Factors Associated with the Severity of Covid-19 in Jeddah, Saudi Arabia – A Retrospective Cohort Study

Wallaa Khalid Albishi[1], Iman K Ramadan[2], Sumyia Mehrin MD Abulkalam[3], Hanan Abdullah Alsaab[4], Mohammed Y. Bin Hayd[5], Mohammad A. AL-Ghamdi[6], Rajaa Al-Raddadi[7]

[1]Department of Community Medicine, King Abdulaziz University. BDS, M.Sc in Public Health (Epidemiology and Biostatics), Jeddah, Saudi Arabia,
[2]Professor Community Medicine, Department of Community Medicine, King Abdulaziz University, Jeddah, Saudi Arabia,
[3]Department of Community Medicine, King Abdulaziz University. MBBS, M.Sc in Public Health (Epidemiology and Biostatics), Jeddah, Saudi Arabia,
[4]Director of Medical Records Department, King Abdullah Medical Complex, Jeddah, Saudi Arabia
[5]Department of Community Medicine, King Abdulaziz University. BHSc, M.Sc in Public Health (Epidemiology and Biostatics), Jeddah, Saudi Arabia,
[6]Department of Community Medicine, King Abdulaziz University. MBBS, M.Sc in Public Health (Epidemiology and Biostatics), Jeddah, Saudi Arabia,
[7]Associate Professor Preventive Medicine, Department of Community Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
Email: Wallaa.Albishi@gmail.com

Abstract: Introduction: SARS-CoV-2 caused a major outbreak in December 2019 in Wuhan, China. The disease was declared a pandemic in March, 2020 by the World Health Organization (WHO). The disease caused over 8 million confirmed cases and almost 450,000 deaths. Our study aims to explore all risk factors associated with Covid-19 severity among hospitalized patients. Methods: Hospital-based records are retrospectively collected from a cohort of admitted RT-PCR COVID -19 positive patients aged 18 years and older. ISARIC data collection form was used to collect all potential risk factors. Logistic regression is used to calculate crude and adjusted OR. Statistical analyses will be done using STATA v.13.0. Results: 224 hospitalized Covid-19 patients were collected. The mean age was 48.6 (SD±15.1) years old. Patients were significantly older among the severe to critical cases than among the mild to moderate cases with a mean of 53.2 (SD±13.4) vs 43.4 (SD±15.2) ($p<0.05$). Having DM was more prevalent among the severe to critical cases than mild to moderate cases (69.9%) vs (30.2%). Having a history of DM (OR=3.18) was significantly associated with a severe form of Covid-19, along with other significant risk factors (<0.05): having a higher BMI (OR=2.04), fever (OR= 3.37), sore throat (OR=0.11), shortness of breath (OR=2.68), RR (OR=1.19), lymphocyte count (OR=0.59), WBC count (OR=1.38) and viral pneumonia (OR=10.03). Conclusion: Older age, being diabetic, dyspnea, decreased lymphocyte count, increased WBC and acquiring viral pneumonia can all significantly predict Covid-19 disease progression.

1. Introduction

Coronaviruses are enveloped RNA viruses that belong to the family Coronaviridae. In December 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) caused a major outbreak in Wuhan, China [1-4]. The virus has been causing multiple outbreaks and deaths and was a major public health concern. The disease was declared by the World Health Organization (WHO) as a pandemic in March, 2020 as it infects more people across the globe [5, 6]. As of June, 2020, the disease has caused over 8 million confirmed cases and almost 450,000 deaths and a reported case-fatality rate 1.6% among the Saudi population [7, 8]. COVID-19 disease has been causing a wide range of symptoms, from asymptomatic and mild illness to hospitalization, viral pneumonia with respiratory failure and death [9-12]. Although epidemiological factors have been previously published, studies exploring the risk factors and predictors associated with the severity of this disease have been scarce. Our study aims to explore other risk factors associated with Covid-19 severity among hospitalized patients by measuring and comparing the epidemiologic, demographic, clinical and laboratory characteristics with Covid-19 severity, as this can help in clinical management of hospitalized patients and reduction of mortality as well as exploring the dose-effect of RAAS medications use and the severity of Covid-19 disease, and to measure the effect of smoking among these patients as it has been recently hypothesized that the increased expression of ACE2 could place patients taking these medications and smokers at a greater risk for the virus or a worsening of the disease outcome by the possible downregulation of ACE2 after infection [13-15].

2. Methods:

Study design:

Hospital-based retrospective cohort study in Jeddah Region. Records are retrospectively collected from a cohort of RT-PCR confirmed Covid-19 patients through nasal or pharyngeal swabs and of age ≥ 18 years old, admitted in King Abdullah Medical Complex database (KAMC) from March 2020 till June 2020 in Jeddah Region. Data was collected from the first entry into the database from March, 2020 till June, 2020. The date of hospital admission will be the index date. KAMC is one of the largest hospitals and was the only one receiving covid-19 cases at the beginning of the pandemic with all cases being referred to this hospital. Patients who were pregnant, with incomplete medical records and those recodes in which patients were not reachable were all excluded from the study. Ministry of Health granted the ethical approval (1442-10056), all patients' information was anonymized for confidentiality. Consent was written by the researcher responsible for the phone call questionnaire and was taken verbally from the participants during the phone call questionnaire.

Data collection:

A modified standardized data collection form was used from the WHO/International Severe Acute Respiratory and Emerging Infection Consortium case record form for Covid-19 [16]. Demographic data was collected from MOH electronic medical records or through contacting patients for missing or incomplete information. Laboratory and medical history, BMI and comorbidities among Covid-19 admitted patients, Medication history including [pre-admission and at admission], clinical signs and symptoms on admission, in-admission vital signs, in-admission radiological findings, management protocol, reported complications and clinical outcomes among Covid-19 admitted patients. Laboratory Investigation included: complete blood count, coagulation profile, renal and liver function, creatine kinase, lactate dehydrogenase, and electrolytes, myocardial enzymes, ferritin and blood glucose levels. Questionnaire created for the collection of missing data and smoking status were based on the CDC classification of smoking status [17].

Endpoint Definitions:

The primary outcome is the severity of Covid-19 disease and is defined and stratified according to the MOH criteria for the disease into mild/moderate, severe and critical [18].

Mild to Moderate Covid-19 cases are defined as PCR-confirmed and are either asymptomatic or have symptoms (no O2 requirements/no evidence of pneumonia).

Severe and Critical Covid-19 Cases: Severe cases are defined as PCR-confirmed and have symptoms of ≥ 1 of the following: Respiratory rate ≥30/min, Blood oxygen saturation ≤93%, PaO2/FiO2 ratio 50% of the lung field within 24- 48 hours. Critical cases defined as having symptoms of ≥ 1 of the following: ARDS, Sepsis, Altered consciousness, Multi-organ failure, Patient with cytokine release syndrome (Serum IL-6 ≥3x upper normal limit, Ferritin >300 ug/L (or surrogate) with doubling within 24 hours, Ferritin >600 ug/L at presentation and LDH >250, Elevated D-dimer (>1 mcg/mL).

Statistical analysis:

Baseline, demographic and laboratory data was presented using Chi-square(X)2 test and for analyzing the categorical data, Fisher's exact test was used when appropriate and t-test was be performed for continuous variables. To measure the risk factors associated with disease severity, univariable and multivariable logistic regression analyses was used. The variables included in multivariable analysis were on the basis of the univariable analysis with a p-value <0.05, and previous findings and clinical importance. Previous studies have shown sex, age, comorbidities such as chronic kidney diseases and chronic pulmonary disease, symptoms such as fever, shortness of breath and cough, laboratory findings (blood leukocyte count and lactose dehydrogenase (LDH), d-dimer) and complications (cardiac injury and hyperglycemia), and drug therapy (corticosteroid, lopinavir/ritonavir, and umifenovir) during hospitalization were associated with severe disease course, thus, the aforementioned variables were added in the multivariable logistic regression analysis as appropriate [11, 19]. A two-sided α of less than 0.05 was considered statistically significant. Statistical analyses were done using STATA v.13.0.

3. Results:

A total of 224 patients were collected. The 224 patients had a mean of 48.6 years (SD±15.1), ranging from 18 years to 93 years. The mean age was 43.4 (SD±15.2) among the mild-to-moderate group compared to the mean age of 53.2 (SD±13.4) in the severe-to-critical group (p=0.000). Over half of the admitted patients (77.2%) were males, and (22.8%) were females. One-hundred-and-sixteen (69.1%) of the patients were employed and only 9 (4.4%) of them were employed as healthcare workers. A higher proportion of the employed patients had a mild to moderate disease severity (56.9%) and (61.5%) of the non-employed were severe to critical cases (p=0.03). All healthcare workers (n=9) experienced mild to moderate disease severity, while 195 of the employed patients were either mild to moderate cases (38.4%) or severe to critical (51.6%) (p=0.003). The proportion of hospitalized patients that were smokers was 10.3% (n=23), and was lower than 33.9% of the non-smokers (n=76). Almost 65.2% of the ever-smokers experienced a mild-to-moderate disease outcome, while 34.8% of them have experienced a severe-to-critical outcome (Table 1). The mean BMI was 30.1 (±5.9) in the severe to critical group compared to a mean of 28 (±7) among the mild to moderate group (p=0.04). Chronic cardiac diseases were significantly more prevalent among the severe to critical cases compared to mild to moderate cases (76.5% vs 23.5%; p=0.04), and diabetes mellitus (69.9% vs 30.1%; p=0.000, Table 1). The most common symptom on admission was shortness of breath (70.2% vs 29.8%), it was significantly more prevalent among the severe to critical cases than in the mild to moderate cases (p<0.05). Sore throat, headache, myalgia and diarrhea were significantly seen more commonly among the mild to moderate patients than severe to critical patients (p<0.05): (63.2% vs 36.8%), (72.4% vs 27.6%), (75% vs 24%), (76.5% vs 23.5%) and

(72% vs 28%) respectively. Upon admission, worse vital signs measurements were exhibited mostly among the severe to critical cases compared to the mild to moderate cases. Temperature mean (37.9 ±9 vs 36.7 ±4; p=0.22), heart rate (92.2 ±16.8 vs 87.9 ±13.3; p=0.04), respiratory rate (21.7 ±7.8 vs 19.4 ±1.3; p=0.003), oxygen saturation (94.5 ±5 vs 97.5 ±1.6; p=0.000), supplemental oxygen (100% vs 0%; p=0.000, Table 1). Laboratory findings were found among the severe to critical cases in comparison to mild to moderate cases: hemoglobin levels (12.6 ±2.3 vs 14 ±3; p=0.000), White blood cells count (8.8 ±4.1 vs 6.1 ±2; p=0.000), lymphocyte count (1.13 ±0.92 vs 1.57 ±0.76; p=0.000), neutrophil count (6.52 ±3.5 vs 3.8 ±1.7; p=0.000), hematocrit (39.6 ±5.9 vs 41.2 ±4.7; p=0.000), platelets (265.6 ±135.9 vs 229.9 ±91.8; p=0.03), INR (1.12 ±0.18 vs 1.04 ±0.1; p=0.004), ALT/SGPT (60.2 ±39.3 vs 46 ±44.4; p=0.02), AST/SGOT (63.4 ±38 vs 37.5 ±32.1; p=0.000), glucose (169.3 ±81.5 vs 135.1 ±50.5; p=0.003), urea/BUN (7.1 ±6.1 vs 3.97 ±2.6; p=0.000), creatinine (128.6 ±167.1 vs 89.8 ±114.3; p=0.049), CRP (22.13 ±18.1 vs 4.1 ±5.7; p=0.000), d-dimer (5.91 ±13.4 vs 0.70 ±0.88; p=0.006), ferritin (924.7 ±494.6 vs 270.9 ±376.4; p=0.000), Hb1c (9.4 ±2.2 vs 7.3 ±1.9; p=0.002, Table 2).Upon chest X-ray (CXR), 80.2% of patients with lung infiltration were severe to critical cases, while 19.8% of them were mild to moderate cases (p=0.000). Patients with lung infiltration on CT (83.3%) were observed among the severe to critical cases vs 16.7% by the mild to moderate cases (p=0.04). As well as 50% of the lung infiltration within 24-48 hours was exhibited only by the severe to critical cases (100% vs 0%; p=0.000, Table 2). Diuretics medication use was mostly given to severe to critical cases (84.6% vs 15.4%) than mild to moderate cases (p=0.02). Corticosteroid was less commonly given to severe to critical cases (14% vs 86%; p=0.000). Nonetheless, immune cytokine therapy (92.3% vs 7.7%; p=0.003), quinolones-based drugs (64.4% vs 35.6%; p=0.02) and antibiotics (67.9% vs 32.1%; p=0.000) were more commonly given to the severe to critical cases than mild to moderate cases. Patients needing oxygen therapy and high flow nasal cannula oxygen therapy were significantly more prevalent among the severe to critical cases, along with non-invasive ventilation, invasive ventilation and tracheostomy insertion (p<0.05). Being admitted to the intensive care unit were most commonly associated with the severe to critical cases (94.9% vs 5.1%; 0.000, Table 3). During hospitalization, patients have presented complications and were mostly common among the severe to critical cases: Viral pneumonia (90.7% vs 9.3%; p=0.000), cardiac arrest (100% vs 0%; p=0.000), cardiac ischemia (100% vs 0%; p=0.03), coagulation disorders/DIC (100% vs 0%; p=0.001), pulmonary embolism (100% vs 0%; p=0.003), acute renal failure (100% vs 0%; p=0.007) and hyperglycemia (78.6% vs 21.4%; p=0.004, Table 3). All patients who were on oxygen therapy after discharge were among the severe to critical cases (p=0.000). Of the 184 Covid-19 patients that were discharged alive, 105 (57.1%) of them were mild to moderate cases, while 79 (42.9%) were severe to critical cases. Among the 224 Covid-19 hospitalized patients, 40 patients died and were all among the severe to critical cases (p=0.000, Table 3). In our multivariate logistic regression (Table 4), variables adjusted for were BMI, Hx. DM, Hx. Fever, Hx. Shortness of breath, Hx. Sore throat, Respiratory rate, Lymphocyte count, WBC count and viral pneumonia. We found body mass index to be significantly associated with disease severity. OR= 2.04 (p=0.021; CI: (1.11 – 3.73)). BMI was treated and analyzed as a continuous variable because it had a better prediction in our model. We also found that being diabetic had an OR= 3.18 (p=0.032; CI: (1.10 – 9.17)). Signs and symptoms such as having a fever was associated with OR= 3.37 (p=0.032; CI: (1.11 – 10.23), shortness of breath OR= 2.68 (p=0.045; CI: (1.02 – 7.02)). Having sore throat was associated with OR= 0.11 adjusted odds of having a severe disease course (p=0.007; CI: (0.02 – 0.54)). Respiratory rate was significantly associated with disease severity, OR= 1.19 (p=0.021; CI: (1.03 – 1.38)). Laboratory tests such as lymphocyte count and white blood cells count were significantly associated with Covid-19 severity. lymphocyte count OR= 1.69 (p=0.022; CI: (0.38 – 0.93)), and WBC is associated with OR= 1.38 (p=0.001; CI: (1.14 – 1.66)) after adjustment. Lastly, the adjusted odds of Covid-19

severity is 10.03 more likely among patients that developed viral pneumonia (p=0.000; CI: (2.16 – 46.6))

Table 1: Sociodemographic and clinical characteristics among hospital admitted COVID 19 patients on admission.

	Total (n=224)	Mild-to-Moderate (n=105)	Severe-to-Critical (n=119)	P-value
Sociodemographic and clinical characteristics of patients on admission				
Age	48.60 ± 15.1 (46.61-50.58)	43.37 ± 15.2 (40.43-46.31)	53.21 ± 13.4 (50.77-55.65)	0.0000*
Sex				
Males	173 (100%)	78 (45.1%)	95 (54.9%)	0.32
Females	51 (100%)	27 (52.9%)	24 (47.1%)	
Employment Status				
Employed	116 (100%)	66 (56.9%)	50 (43.1%)	
Non-employed	52 (100%)	20 (38.5%)	32 (61.5%)	0.027*
Employed as a healthcare Worker				
Yes	9 (100%)	9 (100%)	0 (0%)	
No	195 (100%)	77 (48.4%)	82 (51.6%)	0.003*
Smoking Status at the time of Covid-19 Diagnosis (n=99)				
Ever-smoker	23 (100%)	15 (65.2%)	8 (34.8%)	0.20
Never-smoker	76 (100%)	38 (50%)	38 (50%)	
Body Mass Index	29.2 ± 6.5 (28.2-30.2)	28 ± 7 (26.4-29.7)	30.1 ± 5.9 (28.9-31.4)	0.037*
Hypertension				
Yes	62 (100%)	23 (37.1%)	39 (62.9%)	0.06
No	160 (100%)	82 (51.3%)	78 (48.8%)	
Diabetes Mellitus				
Yes	73 (100%)	22 (30.1%)	51 (69.9%)	0.000*
No	150 (100%)	83 (55.3%)	67 (44.7%)	
Type of Diabetes Mellitus				
Type-I	16 (100%)	2 (12.5%)	14 (87.5%)	0.001*
Type-II	57 (100%)	20 (35.1%)	37 (64.9%)	
None	150 (100%)	83 (55.3%)	67 (44.7%)	
Chronic Cardiac Diseases – Other than Hypertension				
Yes	17 (100%)	4 (23.5%)	13 (76.5%)	0.043*
No	206 (100%)	101 (49%)	105 (51%)	
Chronic Obstructive Pulmonary Diseases				
Yes	2 (100%)	0 (0%)	2 (100%)	0.50
No	220 (100%)	105 (47.7%)	115 (52.3%)	
Chronic Kidney Diseases				
Yes	7 (100%)	1 (14.3%)	6 (85.7%)	0.12
No	215 (100%)	103 (47.9%)	112 (52.1%)	
Malignant Neoplasms				
Yes	1 (100%)	0 (0%)	1 (100%)	1.00
No	222 (100%)	105 (47.3%)	117 (52.7%)	
Fever				
Yes	156 (100%)	68 (43.6%)	88 (56.4%)	0.09
No	66 (100%)	37 (56.1%)	29 (43.9%)	
Cough				
Yes	160 (100%)	71 (44.4%)	89 (55.6%)	0.16
No	62 (100%)	34 (54.8%)	28 (45.2%)	
Sore Throat				
Yes	29 (100%)	21 (72.4%)	8 (27.6%)	0.003*
No	194 (100%)	84 (43.3%)	110 (56.7%)	

Shortness of Breath				
Yes	124 (100%)	37 (29.8%)	87 (70.2%)	0.000*
No	99 (100%)	68 (68.7%)	31 (31.3%)	
Fatigue/Malaise				
Yes	13 (100%)	8 (61.5%)	5 (38.5%)	0.28
No	210 (100%)	97 (46.2%)	113 (53.8%)	
Muscle Ache/Myalgia				
Yes	17 (100%)	13 (76.5%)	4 (23.5%)	0.01*
No	206 (100%)	92 (44.7%)	114 (55.3%)	
Diarrhea				
Yes	25 (100%)	18 (72%)	7 (28%)	0.007*
No	197 (100%)	86 (43.6%)	111 (56.4%)	
Headache				
Yes	25 (100%)	19 (76%)	6 (24%)	0.002*
No	198 (100%)	86 (43.4%)	112 (56.6%)	
Temperature (°C)	37.3 ± 7.1 (36.3-38.2)	36.7 ± 4 (35.9-37.4)	37.9 ± 9 (36.2-39.5)	0.22
Heart Rate (beats/min)	90.1 ± 15.4 (88-92.1)	87.9 ± 13.3 (85.3-90.5)	92.2 ± 16.8 (89-95.3)	0.04*
Respiratory Rate (breaths/min)	20.6 ± 5.8 (19.8-21.3)	19.4 ± 1.3 (19.1-19.6)	21.7 ± 7.8 (20.2-23.2)	0.003*
Systolic Blood Pressure (mmHg)	126.9 ± 15.9 (124.8-129.1)	126.9 ± 16 (123.8-130)	127 ± 15.9 (124-130)	0.95
Diastolic Blood Pressure (mmHg)	73 ± 10.2 (71.6-74.4)	73.9 ± 9.9 (72-75.8)	72.1 ± 10.5 (70.2-74.1)	0.21
Oxygen Saturation (SaO2%)	96 ± 4 (95.4-96.5)	97.5 ± 1.6 (97.2-97.9)	94.5 ± 5 (93.5-95.4)	0.0000*
In-admission Any Supplemental Oxygen				
Yes	89 (100%)	0 (0%)	89 (100%)	0.000*
No	134 (100%)	105 (78.4%)	29 (21.6%)	

Table1: Data are n(%), mean ± SD, (CI),p-values were calculated by X^2 test or Fisher's exact as appropriate.*<0.05.

Table 2: Laboratory and radiological findings among hospital admitted COVID 19 patients on admission.

	Total (n=224)	Mild-to-Moderate (n=105)	Severe-to-Critical (n=119)	P-value
Laboratory and radiological findings of patients on admission				
Hemoglobin (g/dl)	13.2 ± 2.7 (12.9-13.6)	14 ± 3 (13.4-14.6)	12.6 ± 2.3 (12.2-13)	0.0002*
WBC Count (10^9/L)	7.6 ± 3.5 (7.1-8.0)	6.1 ± 2 (5.7-6.5)	8.8 ± 4.1 (8.1-9.6)	0.0000*
Lymphocyte Count (10^3/ µl)	1.33 ± 0.92 (1.2-1.5)	1.57 ± 0.76 (1.42-1.72)	1.13 ± 0.92 (0.95-1.31)	0.0003*
Neutrophil Count (10^3/ µl)	5.23 ± 3.12 (4.82-5.6)	3.8 ± 1.7 (3.4-4.1)	6.52 ± 3.5 (5.9-7.2)	0.0000*
Hematocrit (%)	39.6 ± 5.9 (38.9-40.4)	41.2 ± 4.7 (40.3-42.1)	39.6 ± 5.9 (37.1-39.5)	<0.05* 0.0003
Platelets (10^9/L)	248.7 ± 118.2 (232.8-264.6)	229.9 ± 91.8 (211.8-247.9)	265.6 ± 135.9 (240.3-291)	0.03*
APTT (seconds)	35 ± 24.3 (31.1-39)	30.6 ± 4.4 (29.4-31.9)	37.4 ± 29.7 (31.4-43.3)	0.11
PT (seconds)	14.5 ± 23.6 (10.6-18.3)	12.1 ± 1 (11.8-12.3)	15.7 ± 29.1 (9.9-21.6)	0.37
INR	1.1 ± 0.16	1.04 ± 0.1	1.12 ± 0.18	0.004*

	(1.07-1.12)	(1.01-1.1)	(1.08-1.16)	
ALT/SGPT (U/L)	53.8 ± 42.2 (47.8-59.7)	46 ± 44.4 (36.6-55.4)	60.2 ± 39.3 (52.7-67.7)	0.02*
AST/SGOT (U/L)	51.6 ± 37.6 (46.4-56.9)	37.5 ± 32.1 (30.8-44.3)	63.4 ± 38 (56.1 – 70.6)	0.0000*
Total Bilirubin (µmol/L)	11.9 ± 8.13 (10.6-13.2)	11.1 ± 7.7 (9.1-13.1)	12.4 ± 8.4 (10.7-14.13)	0.34
Glucose (mg/dL)	155 ± 72 (143.7-166.3)	135.1 ± 50.5 (122.7-147.5)	169.3 ± 81.5 (152.5-186.2)	0.003*
Urea/BUN (mmol/L) (Blood Urea Nitrogen)	5.7 ± 5.1 (4.98-6.35)	3.97 ± 2.6 (3.5-4.5)	7.1 ± 6.1 (5.98-8.2)	0.0000*
Creatinine (µmol/L)	110.3 ± 145.7 (90.9-129.7)	89.8 ± 114.3 (67.4-112.1)	128.6 ± 167.1 (97.9-159.3)	0.049*
Sodium (mmol/L)	138.6 ± 11 (137.1-140.1)	138.1 ± 4.5 (137.3-139)	139.02 ± 14.5 (136.4-141.7)	0.55
Potassium (mmol/L)	4.6 ± 10 (3.3-5.92)	3.9 ± 0.43 (3.8-4.0)	5.2 ± 13.7 (2.7-7.7)	0.35
CRP (mg/L)	17.5 ± 17.7 (13.7-21.2)	4.1 ± 5.7 (1.62-6.51)	22.13 ± 18.11 (17.7-26.6)	0.0000*
LDH (U/L)	433.6 ± 238.8 (361.8-505.4)	220.2 ± 55.1 (83.3-357.1)	448.8 ± 238.8 (374.1-523.6)	0.11
Creatine Kinase (U/L)	421.8 ± 802.8 (258.2-585.3)	225.7 ± 508.6 (-45.3-496.7)	461.5 ± 847 (271.8-651.2)	0.29
Troponin I (ng/mL)	0.43 ± 3.9 (-0.26-.11)	1.37 ± 7.6 (-1.42-4.2)	.10 ± 0.39 (0.25-0.19)	0.67
D-dimer (mg/L)	4.1 ± 11.1 (2.3-5.9)	0.70 ± 0.88 (0.46-0.95)	5.91 ± 13.4 (3.2-8.6)	0.006*
Ferritin(ng/mL)	671.4 ± 552.4 (548.4-794.3)	270.9 ± 376.4 (132.8-408.97)	924.7 ± 494.6 (782.6-1066.8)	0.0000*
HbA1c (%)	8.6 ± 2.3 (7.97-9.31)	7.3 ± 1.9 (6.3-8.3)	9.4 ± 2.2 (8.6-10.2)	0.002*
Radiological Findings				
Chest X-Ray (CXR)				
Lung-infiltration	116 (100%)	23 (19.8%)	93 (80.2%)	0.000*
No lung-infiltration	101 (100%)	80 (79.2%)	21 (20.8%)	
Computed Tomography Scan (CT)				
Lung-infiltration	18 (100%)	3 (16.7%)	15 (83.3%)	0.03*
No lung-infilration	33 (100%)	16 (48.5%)	17 (51.5%)	
Lung Infiltrate 50% of the lung field within 24-48 hours				
Yes	64 (100%)	0 (0%)	64 (100%)	0.000*
No	140 (100%)	101 (72.1%)	39 (27.9%)	

Table 2: Data are mean, n(%), (CI),p-values were calculated by X2 test or Fisher's exact as appropriate. WBC= White Blood Cells. APTT= Activated Partial Thromboplastin Time. PT= Prothrombin Time. INR= International Normalized Ratio. ALT/SGPT= Alanine Aminotransferase/Serum-glutamate-pyruvate-transaminase. AST/SGOT=. Aspartate Transaminase/Serum/glutamic-oxaloacetic-transaminase. CRP= C-reactive Protein. LDH= Lactate Dehydrogenase. *<0.05.

Table 3: Treatment, management, complications and outcome among hospital admitted COVID 19 patients on admission.

	Total (n=224)	Mild-to-Moderate (n=105)	Severe-to-Critical (n=119)	P-value
Treatments and management, complications and outcome				
Hypertensive Medications (n=224)				
Yes	35 (100%)	17 (48.6%)	18 (51.4%)	0.83
No	189 (100%)	88 (46.6%)	101 (53.4%)	
Angiotensin Converting Enzyme Medications (n=224)				
Yes	11 (100%)	7 (63.6%)	4 (36.5%)	0.36
No	213 (100%)	98 (46%)	115 (54%)	
Angiotensin Receptor Blockers (n=224)				
Yes	4 (100%)	2 (50%)	2 (50%)	1.00
No	220 (100%)	103 (46.8%)	117 (53.2%)	
Diuretics (n=224)				
Yes	13 (100%)	2 (15.4%)	11 (84.6%)	0.02*
No	211 (100%)	103 (48.8%)	108 (51.2%)	
Corticosteroids (n=224)				
Yes	50 (100%)	43 (86%)	7 (14%)	0.000*
No	174 (100%)	98 (56.3%)	76 (43.7%)	
Immune/Cytokines Therapy (n=224)				
Yes	13 (100%)	1 (7.7%)	12 (92.3%)	0.004*
No	211 (100%)	104 (49.3%)	107 (50.7%)	
Antiviral Medications (n=224)				
Yes	149 (100%)	65 (43.6%)	84 (56.4%)	0.17
No	75 (100%)	40 (53.3%)	35 (46.7%)	
Quinolines Based-drugs (n=224)				
Yes	73 (100%)	26 (35.6%)	47 (64.4%)	0.02*
No	151 (100%)	79 (52.3%)	72 (47.7%)	
Antibiotics (n=224)				
Yes	134 (100%)	43 (32.1%)	91 (67.9%)	0.000*
No	90 (100%)	62 (68.9%)	28 (31.1%)	
Management protocol				
High-flow Nasal Cannula Oxygen Therapy (n=223)				
Yes	44 (100%)	0 (0%)	44 (100%)	0.000*
No	179 (100%)	105 (58.7%)	74 (41.3%)	
Non-invasive Ventilation (n=221)				
Yes	28 (100%)	0 (0%)	23 (100%)	0.000*
No	193 (100%)	104 (53.9%)	89 (46.1%)	
Invasive Ventilation (n=215)				
Yes	32 (100%)	0 (0%)	32 (100%)	0.000*
No	183 (100%)	105 (57.4%)	78 (42.6%)	
Tracheostomy Insertion (n=222)				
Yes	18 (100%)	0 (0%)	18 (100%)	0.000*
No	204 (100%)	104 (51%)	100 (49%)	
Extra Corporeal Life Support (ECLS/ECMO) (n=220)				
Yes	6 (100%)	0 (0%)	6 (100%)	0.03*
No	214 (100%)	105 (49.1%)	109 (50.9%)	
Renal Replacement Therapy (RRT)/Dialysis (n=222)				
Yes	6 (100%)	1 (16.7%)	5 (83.3%)	0.22
No	216 (100%)	104 (48.2%)	112 (51.8%)	
Intensive Care Unit Admission/ICU (n=223)				
Yes	79 (100%)	4 (5.1%)	75 (94.9%)	0.000*
No	144 (100%)	101 (70.1%)	43 (29.9%)	
Complications				
Viral Pneumonia (n=218)				
Yes	43 (100%)	4 (9.3%)	39 (90.7%)	0.000*

No	177 (100%)	101 (57.1%)	76 (42.9%)	
Bacterial Pneumonia (n=217)				
Yes	2 (100%)	0 (0%)	2 (100%)	0.50
No	215 (100%)	105 (48.8%)	110 (51.2%)	
Acute Respiratory Distress Syndrome/ARDS (n=224)				
Yes	3 (100%)	0 (0%)	3 (100%)	0.25
No	221 (100%)	105 (47.5%)	116 (52.5%)	
Cardiac Arrest (n=221)				
Yes	37 (100%)	0 (0%)	37 (100%)	0.000*
No	184 (100%)	105 (57.1%)	79 (42.9%)	
Cardiac Ischemia (n=222)				
Yes	6 (100%)	0 (0%)	6 (100%)	0.03*
No	216 (100%)	104 (48.2%)	112 (51.9%)	
Coagulation Disorders/DIC (n=223)				
Yes	11 (100%)	0 (0%)	11 (100%)	0.001*
No	212 (100%)	105 (49.5%)	107 (50.5%)	
Pulmonary Embolism (n=220)				
Yes	9 (100%)	0 (0%)	9 (100%)	0.004*
No	211 (100%)	105 (49.8%)	106 (50.2%)	
Acute Renal Injury/Acute Renal Failure (n=223)				
Yes	8 (100%)	0 (0%)	8 (100%)	0.008*
No	215 (100%)	105 (48.8%)	110 (51.2%)	
Hyperglycemia (n=222)				
Yes	28 (100%)	6 (21.4%)	22 (78.6%)	0.004*
No	194 (100%)	98 (50.5%)	96 (49.5%)	
Outcome (n=224)				
Discharged Alive	184 (100%)	105 (57.1%)	79 (42.9%)	0.000*
Died	40 (100%)	0 (0%)	40 (100%)	
Post-discharge Oxygen Treatment (n=200)				
Yes	14 (100%)	0 (0%)	14 (100%)	0.000*
No	186 (100%)	105 (56.5%)	81 (43.5%)	

Table 3: Data are mean, n(%), (CI),p-values were calculated by X^2 test or Fisher's exact as appropriate. *<0.05.

Table 4: Multivariate Logistic Regression Model for Possible Predictors of Severity of Covid-19 among KAMC in Jeddah, SA.

	(OR)	**P-value**	(95% CI)	(OR*)	**P-value**	(95% CI)
Viral Pneumonia	12.96	0.000**	(4.44 – 37.8)	10.03	0.000**	(2.16 – 46.6)
Hx. Fever	1.65	0.09	(0.92 – 2.95)	3.37	0.032**	(1.11 – 10.23)
Hx. DM	2.87	0.001**	(1.58 – 5.20)	3.18	0.032**	(1.10 – 9.17)
Hx. Shortness of Breath	5.16	0.000**	(2.91 – 9.15)	2.68	0.045**	(1.02 – 7.02)
BMI	2.06	0.000**	(1.37 – 3.1)	2.04	0.021**	(1.11 – 3.73)
WBC Count (10^9/L)	1.38	0.000**	(1.22 – 1.55)	1.38	0.001**	(1.14 – 1.66)
Respiratory Rate (breaths/min)	1.22	0.001**	(1.08 – 1.36)	1.19	0.021**	(1.03 – 1.38)
Lymphocyte Count (10^3/ µl)	0.49	0.001**	(0.33 – 0.73)	0.59	0.022**	(0.38 – 0.93)
Hx. Sore Throat	0.29	0.005**	(0.12 – 0.69)	0.11	0.007**	(0.02 – 0.54)

*Adjusted OR
** <0.05

4. Discussion:

Males 173 (77.2%) were more affected than females as observed in many of the previous studies [9, 20, 21]. We did not find any significant disparity between males and females with disease severity, ruling out sex as risk factors for Covid-19 severity. We found older age, higher body mass index, presenting higher heart and respiratory rate upon admission and decreased oxygen saturation are commonly presented among our cohort. Additionally, elevated biomarkers such as WBCs, neutrophil count, platelet count, INR, ALT, AST, glucose, urea/BUN, CRP, D-dimer, creatinine, ferritin and HbA1c are all significantly more common among severe to critical Covid-19 patients. Previous studies showed that increased age was an important predictor of Covid-19 severity and mortality [22, 23] This can be explained by the higher proportion of older adults exhibiting comorbidities and age-related chronic diseases than the younger population [24]. Only 4% of the Covid-19 hospitalized patients were smokers in our study, which is a low prevalence of smokers compared to 16% in the general population [25]. This can be due to the age represented by the ever-smokers as the mean age is higher than non-smokers and older age was previously established to be a predictor to disease severity, or the cessation of smoking among the older age group due to the presence of comorbidities as Ho FK et al. mentioned [24]. Previously, Khan A et al. noted that patients who had DM and cardiac diseases are associated with Covid-19 complications and mortality [51]. We found chronic cardiac diseases and diabetes mellitus to be significantly associated with SARS-CoV-2 disease severity. In fact, diabetic patients have 3 times the odds of developing a severe to critical outcome than non-diabetic patients. As mentioned by Lim S et al., elevated glucose level directly increases viral replication thus explaining why hyperglycemia is an independent predictor of morbidity and mortality in patients with Covid-19 [26]. In our current study, it shows that 22 (78.6%) of those who developed hyperglycemia were among the severe to critical cases. Obesity is an important risk factor and plays a role on the immunological responses against viral infections. Body mass index has also been reported as an independent predictor of Covid-19 morbidity and mortality, as body fat accumulates, it places obese individuals at a greater risk for many diseases as well as increased mortality [27, 28]. We found patients at two times the odds of developing severe to a critical outcome with each unit increase in BMI. Similar to previously conducted studies [9, 29], our data shows signs and symptoms such as cough, fever and shortness of breath to be significantly more prevalent among severe to critical cases. These can indicate disease progression and severe damage to the alveoli [30]. Our logistic analysis shows shortness of breath and respiratory rate as independent predictors of a worsened SARS-CoV-2 infection. [20, 21, 30]. Infiltration on CXR and CT were presented highly among the severe to critical cases which acts as an important indicator of disease severity [31]. Lymphocytes have a key role in protecting the body from viral infections [32, 33]. Our data shows, on average, the odds of developing severe to critical cases is 1.69 times more likely with every unit decrease in lymphocyte count. CRP is induced by IL-6 in the liver, it has been elevated in multiple types of inflammation and infections [34]. Severe to critical cases in our study significantly show elevated levels of CRP compared to mild to moderate cases, as well as D-dimer levels. D-dimer elevation upon admission was more prevalent and was associated with increased disease severity and in-hospital mortality [35, 36]. Prior studies show that D-dimer levels greater than 2.0 µg/mL on admission could predict in-hospital mortality among Covid-19 patients. As a response to increased inflammation and hypoxia from Covid-19 illness due to pneumonia, coagulation and fibrinolysis get activated, and is followed by the hypercoagulable state and leading to disseminated intravascular coagulation (DIC) [19]. Thus, D-dimer acts as a crucial biomarker in determining the severity and prognosis of Covid-19 severity and in-hospital mortality. Among our hospital admitted patients with Covid-19 we found DIC to be entirely prevalent among severe to critical cases. Zhang et al., showed a positive protective pattern with the use of renin-angiotensin-aldosterone-system (RAAS)

medications among SARS-CoV-2 infected patients. All-cause mortality was decreased among the ACEi/ARBs group compared to the non-ACEi/ARBs group [37]. We did not observe any statistically significant difference among RAAS medications users and non-users with regards to Covid-19 severity, but it confirms the results found in some previously conducted studies [38, 39]. Viral pneumonia was 90.7% presented among the severe to critical patients in our study. In this current study, about 54% of those patients that died developed Covid-19 viral pneumonia. Along with viral pneumonia, other complications such as pulmonary embolism, cardiac ischemia, acute renal failure and cardiac arrest were almost entirely prevalent among the severe to critical patients. It was suggested that this elevated risk of cardiovascular complications among Covid-19 patients may be attributed to the presence of ACE2 receptors on myocytes and vascular endothelial cells, directly affecting the cardiovascular system. Additionally, it may be due to an increase in cytokines production and plaque rupture and increased cardiac demand [40].

This study faced some limitation. First, this was a retrospective study with data collected from electronic medical records, lack of complete medical records was encountered resulting in a lesser sample size that could have attenuated the relationship for some factors. Second, some information was not recorded such as lifestyle habits, dietary habits, alcohol intake and exercise. Lastly, some biomarkers such as IL-6 and INF-y were not recorded. Despite the limitations, to the best of our knowledge, this is one of the fewest studies done in the Kingdome of Saudi Arabia to study all epidemiological predictors of disease severity with a wide range of population especially with allowance of all residents to be treated in the Kingdom which increases the generalizability. And the first to assess the smoking status and the use of ARBs, ACEi and other medications pre-admission and on-admission with regards to disease severity.

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Pal, M., Berhanu, G., Desalegn, C., & Kandi, V. (2020). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): an update. Cureus, 12(3). doi: https://doi.org/10.7759/cureus.7423
2. Azkur, A. K., Akdis, M., Azkur, D., Sokolowska, M., van de Veen, W., Brüggen, M. C., ... & Akdis, C. A. (2020). Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy, 75(7), 1564-1581. doi: https://doi.org/10.1111/all.14364
3. Phelan, A. L., Katz, R., & Gostin, L. O. (2020). The novel coronavirus originating in Wuhan, China: challenges for global health governance. Jama, 323(8), 709-710. doi: https://doi.org/10.1001/jama.2020.1097
4. Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., ... & Tan, W. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The lancet, 395(10224), 565-574. doi: https://doi.org/10.1016/S0140-6736(20)30251-8
5. Chan, J. F. W., Yuan, S., Kok, K. H., To, K. K. W., Chu, H., Yang, J., ... & Yuen, K. Y. (2020). A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The lancet, 395(10223), 514-523. doi: https://doi.org/10.1016/S0140-6736(20)30154-9
6. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020. (https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020).

7. World Health Organization. Coronavirus disease (COVID-2019) situation reports. 2020. Available on: https://www. WHO. Int/docs/default
8. Johns Hopkins University and Medicine (Coronavirus resource center) https://coronavirus.jhu.edu/data/mortality .
9. Zhang, J., Wang, X., Jia, X., Li, J., Hu, K., Chen, G., ... & Dong, W. (2020). Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clinical microbiology and infection, 26(6), 767-772. doi: https://doi.org/10.1016/j.cmi.2020.04.012
10. Cao, Y., Hiyoshi, A., & Montgomery, S. (2020). COVID-19 case-fatality rate and demographic and socioeconomic influencers: worldwide spatial regression analysis based on country-level data. BMJ open, 10(11), e043560. doi: https://doi.org/10.1136/bmjopen-2020-043560
11. Li, X., Xu, S., Yu, M., Wang, K., Tao, Y., Zhou, Y., ... & Zhao, J. (2020). Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. Journal of Allergy and Clinical Immunology, 146(1), 110-118. doi: https://doi.org/10.1016/j.jaci.2020.04.006
12. Guan, W. J., Liang, W. H., Zhao, Y., Liang, H. R., Chen, Z. S., Li, Y. M., ... & He, J. X. (2020). Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. European Respiratory Journal, 55(5). doi: https://doi.org/10.1183/13993003.00547-2020
13. Alraddadi, B. M., Watson, J. T., Almarashi, A., Abedi, G. R., Turkistani, A., Sadran, M., ... & Madani, T. A. (2016). Risk factors for primary Middle East respiratory syndrome coronavirus illness in humans, Saudi Arabia, 2014. Emerging infectious diseases, 22(1), 49. doi: https://doi.org/10.3201/eid2201.151340
14. Wang, J., Luo, Q., Chen, R., Chen, T., & Li, J. (2020). Susceptibility analysis of COVID-19 in smokers based on ACE2. Preprints 2020, 2020030078. doi: https://doi.org/10.20944/preprints202003.0078.v1
15. Patanavanich, R., & Glantz, S. A. (2020). Smoking is associated with COVID-19 progression: a meta-analysis. Nicotine and Tobacco Research, 22(9), 1653-1656. doi: https://doi.org/10.1093/ntr/ntaa082
16. ISARIC COVID-19 CORE CASE RECORD FORM 05, JUL, 21. Adapted from SPRINT SARI CRF by ISARIC. Licensed under a Creative Commons Attribution-ShareAlike 4.0 International License by ISARIC on behalf of Oxford University.
17. NHIS- Adult Tobacco Use- Glossary – CDC https://www.cdc.gov/nchs/nhis/tobacco/tobacco_glossary.htm.
18. Ministry of Health. Coronavirus Diseases 19 (COVID-19) guidelines. March 2020, version 2.0
19. https://www.moh.gov.sa/en/Ministry/MediaCenter/Publications/Pages/covid19.aspx
20. Sim, B. L. H., Chidambaram, S. K., Wong, X. C., Pathmanathan, M. D., Peariasamy, K. M., Hor, C. P., ... & Goh, P. P. (2020). Clinical characteristics and risk factors for severe COVID-19 infections in Malaysia: A nationwide observational study. The Lancet Regional Health-Western Pacific, 4, 100055. doi: https://doi.org/10.1016/j.lanwpc.2020.100055
21. Al Mutair, A., Alhumaid, S., Alhuqbani, W. N., Zaidi, A. R. Z., Alkoraisi, S., Al-Subaie, M. F., ... & Al-Omari, A. (2020). Clinical, epidemiological, and laboratory characteristics of mild-to-moderate COVID-19 patients in Saudi Arabia: an observational cohort study. European Journal of Medical Research, 25(1), 1-8. doi: https://doi.org/10.1186/s40001-020-00462-x
22. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... & Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet, 395(10223), 497-506. doi: https://doi.org/10.1016/S0140-6736(20)30183-5

23. Shabrawishi, M., Al-Gethamy, M. M., Naser, A. Y., Ghazawi, M. A., Alsharif, G. F., Obaid, E. F., ... & Alwafi, H. (2020). Clinical, radiological and therapeutic characteristics of patients with COVID-19 in Saudi Arabia. PLoS One, 15(8), e0237130. doi: https://doi.org/10.1371/journal.pone.0237130
24. Brodin, P. (2021). Immune determinants of COVID-19 disease presentation and severity. Nature Medicine, 27(1), 28-33. doi: https://doi.org/10.1038/s41591-020-01202-8.
25. Ho, F. K., Petermann-Rocha, F., Gray, S. R., Jani, B. D., Katikireddi, S. V., Niedzwiedz, C. L., ... & Pell, J. P. (2020). Is older age associated with COVID-19 mortality in the absence of other risk factors? General population cohort study of 470,034 participants. PLoS One, 15(11), e0241824. doi: https://doi.org/10.1371/journal.pone.0241824
26. Moradi-Lakeh, M., El Bcheraoui, C., Tuffaha, M., Daoud, F., Al Saeedi, M., Basulaiman, M., ... & Mokdad, A. H. (2015). Tobacco consumption in the Kingdom of Saudi Arabia, 2013: findings from a national survey. BMC public health, 15(1), 1-10. doi: https://doi.org/10.1186/s12889-015-1902-3.
27. Lim, S., Bae, J. H., Kwon, H. S., & Nauck, M. A. (2021). COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nature Reviews Endocrinology, 17(1), 11-30. doi: https://doi.org/10.1038/s41574-020-00435-4
28. Prospective Studies Collaboration. (2009). Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. The Lancet, 373(9669), 1083-1096. doi: https://doi.org/10.1016/S0140-6736(09)60318-4
29. Lenz, M., Richter, T., & Mühlhauser, I. (2009). The morbidity and mortality associated with overweight and obesity in adulthood: a systematic review. Deutsches Ärzteblatt International, 106(40), 641. doi: https://doi.org/10.3238/arztebl.2009.0641
30. Berlin, D. A., Gulick, R. M., & Martinez, F. J. (2020). Severe covid-19. New England Journal of Medicine, 383(25), 2451-2460. doi: https://doi.org/10.1056/NEJMcp2009575
31. Gandhi, R. T., Lynch, J. B., & Del Rio, C. (2020). Mild or moderate Covid-19. New England Journal of Medicine, 383(18), 1757-1766. doi: https://doi.org/10.1056/NEJMcp2009249
32. Li, K., Wu, J., Wu, F., Guo, D., Chen, L., Fang, Z., & Li, C. (2020). The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Investigative radiology. doi: https://doi.org/10.1097/RLI.0000000000000672
33. Malik, P., Patel, U., Mehta, D., Patel, N., Kelkar, R., Akrmah, M., ... & Sacks, H. (2021). Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. BMJ evidence-based medicine, 26(3), 107-108. doi: https://doi.org/10.1136/bmjebm-2020-111536
34. Ponti, G., Maccaferri, M., Ruini, C., Tomasi, A., & Ozben, T. (2020). Biomarkers associated with COVID-19 disease progression. Critical reviews in clinical laboratory sciences, 57(6), 389-399. doi: https://doi.org/10.1080/10408363.2020.1770685
35. Chalmers, S., Khawaja, A., Wieruszewski, P. M., Gajic, O., & Odeyemi, Y. (2019). Diagnosis and treatment of acute pulmonary inflammation in critically ill patients: the role of inflammatory biomarkers. World journal of critical care medicine, 8(5), 59. doi: https://doi.org/10.5492/wjccm.v8.i5.59
36. Yao, Y., Cao, J., Wang, Q., Shi, Q., Liu, K., Luo, Z., ... & Hu, B. (2020). D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. Journal of intensive care, 8(1), 1-11. doi: https://doi.org/10.1186/s40560-020-00466-z.
37. Zhang, L., Yan, X., Fan, Q., Liu, H., Liu, X., Liu, Z., & Zhang, Z. (2020). D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. Journal of thrombosis and haemostasis, 18(6), 1324-1329. doi: https://doi.org/10.1111/jth.14859
38. Zhang, P., Zhu, L., Cai, J., Lei, F., Qin, J. J., Xie, J., ... & Li, H. (2020). Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19.

Circulation research, 126(12), 1671-1681. doi: https://doi.org/10.1161/CIRCRESAHA.120.317134

39. de Abajo, F. J., Rodríguez-Martín, S., Lerma, V., Mejía-Abril, G., Aguilar, M., García-Luque, A., ... & Elvira, C. (2020). Use of renin–angiotensin–aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. The Lancet, 395(10238), 1705-1714. doi: https://doi.org/10.1016/S0140-6736(20)31030-8
40. Li, J., Wang, X., Chen, J., Zhang, H., & Deng, A. (2020). Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. JAMA cardiology, 5(7), 825-830. doi: https://doi.org/10.1001/jamacardio.2020.1624
41. Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., ... & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The lancet, 395(10229), 1054-1062. doi: https://doi.org/10.1016/S0140-6736(20)30566-3