± 17	1.008 (1.002-1.014)	0.005
Heart Rate (bpm)	85.5 ± 16.5	86.5 ± 17.7	0.996 (0.990-1.003)	0.258
Respiratory Rate (irpm)	21.9 ± 6.0	19.9 ± 5.4	1.065 (1.044-1.086)	0.0001
O2 Saturation (%)	89.1 ± 15.3	88.2 ± 22.6	1.002 (0.997-1.007)	0.48

COPD: Chronic obstructive pulmonary disease

Table 3. Univariate analysis of laboratory determinants of mortality in 2954 patients hospitalized with COVID-19 in a Health Network in the Metropolitan Region of Belo Horizonte

-	Deaths (405)	Discharge (2549)	*Hazard ratio (95% CI)*	p
O2 Saturation (%)	89.1 ± 15.3	88.2 ± 22.6	1.002 (0.997-1.007)	0.48
Total Leukocytes	9428.2 ± 5608.2	7695.6 ± 3470.0	1.450 (1.321 – 1.591)	0.0001
Neutrophils	7879.7 ± 4893.5	5837.1 ± 3184.5	1.615 (1.469- 1.775)	0.0001
Lymphocytes	937.1 ± 631.5	1156.6 ± 797.0	0.678 (0.591-0.778)	0.0001
Platelets	190291 ± 76299	226683 ± 81212	0.564 (0.492-0.646)	0.0001
C-reactive Protein	136.2 ± 88.7	81.3 ± 73.4	1.008 (1.007–1.009)	0.0001
Creatinine (mg/dl)	1.53 ± 1.33	1.11 ± 0.97	1.296 (1.192-1.409)	0.0001
D-Dimer	3162.9 ± 2901.5	2150.4 ± 1052.9	1.000(1.000-1.000)	0.23
LDH	480.8 ± 385.8	327.6 ± 129.8	1.004 (1.004-1.005)	0.0001
SGOT	104.5 ± 47.5	54.6 ± 45.8	1.005 (1.003-1.007)	0.0001
Bilirubin	0.64 ± 0,9	0,52 ± 0,8	1.173 (1.010- 1.369)	0,037
Lactate	4,3 ± 0,7	3.1 ± 0,5	1.033 (1.016-1.050)	0.0001
HCO3	22.5 ± 4,6	23.2 ± 3.1	0.940 (0.910-0.970)	0.0001

LDH: LactateDehydrogenase. SGOT: SerumGlutamic-oxaloacetic Transaminase. HCO3: Bicarbonate

The prevalence of comorbidities was high. Hypertension (48.3%), obesity (31.7%), diabetes (23.1%), coronary artery disease (CAD) (6.9%), heart failure (4.3%) were the main identified comorbidities. 5.3% of patients were active smokers. In a univariate analysis, the presence of pathologies was related to an increase in mortality but affected mortality rates differently. When evaluated in a multivariate analysis, only hypertension (HR:1.595, CI:1074-2369) and diabetes (HR: 1.589, CI:1092-2312) were related to increased mortality. The prevalence of comorbidities was high. Hypertension (48.3%), obesity (31.7%), diabetes (23.1%), coronary artery disease (CAD) (6.9%), heart failure (4.3%) were the main identified comorbidities. 5.3% of patients were active smokers. In a univariate analysis, the presence of pathologies was related to an increase in mortality but affected mortality rates differently. When evaluated in a multivariate analysis, only hypertension (HR:1.595, CI:1074-2369) and diabetes (HR: 1.589, CI:1092-2312) were related to increased mortality. The prevalence of comorbidities was high.

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Hemoglobin saturation measured at admission of patients, through pulse oximetry, was not able to predict mortality. Among the tests performed at admission and evaluated in univariate analysis, total leukocytes, neutrophil counts, lymphocyte counts, platelet counts, C-reactive protein (CRP), creatinine, lactic dehydrogenase (LDH), bilirubins, lactate and bicarbonate were able to define prognosis, but when submitted to a multivariate analysis, only PCR (HR: 1012 CI: 1011-1014), SGOT (HR: 1004 CI: 1001-1007), lactate (HR 1039 CI: 1007- 1072), total leukocytes (HR: 1356 CI: 1152-1596) and platelet count (HR: 0465 CI: 0366-0593) were shown to be capable of prognostic evaluation (Table 3 and 4).

DISCUSSION

This series is one of the biggest when accounting for patients treated in the same Hospital Network. Other case series were already published with one of them, similarly, treating patients from the same Hospital Network in New York City[23]. Other notable case series published included three studies, reporting early cases in Wuhan[24-27], cases from the Lombardy region in Italy[28-29] and the largest series ever published, which involved the entire United Kingdom[30]. Possibly due to a younger population, the prevalence of comorbidities was slightly lower in our series compared to New York[23] and the United Kingdom[30], but the most frequent comorbidities were the same. The New York series did not assess the impact of comorbidities on mortality[23]. Our series was able to demonstrate that co-morbidities such as hypertension (HR:1.595, CI:1074-2369) and diabetes (HR:1589, CI:1092-2312) were related to increased mortality.

Obesity, when evaluated in a univariate analysis, proved to be a risk factor, but when evaluated in a multivariate analysis, it did not remain a risk factor for death in our series, but was a factor for increased mortality in the United Kingdom[30].

Table 4. Multivariate analysis of the mortality determinants of 2954 patients hospitalized with COVID-19 in a Health Network in the Metropolitan Region of Belo Horizonte

Variable	HR	(95% CI)	p
Age (Years)	1.074	1.060-1.089	0.0001
Hypertension	1,595	1.074-2.369	0.021
Diabetes	1.589	1.092-2.312	0.016
Respiratory Rate (irpm)	1.053	1.020-1.087	0.001
C-reactive Protein	1.012	1.011-1.014	0.0001
SGOT	1.004	1.001-1.007	0.006
Lactate	1.039	1.007-1.072	0.015
Total Leukocytes	1.356	1.152-1.596	0.0001
Platelets	0.465	0.366-0.593	0.0001

SGOT: Serum Glutamic-oxaloacetic Transaminase.

Several other comorbidities were related to increased mortality, such as chronic lung disease, chronic kidney disease, degenerative neurological disease, dementia, moderate or advanced liver disease and cancer. Diabetes, in this series, was not related to increased mortality, unlike our series, where this was an important factor in mortality (HR:1.589, CI: 1092-2312)[30]. New York patients used ICU in 14.2% of cases, and invasive mechanical ventilation in 12.2%[23]. In the UK, 17% of patients were under ICU care and 10% of them used Invasive Mechanical Ventilation. Also, in the United Kingdom, 55% of patients used a high-flow nasal catheter and 16% of them used non-invasive ventilation[30]. The data above was not evaluated by us. We used both ICU admission(29.3%) and invasive mechanical ventilation (19.3%) in a greater proportion of patients than in the two series mentioned. The use of those devices was, related to an increase in mortality, with 36.3% mortality for patients admitted to the ICU, and 62.5% for those who required mechanical ventilation. This represents a lower mortality when compared to patients from New York, who had a mortality related to mechanical ventilation of 88%[23]. In the UK[30] and Lombardy[29] series, there was no definition of the clinical outcome of patients in a large number of cases, approaching or exceeding 50% of patients, not allowing an adequate comparison[30]. In relation to clinical examination data, during patient admission, it is difficult to predict the risk of death. Systolic blood pressure, heart rate, respiratory rate and saturation were evaluated.Using univariate analysis, heart rate and saturation were discarded as prognosis defining. Systolic blood pressure was also deemed as not prognosis defining after multivariate analysis. This leaves respiratory rate as the only variable that is able to estimate patient prognosis, with HR of 1053 (CI: 1020-1087).

When evaluating common admission laboratory tests, we achieved a better performance than with vital data. We evaluated several of these exams, which are routinelymeasured from the admission of patientswith COVID-19, or even without this pathology. When initially evaluated in a univariate analysis, total leukocytes, neutrophil counts, lymphocyte counts, platelet counts, C-reactive protein, creatinine, LDH, SGOT, bilirubin, lactate, and bicarbonate were all related to good prediction of outcomes. When submitted to a multivariate analysis, only total leukocyte count and platelet count, CRP, SGOT and lactate remained able to predict prognosis. The Wuhan series also evaluated laboratory alterations in terms of clinical outcome[24]. In univariate analysis, they observed that leukocyte count, neutrophil count, lymphocyte count, platelet count, CRP, creatinine, LDH, SGOT, bilirubin, lactate and bicarbonate were different in survivors and non-survivors. When evaluated, in a multivariate analysis however, only SGOT, CRP, lactate, lymphocyte count and platelet count maintained this ability to predict prognosis. Finally, the Wuhan series, like us, explored differences between survivors and non-survivors, and found positive results for leukocyte count, lymphocyte count, platelet count and LDH[24]. They further explored and found significance between survivors and non-survivors for:

Troponin, ferritin, IL-6, and pro-calcitonin, which was not studied by us[24]. D-Dimer, in our series, was not able to predict outcome.

Limitations: The main limitation of this work is its observational and retrospective. We believe that as the data was collected at patient admission and entered previously to the study, it reduced the bias caused by this type of cohort. Another important limitation worth mentioning is that as private hospital, where only private patients are admitted, it may not represent the full demographic set of this metropolitan region, allowing access to only a portion of the population.

CONCLUSIONS

There is a high mortality in hospitalized patients diagnosed with COVID-19, and the presence of increasing age and comorbidities significantly increases mortality and the use of resources in the hospital (ICU admission and Invasive Mechanical Ventilation).

REFERENCES

Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15;395(10223):507-513

Drosten C, Günther S, Preiser W, van der Werf S, Brodt HR, Becker S, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med.* 2003 May 15;348(20):1967-76.

Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. 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. 2020 Apr 28;323(16):1574-1581.

Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020 Apr 30;382(18):1708-1720.

He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med.* 2020 May;26(5):672-675.

Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020 Apr 16;181(2):271-280.e8.

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. Lancet. 2020 Feb 15;395(10223):497-506.

ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020 May 22;369:m1985.

Kimball A, Hatfield KM, Arons M, James A, Taylor J, Spicer K, et al. Public Health – Seattle & King County; CDC COVID-19 Investigation Team. Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility - King County, Washington, March 2020. MMWR Morb Mortal Wkly Rep. 2020 Apr 3;69(13):377-381.

Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, et al. SARS Working Group. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med.* 2003 May 15;348(20):1953-66.

Ma J, Qi X, Chen H, Li X, Zhang Z, Wang H, at al. Coronavirus Disease 2019 Patients in Earlier Stages Exhaled Millions of Severe Acute Respiratory Syndrome Coronavirus 2 Per Hour. *Clin Infect Dis.* 2021 May 18;72(10):e652-e654.

Masters PS, Perlman S. Coronaviridae. In: Knipe DM, Howley PM, eds. Fields virology. 6th ed. Lippincott Williams &Wilkins, 2013: 825-58.

Meng X, Deng Y, Dai Z, Meng Z. COVID-19 and anosmia: A review based on up-to-date knowledge. *Am J Otolaryngol*. 2020 Sep-Oct;41(5):102581.

Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA. 2020 May 12;323(18):1775-1776.

Richardson S, Hirsch JS, Narasimhan M, et al, and the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with covid-19 in the New York City area. JAMA 2020. May 26;323(20):2052-2059.

Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, et al. Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses. Trends Microbiol. 2016 Jun; 24(6):490-502.

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 Mar 17;323(11):1061-1069.

Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ. Presymptomatic Transmission of SARS-CoV-2 - Singapore, January 23-March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020 Apr 10;69(14):411-415.

Weiss SR, Leibowitz JL. Coronavirus pathogenesis. Adv Virus Res. 2011;81:85-164

WHO Coronavirus disease 2019 [Internet]. World Health Organization. 2020 [2020 Feb 14]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019

WHO Director-General's opening remarks at the media briefing on COVID-19: 11 March 2020. Published March 11, 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-themedia-briefing-on-covid-19---11-march-2020

WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance, 25 January 2020. Published January 25, 2020. https://apps.who.int/iris/handle/10665/330854

WHO: World Health Organization. Pneumonia of unknown cause – China. 5 january 2020. https://www.who.int/emergencies/disease-outbreak-news/item/2020-DON229

Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020 May;581(7809):465-469.

Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020 Apr ;323(13):1239-1242.

Wuhan Municipal Health Commission: Report of clustering pneumonia of unknown etiology in Wuhan City. Wuhan Municipal Health Commission, 2019. (http://wjw.wuhan.gov.cn/front/web/showDetail/2019123108989).

Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med*. 2012 Nov 8;367(19):1814-20.

Zhong NS, Zheng BJ, Li YM, Poon, Xie ZH, Chan KH, et al. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. Lancet. 2003 Oct 25;362(9393):1353-8.

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. Lancet. 2020 Mar 28;395(10229):1054-1062.

Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020 Feb 20;382(8):727-733.

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