Natural History and Clinical Course of Symptomatic and Asymptomatic COVID-19 Patients in the Kingdom of Saudi Arabia

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Abstract

Objectives: To analyze symptomatic and asymptomatic COVID-19 patients in Saudi Arabia in terms of initial presentation, risk factors, laboratory findings, clinical outcomes and healthcare utilization.

Methods: All laboratory-confirmed reverse transcription–polymerase chain reaction positive COVID-19 patients who had been tested at three governmental hospitals in Saudi Arabia (two in Riyadh and one in Makkah) between March 8 and May 18, 2020 were included. Demographics, COVID-19 variables, clinical characteristics and healthcare utilization variables were extracted and combined, and a descriptive analysis was conducted. Symptomatic and asymptomatic (on presentation) patients' data were compared.

Results: Eighty percent of the patients were males (81.4% of symptomatic and 73.2% of asymptomatic patients, $P = 0.02$). Moreover, 47.6% and 38.4% of symptomatic and asymptomatic patients were aged 40–64 years, respectively. Fever, cough and breathing difficulties were frequent presenting symptoms. Overall, diabetes (16.4%), hypertension (11.7%), chronic respiratory disease (7.1%) were the most frequent comorbidities, with no differences between the two groups. Symptomatic patients had higher C-reactive protein levels (3.55 vs. 0.30 mg/L; $P < 0.0001$) and lower total lymphocytes (1.41 vs. 1.70; $P = 0.02$). ICU admission and mortality were 12.1% and 4.1% in symptomatic, compared to 6.0% and 2.9% in asymptomatic patients, respectively.

Conclusion: In the studied COVID-19 cohort, symptomatic patients tended to be older, had higher C-reactive protein and more lymphopenia with worse outcome than asymptomatic patients. This granular analysis of COVID-19 cohorts enables identification of at-risk cohorts in future waves, optimizing development of patient pathways and public health interventions.

Keywords: Coronavirus, epidemiology, public health surveillance, SARS-CoV-2, Saudi Arabia, symptoms

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), remains one of the most challenging zoonotic infectious disease faced worldwide. As of February 10, 2021, over 106 million cases of COVID-19 had been reported worldwide that have resulted in > 2 million deaths.[1] In the Kingdom of Saudi Arabia (KSA), which is the largest country in the Arabian Peninsula with a population of 34 million, 370,987 COVID-19 cases had been reported with 6410 deaths as of March 2nd, 2021.[2]

A large proportion of those testing positive for COVID-19 are pauci-symptomatic or asymptomatic.[3] In symptomatic patients, the clinical presentation of COVID-19 varies markedly and is impacted by risk factor groups, including older age and patients with comorbidities.[4] The clinical features of COVID-19 appears to differ in prevalence in different clinical populations.[5]

In the Middle East, few studies have reported the course and clinical presentation of COVID-19 and compared these between symptomatic and asymptomatic patients. Therefore, this study aims to compare the initial presentation, risk factors, laboratory findings and healthcare utilization of symptomatic and asymptomatic COVID-19 patients from KSA.

METHODS

This retrospective study analyzed the clinical data of all laboratory-confirmed reverse transcription–polymerase chain reaction-positive COVID-19 patients who had been tested at three governmental hospitals in KSA (two in Riyadh and one in Makkah) between March 8 and May 18, 2020. This study was approved by the Ethics Committee of Ministry of Health (MoH) (Ref no.: 20-63E) and permissions were obtained from the concerned departments of all three hospitals.

Participants and setting
In KSA, healthcare is available for free at governmental hospitals for nationals, and expatriates typically access the private healthcare system through insurance supplied by their employer. Nonetheless, the Saudi government had passed an order for free COVID-19 treatment across the country to ensure larger accessibility.[6] In addition, the testing facility was freely made available by the MoH at healthcare facilities, all individuals with suspected COVID-19 – either based on symptoms or exposure to those with confirmed COVID-19 – can be tested at these sites. If positive, they are immediately enrolled in the MoH testing and contact tracing program. In the early phase of the pandemic, all patients who tested positive were admitted to hospitals, which was later changed to only include symptomatic patients. To provide data for comparison between symptomatic and asymptomatic patients, this study retrospectively analyzed the data of the initial phase.

All cases presented in this study are from three governmental hospitals, that are part of the Saudi MoH: Al Noor Specialist Hospital, a 500-bed specialized teaching hospital located centrally in Makkah;[7] Prince Mohammed bin Abdulaziz Hospital, a 500-bed hospital in Riyadh that is one of the major hospitals for COVID-19 case referrals;[8] and Al-Imam Abdulrahman Al Faisal Hospital, Riyadh.

Grouping of patients was based on their initial presentation, with those presenting with at least one of the following symptoms were considered symptomatic: fever, cough, shortness of breath (SOB), sore throat, digestive symptoms, rhinorrhea, headache, or other symptoms. In the absence of any of the mentioned symptoms, patients were considered asymptomatic.

Data collection
The following data were collected: demographics (gender, weight, and height), symptoms at presentation, reasons for testing (suspected as per case definition, contact of a positive case or travel history), baseline vitals and laboratory results, complete blood count, liver function, C-reactive protein, lactate dehydrogenase (LDH), D-dimer, alkaline phosphatase, albumin and total bilirubin. Moreover, information regarding treatment received, intensive care unit (ICU) admission, discharge date and survival (i e., death date) were also extracted. Data extraction was done by a single author and was quality checked by another author to ensure accuracy and quality of data.

Statistical analysis
The data were manually entered into a Microsoft Excel (Microsoft Corp, Redmond, WA), and then transferred to SPSS version 25 (SPSS Inc., Chicago, IL, USA) for data cleaning, management and analysis. The collected information is presented as total numbers and valid percentage for categorical variables, and as median and interquartile range (IQR) for continuous variables. Differences between variables for symptomatic and asymptomatic patients were assessed with a Chi-square test or independent *t*-test, as appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

Demographic characteristics

A total of 1051 patients tested positive for COVID-19 in the three hospitals during the included period. Table 1 details the demographic characteristics of these patients. The sample consisted of 80.3% males, with 2.0% being aged ≤18 years and 8.9% aged ≥65 years. Further, 24.7% of the patients were Saudi, 3.1% were healthcare workers, 5.9% were tested due to travel and 16.4% were linked epidemiologically to a confirmed case. In total, 913 (86.9%) patients were symptomatic. Significantly more males were symptomatic than asymptomatic (81.4% vs. 73.2%, respectively; P = 0.02). Moreover, symptomatic patients were more likely to be non-Saudi (P < 0.0001), and were less likely to be linked epidemiologically to a confirmed case (13.9%) compared to asymptomatic patients (32.6%, P < 0.0001).

Comorbidities and symptomatology of the studied patients

The most common comorbidities were diabetes (16.4%), hypertension (11.7%) and chronic respiratory disease (7.1%). Diabetics were more likely to be symptomatic (17.5% vs. 12.0% among non-symptomatic), although the association was not statistically significant (P = 0.15). No significant differences were found in other comorbidities between the two groups. For BMI, data on weight was only available for 551 patients (52.4%), and symptomatic patients were found to more likely be obese than asymptomatic patients (26.6% and 18.8%, respectively, P = 0.09) was observed [Table 2].

In the symptomatic group, the most common symptoms were fever and cough (66.0% and 64.5%, respectively). SOB, sore throat, and digestive symptoms were also frequently reported, although at a lower frequency (26.2%, 20.3% and 6.4%, respectively) [Figure 1]. Headache, fatigue, rhinorrhea or any other symptom were rarely reported.
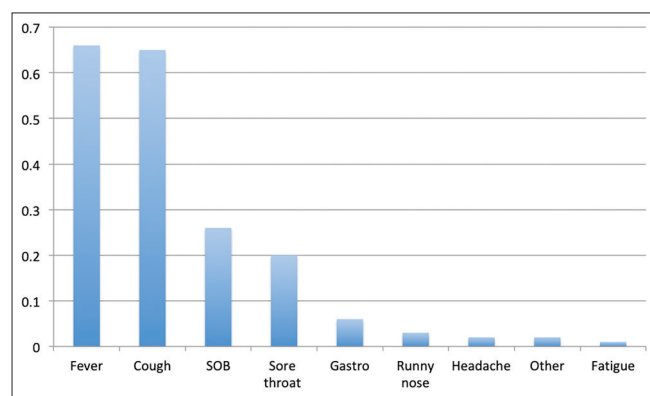
Figure 1: Prevalence of symptoms among patients infected with SARS-CoV-2 who were reported to be symptomatic

Laboratory findings

Overall, no medians were found to be outside the reference ranges. When comparing the two groups, symptomatic patients were found to have significantly higher C-reactive protein levels (3.55 vs. 0.30 mg/L; P = <0.0001) and lower total lymphocyte levels (1.41 vs. 1.70; P = 0.02). Significant difference was not noted in any other studied parameters. Regarding vital signs, symptomatic patients had higher heart rate (95.0 beats/min) than asymptomatic patients (86.0 beats/min) (P < 0.0001) [Table 3].

Healthcare utilization and outcome

Antibiotics and hydroxychloroquine were frequently administered (73.9% and 32.0%, respectively), while steroids and antiviral drugs were less common (14.8% and 20.5%, respectively) [Table 4]. Antibiotics were more frequently administered to symptomatic patients (78.6% vs. 34.5%, P < 0.0001). Similarly, hydroxychloroquine and corticosteroids were more frequently administered to symptomatic patients (34.7% and 14.8%, respectively) than asymptomatic patients (9.2% and 2.5%, respectively) (P < 0.0001 and 0.001, respectively). Oseltamivir use was not significantly different between the two groups.

A total of 11.3% of the patients were admitted to the ICU, with symptomatic patients more likely to be admitted (12.1% vs. 6.0%, P = 0.04). Hospital stay of less than 2 days was rare (10.2%); most were admitted for 2–7 days (52.5%%), followed by 8–14 days (26.8%) and >2 weeks (10.4%). No differences were found between the two groups in terms of lengths of hospital stay. The vast majority (73.3%) of the patients had been discharged at the time of data collection, but about one-fifth (22.8%) remained admitted, while 3.9% had died.

DISCUSSION

The clinical features of patients hospitalized for COVID-19 in the KSA were similar to patients in studies from other parts of the world: a significant number of our patients had underlying medical conditions, and a considerable proportion of patients were asymptomatic.

About 80% of COVID-19 patients in this study were male; similar proportions have been observed in China, Italy and the United States.[9-11] It is currently unclear why COVID-19 infects males at a higher rate, and further research will be needed to understand this epidemiologic trend. The median age in this study (41 years) was noticeably lower than that in other countries. For example, the median age of patients with COVID-19 reported from other countries was between 62 − and 66 − years old in the

Table 1: Demographic, occupation, and reason for testing for patients infected with severe acute respiratory syndrome coronavirus-2 as well as distribution according to symptoms

Category	Level	All (*n*=1051), *n* (%)	Symptomatic (*n*=913), *n* (%)	Asymptomatic (*n*=138), *n* (%)	*P*
Hospital	Riyadh 1	136 (12.9)	104 (11.4)	32 (23.2)	<0.0001
	Riyadh 2	597 (56.8)	504 (55.2)	93 (67.4)	
	Makkah 1	318 (30.3)	305 (33.4)	13 (9.4)	
Gender	Male	844 (80.3)	743 (81.4)	101 (73.2)	0.02
	Female	207 (19.7)	170 (18.6)	37 (26.8)	
Age (years)	≤18	21 (2.0)	13 (1.4)	8 (5.8)	0.01
	19-39	446 (42.7)	383 (42.2)	63 (45.7)	
	40-64	485 (46.4)	432 (47.6)	53 (38.4)	
	≥65	93 (8.9)	79 (8.7)	14 (10.1)	
Nationality	Saudi	260 (24.7)	201 (22.0)	59 (42.8)	<0.0001
	Non-Saudi	791 (75.3)	712 (78.0)	79 (57.2)	
Healthcare worker		28 (3.1)	22 (2.7)	6 (5.7)	0.12
Reason for testing	Linked to travel	62 (5.9)	49 (5.4)	13 (9.4)	<0.0001
	Linked to confirmed case	172 (16.4)	127 (13.9)	45 (32.6)	

Table 2: Comorbidities and body mass index among patients infected with severe acute respiratory syndrome coronavirus-2 as well as distribution according to symptoms

Category	Level	All (*n*=1051), *n* (%)	Symptomatic (*n*=913), *n* (%)	Asymptomatic (*n*=138), *n* (%)	*P*
Comorbidities	Any comorbidity	218 (29.7)	183 (30.1)	35 (28.0)	0.64
	Diabetes	120 (16.4)	105 (17.5)	15 (12.0)	0.15
	Hypertension	86 (11.7)	70 (11.5)	16 (12.8)	0.68
	Cancer	6 (0.8)	5 (0.8)	1 (0.8)	0.98
	Respiratory disease	52 (7.1)	42 (6.9)	10 (8.0)	0.67
	Cardiovascular disease	30 (4.1)	25 (4.1)	5 (4.0)	0.95
	Kidney disease	16 (2.2)	12 (2.0)	4 (3.2)	0.39
	Other	33 (4.5)	23 (3.8)	10 (8.0)	0.04
BMI (kg/m²)	Underweight (<18.5)	10 (1.8)	6 (1.3)	4 (4.7)	0.09
	Normal (18.5-24.9)	206 (37.4)	173 (37.1)	33 (38.8)	
	Overweight (25-29.9)	195 (35.4)	163 (35.0)	32 (37.6)	
	Obese (≥30)	140 (25.4)	124 (26.6)	16 (18.8)	

BMI – Body mass index

United States,[9,12,13] 63 − years old in Italy,[10] and ranged from 49 − to 56 − years old in Wuhan, China.[11,14,15] This could be attributed to the fact that that KSA has a younger population compared to European and Asian countries.[16,17]

Diabetes, hypertension, and chronic lung disease were common comorbidities, similar to previous reports of patients hospitalized for COVID-19,[18-21] It is well established that patients with diabetes are at increased risk of viral infections and related complications,[22] due to impaired immune responses against viral pathogens. Although not yet fully established, it has been postulated that the weakened immune system expedites the progression of COVID-19 in patients with diabetes.[23] Accordingly, those with diabetes are at higher risk of severe disease, need for mechanical ventilation and admission to ICU; these factors likely contribute to the overall poor survival in this subset of patients.[24] Although the pathogenesis of COVID-19 in patients with hypertension or COPD remains poorly understood, both comorbidities are independently associated with a 2.5-and a 5.7-fold risk of COVID-19 disease severity and death, respectively.[4,25,26]

In our cohort, the majority of the patients were symptomatic. Among asymptomatic patients, some developed symptoms during the hospital stay. We believe the percentage of positive asymptomatic is underestimated, as one of the criteria for undertaking a COVID-19 test in KSA is the presence of symptoms or known exposure to a confirmed case. A random community wide testing would provide a more robust understanding of the percentage of asymptomatic patients. Further studies focused on random, unbiased testing of individuals would be necessary to accurately determine the exact percentage of patients who remain asymptomatic. Understanding this proportion is of great importance, as asymptomatic patients are at risk of transmitting the virus.[27,28] In fact, it is believed that the spread of the infection by asymptomatic individuals, combined with the relatively high basic reproduction number (R_0) of 5.7[29] hastened the global pandemic and hindered public health efforts to effectively prevent and control the pandemic. Several studies have attempted to estimate the rate of asymptomatic COVID-19 infection, but the estimates vary widely (from 2% to 52%) and depend on the geographic location and setting.[29-32] Irrespective of the actual value, our results support a low

Table 3: Baseline laboratory results and vital signs for patients infected with severe acute respiratory syndrome coronavirus-2 as well as distribution according to symptoms

Findings	Normal value	Median (IQR)			P
		All (*n*=1051)	Symptomatic (*n*=913)	Asymptomatic (*n*=138)	
WBCs (×10⁹/L)	3.5-9.5	6.6 (3.6)	6.5 (3.6)	6.9 (3.8)	0.91
Hb (g/L)	130-175	143.0 (25.0)	143.0 (25.0)	144.0 (27.0)	0.26
Platelets (×10⁹/L)	150-350	231.0 (106.0)	231.0 (109.0)	230.0 (95.0)	0.89
Neutrophils (×10⁹/L)	1.8-6.3	3.89 (3.16)	3.92 (3.21)	3.66 (3.06)	0.31
Lymphocytes (×10⁹/L)	1-3.3	1.45 (0.85)	1.41 (0.86)	1.70 (0.71)	0.01
CK (U/L)	25-200	123.0 (195.8)	130.5 (211.8)	96.0 (86.0)	<0.0001
ALT (U/L)	10-45	36.0 (34.0)	36.0 (35.0)	31.0 (30.0)	0.20
AST (U/L)	10-40	36.0 (31.0)	37.0 (33.0)	29.0 (17.0)	0.050
Creatinine (μmol/L)	57-111	79.0 (26.1)	79.5 (26.9)	74.5 (24.8)	0.31
Albumin (g/L)	40-55	40.0 (10.0)	39.3 (11.0)	42.0 (8.0)	0.047
Bilirubin (μmol/L)	0-21	9.4 (6.6)	9.6 (6.5)	8.7 (6.2)	0.30
PT (s)	9.5-13.5	13.6 (1.3)	13.6 (1.3)	13.7 (1.1)	0.23
PTT (s)	25-37	35.8 (7.2)	35.8 (7.3)	35.4 (5.1)	0.65
INR	0.8-1.2	1.02 (0.11)	1.02 (0.11)	1.03 (0.11)	0.86
CRP (mg/dL)	0.0-0.40	2.78 (9.08)	3.55 (9.52)	0.30 (1.23)	<0.0001
Erythrocytes sedimentation rate (mm/h)	0-15	26.5 (59.9)	35.0 (66.7)	5.34 (10.9)	<0.0001
LDH (U/L)	50-242	265.0 (196.5)	273.5 (203.0)	209.0 (101.0)	<0.0001
D-Dimer (ng/mL)	0-229	0.91 (1.70)	0.91 (1.50)	0.79 (3.3)	0.65
Ferritin (ng/mL)	15-400	629.1 (1006.1)	629.1 (1005.2)	597.3 (695.0)	0.88
Lactate (mmol/L)	0.5-1	1.66 (0.66)	1.68 (0.70)	-	-
Temperature (°C)	35.5-37.5	37.3 (1.0)	37.4 (1.0)	37.0 (0.5)	<0.0001
HR (beats/min)	60-100	93.0 (23.0)	95.0 (23.0)	86.0 (17.0)	<0.0001
RR (breaths/min)	12-20	20.0 (1.0)	20.0 (1.0)	20.0 (1.0)	<0.0001
SBP (mmHg)	90-120	125.0 (20.0)	125.0 (20.0)	129.0 (20.0)	0.10
DBP (mmHg)	60-90	78.0 (14.0)	78.0 (13.0)	75.0 (15.0)	0.20

AST – Aspartate aminotransferase; ALT – Alanine aminotransferase; CK – Creatine kinase; CRP – C-reactive protein; DBP – Diastolic blood pressure; Hb – Hemoglobin; HR – Heart rate; INR – International normalized ratio; LDH – Lactate dehydrogenase; NLR – Neutrophil-lymphocyte ratio; PT – Prothrombin time; PTT – Partial thromboplastin time; RR – Respiratory rate; SBP – Systolic blood pressure – WBCs – White blood cells; IQR – Interquartile range

Table 4: Intensive care unit admission, management, and outcome of patients infected with severe acute respiratory syndrome coronavirus-2 as well as distribution according to symptoms

Category	Level	All, *n* (%)	Symptomatic (*n*=913), *n* (%)	Asymptomatic (*n*=138), *n* (%)	P
Medication	Antibiotic	596 (73.9)	566 (78.6)	30 (34.5)	<0.0001
	Hydroxychloroquine	258 (32.0)	250 (34.7)	8 (9.2)	<0.0001
	Steroid	94 (14.8)	92 (14.8)	2 (2.5)	0.001
	Oseltamivir	130 (20.5)	117 (21.1)	13 (16.5)	0.34
ICU admission		115 (11.3)	107 (12.1)	8 (6.0)	0.04
Hospital length of stay (days)*	0-1	82 (10.2)	73 (10.4)	9 (8.7)	0.19
	2-7	423 (52.5)	362 (51.6)	61 (58.7)	
	8-14	216 (26.8)	187 (26.7)	29 (27.9)	
	>14	84 (10.4)	79 (11.3)	5 (4.8)	
Outcome	Remained admitted at the time of data collection	240 (22.8)	207 (22.7)	33 (23.9)	0.78
	Discharged	770 (73.3)	669 (73.3)	101 (73.2)	
	Died	41 (3.9)	37 (4.1)	4 (2.9)	

*Among discharged patients. ICU – Intensive care unit

threshold for testing of COVID-19 and stress the need for testing availability to diagnose COVID-19, particularly in asymptomatic patients.

Interestingly, most of the laboratory values were within normal ranges. The degree of abnormalities in the laboratory findings of patients with COVID-19 varies across different studies,[11-15] but the levels of LDH and total lymphocytes are consistently reported as elevated in these patients. In our study, both the LDH and lymphocytes level were within the normal range. It must be noted that

the patients in this study were younger and had fewer comorbidities; presumably, they were healthier and more able to mount an adequate immune response against the virus, which would minimize the degree of laboratory abnormalities. To fully understand the link between age and degree of laboratory abnormalities, future large-scale studies are needed to compare patients with and without laboratory abnormalities, particularly LDH, lymphocyte, ferritin, D-dimer, procalcitonin and interleukin 6 levels. Similarly, the lack of laboratory abnormalities combined with fewer comorbidities and younger age may have

contributed to the study's favorable composite endpoints. Overall, 10% of our cohort was admitted to the ICU, nearly 73% of patients were discharged and <4% died. These rates compared favorably to previously reported values for ICU admission (14%−39%), discharge (26%−66%) and mortality (7%−26%).[9-15,33]

The study had some noteworthy limitations and strengths. The study was a retrospective, cross-sectional analysis, and no patient data were collected after hospital discharge. Further, we were unable to collect the data for several different parameters for a significant proportion of patients. Notwithstanding, the study included COVID-19 patients from hospitals in two large metropolitan cities in KSA. To our knowledge, this is only the third study that describes the characteristics of patients with confirmed COVID-19 hospitalized in the KSA.[34,35] Therefore, this study adds to the growing body of literature characterizing the clinical features of COVID-19. The majority of currently available studies are retrospective in design, limited to single centers and carried out during short time periods. In the future, larger prospective, multi-center studies are required to be conducted over longer observation periods and with a larger sample size. Likewise, more studies are necessary to adequately examine and compare the clinical features and outcomes of patients with COVID-19 and MERS, to facilitate the implementation of optimal prevention and control strategies not only for COVID-19 but also in the event of any future coronavirus outbreaks.

CONCLUSION

In this studied COVID-19 cohort in KSA, about 80% of the patients were male. Symptomatic patients tended to be older, had higher C-reactive protein and more lymphopenia with worse outcome than asymptomatic patients. This granular analysis of COVID-19 cohorts enables identification of at-risk cohorts in future waves, optimizing development of patient pathways and public health interventions.

Ethical considerations
Ethical approval for this study was obtained from the Ethics Committee of Saudi Ministry of Health (Ref no.: 20-63E) on April 22, 2020.

Peer review
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Conflict of interest
There are no conflicts of interest.

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