Cytokines as predictors of COVID-19 severity: evidence from a meta-analysis

To the editor With great interest, we read the articles by Kosmaczewska et al[1] and Marcinkiewicz et al,[2] showing the potential role of cytokines, including interleukin (IL) 6, as predictors of coronavirus disease 2019 (COVID-19) severity. In most cases of COVID-19, the course of the disease is asymptomatic, or the symptoms are so mild that the patient does not require hospitalization. However, some patients experience a sudden deterioration in health. This phenomenon is called a cytokine storm and is caused by an abnormal overresponse of the immune system. Cytokine storms are common complications of COVID-19, influenza, and other coronavirus-induced respiratory diseases such as severe acute respiratory syndrome and Middle East respiratory syndrome. During the course of the disease there is a rapid release of cytokines, that is, proteins which stimulate other immune system cells to specific reactions. Cytokines, including ILs, coordinate the body's response to infection and cause inflammation. Interleukin 6 exerts a multidirectional effect on the cells of the innate and gained immune systems. It plays a key role in initiating and developing an acute inflammatory response by activating cells via the classical route. It also facilitates the development of gained response and directs its course. As shown by Musselman et al,[3] an increase in the concentration of IL-6 and other proinflammatory cytokines also affects the central nervous system, contributing to the occurrence or intensification of symptoms characteristic of both neuropsychological and somatic depression.

To confirm the effect of cytokines as predictors of COVID-19 severity, we performed a meta-analysis following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for reporting systematic reviews and meta-analyses of observational studies.[4] The detailed methodology of the study is described in Supplementary material.

Twenty-four studies reported IL-6 levels in the severe and nonsevere COVID-19. Pooled analysis showed significantly higher IL-6 concentrations in patients with severe disease compared with the nonsevere group (mean difference, 21.9; 95% CI, 17.64–26.16; P <0.001; FIGURE 1). The analysis also showed that higher levels of tumor necrosis factor, IL-2R, IL-4, IL-8, and IL-10 were associated with a more severe course of COVID-19 (Supplementary material). Moreover, the pooled

Study or subgroup[a]	Severe Mean	SD	Total	Nonsevere Mean	SD	Total	Weight, %	Mean difference IV, random, 95% CI
Cai Q, 2020	28.392	9.854	58	9.42	2.1	40	7.4	18.97, 16.35–21.59
Chen L, 2020	72	12	14	34	7	15	6.7	38, 30.78–45.22
Chen LD, 2020	39.513	33.529	25	3.67	1.652	69	5.4	35.84, 22.69–48.99
Chen R, 2020	8.4605	1.1943	203	7.593	1.244	345	7.5	0.87, 0.66–1.08
Chen X, 2020	44.7176	34.8665	27	13.9	7.868	21	5.3	30.82, 17.24–44.39
Gao Y, 2020	38.6	10.458	15	12.628	5.518	28	7	25.97, 20.3–31.65
Guirao JJ, 2020	320.45	220.96	6	29.1573	15.2819	44	0.1	291.29, 114.43–468.15
Guner R, 2020	63.75	48.226	50	17.85	7.767	172	5.3	45.9, 32.48–59.32
Huang H, 2020	23.29	8.4	21	12.1	4.513	43	7.3	11.19, 7.35–15.03
Liu L, 2020 (a)	20.225	9.025	26	5.35	2.336	24	7.3	14.88, 11.28–18.47
Liu L, 2020 (b)	9.35	8.162	7	1.825	2.132	44	6.9	7.52, 1.45–13.6
Qin C, 2020	28.6	7.5	286	17.9	6.2	166	7.5	10.7, 9.42–11.98
Sun Y, 2020	33.6321	28.6428	19	12.55	10.8427	44	5.3	21.08, 7.81–34.35
Xu X, 2020	17.1564	29.6613	41	2.755	1.238	47	6.3	14.4, 5.32–23.49
Xu Y, 2020	20.6	9.45	25	6.375	2.352	44	7.3	14.23, 10.46–17.99
Zeng Z, 2020	37.7835	26.231	224	13.4	3.3	93	7.3	24.38, 20.88–27.88
Total, 95% CI			1047			1239	100	20.2, 14.53–25.87

Heterogeneity: Tau² = 111.01; χ² = 975.27, *df* = 15 (*P* <0.00001); I^2 = 98%
Test for overall effect: *Z* = 6.98 (*P* <0.00001)

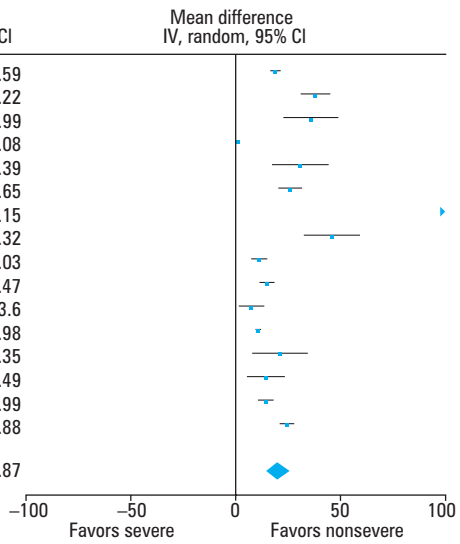

FIGURE 1 Pooled analysis of interleukin 6 concentration in patients with severe and nonsevere coronavirus disease 2019.
a References to all studies are provided in Supplementary material.

analysis revealed that IL-6 and IL-10 concentrations were higher in patients admitted to intensive care units than in patients hospitalized in other units. Additional analysis showed that significantly higher levels of tumor necrosis factor, IL-2R, IL-6, IL-8, and IL-10 were observed among those who died from COVID-19 than among those who survived.

In summary, this meta-analysis is the most up-to-date presentation of the use of ILs as predictors of COVID-19 severity. Simultaneously, the obtained results show that cytokines (including ILs) can be used as independent predictors of the severity of a patient's condition.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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Authors' reply We are grateful to Szarpak et al[1] for their interest in our review article describing the role of immune deregulation in the adverse clinical course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, especially since the results of their meta-analysis confirm the essential role of immune alterations for the development of critical coronavirus disease 2019 (COVID-19). They report significantly higher serum levels of tumor necrosis factor alpha (TNFα), interleukin (IL) 6, IL-2R, IL-4, IL-8, and IL-10 in patients with a more severe clinical course of COVID-19, and emphasize a predictive role of IL-6 and IL-10 cytokines for development of critical disease requiring intensive care support. Their results are also consistent with a recent meta-analysis from 24 clinical studies identifying dramatically elevated levels of IL-6 and IL-10 as the most important clinical predictors of an unfavorable COVID-19 outcome.[2]

Among proinflammatory cytokines and chemokines whose level is elevated in patients with COVID-19, one of the most important is IL-6. It plays a key role in mortality in cytokine release syndrome which may lead to acute respiratory distress syndrome, multiorgan failure, and death, and is also observed in other coronavirus infections, such as severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS). However, it should be noted that a unique cytokine signature of COVID-19 clinical course is systemic elevation of IL-10.[3] Remarkably, elevation of serum IL-10, similarly to IL-6, was found to be mostly significant in patients with COVID-19 admitted to an intensive care unit (ICU). Furthermore, highly upregulated IL-10 and IL-6 were strongly correlated with each other and with biomarkers of inflammation, such as C-reactive protein. Of note, it has also been reported that IL-10 is substantially elevated earlier than IL-6 during COVID-19 development.[3]

The mechanism of this unique SARS-CoV-2 ability to stimulate IL-10 is still unknown. Initially, it was believed that upregulation of IL-10, a cytokine with immunoregulatory properties, is a part of a negative feedback loop induced in response to the rapid accumulation of several proinflammatory cytokines. However, there is a growing body of evidence that the dramatic systemic increase of IL-10 in COVID-19 might instead be involved in pathogenesis of the severity of SARS-CoV-2 infection rather than immunoregulation and inhibition of the immune system. The above suggestion is consistent with the observation that IL-10 strongly correlates with disease severity and poor clinical outcomes,[3] which points to the possibility that IL-10 might play a role in immune activation in COVID-19 patients. Furthermore, serum IL-10 level is associated with levels of other proinflammatory cytokines such as TNF-α, IL-2R, IL-8, IL-18, interferon γ, and granulocyte-macrophage colony-stimulating factor in patients with critical COVID-19.[1,3] The finding of a correlation between elevated levels of IL-10 and an increased population of exhausted $CD8^+TIM3^+PD1^+$ lymphocytes in peripheral blood may indicate a role of IL-10 in overactivation of T cells during COVID-19 progression.[4] A role of IL-10 in aggravated inflammation and organ destruction related to COVID-19 might be strengthened by the direct impact of IL-10 on relative expansion of

the pathogenic cytotoxic $CD8^+$ T cells despite a reduction in the total number of lymphocytes in peripheral blood in critically ill COVID-19 patients.[5]

A meta-analysis performed by Szarpak et al[1] demonstrating significantly higher levels of both pathogenic IL-6 and IL-10 cytokines in patients admitted to the ICU compared with non-ICU patients, together with elevated levels of other proinflammatory cytokines such as TNF-α, IL-2R, and IL-8 in patients who died from COVID-19 complications, seems to support the suggestion of a predictive role of serum cytokine levels for the critical outcome of COVID-19.

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Authors' reply We read with great interest the article by Szarpak et al[1] showing the association between high blood levels of cytokines and the severity of coronavirus disease 2019 (COVID-19). In order to confirm the effect of cytokines, including interleukin 6 (IL-6), as predictors of COVID-19 severity, they performed a meta-analysis. Pooled analysis showed significantly higher IL-6 levels for patients with severe conditions compared with the nonsevere group, and also for patients who died from COVID-19 compared with those who survived. These results are in agreement with our hypothesis and with other studies suggesting the major role of IL-6 in the pathogenesis of COVID-19–induced cytokine storm.[2,3] Moreover, the significantly increased levels of IL-6 in patients with COVID-19 have been considered an independent biomarker for predicting a poor prognosis.[3] However, the levels of inflammatory cytokines in patients with a severe course of COVID-19 are significantly less elevated than in patients with acute respiratory distress syndrome unrelated to COVID-19 or sepsis.[4]

On the other hand, other studies revealed a positive correlation of coagulopathy with cytokine storm in patients with COVID-19. Namely, D-dimer concentration rises early, which indicates that coagulopathy acts as a prodrome of the cytokine storm.[5]

In conclusion, current data suggest that elevated blood levels of IL-6, C-reactive protein, and D-dimer, as well as lymphopenia are the best predictors of the fatal outcome of COVID-19.[4,5]

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