

Continuous Renal Replacement Therapy with oXiris Filter May Not Be an Effective Resolution to Alleviate Cytokine Release Syndrome in non-AKI Patients with Severe and Critical COVID-19

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Research

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Abstract

Background

In this study, we aimed to determine whether continuous renal replacement therapy (CRRT) with oXiris filter may alleviate cytokine release syndrome (CRS) in non-AKI patients with severe and critical coronavirus disease 2019 (COVID-19).

Methods

Non-AKI patients with severe and critical COVID-19 treated between February 14 and March 26, 2020 were included and randomly divided into intervention group and control group according to the random number table. Patients in the intervention group received CRRT with oXiris filter plus conventional treatment, while those in the control group only received conventional treatment. Demographic data were collected and collated at admission. During ICU hospitalization, the serum levels of cytokine and inflammatory chemokines, including IL-2, IL-4, IL-6, IL-10, TNF- α , and IFN- γ , were measured daily to reflect the degree of CRS induced by SARS-CoV-2 infection. Clinical data, including white blood cell count (WBC), neutrophil proportion (NEUT%), lymphocyte count (LYMPH), lymphocyte percentage (LYM%), platelet (PLT), C-reaction protein (CRP), high sensitivity C-reactive protein (hs-CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), albumin (ALB), serum creatinine (SCr), D-Dimer, fibrinogen (FIB), IL-2, IL-4, IL-6, IL-10, TNF- α , IFN- γ , number of hospital days and sequential organ failure assessment (SOFA) score were obtained and collated from medical records during hospitalization, and then compared between the two groups.

Results

Age, and SCr significantly differed between the two groups. Besides the IL-2 level that was significantly lower on day 2 than that on day 1 in the intervention group, and the IL-6 levels that were significantly higher on day 1, and day 2 in the intervention group compared to the control group, similar to the IL-10 level on day 5, there were no significant differences between the groups.

Conclusion

CRRT with oXiris filter may not effectively alleviate CRS in non-AKI patients with severe and critical COVID-19. Thus, its application in these patients should be considered with caution to avoid increasing the unnecessary burden on society and individuals and making the already overwhelmed medical system even more strained (IRB number: IRB-AF/SC-04).

Background

Coronavirus disease 2019 (COVID-19), which has wreaked havoc on the global public health system and economy, is essentially viral sepsis induced by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection, where excessive and uncontrolled systemic immune responses are the real culprit of disease deterioration and death of patients with COVID-19, and not fatal virus infection (13). This further elucidates the core reason for the current ineffectiveness of antiviral drugs used as a treatment against COVID-19 (39). SARS-CoV-2 infection can trigger the excessive production and release of a series of cytokines and inflammatory chemokines, especially marked by IL-6, IL-10, and TNF-a, also known as cytokine release syndrome (CRS) or cytokine storm, which have been revealed to be closely associated with organ injury, disease severity and death in patients with COVID-19 (8, 10, 16). Compared with serum cytokine concentrations in sputum and bronchoalveolar lavage fluid (BALF) are more representative (38). Thus, drawing lessons from the history of researches on sepsis, interventions targeting single cytokines may not be effective. However, short-term corticosteroid treatment based on the treatment concept of alleviating excessive and uncontrolled systemic immune responses is still full of controversy in clinical practice due to significant adverse effects in the middle and late stages of SARS-CoV-2 infection (19, 36). Consequently, it remains unclear how effective the other methods are based on controlling hyper inflammation of SARS-CoV-2 infection.

Continuous renal replacement therapy (CRRT) involves a series of treatment modalities in clinic, during which the patient's blood is drawn out of the body with an external device, and the internal environment is maintained stable based on the working principles of diffusion, convection, and membrane adsorption. The therapeutic purpose of CRRT has evolved from the single replacement of kidney function to support of multiple organ systems via the removal of cytokines and inflammatory mediators. Accordingly, it can be considered for use in acute respiratory distress syndrome (ARDS) induced by current SARS-CoV-2 infection, especially for severe and critical COVID-19 patients with CRS, regardless of the presence of acute kidney injury (AKI) complications (12, 41, 45). Continuous venovenous hemofiltration (CVVH) has occupied the mainstream of CRRT in intensive care units (ICU) due to its superior effectiveness and safety (33). In addition, regional citrate anti-coagulation is currently the main anti-coagulation method for critically ill patients requiring CRRT in clinical practice (18).

oXiris filter is a highly biocompatible modified hemodiafilter with a special heparin-coated design, which can be combined with CRRT in clinical practice. CRRT with oXiris filter can further enhance the clearance of cytokines and inflammatory chemokines, improve clinical symptoms and laboratory indicators, reduce disease severity, and prolong the survival time in critically ill patients with COVID-19 (4, 28, 30). Still, the relevant studies mainly focused on acute or chronic renal failure in patients with COVID-19, which is one of the potential indications for CRRT initiation. Thus far, there are no sufficient clinical data to recommend the application of CRRT with oXiris filter to alleviate CRS in non-AKI patients with severe and critical COVID-19. In our study, we tried to explore the role of CRRT with oXiris filter on CRS in non-AKI patients with severe and critical application. Our findings provide a solid theoretical basis that can guide its clinical application.

Methods Study design

Non-AKI patients with severe and critical COVID-19 treated at COVID-19 treatment center of Heilongjiang province in the First Affiliated Hospital of Harbin Medical University between February 14 and March 26, 2020, were included in this prospective randomized controlled study. These patients were randomly divided into intervention group and control group according to the random number table. Patients in the intervention group received CRRT with oXiris filter plus conventional treatment, while those in the control group only received conventional treatment based on the Diagnosis and Treatment of New Coronavirus Pneumonia (the fifth edition). These patients were dealt with by the same group of experienced intensivists in the ICU.

Demographic data were collected and collated at admission. Clinical data, including white blood cell count (WBC), neutrophil proportion (NEUT%), lymphocyte count (LYMPH), lymphocyte percentage (LYM%), platelet (PLT), C-reaction protein (CRP), high sensitivity C-reactive protein (hs-CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), albumin (ALB), serum creatinine (SCr), D-Dimer, fibrinogen (FIB), IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ, and a number of hospital days were obtained and collated from medical records during hospitalization, and then compared between the two groups. Sequential organ failure assessment (SOFA) scores were calculated during the first 24 h clinical data after ICU admission.

The study was approved by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University (IRB number: IRB-AF/SC-04).

Study Population

In this study, the inclusion criteria were following: (1) admitted to ICU; (2) age \geq 18 years old; (3) confirmed severe and critical patients with COVID-19; (4) non-AKI; (5) written informed consent obtained from patients or guardians; whereas COVID-19 patients who met the following criteria were excluded: (1) uncontrolled malignant tumors with multiple metastases; (2) leukemia; (3) acquired immunodeficiency syndrome (AIDS); (4) obstructive pneumonia caused by pulmonary tumors, severe pulmonary interstitial fibrosis, pulmonary alveolar proteinosis, and allergic alveolitis; (5) chronic organ failure; (6) immunotherapy or organ transplant within 6 months; (7) autoimmune disorder; (8) need extracorporeal membrane oxygenation (ECMO) or extracorporeal carbon dioxide removal (ECCO2R) at ICU admission; (9) patients expected to die within 72 h; (10) pregnant or breastfeeding women; (11) incomplete medical records; (12) any potential conditions endangering the patient's safety. The full panel of experts was responsible for identifying potential conditions that could endanger the safety of enrolled patients.

Diagnosis Of Severe And Critical Covid-19

All enrolled patients were confirmed by detection of SARS-CoV-2 nucleic acid on oropharyngeal swabs, nasopharyngeal swabs, or lower respiratory tract specimens, and then classified into severe or critical cases according to the Diagnosis and Treatment of New Coronavirus Pneumonia (the fifth edition). During ICU hospitalization, the serum concentration of cytokine and inflammatory chemokines, including IL-2, IL-4, IL-6, IL-10, TNF- α , and IFN- γ , were measured on a daily basis to reflect the degree of CRS induced by SARS-CoV-2 infection.

Continuous Renal Replacement Therapy With Oxiris Filter

In this study, a temporary double-lumen central venous catheter (11.5 F) was used to establish vascular access under ultrasound guidance. Patients in the intervention group were managed with 72 h CVVH combined oXiris filter (Baxter International, Deerfield, IL, USA), regional citrate anti-coagulation, and a preand post-dilution ratio of 1:1 on a Prismaflex system (Baxter International, Deerfield, IL, USA). Blood flow rates, dehydration volume, and amount of substitute fluid were individually adjusted according to the different conditions and treatment needs of each patient. Considering the saturation of membrane adsorption, Oxiris filter was changed every 12 hours.

Data Collection

Demographic data, including age, gender, comorbidities, and clinical data, including the severity of COVID-19, SOFA score, WBC, NEUT%, LYMPH, LYM%, PLT, CRP, hs-CRP, ALT, AST, TB, ALB, SCr, D-Dimer, FIB, IL-2, IL-4, IL-6, IL-10, TNF-a, IFN- γ , and a number of hospital days were obtained and collated from medical records during hospitalization by dedicated personnel in our research team. None of the other members of our research team was privy to enrolled patient's personal information beyond what was required for this study.

Statistical Analyses

SPSS 24.0 (SPSS, Inc., Chicago, IL) was used for statistical analyses. Continuous data conforming to normal distribution were described as mean ± standard deviation (SD), while continuous data with non-normal distribution were expressed as median (P25, P75). The measurement data were expressed by frequency. Independent-samples t-test was used to perform inter-group comparison for continuous data with normal distribution, while Mann-Whitney U test was employed for inter-group comparison of abnormally distributed continuous data. The Fisher's exact test was used for comparing measurement data between the two groups. P-values <0.05 were considered to indicate statistical significance.

Results

Comparison of demographic and clinical baseline data between the two groups

As shown in Table 1, age and SCr were significantly different in the two groups (p = 0.026, = 0.049, respectively), despite the randomization process, while no significant difference was observed in the remaining demographic and clinical baseline data.

	Intervention group	Control group	t/z/x ²	Р
Age	67.63±9.87	56.22±9.16	2.470	0.026
Gender(male/female)	7/1	6/3	-	0.576
Hypertension(yes/no)	2/6	4/5	-	0.620
Diabetes(yes/no)	0/8	2/7	-	0.471
Severity of COVID-19(severe/critical)	7/1	8/1	-	1.000
SOFA score	4(3,4)	4(2.5,4.5)	-0.314	0.754
WBC	6.48±2.22	7.69±2.32	-1.099	0.289
NEUT%	80.98±9.71	85.38±5.18	-1.146	0.278
LYMPH	10.68±7.46	8.01±3.84	0.909	0.384
LYM%	0.62±0.34	0.55±0.16	0.473	0.647
PLT	244.50±150.99	247.89±61.98	-0.062	0.951
CRP	46.58±25.65	58.78±58.26	-0.546	0.593
hs-CRP(>10mg/L/other)	7/1	8/1	-	1.000
ALT	26.41(23.83,77.05)	36.35(18.65,58.90)	-0.096	0.923
AST	40.59±24.98	37.39±27.02	0.253	0.804
ТВ	18.37±12.27	30.13±18.83	-1.503	0.154
ALB	27.67±5.39	28.28±2.27	-0.301	0.770
SCr	71.00±17.97	54.73±13.30	2.138	0.049
D-Dimer	1.75(1.38,2.63)	1.93(1.18,25.40)	-0.481	0.630
FIB	5.84±1.30	3.96±2.22	2.100	0.053
IL-2 level at admission	1.10(0.91,1.15)	1.19(1.10,1.23)	-1.263	0.207
IL-4 level at admission	0.59±0.32	1.01±0.76	-1.537	0.153
IL-6 level at admission	13.88(2.67,48.04)	10.46(3.68,25.26)	-0.577	0.564
IL-10 level at admission	6.71±3.97	7.00±3.40	-0.162	0.873
TNF- α level at admission	0.16(0.01,0.49)	0.05(0,0.56)	-0.297	0.767
IFN-y level at admission	0.99±0.11	1.19±0.81	-0.734	0.483
Hospital day	28.63±6.86	28.22±6.38	0.125	0.902

Table 1 Comparison of demographic and clinical baseline data between two groups

Comparison of IL-2 levels between the two groups from day 1 to day 6

As shown in Table 2 and Figure 1, no difference in IL-2 levels was observed, except that the IL-2 level on day 2 was significantly lower (P<0.05) than that on day 1 in the intervention group.

Group	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	X ² _{Mauchy} /P	F _(G-G) /P	F _{group} /P	F _{group*time} /I
Control group	1.5±0.62	0.98±0.70	0.97±0.50	1.20±0.73	1.17±0.85	1.48±0.84	27.95/0.016	3.979/0.012	1.069/0.318	0.854/0.74
Intervention group	1.68±0.63	0.86a±0.47	0.52±0.37	0.68±0.76	1.49±0.89	1.43±0.84				
^a Represent s	ignificant diff	erence compar	ed with day 1							

Comparison of IL-4 levels between the two groups from day 1 to day 6

As shown in Table 3 and Figure 2, no significant difference in IL-4 levels was observed between the two groups from day 1 to day 6.

Comparison of IL-4 levels between the two groups from day 1 to day 6											
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	X ² _{Mauchy} /P	F _(G-G) /P	F _{group} /P	F _{group*time} /I	
Control group	1.36±0.44	0.55±0.49	0.94±1.05	1.41±0.89	1.77±1.19	1.35±0.93	32.784/0.004	1.854/0.152	0.032/0.861	0.385/0.762	
Intervention group	1.08±0.70	0.78±0.68	1.07±1.13	1.17±1.42	1.38±1.41	1.70±1.21					

Comparison of IL-6 levels between the two groups from day 1 to day 6

As shown in Table 4 and Figure 3, no significant difference was found except that the IL-6 levels on day 1 and 2 in the intervention group were significantly higher (P<0.05) than those in the control group.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	X ² _{Mauchy} /P	F/P	F _{group} /P	F _{group*tim}
Control group	1.99±0.99	1.22±2.37	2.31±0.99	2.82±1.46	2.04±0.91	2.07±1.22	20.540/0.119	1.906/0.103	5.972/0.027	1.710/0.
Intervention group	3.41a±0.78	3.25a±0.99	2.93±1.34	3.42±0.62	3.24±1.15	3.20±1.08				

Comparison of IL-10 levels between the two groups from day 1 to day 6

As shown in Table 5 and Figure 4, no significant difference was observed except that the IL-10 levels on day 5 in the intervention group were significantly higher (P<0.05) than the control group.

Table 5 Comparison of IL-10 levels between the two groups from day 1 to day 6											
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	X ² _{Mauchy} /P	F _(G-G) /P	F _{group} /P	F _{group} ,	
Control group	7.45±4.75	5.39±2.19	7.46±4.75	6.59±2.53	5.20±1.74	5.57±2.40	30.709/0.007	0.371/0.521	6.178/0.025	0.474/	
Intervention group	9.33±5.18	7.32±3.80	10.67±9.19	9.54±4.01	9.37a±4.65	11.70±10.29					
^a Represent s	ignificant diff	erence compa	ared with the co	ontrol group							

Comparison of TNF- α levels between the two groups from day 1 to day 6

As shown in Table 6 and Figure 5, no significant differences were found in TNF-a levels when comparing the two groups from day 1 to day 6.

Table 6 Comparison of TNF- α levels between the two groups from day 1 to day 6											
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	X ² _{Mauchy} /P	F _(G-G) /P	F _{group} /P	F _{group*time} /I	
Control group	1.14±0.26	0.73±0.36	1.50±1.53	1.50±1.10	0.90±1.10	1.02±0.62	42.026/0.000	2.096/0.116	0.003/0.959	1.857/0.31(
Intervention group	0.93±0.24	0.65±0.18	0.69±0.41	0.82±0.55	2.36±1.59	1.40±0.73					

Comparison of IFN- $\!\gamma$ levels between the two groups from day 1 to day 6

As shown in Table 7 and Figure 6, no significant difference was found in IFN-y levels when comparing the two groups from day 1 to day 6.

Table 7 Comparison of IFN-γ levels between the two groups from day 1 to day 6										
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	X ² _{Mauchy} /P	F _(G-G) /P	F _{group} /P	F _{group*time}
Control group	1.39±0.32	1.14±0.34	1.26±0.57	1.52±0.68	1.44±0.61	1.44±0.88	110.437/0.000	2.043/0.162	1.613/0.223	1.227/0.3(
Intervention group	1.34±0.37	1.07±0.38	1.22±0.47	2.04±1.51	2.27±1.95	3.10±4.00				

Discussion

Nearly two years have passed since the outbreak of COVID-19 in Wuhan; however, the disease is still rapidly advancing around the world, with the number of SARS-CoV-2 infections and death reaching new records every day. As a novel, highly pathogenic human coronavirus (hCoV), SARS-CoV-2 may continue to pose a persistent and unprecedented threat to global public health security for a considerable time to come. Breakthrough infections caused by adaptive mutations in the SARS-CoV-2 genome prevent universal vaccination from becoming the effective coping strategy against COVID-19 (14). In the absence of available targeted interventions, there is an urgent need to explore effective treatment approaches based on an ongoing understanding of the pathogenesis of SARS-CoV-2 viral infection and disease deterioration to avert irreversible multi-organ failure induced by SARS-CoV-2 infection in clinical practice, especially for severe and critical COVID-19 patients with high mortality. Among them, CRRT with oXiris filter is a highly expected and promising clinical approach (6).

Nearly 20% of patients with COVID-19 tend to develop into severe and critical cases, which usually involve the lungs and manifest as acute respiratory distress syndrome (ARDS) and marked dysregulated immunity (40). Although the exact pathogenesis of SARS-CoV-2 infection and disease deterioration is still poorly understood, CRS characterized by an excessive and uncontrolled systemic inflammatory response has an essential role (21). A significant increase in cytokines and inflammatory chemokines burden was observed in patients with COVID-19, in association with multiple-organ dysfunction, increased disease severity, and adverse clinical outcomes (16, 34, 44). Data from the Chinese Center for Disease Control and Prevention indicated that the overall mortality of COVID-19 was 2.3%, while the mortality of patients with critical COVID-19 was close to 50% and even exceeded 60% in the early stages of the outbreak (40, 42). Some of the survivors, who recovered from severe or critical COVID-19, were reported to suffer from severely impaired pulmonary diffusion capacities and abnormal chest imaging manifestations at 6-months follow-up after SARS-CoV-2 infection (15). It is a realistic clinical need to alleviate organ damage and reduce mortality in patients with severe and critical COVID-19. Regulating inflammatory responses to restore immunological equilibrium and maintain immune homeostasis may be an entry point strategy.

Obviously, organ support therapy alone is not enough for CRS-induced organ injury in patients with COVID-19. Using CRRT for immunomodulation has a long history in clinic for tapering cytokine storms and controlling the associated dysregulation of the immune system. This approach has also been proposed as adjuvant therapy in many diseases, including sepsis (22), septic AKI (35), septic shock (32), severe Middle East Respiratory Syndrome (MERS) (5), severe acute pancreatitis (SAP) with or without ARDS (9, 11), CRS induced by some immunotherapies (7), severe burns (27), etc. Yet, a non-selective way allows harmful and beneficial substances to be simultaneously removed during CRRT (33). Moreover, the potential disadvantages of CRRT, such as technical complications of establishing vascular access, anti-coagulation-related complications, hemodynamic instability, internal environment disturbance, obstacles to the spontaneous recovery of renal function, and huge cost, should not be ignored in clinical practice. As a result, although some studies have confirmed the immunomodulation effect of CRRT, this was not sufficient to influence clinical endpoints and could even prolong the need for organ support (25, 43).

oXiris filter is superficially modified from an AN-69 membrane (polyacrylonitrile) with an additional positively charged polyimide ethylene layer used to enhance the cytokines-adsorbing capacity by ionic bonding and grafted with heparin (3), which was first approved and marketed in Europe in 2009. The addition of the highly adsorptive preheparinized oXiris filter can enhance the ability of CRRT to effectively remove endotoxin, circulating cytokines, and inflammatory chemokines, thus reducing lactate concentration and vasopressors influsion rate, and improving haemodynamic status, systemic perfusion, multi-organ function, and clinical outcomes without related adverse events (3, 31, 32, 35, 37). Therefore, it gained emergency approval from US Food and Drug Administration (FDA) for the clinical treatment of COVID-19 in April 2020 to counter the CRS attack triggered by SARS-CoV-2 infection. Different from shortterm corticosteroid treatment, CRRT with oXiris filter is expected to mitigate circulating cytokines and inflammatory chemokines burden and restore immune homeostasis in COVID-19 patients without a prolonged state of immunosuppression and serious secondary infection.

In our study, CRRT with oXiris filter showed no advantage in removing circulating cytokines and inflammatory chemokines in non-AKI patients with severe and critical COVID-19. The primary reason is that all the selected patients were non-AKI with normal renal clearance, which is significantly different from previous relevant studies that mainly focused on the acute or chronic renal failure patients with seriously damaged renal clearance. In such case, CRRT with or without oXiris filter becomes an important way to clear circulating and inflammatory chemokines. In addition, the levels of IL-6 in patients with severe COVID-19 was usually tens of pg/mL, which was similar to our results and far lower than those in patients with septic shock or CRS induced by Chimeric Antigen Receptor (CAR) T-cell infusion (1, 23). A previous study has confirmed that the immunomodulatory treatment of Afelimomab exerts a protective effect in patients with severe sepsis only when the level of IL-6 exceeds the threshold of 1000 pg/mL (24). The level of IL-6 in our study, which was far from reaching or close to this threshold, may explain these negative results. Furthermore, different inflammatory subphenotypes of COVID-19 may have a certain impact on the production and release of circulating cytokines and inflammatory chemokines (17). Lastly, changes in circulating cytokines and inflammatory chemokines (2, 20, 26, 29).

There are some limitations in the present study. First of all, as this was a small-size single-center study, the possible positive results may be hidden after increasing the number of cases, and the credibility and generalizability of our conclusion may weaken. Second, the duration varies from onset to ICU

admission, which may influence the production and removal of circulating cytokines and inflammatory chemokines to a certain extent, although no significant difference was observed in the clinical baseline data between the two groups except Scr. Third, the monitoring duration of cytokines and inflammatory chemokines levels was limited to 6 days, and thus the medium and long term role of CRRT with oXiris filter in non-AKI patients with severe and critical COVID-19 was not further explored. Finally, the types of cytokines and inflammatory chemokines detection were also limited.

Conclusion

CRRT with oXiris filter may not be an effective method for alleviating CRS in non-AKI patients with severe and critical COVID-19; thus, its application in these patients should be considered with caution to avoid increasing the unnecessary burden on society and individuals and making the already overwhelmed medical system even more overstretched. The findings of our study need to be further confirmed by well-designed large-sample studies.

Declarations

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Ethics Approval and Consent to Participate

Written informed consent was duly obtained from all enrolled patients. The study was approved by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University (IRB-AF/SC-04), and registered at clinicaltrials.gov.cn (ChiCTR2000030265).

Competing interests

The authors declare that they have no competing interests.

Authors' Contributions

K.K., Y.L., Y.G., J.Z., C.W., M.Z., and K.Y. took part in the conception, literature search, study design, statistical analysis, analysis and discussion of results, and manuscript preparation, editing, and review. D.F., W.Y., X.M., M.Y., Y.G., H.L., X.D., Y.J., J.W., W.X., and J.W. provided assistance for the conception, literature search, data acquisition and collation, statistical analysis, analysis and discussion of results, and manuscript preparation. All authors read and approved the final article.

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Consent for publication

All authors read and approved the final version for publication.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures



Figure 1

Longitudinal comparison of IL-2 levels between the two groups from day 1 to day 6.



Figure 2

Longitudinal comparison of IL-4 levels between the two groups from day 1 to day 6.



Figure 3

Longitudinal comparison of IL-6 levels between the two groups from day 1 to day 6.



Figure 4

Longitudinal Comparison of IL-10 levels between the two groups from day 1 to day 6.



Figure 5

Longitudinal comparison of TNF- α levels between the two groups from day 1 to day 6.



Figure 6

Longitudinal comparison of IFN- $\!\gamma$ levels between the two groups from day 1 to day 6