

## Estimation of immune response (IgG) to SARS-COV2 (COVID-19) after the third COVID-19 wave in Egypt, A cross-sectional Study

Mona M. Abdelrahman<sup>1</sup>, Shimaa B. Hemdan<sup>2</sup>,  
Radwa M. Farag<sup>3</sup>, Ahmed N. Nour Eldin<sup>4</sup>, Asmaa R.  
Khalaf<sup>5</sup>, Tasneem M. Bakheet<sup>6</sup> and Noha S. Shafik<sup>7</sup>

<sup>1</sup>Department of Tropical Medicine & Gastroenterology, Faculty of Medicine, Sohag University, Sohag, Egypt.

<sup>2</sup>Department of Medical Biochemistry, Faculty of Medicine, Sohag University, Egypt.

<sup>3</sup>Department of Clinical and Chemical Pathology Department, Faculty of Medicine, Sohag University, Sohag, Egypt.

<sup>4</sup>Department of Internal Medicine, Faculty of Medicine, Sohag University, Sohag, Egypt.

<sup>5</sup>Department of Chest Diseases & Tuberculosis, Faculty of Medicine, Sohag University, Sohag, Egypt.

<sup>6</sup>Department of Public Health & Community Medicine, Faculty of Medicine, Sohag University, Sohag, Egypt.

<sup>7</sup>Department of Medical Microbiology & Immunology, Faculty of Medicine, Sohag University, Sohag, Egypt.

**Corresponding author:** Noha S. Shafik, Medical Microbiology & Immunology Department, Faculty of Medicine, Sohag University, Sohag, Egypt.

Email: [Nohasaber@med.sohag.edu.eg](mailto:Nohasaber@med.sohag.edu.eg)

### Abstract

Since the start of the pandemic, the number of cases has been increased rapidly. Due to asymptomatic and mild cases and restricted testing in many geographic locations, the overall number of actual COVID-19 cases is likely significantly higher than the number of verified cases. Several COVID-19-related comorbid diseases impair immune system function, which has an impact on COVID-19 responsiveness. So, we evaluated the immune response to SARS-CoV-2 after the third wave of COVID-19 and assessed the effect of comorbid diseases on this immune response. The current cross-sectional study was conducted in August 2021 after the third wave of COVID-19. The study included 287 participants. All participants were asked about their epidemiological data, comorbid diseases, data suggesting COVID-19 infection, and precautions measures to minimize the exposure to the disease. Of the 278 participants, 50% had a positive IgG response to COVID-19. Regarding comorbid diseases, the IgG antibody titer was significantly lower in patients with chronic kidney diseases (CKD) on dialysis, ischemic heart disease, and chronic obstructive lung diseases than other participants ( $p= 0.01$ ,  $p= 0.02$ ,  $p= 0.005$ , respectively). Neither precaution measures nor comorbid diseases had a role in risk factors of COVID-19 infections in our participants. In conclusion, high seroprevalence (50%) of SARS-CoV-2 IgG antibody after the third wave of COVID-19 was observed in the current study. Comorbid conditions as hypertension, chronic cardiac diseases, chronic chest problems, and CKD on dialysis could decrease the immune response against COVID-19 infection.

**Keywords:** Immune response, seroprevalence, comorbid diseases, COVID-19, SARS-CoV-2.

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## Introduction

The coronavirus 19 (COVID-19) pandemic was started in late 2019.<sup>1</sup> COVID-19 patients have a wide range of symptoms, ranging from asymptomatic or moderate illness in the majority of cases to severe acute respiratory syndrome (SARS) in others.<sup>2</sup> The main clinical presentations of COVID-19 are similar to those of other respiratory viruses, such as fever and dry cough.<sup>3</sup>

Since the start of the pandemic, the number of cases has increased reaching 281,808,270 confirmed cases of COVID-19 on 27 December 2021.<sup>1</sup> Since the first COVID-19 case was reported on February 14, 2020, Egypt's total number of infected cases by the end of 2021 has surpassed 380,000, with over 21,000 deaths. Up till now, 3 waves of COVID-19 infection were reported. The first wave occurred between March and July 2020, the second wave between November 2020 and February 2021, and the third wave between March 2021 and July 2021.<sup>4</sup>

SARS-CoV-2 remained hard to handle, because of its high infectiousness and spreading mostly through infected patients' respiratory droplets.<sup>5</sup> Due to restricted testing in many geographic locations, the overall number of actual COVID-19 cases is likely significantly higher than the number of verified cases.<sup>3</sup> The continuing increase in the number of COVID-19 is putting a strain on healthcare systems.<sup>6</sup> So, it is essential to evaluate the extent of the exposure to the SARS-CoV-2 virus especially with the occurrence of a large number of asymptomatic infections.<sup>7</sup> Assessing the disease prevalence is critical in both screening and monitoring disease status.<sup>8</sup>

There is an under-estimate in the diagnosis of COVID-19 cases using the polymerase chain reaction (PCR) worldwide because the mild and asymptomatic infections often go undetected.<sup>9</sup>

<sup>10</sup> According to some estimations, the actual asymptomatic share could be as high as 80%.<sup>11</sup> So, some countries adopted mass screening programs using either PCR or anti-SARS-CoV-2 antibody testing<sup>12, 13</sup>

Most COVID-19 infected patients have an IgG antibody response 2 to 3 weeks after disease

onset, though levels may begin to diminish after 3 months.<sup>14</sup> When Smith et al., 2020, evaluated IgG towards SARS-COV2 during April and May 2020, they found that the illness was 10 times more widespread than the number of COVID-19 patients diagnosed by direct detection of the virus by PCR. So, serological testing of IgG against SARS-COV-2 not only evaluated symptomatic patients but also detected asymptomatic and mild cases.<sup>9</sup>

In a symptom-free approach, estimation of seroprevalence can assess the cumulative incidence of COVID-19 infection<sup>15</sup> and evaluate the public health measure.<sup>16</sup> The infection rate and seroprevalence differ from one area to another even in the same country.<sup>9, 16</sup> However, more seroprevalence studies are needed to offer information that takes into account the diversity of specific populations, time of the sample, location, and kind of detected immune responses.<sup>7</sup>

Several COVID-19-related comorbid diseases impair immune system function, which has an impact on COVID-19 responsiveness.<sup>17</sup> So, we evaluated the immune response to SARS-CoV-2 after the third wave of COVID-19 and assessed the effect of comorbid diseases on this immune response.

## Subjects and Methods

The current cross-sectional study was conducted in August 2021 after the third wave of COVID-19. The current study included 287 participants. The first group included 89 chronic kidney disease (CKD) patients on dialysis. Their mean age was 52±16 years, and 52 (58%) of them were males. They were selected as a systematic random sample from the major renal dialysis unit in Sohag governorate (Sohag university renal dialysis unit). The second group included 189 participants, was collected by a simple random sample from health care workers, blood donors, relatives of patients working at or visiting different departments in Sohag university hospitals. Their mean age was 41±17 years, and 107 (56.6%) of them were females. Participants who received any type of COVID-19 vaccine were excluded from the study.

### *Ethical consideration*

The study protocol was reviewed and approved by the Medical Research Ethics Committee of the Faculty of Medicine, Sohag University (No. Soh-Med-21-04-33, dated April 2021). An informed consent was taken from each participant before enrolled in the study.

### *Data collection*

- a. Demographic data including name, occupation, educational level, and residence were collected.
- b. Clinical data were collected, including comorbid diseases (e.g., CKD on dialysis, ischemic heart disease, chronic obstructive lung diseases, and diabetes mellitus), history contact to COVID-19 cases, history or previous or recurrent COVID-19, symptoms suggestive of COVID-19 infection as (Fever, dry or productive cough, sore throat, fatigue, general malaise, headache, dyspnea, diarrhea, loss of taste, anorexia, and rhinorrhea).
- c. Participants were asked about precautions measures to minimize the exposure to COVID-19 as wearing the mask, hand hygiene, social distancing, hand contact, and visiting crowded places.

### *Measuring SARS-CoV-2 IgG*

- a. From each participant a blood sample (5 ml) was collected in a serum collection tube (BD Vacutainer CAT (clot activator tube), BD, Plymouth, UK), under complete aseptic conditions. The blood sample in the tube was centrifuged at a speed of 500 Xg for 3 minutes, then the serum sample isolated.
- b. The enzyme linked immunoassay assay (ELISA) assay: The quantitative assay of IgG anti-SARS-

CoV-2 whole spike protein antibody was carried out by the SERION ELISA agile SARS-CoV-2 IgG test kit (CE marked, Institute Virion/Serion, Diagnostics, Würzburg, Germany), according to the manufacturer's instructions. The signal intensity of the reaction product was proportional to the antibody concentration in the sample and was measured photometrically after specific programming of an Original Multiskan EX ELISA reader (Thermo Electron Corporation, Waltham, US). Samples with a concentration of < 10 U/ml were considered negative, samples with a concentration of 10 – 15 U/ml considered borderline, samples with a concentration of > 15 U/ml considered as positive.

### *Statistical analysis*

The SPSS computer program version 25.0 was used to analyse the data. Quantitative data were expressed as means  $\pm$  standard deviation (SD), median and 25th percentile, and 75th percentile (interquartile range). Qualitative data were expressed as numbers and percentages. The Chi-square test was used for comparing the results of the different groups (negative, positive, and borderline groups). Also, risk estimation and odds ratio were calculated for the predictors of positive COVID-19. A *p* value of <0.05 was considered significant.

## **Results**

The studied groups were divided into three categories according to antibody titer, positive, borderline, and negative group. There was no difference between the three categories regarding socio-demographic data (Table 1).

**Table 1.** Socio-demographic and clinical criteria among the studied groups' population.

		Study categories								p value
		Positive		Borderline		Negative		Total		
		N=140		N=39		N=99		N=278		
		No.	%	No.	%	No.	%	No.	%	
Gender	Male	59	42.1	19	48.7	56	56.6	134	48.2	NS
	Female	81	57.9	20	51.3	43	43.4	144	51.8	
Age	≤20	12	8.6	1	2.6	11	11.1	24	8.6	NS
	21-40	53	37.9	13	33.3	24	24.2	90	32.4	
	41-60	44	31.4	18	46.2	33	33.3	95	34.2	
	>60	31	22.1	7	17.9	31	31.3	69	24.8	
Work	Not working	49	35.0	20	51.3	46	46.5	115	41.4	NS
	Student	23	16.4	1	2.6	12	12.1	36	12.9	
	Employer	32	22.9	5	12.8	24	24.2	61	21.9	
	Free worker	20	14.3	7	17.9	11	11.1	38	13.7	
	Doctor	16	11.4	5	12.8	5	5.1	26	9.4	
	Healthcare worker	0	0.0	1	2.6	1	1.0	2	0.7	
Education level	Illiterate	18	12.9	8	20.5	19	19.2	45	16.2	NS
	Primary	16	11.4	2	5.1	15	15.2	33	11.9	
	Preparatory	42	30.0	10	25.6	27	27.3	79	28.4	
	Secondary	41	29.3	11	28.2	18	18.2	70	25.2	
	University	8	5.7	2	5.1	2	2.0	12	4.3	
	Post graduate degree	15	10.7	6	15.4	18	18.2	39	14.0	
Residence	Rural	65	46.4	19	48.7	43	43.4	127	45.7	NS
	Urban	38	27.1	8	20.5	19	19.2	65	23.4	
	Governorate	37	26.4	12	30.8	37	37.4	86	30.9	
History of contact	Yes	70	50.0	15	38.5	39	39.4	124	44.6	NS
	No	70	50.0	24	61.5	60	60.6	154	55.4	

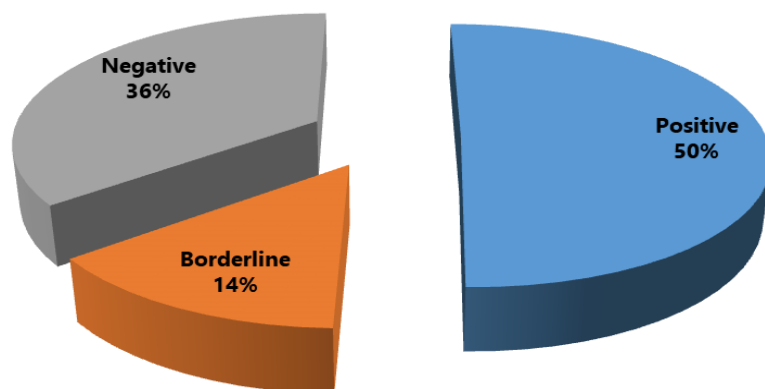
$p > 0.05$  is not significant (NS).

Table 2 shows the SARS-CoV-2 IgG antibody titer. The mean antibody titer of the seropositive patients was  $35.71 \pm 18.12$  U/ml with a median of 32.11 U/ml.

Seroprevalence of IgG antibodies against SARS-CoV-2 was found in 50 % of the studied population (Figure 1).

**Table 2.** The antibody titer among the studied population categories.

Categories	Mean $\pm$ SD	Median	Percentile 25	Percentile 75
Positive group	$35.71 \pm 18.12$	32.11	20.85	47.02
Borderline group	$12.66 \pm 1.65$	12.95	11.10	14.10
Negative group	$7.35 \pm 1.83$	7.68	5.74	9.06
Total	$22.38 \pm 18.71$	15.05	9.04	32.13



**Figure 1.** Prevalence of COVID-19 among the studied population according to IgG results.

Regarding comorbid diseases, the IgG antibody titer was significantly lower in patients with CKD on dialysis, ischemic heart disease, and chronic obstructive lung diseases than other

participants ( $p=0.01$ ,  $p=0.02$ ,  $p=0.005$ , respectively) (Table 3). However, being diabetic did not affect the immune response ( $p=0.4$ ) (Table 3).

**Table 3.** The antibodies titer in the studied population according to comorbid diseases.

Disease	Healthy participants Median (IQR)	Participants with comorbidity Median (IQR)	<i>p</i> value
Diabetes mellitus N=43	15.8 (9-32)	13.9 (9-19)	NS
Hypertension N=59	16.4 (9-32)	10.4 (9-33)	NS
Chronic kidney diseases on dialysis N= 89	16.7 (9.6-31.9)	9.07 (9-32)	0.01
Ischemic heart disease N= 17	15.8 (9.04-32.6)	9.07 (9.04 – 15)	0.02
Chronic obstructive lung diseases N= 15	15.9 (9.04-32.6)	9 (6.9-13.2)	0.005

$p > 0.05$  is not significant (NS)

There was a significant difference between the three categories regarding fever, dry cough, headache, malaise, and dyspnea ( $p=0.04$ ,  $p=0.02$ ,  $p=0.03$ ,  $p=0.02$ ,  $p=0.01$ , respectively). As regard co-morbid conditions there was a

significant difference between groups regarding hypertension, ischemic heart disease, chronic obstructive lung disease, and chronic kidney diseases (CKD) on dialysis. ( $p=0.03$ ,  $p=0.01$ ,  $p=0.0001$ , respectively) (Table 4).

**Table 4.** Symptoms suggestive of COVID-19 infection and comorbid diseases among the studied categories.

	Positive N=140		Borderline N=39		Negative N=99		p value
	No.	%	No.	%	No.	%	
Fever	83	59.3	15	38.5	49	49.5	0.04
Dry cough	80	57.1	18	46.2	39	39.4	0.02
Headache	75	53.6	17	43.6	36	36.4	0.03
Productive cough	61	43.6	12	30.8	35	35.4	NS
Sore throat	59	42.1	13	33.3	31	31.3	NS
Malaise	70	50.0	13	33.3	34	34.3	0.02
Dyspnea	47	33.6	5	12.8	21	21.2	0.01
Diarrhea	36	25.7	9	23.1	24	24.2	NS
Loss of taste or smell	31	22.1	6	15.4	15	15.2	NS
Rhinorrhea	27	19.3	10	25.6	19	19.2	NS
Loss of appetite	29	20.7	8	20.5	23	23.2	NS
COVID-19 infection	47	33.6	13	33.3	27	27.3	NS
Recurrent COVID-19 infection	5	3.6	1	2.6	2	2.0	NS
Comorbid diseases							
Diabetic	18	12.9	6	15.4	19	19.2	NS
Hypertensive	21	15.0	11	28.2	27	27.3	0.03
Chronic kidney disease on dialysis	30	21.4	10	25.6	49	49.5	<0.0001
Chronic obstructive lung diseases	1	0.7	4	10.3	10	10.1	0.002
Ischemic heart diseases	3	2.1	3	7.7	11	11.1	0.01

\*p-value was calculated by Chi-Square Tests.  $p > 0.05$  is not significant (NS).

As regards precautions taken to minimize the exposure to COVID-19, we found that the percentage of antibody response was lower in individuals who followed the precautions, but this did not reach the statistical significance level (Table 5).

When evaluating the risk of acquiring COVID-19 infection, we noticed neither precaution measures nor comorbid diseases had a role in this risk in our participants (Table 6).

**Table 5.** Precautionary measures taken by study population against COVID-19 infection.

	Positive N=140		Borderline N=39		Negative N=99		p-value
	No.	%	No.	%	No.	%	
Mask wearing	100	71.4	33	84.6	77	77.8	NS
Hand hygiene	103	73.6	32	82.1	79	79.8	NS
Social distance	91	65.0	26	66.7	67	67.7	NS
Crowded places	77	55.0	14	35.9	55	55.6	NS
Hand contact	75	53.6	19	48.7	51	51.5	NS

\*p-value was calculated by Chi-Square Tests.  $p > 0.05$  is not significant (NS).

**Table 6.** Risk estimate of acquiring COVID-19 infection.

Risk Estimate	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for mask wearing (Yes / No)	0.714	0.392	1.300
Odds Ratio for hand hygiene (Yes / No)	0.705	0.380	1.307
Odds Ratio for social distance (Yes / No)	0.887	0.514	1.531
Odds Ratio for crowded places (Yes / No)	0.978	0.583	1.641
Odds Ratio for hand contact (Yes / No)	1.086	0.649	1.818
Odds Ratio for hand contact (Yes / No)	1.086	0.649	1.818
Odds Ratio for diabetic (Yes / No)	0.621	0.307	1.256
Odds Ratio for hypertensive (Yes / No)	0.471	0.248	0.893
Odds Ratio for renal disease (Yes / No)	0.278	0.158	0.489
Odds Ratio for chest disease (Yes / No)	0.064	0.008	0.509
Odds Ratio for cardiac (Yes / No)	0.175	0.048	0.646

## Discussion

The current study evaluated the seroprevalence of antibodies against the SARS-CoV-2 in 278 participants during August 2021 immediately after the third wave of COVID-19 in Egypt. We found that 50 % of the 278 participants had a positive IgG response to COVID-19. Several previous studies estimated antibody response to COVID-19 over different periods and in different countries. As the COVID-19 incidence rate increased, the seroprevalence increased as well.<sup>7</sup> To the best of our knowledge, our study was the only one that evaluated the COVID-19 seroprevalence in Egypt in 2021 after the third wave. However, three studies evaluated COVID-19 seroprevalence in Egypt in 2020. In the first study that was conducted from April to October

2020, 34.8% out of 1598 participants were seropositive.<sup>18</sup> The second study was performed from May to October 2020, showed that 28.9% of 4313 participants were seropositive.<sup>19</sup> The third study was a multicenter study involving 82 health care workers during the period from October to December 2020. The reported seroprevalence was 40.3%.<sup>20</sup>

When evaluating the COVID-19 in the neighboring countries, Banjar et al., 2021, reported that during the first half of 2020, 1.4% of 837 blood donors in Saudia Arabia had positive IgG against SARS-CoV-2.<sup>2</sup> While, Alharbi et al., 2021, in the second half of 2020, found that 11% out of 11703 participants in Saudi Arabia had antibody responses to SARS-CoV-2.<sup>7</sup> There was also a rapid increase in the seroprevalence rate in Jordan from 0% in



September 2020 to 27% in February 2021.<sup>21</sup> The seroprevalence in a study in South Sudan during August 2020 was 38% out of 2214 participants.<sup>22</sup> While in May 2020, the reported seroprevalence in a Libyan study was 2.7% out of 219 participants.<sup>23</sup> Mukwege et al., 2021, showed that 14% out of 359 healthcare workers in Panzi hospital in Congo were seropositive.<sup>24</sup> In a systematic metanalysis study about seroprevalence in Africa until April 2021<sup>25</sup>, the reported seroprevalence across African countries was 0% to 45%. While a second metanalysis study reported a seroprevalence ranging from 0 to 63%.<sup>10</sup>

A metanalysis study evaluating the seroprevalence in Europe showed that in June 2020 the seroprevalence ranged from 0.42 to 13.6%. Also, Ward et al., 2021, showed that 6% of the population in England had positive anti SARS-CoV-2 antibody titer.<sup>26</sup> In an Italian study, the reported seroprevalence until April 2020 was 5.6%.<sup>27</sup> The national seroprevalence in a Spanish study until April 2020 was 5%.<sup>28</sup>

In the USA, the seroprevalence until September 2020 ranged from less than 0% to up to 23%.<sup>29</sup> While another American study showed that by May 2021 the seroprevalence reached 22%, however after the introduction of vaccination the seroprevalence rate reached 83% in the same month.<sup>30</sup> In the second quartile of 2020, Smith et al., 2020,<sup>9</sup> found that 3% out of 503 participants in St. Louis, Missouri had positive IgG against SARS-CoV2. During the fourth quartile of 2020 in Manus, Brazil the seroprevalence reached 32.31%.<sup>31</sup> The seroprevalence in the Austrian ski resort of Ischgl in April 2020 reached 42%.<sup>32</sup>

The worldwide seroprevalences until the end of 2020, as reported in a metanalysis was 4.5%.<sup>33</sup> Another metanalysis evaluated the worldwide seroprevalence until August 2020, indicated that the seroprevalence ranged from 0.37% to 22% with a pooled estimate of 3.38%.<sup>34</sup>

We found no difference between participants with positive IgG against SARS-CoV-2 and those with negative antibody response regarding the age, gender, occupation, education level, type of work, and history of contact with patients having COVID-19

infection. Banjar et al., 2021, reported a similar finding regarding age and sex. However, they reported that participants with low educational levels had a higher seropositive rate than others.<sup>2</sup> Lindahl et al., 2020,<sup>3</sup> also reported no association between gender and age and being seropositive. Vaselli et al., 2021<sup>16</sup> and Pollán et al., 2020<sup>28</sup> reported no association between seroprevalence and gender. However, they reported a significant difference in the antibody titer in different age groups. Mukwege et al., 2021, reported that seropositivity is not related to the type of work.<sup>24</sup> In an African metanalysis, Chisale et al., 2021 reported that participants aged 50 years or less had a higher seropositive rate than others.<sup>10</sup> In a British study, Ward et al., 2021, reported that IgG level was higher in black ethnicity, health care workers, those who provide social services in a residence, participants with higher income, and participants with the age from 18-24year.<sup>26</sup> Gudbjartsson et al., 2020, showed that elderly and hospitalized patients had higher antibody responses than others.<sup>35</sup> Lalwani et al., 2021<sup>31</sup> and Galanis et al., 2021<sup>36</sup> reported that men had higher seroprevalence levels than women. While, Girgis et al., 2021, noticed that seroprevalence was high among adult, middle-aged participants, and female gender.<sup>19</sup> Rostami et al., 2021, reported a relationship between the seroprevalence and the income levels.<sup>34</sup>

In the current research, we noticed that fever, headache, cough, malaise, and dyspnea were significantly higher in seropositive participants than seronegative participants. Lindahl et al., 2020, reported that fever and loss of smell were indicators of seropositivity against COVID-19.<sup>3</sup> Also, Gudbjartsson et al., 2020, reported that fever, cough, and anorexia were associated with higher antibody response against SARS-CoV-2.<sup>35</sup> Ward et al., 2021, reported a high level of IgG in patients with severe symptoms and those with a history of close contact with an infected case.<sup>26</sup>

We found that the percentage of IgG response against COVID-19 in participants with hypertension, chronic chest, and cardiac disorders was significantly lower than other participants. We also noticed that being diabetic did not affect the immune response. Alharbi et



al., 2021, noticed that hypertensive individual has a higher percentage of antibody response than non-hypertensive individuals.<sup>7</sup> However, Girgis et al., 2021 and Zheng et al., 2021, showed that seroprevalence was not affected by the presence of comorbid diseases as diabetes or hypertension.<sup>19, 37</sup> However, Krystle et al., 2021, demonstrated that antibody response was higher among hospitalized COVID-19 patients with comorbid diseases.<sup>38</sup>

Despite the increased prevalence of COVID-19 infection in patients with chronic kidney diseases (CKD),<sup>39</sup> we found that participants with chronic kidney diseases had poorer antibodies response against COVID-19 in comparison with other individuals. This can be explained by a poor immune response in patients with chronic CKD. However, Bruno et al., 2021, reported that CKD patients who caught COVID-19 infection had a satisfactory immune response against SARS-CoV-2.<sup>39</sup>

As regards precautions taken to minimize the exposure to COVID-19, we found that the percentage of antibody response was lower in individuals who followed the precautions, but did not reach the statistical significance. Bo et al., 2021,<sup>40</sup> noticed that social distancing has an important role in controlling COVID-19 transmission. In African studies, Mukwege et al., 2021 and Shaweno et al., 2021, reported that immune response was significantly lower in participants who followed preventive precautions against COVID-19.<sup>24, 41.</sup>

When evaluating the risk of acquiring COVID-19 infection, we noticed neither precaution measures nor comorbid diseases had a role in this risk in our participants. However, Lalwani et al., 2021, reported that low income and unavailability of health care services were related to the increase in seroprevalence against COVID-19.<sup>31</sup> Lindahl et al., 2020, showed that history of contact with COVID-19 patients increases the risk of being seropositive to COVID-19.<sup>3</sup> Bobrovitz et al., 2021, in a metanalysis study indicated that the seroprevalence was related to the number of COVID-19 cases in each country.<sup>33</sup> Naranbhai et al., 2020, reported that anosmia and loss of taste were considered risk factors of seropositivity.<sup>42</sup> Shaweno et al., 2021, noticed

that wearing a face mask was associated with a reduced seroprevalence.<sup>41</sup>

In conclusion, high seroprevalence (50%) of SARS-CoV-2 IgG antibody after the third wave of COVID19 is reported in the current study. Comorbid conditions as hypertension, chronic cardiac diseases, chronic chest problems, and CKD on dialysis may decrease the immune response against COVID-19 infection.

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## Author Contributions

All authors contributed to the study conception and design. MMA, NSS, RMF, SBH, ANN, AR and TMB, performed material preparation, data collection and analysis. MMA, wrote the first draft of the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

## Declaration of Conflicting Interests

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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## Ethical approval

The study protocol was reviewed and approved by the Medical Research Ethics Committee of the Faculty of Medicine, Sohag University (No. Soh-Med-21-04-33, dated April 2021). An informed consent was taken from each participant before enrolled in the study.

## Informed consent

A signed consent form was obtained from each study participant.

## ORCID iD

Noha S. Shafik,  <https://orcid.org/0000-0003-2786-7125>

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