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Serum cytokine/chemokine profile and clinical/paraclinical data in COVID-19 deceased and recovered patients

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Abstract

Objectives: The induction of an intense immune response and cytokine storm is proposed to be central in the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The study evaluated serum cytokine/chemokine profiles, and clinical and paraclinical data of COVID-19 deceased and recovered patients in Iran. **Methods:** The severity of disease, clinical data, and routine laboratory and inflammatory cytokine/chemokine responses were retrospectively explored in 60 in-hospital patients in northern Iran. Characteristics of those who deceased (n = 30) were compared to recovered (n = 30), and associations with serum levels of potential disease regulating pro- and anti-inflammatory mediators were studied. **Results:** The serum levels of IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, IP-10, MIP1-α, MCP1, RANTES, and TNF-α were upregulated in all COVID-19 patients when compared to healthy and gender-matched individuals (n = 30). Although with no significant difference between deceased and recovered cases, the serum levels of all cytokines/chemokines tended to be higher in the severely diseased non-surviving patients. Association analyses revealed that all cytokine/chemokine levels (except IL-10) significantly affect the disease outcome. **Conclusion:** This study provides more evidence for the association of cytokine/chemokine levels with the clinical course and outcome of COVID-19. More studies are needed to consider this measurement as an indicator of disease stage and strategy for treatment.

Keywords

coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, cytokine/chemokine profile, clinical/paraclinical data

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Introduction

The coronavirus disease 2019 (COVID-19), caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has swept across the globe, infected more than 535 million people, and killed over 6.31 million.[1] While most develop a mild to moderate disease, the infection appears lethal in a significant proportion of patients (with the range of 3.3–8.8%).[1,2] Growing evidence on the pathogenesis of SARS-CoV-2 indicates a dysregulated and intense immune response as the leading contributor to disease development.[3,4] Although lessons from the previous coronaviruses can be drawn, there is still much to explore on whether SARS-CoV-2 behaves similarly to its predecessors or is characterized by peculiar specificities.[5]

The immune response triggered by SARS-CoV-2 infection acts as a "double-edged sword". A strong response is essential to eliminate viral pathogens, whereas a dysregulated and intense inflammatory response can damage the respiratory tract.[6,7] Studies show that underlying disease, old age, high viral titer, and sustained inflammation (known as cytokine storm) correlate with adverse outcomes of the virus infection.[8] An increased number of innate immune cells such as macrophages/monocytes and neutrophils, and high concentrations of different cytokines and chemokines, were found in critically ill COVID-19 patients.[9–16] It is well hypothesized that the intensity of the cytokine storm in these patients is associated with disease severity and outcomes.

So far, no effective treatment for COVID-19 has been successfully developed.[17] As declared, the intense and uncontrolled inflammation induced by SARS-CoV-2 leads to severe disease, increased morbidity, and mortality, so dampening and downregulating the inflammatory response and reducing its intensity could be a promising therapy.[18,19] Exploring broad with patients in different geographical areas and ethnical groups might pave the way toward controlling SARS-CoV-2 immunopathogenesis.[20] The challenges would be to increase knowledge and understand the physiopathology of COVID-19 and emerging mutants.

The hide-and-seek challenge of immune responses between the host and virus, understanding the viral-induced mechanisms that increase viral infectivity and lead to severe and fatal disease, and the associated intensity and character of the immune response need to be explored and understood. While many studies approved the association between serum cytokine profile and COVID-19 severity and outcome, there are no comprehensive studies from Iran. We aimed to find if any measure could reveal COVID-19 patients are at higher risk of dying.

Materials & Methods

This case-control study was performed on samples and data collected from patients hospitalized between February and December 2020 in the Golestan Province, north of Iran. Sixty confirmed COVID-19 cases, and 30 healthy subjects were enrolled in this study. The mean age for healthy, recovered, and deceased subjects were 40.00 ± 7.22, 56.97 ± 15.75, and 63.30 ± 13.71 years, respectively. The COVID-19 patients were confirmed positive by real-time RT-PCR assay targeting the SARS-CoV-2 nucleoprotein (N) and ORF1ab genes (Pishtazteb, Iran). Blood samples of patients were collected immediately after hospitalization. All COVID-19 patients were included in the severe group, with oxygen saturations <93% and arterial blood oxygen partial pressure (PaO2)/ oxygen concentration (FiO2) ≤ 300 mm Hg and needed intubation and admission to the intensive care unit (ICU). Patients were followed and divided into recovered (n = 30) and deceased (n = 30) groups. Serum samples from 30 healthy individuals collected before the pandemic (during 2018) were used as a control group. Data of age, gender, clinical symptoms and signs, and routine laboratory tests were collected from patient records at admission. The study was approved by the Ethics Committee of Golestan University of Medical Sciences (IR.GOUMS.REC.1399.007) and performed under the declaration of Helsinki for medical research involving human subjects.[21]

Serum samples were stored at −80°C until cytokine and chemokine analysis. The cytokines (IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-17, and TNF-α) and chemokines (IL-8, IP-10, MIP1-α, MCP1, and RANTES) levels were measured with commercial ELISA kits according to the manufacturer's instruction (Invitrogen, USA). The sensitivity of detection for IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, IP-10, MIP1-α, MCP1, RANTES and TNF-α were 4, 0.3, 9.1, 1.3, 1.5, 0.92, 5, 1, 2.1, 0.4, 2, 2, 2.3, 2, and 2.3 pg/mL, respectively. Demographic, clinical, and laboratory data and cytokine/chemokine levels were compared between groups and associations between groups done.

Statistical Analysis

Data were analyzed using SPSS22 software (SPSS Inc, Chicago, Illinois, USA). The normality status of the data was assessed with the Kolmogorov-Smirnov test. The Fisher exact test was used to distribute binary variables in the study groups. Comparing of the mean of continuous variables in the study groups was done using the Mann-Whitney U or Kruskal-Wallis tests, followed by paired comparison using the Tukey post-hoc test. Correlations were assessed by Spearman's rank correlation coefficient. Graphs were produced using SPSS22 software. The results were considered statistically significant if the p-values were <0.05.

Results

Of all cases, 41 (45.6%) and 49 (54.4%) were males and females, respectively. The mean age for healthy, recovered, and deceased subjects were 40.00 ± 7.22, 56.97 ± 15.75, and 63.30 ± 13.71 years, respectively, with significant differences in mean age between healthy, recovered, and deceased subjects ($p < .001$). Clinical data such as fever (61.7%), cough (41.7%), dyspnea (41.7%), headache (38.4%), myalgia (36.7%), sputum (18.3%), diarrhea (16.7%), sore throat (15%), and vomiting (8.3%) were obtained among COVID-19 patients (recovered and deceased). There were differences in symptoms such as dyspnea ($p = .001$), myalgia ($p < .001$), and sputum ($p = .02$) between deceased and recovered COVID-19 cases. Demographic and clinical data are shown in Table 1.

Laboratory data of WBC (White Blood Cells), RBC (Red Blood Cells), Hb (Hemoglobin), HCT (Hematocrit), MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin), MCHC (Mean Corpuscular Hemoglobin Concentration), PLT (Platelet Cells), RDW (Red Cell Distribution Width), MPV (Mean Platelet Volume), PDW (Platelet Distribution Width), P-LCR (Platelet-large cell ratio), ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), ALP (Alkaline Phosphatase), CPK (Creatinine Phosphokinase), LDH (Lactate Dehydrogenase), Mg (Magnesium), PMN (Polymorph Nuclear Leukocytes), Lymph (Lymphocyte), and electrolytes were statistically analyzed in all groups. The results revealed that ALP ($p < .001$), Calcium ($p < .001$), Phosphorus, ($p = .002$), PMN ($p = .003$), and monocyte counts ($p < .001$) were significantly higher, and PLT ($p = .036$) was significantly lower in deceased versus recovered. Moreover, significant differences were observed between COVID-19 patients and healthy subjects. Details of laboratory data are shown in Table 2.

ELISA analyses showed levels of IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, IP-10, MIP1-α, MCP1, RANTES, and TNF-α significantly higher in COVID-19 patients compared to healthy individuals (Figure 1 and Figure 2). Although with no significant difference between recovered and deceased cases, the serum levels of all cytokines/chemokines tended to be higher in the severely diseased non-surviving patients (supplementary File 1). Association analyses between cytokine/chemokine levels and clinical data revealed that all cytokine/chemokine levels (except IL-10) significantly affected the clinical course and outcome of COVID-19. Moreover, we found significant associations between MIP1-α with cough in the recovered group, IL-12 with dyspnea in the deceased group, MCP-1 with myalgia in recovered groups, IL-1β with dyspnea in the deceased and recovered groups, MIP1-α with headache in the deceased group, IL-6 and MIP1-α with diarrhea in the recovered group, and IP-10 with vomiting in deceased and recovered groups. Associations between cytokine/chemokine levels and clinical data are shown in Table 3.

Significant correlations between cytokine/chemokine levels and laboratory data were identified. In the deceased group, there were several correlations; IFN-γ with PDW, urea and ALP; IL-1β with LDH; IL-2 with Mg and eosinophils; IL-4 with MCHC, urea and Potassium; IL-5 with urea, creatinine, and Mg, IL-6 with Sodium; IL-8 with RDW, MPV, and LDH; IL-12 with MPV, PDW, P-LCR, and Calcium; IL-17 with PLT and Potassium; IP-10 with ALP; MCP-1 with Potassium; MIP1-α with PLT, MPV, PDW, P-LCR and Potassium; RANTES with MCHC and RDW, and TNF-α with RDW. In the recovered group, there was a significant correlation between levels of IFN-γ with PMN and eosinophils; IL-1β with PLT; IL-2 with Potassium and ALP; IL-4 with PLT; IL-5 with PLT and Lymph; IL-6 with RDW, AST, ALP, and LDH; IL-8 with PLT and

Table 1. Demographic and clinical data in healthy, recovered, and deceased cases.

Variables	Healthy, N (%)	Recovered, N (%)	Deceased, N (%)	*p*-value
Gender				
Female	16 (53.3)	18 (60)	15 (50)	0.73*
Male	14 (46.7)	12 (40)	15 (50)	
Age (Mean±SD)	40 ± 7.22	56.97 ± 15.75	63.30 ± 13.71	<0.001
Symptoms				
Fever	—	17 (56.7)	20 (66.7)	0.63**
Cough	—	13 (43.3)	12 (40)	0.50**
Dyspnea	—	8 (26.7)	17 (56.7)	0.001**
Headache	—	11 (36.7)	12 (40)	0.82**
Myalgia	—	19 (63.3)	3 (10)	<0.001**
Sputum	—	2 (6.7)	9 (30)	0.02**
Diarrhea	—	3 (10)	7 (23.3)	0.16**
Sore throat	—	5 (16.7)	4 (13.3)	0.500**
Vomiting	—	2 (6.7)	3 (10)	0.641**

*Chi square test, **Fisher exact test.

Table 2. Laboratory data in healthy, recovered, and deceased cases.

Variables	Group	Mean ± SD	*p*-value	Group	*p*-value	Group	*p*-value	Group	*p*-value
WBC (μ.l)	Deceased Healthy Recovered	10.11 ± 4.93 6.72 ± 1.93 10.31 ± 5.46	.003	Deceased Healthy	.004	Deceased Recovered	.998	Healthy Recovered	.005
RBC (μ.l)	Deceased Healthy Recovered	4.13 ± 0.35 4.67 ± 0.59 4.10 ± 0.63	<.001	Deceased Healthy	.001	Deceased Recovered	.95	Healthy Recovered	<.001
Hb (mg.dl)	Deceased Healthy Recovered	11.49 ± 1.78 12.06 ± 1.72 11.85 ± 2.7	.493	Deceased Healthy	—	Deceased Recovered	—	Healthy Recovered	—
HCT (%)	Deceased Healthy Recovered	34.80 ± 4.95 37.27 ± 4.18 35.57 ± 5.64	.148	Deceased Healthy	—	Deceased Recovered	—	Healthy Recovered	—
MCV (FL)	Deceased Healthy Recovered	86.22 ± 5.43 80.48 ± 7.43 87.25 ± 5.87	<.001	Deceased Healthy	.002	Deceased Recovered	.803	Healthy Recovered	<.001
MCH (pg)	Deceased Healthy Recovered	27.96 ± 2.22 26.18 ± 3.12 29.06 ± 2.03	<.001	Deceased Healthy	.020	Deceased Recovered	.207	Healthy Recovered	<.001
MCHC (%)	Deceased Healthy Recovered	34.45 ± 1.89 32.19 ± 1.40 33.33 ± 1.27	<.001	Deceased Healthy	<.001	Deceased Recovered	.170	Healthy Recovered	.014
PLT (mm3.µl)	Deceased Healthy Recovered	155.57 ± 79.64 239.57 ± 57.11 212 ± 114.21	.001	Deceased Healthy	.001	Deceased Recovered	.036	Healthy Recovered	.44
RDW (µm)	Deceased Healthy Recovered	47.36 ± 4.18 12.88 ± 0.43 47.15 ± 4.30	<.001	Deceased Healthy	<.001	Deceased Recovered	.978	Healthy Recovered	<.001
MPV(fl)	Deceased Healthy Recovered	10.25 ± 1.08 NA 9.94 ± 1.06	.257	Deceased Healthy	—	Deceased Recovered	—	Healthy Recovered	—
PDW (%)	Deceased Healthy Recovered	13.64 ± 3.28 NA 13.23 ± 2.88	.612	Deceased Healthy	—	Deceased Recovered	—	Healthy Recovered	—
P-LCR (ng.ml)	Deceased Healthy Recovered	27.31 ± 7.79 NA 26.30 ± 7.74	.60	Deceased Healthy	—	Deceased Recovered	—	Healthy Recovered	—
Urea (mg.dl)	Deceased Healthy Recovered	59.37 ± 56.55 30.77 ± 4.55 64.07 ± 50.26	.008	Deceased Healthy	.035	Deceased Recovered	.909	Healthy Recovered	.011
Creatinine (mg.dl)	Deceased Healthy Recovered	2.01 ± 1.73 1.07 ± 0.89 1.43 ± 1.16	.012	Deceased Healthy	.009	Deceased Recovered	.153	Healthy Recovered	.478
AST (IU.L)	Deceased Healthy Recovered	60.43 ± 65.69 22.66 ± 6.73 68.83 ± 140.60	.119	Deceased Healthy	.248	Deceased Recovered	.931	Healthy Recovered	.127
ALT (IU.L)	Deceased Healthy Recovered	57.47 ± 39.59 23 ± 8.04 42.50 ± 31.66	<.001	Deceased Healthy	<.001	Deceased Recovered	.129	Healthy Recovered	.033
ALP (IU.L)	Deceased Healthy Recovered	264.97 ± 87.89 173.48 ± 40.25 170.13 ± 77.89	<.001	Deceased Healthy	<.001	Deceased Recovered	<.001	Healthy Recovered	.986
LDH (U.L)	Deceased Healthy Recovered	856.13 ± 735.36 NA 645.80 ± 299.10	.152	Deceased Healthy	—	Deceased Recovered	—	Healthy Recovered	—

(continued)

Table 2. (continued)

Variables	Group	Mean ± SD	*p*-value	Group	*p*-value	Group	*p*-value	Group	*p*-value
CPK (U.L)	Deceased Healthy Recovered	413.97 ± 560.63 NA 147.73 ± 82.80	.013	Deceased Healthy	—	Deceased Recovered	—	Healthy Recovered	—
Mg (mEq.L)	Deceased Healthy Recovered	2.05 ± 0.55 NA 1.74 ± 0.26	.009	Deceased Healthy	—	Deceased Recovered	—	Healthy Recovered	—
Ca (mg.dl)	Deceased Healthy Recovered	8.05 ± 0.36 9.17 ± 0.36 8.88 ± 0.72	<.001	Deceased Healthy	<.001	Deceased Recovered	<.001	Healthy Recovered	.271
P (mg.dl)	Deceased Healthy Recovered	4.30 ± 0.60 3.87 ± 0.58 3.78 ± 0.49	.002	Deceased Healthy	<.001	Deceased Recovered	.002	Healthy Recovered	.889
Na (mEq.L)	Deceased Healthy Recovered	135.46 ± 23.12 NA 138.16 ± 3.97	.530	Deceased Healthy	—	Deceased Recovered	—	Healthy Recovered	—
K (mEq.L)	Deceased Healthy Recovered	3.96 ± 0.35 NA 4.08 ± 0.72	.418	Deceased Healthy	—	Deceased Recovered	—	Healthy Recovered	—
PMN (%)	Deceased Healthy Recovered	86.97 ± 5.98 56.97 ± 5.49 81.07 ± 8.21	<.001	Deceased Healthy	<.001	Deceased Recovered	.003	Healthy Recovered	<.001
Lymph (%)	Deceased Healthy Recovered	9.80 ± 6.08 38.63 ± 5.46 13.17 ± 8.08	<.001	Deceased Healthy	<.001	Deceased Recovered	.127	Healthy Recovered	<.001
Monocyte (%)	Deceased Healthy Recovered	1.60 ± 0.67 2.93 ± 1.01 2.90 ± 1.26	<.001	Deceased Healthy	<.001	Deceased Recovered	<.001	Healthy Recovered	.991
Eosinophil (%)	Deceased Healthy Recovered	1.53 ± 0.62 1.47 ± 0.83 1.87 ± 0.97	.135	Deceased Healthy	.947	Deceased Recovered	.262	Healthy Recovered	.147

WBC: White Blood Cells, RBC: Red Blood Cell, Hb: Hemoglobin, HCT: Hematocrit, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, PLT: Platelet Cells, RDW: Red Cell Distribution Width, MPV: Mean Platelet Volume, PDW: Platelet Distribution Width, P-LCR: Platelet-large cell ratio, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase, CPK: Creatinine Phosphokinase, LDH: Lactate Dehydrogenase, Mg: Magnesium, Ca: Calcium, P: Phosphorus, Na: Sodium, K: Potassium, PMN: Polymorph nuclear leukocytes, Lymph: Lymphocyte, NA: Not Available.

CPK; IL-10 with age and Sodium; IL-12 with MCV and MCH; IL-17 with HCT, PLT, and Sodium; IP-10 with ALT; MCP-1 with Phosphorus; MIP1-α with Sodium; RANTES with MCHC; TNF-α with WBC and Mg. The correlation between cytokine/chemokine levels and laboratory data is shown in Table 4.

Discussion

The present study confirms previous studies where fever, cough and dyspnea are the most common clinical symptoms in COVID-19 disease.[19,20] We found that some laboratory findings (ALP, Calcium, Phosphorus, PMN, monocyte counts, and PLT) are associated with an increased risk of death and may be considered predictors of disease severity. Also, significant differences were found between COVID-19 patients and healthy. Association analyses between cytokine/chemokine levels and clinical data revealed that cytokine/chemokine levels (except IL-10) were significantly associated with symptoms in COVID-19 patients. Previous studies have demonstrated that fever, cough, and sputum are the most common clinical symptoms and findings, whereas myalgia, diarrhea, and vomiting have been reported less common,[22,23] similar to reports on infections like seasonal influenza, SARS and MERS.[24,25] Reports on epidemiological characteristics of COVID-19 revealed that nearly 80% of patients are asymptomatic or have a mild disease.[26,27] In contrast, all individuals in this study had severe disease, and fever, cough, and dyspnea are the most frequently reported clinical findings in COVID-19 patients.[28]

Our data revealed early elevated LDH and PMN in COVID-19 patients compared to healthy, as well as low platelet counts. This implies that assessing inflammation

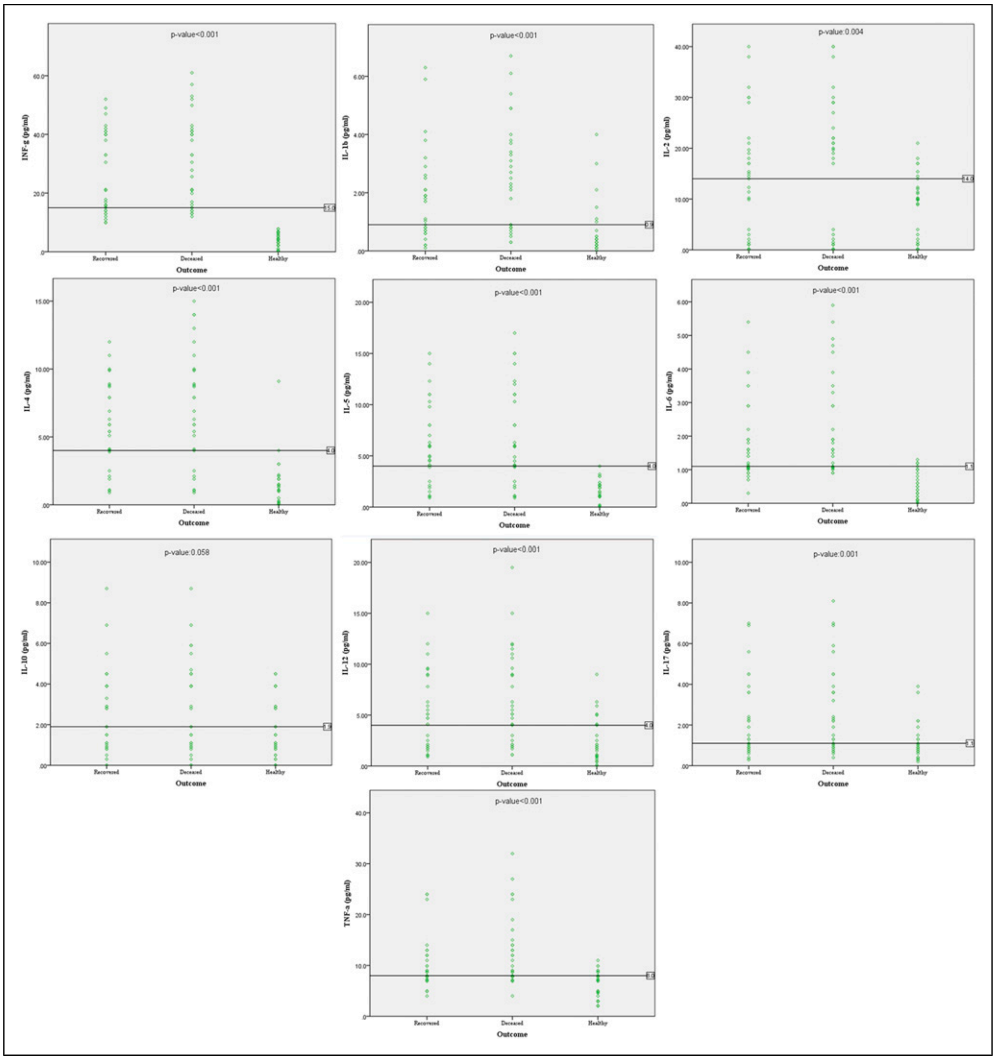

Figure 1. The levels of cytokines in healthy, recovered and deceased case. The serum concentration of IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-17, and TNF-α from 60 COVID-19 patients and 30 controls were analyzed immediately after hospital admission. Median with range was presented.

markers may be critical for early detection of suspected cases and may help in identifying patients at risk of developing severe disease.[29] Previous studies revealed that lymphopenia and albuminuria are other common findings,[28,30] in accordance with this study that found lymphopenia and/or an elevation in WBC as prognostic factors in COVID-19 patients. The marked lymphopenia may indicate that the virus directly or indirectly affect lymphocytes.[28] SARS-CoV-2 epidemiological studies showed lymphopenia, thrombocytopenia and leukocytosis, and increased levels of LDH, AST, ALT and creatinine, to be the frequently reported laboratory abnormalities.[31] This indicates that COVID-19 infection indirectly affects the liver and other organs.[32] This seems important as abnormal liver function and kidney tests are associated with increased mortality rates and poor prognosis[33,34] in line with our findings. Also, coagulation measures like PT and PTT seem to be important when evaluating prognosis in a COVID-19 patient, as well as decreased platelet counts.[35] Moreover, acute phase factors including CRP, LDH and ferritin are all associated with disease severity in COVID-19.[33] these elements could be considered to evaluate the patient's disease condition and prognosis.

SARS-CoV-2, crossing the respiratory barriers and invading host cells, lead to elevation of proinflammatory cytokine/chemokine and stimulation of the cytokine storm. Some of the biomarkers analyzed here, are potent anti-inflammatory cytokines that inhibits production of proinflammatory cytokines, supposed to result in a diminution of pathological inflammation, and these are activated in parallel with proinflammatory cytokines.[5] The complex network of cytokine/chemokine interactions in COVID-19

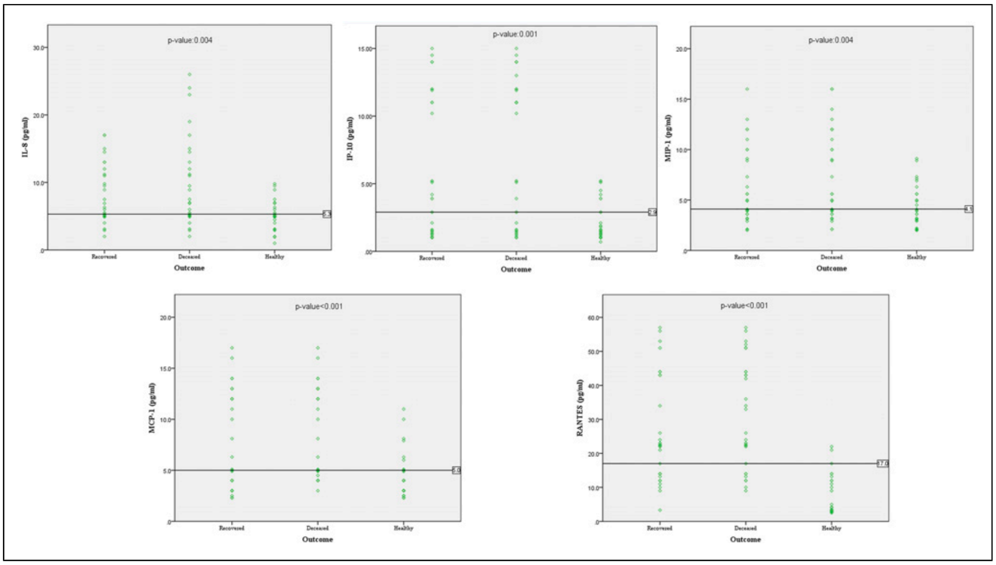

Figure 2. The levels of chemokines in healthy, recovered and deceased case. The serum concentration of IL-8, IP-10, MIP1-α, MCP1, and RANTES from 60 COVID-19 patients and 30 controls were analyzed immediately after hospital admission. Median with range was presented.

disease is therefore challenging to explore and understand and modulation of immune cell activation, recruitment and involvement in the inflammatory response. We examined expression levels of 15 cytokines/chemokines in deceased and recovered COVID-19 patients and healthy subjects. We detected over-expression of IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, IP-10, MIP-1, MCP1, RANTES, and TNF-α in COVID-19 patients compared to healthy subjects of both genders. However, none of these cytokines/chemokines were significantly different between recovered and deceased patients, although they tended to be higher in the deceased group (1.15-1.86-fold). These mediators have also been studied by Chen et al. who observed increased expression of IL-2R and IL-6, proposed to predict the severity of COVID-19 pneumonia and the prognosis of their patients.[36] While many studies approved the association between cytokine/chemokine profiles and COVID-19 clinical course and outcomes, there are no comprehensive studies in this area.

The elevation in IL-5 was correlated with lymphopenia and elevated IFN-γ level, one of the main acute phase cytokines, but with no difference between deceased and recovered patients. We found no difference in cytokine/chemokine patterns between deceased and recovered COVID-19 patients, in contrast to previously reported higher levels of IL-6 in ICU-admitted patients, compared to milder cases.[37] Chen et al. studied critical, severe and mild COVID-19 patients,[36] and in accordance with us found no differences in IL-1, IL-8 and TNF-α. In a study from China, the chemokine RANTES was significantly elevated in patients with mild but not severe disease, even in an early stage of infection.[29] In contrast, we found similar levels of RANTES in deceased and recovered patients, above levels in healthy individuals. We proved elevated IFN-γ levels compared to healthy, in accordance with a recent report on nucleoprotein-related IFN-γ secretion in COVID-19 patients.[38] Hu et al. studied recovered COVID-19 patients and found elevated levels of IFN-γ to protect against development of lung fibroses.[39] While the study did not evaluated outcomes such as lung fibrosis in this study, we noticed similar levels of IFN-γ in recovered and deceased patients. Previous studies have suggested that IL-1β and IL-6 are key pro-inflammatory biomarkers in initiation of the acute phase response, resulting in a broad range of local and systemic events such as fever and recruitment of leukocytes.[18,19] Increased IL-17 in patients with COVID-19 pneumonia has been observed in other studies,[40] and Th-17 cells contribute in the cytokine storm triggered by SARS-CoV-2.[41] Further, elevations of IL-2, IL-4 and IL-17 levels are observed in COVID-19 patients' serums with prominent lung damage.[40] Studies on TNF-α highlight differences in immunological responses during COVID-19 infection, dependent on disease severity.[5] Due to several studies reporting an increase in TNF-α, it has been proposed that TNF-α should be the target for immunoregulatory therapies in COVID-19 disease.[19,20]

SARS-CoV-2 has been reported to stimulate IL-1β increase that sequentially triggers elevation of other pro-inflammatory cytokines, including IL-6 and TNF-α.[16] Although, we detected elevation of such cytokines in COVID-19 patients, we could not show different levels in deceased compared to recovered patients. We assessed

Table 3. Association between cytokine/chemokine levels and clinical data.

Variables		IFN-γ	IL-1β	IL-2	IL-4	IL-5	IL-6	IL-8	IL-10	IL-12	IL-17	IP-10	MCP-1	MIP-1α	RANTES	TNF-α
Outcome																
Deceased		30.66 ± 14.98	2.47 ± 1.84	18.45 ± 12.79	7.26 ± 4.13	7.12 ± 4.65	2.32 ± 1.49	9.65 ± 6.59	2.99 ± 2.25	6.59 ± 4.58	2.78 ± 2.17	7.13 ± 5.30	8.39 ± 4.41	7.23 ± 4.33	30.85 ± 15.59	12.92 ± 6.91
Healthy		3.99 ± 2.22	0.64 ± 0.90	9.15 ± 5.91	1.53 ± 1.73	1.67 ± 0.89	0.47 ± 0.41	5.17 ± 2.05	1.73 ± 1.47	2.37 ± 2.15	1.07 ± 0.89	2.22 ± 1.42	4.39 ± 2.28	4.10 ± 2.14	7.25 ± 5.88	6.42 ± 2.55
Recovered		26.19 ± 13.8	1.90 ± 1.55	14.94 ± 11.69	5.98 ± 3.20	6.09 ± 3.88	1.76 ± 1.20	8.05 ± 4.31	2.63 ± 2.10	5.02 ± 3.77	2.17 ± 1.91	5.85 ± 5.06	7.29 ± 480	6.24 ± 3.76	26.09 ± 15.50	10.35 ± 5.12
***p*-value**		<.001	<.001	.004	<.001	<.001	<.001	.004	.058	<.001	.001	.001	<.001	.004	<.001	<.001
Deceased	**Male**	29.43 ± 12.76	2.51 ± 1.98	21.61 ± 13.14	8.84 ± 3.80	7.73 ± 4.63	2.27 ± 1.71	9.80 ± 7.59	2.92 ± 2.09	5.61 ± 3.83	2.74 ± 2.29	6.35 ± 4.89	7.32 ± 4.20	6.95 ± 4.49	29.35 ± 13.68	10.72 ± 5.61
	Female	31.90 ± 17.29	2.42 ± 1.75	15.30 ± 12.04	5.68 ± 3.95	6.52 ± 4.75	2.37 ± 1.30	9.50 ± 5.69	3.06 ± 2.48	7.58 ± 5.16	2.83 ± 2.12	7.92 ± 5.74	9.46 ± 4.50	7.50 ± 4.31	32.34 ± 17.64	15.11 ± 7.56
***p*-value**		.693	.88	.394	.29	.29	.547	.64	.91	.299	.83	.289	.218	.575	.589	.056
Healthy	**Male**	3.52 ± 1.89	0.79 ± 1.19	9.76 ± 6.30	1.46 ± 1.14	1.92 ± 1.02	0.50 ± 0.47	5.46 ± 2.65	1.96 ± 1.73	2.42 ± 2.11	1.20 ± 0.92	2.00 ± 1.20	3.75 ± 1.24	4.42 ± 2.35	8.69 ± 6.33	6.77 ± 2.42
	Female	4.40 ± 2.45	0.50 ± .57	8.61 ± 5.71	1.59 ± 2.16	1.44 ± 0.72	0.44 ± 0.36	4.91 ± 1.38	1.53 ± 1.23	2.33 ± 2.24	0.96 ± 0.88	2.41 ± 1.60	4.96 ± 2.83	3.81 ± 1.96	6 ± 5.34	6.11 ± 2.69
***p*-value**		.252	.80	.983	.69	.21	.917	.63	.80	.917	.21	.771	.389	.545	.453	.33
Recovered	**Male**	21.85 ± 12.01	1.81 ± 1.58	13.45 ± 10.78	6.01 ± 3.32	6.35 ± 4.48	1.73 ± 1.03	6.62 ± 3.06	3.05 ± 2.43	6.05 ± 4.18	2.49 ± 2.37	6.15 ± 5.25	7.1 ± 5.01	5.74 ± 3.41	27.51 ± 17.35	10.90 ± 6.45
	Female	29.08 ± 14.47	1.96 ± 1.57	15.93 ± 12.47	5.96 ± 3.22	5.91 ± 3.55	1.78 ± 1.32	9.01 ± 4.81	2.36 ± 1.87	4.34 ± 3.42	1.95 ± 1.58	5.64 ± 5.08	7.42 ± 4.79	6.57 ± 4.03	25.14 ± 14.59	9.98 ± 4.19
***p*-value**		.362	.91	.672	.83	.81	.735	.35	.45	.290	.73	.932	.671	.687	.983	.58
Fever																
Deceased	**Yes**	32.38 ± 16.65	2.76 ± 1.94	17.12 ± 12.80	6.73 ± 3.92	7.14 ± 4.80	2.30 ± 1.47	9.41 ± 6.45	3.13 ± 2.13	7.13 ± 4.93	3.15 ± 2.45	6.99 ± 5.19	8.24 ± 4.23	7.72 ± 4.60	31.05 ± 15.94	13.20 ± 7.03
	No	27.2 ± 10.88	1.88 ± 1.54	21.13 ± 13	8.34 ± 4.54	7.10 ± 4.58	2.36 ± 1.62	10.14 ± 7.20	2.71 ± 2.57	5.52 ± 3.77	2.05 ± 1.26	7.41 ± 5.79	8.70 ± 4.98	6.25 ± 3.78	30.45 ± 15.70	12.35 ± 7.01
***p*-value**		.538	.194	.523	.32	.93	.930	.89	.64	.367	.28	.965	.723	.209	.965	.71
Recovered	**Yes**	28.30 ± 13.63	1.95 ± 1.3	15.12 ± 11.80	5.18 ± 3.11	6.35 ± 3.31	2.35 ± 1.40	8.96 ± 4.55	2.63 ± 2.10	5.13 ± 2.93	2.17 ± 1.91	5.99 ± 5.19	6.40 ± 4.23	6.72 ± 4.65	26.05 ± 11.94	10.35 ± 5.12
	No	26.8 ± 12.88	1.90 ± 1.55	14.13 ± 9.21	5.98 ± 3.20	6.09 ± 3.88	1.36 ± 1.62	8.05 ± 4.31	2.45 ± 2.11	4.62 ± 3.75	1.98 ± 1.75	5.41 ± 4.79	5.70 ± 3.98	6.25 ± 3.88	25.45 ± 11.70	9.86 ± 4.96
***p*-value**		.621	.43	.498	.61	.56	.846	.67	.95	.695	.45	.951	.965	.469	.841	.44
Cough																
Deceased	**Yes**	26.53 ± 12.23	2.20 ± 2.12	13.92 ± 12.54	7.31±4.64	5.16 ± 3.45	1.99 ± 1.13	8.15 ± 5.53	2.45 ± 2.03	6.74 ± 4.51	2.96 ± 2.39	5.50 ± 5.20	8.26 ± 4.28	8.83 ± 4.18	30.37 ± 16.03	14.79 ± 7.88
	No	33.42 ± 16.31	2.64 ± 1.66	21.47 ± 12.37	7.23 ± 3.90	8.43 ± 4.96	2.54 ± 1.69	10.65 ± 7.19	3.34 ± 2.38	6.50 ± 4.75	2.67 ± 2.07	8.22 ± 5.22	8.47 ± 4.62	6.16 ± 4.21	31.16 ± 15.75	11.67 ± 6.10
***p*-value**		.299	.26	.054	.76	.09	.656	.58	.24	.916	.62	.175	.815	.051	.899	.25
Recovered	**Yes**	22.87 ± 13.33	1.64 ± 0.64	11.77 ± 10.58	6.04 ± 3.73	5.11 ± 3.30	1.39 ± 0.673	8.22 ± 4.62	2.56 ± 2.01	5.01 ± 4.64	2.02 ± 1.85	4.47 ± 3.98	7.37 ± 4.65	7.86 ± 3.90	25.26 ± 14.98	12.35 ± 6.86
	No	28.73 ± 14	2.10 ± 1.49	17.37 ± 12.23	5.93 ± 2.85	6.83 ± 4.21	2.05 ± 1.43	7.83 ± 4.03	2.68 ± 2.23	5.04 ± 3.10	2.28 ± 2.01	6.90 ± 5.65	7.22 ± 5.05	5 ± 3.22	26.72 ± 16.32	8.81 ± 2.56
***p*-value**		.315	.39	.187	.86	.35	.544	.95	.96	.476	.98	.335	.801	.016	.917	.18
Sputum																
Deceased	**Yes**	28.16 ± 16.71	2.13 ± 1.66	15 ± 13.95	5.85 ± 4.69	5.12 ± 4.15	2.38 ± 1.51	9.77 ± 7.29	4.11 ± 2.58	7.75 ± 4.83	3.32 ± 2.09	6.69 ± 5.33	8.20 ± 4.99	7.70 ± 4.40	26.50 ± 16.50	12.76 ± 5.11
	No	31.73 ± 14.49	2.61 ± 1.93	19.93 ± 12.31	7.87 ± 3.83	7.98 ± 4.67	2.29 ± 1.52	9.60 ± 6.46	2.51 ± 1.97	6.11 ± 4.49	2.56 ± 2.21	7.32 ± 5.41	8.47 ± 4.27	7.02 ± 4.41	32.71 ± 15.21	12.98 ± 7.67
***p*-value**		.455	.61	.341	.23	.10	0964	.92	.18	.287	.27	.856	.802	.454	.330	.54
Recovered	**Yes**	15 ± 0.01	1.75 ± 1.20	9.55 ± 10.53	3.90 ± 4.24	6.60 ± 8.06	2.75 ± 2.47	4.60 ± 2.40	6.60 ± 2.96	6.31 ± 4.66	2.25 ± 1.90	9.21 ± 7.49	10 ± 9.89	5.61 ± 4.94	32.5 ± 28.99	9.10 ± 2.68
	No	26.99 ± 13.95	1.91 ± 1.59	15.33 ± 11.85	6.13 ± 3.16	6.05 ± 3.71	1.69 ± 1.11	8.30 ± 4.33	2.35 ± 1.78	4.93 ± 3.79	2.16 ± 1.95	5.61 ± 4.96	7.1 ± 4.53	6.28 ± 3.77	25.63 ± 14.96	10.43 ± 5.27
***p*-value**		.318	.73	.647	.36	.86	.739	.27	.37	.454	.83	.261	.616	.647	.835	.73
Myalgia																
Deceased	**Yes**	33.54 ± 15.67	2.45 ± 1.90	19.43 ± 12.64	7.46 ± 3.78	7.47 ± 4.60	2.25 ± 1.48	10.49 ± 7.39	2.44 ± 1.73	8.01 ± 4.86	3.15 ± 2.20	7.59 ± 4.78	7.92 ± 4.11	7.82 ± 4.53	29.33 ± 14.12	13.384 ± 7.51
	No	25.71 ± 12.89	2.49 ± 1.82	16.76 ± 13.48	6.92 ± 4.86	6.53 ± 4.89	2.44 ± 1.58	8.20 ± 4.90	3.93 ± 2.79	4.16 ± 2.83	2.15 ± 2.05	6.34 ± 6.26	9.21 ± 5.01	6.21 ± 3.96	33.47±18.27	12.11 ± 6.05
***p*-value**		.212	.98	.635	.62	.54	.714	.63	.10	.020	.14	.518	.729	.211	.651	.73
Recovered	**Yes**	25.61 ± 12.78	3.03 ± 2.84	13.1 ± 21.59	4.43 ± 2.89	4.46 ± 2.91	1.81 ± 0.41	10.30 ± 6.12	1.13 ± 1.0	4.31 ± 2.81	1.80 ± 0.87	1.51 ± 0.55	13.33 ± 0.57	5.73 ± 3.72	27.11 ± 21.22	13.26 ± 8.45
	No	26.21 ± 14.13	1.77 ± 1.37	15.15 ± 10.78	6.15 ± 3.24	6.27 ± 3.97	1.76 ± 1.26	7.80 ± 4.14	2.80 ± 2.13	5.10 ± 3.90	2.21 ± 2.02	6.33 ± 5.12	6.62 ± 4.58	6.30 ± 3.83	25.98 ± 15.28	10.02 ± 4.76
***p*-value**		.756	.46	.468	.53	.72	.316	.51	.20	.945	.86	.067	.026	.782	.890	.53
Dyspnea																
Deceased	**Yes**	34.03 ± 14.56	3.08 ± 2.11	16.84 ± 12.66	6.96 ± 3.84	6.11 ± 3.78	1.89 ± 1.04	9.96 ± 7.53	2.65 ± 1.97	7.07 ± 4.64	2.54 ± 2.39	7.51 ± 5.21	8.91 ± 4.24	7.94 ± 4.25	31.57 ± 14.78	13.33 ± 5.79
	No	26.26 ± 14.93	1.66 ± 1.01	20.56 ± 13.16	7.66 ± 4.61	8.44±5.46	2.88 ± 1.83	9.25 ± 5.40	3.43 ± 2.59	5.97 ± 4.61	3.11±1.89	6.63 ± 5.59	7.73 ± 4.71	6.31 ± 4.43	29.91 ± 17.18	12.60 ± 7.82
***p*-value**		.149	.044	.489	.75	.32	.285	.95	.43	.391	.23	.276	.255	.216	.769	.52
Recovered	**Yes**	28 ± 13.40	2.98 ± 1.02	17.56 ± 10.23	4.56 ± 2.36	6.51 ± 35	2.06 ± 1.30	8.15 ± 3.98	2.63 ± 2.10	6.86 ± 3.21	1.63 ± 0.42	5.21 ± 4.25	6.98 ± 3.64	6.95 ± 3.20	27.85 ± 1.41	10.35 ± 5.12
	No	26.19 ± 13.80	1.01 ± 1.15	14.94 ± 11.69	5.98 ± 3.20	6.09 ± 3.88	1.76 ± 1.21	8.0567 ± 4.31	1.96 ± 1.45	5.02 ± 3.77	2.17 ± 1.91	5.85 ± 5.16	7.29 ± 4.81	6.24 ± 3.76	26.09 ± 15.52	9.88 ± 4.13
***p*-value**		.458	.050	.647	.31	.41	.397	.42	.28	.632	.41	.436	.541	.841	.541	.85
Sore throat																
Deceased	**Yes**	31.52 ± 18.26	3.05 ± 1.74	14.87 ± 16.31	3.77 ± 1.34	7.22 ± 6.71	2.27 ± 1.12	6.45 ± 5.53	3.12 ± 3.00	3.77 ± 1.34	1.92 ± 1.75	4.42 ± 5.03	7.72 ± 4.59	3.52 ± 0.95	39.75 ± 18.83	10.40 ± 3.19
	No	30.53 ± 14.84	2.38 ± 1.87	19.01 ± 12.47	7.80 ± 4.16	7.11 ± 4.43	2.33 ± 1.56	10.15 ± 6.70	2.96 ± 2.19	7.03 ± 4.75	2.92 ± 2.22	7.55 ± 5.31	8.49 ± 4.47	7.81 ± 4.38	29.4 ± 14.99	13.30 ± 7.28

(continued)

Table 3. (continued)

Variables		IFN-γ	IL-1β	IL-2	IL-4	IL-5	IL-6	IL-8	IL-10	IL-12	IL-17	IP-10	MCP-1	MIP-1α	RANTES	TNF-α
p-value		.976	.39	.669	.54	.83	.783	.20	.85	.189	.44	.328	.539	.076	.285	.56
Recovered	**Yes**	34.61 ± 17.27	2.70 ± 1.14	14.30 ± 12.89	4.10 ± 1.37	5.84 ± 3.15	1.99 ± 1.14	8.16 ± 6.13	2.66 ± 2.18	5.36 ± 3.38	2.66 ± 2.23	4.58 ± 4.37	4.68 ± 3.11	3.94 ± 1.24	30.31 ± 16.43	10.92 ± 3.002
	No	24.51 ± 12.76	1.74 ± 1.59	15.07 ± 11.72	6.36 ± 3.34	6.14 ± 4.06	1.72 ± 1.22	8.03 ± 4.02	2.63 ± 2.13	4.96 ± 3.91	2.07 ± 1.88	6.11 ± 5.24	7.81 ± 4.95	6.71 ± 3.93	25.25 ± 15.53	10.23 ± 5.49
p-value		.172	.97	.978	.14	.98	.597	.80	.91	.636	.50	.802	.154	.253	.559	.32
Headache																
Deceased	**Yes**	32.21 ± 14.71	2.73 ± 2.35	15.83 ± 12.91	7.44 ± 4.11	5.64 ± 3.29	2.17 ± 1.36	11.86 ± 7.89	3.25 ± 1.96	7.32 ± 4.47	2.97 ± 2.55	6.99 ± 5.01	8.29 ± 4.64	9.46 ± 4.43	25.61 ± 12.23	14.05 ± 8.57
	No	29.49 ± 15.53	2.26 ± 1.37	20.45 ± 12.71	7.12 ± 4.27	8.26 ± 5.28	2.43 ± 1.62	7.97 ± 5.01	2.78 ± 2.49	6.04 ± 4.71	2.64 ± 1.90	7.24 ± 5.66	8.47 ± 4.37	5.52 ± 3.49	34.86 ± 17.12	12.05 ± 5.45
p-value		.691	.73	.335	.72	.18	.850	.17	.50	.267	.96	.675	.768	.007	.154	.63
Recovered	**Yes**	34.25 ± 5.31	4.00 ± 2.68	10 ± 9.89	7.90 ± 2.82	6.95 ± 1.48	1.15 ± 0.63	8.55 ± 4.87	2.9 ± 0.01	3.9 ± 2.82	0.55 ± 0.21	9.55 ± 6.29	10 ± 8.48	8.45 ± 6.43	22 ± 1.41	7.90 ± 0.14
	No	25.62 ± 14.08	1.75 ± 1.40	15.31 ± 11.89	5.84 ± 3.23	6.02 ± 4.0	1.81 ± 1.22	8.02 ± 4.36	2.61 ± 2.17	5.10 ± 3.86	2.28 ± 1.93	5.58 ± 5.01	7.11 ± 4.63	6.08 ± 3.64	26.38 ± 16.03	10.52 ± 5.26
p-value		.506	.12	.708	.33	.50	.405	.80	.61	.901	.061	.228	.428	.559	.967	.53
Diarrhea																
Deceased	**Yes**	33.12 ± 13.40	2.64 ± 2.02	18.80 ± 13.28	7.67 ± 3.81	7.87 ± 5.44	2.89 ± 1.79	8.74 ± 7.99	2.32 ± 1.67	8.50 ± 3.94	2.62 ± 2.28	10.01 ± 3.20	7.28 ± 3.83	7.85 ± 5.33	37.85 ± 16.62	14.37 ± 8.89
	No	29.91 ± 15.63	2.41 ± 1.82	18.35 ± 12.94	7.14 ± 4.30	6.90 ± 4.49	2.15 ± 1.39	9.93 ± 6.29	3.19 ± 2.40	6.01 ± 4.68	2.83 ± 2.18	6.25 ± 5.56	8.73 ± 4.61	7.03 ± 4.11	28.71 ± 15	12.47 ± 6.37
p-value		.462	.75	.864	.62	.75	.269	.31	.44	.105	.82	.202	.388	.863	.134	.86
Recovered	**Yes**	29.33 ± 13.86	1.30 ± 1.66	18.91 ± 11.54	9.56 ± 2.15	10.16 ± 7.52	3.61 ± 1.96	8.33 ± 7.55	0.96 ± 0.11	4.21 ± 4.16	1.73 ± 1.69	4.78 ± 6.25	4.81 ± 2.98	2.66 ± 0.58	31 ± 22.11	8.23 ± 1.49
	No	25.84 ± 14.015	1.96 ± 1.55	14.50 ± 11.84	5.58 ± 3.07	5.63 ± 3.21	1.56 ± 0.93	8.02 ± 4.03	2.82 ± 2.13	5.11 ± 3.80	2.22 ± 1.96	5.97 ± 5.05	7.57 ± 4.92	6.64 ± 3.75	25.54 ± 15.08	10.58 ± 5.34
p-value		.729	.32	.604	.61	.25	.049	.55	.14	.678	.67	.350	.331	.011	.489	.40
Vomiting																
Deceased	**Yes**	36.6 ± 21.40	3.20 ± 2.30	21.36 ± 20.07	6.34 ± 6.79	5.71 ± 5.65	1.29 ± 0.53	12.06 ± 6.54	4.20 ± 1.57	12.16 ± 7.20	4.56 ± 3.30	13.66 ± 1.52	9.66 ± 4.04	7.76 ± 3.02	31.83 ± 16.60	12.63 ± 2.56
	No	30.01 ± 14.51	2.38 ± 1.81	18.13 ± 12.26	7.37 ± 3.92	7.28 ± 4.62	2.43 ± 1.53	9.38 ± 6.67	2.85 ± 2.30	5.97 ± 3.92	2.59 ± 2.01	6.41 ± 5.07	8.25 ± 4.50	7.17 ± 4.51	30.74 ± 15.80	12.95± 7.26
p-value		.489	.44	.678	.55	.51	.146	.28	.29	.084	.31	.019	.602	.510	.972	.44
Recovered	**Yes**	16 ± 7.07	0.56 ± 0.21	27 ± 18.38	4.05 ± 0.07	6.95 ± 4.03	0.98 ± 0.12	10.50 ± 0.98	1.80 ± 1.41	7.3 ± 3.11	0.85 ± 0.07	14.5 ± 0.70	12 ± 0.0	9.15 ± 2.61	22.25 ± 0.35	7.45 ± 3.46
	No	26.92 ± 13.94	1.99 ± 1.56	14.08 ± 11.08	6.12 ± 3.27	6.02 ± 3.94	1.82 ± 1.22	7.88 ± 4.41	2.69 ± 2.14	4.86 ± 3.81	2.26 ± 1.95	5.23 ± 4.65	6.95 ± 4.79	6.03 ± 3.77	26.36 ± 16.03	10.5 ± 5.20
p-value		.298	.10	.280	.33	.80	.170	.27	.45	.261	.26	.027	.210	.182	.934	.47

Table 4. Correlation between cytokine/chemokine levels and laboratory data.

Outcome	Variables	IFN-γ	IL-1β	IL-2	IL-4	IL-5	IL-6	IL-8	IL-10	IL-12	IL-17	IP-10	MCP-1	MIP-1α	RANTES	TNF-α
Deceased	**WBC (μl)**	r = 0.219	0.325	−0.232	−0.058	0.023	−0.069	0.031	0.046	0.193	0.112	0.009	−0.035	0.355	−0.044	0.064
		p = 0.245	0.080	0.218	0.761	0.905	0.716	0.869	0.810	0.307	0.555	0.960	0.853	0.054	0.818	0.737
	RBC (μ/l)	r = 0.136	0.020	0.126	−0.103	−0.096	−0.246	0.055	0.286	0.178	−0.107	−0.169	0.108	0.184	−0.218	0.272
		p = 0.474	0.918	0.505	0.586	0.612	0.189	0.773	0.125	0.347	0.574	0.371	0.570	0.330	0.247	0.145
	Hb (mg/dl)	r = 0.280	0.300	−0.012	−0.199	0.017	−0.073	0.013	−0.033	0.085	0.069	0.271	0.027	0.119	0.180	−0.199
		p = 0.134	0.107	0.952	0.291	0.930	0.700	0.945	0.863	0.654	0.719	0.147	0.886	0.531	0.340	0.292
	HCT (%)	r = 0.268	0.225	0.047	−0.112	−0.051	−0.048	0.103	0.001	0.066	−0.059	0.242	0.115	0.187	0.231	−0.219
		p = 0.152	0.232	0.804	0.554	0.790	0.802	0.588	0.996	0.728	0.757	0.199	0.544	0.322	0.219	0.245
	MCV (fl)	r = 0.130	−0.053	0.255	−0.015	−0.087	0.007	0.324	−0.345	−0.051	0.006	−0.153	0.329	0.184	0.028	0.185
		p = 0.495	0.782	0.174	0.937	0.646	0.971	0.081	0.062	0.791	0.975	0.419	0.076	0.331	0.881	0.327
	MCH (pg)	r = 0.275	−0.074	0.281	0.002	0.085	−0.033	0.348	−0.060	0.087	0.253	0.253	−0.184	0.010	−0.234	0.060
		p = 0.142	0.698	0.133	0.991	0.657	0.861	0.059	0.754	0.649	0.177	0.178	0.331	0.956	0.214	0.751
	MCHC (%)	r = 0.002	0.096	0.048	−0.578**	0.045	0.116	0.000	0.147	0.149	0.162	0.145	0.128	−0.223	0.371*	−0.027
		p = 0.993	0.615	0.801	0.001	0.813	0.540	0.998	0.437	0.431	0.393	0.444	0.501	0.235	0.044	0.889
	PLT (mm3/μl)	r = 0.254	0.182	−0.087	−0.037	−0.182	0.092	−0.016	0.018	0.319	0.394*	0.125	0.048	0.387*	−0.183	0.302
		p = 0.176	0.337	0.646	0.845	0.336	0.630	0.931	0.924	0.086	0.031	0.509	0.802	0.035	0.334	0.104
	RDW (μm)	r = −0.058	−0.197	0.054	0.245	0.001	−0.242	0.324	0.149	0.164	0.088	0.106	−0.135	0.242	−0.398*	0.373*
		p = 0.761	0.298	0.776	0.192	0.997	0.198	0.080	0.431	0.387	0.643	0.576	0.478	0.197	0.029	0.042
	MPV (fl)	r = 0.328	−0.037	−0.223	−0.177	−0.289	−0.090	0.364*	−0.042	0.415*	0.298	0.098	0.160	0.568**	−0.102	0.312
		p = 0.077	0.844	0.237	0.348	0.121	0.635	0.048	0.825	0.022	0.109	0.606	0.398	0.001	0.593	0.094
	PDW (%)	r = 0.407*	−0.051	−0.101	−0.099	−0.131	−0.051	0.266	−0.054	0.461*	0.196	0.115	0.186	0.510**	0.006	0.296
		p = 0.026	0.790	0.595	0.603	0.490	0.790	0.155	0.777	0.010	0.299	0.545	0.325	0.004	0.975	0.112
	P-LCR (ng/ml)	r = 0.355	−0.095	−0.105	−0.071	−0.148	−0.155	0.325	−0.032	0.484**	0.230	0.119	0.158	0.590**	−0.055	0.293
		p = 0.054	0.618	0.582	0.709	0.435	0.414	0.080	0.866	0.007	0.220	0.533	0.404	0.001	0.774	0.116
	Urea (mg/dl)	r = 0.416*	0.130	0.063	0.425*	0.389*	−0.080	0.167	−0.242	−0.065	0.037	−0.097	−0.291	0.030	−0.161	−0.136
		p = 0.022	0.493	0.742	0.019	0.034	0.674	0.377	0.198	0.732	0.848	0.610	0.118	0.876	0.396	0.474
	Cr (mg/dl)	r = 0.267	0.186	0.272	0.177	0.405*	−0.054	0.348	0.002	−0.061	−0.088	−0.032	0.072	0.000	0.044	−0.280
		p = 0.153	0.325	0.146	0.350	0.026	0.778	0.059	0.990	0.749	0.644	0.865	0.705	0.999	0.816	0.134
	AST(IU/L)	r = −0.206	−0.220	−0.030	0.215	−0.100	−0.217	−0.092	0.083	−0.034	0.132	0.027	−0.049	−0.324	−0.240	−0.025
		p = 0.274	0.243	0.877	0.255	0.600	0.250	0.627	0.661	0.860	0.485	0.889	0.798	0.081	0.202	0.896
	ALT (IU/L)	r = 0.051	0.175	0.065	0.072	−0.070	−0.012	−0.115	−0.049	0.116	−0.325	0.069	0.139	0.062	−0.108	0.320
		p = 0.789	0.355	0.735	0.704	0.715	0.952	0.546	0.796	0.543	0.080	0.716	0.465	0.746	0.569	0.084
	ALP (IU/L)	r = −0.376*	−0.075	−0.114	−0.004	−0.040	−0.010	−0.086	−0.110	−0.281	−0.172	−0.415*	0.227	−0.195	0.143	0.191
		p = 0.040	0.692	0.547	0.985	0.834	0.960	0.651	0.564	0.132	0.364	0.023	0.229	0.303	0.452	0.311
	LDH (U/L)	r = −0.013	0.380*	−0.168	0.174	−0.115	0.116	−0.434*	−0.094	−0.098	0.145	−0.038	0.046	−0.243	−0.127	−0.013
		p = 0.944	0.039	0.374	0.359	0.545	0.543	0.016	0.622	0.606	0.445	0.842	0.811	0.196	0.505	0.944
	CPK (U/L)	r = −0.236	−0.238	0.081	0.233	0.338	−0.225	0.043	−0.272	−0.114	−0.095	−0.340	0.049	0.072	0.184	−0.222
		p = 0.210	0.206	0.670	0.216	0.068	0.231	0.822	0.146	0.549	0.618	0.066	0.799	0.706	0.331	0.237
	Ca (mg/dl)	r = 0.062	−0.006	−0.187	0.096	0.248	−0.212	0.084	0.247	0.514**	0.140	0.210	0.121	−0.088	0.092	−0.140
		p = 0.750	0.976	0.332	0.622	0.195	0.269	0.664	0.196	0.004	0.469	0.274	0.533	0.650	0.634	0.469
	P (mg/dl)	r = −0.254	0.049	−0.208	0.065	0.055	−0.055	−0.025	0.071	0.020	−0.277	−0.071	−0.374*	−0.336	−0.030	−0.259
		p = 0.176	0.798	0.270	0.731	0.775	0.772	0.896	0.710	0.918	0.139	0.709	0.042	0.070	0.876	0.167
	Mg (mEq/L)	r = −0.174	0.290	0.540**	−0.335	−0.613**	−0.076	−0.053	−0.025	0.064	0.062	0.292	0.170	0.101	−0.179	0.182
		p = 0.357	0.120	0.002	0.070	0.000	0.690	0.782	0.896	0.738	0.747	0.118	0.369	0.597	0.343	0.337
	Na (mEq/L)	r = −0.234	0.167	0.165	0.087	−0.002	−0.410*	−0.025	0.209	0.230	0.169	0.200	0.112	0.065	0.177	−0.265
		p = 0.212	0.376	0.385	0.648	0.992	0.024	0.898	0.268	0.220	0.372	0.290	0.556	0.732	0.351	0.157
	K (mEq/L)	r = 0.124	0.222	−0.353	0.391*	0.121	0.062	0.002	0.233	0.090	0.369*	0.292	0.178	−0.422*	0.005	−0.345
		p = 0.515	0.238	0.056	0.032	0.523	0.744	0.993	0.215	0.637	0.045	0.117	0.348	0.020	0.979	0.062
	PMN (%)	r = 0.048	0.166	0.010	0.110	−0.159	0.058	−0.051	−0.019	0.131	0.341	0.044	0.127	−0.047	0.073	−0.180
		p = 0.802	0.380	0.957	0.564	0.402	0.760	0.790	0.920	0.491	0.065	0.818	0.504	0.805	0.701	0.342
	Lymph (%)	r = −0.152	−0.158	0.082	−0.079	0.142	−0.049	−0.003	0.056	−0.185	−0.335	−0.109	−0.143	0.185	−0.024	0.213
		p = 0.422	0.405	0.668	0.679	0.454	0.799	0.986	0.768	0.328	0.071	0.567	0.451	0.328	0.900	0.257
	Monocyte (%)	r = −0.029	0.225	0.099	−0.076	−0.028	−0.135	0.001	0.047	0.203	−0.126	−0.038	−0.123	−0.294	−0.242	0.192
		p = 0.878	0.231	0.602	0.691	0.882	0.478	0.997	0.803	0.281	0.507	0.843	0.518	0.115	0.198	0.309
	Eos (%)	r = 10.000	−0.049	−0.379*	0.002	0.106	0.012	0.155	−0.179	−0.236	0.183	0.032	−0.093	−0.069	−0.137	0.018
		p = <00.001	0.796	0.039	0.993	0.579	0.948	0.414	0.343	0.209	0.333	0.868	0.624	0.717	0.469	0.926

(continued)

Table 4. (continued)

Outcome	Variables	IFN-γ	IL-1β	IL-2	IL-4	IL-5	IL-6	IL-8	IL-10	IL-12	IL-17	IP-10	MCP-1	MIP-1α	RANTES	TNF-α
Healthy	**WBC (µl/l)**	r = 0.082	0.149	0.056	−0.462*	−0.222	0.190	−0.058	0.123	−0.061	−0.394*	0.100	0.055	0.210	0.193	−0.300
		p = 0.667	0.432	0.770	0.010	0.239	0.316	0.760	0.517	0.747	0.031	0.597	0.771	0.265	0.306	0.107
	RBC (µ/l)	r = −0.207	0.211	−0.246	−0.049	−0.061	−0.364*	0.065	0.076	0.029	−0.125	0.151	0.074	0.158	−0.014	−0.299
		p = 0.272	0.263	0.191	0.797	0.749	0.048	0.733	0.689	0.881	0.511	0.427	0.697	0.404	0.942	0.108
	Hb (mg/dl)	r = 0.041	0.048	−0.245	−0.005	−0.087	0.076	−0.118	0.191	0.028	−0.028	0.133	−0.050	0.167	0.089	−0.373*
		p = 0.828	0.800	0.193	0.978	0.648	0.689	0.535	0.312	0.882	0.882	0.484	0.793	0.379	0.641	0.042
	HCT (%)	r = 0.000	0.044	−0.285	0.011	−0.125	−0.012	−0.113	0.102	0.050	−0.013	0.188	0.033	0.072	0.085	−0.359
		p = 0.998	0.817	0.127	0.952	0.509	0.950	0.554	0.593	0.791	0.946	0.320	0.862	0.705	0.656	0.051
	MCV (fl)	r = 0.183	−0.370*	0.317	0.046	0.076	0.475**	−0.081	0.086	0.066	0.290	0.062	0.052	−0.142	0.097	0.197
		p = 0.334	0.044	0.087	0.810	0.692	0.008	0.672	0.650	0.730	0.120	0.746	0.784	0.453	0.609	0.297
	MCH (pg)	r = 0.241	−0.230	−0.125	−0.131	−0.182	0.582**	−0.082	0.052	0.177	−0.077	−0.017	0.008	−0.082	0.336	−0.212
		p = 0.199	0.221	0.510	0.491	0.335	0.001	0.666	0.784	0.350	0.687	0.931	0.965	0.666	0.070	0.260
	MCHC (%)	r = −0.084	0.050	−0.110	−0.019	−0.082	0.207	−0.207	0.151	0.165	−0.024	0.037	−0.109	−0.029	0.209	−0.259
		p = 0.661	0.794	0.561	0.921	0.667	0.273	0.273	0.427	0.384	0.898	0.844	0.567	0.879	0.268	0.167
	PLT (mm3/µl)	r = 0.005	0.109	0.198	−0.188	−0.165	0.246	0.041	0.128	−0.078	−0.200	0.044	−0.045	0.125	0.079	−0.104
		p = 0.979	0.565	0.294	0.319	0.384	0.190	0.832	0.501	0.682	0.290	0.819	0.815	0.509	0.678	0.586
	RDW (µm)	r = −0.704	0.595	0.036	0.000	0.667	0.821*	−0.334	0.306	−0.519	−0.750	0.000	0.164	0.357	−0.071	−0.036
		p = 0.077	0.159	0.939	10.000	0.102	0.023	0.465	0.504	0.233	0.052	10.000	0.726	0.432	0.879	0.939
	MPV (fl)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	PDW (%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	P-LCR (ng/ml)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Urea (mg/dl)	r = 0.372*	−0.256	0.067	−0.256	−0.315	0.123	0.008	−0.074	−0.397*	−0.031	−0.127	−0.091	−0.074	−0.116	0.149
		p = 0.043	0.171	0.725	0.172	0.090	0.516	0.966	0.698	0.030	0.870	0.503	0.631	0.697	0.543	0.431
	Cr (mg/dl)	r = 0.053	−0.008	−0.237	−0.125	−0.299	−0.206	−0.032	0.005	−0.187	−0.037	−0.039	−0.039	0.119	−0.067	−0.188
		p = 0.781	0.967	0.206	0.511	0.108	0.274	0.866	0.980	0.323	0.846	0.840	0.838	0.530	0.726	0.320
	AST (IU/L)	r = −0.274	0.381*	−0.414*	0.145	0.290	−0.060	−0.290	0.066	−0.189	−0.164	0.084	0.184	0.184	−0.034	0.126
		p = 0.151	0.042	0.026	0.452	0.128	0.756	0.128	0.735	0.327	0.397	0.664	0.340	0.339	0.862	0.516
	ALT (IU/L)	r = 0.254	−0.119	0.116	−0.043	−0.246	0.207	0.141	−0.207	0.018	0.063	0.268	0.054	0.028	−0.019	−0.066
		p = 0.175	0.532	0.541	0.823	0.189	0.272	0.457	0.273	0.924	0.742	0.152	0.775	0.882	0.920	0.727
	ALP (IU/L)	r = 0.100	0.355	−0.150	0.031	−0.079	−0.084	−0.160	−0.091	0.432	−0.198	0.228	0.311	−0.197	0.050	0.140
		p = 0.665	0.114	0.517	0.895	0.732	0.718	0.489	0.694	0.050	0.390	0.320	0.170	0.391	0.830	0.546
	LDH (U/L)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	CPK (U/L)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Ca (mg/dl)	r = 0.098	0.465	0.042	0.280	−0.054	−0.036	0.053	−0.670*	0.385	−0.652*	0.519	0.266	−0.424	0.512	−0.580*
		p = 0.763	0.127	0.898	0.379	0.869	0.912	0.870	0.017	0.216	0.021	0.084	0.404	0.170	0.089	0.048
	P (mg/dl)	r = 0.509	0.244	0.293	−0.227	0.108	0.370	−0.028	0.383	0.258	0.076	−0.323	−0.310	−0.150	−0.058	−0.144
		p = 0.091	0.445	0.355	0.479	0.738	0.236	0.931	0.219	0.417	0.814	0.306	0.327	0.642	0.858	0.656
	Mg (mEq/L)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Na (mEq/L)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	K (mEq/L)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	PMN (%)	r = −0.200	0.323	0.084	0.271	−0.361*	−0.245	0.028	0.357	0.139	0.157	−0.310	−0.214	0.146	0.320	0.144
		p = 0.289	0.082	0.660	0.147	0.050	0.191	0.884	0.053	0.464	0.407	0.095	0.255	0.441	0.085	0.449
	Lymph (%)	r = 0.132	−0.308	−0.075	−0.256	0.372*	0.231	−0.075	−0.296	−0.163	−0.151	0.317	0.207	−0.121	−0.338	−0.169
		p = 0.485	0.097	0.695	0.172	0.043	0.220	0.695	0.112	0.390	0.425	0.088	0.273	0.523	0.067	0.373
	Monocyte (%)	r = −0.184	0.273	−0.042	−0.209	−0.234	−0.285	0.186	−0.249	0.014	0.223	−0.240	0.105	−0.085	0.010	0.292
		p = 0.331	0.144	0.826	0.268	0.213	0.128	0.326	0.185	0.942	0.236	0.201	0.582	0.655	0.958	0.117
	Eos (%)	r = 10.000	−0.292	−0.123	0.381*	0.228	0.435*	0.206	−0.039	0.105	−0.265	0.226	0.013	−0.132	0.157	−0.331
		<00.001	0.118	0.518	0.038	0.226	0.016	0.275	0.838	0.583	0.157	0.229	0.944	0.488	0.406	0.074

(continued)

Table 4. (continued)

Outcome	Variables	IFN-γ	IL-1β	IL-2	IL-4	IL-5	IL-6	IL-8	IL-10	IL-12	IL-17	IP-10	MCP-1	MIP-1α	RANTES	TNF-α
Recovered	**WBC (μl)**	r = 0.035	0.191	−0.255	−0.221	−0.098	0.010	−0.081	0.079	0.164	−0.297	0.126	0.299	0.244	0.065	0.582**
		p = 0.855	0.313	0.174	0.240	0.607	0.959	0.672	0.677	0.388	0.111	0.508	0.109	0.193	0.731	0.001
	RBC (μ/l)	r = 0.080	−0.019	0.055	−0.252	−0.152	0.069	0.068	0.283	−0.034	0.336	−0.064	0.087	−0.150	0.133	0.052
		p = 0.675	0.922	0.773	0.180	0.423	0.719	0.720	0.130	0.860	0.069	0.737	0.646	0.429	0.483	0.783
	Hb (mg/dl)	r = 0.184	0.191	0.063	−0.141	−0.068	0.134	0.015	0.112	−0.202	0.303	−0.074	0.000	−0.218	0.184	−0.023
		p = 0.329	0.312	0.740	0.458	0.722	0.482	0.938	0.556	0.283	0.103	0.699	10.000	0.248	0.330	0.903
	HCT (%)	r = 0.246	0.097	0.052	−0.162	−0.151	0.168	0.016	0.173	−0.136	0.388*	−0.088	−0.032	−0.200	0.134	0.149
		p = 0.190	0.611	0.784	0.393	0.426	0.373	0.934	0.360	0.474	0.034	0.645	0.867	0.289	0.481	0.431
	MCV (fl)	r = 0.129	0.104	−0.203	0.214	−0.104	0.204	−0.181	−0.343	−0.486**	0.173	−0.322	−0.262	−0.202	−0.253	0.230
		p = 0.496	0.586	0.283	0.256	0.585	0.279	0.339	0.063	0.006	0.361	0.082	0.161	0.284	0.178	0.221
	MCH (pg)	r = 0.150	0.237	−0.201	0.183	−0.033	0.304	−0.203	−0.354	−0.576**	0.093	−0.223	−0.176	−0.301	−0.089	0.069
		p = 0.429	0.207	0.286	0.333	0.861	0.102	0.282	0.055	0.001	0.625	0.235	0.352	0.106	0.641	0.717
	MCHC (%)	r = −0.060	0.128	0.086	−0.140	0.121	0.149	−0.183	−0.144	−0.197	0.016	0.074	0.173	−0.149	0.386*	−0.353
		p = 0.751	0.499	0.650	0.462	0.525	0.432	0.333	0.448	0.297	0.933	0.698	0.361	0.431	0.035	0.056
	PLT (mm3/μl)	r = −0.021	0.451*	0.045	0.373*	0.458*	0.139	−0.485**	−0.240	0.042	−0.371*	−0.020	0.084	−0.139	0.138	0.011
		p = 0.911	0.012	0.814	0.042	0.011	0.465	0.007	0.201	0.824	0.044	0.918	0.657	0.463	0.468	0.952
	RDW (μm)	r = −0.312	−0.246	0.005	0.004	−0.102	−0.361*	0.042	0.133	−0.050	0.229	0.134	−0.122	0.046	−0.288	0.136
		p = 0.094	0.190	0.980	0.985	0.590	0.050	0.826	0.484	0.791	0.224	0.481	0.521	0.810	0.122	0.475
	MPV (fl)	r = 0.093	−0.245	−0.030	0.024	−0.242	−0.198	0.137	0.016	0.078	0.337	−0.034	−0.199	0.303	0.088	−0.013
		p = 0.627	0.192	0.875	0.902	0.197	0.294	0.471	0.933	0.680	0.069	0.859	0.292	0.103	0.644	0.948
	PDW (%)	r = 0.154	−0.233	−0.120	−0.019	−0.349	−0.074	0.149	0.022	0.061	0.195	−0.121	−0.146	0.235	0.126	0.079
		p = 0.415	0.214	0.529	0.919	0.059	0.698	0.431	0.907	0.748	0.303	0.524	0.443	0.211	0.508	0.678
	P-LCR (ng/ml)	r = 0.114	−0.313	−0.044	0.009	−0.249	−0.221	0.224	−0.010	0.087	0.245	−0.083	−0.148	0.359	0.103	0.017
		p = 0.547	0.092	0.817	0.960	0.184	0.240	0.235	0.957	0.649	0.192	0.663	0.434	0.051	0.588	0.928
	Urea (mg/dl)	r = −0.176	−0.124	−0.044	−0.197	−0.292	0.023	0.017	0.183	−0.118	0.139	0.245	0.008	0.068	0.045	0.247
		p = 0.353	0.515	0.817	0.296	0.117	0.904	0.927	0.333	0.536	0.465	0.192	0.968	0.719	0.813	0.188
	Cr (mg/dl)	r = −0.034	0.053	0.189	0.167	−0.026	−0.313	0.240	−0.043	−0.120	0.018	−0.052	−0.061	0.284	−0.183	0.061
		p = 0.860	0.779	0.318	0.377	0.893	0.092	0.202	0.823	0.529	0.924	0.786	0.749	0.129	0.334	0.748
	AST (IU/L)	r = −0.347	0.227	−0.090	−0.147	−0.045	−0.380*	−0.102	0.207	0.050	0.153	−0.024	−0.063	0.201	−0.001	0.104
		p = 0.060	0.228	0.636	0.438	0.813	0.039	0.593	0.273	0.795	0.419	0.898	0.741	0.287	0.997	0.585
	ALT(IU/L)	r = 0.019	0.118	0.033	0.022	0.008	0.195	0.147	0.003	0.020	0.159	−0.383*	−0.106	−0.315	0.313	−0.113
		p = 0.922	0.533	0.863	0.906	0.966	0.301	0.437	0.987	0.915	0.401	0.037	0.576	0.090	0.093	0.554
	ALP (IU/L)	r = 0.105	−0.240	0.546**	0.158	0.249	−0.374*	0.176	−0.002	0.205	0.109	0.125	−0.214	0.065	0.050	−0.329
		p = 0.582	0.202	0.002	0.405	0.185	0.042	0.353	0.992	0.276	0.565	0.511	0.257	0.733	0.792	0.076
	LDH (U/L)	r = −0.203	−0.123	0.286	−0.087	0.102	−0.413*	0.191	0.020	0.144	0.124	0.021	−0.209	0.140	−0.147	−0.322
		p = 0.281	0.517	0.125	0.647	0.593	0.023	0.311	0.917	0.449	0.514	0.913	0.269	0.461	0.438	0.083
	CPK (U/L)	r = 0.240	−0.197	0.158	0.090	−0.031	−0.248	0.467**	−0.003	0.188	−0.209	−0.259	−0.035	0.289	−0.130	0.058
		p = 0.201	0.298	0.406	0.635	0.871	0.187	0.009	0.988	0.320	0.267	0.167	0.853	0.122	0.493	0.759
	Ca (mg/dl)	r = 0.129	0.001	0.264	−0.236	−0.077	−0.270	0.200	−0.194	0.163	−0.235	0.140	−0.017	−0.248	−0.126	−0.207
		p = 0.496	0.996	0.159	0.209	0.686	0.149	0.289	0.304	0.389	0.211	0.462	0.930	0.187	0.509	0.272
	P (mg/dl)	r = −0.073	−0.029	0.006	0.124	0.280	0.209	0.059	0.198	−0.122	−0.210	−0.060	−0.375*	−0.005	0.189	0.121
		p = 0.700	0.879	0.975	0.514	0.134	0.268	0.759	0.293	0.522	0.265	0.754	0.041	0.980	0.317	0.524
	Mg (mEq/L)	r = 0.214	−0.087	0.058	0.003	−0.214	−0.104	−0.030	0.141	0.057	−0.280	0.257	0.026	−0.101	−0.061	−0.400*
		p = 0.256	0.649	0.762	0.986	0.255	0.584	0.875	0.457	0.763	0.135	0.170	0.893	0.595	0.750	0.029
	Na (mEq/L)	r = −0.325	0.212	−0.130	0.065	0.004	−0.217	−0.164	0.404*	−0.026	−0.382*	0.299	−0.313	−0.469**	0.055	−0.274
		p = 0.080	0.262	0.493	0.732	0.984	0.250	0.388	0.027	0.891	0.037	0.108	0.092	0.009	0.773	0.143
	K (mEq/L)	r = 0.128	0.105	−0.447*	0.288	0.006	−0.317	0.043	−0.087	0.087	0.010	0.142	0.029	−0.116	−0.249	−0.095
		p = 0.500	0.579	0.013	0.122	0.976	0.088	0.822	0.648	0.648	0.958	0.454	0.879	0.542	0.185	0.619
	PMN (%)	r = −0.491**	−0.039	−0.034	−0.105	−0.307	−0.125	−0.039	0.187	0.082	0.005	−0.182	0.079	0.220	0.110	0.129
		p = 0.006	0.837	0.860	0.580	0.099	0.510	0.838	0.324	0.666	0.980	0.335	0.677	0.243	0.563	0.497
	Lymph (%)	r = 0.261	0.203	−0.042	0.276	0.407*	0.183	−0.022	0.071	−0.203	0.005	0.089	−0.181	−0.151	−0.089	−0.032
		p = 0.164	0.281	0.825	0.139	0.026	0.334	0.908	0.709	0.281	0.979	0.642	0.339	0.424	0.642	0.868
	Monocyte (%)	r = 0.340	−0.215	0.221	−0.011	0.083	0.088	−0.263	−0.071	0.091	−0.016	−0.141	−0.047	0.009	0.246	−0.003
		p = 0.066	0.253	0.242	0.955	0.662	0.643	0.161	0.708	0.634	0.935	0.458	0.805	0.963	0.189	0.989
	Eos (%)	r = 10.000	0.105	0.176	0.138	0.233	0.283	0.113	−0.074	−0.229	0.126	−0.038	0.004	−0.009	−0.310	0.063
		p = <00.001	0.580	0.353	0.468	0.216	0.130	0.552	0.697	0.223	0.506	0.843	0.983	0.962	0.096	0.740

(continued)

Table 4. (continued)

Outcome	Variables	IFN-γ	IL-1β	IL-2	IL-4	IL-5	IL-6	IL-8	IL-10	IL-12	IL-17	IP-10	MCP-1	MIP-1α	RANTES	TNF-α
Total	**WBC (µl/l)**	r = 0.345**	0.354**	−0.048	0.106	0.168	0.277**	0.086	0.179	0.257*	−0.024	0.222*	0.253*	0.354**	0.284**	0.357**
		p = 0.001	0.001	0.656	0.321	0.113	0.008	0.420	0.092	0.014	0.821	0.035	0.016	0.001	0.007	0.001
	RBC (µ/l)	r = −0.317**	−0.172	−0.127	−0.345**	−0.322**	−0.386**	−0.094	0.108	−0.137	−0.114	−0.171	−0.101	−0.040	−0.291**	−0.180
		p = 0.002	0.104	0.233	0.001	0.002	0.000	0.376	0.312	0.197	0.285	0.107	0.342	0.709	0.005	0.090
	Hb (mg/dl)	r = 0.030	0.090	−0.090	−0.119	−0.086	−0.031	−0.080	0.073	−0.056	0.086	0.069	−0.089	−0.012	0.059	−0.220*
		p = 0.776	0.398	0.399	0.263	0.422	0.768	0.455	0.492	0.598	0.421	0.520	0.405	0.910	0.579	0.037
	HCT (%)	r = −0.049	−0.013	−0.106	−0.166	−0.185	−0.105	−0.065	0.051	−0.098	0.026	0.035	−0.086	−0.033	−0.039	−0.229*
		p = 0.647	0.904	0.321	0.117	0.082	0.326	0.540	0.630	0.359	0.807	0.741	0.420	0.760	0.717	0.030
	MCV (fl)	r = 0.472**	0.210*	0.218*	0.367**	0.313**	0.452**	0.210*	−0.066	0.119	0.321**	0.063	0.188	0.131	0.293**	0.374**
		p = 0.000	0.047	0.039	0.000	0.003	0.000	0.046	0.536	0.264	0.002	0.555	0.077	0.220	0.005	0.000
	MCH (pg)	r = 0.427**	0.208*	0.123	0.268*	0.255*	0.356**	0.171	−0.039	0.107	0.229*	0.167	0.029	0.047	0.255*	0.160
		p = <0.001	0.050	0.248	0.011	0.015	0.001	0.107	0.714	0.315	0.030	0.116	0.786	0.660	0.015	0.132
	MCHC (%)	r = 0.384**	0.406**	0.120	0.154	0.311**	0.446**	0.074	0.131	0.296**	0.266*	0.248*	0.293**	0.081	0.542**	0.168
		p = <00.001	<00.001	0.261	0.146	0.003	<00.001	0.489	0.219	0.005	0.011	0.019	0.005	0.451	0.000	0.113
	PLT (mm3/µl)	r = −0.240*	−0.020	−0.112	−0.169	−0.126	−0.200	−0.302**	−0.193	−0.127	−0.257*	−0.104	−0.164	−0.085	−0.237*	−0.175
		p = 0.023	0.855	0.292	0.111	0.235	0.058	0.004	0.068	0.232	0.014	0.330	0.123	0.424	0.024	0.099
	RDW (µm)	r = 0.023	0.855	0.292	0.111	0.235	0.058	0.004	0.068	0.232	0.014	0.330	0.123	0.424	0.024	0.099
		p = 0.198	0.908	0.212	0.007	0.178	0.870	0.003	0.181	0.077	0.110	0.054	0.676	0.066	0.902	0.006
	MPV (fl)	r = 0.229	−0.100	−0.101	−0.074	−0.260*	−0.092	0.257*	0.012	0.266*	0.326*	0.027	0.017	0.451**	0.026	0.166
		p = 0.078	0.446	0.442	0.574	0.045	0.484	0.047	0.928	0.040	0.011	0.837	0.898	0.000	0.842	0.206
	PDW (%)	r = 0.290*	−0.126	−0.078	−0.052	−0.227	−0.050	0.211	−0.013	0.278*	0.199	−0.008	0.047	0.385**	0.086	0.179
		p = 0.290*	−0.126	−0.078	−0.052	−0.227	−0.050	0.211	−0.013	0.278*	0.199	−0.008	0.047	0.385**	0.086	0.179
	P-LCR (ng/ml)	r = 0.242	−0.190	−0.046	−0.023	−0.192	−0.166	0.270*	−0.012	0.295*	0.239	0.015	0.029	0.484**	0.037	0.155
		p = 0.063	0.146	0.728	0.860	0.141	0.204	0.037	0.925	0.022	0.066	0.909	0.825	0.000	0.780	0.238
	Urea (mg/dl)	r = 0.375**	0.163	0.201	0.324**	0.294**	0.198	0.185	0.031	0.046	0.121	0.173	−0.028	0.154	0.182	0.135
		p = <00.001	0.125	0.058	0.002	0.005	0.061	0.082	0.773	0.667	0.257	0.102	0.795	0.147	0.087	0.205
	Cr (mg/dl)	r = 0.314**	0.240*	0.272**	0.336**	0.311**	0.118	0.311**	0.066	0.080	0.104	0.071	0.184	0.232*	0.207*	0.087
		p = 0.003	0.023	0.009	0.001	0.003	0.268	0.003	0.535	0.451	0.327	0.503	0.083	0.027	0.050	0.413
	AST (IU/L)	r = 0.416**	0.474**	0.157	0.469**	0.433**	0.359**	0.109	0.226*	0.272**	0.311**	0.253*	0.279**	0.241*	0.426**	0.358**
		p = <0.001	<00.001	0.142	<0.001	<0.001	0.001	0.310	0.033	0.010	0.003	0.017	0.008	0.023	<0.001	0.001
	ALT (IU/L)	r = 0.543**	0.392**	0.256*	0.400**	0.352**	0.526**	0.259*	0.102	0.360**	0.246*	0.201	0.280**	0.144	0.514**	0.343**
		p = <0.001	<0.001	0.015	<0.001	0.001	<0.001	0.014	0.340	<0.001	0.019	0.058	0.008	0.176	<00.001	0.001
	ALP (IU/L)	r = 0.216	0.131	0.283*	0.223*	0.219*	0.132	0.173	0.042	0.250*	0.105	0.128	0.180	0.085	0.242*	0.159
		p = 0.053	0.245	0.011	0.045	0.050	0.241	0.123	0.708	0.024	0.350	0.253	0.107	0.451	0.030	0.155
	LDH (U/L)	r = −0.083	0.184	0.102	0.063	0.002	−0.120	−0.127	−0.018	0.074	0.130	0.019	−0.054	−0.054	−0.097	−0.128
		p = 0.526	0.160	0.436	0.632	0.987	0.361	0.332	0.889	0.576	0.321	0.888	0.684	0.683	0.461	0.331
	CPK (U/L)	r = 0.131	0.007	0.198	0.202	0.138	0.042	0.193	0.003	0.152	0.001	−0.091	0.149	0.157	0.123	0.118
		p = 0.318	0.958	0.130	0.121	0.293	0.751	0.139	0.985	0.247	0.995	0.489	0.256	0.230	0.348	0.368
	Ca (mg/dl)	r = 0.148	−0.321**	−0.227	−0.225	−0.252*	−0.375**	−0.218	−0.170	0.136	−0.378**	−0.036	−0.190	−0.397**	−0.122	−0.389**
		p = 0.218	0.006	0.056	0.059	0.034	0.001	0.068	0.156	0.258	0.001	0.763	0.113	0.001	0.309	0.001
	P (mg/dl)	r = −0.128	0.133	0.056	0.151	0.231	0.155	0.137	0.217	0.002	−0.011	0.027	−0.236*	−0.005	0.152	0.051
		p = 0.283	0.264	0.641	0.205	0.051	0.193	0.250	0.067	0.984	0.930	0.822	0.046	0.965	0.202	0.668
	Mg (mEq/L)	r = −0.058	0.158	0.375**	−0.165	−0.407**	−0.082	0.050	0.068	0.062	−0.034	0.303*	0.139	0.071	−0.073	−0.028
		p = 0.660	0.228	0.003	0.208	0.001	0.533	0.707	0.604	0.639	0.795	0.019	0.289	0.589	0.577	0.831
	Na (mEq/L)	r = −0.293*	0.237	0.019	0.071	0.006	−0.298*	−0.050	0.330*	0.121	−0.071	0.300*	−0.098	−0.181	0.126	−0.226
		p = 0.023	0.069	0.888	0.588	0.961	0.021	0.704	0.010	0.357	0.589	0.020	0.456	0.167	0.337	0.083
	K (mEq/L)	r = 0.143	0.123	−0.394**	0.319*	0.034	−0.146	0.002	0.038	0.097	0.138	0.197	0.086	−0.253	−0.146	−0.183
		p = 0.275	0.348	0.002	0.013	0.797	0.265	0.986	0.770	0.460	0.293	0.132	0.513	0.051	0.267	0.163
	PMN (%)	r = −0.025	0.713**	0.482**	0.305**	0.459**	0.497**	0.605**	0.336**	0.286**	0.481**	0.299**	0.355**	0.396**	0.340**	0.594**
		p = 0.813	<0.001	<0.001	0.003	<0.001	<0.001	<0.001	0.001	0.006	0.000	0.004	0.001	<0.001	0.001	<0.001
	Lymph (%)	r = −0.061	−0.679**	−0.478**	−0.249*	−0.430**	−0.469**	−0.604**	**−0.272****	−0.321**	−0.458**	−0.305**	−0.372**	−0.343**	−0.332**	−0.564**
		p = 0.568	<0.001	<0.001	0.018	<0.001	<0.001	<0.001	0.009	0.002	<0.001	0.003	<0.001	0.001	0.001	<0.001
	Monocyte (%)	r = 0.088	−0.279**	−0.155	−0.196	−0.251*	−0.255*	−0.323**	−0.198	−0.028	−0.189	−0.264*	−0.182	−0.281**	−0.111	−0.193
		p = 0.408	0.008	0.144	0.064	0.017	0.015	0.002	0.062	0.791	0.074	0.012	0.086	0.007	0.296	0.068
	Eos (%)	r = 1.000	0.099	0.020	0.182	0.196	0.227*	0.201	−0.031	−0.093	0.076	0.108	0.017	−0.014	−0.052	0.074
		p = <0.001	0.355	0.848	0.087	0.065	0.031	0.058	0.770	0.385	0.476	0.310	0.874	0.898	0.627	0.488

WBC: White Blood Cells, RBC: Red Blood Cell, Hb: Hemoglobin, HCT: Hematocrit, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, PLT: Platelet Cells, RDW: Red Cell Distribution Width, MPV: Mean Platelet Volume, PDW: Platelet Distribution Width, P-LCR: Platelet-large cell ratio, Cr: Creatinine, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase, CPK: Creatinine Phosphokinase, LDH: Lactate Dehydrogenase, Mg: Magnesium, Ca: Calcium, P: Phosphorus, Na: Sodium, K: Potassium, PMN: Polymorph nuclear leukocytes, Lymph: Lymphocyte, NA: Not Available.

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

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

r = Correlation coefficient.

p = *p*-value.

correlations and associations between different cytokines, between cytokines and outcomes (healthy, recovered, deceased), and routine laboratory tests. In contrast to previous studies,[16,40] we did not find IL-6 to be correlated to WBC counts, PMN percentage or fever. However, IFN-γ was correlated to increased numbers of PMN, and suggested to be the major trigger of early inflammatory response in COVID-19 disease. IL-1β, IL-4, IL-5, IL-17, and MIP-1α were all correlated with decreased PLT counts. Levels of IL-4 and IL-5 were correlated with increased urea and creatinine, indicative of kidney organ failure. Liver failure is suspected with raised liver enzymes and these were correlated to levels of IFN-γ, IL-2, IL-6 and IP-10.

Pro-inflammatory cytokine/chemokine have a key role in viral infections through activating the adaptive immune cells; whereas an unbalanced pro- versus anti-inflammatory response can result in damage of lung tissue in the course of the infection.[42] Recent studies showed that key pro-inflammatory cytokines and chemokines, including IFN-γ, IL-2, CCL2, and CCL3, can be anti-inflammatory mediators.[43,44] Similarly, anti-inflammatory effectors such as IL-10, under certain conditions and in combination with other cytokines, may induce a pro-inflammatory response.[45] We found similar cytokine patterns in recovered and deceased COVID-19 patients, possibly suggesting a regulatory mechanism of cytokine secretion in severe COVID-19 disease. A limitation in this study was the lower age in COVID-19 patients compared to controls. However, differences between patients with COVID-19 disease and healthy were substantial and highly significant for all measures. Therefore, the age differences should be acceptable for conclusions. There are discrepancies between our and other studies as discussed above, maybe because of differences in sample size, ethnicity, age, comorbidities, time of sampling, as well as season and climate differences. The limited number of cases when performing the study may be led to a reduced study's power in showing statistically significant differences in different parameters.

Conclusion

This study provides more evidence for the association of cytokine/chemokine levels with the clinical course and outcome of COVID-19 disease. More studies are needed to explore if this measures could be an indicator of disease stage, help in strategy for treatment and/or prognosis for outcome.

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Author contributions

AT conceptualized and designed the study. BA and EB did the experiments and collected data. AR carried out the initial data analyses. BA and EB drafted the initial manuscript. AT and BN coordinated and supervised data collection, and critically reviewed the manuscript. ATb, HRN, BN, and AM reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Ethics approval

The study was approved by the Ethics Committee of Golestan University of Medical Sciences (IR.GOUMS.REC.1399.007).

Informed consent

Written informed consent was obtained from all subjects before the study.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material; further inquiries can be directed to the corresponding authors.

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Supplemental Material

Supplemental material for this article is available online.

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Appendix

Abbreviations

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
PCR	Polymerase chain reaction
ELISA	Enzyme-linked immunosorbent assay
IFN	Interferon
IL	Interleukin
IP-10	Interferon gamma-induced protein 10
MIP1-α	Macrophage Inflammatory Proteins 1-alpha
MCP-1	Monocyte chemoattractant protein-1
TNF	Tumor necrosis factor
WBC	White Blood Cells
RBC	Red Blood Cell
Hb	Hemoglobin
HCT	Hematocrit
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
PLT	Platelet Cells
RDW	Red Cell Distribution Width
MPV	Mean Platelet Volume
PDW	Platelet Distribution Width
P-LCR	Platelet-large cell ratio
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ALP	Alkaline Phosphatase
CPK	Creatinine Phosphokinase
LDH	Lactate Dehydrogenase
Mg	Magnesium
PMN	Polymorph nuclear leukocytes
Lymph	Lymphocyte
PT	Prothrombin time.