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RESEARCH ARTICLE

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Fatal outcome of severe fever with thrombocytopenia syndrome (SFTS) and severe and critical COVID-19 is associated with the hyperproduction of IL-10 and IL-6 and the low production of TGF-β

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Abstract

Severe fever with thrombocytopenia syndrome virus (SFTSV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause the hyperproduction of inflammatory cytokines, which have pathological effects in patient including severe or fatal cytokine storms. To characterize the effect of SFTSV and SARS-CoV-2 infection on the production of cytokines in severe fever with thrombocytopenia syndrome (SFTS) and COVID-19 patients, we performed an analysis of cytokines in SFTS and COVID-19 patients and also investigated the role of interleukin-10 (IL-10) in vitro studies: lipopolysaccharide-induced THP-1-derived macrophages, SFTSV infection of THP-1 cells, and SARS-CoV-2 infection of THP-1 cells. In this study, we found that levels of both IL-10 and IL-6 were significantly elevated, the level of transforming growth factor-β (TGF-β) was significantly decreased and IL-10 was elevated earlier than IL-6 in severe and critical COVID-19 and fatal SFTS patients, and inhibition of IL-10 signaling decreased the production of IL-6 and elevated that of TGF-β. Therefore, the hyperproduction of IL-10 and IL-6 and the low production

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of TGF-β have been linked to cytokine storm-induced mortality in fatal SFTS and severe and critically ill COVID-19 patients and that IL-10 can play an important role in the host immune response to severe and critical SARS-CoV-2 and fatal SFTSV infection.

KEYWORDS
COVID-19, cytokine storm, IL-10, IL-6, SFTS, TGF-β

1 | INTRODUCTION

Severe fever with thrombocytopenia syndrome virus (SFTSV, officially named *Dabie bandavirus*) an emerging tick-borne virus in Asia, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and avian influenza A (H5N1) viruses can cause severe and often fatal disease that is characterized by hyperinflammation with features of cytokine storm.[1–5]

The cytokine storm is a common pathogenic characteristic, namely, imbalanced immune responses with an exaggerated inflammatory cytokine reaction, excessive activation of immune cells, and life-threatening systemic inflammatory syndromes, which can cause serious pathological changes and result in multiorgan dysfunction.[1–11]

Interleukin 6 (IL-6) is a proinflammatory cytokine with pivotal roles in inflammation and a key cytokine in cytokine syndrome-induced mortality.[5–11]

IL-10 is a regulatory cytokine with pleiotropic roles in the immune system and is known to be an important immunoregulatory cytokine.[12] However, fatal severe fever with thrombocytopenia syndrome (SFTS) and severe and critical coronavirus disease 2019 (COVID-19) had significantly higher serum levels of IL-10 than those of patients with mild to moderate and nonfatal illness; in addition, systemic hyperproduction of both IL-6 and IL-10 can generate a cytokine storm, which contributes to their pathology, is more strongly correlated with the outcome of death, and viral load is not strongly correlated with outcomes (for severe disease with an ultimate outcome of recovery or death) than IL-6 and IL-10 levels in patients with an SFTSV infection and the relationship between mean cycle threshold (C_t) values of real time RT-PCR and severity of disease remain disputable and not clearly defined in COVID-19.[5,7,9,10]

Transforming growth factor-β (TGF-β) is a regulatory cytokine with pivotal functions in the control of inflammation. SARS-CoV-2 induces a TGF-β-dominated chronic immune response in severe COVID-19 while TGF-β was downregulated in SFTS patients compared with healthy controls.[12–15]

In this study, we found that the levels of IL-6 and IL-10 were significantly higher and produced at robust levels in fatal SFTS patients and severe and critically ill COVID-19. In contrast, TGF-β was significantly lower in fatal SFTS and severe and critical COVID-19 patients than in patients with nonfatal SFTS patients and mild to moderate COVID-19. Namely, elevated levels of IL-6 and IL-10 and decreased levels of TGF-β have been linked to severe inflammation and fatality SFTS and in COVID-19 patients.

We also found that IL-10 is elevated earlier than IL-6 and TGF-β, and the blocking of IL-10 signaling using an antibody against the IL-10 receptor can reduce IL-6 production and increase TGF-β production in lipopolysaccharide (LPS)-induced, SFTSV and SARS-CoV-2-infected immune cells, respectively, suggesting that IL-10, IL-6, and TGF-β may contribute to disease severity in SFTS COVID-19 and patients.

Therefore, IL-10 plays an important role in the host immune response to severe and critical SARS-CoV-2 and fatal SFTSV infection, and these results demonstrated that targeting IL-10 signaling using a monoclonal antibody against the IL-10 receptor is a potential immune-based intervention against fatal SFTS and severe and critically ill COVID-19 disease.[7,10]

2 | MATERIAL AND METHODS

2.1 | SFTS patients

We performed a retrospective study on eligible patients with SFTS from May 2013 to April 2022. During the study period, 84 patients were confirmed to be positive for partial small (S) and large (L) segments of SFTSV RNA using real-time RT-PCR.[16]

Of these patients, 65 confirmed patients were analyzed in the present study (Table S1). The study was approved by the Institutional Review Board (IRB) at the Jeju National University Hospital (IRB file no. 2021-03-012) and the study design and baseline characteristics of SFTS patients are available in the Data S1.

2.2 | COVID-19 patients

We performed a retrospective study on eligible patients with COVID-19 from August 2020 to July 2021.

During the study period, 188 confirmed patients were admitted, and 109 of these patients were analyzed in the present study (Table S2). The study was approved by the IRB at the Jeju National University Hospital (IRB file no. 2020-10-019), and the study design and baseline characteristics of COVID-19 patients are available in the Data S2.

2.3 | Analyses of cytokines in SFTS and COVID-19 patients

To characterize the effect of SFTSV and SARS-CoV-2 infection on the production of serum cytokines in SFTS and COVID-19 patients, IL-2, IL-4, IL-6, IL-10, IL-17A, interferon-γ (IFN-γ), and tumor necrosis factor (TNF-α) were measured using human Th1/Th2/Th17 CBA kits (BD Bioscience) according to the manufacturer's instructions, with minor modifications. Sample acquisitions were performed with a FACS Canto II flow cytometer and analyzed by FCAP Array software version 3.0 (BD Bioscience). All statistical analyses were performed using SPSS 22.0 (SPSS, an IBM Company). TGF-β was measured in the collected serum using a TGF-β-1 Human ELISA Kit (Thermo Fisher Scientific) according to the manufacturer's protocols.

To compare the mean difference between patients with fatal and nonfatal SFTS disease and between patients with severe and critical and mild to moderate COVID-19 disease, we usually used a two-sample *t*-test. When using this method, we checked some assumptions, such as normality, equal variance, and independence. When these assumptions were not met, we used a nonparametric two-sample *t*-test called the Wilcoxon–Mann–Whitney test.[7] $p < 0.05$ indicated statistical significance.

2.4 | THP-1 cells, SFTSV, and SARS-CoV-2

The human monocytic cell line THP-1 (ATCC TIB-202) was used to model macrophages. THP-1 cells were cultured in RPMI-1640

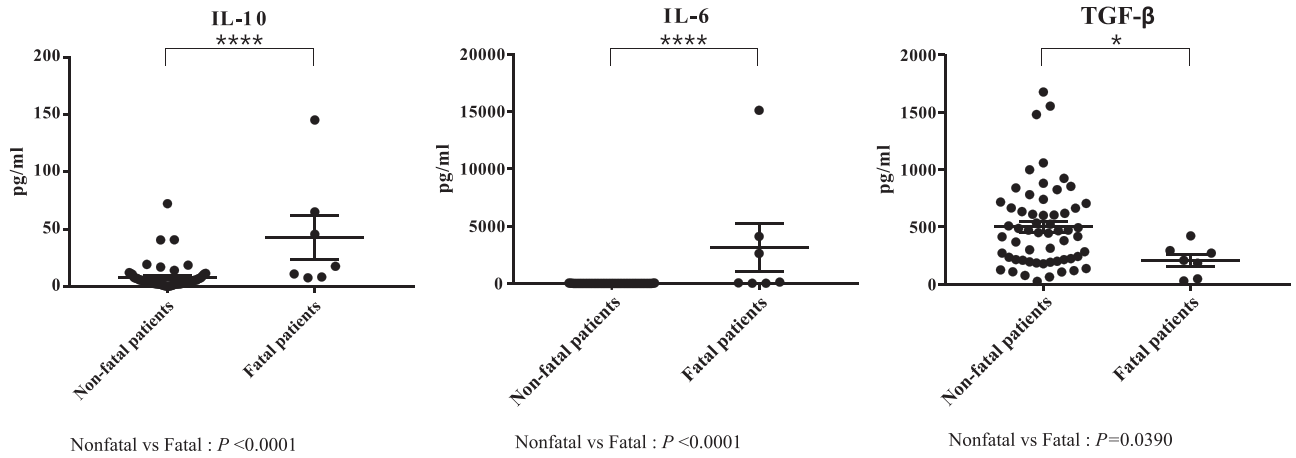

FIGURE 1 The serum levels of IL-6, IL-10, and TGF-β in SFTS patients with nonfatal and fatal diseases. The serum concentrations of IL-6, IL-10, and TGF-β from SFTS patients (total 65; nonfatal [$n = 58$] and fatal [$n = 7$]) were analyzed immediately after hospital admission. Each dot shows the cytokine concentration in an individual, and the horizontal bars indicate the respective group median.

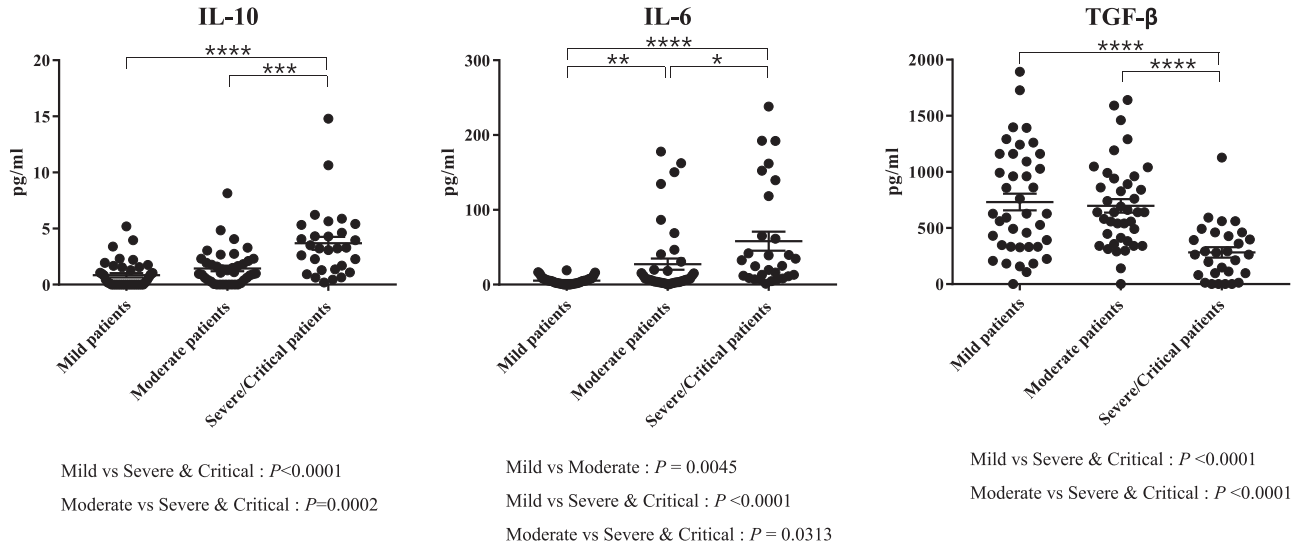

FIGURE 2 The serum levels of IL-6, IL-10, and TGF-β between mild to moderate patients and severe and critically ill COVID-19 patients. The serum concentrations of IL-6, IL-10, and TGF-β from COVID-19 patients (total 109; mild [$n = 40$], moderate [$n = 40$], and severe [$n = 27$] and critical [$n = 2$]) were analyzed immediately after hospital admission. Each dot shows the cytokine concentration in an individual, and the horizontal bars indicate the respective group median.

TABLE 1 Kinetics of IL-6, IL-10, and TGF-β concentrations in SFTS patients from May 2020 to April 2022.

Patients	Age (years)/sex	Severity	Outcome	Date[a]	IL-10	IL-6	TGF-β
P01-20	84/M	Mild	Recovered	18 May 2020	13.259	43.305	161.038
				21 May 2020	12.426	42.648	132.077
				23 May 2020	**4.657**	23.149	97.104
				25 May 2020	8.833	**4.356**	**448.197**
P02-20	79/F	Moderate	Recovered	27 May 2020	7.533	7.984	258.852
				29 May 2020	32.152	15.971	84.536
				31 May 2020	76.281	22.075	136.448
				2 Jun 2020	21.759	12.591	109.945
				4 Jun 2020	**2.335**	15.526	104.481
				6 Jun 2020	1.943	**3.162**	**224.973**
				7 Jun 2020	3.673	9.688	390.273
				8 Jun 2020	0	1.787	383.989
P03-20	61/F	Severe	Recovered	29 Jul 2020	8.414	132.111	188.907
				31 Jul 2020	35.568	332.601	182.077
				2 Aug 2020	12.842	86.302	228.525
				3 Aug 2020	**6.648**	46.122	95.464
				5 Aug 2020	3.416	**7.367**	**112.678**
				7 Aug 2020	4.912	2.55	152.022
				9 Aug 2020	3.459	4.356	266.776
				10 Aug 2020	0	9.315	300.929
				12 Aug 2020	0.675	11.089	233.443
				14 Aug 2020	3.028	15.272	494.918
				16 Aug 2020	4.401	8.943	276.885
				17 Aug 2020	2.074	8.819	224.699
P04-20	48/M	Severe	Recovered	3 Sep 2020	59.476	47.416	229.617
				5 Sep 2020	83.077	34.035	191.639
				7 Sep 2020	16.216	30.109	152.022
				9 Sep 2020	**9.796**	203.173	450.383
				11 Sep 2020	7.701	**21.556**	**1553.661**
				14 Sep 2020	1.856	6.381	633.989
P01-21	77/F	Mild	Recovered	28 Apr 2021	4.743	5.41	533.443
				30 Apr 2021	**1.424**	104.992	255.574
				4 May 2021	1.008	**48.222**	**826.339**
P02-21	57/M	Mild	Recovered	26 Jul 2021	18.633	13.196	317.049
				27 Jul 2021	**6.179**	6.589	800.109
				30 Jul 2021	0.694	**3.823**	**1037.814**
P03-21	63/M	Mild	Recovered	10 Aug 2021	15.056	16.629	438.1
				12 Aug 2021	2.001	6.475	619.1
P04-21	60/M	Severe	Death	12 Aug 2021	79.097	119.866	1298.5

TABLE 1 (Continued)

Patients	Age (years)/sex	Severity	Outcome	Date[a]	IL-10	IL-6	TGF-β
P05-21	73/M	Mild	Recovered	07 Sep 2021	18.999	6.078	571
				10 Sep 2021	**1.903**	8.18	442.9
				13 Sep 2021	0.872	**1.638**	**764**
				16 Sep 2021	0.738	2.268	1058.9
P06-21	73/F	Severe	Recovered	11 Nov 2021	0.94	259.88	3828.8
				13 Nov 2021	0.26	222.3	1791.3
				16 Nov 2021	2.28	206.1	3941.3
				18 Nov 2021	**0.2**	77.72	2753.8
				22 Nov 2021	0.08	**35.7**	**3466.3**
				29 Nov 2021	0.06	36.72	4078.8
P01-22	48/M	Mild	Recovered	26 Apr 2022	**7.435**	2.662	128.75
				28 Apr 2022	1.864	**1.944**	**216.25**
				29 Apr 2022	1.19	1.096	16.25

Note: Unit: pg/mL.

[a]The hospitalization and sampling date.

medium (Gibco) supplemented with 10% fetal bovine serum (FBS) (Gibco), 1% penicillin–streptomycin (Gibco), 200 mM L-glutamin (Gibco), and 55 mM 2-mercaptoethanol (Gibco) and kept in a humidified 5% CO_2 incubator at 37°C.

THP-1 cells were differentiated into a macrophage phenotype at a density of 2–4 × 10^5 cells/mL in 100 mm Cell Culture Dish (Corning Ins.), treated with 100 ng/mL phorbol myristate acetate (PMA) (Sigma-Aldrich) for 24 h, washed and suspended in culture medium without PMA.

SFTSV (GenBank accession no. MN329148-MN329150) was isolated from a Korean SFTS patient. The virus was propagated and titrated in Vero E6 cells (ATCC CRL-1586), which were cultured in Dulbecco's modified Eagle's medium (DMEM) (Gibco) supplemented with 10% FBS.

SARS-CoV-2/BA.1.1 was isolated from a nasopharyngeal swab taken from a patient with COVID-19. The virus was propagated and titrated in Vero E6 cells (ATCC CRL-1586), which were cultured in DMEM (Gibco) supplemented with 2% FBS and 1% penicillin–streptomycin (Gibco).[17]

2.5 | LPS-induced THP-1-derived macrophages to investigate the role of IL-10 and IL-6

THP-1 cells were divided into three different treatment groups: THP-1 cells treated with LPS (2 μg/mL) (Sigma-Aldrich) as the control group; cells treated with LPS (2 μg/mL) (Sigma-Aldrich) and IL-6R polyclonal antibody (10 μg/mL) (Invitrogen); and cells treated with LPS (2 μg/mL; Sigma-Aldrich) and IL-10RA polyclonal antibody (10 μg/mL) (Invitrogen).

The three different treatment groups were stimulated for 6, 12, 24, and 48 h, and the levels of IL-2, IL-4, IL-6, IL-10, IL-17A, IFN-γ, and TNF-α were measured in the collected supernatants using human Th1/Th2/Th17 CBA kits (BD Bioscience) according to the manufacturer's instructions, with minor modifications. Sample acquisitions were performed with a FACS Canto II flow cytometer and analyzed by FCAP Array software version 3.0 (BD Bioscience). TGF-β was measured in the collected supernatants using a TGF-β-1 Human ELISA Kit (Thermo Fisher Scientific) according to the manufacturer's protocols.[7]

2.6 | Investigating the role of IL-10 in SFTSV infected THP-1-derived macrophages

To investigate the role of IL-10 in SFTSV-infected THP-1 cells, THP-1 cells were infected with SFTSV at a multiplicity of infection (MOI) of 1, and SFTSV-infected THP-1 cells were divided into two different treatment groups: SFTSV-infected THP-1 cells were used as the control group, and SFTSV-infected THP-1 cells were treated with the IL-10RA polyclonal antibody (10 μg/ml) (Invitrogen). The two different treatment groups were incubated for 6, 12, 24, and 48 h, and the levels of IL-2, IL-4, IL-6, IL-10, IL-17A, TNF-α, and IFN-γ were measured using human Th1/Th2/Th17 CBA kits (BD Bioscience) according to the manufacturer's instructions, with minor modifications. Sample acquisitions were performed with a FACS Canto II flow cytometer and analyzed by FCAP Array software version 3.0 (BD Bioscience). TGF-β was measured in the collected supernatants using

a TGF-β-1 Human ELISA Kit (Thermo Fisher Scientific) according to the manufacturer's protocols.[7]

2.7 | Investigating the role of IL-10 in SARS-CoV-2 infected THP-1-derived macrophages

To investigate the role of IL-10 in SARS-CoV-2-infected THP-1 cells, THP-1 cells were infected with SARS-CoV-2 at a MOI of 0.01, and these SARS-CoV-2-infected THP-1 cells were divided into two different treatment groups: SARS-CoV-2-infected THP-1 cells as the control group and SARS-CoV-2-infected THP-1 cells treated with the IL-10RA polyclonal antibody (10 μg/mL) (Invitrogen). The two different treatment groups were incubated for 6, 12, 24, and 48 h, and the levels of IL-2, IL-4, IL-6, IL-10, IL-17A, IFN-γ, and TNF-α were measured using human Th1/Th2/Th17 CBA kits (BD Bioscience) according to the manufacturer's instructions, with minor modifications. Sample acquisitions were performed with a FACS Canto II flow cytometer and analyzed by FCAP Array software version 3.0 (BD Bioscience). TGF-β was measured in the collected supernatants using a TGF-β-1 Human ELISA Kit (Thermo Fisher Scientific) according to the manufacturer's protocols.[7,18]

3 | RESULTS

3.1 | Levels of serum IL-6, IL-10, and TGF-β in SFTS and COVID-19 patients

Among SFTS patients, serum IL-6 and IL-10 concentrations in those with fatal disease were significantly higher than those in patients with nonfatal disease, and TGF-β concentrations in the former were significantly lower than those in the latter during the initial clinical course of hospitalization (Figure 1; Table S3).

However, there were no statistically significant differences in serum levels of IL-2, IL-4, IL-17A, IFN-γ, and TNF-α between patients with fatal disease and those with nonfatal disease (Figure S1; Table S3).[7]

In COVID-19 patients, serum IL-6 and IL-10 concentrations in patients with severe and critical disease were significantly higher than those in patients with mild to moderate disease, and TGF-β concentrations in patients with severe and critical disease were significantly lower than those in patients with mild to moderate disease during the initial clinical course of hospitalization (Figure 2; Table S4).

However, similar to the results of SFTS patients, there were no statistically significant differences in plasma levels of IL-2, IL-4, IL-17A, IFN-γ, and TNF-α between patients with mild to moderate and severe/critical disease (Figure S2; Table S4).

TABLE 2 Kinetics of IL-10, IL-6, and TGF-β concentrations in patients with nonfatal severe COVID-19.

Patients	Age (years)/sex	Severity	Outcome	Date[a]	IL-10	IL-6	TGF-β
P01-20	73/M	Severe	Recovered	1 Jan 2020	**5.416**	161.304	284
				8 Jan 2020	3.154	**52.223**	**484**
				11 Jan 2020	1.129	11.514	744
P02-20	71/F	Severe	Recovered	4 Jan 2020	1.129	8.53	1244
P03-20	70/F	Severe	Recovered	19 Feb 2020	**4.007**	36.857	784
				27 Feb 2020	2.15	**17.536**	**984**
P04-20	59/M	Severe	Recovered	28 May 2020	**7.93**	62.25	184
				3 Jun 2020	2.869	**82.671**	**464**
P05-20	67/M	Severe	Recovered	27 Mar 2020	2.582	6.655	884
				31 Mar 2020	1.424	2.603	764
				5 Apr 2020	0.981	5.251	784
P06-20	31/M	Severe	Recovered	14 Apr 2020	0.529	3.538	304
				24 Apr 2020	0.529	4.473	324
P01-21	74/M	Severe	Recovered	1 Jan 2021	**4.289**	211.011	384
				11 Jan 2021	1.716	**17.695**	**544**
P02-21	50/F	Severe	Recovered	22 May 2021	**5.135**	99.97	144
				31 May 2021	2.439	**5.563**	**864**
P03-21	62/M	Severe	Recovered	14 Jun 2021	**3.439**	9	44
				30 Jun 2021	1.57	**7.123**	**824**

Note: Unit: pg/mL.

[a]The hospitalization and sampling date.

In this study, we found that the levels of serum IL-6, IL-10, and TGF-β were significantly associated with the outcomes of patients with SFTSV and SARS-CoV-2 (Figures 1 and 2).[7,9,10,14,15]

3.2 | Kinetics of IL-6, IL-10, and TGF-β in SFTS and COVID-19 patients

We studied the kinetics of the IL-6, IL-10, and TGF-β levels in patients with nonfatal SFTS and severe COVID-19 patients, and the results showed that IL-10 is elevated earlier than IL-6 (Tables 1 and 2).[7] In contrast, TGF-β is decreased later (Tables 1 and 2).

Therefore, we studied the correlation between IL-6, IL-10, and TGF-β in LPS-induced THP-1-derived macrophages treated with IL-6R and IL-10RA polyclonal antibodies. The results showed that the level of IL-6 was decreased and that of TGF-β increased when we treated with the IL-10RA polyclonal antibody (Figure 3; Table S5).

However, there were no significant differences between IL-6, IL-10, and TGF-β in LPS-induced THP-1-derived macrophages treated with the IL-6R polyclonal antibody (Figure 3; Table S5).

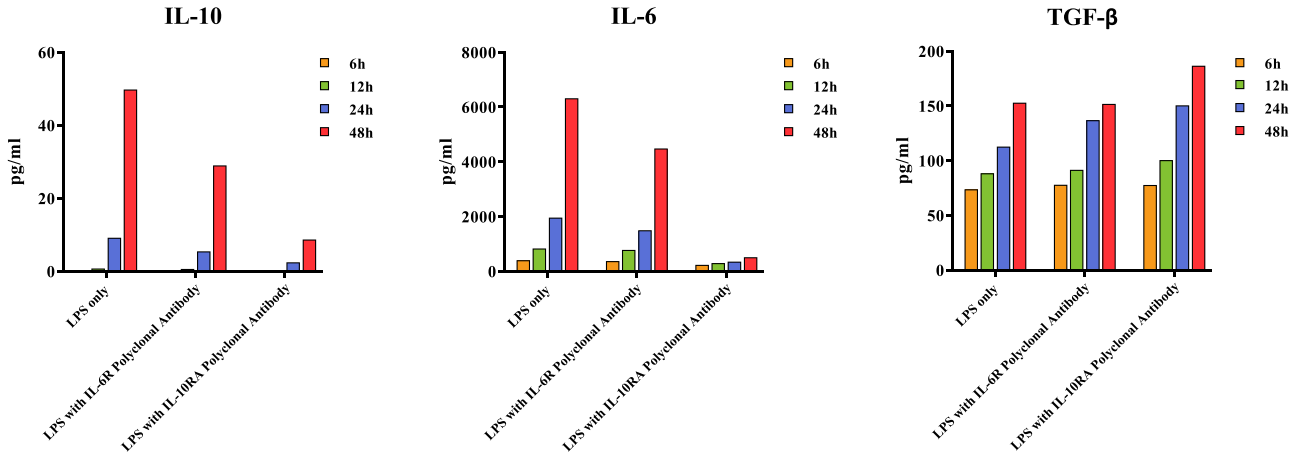

FIGURE 3 The lipopolysaccharide (LPS)-induced IL-6 concentration in THP-1 cells is suppressed by the IL-10RA polyclonal antibody, and the LPS-induced TGF-β concentration in THP-1 cells is induced by the IL-10RA polyclonal antibody. Human monocyte THP-1 cells were treated with LPS (10 μg/mL), LPS + IL-10RA polyclonal antibody (10 μg/mL) or LPS + IL-6R polyclonal antibody for 6, 12, 24, and 48 h, and the levels of IL-6 and IL-10 were measured using human Th1/Th2/Th17 CBA kits (BD Bioscience). TGF-β was measured in the collected supernatants using a TGF-β-1 Human ELISA Kit (Thermo Fisher Scientific) according to the manufacturer's protocols. [10].

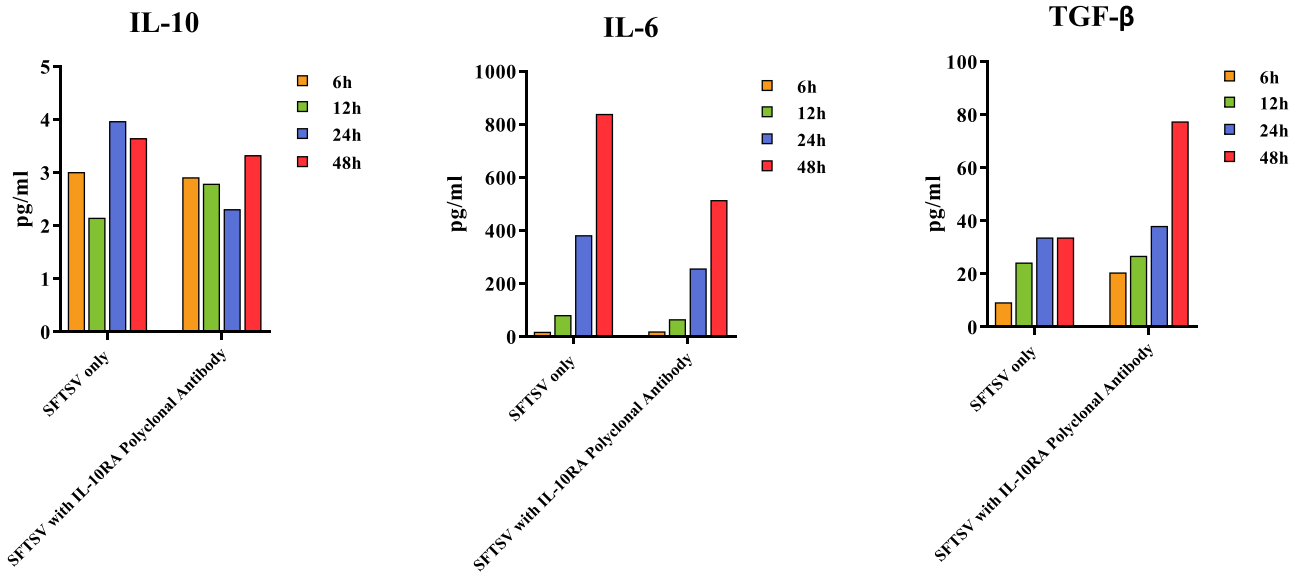

FIGURE 4 IL-6 concentration in SFTSV-infected THP-1 cells is suppressed by IL-10RA polyclonal antibody and TGF-β concentration in SFTSV-infected THP-1 cells is induced by IL-10RA polyclonal antibody. Human monocyte THP-1 cells were infected with SFTSV with IL-10RA polyclonal antibody for 6, 12, 24, and 48 h, and the levels of IL-6 and IL-10 were measured using human Th1/Th2/Th17 CBA kits (BD Bioscience). TGF-β was measured in the collected supernatants using a TGF-β-1 Human ELISA Kit (Thermo Fisher Scientific) according to the manufacturer's protocols [10].

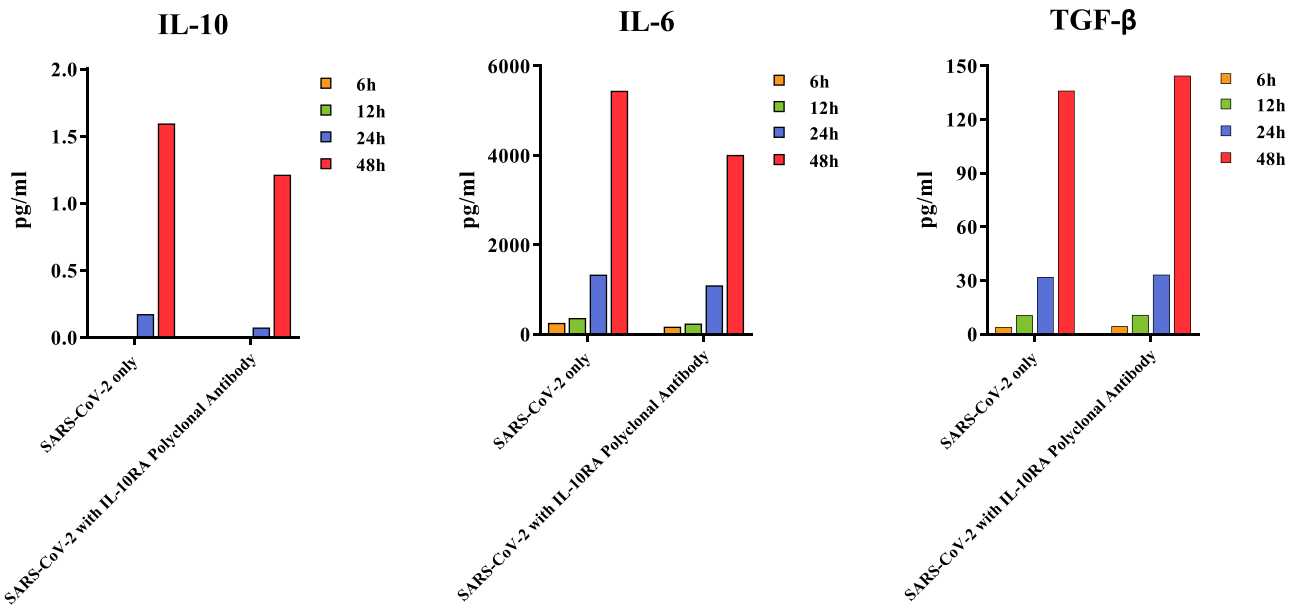

FIGURE 5 IL-6 concentration in SARS-CoV-2-infected THP-1 cells is suppressed by IL-10RA polyclonal antibody and TGF-β concentration in SARS-CoV-2-infected THP-1 cells is induced by IL-10RA polyclonal antibody. Human monocyte THP-1 cells were infected with SARS-CoV-2 or SARS-CoV-2 with IL-10RA polyclonal antibody for 6, 12, 24, and 48 h, and the levels of IL-6 and IL-10 were measured using human Th1/Th2/Th17 CBA kits (BD Bioscience). TGF-β was measured in the collected supernatants using a TGF-β-1 Human ELISA Kit (Thermo Fisher Scientific) according to the manufacturer's protocols [10].

We also treated THP-1-derived macrophages infected with SFTSV and SARS-CoV-2 with the IL-10RA polyclonal antibody to determine the role of IL-10 in SFTSV and SARS-CoV-2 infection and the results were similar to those for LPS-induced THP-1-derived macrophages: the level of IL-6 was decreased and that of TGF-β increased (Figures 4 and 5; Tables S6 and S7).

4 | DISCUSSION

Fatal SFTS and severe and critically ill COVID-19 patients develop a pathological state termed cytokine release syndrome.[1,3–11]

Cytokine release syndrome can be triggered by infections and is characterized by rapid and prolonged systemic elevation of inflammatory cytokines and chemokines, and IL-6 is a proinflammatory cytokine and a key cytokine in cytokine release syndrome-induced mortality.[1,3–11]

Serum IL-10 is an important anti-inflammatory cytokine.[12] However, the serum IL-10 concentration was significantly higher in fatal SFTS, severe and critically ill COVID-19, and H5N1 patients and, like IL-6, can predict poor outcomes in SFTS and COVID-19 patients (Figures 1 and 2).[5,7,9,10]

In this study, we found that TGF-β concentrations were significantly lower in fatal SFTS and severe and critical COVID-19 patients (Figures 1 and 2). Namely, the hyperproduction of IL-6 and IL-10, which is a feature of cytokine storms, and the low production of TGF-β have been linked to cytokine storm-induced mortality in fatal SFTS and severe and critically ill COVID-19 patients (Figures 1 and 2).

Furthermore, IL-10 was elevated earlier than IL-6, and TGF-β was decreased later than IL-10 in SFTS and COVID-19 patients (Tables 1 and 2).

When we blocked IL-10 signaling using an antibody against the IL-10 receptor, the production of IL-6 was decreased, and the production of TGF-β was increased (Figures 3–5; Table S5–S7).

IL-10 is usually known as an anti-inflammatory cytokine.[12] However, IL-10 can also be an immune-activating and proinflammatory cytokine in some autoimmune diseases, cancers, and severe and critically ill COVID-19 patients. Patients with fatal SFTS and H5N1 present with dramatically elevated serum IL-10 concentrations that correlate with disease severity.[5,7,9–11]

Fatal SFTS and severe and critically ill COVID-19 patients present with dramatically elevated serum levels of IL-10 and IL-6 and dramatically decreased serum levels of TGF-β that correlate with disease severity.

When we blocked the signal of IL-10 using an antibody against the IL-10 receptor, IL-6 was decreased and TGF-β was elevated in the THP-1-cell study (Figures 3–5).

Therefore, we suggest that IL-10 can induce the production of IL-6 and inhibit the production of TGF-β in cytokine storms and might play a pathological role in SFTS and COVID-19 disease progression and also propose that IL-10 may be a potential target for reducing SFTS and COVID-19 mortality.

5 | CONCLUSION

In conclusion, our findings demonstrated that IL-10 is a potential target for the treatment of SFTSV and SARS-CoV-2-related immunopathology.

Therefore, blockade of IL-10 signaling using monoclonal antibodies against the IL-10 receptor is a promising therapeutic for treating fatal SFTS and severe and critically ill COVID-19 patients.[7,10]

AUTHOR CONTRIBUTIONS

Keun Hwa Lee conceived of the research and designed the study. Keun Hwa Lee acquired the funding. Keun Hwa Lee, Kyung-Mi Lee, Nam-Hyuk Cho, Su Yeon Kang, and Jeong Rae Yoo wrote the manuscript. Su Yeon Kang, Jeong Rae Yoo, Yejin Park, So-Hee Kim, Sang Taek Heo, Seong Hyeon Park, Misun Kim, Songhyeok Oh, Tae-Jin Kim, Moo-Seung Lee, and Jung Mogg Kim performed the experiments. Keun Hwa Lee, Kyung-Mi Lee, Nam-Hyuk Cho, Su Yeon Kang, and Jeong Rae Yoo analyzed the data. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used to support the results of this study are available from the corresponding author (Keun Hwa Lee) upon reasonable request.

ETHICS STATEMENT

This study was reviewed and approved by the Local Research Ethics Committee of the Jeju National University Hospital. Informed consent was obtained from all patients following the principles of the Helsinki Declaration.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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