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Original article

Clinical characteristics, risk factors, and rate of severity of a nationwide COVID-19 Saudi cohort

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ABSTRACT

Objective: To evaluate COVID19 patients' clinical characteristics, risk factors, and COVID-19 severity at baseline and over one month following hospitalization.
Design, setting, and participants: This prospective cohort study of 598 Saudi COVID19 patients recruited from 4 major medical institutions nationwide between June 01, 2020, and February 28, 2021. Patients were stratified into different demographic characteristics and COVID-19 severity scale.
Results: Of the 598 hospitalized adult COVID19 patients (mean [range] age, 57 [46 to 65] years; 59% male), 300 (50.16%) had severe clinical COVID-19. Comorbidity was high among hospitalized patients (73.5 %), with diabetes mellitus (n=; 46%) and hypertension (n=; 41%) being the most common prevalent. In a multivariate logistic regression model, patient demographics and clinical factors such as age (odds ratio [OR], 1.014 per year; 95% CI, 1.003–1.025), male sex (OR, 1.63; 95% CI, 1.02–2.62), diabetes mellitus (OR, 1.63; 95% CI, 1.06–2.49), obesity (OR, 1.93; 95% CI, 1.26–2.94), oxygen saturation<92% (OR, 4.83; 95% CI, 2.96–7.86), and high neutrophil to lymphocyte ratio (OR, 3.74 per unit; 95% CI, 1.96–7.14) were independently associated with higher COVID-19 severity. Moreover, more than 60% of male patients and middle-aged patients (40–60 years) were associated with the use of COVID-19 medications, including favipiravir and dexamethasone, during their hospital stay. Additionally, the rate of invasive mechanical ventilation was the highest in female patients (61.5%) and in middle-aged patients (46.2%). However, the death rate was slightly higher in males (56%) than in female patients and in elderly patients (52%). In Cox proportional analysis, age associated with increased risk of 60-days mortality (Hazard ratio; HR, 1.05 per year; 95% CI, 1.018–1.098). Additionally, the Riyadh region associated with more COVID-19 cases required invasive respiratory support (57.7%) and Jeddah was associated with more deceased COVID-19 cases (44%).
Conclusions: The data shows that comorbidity is associated with hospitalization among COVID-19 patients, which indicates the level of severity. Infection during the winter season (November), male gender, elderly, and those with pre-existing diabetes mellitus or obesity were associated with higher COVID-19 clinical severity.

1. Introduction

More than two years into this pandemic crisis, SARS-CoV-2 had catastrophic effect infecting more than 200 million people and resulting in more than 4 million deaths. Infection with SARS-CoV-2 causes COVID-19 disease, a disease characterized by viral pneumonia, which can lead to mortality or persistent morbidity in some survivors. Moreover, the research in COVID-19 has been delayed due to the lack of access to nationwide COVID-19 patient

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clinical data (Bennett et al., 2021). Researchers in the United States (Bennett et al., 2021) and European countries (Williamson et al., 2020; Butt et al., 2020) have assessed patient-level data analysis within their cohort of COVID-19 patients to inform therapeutic decisions and clinical interventions; however, such as investigation is still lacking in most of gulf countries including Saudi Arabia. Thus, a large, multicenter, representative clinical study is urgently needed by the Saudi health care practitioners and policymakers to develop predictive and diagnostic models and/or design computer based clinical decision tools to inform therapeutic and clinical decisions.

To address these gaps, we have collected data from hospitalized COVID-19 patients across different cities in Saudi Arabia. This study provides a detailed patient-level clinical data of the largest cohort of Saudi COVID-19 patients to date. This cohort is from different geographic regions in Saudi Arabia. We assessed demographic, clinical characteristics, as well as COVID-19-related data of patient on admission.

2. Methods

2.1. Study design and participants

This was a prospective, multicenter observational study that included consecutive adults 18 years or older with positive COVID-19 test results and hospitalized between June 2020 and January 2021 in any of the following four most populated regions of Saudi Arabia; central region (Riyadh), western region (Macca), eastern region (Dammam), and northern region (Al-Qassim). Diagnosis of COVID-19 was confirmed by polymerase chain reaction (PCR) test detecting presence of SARS-CoV-2. Moderate COVID-19 was defined by PCR-positive COVID-19 cases requiring hospitalization, while severe COVID-19 was defined by PCR-positive hospitalized COVID-19 patients requiring high-flow oxygen therapy or non-invasive ventilation respiratory support (Marshall et al., 2020).

The Saudi Ministry of Health, Saudi Arabia, has approved the study (IRB # 20–85-M). The data reported in this study was further approved separately by the IRB of each institution in Riyadh (Riyadh), Macca (Jeddah), Dammam, and Al-Qassim (Buraydah). A written informed consent was granted from each of the included patient on admission, and those who did not give the consent were excluded. There were no further exclusion criteria.

2.2. Variable definitions

A standard data collection form was used to collect patients' information on demographic and pre-existing conditions at admission, as well as in-hospital observational outcomes, including laboratory measures, vital signs, or medication. The data was complete for outcome analysis needed for identification of patient-specific factors associated with COVID-19 severity and/or mortality.

2.3. Statistical analysis

Chai-square for categorical variables, and Student *t*-test or Mann-Whitney *U* test for continuous variables depending on the skewness of data were used to compare baseline clinical characteristics between hospitalized patients with moderate or severe COVID-19. Moreover, the associations of patient-specific factors with disease severity were evaluated using multivariate regression models and with 60-day mortality with Cox proportional hazards regression model. Analyses was performed using R software (v 3.0.2), SPSS Version 26 (IBM Corporation, Chicago, USA), and Graphpad Prism 7 (GraphPad Software Inc., San Diego, USA). For all analyses, P-values < 0.05 were considered significant.

3. Results

3.1. Study cohort

As between June 2020 and January 2021, the study cohort included 598 adults from different regions of Saudi Arabia (mean [range] age, 57 [46 to 65] years; 59% male) who had positive COVID-19 PCR test at one of the following sites; 55.7% from Riyadh, 19.7% from Al-Qassim, 13.2% from Jeddah, and 11.4% from Dammam (Fig. 1). The data shows the greater number of laboratory-confirmed COVID-19-positive cases in Riyadh in September 2020. (Fig. 1). Moreover, the number of severe COVID-19-positive cases admitted to the hospital were highest in November 2020 (77.1%) [Fig. 2].

3.2. Demographic Characteristics, Comorbidities, and obesity

The age distribution for hospitalized patients was relatively older during December and January 2020, and younger during the summer (Fig. 3). Of these hospitalized patients, 73.5% had at least 1 comorbidity; with diabetes mellitus (DM) or hypertension being the most prevalent (46% for DM, and 41% for hypertension) (Table 1). Obesity, defined as mean body mass index (BMI) of 30 and above was for 43% of COVID-19 cases (Table 1). In a multivariate logistic regression model, age (odds ratio [OR], 1.014 per year; 95% CI, 1.003–1.025), male sex (OR, 1.63; 95% CI, 1.02–2.62), DM (OR, 1.63; 95% CI, 1.06–2.49), and obesity (OR, 1.93; 95% CI, 1.26–2.94) were independently associated with higher COVID-19 severity (Fig. 4).

3.3. Laboratory measurements

Overall, values of oxygen saturation (SpO2), laboratory and immune inflammatory markers were measured for all patients at baseline (Table 1). Of interest, early on admission, oxygen saturation<92% (OR, 4.83; 95% CI, 2.96–7.86), and high neutrophil to lymphocyte ratio (OR, 3.74 per unit; 95% CI, 1.96–7.14) were associated with severity of COVID-19.

3.4. Treatments

Overall, the majority of patients (62%) of the hospitalized cohort received azithromycin antimicrobial agent with the peak of its use been in September for all the clinical severity groups (5A). Antiviral therapies against SARS-CoV-2 were administrated to 23% (favipiravir), 1.3% (remdesivir), and 0.7% (lopinavir and ritonavir) of patients. Additionally, 24.5% received dexamethasone as supportive medication. In line with this, severe COVID-19 or deceased COVID-19 cases had a similar pattern for dexamethasone and favipiravir use, with the highest rate of use been in August and October 2020 (Fig. 5B and 5C). Moreover, middle-aged patients (40–60 years) and male patients were associated with higher rate of dexamethasone (48.5% in middle-aged patients and 63.9% in male patients) and favipiravir use (50% in middle-aged patients and 37.8% in male patients) compared to their counterparts, which may reflect their presentation with greater COVID-19 clinical severity (Fig. 5D and 5E).

Of the hospitalized cohort of COVID-19 patients, 4% required invasive respiratory support (mechanical ventilatory support). Moreover, 2.5% received treatment for cardiovascular support, and 6.5% received continuous renal replacement therapy (Table 1).

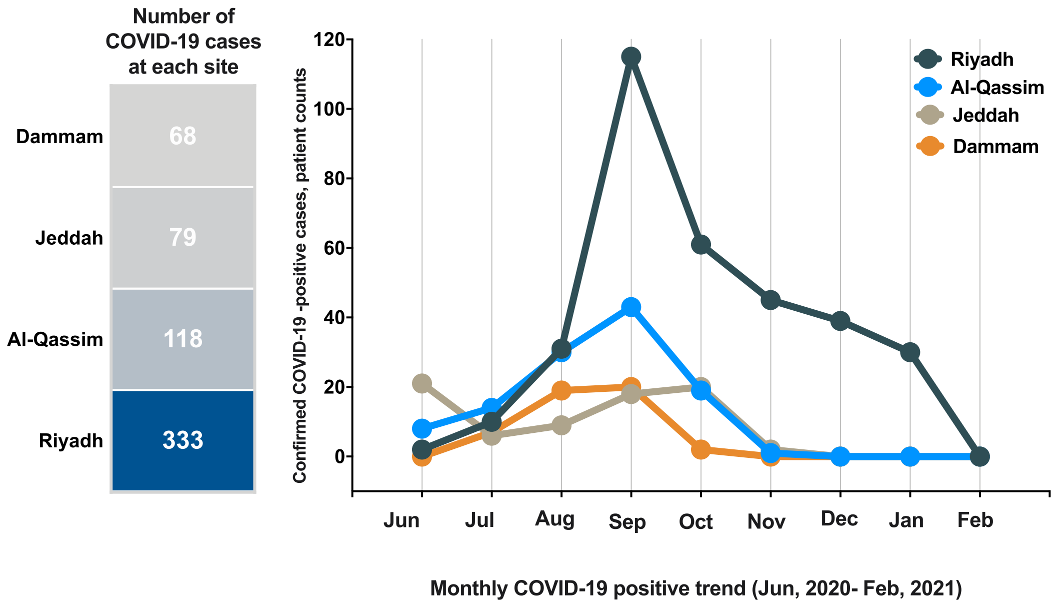

Fig. 1. The geographic distribution of laboratory-confirmed COVID-19-positive hospitalized cases in COVID-19 Saudi cohort (N = 598). The data shows the greater number of laboratory-confirmed COVID-19-positive cases in the Riyadh region in September 2020 (115 COVID-19-cases out of 598 COVID-19 Saudi cohort).

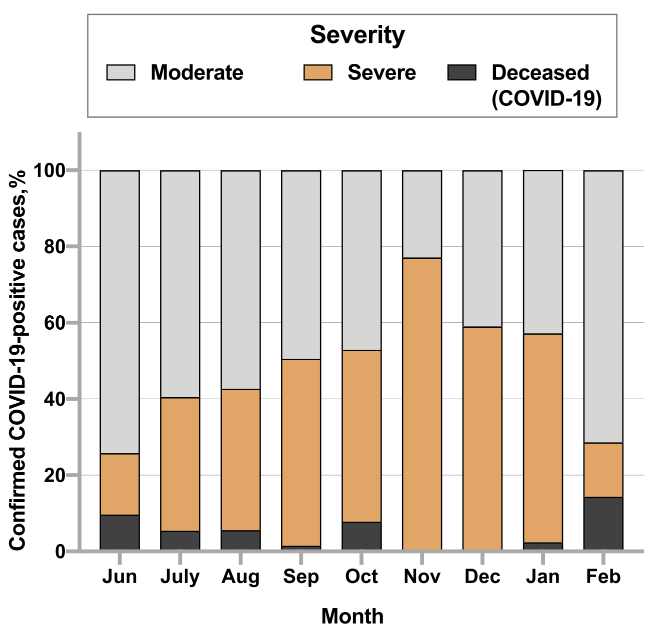

Fig. 2. Distribution of the COVID-19-related severity over the study time. The number of severe COVID-19-positive cases admitted to the hospital were highest in the late fall (November 2020, 77.1%), and the early winter (December 2020, 59%).

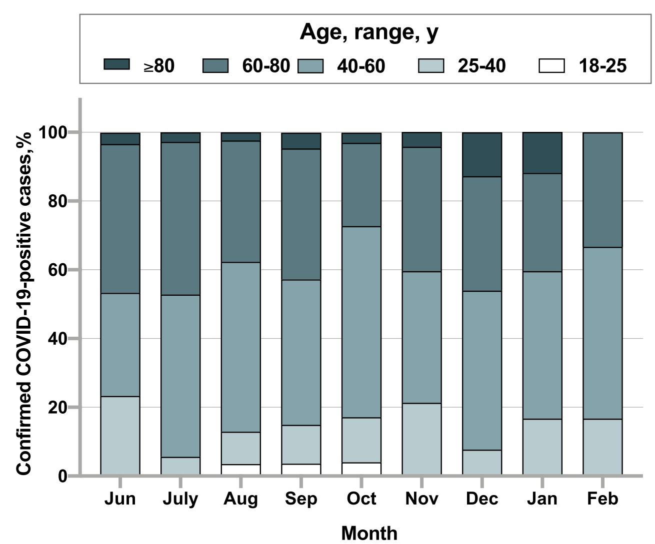

Fig. 3. Age distribution of hospitalized patients over the study time. Older COVID-19 patients (≥80 years old) were more prominent in the winter, with more younger patients (<40 years old) in the summer.

3.5. Clinical course of COVID-19 and death

Of the 598 adults with SARS-CoV-2, 51 (8.5%) had a severe clinical course of COVID-19 (required mechanical ventilation 4%, or death 4%- Table 1). The rate of invasive mechanical ventilation was higher in middle-aged patients (46.2%) and female patients (61.5%) compared to other groups (Fig. 6A and 6B). Moreover, the rate of death was higher in elderly (n = 25; 40–60 yrs [n = 9;36%], 60–80 yrs [n = 13; 52%], and greater than 80 yrs [n = 3; 12%]) and in male patients (n = 14; 56%) (Fig. 6A-6D). In the multivariate survival analysis age factor associated with increased risk of 60-days mortality from COVID-19 (Hazard ratio; HR, 1.05 per year; 95% CI, 1.018–1.098). Our data also indicate the site-level variation in the rate of invasive respiratory needs and mortality among different reported cities. As such, a higher rate of hospitalized patients with COVID-19 in Riyadh needed invasive ventilation support (57.7%) and the rate of deceased COVID-19 cases was highest in Jeddah (34.6%) (Fig. 6C and 6D).

4. Discussion

This cohort study describes the largest Saudi cohort of hospitalized COVID-19 patients to date, including 598 adults who tested positive for COVID-19. The study shown data of many clinical and laboratory values of Saudi hospitalized COVID-19 patients with different demographic distribution, age groups, and clinical severities. Understanding this data may provide insights that may help decision making related to prevention, treatment, and

Table 1
Characteristics and clinical course of the patients with confirmed SARS-COV-2.

Variables	Total (n = 598)	Moderate (n = 298)	Severe (n = 300)	*P-Value*
Age (years), mean ± SD	57 (46–65)	56 (44–64)	58 (48–66)	0.015
Male sex, n (%)	352 (59)	169 (57)	183 (61)	0.163
O2 saturation at admission, mean (SD)	93 (5)	96 (94–98)	92 (89–95)	<0.001
Pre-Existing Conditions, n (%)				
Diabetes	272 (46)	119 (40)	153 (51)	0.004
Hypertension	244 (41)	108 (36)	136 (45)	0.016
Obesity (BMI greater than 30)	259 (43)	111 (37)	148 (49)	0.002
Chronic pulmonary disease	63 (11)	26 (9)	37 (12)	0.096
Liver disease	3 (0.5)	1 (0.3)	2 (0.7)	0.503
Renal disease	38 (6)	17 (6)	21 (7)	0.315
Laboratory Data				
White cell count (3.9–11.10 $\times$ 10^9 per L)	6.3 (4.7–8.9)	6.0 (4.5–8.6)	7.0 (5.1–9.1)	0.103
Neutrophils (1.35–7.5 $\times$ 10^9 per L)	4.8 (3.2–7.4)	4.2 (2.7–7.3)	5.2 (3.6–7.5)	0.029
Lymphocytes (1.5–4.3 $\times$ 10^9 per L)	1.1 (0.8–1.6)	1.2 (0.8–1.7)	1.0 (0.7–1.5)	0.683
Neutrophil to lymphocyte ratio (0.78–3.53)	4. 4 (2.6–6.9)	3.6 (2.2–5.6)	4.8 (3.1–7.9)	<0.001
Platelets (115–435 $\times$ 10^9 per L)	213 (171–277)	224 (182–293)	204 (164–268)	0.001
Prothrombin time (10–13 sec)	13.6 (12.9–14.5)	13.5 (12.7–14.5)	13.6 (12.9–14.4)	0.429
aPTT (30–40 sec)	34.6 (31.6–38.3)	32.8 (30.1–37.1)	35.2 (32.6–39.9)	0.172
D Dimer (0–0.5 μ/mL)	0.8 (0.5–1.3)	0.6 (0.3–1.3)	0.8 (0.5–1.3)	0.398
Lactate dehydrogenase (125–220 U/L)	322 (265–404)	305 (246–366)	334 (273–408)	0.980
Alanine transaminase (0–55 U/L)	33 (21–50)	33 (21–52)	32.5 (21–50)	0.279
Aspartate transaminase (5–34 U/L)	40.5 (30–58)	34.8 (25–52)	45 (34–61)	0.035
Bilirubin (3–20 μmol/L)	8.05 (6.1–11.1)	7.7 (5.7–11)	8.3 (6.4–11)	0.629
BUN (2.1–8.5 mmol/L)	4.6 (3.4–7)	4.4 (3.2–6.9)	4.6 (3.4–7.1)	0.259
Creatinine (49–90 μmol/L)	77.1 (66–96)	78.8 (65–96)	75.8 (66–96)	0.327
Troponin I (0.4–0.04 ng/mL)	0.23 (0.05–0.41)	0.16 (0.003–0.33)	0.25 (0.02–0.49)	0.651
Hospital treatment, n (%)				
Antibiotics				
Azithromycin, n (%)	372 (62)	167 (56)	205 (68)	0.002
Ceftriaxone, n (%)	260 (44)	146 (49)	114 (38)	0.008
Cefuroxime, n (%)	194 (32)	49 (16)	145 (48)	<0.001
Meropenem, n (%)	39 (6.5)	6 (2)	33 (11)	<0.001
Vancomycin, n (%)	22 (4)	8 (3)	14 (5)	0.277
Imipenem, n (%)	18 (3)	7 (2)	11 (4)	0.474
Hydroxychloroquine	7 (1.2)	7 (1.2)	–	–
Antiviral agents				
Favipiravir, n (%)	138 (23)	104 (35)	52 (17)	<0.001
Remdesivir, n (%)	8 (1.3)	5 (2)	3 (1)	0.504
Supportive medications				
Dexamethasone, n (%)	147 (25)	118 (39)	119 (39)	0.837
Enoxaparin, n (%)	67 (11)	60 (20)	178 (59)	<0.001
Hospitalization duration (days), median (IQR)	25 (13)	22 (11)	27 (13)	0.483
Hospital outcomes				
ARDS, n (%)	25 (4)	1 (0.3)	24 (8)	<0.001
Arrythmia, n (%)	3 (0.5)	2 (0.7)	1 (0.3)	0.623
Acute Cardiac Injury, n (%)	14 (2)	3 (1)	11 (3.7)	0.028
Acute kidney Injury, n (%)	39 (6.5)	11 (4)	28 (9)	0.004
Sepsis, n (%)	8 (1.3)	2 (0.7)	6 (2)	0.286
Mechanical ventilation support, n (%)	26 (4)	0	26 (9)	<0.001
Death, n (%)	25 (4)	3 (1)	22 (7)	<0.001

Data are n (%) or median (IQR).

support to be provided, as well as may help manoeuver strategies to ensure better providing health care for patients in these health care facilities.

Heterogeneity of patients' demographic data, including age, BMI, and pre-existing conditions (e.g., obesity), made it difficult to interpretate the outcome of COVID-19 illness. This study found that among hospitalized patients with COVID-19, male patients, middle-aged patients and those with obesity, or diabetes mellitus had higher clinical severity, which is in line with previous reports (Tartof et al., 2020; Hyrich and Machado, 2021; Moon et al., 2020). In line with this, a higher rate of COVID-19 medications use, including azithromycin, favipiravir, and dexamethasone, was in male patients and middle-aged hospitalized patients with COVID-19. Some medications have been no longer supported for COVID-19 (e.g., azithromycin); other medication are the subject of further investigation (e.g., favipiravir and dexamethasone). For most treatments, the effects has not been assessed in proper randomized clinical trials. However, ongoing monitoring for the efficacy of these regiments in observational study such as ours will be important.

Our study has distinctive features that separate it from other COVID-19 patient-level data. First, this study is the first nationwide cohort study that patient data were collected prospectively from the hospital settings. Furthermore, it combines patient-level clinical data from major clinical sites in Saudi Arabia (Riyadh, Al-Qassim, Jeddah, and Dammam), showing that there is site-based variation in critical values, such as invasive respiratory needs, and death; as Riyadh site was associated with more cases of COVID-19 hospitalized patients with need for invasive respiratory support and Jeddah was associated with more deceased COVID-19 cases. Similarly, significant site-level variation in the rate of invasive respiratory needs, or in-hospital death from COVID-19 has been reported from other populations (Gupta et al., 2020; Auld et al., 2020). Most of the Saudi reports of COVID-19 clinical data were collected retrospectively from patient medical records, and/or were based in a single hospital site or COVID-19 health care cen-

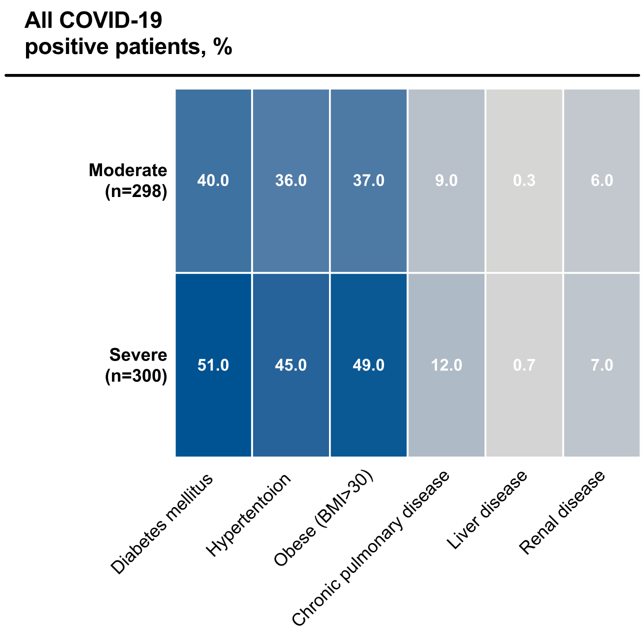

Fig. 4. Comorbidity distribution of the COVID-19 Saudi cohort (N = 598). Pre-existing chronic liver disease was present in around two-thirds of severe COVID-19 cases (66.7%) and one third of moderate COVID-19 cases (33.3%).

ter in a particular region of Saudi Arabia (A. Malhani et al., 2021;16 (6):e0252984.; Abohamr et al., 2020; Al Mutair et al., 2020; Al Sulaiman et al., 2021). Our methods of data curation from the major clinical sites in Saudi Arabia, ensures a robust nationwide data platform, which overcome the difficulties of relying on a single-site level clinical data quality assurance. Moreover, our report provides patient-level data which is fully analyzable and can be used to develop accurate models to predict COVID-19 severity based on the clinical data available on admission. As a result, multivariate analysis of baseline patient demographics revealed that advanced age, male sex, and individual with DM and obesity were at greater risk of severe COVID-19. Moreover, analysis of clinical and laboratory data on admission showed that low oxygen saturation (<92%) and high NLR value associated with disease severity. These results may support the hypothesis that disease severity can be predicted using patients' data available early in a hospital course. In addition, the findings from these models could be the base of therapeutics and decision support tools in the kingdom. However, development of these clinical decision tools would also require internal validation in large cohort of patients, and consideration of any outliner effects.

The study's strength is that this study revealed a month-over-month trend in the pattern of COVID-19 severity cases admitted to hospitals between June 2020 to February 2021, as well as unpredicted changes over time in treatment patterns for hospitalized patients with different clinical severity. The hospital admission rate of severe cases of COVID-19, as well as the treatment regimens for hospitalized patients with severe COVID-19 were more prominent in the Fall, 2020. In contrast with the prior data from COVID-19 cohorts in the US, where the severe cases were more likely to be admitted during Spring 2020 (Bennett et al., 2021). Moreover; another report from different regions of the US indicated that excess deaths from COVID-19 occurred more in the Fall (Woolf et al., 2021). This national-level difference in the admission rate for severe cases of COVID-19 and the number of deaths from COVID-19 desire further consideration and alerts. The contribution of the emerging SARS-CoV-2 variants such as Alpha; Beta, Gamma and Delta in these seasons to the rate of infection and level of

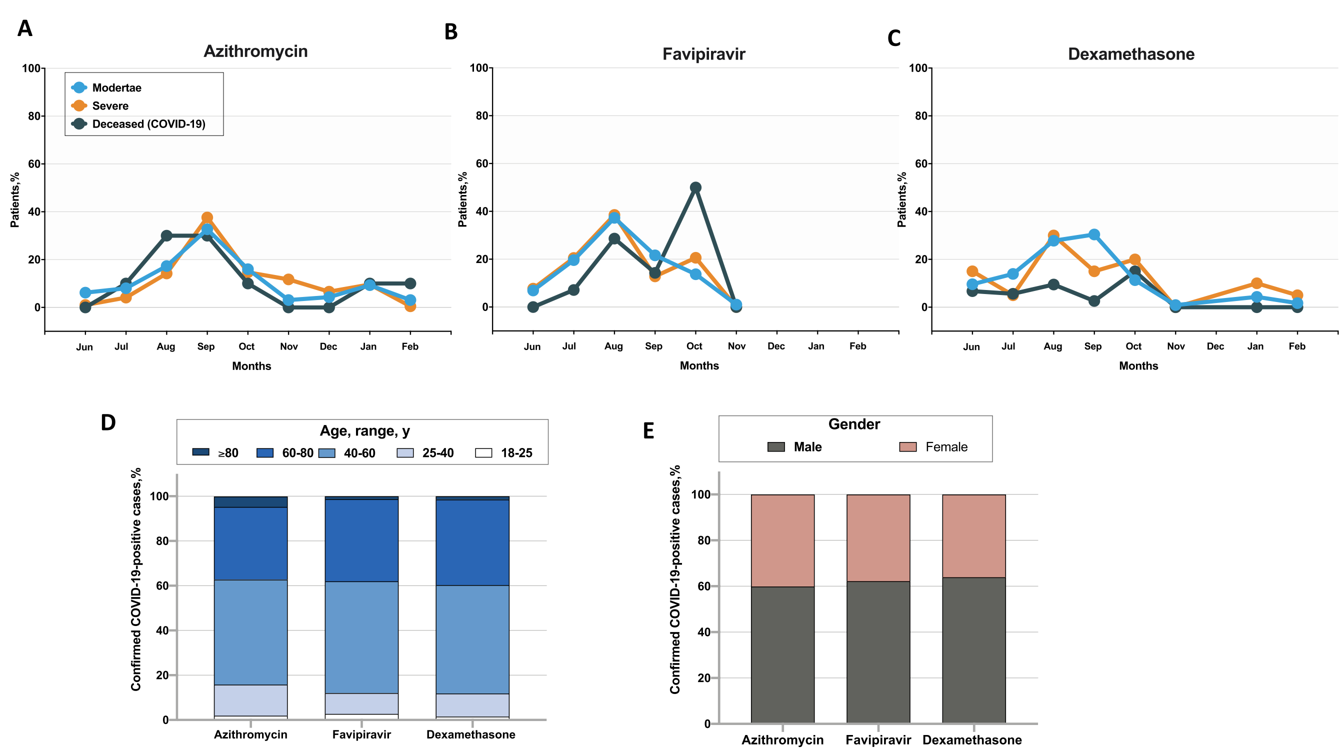

Fig. 5. Antimicrobial and immunosuppressive medication use over the study time. Trends of antimicrobial (A) azithromycin and (B) favipiravir, and immunomodulatory (C) dexamethasone treatment regimens for hospitalized patients during the study time. The use of antimicrobial and immunosuppressive medication in relation with patients (D) gender, and (E) age groups.

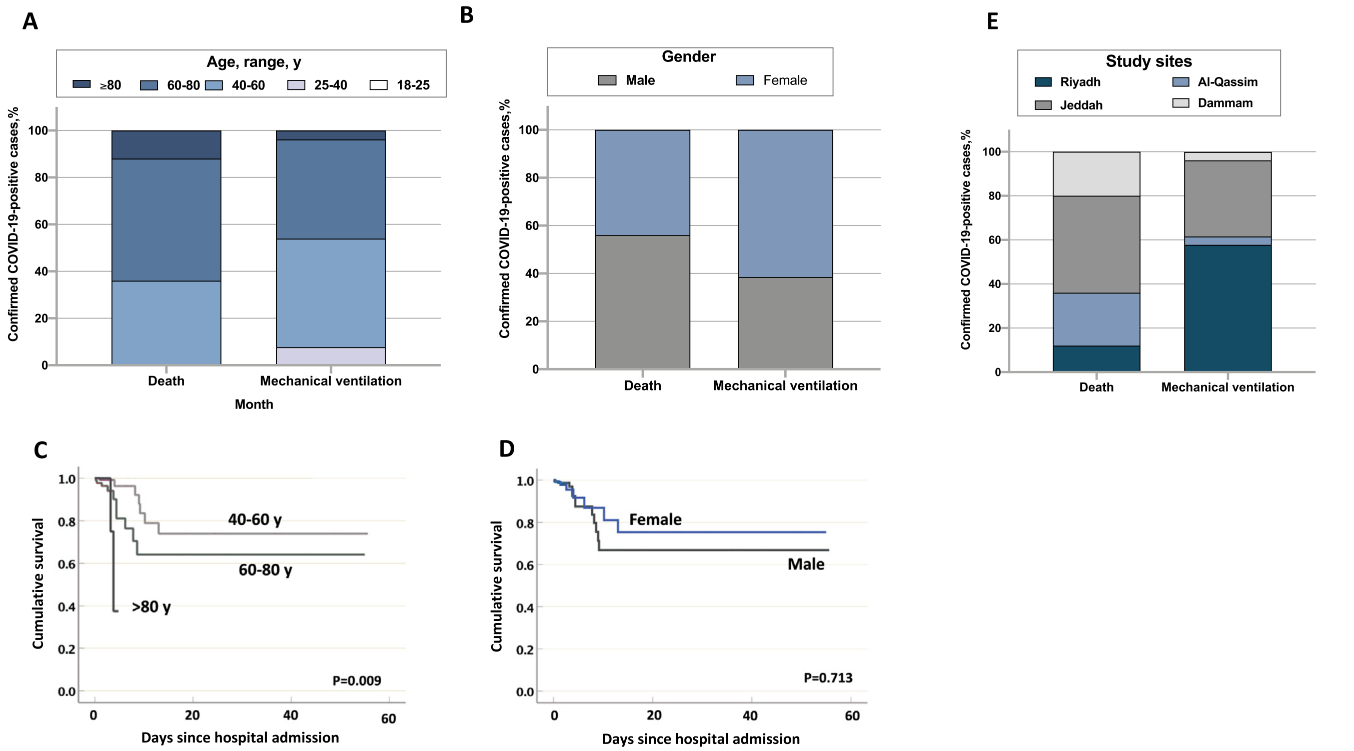

Fig. 6. Clinical severity distribution according to patient specific-factors. Mortality and need for mechanical ventilation were evaluated in relation with patients (A) gender, (B) age groups, and the (C) admitted sites.

severity should not be excluded (Tao et al., 2021). Additionally; pandemic control measures and lifting restrictions in some regions earlier than others might be among the reasons for this visualized difference in COVID-19 survival outcomes.

5. Limitation

This study has several limitations. The data is combined from different hospitals across Saudi Arabia that might vary in the way health care systems document and handle the data. Some sites also have missingness of some variables. Moreover, detailed information of respiratory support variables, such as oxygen flow, the fraction of inspired oxygen, and ventilator settings, was not fully available.

6. Conclusion

This is the first multicenter patient-level cohort of COVID19 Saudi patients from all over the kingdom. The data shows that the rate of COVID-19 severe cases was the highest in November 2020, and mostly admitted to Riyadh city. Male patients, elderly, and those with DM or obesity were associated with higher COVID-19 clinical severity.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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