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Original article

The seroprevalence of SARS-CoV-2 IgG antibodies among asymptomatic blood donors in Saudi Arabia

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ABSTRACT

Background: In late 2019, cases of severe pneumonia with unidentified etiology began to emerge in Wuhan, China, before progressively spreading first nationally and then globally.

The current study sought to investigate the seroprevalence of immunoglobulin G (IgG) antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among blood donors in Al-Madinah, Saudi Arabia. To our knowledge, this is the first study in Saudi Arabia to screen blood donors who were not known to be previously infected with SARS-CoV-2.

Methods: This study was a cross-sectional study to assess individuals who donated blood to the central blood bank in Al-Madinah between mid-May and mid-July 2020. An enzyme-linked immunosorbent assay (ELISA) was designed and established to detect antibodies directed against the SARS-CoV-2 spike protein in serum samples. A total of 1,212 healthy blood donors participated in this study. The donors were males and met the requirements for blood donation during the COVID-19 pandemic period in Saudi Arabia.

Results: The SARS-CoV-2 seroprevalence among blood donors in Al-Madinah was 19.31% (n = 234/1212; 95% confidence interval: 17.12%–21.64%). No statistically significant difference was identified in seropositivity according to age. However, significant differences ($p < 0.001$) were identified according to ABO blood groups, with those with type A blood presenting the highest rate of seropositivity (29.18%) compared with the other blood groups (12.65% for type B, 16.36% for type AB, and 15.11% for type O).

Conclusion: A high prevalence of SARS-CoV-2 antibodies was detected among blood donors in Al-Madinah, which indicated a high level of exposure to the virus within the population. This further suggested that as high as one-fifth of the population may have acquired innate immunity against the virus.

1. Introduction

During late 2019, cases of severe pneumonia with an unidentified etiology began to emerge in Wuhan, China, before spreading first nationally and then globally. A novel beta coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the causative pathogen of this condition, which was later named coronavirus disease 2019 (COVID-19). Within months, COVID-19 cases were reported in almost every country worldwide (Cucinotta and Vanelli, 2020, Du et al., 2020).

On March 2, 2020, a Saudi man in the Eastern Province who was traveling from Iran was confirmed as positive for SARS-CoV-2 infection (Alsofayan et al., 2020). At the time, the Saudi Ministry of Health (MOH) took the case seriously, and isolated the patient and all of his contacts. However, the subsequent domestic spread of the virus was dramatic, with several cases reported in the same region. The initial cases were classified as originating among citizens returning from Iran, who likely imported the virus, whereas the later cases were traced to incidents of local community transmission.

Globally, the total number of confirmed SARS-CoV-2 cases reached 58 million, and 1,380,088 deaths as accessed on 21-11-2020. (https://www.worldometers.info/coronavirus/).

In Saudi Arabia, the total number of confirmed COVID-19 cases were 354,813, including 342,404 recovered cases and 5,745 deaths.

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A total of 28,713 cases, including 27,779 recoveries, 410 active cases, and 140 deaths, have been reported for Al-Madinah. These numbers suggested a recovery rate of greater than 96% and a case fatality rate (CFR) of 0.49% (https://covid19.moh.gov.sa/ accessed on 21-11-2020).

A comprehensive, multicenter study conducted in Saudi Arabia indicated that the median incubation period for the virus was six days. The most common symptoms included cough (89.4%), fever (85.6%), and sore throat (81.6%), and 20.1% of infected patients were found to present with underlying comorbidities (Alsofayan et al., 2020). Saudi Arabia had previously experienced an outbreak of the Middle East respiratory syndrome-related coronavirus (MERS-CoV), which began in 2012 and lasted for a few years (Al-Raddadi et al., 2020).

Reverse-transcription-polymerase chain reaction (RT-PCR) is the gold-standard method for identifying and confirming SARS-CoV-2 infection (Cao et al., 2020). However, this technique cannot detect previous, nonactive viral infections. Therefore, serological tests might represent a useful method through which to investigate the prevalence of previous SARS-CoV-2 infections within the community, which would support the continued efforts to minimize the viral transmission rate and the design of sensible public health policies.

Scientists have thoroughly investigated the characteristics, clinical presentation, and risk factors associated with individuals who have experienced SARS-CoV-2 infections (Sanche et al., 2020). Among the risk factors that have been identified as influencing numerous infectious diseases, is the ABO blood group polymorphism, which has been associated with the differential spread of several pathogens (Chen et al., 2020b). To date, a number of investigators have explored the level of host vulnerability to infections with coronaviruses, such as SARS-CoV-2, according to the blood type or the presence of anti-histo-blood group antibodies (Cheng et al., 2005).

To better understand the persistent spread of the SARS-CoV-2 virus, to identify individuals who are or were previously infected, and to monitor the immune response to SARS-CoV-2 exposure longitudinally, reliable and robust tests for SARS-CoV-2 detection and immunological observation are necessary and have been developed globally. In this study, we measured the levels of IgG antibodies targeting the SARS-CoV-2 spike (S) protein during the peak period of the COVID-19 pandemic in Al-Madinah, Saudi Arabia. In addition, the distribution of IgG-positive cases was examined according to ABO blood groups. The present findings shed light on the magnitude of SARS-CoV-2 exposure among the Al-Madinah population in Saudi Arabia.

2. Materials and methods

2.1. Study setting

The present study recruited blood donors who visited the central blood bank in Al-Madinah, Saudi Arabia, which is the primary blood bank in the region and supplies to almost all the government and private hospitals in Al-Madinah. It is one of the most highly ranked blood banks in Saudi Arabia and has been certified and accredited by the Saudi Central Board for Accreditation of Healthcare Institutions (CBAHI), the official agency authorized to grant accreditation certificates to all government and private healthcare facilities in Saudi Arabia.

2.2. Study subjects

At the blood bank, potential blood donors had to respond to a printed questionnaire and undergo a short-term health screening administered by the blood bank physician. To obtain approval to donate blood, individuals had to fulfill the donation eligibility criteria, which were defined by the Saudi MOH according to the regulations and standards established by the American Association of Blood Banks (AABB, http://www.aabb.org/tm/donation/Pages/donatefaqs.aspx, accessed on 21-11-2020)

Eligible participants for this study were those with no current COVID-19 symptoms and no confirmed previous SARS-CoV-2 infection. Blood donors were excluded if they were diagnosed with existing diseases or presented with physically identifiable symptoms of any infection, including cough, sore throat, or fever. All participants were confirmed to be free from all viral infections, including hepatitis B and C, human immunodeficiency virus (HIV) 1 and 2, and human T-cell leukemia-lymphoma virus.

After being approved for blood donation, all eligible blood donors were included in this study as long as they signed the informed consent form and had not been previously tested positive for SARS-CoV-2 infection.

All blood donations were completed at the central blood bank in Al-Madinah. This study was approved by the research ethics committee of the General Directorate of Health Affairs in Al-Madinah (IRB number: 496). Informed consent was obtained from all participants.

2.3. Participant blood samples

A total of 1,212 residual serum samples, which remained after the routine screening of blood from eligible blood donors, obtained between mid-May and mid-July 2020, were screened for the presence of anti–SARS-CoV-2 IgG antibodies.

2.4. Enzyme-linked immunosorbent assay (ELISA)

An enzyme-linked immunosorbent assay (ELISA) was adapted for use in this study, according to a previously established protocol, with slight modifications (Mahallawi, 2017, Mahallawi et al., 2013). In brief, a 96-well ELISA plate (Costar; Corning, Corning, NY, USA) was coated with the SARS-CoV-2 recombinant S protein (Sino Biological, Beijing, China). The SARS-CoV-2 S protein was reconstituted in phosphate-buffered saline (PBS; pH 7.2), and the plates were coated with 100 μL/well of SARS-CoV-2 S protein, at an optimal concentration of 2 μg/mL. The plates were then covered with an adhesive seal and incubated overnight at 4 °C. The plates were then washed five times with washing buffer (PBS containing 0.05% Tween-20; Sigma-Aldrich, St. Louis, MO, USA), using an automated microplate washer (Elx50; Bio Tek, Winooski, VT, USA). The plates were then blocked with 150 μL/well blocking buffer [PBS containing 0.05% fetal bovine serum (FBS) that was heat-inactivated at 56 °C for 60 min; Sigma-Aldrich] for one hour at room temperature. Serum samples were then diluted (1:100) using a blocking buffer and added at 100 μL/well. The plates were incubated again for 30 min at room temperature and washed five more times with washing buffer. A specific alkaline phosphatase-conjugated goat anti-human IgG secondary antibody (1:1,000 in blocking buffer, Sigma-Aldrich) was then added at 100 μL/well, and the plates were incubated at room temperature for 30 min before again being washed five times with washing buffer. Finally, 100 μL/well of the ready-prepared substrate, p-nitrophenyl phosphate (p-NPP, Sigma-Aldrich), was added. The plates were maintained in the dark, away from direct light, until color developed. After 30 min, 100 μL of the stopping solution (1.2 N sodium hydroxide, Reagecon , UK), was added to all the wells to terminate the reaction. The optical density at 405 nm was measured using a microplate reader (ELX800; BioTek).

The sample was defined as ELISA-antibody-positive if the OD_{405} value was three standard deviations (SDs) above the mean value of the negative control. The calculated cutoff OD_{405} value (mean negative control value + 3 SDs) was 0.19 + (3 × 0.033) = 0.29.

Background values were obtained while performing the assay to ensure that the OD values represented the actual antibody levels in each sample. The background value was deducted from all OD_{405} values prior to calculating the cutoff. Additionally, all seropositive samples were confirmed by the central blood bank serology department, using chemiluminescent microparticle immunoassay (CMIA), which has a sensitivity of 99.99% and has previously been reported to obtain results with 98% similarity to those obtained using the current ELISA analysis.

2.5. Statistical analyses

Statistical analyses were conducted using Stata 16.1 (StataCorp LLC, College Station, TX, USA). The outcome variable was SARS-CoV-2 seropositivity, defined as an OD_{405} value of 0.30 or higher. Independent variables included age, blood group, and hemoglobin levels. Age was divided into the following seven categories: 18–24 years, 25–29 years, 30–34 years, 35–39 years, 40–44 years, 45–49 years, and 50 years or older. Seropositivity outcomes were compared in the different age groups as well as among the different blood type groups. Statistical significance for both comparisons was assessed using the Chi-square test. An analysis of variance (ANOVA) was used to compare means among groups, whereas Levene's test was used to review the homogeneity of variance.

3. Results

3.1. Distribution of seropositivity by age and blood type

A total of 1,212 blood samples were obtained from blood donors in Al-Madinah and included in this study. All the donors were men, of various nationalities, including 847 (70%) classified as Saudi, 253 (20.85%) classified as Asian, and 113 (9.3%) classified as Africans. The mean age of the participants was 31.73 ± 9.05 years, ranging from 18 to and 64 years. Among all participants, 234 [19.31%; 95% confidence interval (CI): 17.12%–21.64%] were positive for anti-SARS-CoV-2 IgG antibodies. The seropositivity rate varied among the age groups, ranging from 16.03% among participants of 35–39 years to 21.53% among participants in the age group, 30–34 years (Table 1). However, the observed differences between the age groups were not statistically significant (p = 0.910).

The seropositivity rate also varied significantly according to blood type, ranging from 12.65% among those in the type B group to 29.18% among those in the type A group (Table 2, p < 0.001).

The mean hemoglobin level was 15.4 g/dL (95% CI: 15.25–15.55) among seropositive cases, compared with 15.53 g/dL (95% CI: 15.45–15.60) among seronegative cases, which was not significantly different (p = 0.146).

3.2. Antibody levels among positive cases

The effects of age and blood group on the antibody level (as a continuous variable) in seropositive cases were also investigated. The mean antibody value among positive cases was 1.12 units/mL (95% CI: 1.07–1.16), ranging from 0.88 units/ml in participants aged 45–49 years to 1.20 units/mL in participants aged 30–34 years (Table 3). Two-way ANOVA revealed no significant differences between the mean values according to either age or blood type.

4. Discussion

Seroepidemiological research can identify the fraction of asymptomatic or subclinical infections in the overall population. Furthermore, because SARS-CoV-2 is a novel virus, the surveillance of antibody seropositivity is likely to offer valuable information regarding the true magnitude of the infection (https://www.who.int/publications/i/item/WHO-2019-nCoV-Seroepidemiology-2020.2).

The gradual return to pre-pandemic levels of social and economic activity will require the performance of persistent and active surveillance to quickly identify local outbreaks, conduct contact tracing, and dictate quarantine measures. In addition, those individuals who have been identified to be the most vulnerable to severe COVID-19 infections must remain under enhanced protection. Understanding how protective immunity against COVID-19 develops in the population at large and in specific groups, such as healthcare professionals, is also a crucial goal. A thorough assessment of the duration of protective immunity will be critical for determining the necessary measures to prevent and respond to future waves of SARS-CoV-2 infection. Such information must be gathered widely from various locations worldwide to reflecting the unique local conditions (Noh et al., 2020, Stringhini et al., 2020).

Therefore, defining the prevalence of SARS-CoV-2 among blood donors will give an insight into the virus' spread among healthy people, which can assist in the development of approaches designed to diminish transmission, particularly given the current overall lack of seroprevalence assessments.

However, limited reports have examined the incidence of SARS-CoV-2 among blood donors to date. Our results suggest the existence of a high prevalence of SARS-CoV-2 antibodies among the population of a large city in Saudi Arabia relative to the findings reported by other globally conducted studies. According to available hospital data (MOH database), few individuals have been infected by the virus to date, which, together with our findings, suggests the existence of a significant number of asymptomatic cases in the Al-Madinah population.

Table 1
Distribution of seropositive cases by age group.

	Negative		Positive		Total	
Age group (years)	**No.**	**%**	**No.**	**%**	**No.**	**%**
18–25	222	79.86	56	20.14	278	100
24–29	265	81.04	62	18.96	327	100
30–34	164	78.47	45	21.53	209	100
35–39	110	83.97	21	16.03	131	100
40–44	115	81.56	26	18.44	141	100
45–49	53	79.1	14	20.9	67	100
≥ 50	49	83.05	10	16.95	59	100
Total	978	80.69	234	19.31	1212	100

Table 2
Distribution of seropositive cases by blood type.

	Negative		Positive		Total	
Blood type	**No.**	**%**	**No.**	**%**	**No.**	**%**
O	427	84.89	76	15.11	503	100
A	284	70.82	117	29.18	401	100
B	221	87.35	32	12.65	253	100
AB	46	83.64	9	16.36	55	100
Total	978	80.69	234	19.31	1212	100

Table 3
Summary statistics of antibody level by age and blood groups.

	N	**Mean** (units/ml)	**SD**	**SE**	**95% CI**		**p-value***
Overall	234	1.12	0.38	0.02	1.07	1.16	
Age group (years)							
18–25	56	1.08	0.40	0.05	0.97	1.18	0.164
24–29	62	1.15	0.40	0.05	1.05	1.25	
30–34	45	1.20	0.35	0.05	1.10	1.31	
35–39	21	1.14	0.39	0.09	0.97	1.31	
40–44	26	1.12	0.38	0.07	0.98	1.27	
45–49	14	0.88	0.31	0.08	0.72	1.05	
$\geq$ 50	10	0.97	0.29	0.09	0.79	1.15	
Blood group							
O	76	1.11	0.39	0.04	1.02	1.20	0.909
A	117	1.11	0.37	0.03	1.05	1.18	
B	32	1.17	0.41	0.07	1.02	1.31	
AB	9	0.99	0.38	0.13	0.74	1.24	

* Calculated by two-way ANOVA.

The seroprevalence of asymptomatic SARS-CoV-2 infections has been reported by a few researchers from other countries. One of the most famous studies to date was conducted among the Diamond Prince cruise population, which identified 17.9% of 3,063 travelers as being asymptomatic among the total cases (Mizumoto et al., 2020). Another population-based serological survey study, performed in the county of Santa Clara in California, the United States, reported a 2.8% SARS-CoV-2 seroprevalence (Zwald et al., 2020)

In Italy, a study conducted at the beginning of April 2020 suggested that a minimum of 10% seropositivity existed. Additionally, the municipality of Gangelt in Germany recorded a total of 14% seropositivity (Anand et al., 2020, Klein et al., 2020). Recent preliminary results reported for a mass population screening study performed on a random sample of 562 subjects in Italy showed that the overall seroprevalence was approximately 22.6% (Pagani et al., 2020).

A number of researchers worldwide have begun conducting analyses and serological surveys among their respective populations to determine the incidence of SARS CoV-2 antibodies. The initial results of these studies already indicate a highly variable array of conclusions regarding the current state of SARS CoV-2 infections. A study in New York state used sera collected from April 19 to April 28, around 8 weeks after community transmission was first recognized in New York City. A seroprevalence of 22.7% was estimated (Rosenberg et al., 2020), conforming with our data. No other serological surveys have been reported for any population in the entire Saudi Arabia region to date.

Globally, similar serological surveys, with reduced SARS-CoV-2 antibody seropositivity rates, have been reported among blood donors. For example, a Brazilian study reported a seroprevalence of 3.3% among blood donors aged 18–69 years, which was higher than the reported rates of 1.7% and 2.7% in seroprevalence surveys among blood donors that were performed in Denmark and the Netherlands, respectively (Amorim Filho et al., 2020).

The spread of SARS-CoV-2 represents a major, global, current health crisis. The burden on government continues to increase with the catastrophic expansion of new cases, particularly due to the rapid infectivity of the virus. No globally approved vaccine exists yet, although a few are in various phases of clinical trial (Chen et al., 2020a). Several cases of reinfection have been reported, although protection from reinfection has also been reported (Mahallawi, 2020). Consequently, the monitoring of seropositive cases at the international level will facilitate the establishment of conclusive data regarding the virus and its behavior in various populations.

Our results also suggested a lack of association between seroprevalence and age. However, recent evidence has accumulated to support the increased vulnerability to infection with increasing age. The age-dependent pattern of disease severity has been well-established; however, the underlying reasons for the differential spread of the virus among different age groups remain unclear (Goldstein et al., 2020).

The current study encompasses the first serological survey of SARS-CoV-2 infections among asymptomatic individuals in Al-Madinah, Saudi Arabia. This study included a multinational population having a very wide range of careers and from both rural and urban settings. Therefore, this study presents a high value and applicability, offering a preview of the prevalence of SARS-CoV-2 antibodies among asymptomatic individuals in Al-Madinah. This type of study is important to perform for several reasons: to monitor the disease and trace its occurrence within the population; to identify the rate of asymptomatic individuals among the community; and to build support for the performance of more comprehensive surveys across the country, to measure the actual prevalence of the virus in all areas and reflect a full picture of the disease spread within the country. Finally, this study is key to the identification of those with high antibody titrations, for potential future plasma donations for therapy of severe, hospitalized COVID-19 patients. Although contradictory reports exist regarding the effec-

tiveness of convalescent plasma therapy (Chai et al., 2020), a recent study suggested the potential effectiveness of plasma therapy against COVID-19, especially among severe patients (Liu et al., 2020).

Additionally, recognizing the incidence of SARS-CoV-2 infections among asymptomatic individuals is of vital importance. Healthy people in epidemic regions may be similarly infected and remain asymptomatic, acting as major viral transmission reservoirs. Moreover, herd immunity is partially associated with the extent of infection within a community (Li et al., 2020). By observing the levels of infection, future decisions regarding the initiation or reduction of social distancing directives can be better managed to decrease the potential for successive endemic occurrences (Amorim Filho et al., 2020). Although the present study revealed a high prevalence of SARS-CoV-2 seropositivity relative to those reported in other countries, the level remains far from the 60%–70% level that has been proposed to be necessary for the establishment of herd immunity (Anderson et al., 2020).

A relationship appears to exist between an individual's ABO blood type and the possibility of contracting a SARS-CoV-2 infection following exposure. Type A blood donors showed the highest frequency of anti–SARS-CoV-2 IgG antibodies, which agreed with the results of a recent meta-analysis showing that SARS-CoV-2–positive individuals were more likely to have type A blood than the other blood types (Golinelli et al., 2020). Another study performed by Guillon et al. reported that a monoclonal anti–A antibody or a natural plasma-derived anti–A antibody was able to definitely inhibit the SARS-CoV-2 S protein/ACE2-dependent adhesion to ACE2-expressing cell lines (Guillon et al., 2008). Consequently, the ABO polymorphism might have considerable impact on SARS-CoV-2 susceptibility, linking a number of infected individuals and increasing the relevance of kinetic studies performed during the SARS outbreak in 2002 to 2003 (Golinelli et al., 2020).

Our study has a few limitations. The sample was limited to successfully screened blood donors in Al-Madinah and may not represent the population of Al-Madinah or the wider population of Saudi Arabia. No females were included in this study because there were very few female blood donors. In addition, the study only measured the IgG antibody isotype; testing for viral nucleic acid and IgM antibodies should be performed in future studies to observe the kinetics of the virus prevalence.

In conclusion, the prevalence of SARS-CoV-2 antibodies among blood donors in Al-Madinah was high. No significant differences were observed in the occurrence of anti–SARS-CoV-2 IgG antibody according to age. However, significant differences were identified according to the ABO blood type, with type A donors showing the highest frequency of anti–SARS-CoV-2 IgG antibodies.

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