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Clinical Presentation and Outcome of Hospitalized Patients With COVID-19 in the First and Second Waves in Saudi Arabia

Salma AlBahrani¹, Nayef AlAhmadi², Safa Hamdan², Noura Elsheikh², Assim Osman², Sharifah Almuthen², Ghadeer N Almajed², Arwa H Alkhuraim², Arulanantham Zechariah Jebakumar³, Jaffar A. Al-Tawfiq^{4,5,6,*}

¹ Infectious Disease Unit, Specialty Internal Medicine, King Fahd Military Medical Complex, Dhahran, Saudi Arabia

² Internal Medicine Department, King Fahd Military Medical Complex, Dhahran, Saudi Arabia

³ Vice deanship of postgraduate studies and Research, Prince Sultan Military College of Health Sciences, Dhahran, Saudi Arabia

⁴ Infectious Disease Unit, Specialty Internal Medicine, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia

⁵ Infectious Disease Division, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

⁶ Infectious Disease Division, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

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ABSTRACT

Introduction: The world had witnessed the occurrence of multiple waves of the SARS-CoV-2. Data comparing the clinical characteristics and outcomes of hospitalized patients in Saudi Arabia during the first and second waves are lacking. This study compares the characteristics and the outcomes of patients in these 2 waves.

Methods: This is a retrospective case series of hospitalized patients with confirmed SARS-CoV-2. We compared epidemiological, demographic, laboratory, and clinical data.

Results: The study included hospitalized patients admitted up to February 28, 2021 as the first wave and those admitted from March 1, 2021 as the second wave. There were 378 patients in the first wave and 241 patients in the second wave. Patients in the first wave were significantly younger (mean age and SD of 47.5 ± 20 vs 55.3 ± 18.2 years; $p < 0.001$). In relation to symptoms, shortness of breath, wheezes, myalgia, tachypnea, and respiratory distress were significantly more common in the second wave than the first wave. On the other hand, sore throat was more common in the first wave than the second wave. Patients in the second wave had higher mean values of lymphocytes count, platelet counts, and ALT than those in the first wave. Patients in the first wave were more likely to receive antibiotics and antiviral therapy and had higher death rate (16.2% vs 8.4%; $p = 0.001$).

Conclusion: The study showed that patients in the second wave were younger and had a lower rate of death than the first wave.

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Introduction

Coronavirus disease-19 (COVID-19), produced by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic, giving rise to a serious health threat globally. Most people infected with the SARS-CoV-2 virus had experienced mild to moderate respiratory illnesses and recovered without special treatment. Older people with underlying medical prob-

lems, such as cardiovascular disease, diabetes mellitus, chronic respiratory disease, and cancer, are more likely to develop serious illnesses (Pradhan et al., 2020). The present pandemic is characterized by multiple waves, causing disease at different times around the globe. Many countries have experienced multiple waves of SARS-CoV-2 outbreaks. During the 2020 pandemic, initial data show that characteristics varied between waves (Iftimie et al., 2021). In comparison with the second wave, the proportion of local clusters (24.8% vs 45.7%) was lower in the third wave, and personal contact transmission (38.5% vs 25.9%) and unknown routes of transmission (23.5% vs 20.8%) were higher (Seong et al., 2021). Consequently, many governments and health authorities, includ-

* Corresponding author: Dr. Jaffar A. Al-Tawfiq, Johns Hopkins Aramco Healthcare, Dhahran 31311, Saudi Arabia. Tel: +966-13-870-7794.

E-mail addresses: jaffar.tawfiq@jhah.com, jaltawfi@yahoo.com (J.A. Al-Tawfiq).

ing the World Health Organization (WHO) and the Saudi Ministry of Health, have been actively educating people to take preventive measures to reduce the spread of the virus, including social distancing and personal hygiene (Farooq et al., 2021; Godman et al., 2020).

In the Kingdom of Saudi Arabia (KSA), the first COVID-19 case was reported in March 2020 (Aljishi et al., 2021). The first wave subsequently developed and ended December 2020, and second wave began approximately February, 2021. As part of the strategies to curtail the pandemic, the KSA applied multiple steps, including vaccination, to decrease the spread of the disease (Al-Tawfiq et al., 2020b; Al-Tawfiq and Memish, 2020). The vaccination strategy included the introduction of step-wise COVID-19 vaccination programs initially with Pfizer-BioNTech messenger RNA (mRNA) vaccine (BNT162b2) and then the ChAdOx1-S (Assiri et al., 2021).

Differences between patients in different waves were evaluated in a few studies. In a study from Spain, patients with severe symptoms were found more frequently in the first wave (27.8%) than the second wave (10.6%, $P = 0.03$) (Soriano et al., 2021). Previous studies from the KSA described the epidemiology, clinical features, ICU admission, and therapy of COVID-19 patients mainly during the first wave of the pandemic (Al-Omari et al., 2020; Al-Tawfiq et al., 2020a, 2020b; Aljishi et al., 2021; Al Mutair et al., 2020). In this study, we compare the characteristics of patients and outcome during the first and the second wave of the pandemic.

Materials and Methods

We conducted a retrospective cohort study of all admitted cases of COVID-19 in a single medical center in the KSA. We collected the demographics, clinical presentation, underlying comorbidities, and outcomes and according to the first and second wave. Patients admitted up to February 28, 2021 were grouped into the first wave and those admitted from 1st March 2021 into the second wave. The only inclusion criterion was to be a hospitalized patient with a confirmed diagnosis of SARS-CoV-2 by PCR. SARS-CoV-2 infection was confirmed by RT-PCR using swab samples from the upper respiratory tract (nasopharyngeal/oropharyngeal exudate) and from the lower respiratory tract (sputum/endotracheal aspirate/bronchoalveolar lavage/bronchial aspirate) as described previously (Aljishi et al., 2021). This study was approved by the institutional review board of the King Fahad Military Medical Complex (AFHER-IRB-2020-034).

Statistical Analysis

We summarized the characteristics for continuous and categorical data as numbers and percentages. Characteristics were compared using descriptive statistics, and categorical data were compared using the chi-square test (to find the association between first and second wave among the demographic and symptoms). We used independent sample *t* test to compare the quantitative variables between first and second wave. Bivariate logistic regression was applied to find relationship between the dependent variable status of the patient (dead or alive) and the independent variables, such as symptoms and comorbidities, to find the associated factors. A P -value <0.05 has been considered for statistical significance. The statistical analysis has been done in SPSS (Statistical Package for Social Sciences) Package with version 27.

Results

During the study period, 619 patients with SARS-CoV-2 infection, confirmed by RT-PCR, were admitted to the hospital. The number of patients admitted was 378 in the first wave and 241 in the second wave. Those in the first wave were significantly

Table 1
Demographic Data and Underlying Comorbidities Comparison Between Patients in the First and Second Wave

Variables	First wave (n= 378)	Second wave (n= 241)	P-value
Male	240 (63.5)	114 (47.7)	$< 0.0001^*$
Female	138 (36.5)	125 (52.3)	
Lung Disease	44 (11.6)	32 (13.4)	0.51
Cardiac Disease	90 (23.8)	60 (25.2)	0.69
Diabetes Mellitus	182 (48.1)	114 (47.9)	0.95
COPD	3 (0.8)	0	0.17
Cancer	5 (1.3)	6 (2.5)	0.28
Hemodialysis	12 (3.2)	16 (6.7)	0.04*
ESRD	39 (10.3)	27 (11.3)	0.69
Heart Failure	75 (19.8)	46 (19.5)	0.92

Table 2
Symptomatology comparison between the 2 waves

Symptoms	First wave (n= 378)	Second wave (n= 241)	P-value
Fever	256 (67.7)	165 (69.3)	0.68
Shivering	43 (11.4)	35 (14.6)	0.23
Shortness of Breath	205 (54.2)	159 (66.5)	0.002*
Chest Pain	46 (12.2)	27 (11.3)	0.74
Wheezes	5 (1.3)	25 (10.5)	$< 0.0001^*$
Cough	296 (78.3)	195 (81.6)	0.32
Hemoptysis	4 (1.1)	5 (2.1)	0.3
Sore throat	65 (17.2)	22 (9.2)	0.005*
Headache	51 (13.5)	41 (17.2)	0.21
Myalgia	94 (24.9)	90 (37.7)	$<0.0001^*$
Vomiting	78 (20.6)	43 (18.0)	0.52
Diarrhea	75 (19.8)	50 (20.9)	0.75
Tachypnea	77 (20.4)	98 (41.0)	$<0.0001^*$
Respiratory Distress	115 (30.4)	105 (44.1)	$<0.0001^*$

Table 3
Clinical Data Comparison Between Patients in the First and Second Wave

	First wave (n= 378)	Second wave (n= 241)	P-value
ICU Admission	145 (38.4)	98 (40.7)	0.57
Mechanically Ventilated	70 (18.5)	41 (17.0)	0.63
In hospital Methyl prednisone	327 (87.9)	220 (92.1)	0.1
Antibiotics given	140 (37.0)	67 (27.9)	0.02*
Antiviral given	20 (5.3)	5 (2.1)	0.04*
Death	61 (16.2)	19 (8.4)	0.001*

* Significant P value

younger (mean age and SD of 47.5 ± 20 vs 55.3 ± 18.2 years, in the first and second wave, respectively; $p <0.001$) and the second wave patients were more likely to be on hemodialysis (6.7% vs. 3.2%, $P =0.04$) (Table 1).

In relation to symptoms, there were significant differences in the presence of shortness of breath, wheezes, sore throat, myalgia, tachypnea, and respiratory distress (table 2). These symptoms were more common in the second wave than the first wave, except for sore throat where it was more common among patients in the first wave than in the second wave. Patients in the first wave were more likely to receive antibiotics and antiviral therapy and had higher death rate (Table 3). Patients in the second wave had higher mean values of lymphocytes count, platelet counts, and ALT than those in the first wave (Table 4).

Of all the admitted patients, a comparison between those who survived and those who died showed that diabetes mellitus, heart failure, shortness of breath, myalgia, tachypnea, oxygen saturation, and admission to the ICU were significant different with higher odds ratio among patients who died (Table 5). In the second wave, 54 (22.4%) of 241 patients with documented vaccination status had received at least 1 dose of COVID-19 vaccine (14.5% had 1 dose

Table 4
Comparison of Laboratory Data of Patients in the First and Second Wave

	Patient group	N	Mean	Std. Deviation	Std. Error Mean	P-value
Age (years)	First wave	378	47.5	20.0	1.0	0.000*
	Second wave	240	55.3	18.2	1.2	
WBC	First wave	377	8.9	6.3	0.3	0.32
	Second wave	238	9.6	10.0	0.7	
PMN	First wave	377	120.8	2261.9	116.5	0.74
	Second wave	239	190.5	2868.0	185.5	
Lymph%	First wave	377	22.2	15.0	0.8	0.01*
	Second wave	236	25.3	14.6	0.9	
Platelet	First wave	377	256.0	118.4	6.1	0.006*
	Second wave	238	285.4	146.0	9.5	
ALT	First wave	377	9.4	409.6	21.1	0.01*
	Second wave	239	649.2	4812.7	311.3	
AST	First wave	377	63.6	67.1	3.5	0.25
	Second wave	239	235.5	2878.6	186.2	
LDH	First wave	377	293.2	342.6	17.6	0.08
	Second wave	229	377.0	830.9	54.9	
D-dimer	First wave	376	3.4	8.6	0.4	0.56
	Second wave	226	4.1	17.9	1.2	
Ferritin	First wave	377	795.0	1070.9	55.2	0.09
	Second wave	235	607.6	1625.9	106.1	
CRP	First wave	365	100.7	85.0	4.4	0.27
	Second wave	231	185.9	1479.1	97.3	
Procalcitonin	First wave	371	0.7	6.2	0.3	0.09
	Second wave	234	2.5	18.1	1.2	

Table 5
Comparison between patients who died and those who survived using bivariate logistic regression

Characteristics	B	S.E.	P-value	Odds Ratio	95% C.I. for Odds ratio	
					Lower	Upper
Diabetes mellitus	1.1	0.5	.025*	3.1	1.2	8.6
Cardiac disease	-1.4	0.9	0.1	0.2	0	1.3
Lung disease	0.8	0.6	0.2	2.2	0.6	7.6
COPD	3	1.5	0	19.3	1	369.8
Heart Failure	4.2	0.9	<.001*	67.8	11.6	396.8
ESRD	0.4	0.7	0.6	1.5	0.4	6.5
Hemodialysis	1.5	1	0.1	4.3	0.6	29.6
Cancer	-18.9	11084.4	1	0	0	.
Fever	0.6	0.5	0.3	1.8	0.6	5.3
Shivering	-0.1	0.7	0.9	0.9	0.2	3.7
Shortness of Breath	-1.5	0.5	.008*	0.2	0.1	0.7
chest pain	-1.1	0.9	0.2	0.3	0.1	1.8
Wheezes	-1	0.8	0.2	0.4	0.1	1.8
Cough	-1.1	0.6	0.1	0.3	0.1	1
Hemoptysis	0.1	1.6	0.9	1.1	0	27.3
Sore Throat	0.4	0.8	0.6	1.5	0.3	7.4
Head ache	-0.4	0.9	0.6	0.7	0.1	3.6
Myalgia	-1.7	0.6	.007*	0.2	0.1	0.6
Vomiting	-0.7	0.7	0.3	0.5	0.1	1.7
Diarrhea	-0.1	0.6	0.8	0.9	0.3	2.7
Tachypnea	1.5	0.7	.034*	4.7	1.1	19.6
Respiratory Distress	0.7	0.7	0.4	1.9	0.5	7.9
Oxygen Saturation	1.4	0.5	.008*	4.1	1.5	11.4
Admitted to ICU	1.2	0.5	.022*	3.4	1.2	9.8
Vaccine Status	-0.25	0.53	0.64	0.78	0.275	2.203
First wave vs. second wave	0.74	0.28	0.008*	2.10	1.22	3.62

* Significant at 95%

and 7.9% had 2 doses). However, there was no statistically significant difference in the mortality in relation to vaccination status (Table 5).

Discussion

The most common underlying comorbidities in the 2 waves were diabetes mellitus, cardiac diseases, and heart failure. Similarly, in a study from Spain, the most common underlying diseases were cardiovascular diseases, type 2 diabetes mellitus, and chronic neurological diseases (Iftimie et al., 2021). In the first wave in the KSA, one study showed the following comorbidities: G6PD

deficiency (33%), hypertension (27%), and diabetes mellitus (26%) (Aljishi et al., 2021). In both waves, the most common symptoms were cough, fever, and shortness of breath. In a previous study during the first wave in the KSA, sore throat and runny nose in addition to the mentioned symptoms were common as well (Aljishi et al., 2021). Similarly, in a study from Spain, the common signs and symptoms in both waves were fever, dyspnea, and cough (Iftimie et al., 2021).

Regarding the laboratory data, we found that patients in the second wave had higher mean values of lymphocytes count, platelet counts, and ALT but no difference in inflammatory markers. One study showed lower inflammatory markers during the

second wave, and that neutrophils and lymphocytes were higher (Asghar et al., 2021). It was suggested that increased inflammatory markers is associated with severe diseases (Fomina et al., 2020). In this study, we found gender and age differences among hospitalized patients in the first and second wave. In a study from Spain, there was no difference in age or gender between the first and second wave (Soriano et al., 2021). In another study, admitted patients during the second wave were considerably younger (67 vs 58 years, $p < 0.001$) but there was no difference in relation to sex (Iftimie et al., 2021). However, in a study from 14 countries, there was no difference in relation to age in the 2 waves (Ioannidis et al., 2021). Also, in one study, the percentage of males infected in the second wave was 47.2% versus 31% in the first wave (Alves-Cabratosa et al., 2022). This difference might be related to the uptake of the vaccine and the priority groups of those older than 60 years of age in the initial phase of the vaccine in KSA (Assiri et al., 2021).

The death rate was significantly higher in the first wave than the second wave (16.2% vs 8.4%, respectively; $P = 0.001$). A previous study from the KSA during the first wave showed a death rate of 16% (Barry et al., 2021a) and another study showed a mortality rate of 11.8% (Alhumaid et al., 2021). It was suggested that the first wave was associated with higher inoculum than the second wave and this may have led to a higher rate of death (Guallar et al., 2020). In Italy, the second wave, August 2020–February 2021, was associated with high incidence of COVID-19 but was associated with lower admissions to intensive care units and lower total deaths in comparison with the first wave (Coccia, 2021). The use of steroids was found to benefit patients with severe disease, and this was clearly demonstrated in the landmark RECOVERY trial with the use of dexamethasone (6 mg intravenous or orally once a day) and was published February 2021 (RECOVERY Collaborative Group, 2020). However, the use of corticosteroids was not different in the 2 waves in this study. However, in another study, the use of steroids was more frequent in the second wave than the first wave (Iftimie et al., 2021). Another explanation is the age of included patients. One study reported that an odds ratio of mortality was higher with increasing age (OR: 1.079, 95% CI: 1.063; 1.094) (Domingo et al., 2021).

The impact of the first two-waves on countries is variable. A study evaluated the impact of the second wave in the African continent and showed a more severe second wave than the first wave (Salyer et al., 2021). In a study from India, patients in the second wave had higher ICU rates (26.1 vs 13.4%, $p < 0.001$) and higher in-hospital death rate (29.9 vs 18.2%, $p < 0.001$) (Ranganathan et al., 2021). It also noted that ICU admission was associated with higher mortality than non-ICU admission, and there is a disparity in the outcomes of patients with COVID-19 (Al-Tawfiq et al., 2020a; Tirupathi et al., 2020). The exact reasons for the decreased death rates in the second wave are not well characterized. The first wave could have caused increased burden in hospitals, and this may have contributed to the increased mortality. Since vaccination was introduced in KSA at the end of December 2020 and was aimed at older adults initially, this may explain higher hospitalization of the younger age group in the second wave. During the initial launch of the COVID-19 vaccination in KSA, the rate of vaccine acceptance was low and only 33.3% of 1058 surveyed healthcare workers were enrolled to receive or had already received the vaccine between December 27, 2020 and January 3, 2021 (Barry et al., 2021b). Another study showed only 20.9% were willing to receive the RNA BNT162b2 vaccine (Temsah et al., 2021). However, additional strategies were successful in achieving a high rate of vaccination among residents and citizens in KSA.

We had no sequencing data on the identified SARS-CoV-2 during this study. However, the second wave in the KSA was thought to be predominantly secondary to the delta variant. In a preprint

study of 320 SARS-CoV-2 samples obtained April–June 2021, 40.9% of the samples were of the delta variant, 15.9% were beta variant, and 11.6% were alpha variant (Alhamlan et al., 2021). In a study from a neighboring country, Qatar, the case fatality rate in patients with the delta variant was 2.4% and was not statistically different from the 1.1% in patients with the beta variant (Butt et al., 2022). However, in a systematic analysis, the delta variant was associated with the highest risk of admission to the ICU and higher death rate than the alpha and beta variants, and that the beta variant was associated with a higher risk of hospitalization than the wild-type variant (Lin et al., 2021).

To the best of our knowledge, this is the first study of the comparison of hospitalized patients in the first wave and the second wave in the KSA. However, the study has a few limitations. First, the study is a single-center study and an additional multi-center study is needed to elucidate the differences between these 2 waves. The study is limited by the nature of retrospective analysis and the lack of genotyping of the SARS-CoV-2 isolates. Thus, the classification was based on epidemiologic timing of the waves.

Conflict of Interest

All authors have no conflict of interest to declare

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Ethical Approval

The institutional review board of the King Fahad Military Medical Complex approved the study (AFHER-IRB-2020-034).

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