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RESEARCH ARTICLE

Cytokine fingerprint differences following infection and vaccination – what can we learn from COVID-19?

Shira Cohen Rubin[1*], Nadav Zacks[1], Ori Wand[2], Ophir Freund[3], Evgeni Gershman[3], Anna Breslavsky[2], Rotem Givoli-Vilensky[1], Anat Tzurel Ferber[2], Natalya Bilenko[1,4], Amir Bar-Shai[3]

[1] Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel
[2] Division of Pulmonary Medicine, Barzilai University Medical Center, Ashkelon, and Ben-Gurion University of the Negev, Beer-Sheva, Israel
[3] The Institute of Pulmonary Medicine, Tel-Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[4] Medical Office of Southern District, Ministry of Health, Ashkelon, Israel

Correspondence: Shira Cohen Rubin
<scohe@post.bgu.ac.il>

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ABSTRACT. COVID-19 vaccination and acute infection result in cellular and humoral immune responses with various degrees of protection. While most studies have addressed the difference in humoral response between vaccination and acute infection, studies on the cellular response are scarce. We aimed to evaluate differences in immune response among vaccinated patients versus those who had recovered from COVID-19. *Materials and Methods:* This was a prospective study in a tertiary medical centre. The vaccinated group included health care workers, who had received a second dose of the BNT162b2 vaccine 30 days ago. The recovered group included adults who had recovered from severe COVID-19 infection (<94% saturation in room air) after 3-6 weeks. Serum anti-spike IgG and cytokine levels were taken at entry to the study. Multivariate linear regression models were applied to assess differences in cytokines, controlling for age, sex, BMI, and smoking status. *Results:* In total, 39 participants were included in each group. The mean age was 53 ±14 years, and 53% of participants were males. Baseline characteristics were similar between the groups. Based on multivariate analysis, serum levels of IL-6 (β=-0.4, p<0.01), TNFα (β=-0.3, p=0.03), IL-8 (β=-0.3, p=0.01), VCAM-1 (β=-0.2, p<0.144), and MMP-7 (β=-0.6, p<0.01) were lower in the vaccinated group compared to the recovered group. Conversely, serum anti-spike IgG levels were lower among the recovered group (124 vs. 208 pg/mL, p<0.001). No correlation was identified between antibody level and any of the cytokines mentioned above. *Conclusions:* Recovered COVID-19 patients had higher cytokine levels but lower antibody levels compared to vaccinated participants. Given the differences, these cytokines might be of value for future research in this field.

Key words: Immunity; SARS-CoV-2; pro-inflammatory; cytokines; vaccination.

Coronavirus disease (COVID-19) is caused by the highly transmissible novel human pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinical manifestations of SARS-CoV-2 infection range from asymptomatic infection to fatal disease, and some studies suggest that approximately 32-87% of patients suffer from post-acute sequelae of COVID-19 (PASC), most commonly fatigue and dyspnoea [1-4].

The morbidity and mortality associated with SARS-CoV-2 infection prompted the rapid development of vaccines. In December 2020, two doses of the Pfizer-BioNTech's BNT162b2 mRNA vaccine were granted emergency use authorization by the U.S. Food and Drug Administration (FDA) [5]. After emerging evidence of waning in vaccine effectiveness, the FDA approved the administration of a third vaccine dose, also known as a "booster" shot, given five months after the first two doses [6].

Both SARS-CoV-2 infection and the BNT162b2 vaccine induce cellular and humoral immune responses, with various degrees of protection. Still, there are differences in the immune response between vaccinated and infected patients. For example, unlike following infection, only S1 protein antibodies are produced after vaccination with BNT162b2 since the vaccine does not contain the N protein gene [7]. Regarding COVID-19 infection, several concerns have been raised about the rapid decline of antibodies after viral clearance, particularly in mild cases [8]. However, cellular responses, and specifically T-cell responses, were observed in the majority of people with COVID-19 infection and may be more potent and persistent than the humoral response [9, 10]. The BNT162b2 vaccine also generates significant T-cell responses which could be of interest as a marker of protection [11].

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Cytokines are essential for acquired immunity, both cellular and humoral, and play a role in modulating a variety of biological processes [12, 13]. Analyses of cytokine expression have provided valuable insight into some of the immune mechanisms involved in protection and recovery from many infectious agents [14-16]. Both infection- and vaccine-induced changes in serum cytokines have been shown to coincide with activation of T cells and innate cells [17, 18]. These findings suggest that cytokine profiles after viral exposure could potentially serve as biomarkers of immune activation and even yield useful information regarding vaccine efficacy.

In this proof-of-concept study, we aimed to evaluate differences in immune responses between individuals who were either vaccinated or had recovered from COVID-19. By comparing the cytokine and chemokine profiles between these two groups, we hoped to provide a proof-of-concept for their use as a marker of immunity against COVID-19 infection and shed light on the inflammatory cascade in COVID-19 infection and vaccination.

METHODS

Ethical considerations

The study was approved by the Ethics Committee and Institutional Review Board of Barzilai University Medical Center (No. BRZ-0082-22). The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants signed an informed consent form prior to study enrolment. Results are reported according to STROBE statement guidelines.

Study design and population

This prospective observational study was performed in a tertiary medical centre in Southern Israel between 2020-2021 and included two groups of adult participants (≥18 years) who signed an informed consent form:

1. The vaccinated group - health care workers (HCWs) of the Barzilai University Medical Center (BUMC) in Ashkelon who received two doses of the BNT162B2 vaccine, 21 days apart, as a part of the national vaccination program in Israel. All included participants in this group underwent serological tests 30 days after the second dose of the vaccine. HCWs with a confirmed SARS-CoV-2 infection (based on either positive RT-PCR from nasopharyngeal swabs, or positive antibodies against the nucleocapsid antigen anti-N), before or during the study, were excluded.
2. The recovered group - patients who had recovered from severe COVID-19 and were treated in the pulmonary outpatient clinic of BUMC afterwards. All included participants in this group had a diagnosis of COVID-19 infection based on positive RT-PCR from a nasopharyngeal swab and underwent a serological test 3-6 weeks after recovery from COVID-19. Severe illness was defined as SpO_2 <%94 on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, or a respiratory rate >30 breaths/minute (42).

Immunosuppressed patients, patients with autoimmune diseases and participants lacking the necessary socio-demographic information were excluded from the study.

Study procedures

Serum for cytokine level measurement was collected during the serological test, 30 days after the second dose of the vaccine in the vaccinated group and 3-6 weeks after recovery from COVID-19 in the recovered group. At the time of collection, all participants were asked to complete a personal questionnaire which included sociodemographic data and medical history. We collected sociodemographic and anthropometric variables, self-reported smoking status (ever/never), and self-reported chronic conditions (yes/no). Additional information included comorbidities such as immunosuppressive states, chronic kidney disease (CKD), hypertension (HTN), diabetes mellitus (DM), and dyslipidaemia. Cytokine and chemokine levels were measured using the Human Premixed Multi Analyte Kit and the Human HS Cytokine Premixed Kit (both manufactured by R&D Systems, Inc., MN, USA). We measured chitinase 3, matrix metalloproteinase-7 (MMP-7), chemokine ligand 2 (CCL2), matrix metalloproteinase-12 (MMP-12), thymic stromal lymphopoietin (TSLP), vascular cell adhesion protein-1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), surfactant protein-D (SP-D), myeloperoxidase (MPO), cancer antigen 15-3 (CA15-3), tumour necrosis factor alpha (TNFα), vascular endothelial growth factor (VEGF), interleukin-2 (IL-2), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), and interferon gamma (IFNγ). Participants were also tested for COVID-19 S1/S2 IgG type antibodies (Abs) using the Liaison chemiluminescent immunoassay kit (DiaSorin, Saluggia, Italy).

Cytokine levels, measured in pg/mL, and IgG anti-S antibody levels, measured in AU/mL, were documented and compared between the study groups. We also investigated associations and correlations between cytokine levels and antibody results relative to time from vaccine/recovery to measurement.

Statistical analysis

Descriptive analyses were performed to evaluate the characteristics of each study group and the overall cohort. Continuous variables are presented as mean (± standard deviation) or median (inter-quartile range) for normally and non-normally distribution, respectively. Normality of distribution was evaluated with the Shapiro-Wilk test. Categorical variables are presented as sum (percentage from total). *P* values lower than 0.05 were considered significant.

Cytokine and antibody levels were compared between the groups (vaccinated / recovered) using independent T-tests for normally distributed samples and the Mann-Whitney U test for non-normally distributed samples.

Multivariate linear regression models were used to detect unique and independent predictors for high levels of each cytokine that showed significant association in univariate analysis. The models included the following variables: patient group, sex, age, BMI, smoking status,

and any other significant variables from the univariate analysis. In addition, to account for the difference in time from vaccination/recovery to testing, for cases in which cytokines significantly correlated with time, we included duration (in days) in the multivariate model. Betas and 95% confidence interval (CI) were calculated using these models. Data analysis and statistical procedures were conducted using SPSS 25.0 ® (SPSS, Chicago, IL), MATLAB 2021 ® software.

RESULTS

Participant characteristics

Overall, 39 subjects were included in the vaccinated group and 39 in the recovered group. No participants were excluded. The alpha variant of the virus was found in all participants. The general characteristics of the overall cohort and comparison between the groups are reported in *table 1*. Our study population was relatively young (52.90 ± 14.16 years old) and most were males (41; 53%). The most common comorbidity was hypertension (29.4%). There were no differences in comorbidities between the groups. Of note, none of the patients had chronic kidney disease or chronic respiratory disease. The median time from recovery to laboratory measurements was 32 days (29-38), while the median time from vaccination to laboratory measurements was 29 days (28-30).

Cytokines

Cytokines that did not show any variance in measurement were excluded from this study; this was the case for MPO, CA15-3, and IFNγ due to measuring limitations, and these were excluded from further analysis.
The median cytokine concentrations in each group (vaccinated group and recovered group) are summarized in *figure 1* and *table 2*. Serum levels of MM-7, IL-6, VCAM1, TNFα and IL-8 were significantly higher in the recovered group compared to the vaccinated group. IL-1β levels were higher in the vaccinated group, although only with borderline statistical significance (p=0.05). For all other cytokines, there were no differences in levels between the two groups. Of note, MMP-7, VCAM1, and IL-8 showed significant correlations with time, while this was not the case for TNFα and IL-6.
Based on multivariate analysis, recovery from COVID-19 infection was an independent predictor for higher levels of MMP-7, IL-6, VCAM1, TNFα and IL-8 (*table 3*). The detailed analyses for each cytokine are presented in *supplementary tables S1 to S5* in the appendix. We found no other independent predictors among the other variables in the multivariate analyses, including sex, age, BMI, smoking status, and time from vaccination/recovery to measurement.

Association between cytokines and COVID-19 IgG (S1-S2) antibody

When comparing the mean anti-COVID-19 IgG (S1-S2) levels of each group, we found higher levels of IgG S1-S2 in the vaccinated group (208 vs. 124 pg/mL; p<0.001). In addition, antibody levels exhibited a negative correlation with time to measurement (r=-0.46, p<0.01). After adjusting for time to measurement using a multivariate linear regression, the difference between groups remained significant (Beta=0.422, p<0.01).
As seen in *table 4*, IL-1β, IL-2 and IL-10 exhibited positive correlations with anti-COVID-19 IgG (p=0.019, p<0.001, p<0.001, respectively). As mentioned above, these cytokines were not found to be significantly different between the two study groups. Moreover, in a sub-analysis of the study cohort divided by group (vaccinated and recovered group), we did not find any additional associations between antibody and cytokine level.

DISCUSSION

The COVID-19 outbreak highlighted the importance of vaccination for controlling the spread of viral infections [19]. Vaccines had an immense effect on disease spread and severity [20, 21]. A number of studies have noted the potential of measuring cytokine levels as indicators of cell-mediated immunity and protection from infection by different infectious diseases [15, 22]. Several

Table 1.
Demographics and characteristics of the sample.

	All	Recovered group	Vaccinated group	
	Mean (± std. deviation) [median] or N (%)			
Category	**N=78 (%)**	**N=39 (%)**	**N=39 (%)**	***p*-value**
Sex				0.503
Male	41 (52.6%)	22 (56.4%)	19 (48.7%)	
Female	37 (47.4 %)	17 (43.6 %)	20 (51.3%)	
Age	52.90 (±14.16) [55.00]	52.44 (± 15.01) [54.00]	53.36 (± 13.34) [55.00]	0.716
BMI	28.05 (±5.5) [27.450]	30.33 (± 6.17) [28.70]	25.77 (± 3.55) [26.60]	0.495
Smokers (ever smoked)	23 (29.5 %)	15 (38.5%)	8 (20.5%)	0.084
Comorbidities				
HTN	23 (29.4%)	10 (25.6%)	13 (33.3%)	0.463
DM	17 (21.7%)	11 (28.2%)	6 (15.3%)	0.175
Dyslipidaemia	19 (24.3%)	12 (30.7%)	7 (17.9%)	0.192

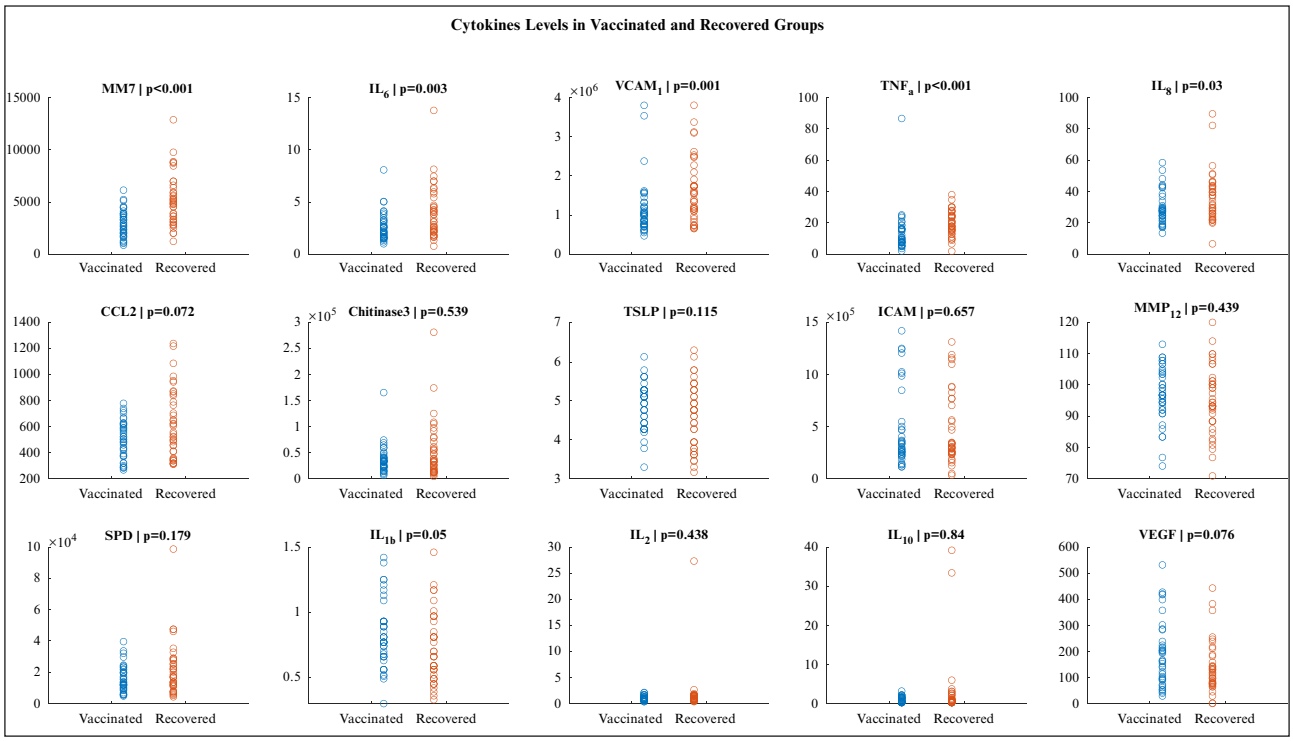

Figure 1.
Cytokine levels in the vaccinated and recovered group. The vertical axis refers to cytokine level (pg\mL).

Table 2.
Mean cytokine levels in the COVID-19 recovered group and vaccinated group.

Cytokine (pg/mL)	*Vaccinated*	*Recovered*	*p value*
Chitinase3	33566 [22408 ; 41747]	34852 [17567 ; 71293]	0.539
MM7	2824 [2015 ; 3885]	4886 [3283 ; 6374]	**<0.001**
CCL2	504.06 [378.81 ; 616.17]	558.41 [409.78 ; 839.27]	0.072
MMP12	97.106 ± 8.817	95.379 ± 10.683	0.439
TSLP	4.868 ± 0.594	4.607 ± 0.832	0.115
VCAM1	1003820 [766907 ; 1320047]	1536770 [1098280 ; 2096489]	**0.001**
ICAM	304273 [236968 ; 501684]	330464 [247791 ; 768254]	0.657
SPD	13610 [9983 ; 21599]	17013 [11286 ; 27639]	0.179
TNFα	9.42 [7.46 ; 16.29]	19.29 [14.66 ; 24.92]	**<0.001**
VEGF	162.21 [91.88 ; 238.22]	117.14 [76.72 ; 181.92]	0.076
IL-2	0.87 [0.77 ; 1.24]	0.95 [0.74 ; 1.48]	0.438
IL-1β	0.77 [0.66 ; 0.93]	0.66 [0.49 ; 0.93]	0.050
IL-6	2.21 [1.69 ; 3.24]	3.41 [2.16 ; 5.43]	**0.003**
IL-8	27.5 [22.74 ; 33.9]	33.7 [25.58 ; 43.55]	**0.030**
IL-10	0.78 [0.3 ; 1.48]	0.77 [0.27 ; 2.08]	0.840

Normally distributed variables are shown as mean ± standard deviation and were compared using the T-test. Non-normally distributed variables are shown as median [Q1; Q3] and were compared using Mann-Whitney U tests.

studies have evaluated the immune response to COVID-19 natural infection and to vaccination. The majority have focused on the humoral response, which is more readily measurable [23-25], while the dynamics of cell-mediated immunity has been less commonly described. Thus, in this proof-of-concept study, we compared cytokine and COVID-19 antibody levels in recovered and vaccinated individuals to evaluate the differences in immune responses between those two groups.

We found that serum levels of IL-6, TNFα, IL-8, VCAM-1, and MMP-7 were higher in the recovered group compared to the vaccinated group, independent of other baseline characteristics. IL-6, TNFα, and IL-8 are pro-inflammatory mediators that play crucial roles in the immune response against viral infection and in other inflammatory diseases [15, 23, 26]. IL-6 mobilizes immune cells to the site of infection and promotes the production of virus-specific antibodies [26]. TNFα and IL-8 are chemotactic factors that promote the recruitment of neutrophils and monocytes to the site of

Table 3.
Correlation between cytokine level and vaccinated patients compared with recovered patients, controlled for background confounders using a multivariate linear regression model.

		95% CI		
Variable	**B**	**Lower bound**	**Upper bound**	***p***
MMP-7	-0.540	-3458	-1329	<0.001
IL-6	-0.425	-2.81	-0.75	0.001
VCAM-1	-0.218	-755373	53621	0.140
TNFα	-0.294	-12.52	-0.83	0.025
IL-8	-0.342	-16.79	-1.87	0.015

Data were controlled for sex, age, BMI and smoking status using a multivariate linear regression model, and time from vaccination/recovery using univariate analysis.

infection [28]. Cell adhesion molecules, like VCAM-1, allow immune cells to attach to infected cells and destroy them [29]. As a matrix metalloproteinase, MMP-7 breaks down infected cells, promoting their elimination [30]. Together, these cytokines work to activate and coordinate the immune response against viral infections, ultimately helping to eliminate the virus from the body during infection.

A possible explanation for the differences we found in this study lies in the cytokine response to COVID-19 compared with COVID-19 vaccination. COVID-19 natural infection results in exposure of the upper airway epithelium to the virus, promoting the local immune response. Inflammation begins when the virus replicating in local macrophages, resulting in apoptosis. Macrophages and T cells that release inflammatory cytokines are activated by Toll-like receptor ligands, such as liposaccharide (LPS), DNA, RNA, and other microbial components [31]. Consequently, patients with severe COVID-19 have considerably higher blood levels of IL-2, IL-6, TNFα, IL-1, IL-10, IFNγ, IL-8/CXCL8, and CXCL10/IP-10, leading to a more pronounced inflammatory state ("cytokine storm"), resulting in detrimental prognosis [32]. Experimental models have demonstrated that COVID-19 exposure generates a significant induction of monocyte- and neutrophil-associated chemokines (CCL2 and CCL8, and CXCL2 and CXCL8, respectively), further supporting the mentioned hypothesis [33]. Still, like COVID-19 infection, vaccines induce both cellular and humoral responses, with mixed reports on the dominant factor between them [34, 35]. A study by Wang *et al*. analysed the immune response after vaccination and showed a strong correlation among cytokines at 40 days after the second vaccine that waned over time [36]. Therefore, although the magnitude of cytokine dynamics after vaccination may be of smaller magnitude compared with that of recovered patients, it should not be ignored as a point of interest in future research.

In contrast to cytokine levels, serum anti-spike IgG levels were lower among the recovered group compared to the vaccinated group, even after adjustment for time to serum measurement. Despite lower antibody response rates in COVID-19 recovered patients in previous studies, both prior infection and vaccination have been shown to be effective in preventing COVID-19 infection 45 days after viral exposure [37, 38]. These results emphasize the assumption that the type of immune response generated by the vaccine and natural infection differ. As a result, specific cytokines might prove to be of added value alongside antibody levels, although this could not be directly concluded from our findings.

This study has several limitations. The sample size was relatively small, and thus its outcomes should be considered as a proof of concept for further studies to explore. We compared vaccinated HCWs with recovered patients from the general population. Therefore, the study population might not appropriately represent the parent population, which could affect the generalizability of our results. Furthermore, it is possible that patients who chose to visit the pulmonary clinic were those with

Table 4.
Correlation between cytokines and COVID-19 IgG (S1-S2) antibodies.

	Sum of squares	**Mean square**	**F**	***p-value***
MMP-7 * S1S2	298442279.962	4388857.058	0.466	0.963
CCL2 * S1S2	3158319.671	46445.878	0.976	0.570
VCAM1 * S1S2	40604508248348.900	597125121299.248	0.750	0.763
MMP12 * S1S2	6873.325	101.078	1.912	0.147
Chitinase3 * S1S2	127827064434.718	1879809771.099	1.446	0.286
TSLP * S1S2	38.811	0.571	2.305	0.088
ICAM * S1S2	8823488654446.010	129757186094.794	1.332	0.339
SPD * S1S2	12930320438.872	190151771.160	1.227	0.396
CA153 * S1S2	268339.015	3946.162	0.920	0.616
TNFα * S1S2	9303.237	136.812	1.644	0.214
VEGF * S1S2	876157.702	12884.672	0.878	0.652
IL-1β * S1S2	5.289	0.078	3.709	**0.019**
IL-2 * S1S2	693.733	10.202	30.959	**<0.001**
IL-6 * S1S2	305.340	4.490	1.118	0.465
IL-8 * S1S2	12032.689	176.951	0.638	0.857
IL-10 * S1S2	2514.257	36.974	194.169	**<0.001**

remaining symptoms, which could have created a selection bias. Additionally, it is important to consider that there may be individual differences in how the immune system responds to natural infection versus vaccination. This could have led to variation in the levels of inflammatory markers and other immune responses between individuals, regardless of whether they were vaccinated or had natural infection. Finally, follow-up measurements of cytokine and antibody levels were not obtained, therefore we were unable to examine their dynamics in both groups or evaluate the association between cytokines and clinical outcomes, both of which should be the aim of future studies in this field.

In conclusion, to our knowledge, this study is among the few comparing cytokine and antibody responses after COVID-19 vaccination and infection. We found discordant responses between the groups, with higher cytokine levels among the recovered group and higher antibody levels in the vaccinated group. This research may pave the way for further studies focusing on cytokine profiles following vaccination and recovery, as possible markers with added value.

DISCLOSURE

Financial support: none. Conflicts of interest: none.

Author Contributions: S.C.R and A.B.S. conceived and designed the study. S.C.R., N.Z. and A.B.S. drafted the manuscript. S.C.R., N.Z., O.F., and E.G. performed data analysis. O.W., A.B, R.G.V., and N.B. performed data acquisition. A.B.S. supervised the project. All authors critically revised the manuscript and approved the final version.

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