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Original Article

Predictors of anti-SARS-CoV-2 seropositivity: An Egyptian population-based study

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ABSTRACT

Background: Population-based studies on the determinants of COVID-19 seroprevalence constitute a cornerstone in guiding appropriate preventive measures. Such studies are scarce in Egypt, thus we conducted this study to explore risk factors for SARS-CoV-2 seropositivity.

Methods: This survey included 2919 participants from 10 Egyptian governorates. Sera were tested for SARS-CoV-2 spike (S) and nucleocapsid (N) antibodies. Univariate and multivariate analyses were performed to identify associated factors and predictors of seropositivity regarding sociodemographic factors, clinical data, and personal practices of participants. A subgroup analysis was performed to investigate the occupational risks of seropositivity.

Results: Seropositivity was recorded in 1564 participants (53.6%). Independent predictors of seropositivity included non-smokers (aOR = 1.817; 95% CI: 1.407–2.346, $p = 0.000$), having blood group A (aOR = 1.231; 95% CI: 1.016–1.493, $p = 0.034$), a history of COVID-19 infection (aOR = 2.997; 95% CI: 2.176–4.127, $p = 0.000$), COVID-19 vaccination (aOR = 4.349; 95%CI: 2.798–6.759, $p = 0.000$), higher crowding index (aOR = 1.229; 95% CI: 1.041–1.451, $p = 0.015$), anosmia and/or ageusia (aOR = 3.453; 95% CI: 2.661–4.481, $p = 0.000$) and history of fever (aOR = 1.269; 95% CI: 1.033–1.560, $p = 0.023$). Healthcare worker and Obesity/overweight were additional significant predictors of seropositivity among the working participants (aOR = 1.760; 95% CI: 1.301–2.381, $p = 0.000$ and aOR = 1.384; 95% CI: 1.059–1.808, $p = 0.019$, respectively). Additional factors showing association with seropositivity in the univariate analysis were: female gender, age group (15–39 years), higher educational level (preparatory and above), lack of environmental disinfection and having roommates at the workplace. There was a positive correlation between the titers of both antibodies. Age was weakly correlated with anti-S titer, while anti-N was significantly correlated with the number of protective measures applied by the participants. Both antibodies were significantly correlated with adult BMI, while both were significantly negatively correlated with the smoking index.

Conclusions: SARS-CoV-2 seropositivity was associated with some personal and behavioral and occupation-related factors. Fever and anosmia and/or ageusia were the symptoms mostly associated with seropositivity.

1. Introduction

Evidence has suggested a link between disadvantaged socioeconomic factors and the increased risk of infectious disease in general, including Coronavirus disease-19 (COVID-19). Such factors might influence disease incidence, transmission, severity, and mortality. As with other infectious diseases, predictors of COVID-19 infection may include personal factors, medical history, educational level, nutritional status, besides working and housing conditions [1]. Thus, effective strategies for predicting risk factors for infection transmission should include all the mentioned factors. Sociodemographic and behavioral determinants of infection are not fully studied, especially in communities with lower socioeconomic status, due to the absence of these data from medical

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records, limiting the possibility of studying the evolution of diseases with regards to these determinants [2]. Risk-stratification would identify vulnerable groups in the community and address them with suitable preventive measures. This study aimed to identify sociodemographic, behavioral, medical, and work-related determinants of COVID-19 seropositivity among a large sector of the Egyptian population.

2. Materials and methods

This cross-sectional survey was a part of a project on the seroprevalence of SARS-CoV-2. It was conducted throughout the period between January and June 2021, which coincided with the second and third waves of the COVID-19 pandemic in Egypt. At the time of the study, COVID-19 vaccines were not available to the public, but were reserved primarily for healthcare workers.

2.1. Sample size

A minimum sample size of 1960 participants were required based on previously reported frequency of COVID-19 infection among SARS-CoV-2 IgG seropositive patients of 35.8% [3], with a margin of error 3% at 95% confidence level and a design effect of 2. The sample size was calculated using Epi-Info 7 software.

2.2. Sampling technique

A total of 2919 participants were allocated from ten randomly selected Egyptian governorates representing Lower and Upper Egypt. The study was conducted using a multistage stratified cluster sample technique. Stratification was done based on gender and age to include both genders and all age groups. According to the Ministry of Health and Population reports, the most affected districts within each governorate were included in the survey in the first stage. In the second stage, a random sample was included within each district based on the WHO method for surveying. Convenient sampling was adopted for participant allocation. The authors described more details on sampling elsewhere (unpublished data).

2.3. Data collection methods and tools

Extensive literature review of published studies at that time (through September 2020) was done, and the most relevant 90 articles on Google scholar and PubMed were selected and reviewed by our authors. Keywords for the search were “COVID-19–SARS-CoV-2 immune response–risk factors for COVID-19 infection". Risk factors for COVID-19 exposure were selected from the reviewed studies along with authors’ suggestions. Accordingly, a structured interview questionnaire sheet was designed. The questionnaire included 90 items categorized into 4 sections; sociodemographic, behavioral, medical, and workplace data. The data included: residence (urban/rural), age, gender, education, marital status, comorbidities, smoking history, history of COVID-19 diagnosis. The smoking index was calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. Height and weight were measured for all study participants. The World Health Organization (WHO) child growth standards were used to calculate BMI-for-age for children (≤18 years old) [4]. For adults, BMI was calculated as weight in kilograms divided by height in meters squared [4]. Obesity among 2- to 18-year-olds was defined as a BMI at or above the 95th percentile of children of the same age, while obesity among adults was defined as BMI 30 or above. Risk factors for exposure to SARS-CoV-2 were included, such as the use of public transportation, history of travel abroad within the last 6 months, the utilization/practice of preventive measures (wearing masks/ washing hands/using soap for hand washing/use of hand disinfectant and social distancing [each variable was recorded in a binary manner: yes/no]). The sum of preventive measures questions was calculated and categorized into not done (0), partially done (1-4), and completely done (5). Work-related risk factors included being a healthcare worker (HCW), practice of surface disinfection and the use of air conditioner at work as well as the number of days working online.

Data regarding the history of COVID-19 symptoms during the last six months were collected (eg, fever, dyspnea, diarrhea, anosmia, and/or ageusia). Positive history of COVID-19 diagnosis was recorded based on the participant’s reporting a COVID-19 diagnosis by his/her physician. The initial diagnostic method was also reported, as one of the following: clinical symptoms, chest computed tomography (CT), laboratory tests (including elevated D-dimer, ferritin, erythrocyte sedimentation rate, leukopenia, lymphopenia, or lymphocytosis), rapid antigen test and polymerase chain reaction (PCR) for SARS-CoV-2.

A pilot study was conducted before the implementation of the research, on a group of 50 randomly selected participants. This was done to test for the feasibility of recruitment and randomization of participants as well as for validation of the questionnaire.

After obtaining written informed consent, a 3 mL venous blood sample was collected from each participant for anti-S and anti-N testing. Serum samples were separated by centrifugation at 3000 rpm, and serum was stored at –20°C frozen until further processing. All 2919 samples were tested for anti-S, and only 1756 of them were additionally tested for anti-N (due to financial and logistic constraints). The anti-SARS-CoV-2 Quantivac enzyme-linked immunosorbent assay (ELISA; EuroImmun) was used to detect immunoglobulin class IgG against the S1 domain of the viral spike protein. In addition, antibodies

against viral nucleocapsid were detected by a commercially available electrochemiluminescence immunoassay kit "Elecsys" anti- SARS-COV-2 kit (Roche) run on the Cobas® e411 automated platform (Roche Diagnostics). A positive serological result was recorded if either-or-both antibodies (anti-S, anti-N) were positive, as both indicate a previous viral infection.

2.4. Data analysis

After data were extracted, it was revised, coded, and fed to statistical software IBM SPSS version 25 (SPSS, Inc). All statistical analysis was done using two-tailed tests. *p*-Values less than 0.05 were statistically significant. Continuous variables were presented as median, while categorical variables were presented as frequencies and percentages. Chi-squared test (χ^2) was used to test the association between categorical variables, while Spearman correlation coefficient (*r*) was used to test the association between SARS-Co-V-2 anti-S and anti-N and other continuous variables. Multiple logistic regression analysis was used to control for confounding factors and investigate significant seropositivity predictors; all variables with a *p*-value < 0.2 in univariate analysis were included in the regression model.

Correlation matrix was performed for all variables before regression analysis and a correlation coefficient of more than 0.5 was pre-specified to omit one of the correlated variables. For handling the missing data (where "not applicable" is the response), 2 models were performed. The first model (Model 1, n = 2919) included all variables with *p*-values < 0.2 in the univariate analysis, except for "occupation related variables". The second model (Model 2) was constructed as a sub-group analysis (n = 1647) and included adults who were currently working at the time of the study, to investigate occupation–related risks of seropositivity. Model 2 included all variables with *p*-value < 0.2 in the univariate analysis, including occupation related factors.

3. Results

A total of 2919 participants were included, with females constituting 57.4% of participants. The age of the participants ranged between 2 and 90 years old, with an overall median age of 38.0 years. The most prevalent age group (35.5%) was "40–59 years". Children below 18 years of age constituted 20.14% while the elderly (60+) were the least prevalent age group (10.8%). Detailed descriptive data on the characteristics of our study participants are available in another publication by the same authors (unpublished data). Seropositivity was recorded in 1564 participants (53.6%). The anti-S and anti-N titres had a median and interquartile range of 6.50, 34.20 RU/mL and 1.0, 30.71 COI, respectively.

Using univariate logistic analysis, females had a 24.9% increase in the odds of seropositivity compared to males; Odds ratio (OR) 95% CI = 1.249 (1.078–1.447), $p = 0.003$. Compared to children below 15 years of age (seropositivity = 49%), the odds of seropositivity were higher among 15–29 years (OR = 1.300; 95% CI =1.007–1.678, $p = 0.044$) and those 30–39 years of age (OR = 1.285; 95% CI = 1.008–1.638, $p = 0.043$). Participants with higher educational levels had significantly higher seropositivity rates than illiterate adults (Table 1). Interestingly, non-smokers were found to have an 86% increase in the odds of seropositivity compared to smokers ($p = 0.000$). A significant inverse relationship (OR = 1.937; 95% CI: 1.265–2.968, $p = 0.002$) was seen with seroprevalence among smokers. Participants with blood group A had the highest seropositivity rate while group O had the lowest (OR = 1.249, 95% CI: 1.042–1.496, $p = 0.016$). Overweight/obese participants (including adults and children) had significantly higher seroprevalence rates compared to those with normal weights (OR = 1.308; 95% CI: 1.107–1.545, $p = 0.002$. Comorbidities were collectively studied as a single category since their individual analysis revealed no significant increase in seropositivity (data not shown; Table 1).

Contact with a COVID-19 patient raised the odds of seropositivity by 38% (95% CI: 1.187–1.607, $p = 0.000$). The highest odds of seropositivity were observed with two factors: history of previous COVID-19 infection (OR = 4.497; 95% CI: 3.424–5.906, $p = 0.000$) and receiving COVID-19 vaccination (OR = 4.145; 95% CI: 2.753–6.242, $p = 0.000$). Healthcare workers had a 28% higher risk of seropositivity compared to non-healthcare workers (95% CI: 1.162–1.691, $p = 0.018$). Participants who reported having one or more roommates at work were more seropositive than those without (56.2% and 47.1%, respectively) with higher odds of seropositivity (OR = 1.441, 95% CI: 1.135–1.829, $p = 0.003$). Lack of environmental disinfection raised the odds of seropositivity (OR = 1.339; 95% CI: 1.098–1.634, $p = 0.004$) compared to participants reporting surface environmental disinfection at work (Table 2**)**. Concerning symptoms of COVID-19, on univariate analysis, several of them were significantly associated with seropositivity: fever, cough, dyspnea, fatigue, sleep problems and myalgia/arthralgia, anosmia, and/or ageusia. Compared to asymptomatic participants, those who had 5 or more symptoms had the highest seropositivity odds (OR = 2.172; 95% CI: 1.744–2.706, $p = 0.000$), followed by those with 3–4 symptoms (OR = 1.478; 95% CI: 1.200–1.820; Table 3**)**.

Two models were constructed to predict risk factors for seropositivity regarding sociodemographic factors, clinical data and personal practices of participants (Model 1), and a subgroup analysis for occupational risks of seropos-

Table 1
Distribution of 2919 Egyptian participants according to their sociodemographic, personal characteristics and SARS-CoV-2 antibody seropositivity.

	SARS-CoV-2 antibodies				Crude OR (95% CI; LL-UL)	*p*-value
	Seronegative (n = 1355)		Seropositive (n = 1564)			
	No.	%	No.	%		
Gender						
Male	617	49.6%	627	50.4%	Ref.	
Female	738	44.1%	937	55.9%	1.249 (1.078–1.447)[a]	0.003
Age (years)						
>15	233	51.0%	224	49.0%	Ref.	
15–29	220	44.4%	275	55.6%	1.300(1.007–1.678)[a]	0.044
30–39	276	44.7%	341	55.3%	1.285(1.008–1.638)[a]	0.043
40–59	472	45.6%	564	54.4%	1.243(0.997–1.549)	0.053
60+	154	49.0%	160	51.0%	1.081(0.811–1.441)	0.597
Residence						
Urban	919	45.3%	1110	54.7%	1.160 (0.991–1.358)	0.065
Rural	436	49.0%	454	51.0%	Ref.	
Educational level (n = 2201 adults older than 23)						
Illiterate/ Primary	236	51.4%	223	48.6%	Ref.	
Preparatory/ Secondary	336	44.0%	428	56.0%	1.348 (1.069–1.700)[a]	0.012
University and higher	438	44.8%	540	55.2%	1.305 (1.045–1.629)[a]	0.019
Marital status (n = 2331)						
Single	165	48.8%	173	51.2%	Ref.	
Married	817	45.8%	967	54.2%	1.129 (0.894–1.425)	0.307
Divorced/Widowed	89	42.6%	120	57.4%	1.286 (0.909–1.820)	0.156
Crowding Index						
< 1	639	48.0%	691	52.0%	Ref.	
1+	716	45.1%	873	54.9%	1.128 (0.974-1.305)	0.107
Comorbidities[b]						
No	978	46.7%	1118	53.3%	Ref.	
Yes	377	45.8%	446	54.2%	1.035 (0.880–1.217)	0.678
Smoking status						
No	1092	44.1%	1385	55.9%	1.864 (1.517–2.289)[a]	0.000
Yes	263	59.5%	179	40.5%	Ref.	
Exercise						
Never	213	44.7%	263	55.3%	1.076 (0.873–1.325)	0.491
Occasionally	478	47.0%	539	53.0%	0.983 (0.836–1.154)	0.831
Consistently	664	46.6%	762	53.4%	Ref.	
Dietary habits						
Poor	97	46.4%	112	53.6%	Ref.	
Fair	1087	46.6%	1245	53.4%	0.992(0.747–1.317)	0.956
Good	171	45.2%	207	54.8%	1.048(0.747–1.471)	0.785
Blood group						
A	438	44.2%	553	55.8%	1.249 (1.042–1.496)[a]	0.016
B	347	45.6%	414	54.4%	1.180 (0.972–1.432)	0.094
AB	122	45.9%	144	54.1%	1.167 (0.887–1.536)	0.269
O	448	49.7%	453	50.3%	Ref.	
RH						
Positive	1256	46.3%	1454	53.7%	1.042(0.786–1.381)	0.775
Negative	99	47.4%	110	52.6%	Ref.	
Pregnancy (n = 988)						
No	400	42.8%	534	57.2%	Ref.	
Yes	22	40.7%	32	59.3%	1.090 (0.624–1.904)	0.763
BMI						
Normal weight	386	51.2%	368	48.8%	Ref.	
Underweight	26	56.5%	20	43.5%	0.807(0.443–1.470)	0.483
Overweight/obese	943	44.5%	1176	55.5%	1.308(1.107–1.545)[a]	0.002

[a] Significant results $p < 0.05$.
[b] Comorbidities included Diabetes mellitus, hypertension, chronic liver, kidney, lung, and heart diseases.

itivity (Model 2). According to (Model 1), the following were independent predictors for seropositivity: Being a non-smoker (aOR= 1.817; 95% CI: 1.407–2.346, $p = 0.000$), having blood group A (aOR = 1.231; 95% CI: 1.016–1.493, $p = 0.034$), having a history of COVID-19 infection (aOR = 2.997; 95% CI: 2.176–4.127, $p = 0.000$), being vaccinated against COVID-19 (aOR = 4.349; 95% CI: 2.798–6.759, $p = 0.000$), higher crowding index (aOR = 1.229; 95% CI: 1.041–1.451, $p = 0.015$), anosmia and/or ageusia (aOR = 3.453; 95% CI: 2.661–4.481, $p = 0.000$) and fever (aOR = 1.269; 95% CI: 1.033–1.560, $p = 0.023$). Model 2 showed that, being a healthcare worker, was the only significant occupation-related predictor of seropositivity (aOR = 1.760; 95% CI: 1.301–2.381, $p = 0.000$; Table 4).

There was a positive correlation between the titres of both anti-N and anti-S ($r = 0.819$). Age was weakly correlated with anti-S titer ($r = 0.041$). Both anti-S and anti-N titres were significantly correlated with adult BMI ($r = 0.117$ and 0.100 respectively), while both antibodies were significantly negatively correlated with the smoking index. Both antibodies significantly correlated with

Table 2
Risk factors for SARS-CoV-2 exposure associated with antibody seropositivity among 2919 Egyptian participants.

Risk factors for SARS-CoV-2 exposure	SARS-CoV-2 antibodies				Crude OR (95% CI;LL-UL)	*p*-value
	Seronegative (n = 1355)		Seropositive (n = 1564)			
	No.	%	No.	%		
Practicing COVID-19 protective measures						
Not done	385	49.3%	396	50.7%	1.029 (0.656–1.613)	0.902
Partially done	928	45.2%	1126	54.8%	1.213 (0.784–1.877)	0.385
Completely done	42	50.0%	42	50.0%	Ref.	
Use of public transportation						
No	145	46.9%	164	53.1%	Ref.	
Yes	1210	46.4%	1400	53.6%	1.023 (0.808–1.296)	0.851
History of travel abroad within the last six months						
No	1343	46.4%	1553	53.6%	Ref.	
Yes	12	52.2%	11	47.8%	0.793(0.349–1.802)	0.579
History of COVID-19 infection						
Never	1286	50.5%	1260	49.5%	Ref.	
Yes	69	18.5%	304	81.5%	4.497 (3.424–5.906)[a]	0.000
Contact with COVID-19 patient						
No	904	49.4%	926	50.6%	Ref.	
Yes	451	41.4%	638	58.6%	1.381 (1.187–1.607)[a]	0.000
Vaccination status against COVID-19						
Not vaccinated	1326	48.0%	1434	52.0%	Ref.	
Vaccinated	29	18.2%	130	81.8%	4.145(2.753–6.242)[a]	0.000
Occupational risks (n = 1647)	Seronegative (n = 753)		Seropositive (n = 894)			
Occupation						
Non-HCWs	483	48.1%	521	51.9%	Ref.	
HCWs	270	42.0%	373	58.0%	1.281 (1.049–1.564)[a]	0.015
Having roommates at work						
No	181	52.9%	161	47.1%	Ref.	
Yes	572	43.8%	733	56.2%	1.441 (1.135–1.829)[a]	0.003
Environmental disinfection						
No	432	42.9%	575	57.1%	1.339 (1.098–1.634)[a]	0.004
Yes	321	50.2%	319	49.8%	Ref.	
Rooms are well-ventilated						
Yes	620	44.0%	790	56.0%	1.629 (1.235–2.150)[a]	0.001
No	133	56.1%	104	43.9%	Ref.	
Use of air conditioner at work						
No	617	44.9%	757	55.1%	1.218 (0.939–1.580)	0.137
Yes	136	49.8%	137	50.2%	Ref.	
Number of days working online/week						
1–3	157	50.5%	154	49.5%	Ref.	
4–5	145	44.6%	180	55.4%	1.266 (0.927–1.729)	0.139
6–7	451	44.6%	560	55.4%	1.266 (0.981–1.633)	0.069

[a] Significant results $p < 0.05$.
HCWs :Health care workers.

the number of COVID-19 symptoms ($r = 0.152$ for each antibody; Fig. 1).

4. Discussion

This population-based cross-sectional showed a high seroprevalence (53.6%) among the study participants, reflecting high COVID-19 infection rates in the community (since vaccines were available only to HCWs during the study period). Seropositivity for SARS-CoV-2 was studied in relation to several possible risk factors.

Females had a 24.9% increase in the odds of seropositivity compared to males; (55.9% vs 50.4%, respectively), (OR; 95% CI: 1.249 (1.078–1.447), $p = 0.003$. However, "being female" was not a significant predictor of seropositivity after adjusting for co-variables, which was in line with a study in United Arab Emirates [5]. Similar to our study, a multicenter European study reported a higher proportion of female COVID-19 patients (63%) than males (37%), with higher rates of olfactory and gustatory complications [6]. In a study on the psychological effect of the pandemic on both genders, females had higher levels of stress, anxiety, and depression [7]. The psychological stress and its detrimental effect on the immune system might be a reason for female infection and seropositivity.

In contrast, several other studies report mechanisms of female protection against COVID-19 infection. These included the protective effect of estradiol which enhances the adaptive and innate immune systems, in addition to the protective effect of the X chromosome against susceptibility to viral infections among females [8,9]. Moreover, Ma et al. reported that estrogen can directly inhibit SARS-CoV-2 replication by regulating cell metabolism, reducing the incidence of SARS-CoV-2 infection [10].

Table 3
Association of history of COVID-19 symptoms and seropositivity of anti-SARS-CoV-2 antibodies.

COVID-19 symptoms in the past 6 months	SARS-CoV-2 antibodies				Crude OR (95% CI;LL-UL)	*p*-value
	Seronegative (n = 1355)		Seropositive (n = 1564)			
	No.	%	No.	%		
Fever						
Yes	284	36.7%	489	63.3%	1.715 (1.44–2.031)[a]	0.000
No	1071	49.9%	1075	50.1%	Ref.	
Cough						
Yes	444	42.8%	594	57.2%	1.256 (1.079–1.464)[a]	0.003
No	911	48.4%	970	51.6%	Ref.	
Diarrhea						
Yes	279	44.2%	352	55.8%	1.120 (0.938–1.337)	0.210
No	1076	47.0%	1212	53.0%	Ref.	
Dyspnea						
Yes	171	38.9%	269	61.1%	1.438 (1.169–1.769)[a]	0.001
No	1184	47.8%	1295	52.2%	Ref.	
Anosmia and/or Ageusia						
Yes	97	19.7%	395	80.3%	4.382 (3.4610–5.548)[a]	0.000
No	1258	51.8%	1169	48.2%	Ref.	
Rhinorrhea						
Yes	434	44.2%	549	55.8%	1.148 (0.984–1.339)	0.080
No	921	47.6%	1015	52.4%	Ref.	
Fatigue						
Yes	270	36.8%	464	63.2%	1.695 (1.427–2.013)[a]	0.000
No	1085	49.7%	1100	50.3%	Ref.	
Myalgia/arthralgia						
Yes	258	37.4%	432	62.6%	1.623(1.362–1.933)[a]	0.000
No	1097	49.2%	1132	50.8%	Ref.	
Eye redness						
Yes	90	41.3%	128	58.7%	1.253 (0.947–1.658)	0.114
No	1265	46.8%	1436	53.2%	Ref.	
Sleep problems						
Yes	123	34.9%	229	65.1%	1.718 (1.362–2.168)[a]	0.000
No	1232	48.0%	1335	52.0%	Ref.	
Number of reported COVID-19 symptoms						
0	527	52.5%	477	47.5%	Ref.	
1–2	412	49.5%	420	50.5%	1.126 (0.937–1.354)	0.205
3–4	240	42.8%	321	57.2%	1.478 (1.200–1.820)[a]	0.000
5+	176	33.7%	346	66.3%	2.172 (1.744–2.706)[a]	0.000

[a] Significant results $p<0.05$.

Table 4
Models of logistic regression for predictors of SARS-CoV-2 seropositivity.

	Model 1 (n = 2919)		Model 2 (n = 1647)	
	Adjusted odds ratio (aOR) (95% CI;LL-UL)	*p*-value	Adjusted odds ratio (aOR) (95% CI;LL-UL)	*p*-value
Gender				
Male	Ref.		Ref.	
Female	0.995(0.830–1.194)	0.960	1.073(0.815–1.413)	0.615
Age (years)				
>15	Ref.		Ref.	
15–29	1.211(0.918–1.597)	0.175	2.947(0.547–15.890)	0.209
30–39	0.985(0.741–1.310)	0.918	2.211(0.411–11.882)	0.355
40–59	1.041(0.802–1.351)	0.764	2.524(0.473–13.463)	0.278
60+	1.099(0.788–1.533)	0.577	3.194(0.572–17.831)	0.186
Residence				
Urban	0.946(0.796–1.124)	0.524	0.799(0.603–1.060)	0.120
Rural	Ref.		Ref.	
Crowding Index				
< 1	Ref.		Ref.	
1+	1.229 (1.041–1.451)[a]	0.015	1.355(1.086–1.690)[a]	0.007
Smoking status				
No	1.817(1.407–2.346)[a]	0.000	2.052 (1.525–2.763)[a]	0.000
Yes	Ref.		Ref.	
Blood group				
A	1.231(1.016–1.493)[a]	0.034	1.065(0.813–1.394)	0.648
B	1.167(0.950–1.433)	0.142	1.153(0.869–1.529)	0.324

(*continued on next page*)

Table 4 (*continued*)

	Model 1 (n = 2919)		Model 2 (n = 1647)	
	Adjusted odds ratio (aOR) (95% CI;LL-UL)	*p*-value	Adjusted odds ratio (aOR) (95% CI;LL-UL)	*p*-value
AB	1.058(0.787–1.423)	0.707	0.933(0.622–1.399)	0.737
O	Ref.		Ref.	
BMI				
Normal weight	Ref.		Ref.	
Underweight	0.710(0.376–1.341)	0.291	0.783(0.120–5.083)	0.848
Overweight/obese	1.193(0.987–1.441)	0.068	1.384(1.059–1.808)[a]	0.019
History of COVID-19 infection				
Never	Ref.		Ref.	
Yes	2.997(2.176–4.127)[a]	0.000	3.350(2.307–4.863)[a]	0.000
Contact with COVID-19 patient[b]				
No	Ref.			
Yes	0.876(0.728–1.053)	0.160	—	
Vaccination status against COVID-19				
Not vaccinated	Ref.		Ref.	
Vaccinated	4.349(2.798–6.759)[a]	0.000	5.979(3.655–9.779)[a]	0.000
Reported COVID-19 symptoms in past 6 months				
Fever				
No	Ref.		Ref.	
Yes	1.269(1.033–1.560)[a]	0.023	1.544(1.154–2.065)[a]	0.003
Cough				
No	Ref.		Ref.	
Yes	0.947(0.782–1.146)	0.573	0.824(0.635–1.070)	0.147
Dyspnea				
No	Ref.		Ref.	
Yes	0.916(0.713–1.178)	0.494	0.915(0.654–1.281)	0.605
Anosmia and/or Ageusia				
No	Ref.		Ref.	
Yes	3.453(2.661–4.481)[a]	0.000	3.306(2.355–4.640)[a]	0.000
Rhinorrhea				
No	Ref.		Ref.	
Yes	0.998(0.832–1.196)	0.982	1.126(0.882–1.437)	0.342
Fatigue				
No	Ref.		Ref.	
Yes	1.089(0.783–1.515)	0.612	0.853(0.556–1.309)	0.466
Myalgia/arthralgia				
No	Ref.		Ref.	
Yes	0.886(0.631–1.242)	0.482	0.961(0.628–1.469)	0.854
Eye redness				
No	Ref.		Ref.	
Yes	0.812(0.586–1.125)	0.210	0.704(0.460–1.077)	0.105
Sleep problems				
No	Ref.		Ref.	
Yes	1.010(0.758–1.347)	0.945	1.174(0.819–1.685)	0.382
Occupational risks (n = 1647)				
Occupation				
Non- HCWs			Ref.	
HCWs			1.760(1.301–2.381)[a]	0.000
Having roommates at work				
No			Ref.	
Yes			1.047(0.772–1.420)	0.767
Environmental disinfection				
No			1.058(0.828–1.353)	0.652
Yes			Ref.	
Rooms are well-ventilated				
No			Ref.	
Yes			1.308(0.921–1.858)	0.134
Use of air conditioner at work				
No			1.235(0.912–1.672)	0.172
Yes			Ref.	
Number of days working online/week				
1–3			Ref.	
4–5			1.398(0.988–1.978)	0.058
6–7			1.301(0.957–1.769)	0.094

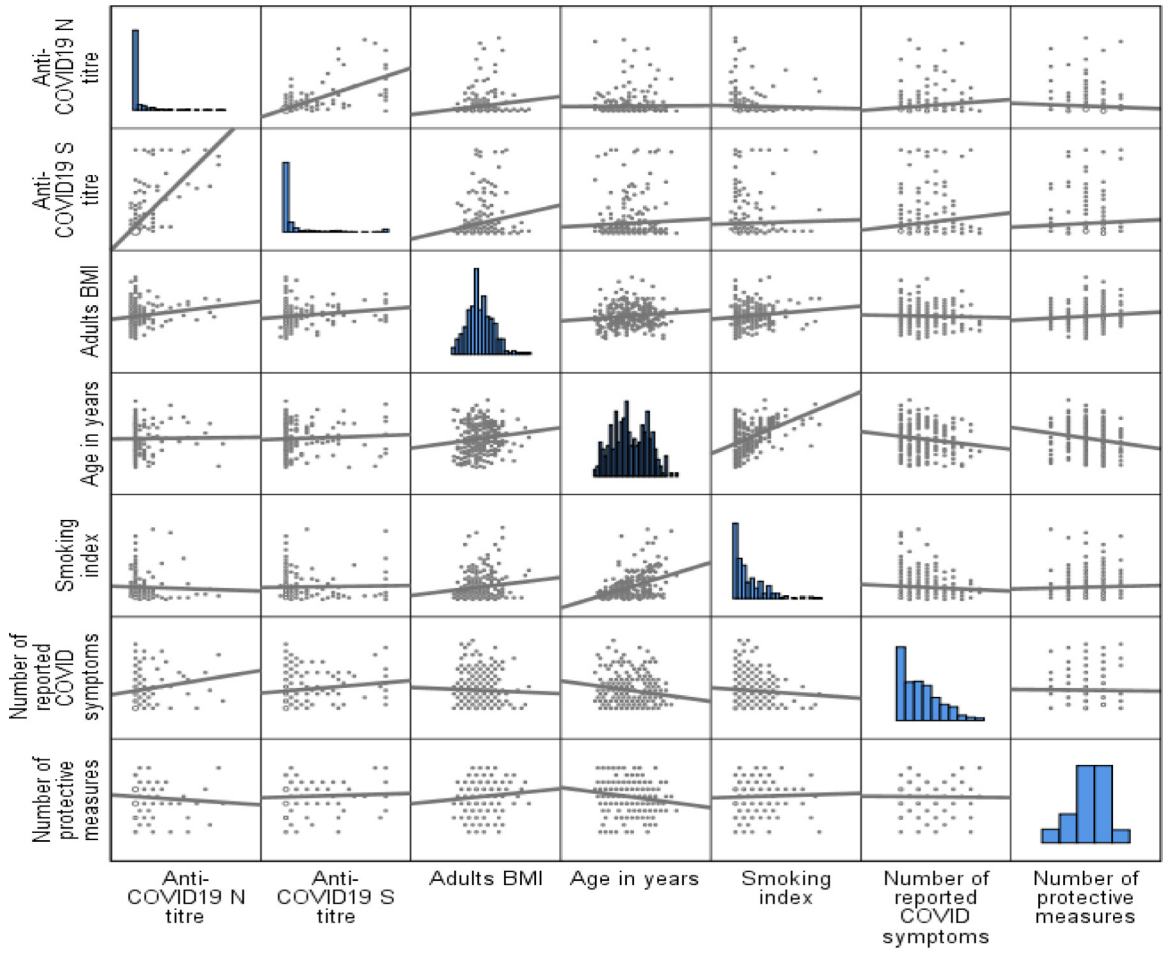
HCWs, healthcare workers.

Model 1; The overall model is statistically significant, $\chi 2 = 351.066$, $p = 0.00$, Nagelkerke R2 = 0.153, Percentage accuracy = 62.5%.

Model 2; The overall model is statistically significant, $\chi 2 = 309.163$, $p = 0.00$, Nagelkerke R2 = 0.229, Percentage accuracy = 67.6%.

[a] Significant results $p < 0.05$.

[b] Contact with COVID patient was omitted from model 2 as it was highly correlated with the occupation.



Spearman correlation		Anti-COVID19 S titre	Anti-COVID19 N titre	Age in years	Smoking index	Number of reported COVID-19 symptoms	Adults BMI
Anti-COVID19 S titre	r	1.000	0.819**	0.041*	-0.195**	0.152**	0.117**
Anti-COVID19 N titre	r	0.819**	1.000	0.021	-0.116*	0.152**	0.100**

**Correlation is significant at the 0.01 level (2-tailed)
*Correlation is significant at the 0.05 level (2-tailed)

Fig. 1. Factors with significant correlation with COVID–19 anti-S and anti-N titers.

In univariate analysis, the age group "15–29 years" was a predictor for seropositivity. Age was also significantly correlated with anti-S titer (r = 0.041), denoting a more mature immune response among adults compared to children. Elderly participants, however, had lower (yet insignificant) seropositivity compared to younger adults. This might be explained by the fact that aging accelerates the rapid decline in humoral immunity owing to qualitative decline in memory B cells and plasma cells, and expansion of the proinflammatory subset of B cells [11].

Interestingly, the significance of age and gender that was present on univariate analysis was lost in both models of multivariate regression, indicating the relatively limited role of age and gender compared to other risk factors of seropositivity.

In our study, there was a significant correlation between BMI among adults and the titres for both anti-S and anti-N antibodies (r = 0.117 and 0.100, respectively). Moreover, in Model 2 of regression analysis, “being obese/overweight” was a significant predictor of seropositivity among working participants (aOR = 1.384; 95%CI: 1.059–1.808, p = 0.019). A study in the United Arab Emirates reported similar results [5]. Sheridan et al. reported that BMI values correlated positively with a higher initial increase in IgG antibodies detected after trivalent influenza vaccine, but, 12 months after vaccination, subjects with higher BMI noted a greater decline in antibody titres as well as a defective $CD8^+$ T-cell response in obese compared with healthy weight individuals, resulting in impaired protection against infection [12]. However, our study could not conclude such observation, owing to its cross-sectional nature.

In contrast to our findings, Pellini et al. reported higher anti-S among individuals with lower BMI as compared to obese participants receiving the Pfizer anti-COVID-19 mRNA vaccine [13], and Watanabe et al. reported

lower COVID-19 mRNA vaccine-induced antibody titers among participants with central obesity, independent of BMI [14]. Adipose tissue stores adipokines and cytokine-like substances, which act as a bridge between cellular metabolism and immune responses and result in immune dysregulation in obese patients [12–14].

In our study, a considerably large number of children (≤18 years) were included (n = 588, 20.14%), which allowed analysis of their BMI in relation to seropositivity. Unlike BMI among adults, the association between BMI and seropositivity was not significant among children, denoting a possible variable inter-relationship between humoral immune response and adipose tissues among children and adults. This observation requires investigation in future studies.

The impaired immune response among patients with comorbidities might be attributed to the disease mechanisms resulting in metabolic disorders that impair lymphocyte and macrophage functions [13,15]. In our study, surprisingly, the presence of comorbidities was not found to be associated with a significant increase in seropositivity. A large American population-based study identified obesity as the most common established risk factor for seropositivity (41.0%), followed by diabetes mellitus (24.0%) and chronic kidney disease (18.4%) [15]. However, their study included analysis of obesity and chronic diseases only, without analyzing personal and behavioral characteristics, as our study did. Our results suggest that, other risk factors (personal/behavioral) might be stronger determinants for acquiring COVID-19 rather than the presence of comorbidities. Several studies document the aggravating role of comorbidities on the severity of COVID-19 and poor prognosis among patients [15–17]; however this was beyond the scope of our study.

Participants with higher educational levels were more seropositive than illiterate adults (OR = 1.305; 95% CI: 1.045–1.629). This might be explained by the excepted longer working hours by educated people compared to illiterates or those with less education, which might expose them more to infection. However, this significance was lost after adjusting for co-variables, suggesting that more factors might be stronger determinants for seropositivity.

Occupation is likely to be a determinant of COVID-19 infection and disease severity and mortality. This was notably reported in studies on COVID-19 among teachers, healthcare workers and crew on-board cruise ships [2,18]. In our study, Model 2 identified “being a healthcare worker” as a significant predictor of seropositivity among adults who had an occupation (aOR = 1.760; 95% CI: 1.301–2.381, $p = 0.000$). Prevalence of COVID-19 infection and risk factors among this group of HCWs were discussed by the same authors elsewhere [19].

According to the WHO, smoking may increase the risk and severity of COVID-19 and death in hospitalized patients. However, the WHO declared that there are currently no peer-reviewed studies that have evaluated the risk of SARS-CoV-2 infection among smokers, which necessitates population-based studies to address this observation [20]. The WHO suggests that smokers may be more vulnerable to contracting COVID-19, as the act of smoking involves contact of fingers (and possibly contaminated cigarettes) with the lips, which increases the possibility of transmission of viruses from hands to the mouth [20].

Surprisingly, in our study, non-smokers were found to have an increased odds of seropositivity compared to smokers (aOR = 1.817; 95% CI: 1.407–2.346, $p = 0.000$). Among smokers, titres of both antibodies were significantly negatively correlated with the smoking index. Watanabe et al. also reported lower antibodies following COVID-19 mRNA vaccine among smokers [14]. An explanation for this reduced antibody prevalence and titer among smokers might be due to a direct inhibitory effect of nicotine on antibody formation. A second explanation for this reduced seropositivity among smokers is the so-called, "smoker’s paradox," wherein smokers might be protected from infection and severe complications of COVID-19 [21,22]. Less frequent complications were observed among smokers with COVID-19 in some studies, which was attributed to the anti-inflammatory effect of nicotine, a blunted immune response in smokers (reducing the risk of a cytokine storm), increased nitric oxide in the respiratory tract (which may inhibit replication of SARS-CoV-2 and its entry into cells) and the observed up-regulation of ACE2, an anti-inflammatory protein, in the lower respiratory tract, compared to non-smokers [23]. The contradictory hypotheses about the role of smoking in the context of COVID-19 should always be interpreted with caution by physicians due to the well-established hazards of smoking, including lung cancer and chronic lung diseases [22]. This observation of reduced antibodies among smokers and its implications deserves further analysis and more insight.

Having blood group A was an independent predictor of seropositivity (aOR = 1.231; 95% CI: 1.016–1.493, $p = 0.034$). Similarly, Zhao et al. [24] (Wuhan, China) reported that blood group A was associated with an increased risk of infection with SARS-CoV-2, whereas blood group O was associated with the lowest risk. In contrast, Guillon et al. [25] reported that anti-A antibodies inhibited the adhesion of SARS-CoV S protein-expressing cells to ACE2-expressing cell lines in a study on SARS-CoV which would be similar to the case of SARS-CoV-2 [24]. Zietz et al. [26] also reported that the risk of intubation was less among blood group A and increased among AB and B types, compared with type O, while the risk of death was increased for type AB and decreased for types A and B, with an overall protective effect of Rh-negative blood type for all 3 outcomes. In our study, there was no association between the Rh group and seropositivity for SARS-CoV-2. The clinical implications of the ABO group

as predictors of infection might be in the form of increased personal precautionary measures among high-risk blood groups as well as closer medical observation in case of actual infection (24).

In our study, contact with a COVID-19 patient raised the odds of seropositivity by 42% (95% CI: 1.159–1.763). Moreover, higher crowding index was an independent predictor of seropositivity (aOR = 1.229; 95%CI: 1.041–1.451, $p = 0.015$). A study reported a higher risk of seropositivity among those having contact with COVID-19 infections (OR = 4.26; 95% CI: 2.05–8.88) [5]. Such findings justify the importance of social distancing in combatting the pandemic.

Being vaccinated against COVID-19 raised the odds of seropositivity (aOR = 4.349; 95% CI: 2.798–6.759, $p = 0.000$), and exceeded that for having a history of COVID-19 infection (aOR = 2.997; 95% CI: 2.176–4.127, $p = 0.000$). In another published work by the authors of this manuscript, anti-S positivity was significantly higher in those who had COVID-19 infection prior to vaccination (97.8%) than those who had not (77.3%; $p < 0.002$), emphasizing the aggravating role of previous infections in seropositivity among vaccinated individuals [19]. Two studies reported that antibody responses induced by vaccination were significantly higher than those induced by natural infection, and suggested that vaccination is still critical even for those naturally infected or diagnosed with COVID-19 [27,28].

Several factors were analyzed in our study concerning the work environment and its role in exposure to SARS-Co-V-2. In line with our result about crowding index as predictor of seropositivity, having roommates at work was significantly associated with seropositivity (OR = 1.441, 95% CI: 1.135–1.829, $p = 0.003$). According to McQuade et al. [29], living in a multifamily residence or apartment was a predictor of seropositivity. Overcrowded housing has been associated with an increased risk of other infections such as tuberculosis [30] and infections by Epstein–Barr virus [31]. Local authorities should thus avoid overcrowded rooms at different work locations, especially during pandemics.

Seropositivity was also associated with lack of surface environmental disinfection at work (OR = 1.339; 95% CI: 1.098–1.634, $p = 0.004$) compared to participants reporting surface environmental disinfection at work. This is expected, owing to the reported viral infectivity, which is reported to last on various environmental surfaces for different durations of time. Surprisingly, participants reporting having well-ventilated rooms at the workplace had significantly higher seropositivity rates than those without (OR = 1.629; 95%CI: 1.235–2.150, $p = 0.001$). This might be explained by the subjective nature of our question, which was not accompanied by actual calculation of the room volume and the number of persons occupying it. According to the WHO guidelines on good indoor ventilation in the context of COVID-19, the minimum recommended ventilation rate in non-residential settings is 10 Liters/seconds/person, and cross ventilation should be enabled, either through doors or the use of pedestal fans [32].

The number of reported symptoms also correlated with anti-S and anti-N titres. On univariate analyses, the following symptoms were significantly associated with seropositivity: cough, dyspnea, fatigue, sleep problems, and myalgia/arthralgia, with “fever” and “anosmia and/or ageusia” being also predictors in multivariate regression (aOR = 3.453; 95% CI: 2.661–4.481, $p = 0.000$) and aOR = 1.269; 95% CI: 1.033–1.560, $p = 0.023$, respectively). This high prevalence of loss of taste and smell was reported in other studies, with a pooled prevalence of 48.47% among 19,424 COVID-19 patients from 27 studies [33]. An Emirati study reported that loss of taste and/or smell was strongly associated with seropositivity [5]. The underlying pathological mechanism might again be explained by the high concentration of ACE2 in olfactory cells [33].

A limitation of this study was the reliance on self-reported medical history as well as behavioral factors, which might have been subject to imprecision due to recall bias or other forms of bias, and thus might have underestimated the investigated risk factors.

In conclusion, we identified other personal factors, such as smoking, age, education, among others, to be more important predictors of seropositivity than gender, comorbidities, and the use of personal protective measures. Based on the results of our study, participants at risk should seriously consider lifestyle modifications for their modifiable-risk factors, including weight control, social distancing, and more precautionary measures at work, such as surfaces disinfection and reducing the numbers of work-mates per room. Individuals with identified risk factors should also be more cautious and consistent in applying anti-COVID-19 preventive measures.

Availability of data and materials

Available and kept confidential.

Authors’ contributions

E.M. El-Ghitany, (1) conception and design of the work, analysis and interpretation of data and (2) revising the work critically for important intellectual content; and (3) revision and final approval of the version to be published; and (4) obtained funding; administrative, technical, material support and study supervision. A. Ashour, (1) Substantial contributions to analysis and interpretation of data for the work; and (2) drafting of the work; and (3) final approval of the version to be published. A. G. Farghaly; (1) contributions to design of the work; and

(2) final approval of the version to be published; and (3) study supervision. M.H.Hashish; (1) substantial contributions to the ELISA testing, and (2) final approval of the version to be published. F. E.A.Omran; (1) ELISA testing, (2) results interpretation, (3) drafting the abstract, (4) final approval of the version to be published

Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics statement

The study was conducted in compliance with the Helsinki Declaration and was approved by the Institutional Review Board (IRB) Committee, Faculty of Medicine, Alexandria University; IRB number: 00012098–FWA number: 00018699, serial number: 0305136. Administrative approval was taken from each healthcare setting before study onset.

Informed consent

Anonymity and confidentiality of participants were ensured and written informed consent was obtained from each patient.

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