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The abundance of Interleukin-22, 37, and 38 post-vaccination and following COVID-19 recuperation

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ABSTRACT

The SARS-CoV-2 virus causes a contagious disease known as Coronavirus Disease 2019 (COVID-19). It began spreading globally in 2019 and is still producing pandemics today. Different COVID-19 vaccinations offer protection against this illness. Pfizer-BioNTech and Sinopharm were the two vaccine manufacturers with the highest usage in Iraq. Both vaccines use a different method to activate the immune system. This study seeks to compare the IL-22, IL-37, and IL-38 levels in those who received either the Sinopharm or the Pfizer-BioNTech COVID-19 vaccination. IL-22, IL-37, IL-38 levels have been shown to be upregulated in COVID-19 patients. In this study, IL-22, IL-37, and IL-38 levels were tested in 80 healthy controls and 100 COVID-19 patients 14–21 days after recovery. Additionally, people who received the Sinopharm or Pfizer-BioNTech vaccine (50 each) were monitored 21 days after the first dosage and 21 days after the second dose. In comparison to controls, serum levels were noticeably higher in recovered patients. Except for the first dosage of Pfizer BioNTech, the first and second doses of Sinopharm and Pfizer BioNTech were linked to considerably higher levels of IL-22, IL-37, and IL-38 compared to controls or recovered patients. where IL-22, IL-37, and IL-38 levels did not show significant differences compared to recovered patients. In conclusion, lower IL-37 and IL-38 molecule levels were linked to recovery from COVID-19, although these levels remained considerably greater in recovered patients compared to uninfected controls. Vaccination with Sinopharm or Pfizer-BioNTech confirmed the up-regulating effects of SARS-CoV-2 on IL-22, IL-37, and IL-38 levels.

Keywords: *COVID-19 Recovery; IL-22; IL-37; IL-38; Sinopharm; Pfizer-BioNTech; Vaccine.*

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INTRODUCTION

SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19), is a novel, highly contagious respiratory virus that has rapidly and uncontrollably spread throughout the world, raising global public health concerns (Huang et al., 2021; Hu et al., 2021). Therefore, efforts have been intensified to control SARS-CoV-2 infection through the development of vaccine strategies. More than 200 COVID-19 vaccines have been developed and are either in clinical or pre-clinical trials (WHO, 2021; Hamed et al., 2022). Of these, Sinopharm (an inactivated whole-virus vaccine) and Pfizer-BioNTech (messenger RNA vaccine) have received authorization for emergency usage in various countries, including Iraq (Al Khames Aga et al., 2021). In most cases, they are given in two doses with an interval of 21 days (Hadj Hassine, 2022 , Sharma et al.,2021) .

Inflammation is one of its most notable characteristics, and a hyper-inflammatory response is associated with an unfavorable outcome and even an increased risk of death (Wong, 2021). SARS-CoV-2 has been linked to an uncontrolled systemic inflammatory response caused by the release of large amounts of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, IL-17A, and tumor necrosis factor (TNF)-α. These cytokines appear to be a major contributor to COVID-19-associated pneumonia and widespread lung damage (Darif et al., 2021). Besides, anti-inflammatory cytokines also showed dysregulated production in COVID-19 patients possibly in response to the pro-inflammatory environment (Notz et al., 2020). Among the pro-inflammatory and anti-inflammatory cytokines that have shown dysregulated production in COVID-19 patients are the recently discovered members of the IL-1 (IL-37 and IL-38) and IL-10 (IL-22) cytokine families (Ahmed and Ad'hiah, 2021; Ahmed Mostafa et al., 2022; Al-bassam et al., 2022).

IL-37 is an anti-inflammatory cytokine known for its ability to suppress inflammation and the innate immune response by inhibiting the production of pro-inflammatory cytokines, thereby reducing the pathophysiological effects of inflammation (Su and Tao, 2021). Low levels of IL-37 have been found in patients with COVID-19, especially those who are severely ill (Ahmed and Ad'hiah, 2021; Li et al., 2021). IL-38 is an additional cytokine of the IL-1 family of cytokines that exhibit anti-inflammatory effects in a number of inflammatory, autoimmune and infectious diseases (Fazeli et al., 2022). In COVID-19 although not well explored, IL-38 has been the subject of controversy with one study reporting increased systemic levels in patients compared to controls (Gao et al., 2021), and another study showing no significant differences between patients and controls (Al-bassam et al., 2022). However, in both studies, IL-38 was linked to the severity of COVID-19. IL-22 is the next focus of this study, and it is interesting to note that this cytokine has both pro-inflammatory and anti-inflammatory functions and is thus a key player in controlling inflammatory reactions caused by infectious pathogens (Arshad et al., 2020). Besides, significantly elevated levels of IL-22 have been reported in the serum of COVID-19 patients under 16 years of age (Ahmed Mostafa et al., 2022). Furthermore, IL22R1, the cellular receptor for IL-22, showed abnormal expression in blood myeloid cells and CD4+ T cells during SARS-CoV-2 infection (Albayrak et al., 2022).

Accordingly, IL-22, IL-37, and IL-38 may play a significant role in the pathogenesis of COVID-19. However, the response of these cytokines to recovery from COVID-19 or vaccination against the disease has not been explored. Therefore, this study aimed to investigate this issue by analyzing serum IL-22, IL-37, and IL-38 levels in patients who had recovered from COVID-19 and individuals who received the vaccine.

MATERIALS AND METHODS

Populations studied

The Ethics Committee of the Iraqi Ministry of Health and Environment approved the study protocol (Ref. No.: BCSMU/0122/0006Z). Informed consent according to the Declaration of Helsinki was obtained from all participant were informed of the objectives of the study, agreed to participate, and provided written consent. The study was conducted during the period from January to June 2022 on 280 individuals divided into four groups. The first group (post-recovery; PR) included 100 patients who had recovered from COVID-19 and had been discharged from hospital and were included in the study 14-21 days after recovery.

Nasopharyngeal swab test for SARS-CoV-2 RNA was negative in the PR group (RealLine SARS-CoV-2 kit, Bioron Diagnostics GmbH). The second group (CTRL) included 80 blood donors who did not have SARS-CoV-2 infection and whose serum was negative for the antibody panel in the blood bank. The third (post-Sinopharm; PS) and fourth (post-Pfizer-BioNTech; PP) groups included individuals vaccinated with Sinopharm (Vero Cell; Beijing Institute of Biological Products Co., Ltd) and Pfizer-BioNTech (mRNA COMINARTY vaccine; Mainz, Germany/New York, United States), respectively (50 individuals each). PS and PP individuals were included in the study 21 days post the first (PS1D and PP1D, respectively) and second (PS2D and PP2D, respectively) doses of each vaccine. Only participants aged 18 years and over of both genders were included. Pregnant women (Nori W et al., 2022), diabetes, hypertension and smokers were excluded (Ahmed Saeed H et al., 2022). Baseline laboratory data for all participants included hemoglobin (Hb), red blood cell (RBC) count, platelet count, white blood cell (WBC) count and erythrocyte sedimentation rate (ESR).

IL-22, IL-37 and IL-38 immunoassay

Enzyme-linked immunosorbent assay (ELISA) kits were used to measure serum IL-22, IL-37 and IL-38 levels. The kits were provided by MyBioSource, Inc., USA (Catalogue number: MBS2020570, MBS165041 and MBS269990, respectively), and instructions of manufacture were followed. The standard curve range of the kits was 0-1000 pg/mL (IL-22), 0-400 ng/L (IL-37) and 0-500 pg/mL (IL-38).

Statistical analysis

Categorical variables were given as number and frequency (percentage), parametric variables as mean and standard deviation (SD), and non-parametric variables as median and interquartile range (IQR: 25-75%). Significance was determined using Pearson's Chi-square test (categorical variables), one-way analysis of variance test (parametric variables) or Mann-Whitney U test (non-parametric variables). Spearman's rank correlation analysis was performed to estimate correlation coefficient (rs) between cytokines. The level of significance was set at probability (p) ≤ 0.05. Statistical analysis was performed using GraphPad Prism version 9.4.1 (San Diego, CA, USA).

RESULTS

Baseline data

The mean age (±SD) of participants in the PR group was significantly higher than that in the CTRL, PS, and PP groups (58.4 ± 15.1 vs. 39.1 ± 7.5, 38.3 ± 9.8, and 39.1 ± 8.7 years, respectively; $p < 0.001$). The frequency of age groups (< 40 and ≥ 40 years) was also significantly different with 84.0% of PR patients in the age group ≥ 40 years, but lower in the CTRL, PS and PP groups were lower (41.3, 44.0 and 44.0% respectively, $p < 0.001$). Male and female frequencies showed no significant differences between the PR, CTRL, PS, and PP groups ($p = 0.096$). WBC, platelet count, and Hb levels were significantly different between these groups but were within the normal reference range. ESR was significantly elevated in the PR, PS, and PP groups compared to the CTRL group (Table 1).

Serum IL-22 levels

Median IL-22 levels were significantly elevated in the serum of the PR group compared to the CTRL group (27.8 [IQR: 21.1-36.9] vs. 15.0 [IQR: 13.3-17.1] pg/mL; $p < 0.001$). Regarding the individuals who received Sinopharm, PS1D and PS2D subjects showed similar levels of IL-22 (42.6 [IQR: 35.3- 52.1] and 43.2 [IQR: 25.4-64.7] pg/mL, respectively; $p = 0.4$), but these levels were significantly higher than either the CTRL group ($p < 0.001$) or the PR group ($p < 0.001$ and $= 0.037$, respectively). In the case of Pfizer-BioNTech, PP1D individuals showed significantly elevated levels of IL-22 (26.7 [IQR: 20.6-40.9] pg/mL; $p < 0.001$) compared to the CTRL group, while the difference was not significant compared to the PR group ($p = 0.883$). However, IL-22 levels were significantly higher in the PP2D individuals (73.2 [IQR: 58.7-84.2] pg/mL; $p < 0.001$) than in the PR, CTRL, or PP1D groups. When Sinopharm was compared with Pfizer-BioNTech, PS1D was associated with significantly elevated IL-22 levels compared to PP1D ($p < 0.001$), while the opposite observation was made when PS2D was compared with PP2D ($p < 0.001$) (Figure 1).

Serum IL-37 levels

Median IL-37 levels were significantly higher in the PR group than in the CTRL group (81.5 [IQR: 66.8-105.2] vs. 60.1 [IQR: 46.1-83.0] ng/L; $p < 0.001$). IL-37 levels were also significantly elevated in PS1D and PS2D individuals (146.9 [IQR: 126.8-194.8] and 185.1 [IQR: 156.9-203.5] ng/L, respectively) compared to the CTRL or PR group ($p < 0.001$), but there were no significant differences between PS1D and PS2D in this context ($p = 0.135$). For Pfizer-BioNTech, IL-37 levels were significantly higher in PP2D individuals (185.0 [IQR: 146.0-231.2] ng/L; $p < 0.001$) than in PP1D (89.5 [IQR: 58.8-134.4] ng/L), CTRL or PR group. In PP1D individuals, IL-37 levels were significantly higher compared to the CTRL group ($p < 0.001$), while no significant differences were found compared to PR levels ($p = 0.43$). The first dose of Sinopharm (PS1D) induced significantly elevated levels of IL-37 compared to the first dose of Pfizer-BioNTech (PP1D; $p < 0.001$), while there were no significant differences between the levels of the PS2D and PP2D groups ($p = 0.659$) (Figure 2).

Serum IL-38 levels

The median levels of IL-38 were significantly increased in the PR group compared to the CTRL group (108.4 [IQR: 77.5-155.4] vs. 58.8 [IQR: 54.3-65.1] pg/mL; $p < 0.001$). In the case of Sinopharm, IL-38 levels were significantly higher in PS1D and PS2D individuals (95.3 [IQR: 65.4-123.8] and 96.2 [64.2-156.6] pg/mL, respectively) than in the CTRL group ($p < 0.001$), while there were no significant differences compared to the PR group ($p = 0.059$ and 0.092, respectively) or between the PS1D and PS2D groups ($p = 0.862$). Regarding Pfizer-BioNTech, both PP1D and PP2D individuals showed significantly elevated levels of IL-38 (70.0 [63.0-81.7] and 106.8 [78.2-138.8] pg/mL; $p = 0.001$ and < 0.001, respectively) compared with the CTRL group. Besides, IL-38 levels were significantly higher in PP2D individuals than in PP1D individuals ($p < 0.001$). When the comparison was made with PR, a different trend was observed. IL-38 levels were significantly decreased in the PP1D individuals compared the PR group ($p < 0.001$), while there were no significant differences between the PP2D and PR groups ($p = 0.521$). IL-38 levels were significantly higher in PS1D individuals than in PP1D individuals ($p = 0.003$), while these levels did not show significant differences between PS2D and PP2D individuals ($p = 0.365$) (Figure 3).

Stratification of cytokine levels by age group and gender

Serum IL-22, IL-37, and IL-38 levels were stratified by age group (< 40 and ≥ 40 years) and gender in the PR, CTRL, PS1D, PS2D, PP1D and PP2D groups. The Mann-Whitney U test showed no significant differences in each stratum, except for IL-38 levels in the PS1D age groups. IL-38 levels were significantly elevated in the age group < 40 years compared to the age group ≥ 40 years (110.1 [IQR: 91.1-134.3] vs. 77.5 [IQR: 63.2-120.4] pg/mL; $p = 0.048$) (Table 2).

Spearman's rank correlation analysis

Spearman's rank correlation analysis of IL-22, IL-37, and IL-38 was performed in the CTRL, PR, PS1D, PS2D, PP1D, and PP2D groups and presented as a heat-map (Figure 4). The CTRL and PR groups shared a significant positive correlation between IL-37 and IL-38 ($rs = 0.477$; $p < 0.001$ and $rs = 0.306$; $p = 0.002$, respectively). In PP1D, IL-22 showed significant positive correlations with IL-37 ($rs = 0.544$, $p < 0.001$) and IL-38 ($rs = 0.359$; $p = 0.01$). For PS1D, PS2D and PP2D, no significant correlation was found between IL-22, IL-37, and IL-38.

TABLE 1: Baseline data for study groups.

Data; mean ± SD or n (%)	PR n = 100	CTRL n = 80	Sinopharm n = 50		Pfizer-BioNTech n = 50		*p*-value
			PS1D	PS2D	PP1D	PP2D	
Age; years	58.4 ± 15.1	39.1 ± 7.5	38.3 ± 9.8		39.1 ± 8.7		< **0.001**
Age group							
< 40 years	16 (16.0)	47 (58.8)	28 (56.0)		28 (56.0)		< **0.001**
≥ 40 years	84 (84.0)	33 (41.3)	22 (44.0)		22 (44.0)		
Gender							
Male	49 (49.0)	37 (46.3)	32 (64.0)		20 (40.0)		0.096
Female	51 (51.0)	43 (53.8)	18 (36.0)		30 (60.0)		
WBC; × 10^9/L	8.8 ± 3.5	7.1 ± 1.5	9.4 ± 2.4	7.9 ± 2.2	7.6 ± 2.2	8.7 ± 2.3	< **0.001**
ESR; mm/h	37.0 ± 18.2	7.3 ± 4.2	14.2 ± 7.7	24.1 ± 7.9	21.1 ± 6.9	18.4 ± 8.6	< **0.001**
RBC; × 10^{12}/L	4.8 ± 0.8	4.7 ± 0.4	5.1 ± 0.7	4.9 ± 0.6	4.9 ± 0.8	5.0 ± 0.5	0.2
Hb; g/dL	12.8 ± 2.4	14.2 ± 0.9	13.6 ± 2.1	14.3 ± 2.3	13.4 ± 1.9	13.7 ± 1.7	< **0.001**
Platelets; × 10^9/L	278 ± 92	237 ± 36	278 ± 76	267 ± 70	265 ± 82	252 ± 63	**0.003**

PR: 14-21 days post-recovery from COVID19; CTRL: Controls; PS1D: 21 days post-first dose of Sinopharm; PS1D: 21 days post-second dose of Sinopharm; PP1D: 21 days post-first dose of Pfizer-BioNTech; PP2D: 21 days post-second dose of Pfizer-BioNTech; SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2; WBC: White blood cell; ESR: Erythrocyte sedimentation rate; RBC: Red blood cell; Hb: Hemoglobin; p: Probability of Pearson's Chi-square test (to compare categorical variables) or one-way analysis of variance test (to compare parametric variables); Significant p-value is indicated in bold.

TABLE 2: Median (interquartile range) of IL-22, IL-37 and IL-38 serum levels stratified by age group and gender in study groups.

Group		IL-22; pg/mL	*p*-value	IL-37; ng/L	*p*-value	IL-38; pg/mL	*p*-value
PR	< 40 years	29.4 (18.9-39.3)	0.975	99.1 (76.7-123.1)	0.103	114.4 (78.8-147.5)	0.918
	≥ 40 years	27.5 (21.2-36.5)		80.2 (64.9-103.2)		108.4 (77.4-155.8)	
	Male	26.9 (20.3-36.5)	0.167	81.3 (70.3-106.2)	0.288	118.7 (82.9-156.3)	0.379
	Female	28.8 (22.0-37.5)		82.3 (62.3-104.1)		104.2 (76.5-154.7)	
CTRL	< 40 years	14.6 (12.5-16.6)	0.142	58.3 (45.7-74.9)	0.414	58.6 (53.2-74.4)	0.42
	≥ 40 years	15.4 (13.9-18.2)		62.9 (46.2-89.3)		60.2 (57.2-73.9)	
	Male	14.7 (13.2-16.8)	0.566	60.6 (47.4-83.0)	0.398	58.0 (54.3-74.4)	0.327
	Female	15.2 (13.4-17.2)		55.0 (43.5-83.0)		60.8 (54.3-73.9)	
PS1D	< 40 years	42.8 (35.5-52.5	0.83	155.5 (128.1-195.8)	0.423	110.1 (91.1-134.3)	**0.048**
	≥ 40 years	42.5 (32.2-50.2)		142.3 (125.6-177.5)		77.5 (63.2-120.4)	
	Male	38.7 (34.5-50.1)	0.106	143.6 (126.4-181.9)	0.479	100.5 (64.3-125.3)	0.701
	Female	45.0 (41.1-58.6)		156.9 (133.4-195.1)		95.3 (90.6-115.3)	
PS2D	< 40 years	48.9 (24.9-63.6)	0.984	183.9 (138.3-203.3)	0.47	121.2 (70.6-152.9)	0.257

	≥ 40 years	37.9 (27.2-66.8)		185.1 (173.5-203.4)		78.3 (53.2-154.7)	
	Male	39.7 (21.7-65.0)	0.363	179.3 (145.4-202.9)	0.125	78.3 (63.6-128.9)	0.13
	Female	43.5 (30.4-61.2)		190.9 (180.7-209.6)		135.6 (80.1-164.5)	
PP1D	< 40 years	28.4 (21.4-41.3)	0.257	89.5 (57.0-138.7)	1.0	71.6 (62.1-83.6)	0.653
	≥ 40 years	24.3 (19.7-29.4)		87.7 (61.1-122.1)		69.8 (64.8-77.1)	
	Male	25.1 (18.2-37.4)	0.185	89.6 (59.3-133.0)	0.828	70.8 (62.2-79.5)	0.566
	Female	27.6 (21.7-41.7)		89.5 (58.8-140.4)		70.0 (63.1-82.6)	
PP2D	< 40 years	69.6 (57.8-79.4)	0.184	198.2 (144.8-231.9)	0.86	109.1 (77.2-140.0)	0.47
	≥ 40 years	76.4 (66.4-88.8)		174.1 (147.1-231.2)		102.6 (78.8-129.9)	
	Male	68.9 (57.0-80.9)	0.191	201.5 (148.0-235.0)	0.878	107.3 (89.2-140.9)	0.797
	Female	73.3 (66.8-84.2)		178.5 (146.1-226.6)		106.4 (76.2-137.6)	

PR: 14-21 days post-recovery from COVID19; CTRL: Controls; PS1D: 21 days post-first dose of Sinopharm; PS1D: 21 days post-second dose of Sinopharm; PP1D: 21 days post-first dose of Pfizer-BioNTech; PP2D: 21 days post-second dose of Pfizer-BioNTech; p: Two-tailed probability of Mann-Whitney U test (significant p-value is indicated in bold).

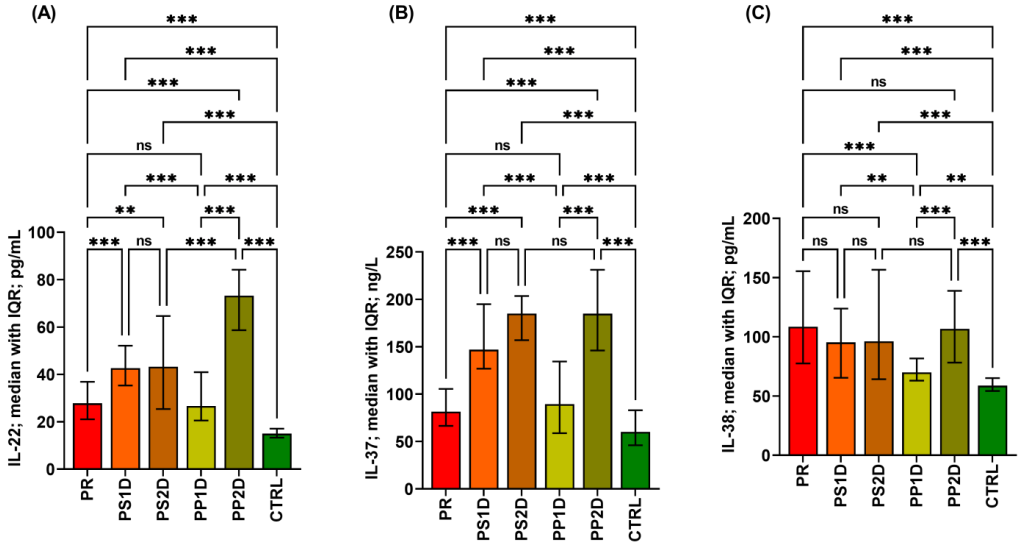

FIGURE 1: Column bar graph of serum IL-22 (A), IL-37 (B), and IL-38 (C) levels in the studied groups: PR (14-21 days post-recovery from COVID19; n = 100), PS1D (21 days post-first dose of Sinopharm; n = 50), PS2D (21 days post-second dose of Sinopharm; n = 50), PP1D (21 days post-first dose of Pfizer-BioNTech; n =50), PP2D (21 days post-second dose of Pfizer-BioNTech; n = 50), and CTRL (uninfected controls; n = 80). Columns indicate median. Bars indicate interquartile range (IQR). Significance was determined using Mann-Whitney U test (**p < 0.01; ***p < 0.001; ns: not significant).

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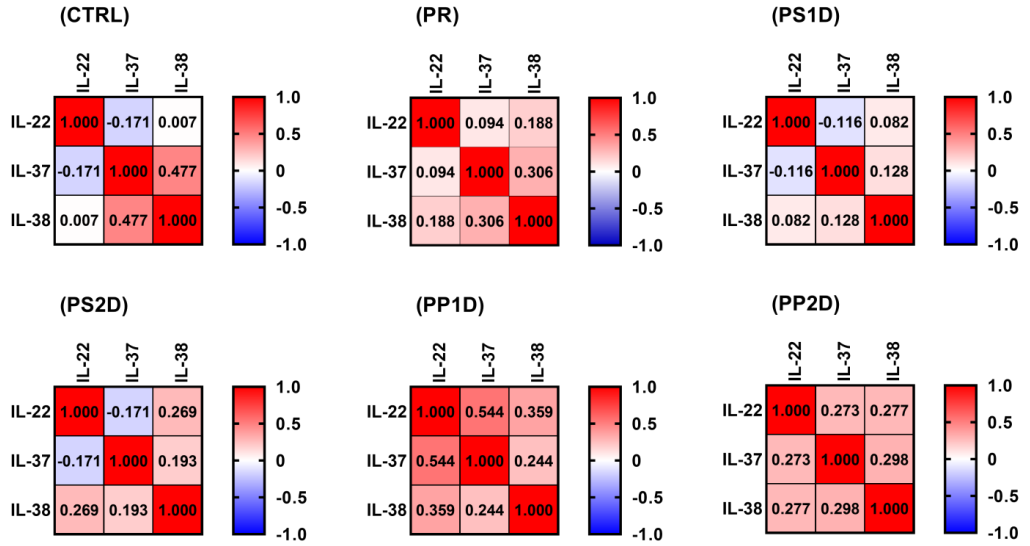

FIGURE 2: Heat-map of Spearman's correlations between serum IL-22, IL-37 and IL-38 levels measured in the studied groups: CTRL (uninfected controls; n = 80), PR (14-21 days post-recovery from COVID19; n = 100), PS1D (21 days post-first dose of Sinopharm; n = 50), PS2D (21 days post-second dose of Sinopharm; n = 50), PP1D (21 days post-first dose of Pfizer-BioNTech; n = 50), and PP2D (21 days post-second dose of Pfizer-BioNTech; n = 50). Values inside squares indicate the Spearman's correlation coefficient.

DISCUSSION

The immune system, through its cellular mediators and cytokines, plays an important role in controlling the SARS-CoV-2 infection, regardless of its exacerbation and severity. Examining the profile of cytokines and their interactions may contribute to expanding our understanding of their role in disease recovery or in response to vaccination. Among the important cytokines are IL-22, IL-37, and IL-38. Recent pieces of literature have indicated their association with the pathogenesis of SARS-CoV-2 infection due to their dysregulated levels in the serum of patients. However, this intended investigation clarifies these vague issues. The three cytokines' serum levels were assessed in patients following COVID-19 recovery on the one hand and in healthy individuals following two doses of Sinopharm or PfizerBioNTech vaccination on the other hand. In light of this, levels of IL-22, IL-37, and IL-38 were found to be up-regulated 14–21 days after recovery from COVID-19. In comparison, in the case of vaccination, there were also such changes in serum levels, but the pattern of these changes depended on the type of vaccine (Sinopharm or Pfizer-BioNTech) and its dose (first or second dose).

Inflammatory, anti-inflammatory, and natural cytokine antagonist cytokines are among the several cytokines that control the process of inflammation, and any imbalanced production of any of those pro- or anti-inflammatory cytokines is the key to triggering the inflammatory response that distinguishes COVID-19 pathophysiology. It is the outcome of successive inflammatory and anti-inflammatory immune activities, depending on the stage under study, and directed towards stopping further responses in those recovering from the infection or in recipients of the second dose of the vaccine and after successfully dealing with the antigen and going to the state of immune homeostasis.

IL-22 levels have been correlated with recovery from COVID-19 because they were significantly higher in the PR group than in the CTRL group. In addition, a higher level of elevation was recorded following the first and second doses of Sinopharm (PS1D and PS2D groups). A notable elevation was also recorded following the second dose of Pfizer-BioNTech (PP2D group), with the highest levels being found in this group. The production of cytokines such as IL-6, IL-7, IL-22, IL-17, and several others causes a severe cytokine storm during the COVID-19 fast advancement phase (Chi Y et al., 2020).

This increase in IL-22 levels could be attributed to its dual role as a protective or pathogenic factor during inflammatory and infectious diseases. (S. Ivanov et al., 2013). It has a role in tissue regeneration and regulation of host defense at barrier surfaces. It's also been linked to a number of inflammatory tissue conditions (Alcorn JF, 2020). Despite its protective role, IL-22 may be detrimental when it is not tightly regulated. Indeed, this cytokine contributes to the pathology observed in several inflammatory and autoimmune diseases. although it induces lung epithelial cells to express chemicals that attract neutrophils to sites of infection (D. Wu et al., 2020). IL-22 also reduces lung inflammation and maintains pulmonary epithelial integrity, an effect associated with a more controlled secondary bacterial infection after influenza. (S. Ivanov et al., 2013). IL-22's helpful effects on host defense have been investigated in a number of different ways. IL-22's roles in host defense against pathogens can be divided into three categories. First, by encouraging epithelial proliferation, IL-22 aids in maintaining and reestablishing the function of the epithelial barrier following infection. Second, like IL-17 and TNF-, IL-22 stimulates the production of antimicrobial proteins involved in host defense in the colon and airways. (Behnsen J. et al., 2014) Overall, IL-22's main purpose is to support the integrity of the mucosal barrier, which prevents bacterial multiplication and spread. As for what is related to IL-37, levels were significantly higher in the patient's sera post-recovery (PR) compared to controls (CTRL). Its levels were also significantly elevated in PS1D and PS2D compared to CTRL and PR, but there were no significant differences between PS1D and PS2D themselves. While at Pfizer-BioNTech, it was found that IL-37 levels were significantly higher in PP2D than in PP1D and even in PR in addition to CTRL. In PP1D, levels were significantly higher than those in CTRL, while no significant differences were found compared to PR. The particular characteristics of the given vaccine, the dosing schedule, and the variation in the immune status of the study participants all influence such discrepancies. The difference in therapeutic and nutritional protocols for patients also has a significant impact.

The recovery of COVID-19 was linked to an increase in IL-37, an anti-inflammatory cytokine that inhibits the production of a number of constitutive or induced pro-inflammatory cytokines (Liu W et al., 2020). TGF-β, an immunosuppressive cytokine, can also be increased by IL-37 (Nold MF et al., 2010).

Here, elevated levels of IL-37 properly downregulate pro-inflammatory cytokines, which in turn may be responsible for COVID-19's slower immunopathogenesis. For the first time, a recent study revealed that pro-inflammatory cytokines linked to inflammation in COVID-19, notably those of the IL-1 family, can be inhibited by IL-37 (Conti P et al., 2020).

Similarly, IL-38 levels were significantly higher in PR compared to CTRL. For those vaccinated with Sinopharm, IL-38 levels were significantly elevated in PS1D and PS2D compared to CTRL, while there were no significant differences compared to PR or between PS1D and PS2D themselves. Regarding Pfizer-BioNTech, both PP1D and PP2D showed significantly elevated levels of IL-38 compared to CTRL. Still, PP1D levels were significantly lower than PR, while no significant differences were found between PP2D and PR, and PP2D levels were significantly higher than PP1. Critically sick patients had lower levels of IL-38 than patients with less severe illnesses (Gao et al., 2021), demonstrating that elevated levels of IL-38 predict the course of healing via counterbalancing inflammatory cytokines.

Correlation analysis of IL-22, IL-37, and IL-38 was achieved in the CTRL, PR, PS1D, PS2D, PP1D, and PP2D groups (Figure 4). The CTRL and PR groups shared a significant positive correlation between IL-37 and IL-38; this finding could point towards a biological relationship between both interleukins. In PP1D, IL-22 showed significant positive correlations with IL-37 and IL-38. The SARS-CoV-2 infection's immunological mode of action is comparable to Pfizer's method and BioNTech's of producing virus-neutralizing antibodies. For PS1D, PS2D, and PP2D, no significant correlation was found between IL-22, IL-37, and IL-38.

The current findings and their implications lead us to believe that it may be crucial to use anti-inflammatory cytokines in a controlled manner in order to curb the overactive and harmful effects of inflammatory cytokines.

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In conclusion, recovery from COVID-19 was associated with lower levels of IL-37 and IL-38 molecules, but these levels were still significantly higher in recovered patients than in uninfected controls. Vaccination with Sinopharm or Pfizer-BioNTech confirmed the upregulating effects of SARS-CoV-2 on IL-22, IL-37, and IL-38 levels. Highly harmful virus copies could be prevented primarily through vaccination to fulfill herd immunity (Mahmood, 2020).

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