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Serum IP-10 and IL-7 levels are associated with disease severity of coronavirus disease 2019

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ABSTRACT

We quantified the serum levels of 34 cytokines/chemokines in 30 patients with SARS-CoV-2 infection. Elevated levels of IP-10 and IL-7 were detected in the acute and convalescent stages of the infection and were highly associated with disease severity.

1. Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a severe threat to the international community. Patients with COVID-19 are clinically characterized by fever, cough, fatigue, sputum production, lymphocytopenia, and radiographic evidence of pneumonia [1]. Death may result from sepsis, respiratory failure, and acute respiratory distress syndrome (ARDS) due to alveolar damage or multiple organ dysfunction caused by systemic inflammation [1] Cytokines/chemokines have long been thought to play an essential role in immunity and immunopathology during virus infections. Although increased serum levels of several inflammatory cytokines and chemokines were associated with disease severity and death of SARS-CoV-2 [1–5], the results of these studies were discrepancies. The pathogenesis of COVID-19 is poorly understood, and factors associated with severity remain elusive. Therefore, to further understand the immuno-pathogenesis of SARS-CoV-2, we studied the expression profile of cytokines/chemokines in the serum of patients with COVID-19.

2. Methods

2.1. Patients and clinical samples

From January to February 2020, a total of 30 COVID-19 patients and individuals with asymptomatic infection of SARS-CoV-2 were identified at the Fifth Hospital of Shijiazhuang, Shijiazhuang City, Hebei Province, China. All COVID-19 patients and individuals with asymptomatic infection of SARS-CoV-2 were laboratory-confirmed by real-time reverse-transcription polymerase chain reaction (RT-PCR) using a SARS-CoV-2 nucleic acid detection kit (Cat No. DA0930-DA0932, DAAN GENE Ltd., Guangzhou, China). After the confirmation diagnose, COVID-19 patients and individual with asymptomatic infection of SARS-CoV-2 were recruited to participate the study. After obtaining informed consent, serum samples were collected from participants at the acute and convalescent stages of infection. We defined the definition of acute and convalescent stages based on the symptoms of the patients after infection. The acute stage always correlated with fever, cough, fatigue, expectoration, dyspnea, chills, and so on, and the convalescent stages correlated symptoms were significantly improved. Therefore, the acute stage was defined as within 2 weeks after symptom onset for

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symptomatic patients and after first RT-PCR positive RNA detection of SARS-CoV-2 for asymptomatic infection, and the convalescent stage was defined between 2 and 4 weeks after symptom onset for symptomatic patients and after first RT-PCR positive RNA detection of SARS-CoV-2 for asymptomatic infection. The disease severity were categorized depending on the severity of illness according to the Diagnosis and Treatment Plan for New Coronavirus Infected Pneumonia (Trial Seventh Edition) by the National Health and Health Commission of China [6]. Twenty-four serum samples from healthy adults with matched age and sex were used as normal control samples. The exclusion criteria for serum samples from healthy adults were as follows: individual who had an acute or chronic infectious disease, any clinically significant disorder (e.g. depressive disorder and anxiety disorder), any medication with known influence on immunological factors. The study was conducted following the Declaration of Helsinki, and the Ethical Committee of the Fifth Hospital of Shijiazhuang approved this study (2020008).

2.2. Cytokine measurement

The concentration of serum cytokines/chemokines (interferon alpha [IFN-α], IFN-γ, IL [interleukin]-1β, IL-1α, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 p70, IL-13, IL-15, IL-17A, IL-18, IL-21, IL-22, IL-23, IL-27, IL-31, tumor necrosis factor alpha [TNF-α], TNF-β, interferon gamma-induced protein 10 [IP-10], monocyte chemoattractant protein 1 [MCP-1], macrophage inflammatory protein-1α [MIP-1α], MIP-1β, regulated on activation and normal T cell expressed and secreted [RANTES], stromal-cell-derived factor 1 Alpha [SDF1α], Eotaxin, granulocyte-macrophage colony stimulating factor [GM-CSF], growth-regulated oncogene alpha [GRO-α]) were quantified using Cytokine & Chemokine Convenience 34-Plex Human ProcartaPlex™ Assay (EPXR340-12167-901, Invitrogen), according to the manufacturer's protocol.

2.3. Statistical analysis

Comparison of clinical parameters among severe, moderate, and asymptomatic patients was calculated by non-parametric Mann-Whitney test (for continuous variables) or Pearson χ^2 test on cross table (for categorical variables). For multiple groups, comparisons were made by two-way ANOVA or non-parametric Kruskal–Wallis test followed by multiple comparisons. $P < 0.05$ was considered to indicate a significant difference.

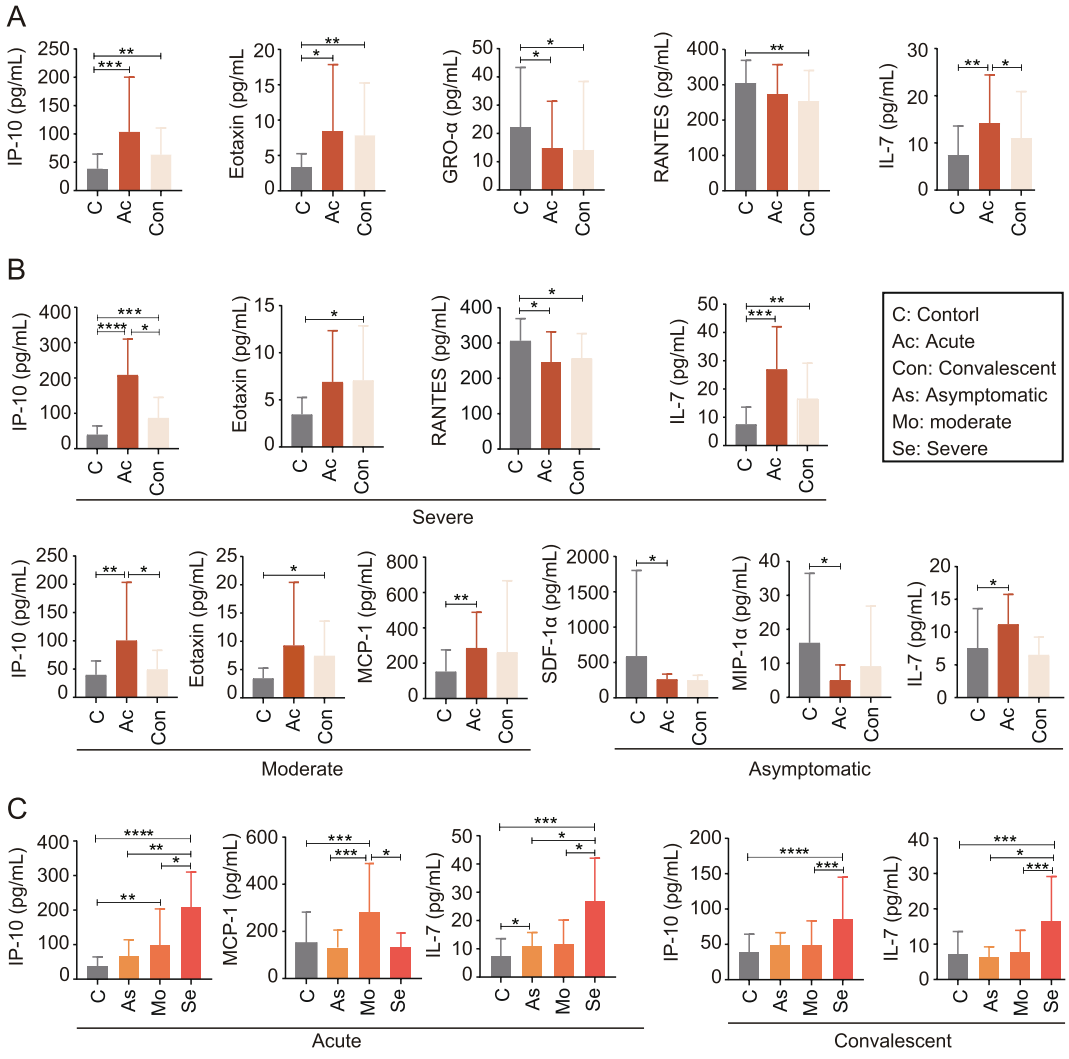

Fig. 1. Serum cytokine and chemokine levels in patients with severe acute respiratory syndrome coronavirus 2 infection. A, Levels in the acute (n = 47) and convalescent (n = 64) serum samples. B, Levels in the acute (n = 8, 19, and 20 for severe, moderate, and asymptomatic) and convalescent (n = 24, 35, and 5 for severe, moderate, and asymptomatic) serum samples by disease severity. C, Levels in serum samples of severe, moderate, and asymptomatic patients by infection stage. IL, interleukin; IP, interferon gamma-induced protein; GRO, growth-regulated oncogene; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; RANTES, regulated on activation and normal T cell expressed and secreted. One-way analysis of variance (ANOVA) was used for statistical analysis. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

3. Results

3.1. Study patients and serum samples

Twenty-one patients (5 severe and 16 moderate) and 9 subjects with asymptomatic infection were enrolled (Supplemental Table1). Older age was associated with severe disease (Supplemental Table 1; $P < 0.05$). In addition, the decrease in lymphocytes was observed in patients with severe disease (Supplemental Table 2). More demographic and clinical information of patients is provided in Supplementary Table 2. In total, 111 serum samples, including 47 serum samples of acute stage of infection and 64 serum samples of convalescent stage of infection, were collected (Supplemental Table1).

3.2. Serum cytokines profiles in acute and convalescent

Among 34 cytokines/chemokines tested, the levels of 23 cytokines/chemokines were undetectable in the serum of patients and controls. Therefore, the remaining 11 cytokines/chemokines (IP-10, Eotaxin, RANTES, MCP-1, SDF-1α, MIP-1β, MIP-1α, Gro-α, IL-7, IL-8, and IL-18) were further analyzed. We first analyzed expression profiles of the 11 cytokines/chemokines between acute and convalescent serum (Fig. 1A). The levels of IP-10 and Eotaxin were significantly higher in both acute ($P = 0.0001$ and 0.030, respectively) and convalescent ($P = 0.008$ and 0.008, respectively) sera compared with control subjects. The level of IL-7 was significantly higher in the acute serum compared to the convalescent serum ($P = 0.025$) and control subjects ($P = 0.002$). In contrast, there were significantly decreased levels of GRO-α in the acute ($P = 0.0317$) and convalescent ($P = 0.0143$) sera and RANTES in the convalescent ($P = 0.0036$) sera compared with the control subjects. No significant differences were observed for the levels of the other six cytokines/chemokines between patients and control subjects (Supplemental Fig. 1).

3.3. Serum cytokines profiles between acute and convalescent of disease severity

We further sub-analyzed the levels of these 11 cytokines/chemokines between the acute and convalescent phases of each group of patients (Fig. 1B). For severe patients, the levels of IP-10 and IL-7 were significantly higher in the acute and convalescent sera than control subjects. Besides, the level of IP-10 in the acute serum was substantially higher than the convalescent serum ($P = 0.029$). RANTES level in acute and convalescent sera was lower compared with controls ($P = 0.038$ and 0.017, respectively). A higher level of Eotaxin was observed in the convalescent serum compared with controls ($P = 0.02$), but no difference was found compared with the acute serum. For moderate patients, a significantly higher level of IP-10 was also detected in the acute serum compared with the convalescent serum and control subjects ($P = 0.042$ and 0.004, respectively). We also found a higher level of MCP-1 in the acute serum and of Eotaxin in the convalescent serum compared with control subjects ($P = 0.002$ and 0.013, respectively). For patients with asymptomatic infection, IL-7 level in the acute serum was significantly higher than compared to the control subjects ($P = 0.026$), whereas patients at the acute phase had lower levels of SDF-1α and MIP-1α compared with controls ($P = 0.028$ and 0.034, respectively).

3.4. Serum cytokines profiles and disease severity in acute and convalescent

Next, we evaluated the levels of these 11 cytokines/chemokines for disease severity in acute and convalescent sera. In the acute phase (Fig. 1C), severe patients had higher levels of IP-10 and IL-7 compared with moderate ($P = 0.014$ and 0.002, respectively) and asymptomatic ($P < 0.0001$ and $= 0.021$, respectively) patients as well as control subjects ($P < 0.0001$ and $= 0.0002$, respectively). We observed a higher level of MCP-1 in moderate patients compared with other groups. At the convalescent phase, severe patients had higher levels of IP-10 and IL-7 compared with moderate ($P = 0.0005$ and 0.0003, respectively) and asymptomatic patients ($P = 0.020$ for IL-7) and controls ($P < 0.0001$ and $= 0.0005$, respectively).

3.5. Cytokine profiles in three individuals

Because several of the 23 undetectable cytokines were detected in three patients, we tried to describe the dynamic levels of these cytokines in sequential serum samples from these three patients. As shown in Fig. 2, seven cytokines (IFN-γ, IL-2, IL-22, IL-1α, IL-1RA, IL-21, and IL-27) were elevated in the serum of patient A with severe illness. The level of IFN-γ gradually increased and peaked at 22 days post-illness onset and then began to decrease but remained at a high-level 29 days post-illness onset. The levels of IL-22 and IL-1α decreased over time, and the level of IL-1α was nearly undetectable 28 days post-illness onset. The levels of IL-1RA and IL-21 decreased over time, although an occasionally increased level was detected. The levels of IL-27 and IL-2 fluctuated over time, but the level of IL-27 elevated 19 days post-illness onset. Twelve cytokines (IFN-γ, IFN-α, IL-2, IL-6, IL-15, IL-17A, IL-22, IL-23, IL-27, IL-9, IL-31, and TNF-β) were elevated in the serum of patient B who had a moderate illness. The levels of 11 cytokines (IFN-γ, IFN-α, IL-2, IL-6, IL-15, IL-17A, IL-22, IL-23, IL-9, IL-31, and TNF-β) declined over time, although the levels of several of them had a slight increase on day 23 post-illness onset. There were no visible changes for the level of IL-22 before day 19 of illness, but a significant elevation was observed on day 23 post-illness onset. We also found a quick decline level for IL-6 compared with other cytokines. In contrast, only three cytokines (IL-1α, IL-15, and IL-22) were elevated in serum within ten days after the first SARS-CoV-2 detection of patient C, who was asymptomatic. It seems that the levels of IL-1α and IL-22 had an increasing trend but a declining pattern for IL-15.

4. Discussion

In this study, we measured the cytokine/chemokine responses in serum of patients with SARS-CoV-2 infection. Our results revealed a minimal pro-inflammatory cytokine/chemokine response after infection of SARS-CoV-2 as there were no increase in levels of most pro-inflammatory cytokines/chemokines that have been implicated in immune reactions against viruses, such as IFN-γ, TNF-α, IL-1β, IL-6, and so on.

Previous studies have shown that increased amounts of pro-inflammatory cytokines in serum (e.g., IL-1β, IL-6, IL-12, IFN-γ, IP-10, and MCP-1) were associated with disease severity in SARS patients [7–9]. MERS-CoV infection could also induce increased concentrations of pro-inflammatory cytokines/chemokines (IFN-γ, TNF-α, IL-6, IL-15, IL-17, IL-1RA, IP-10, and MCP-1) [10,11]. For the patients with SARS-CoV-2 infection, high amounts of IL-1β, IFN-γ, IP-10, and MCP-1 were observed, and high concentrations of GCSF, IP-10, MCP-1, MIP-1A, and TNF-α were associated with disease severity (i.e., higher levels in intensive care unit (ICU) patients) [1–5]. However, most pro-inflammatory cytokines/chemokines, such as IL-2, IL-6, IL-10, IFN-γ and TNF-α [3,12–14], were not detected in patients of our study. A similar result was also observed in another study where only minimal pro-inflammatory cytokines/chemokines were found in a COVID-19 patient [15]. In the present study, although 11 (IP-10, Eotaxin, RANTES, MCP-1, SDF-1α, MIP-1β, MIP-1α, Gro-α, IL-7, IL-8, and IL-18) cytokines/chemokines were detected in patients, only 5 of them had a showed a significant elevated or decreased level compared with control subjects, including increased levels of IP-10, Eotaxin, and IL-7, and declined levels of RANTES and GRO-α. The Increased plasma levels of IL-7 and IP-10 were also observed in intensive care unit (ICU) patients compared with non-ICU patients [16]. Recent studies also reported that higher level of IL-7 was associated with the severity of COVID-19

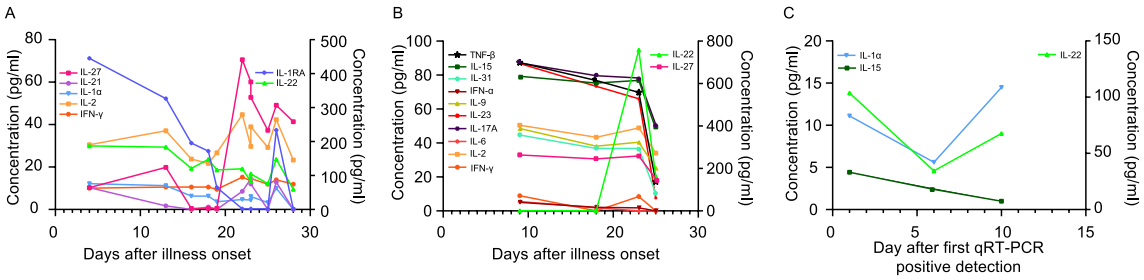

Fig. 2. Cytokine and chemokine levels in sequential serum samples of 3 patients (patients A, B, and C). Patients A, B, and C had 11, 4, and 3 different sampling time-points, respectively. IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

[12,17,18]. In this study, severe patients showed a decreased of lymphocytes and an elevated level of IL-7, indicating that IL-7 was associated with lymphocytes returning to a reference level, appearing to reverse a pathologic hallmark of COVID-19. IP-10 has been reported as an excellent biomarker for the prediction of COVID-19 progression and can be related to the risk of death in COVID-19 patients [5,14,19,20]. Consistent with the previous study, we found that IP-10 was augmented markedly in the serum of patients at an early stage but remained at a high level during the convalescent stage in severe and moderate patients. In addition, a similar profile of IL-7 was observed. IL-6 was recognized as the main cytokines related to the severity of COVID-19 [12,21–23], but we did not detected IL-6 in both patients and control subjects in this study, the possible reason is the different methods of measurement of the cytokines.

The limited number of patients recruited in this study, however, was an obstacle to reaching a conclusion. The second weakness of this study is the absence of viral load data. Consequently, we could not define the relationship between viral load and the magnitude of the cytokine/chemokine response. Nevertheless, our study provides valuable information about the profiles of cytokines/chemokines during SARS-CoV-2 infection at the early period of infection and shows that the production of IP-10 and IL-7 are the main effectors of the early innate immune response against SARS-CoV-2. The early elevation of IP-10 and IL-7 may be early markers of infection and disease severity that could be useful in estimating the clinical situation of patients with SARS-CoV-2 infection.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

Mai-Juan Ma, Er-Hei Dai, and Xiang-Na Zhao conceived the study. Yu-Ling Wang, Hui-Xia Gao, Yu-Zhen Liu, Jian-Hua Lu, Li Li, Hai-Bin Wang, Lei Zhao, Yan-Xiao Rong, Lin Yao, and Li-Juan Duan collected clinical samples and performed the data collation. Guo-Lin Wang, Hui-Xia Gao, Yu-Ling Wang and Xiao Wei performed experiments and data analysis. Xiang-Na Zhao, Er-Hei Dai, and Mai-Juan Ma drafted the manuscript. Benjamin D. Anderson reviewed and edited the manuscript. All authors reviewed and approved the final manuscript. Guo-Lin Wang, Yu-Ling Wang, Hui-Xia Gao, and Xiao Wei joint as first authors.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2021.155500.

References

[1] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, S. Liu, P. Zhao, H. Liu, L. Zhu, Y. Tai, C. Bai, T. Gao, J. Song, P. Xia, J. Dong, J. Zhao, F.S. Wang, Pathological findings of COVID-19 associated with acute respiratory distress syndrome, The Lancet. Respirat. Med., 2020.

[2] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet (London, England) 395 (10223) (2020) 497–506.

[3] G. Chen, D. Wu, W. Guo, Y. Cao, D. Huang, H. Wang, T. Wang, X. Zhang, H. Chen, H. Yu, X. Zhang, M. Zhang, S. Wu, J. Song, T. Chen, M. Han, S. Li, X. Luo, J. Zhao, Q. Ning, Clinical and immunological features of severe and moderate coronavirus disease 2019, J. Clin. Invest. 130 (5) (2020) 2620–2629.

[4] C. Qin, L. Zhou, Z. Hu, S. Zhang, S. Yang, Y. Tao, C. Xie, K. Ma, K. Shang, W. Wang, D.S. Tian, Dysregulation of immune response in patients with COVID-19 in Wuhan, China, Clin. Infect. Dis. (2020).

[5] Y. Yang, C. Shen, J. Li, J. Yuan, J. Wei, F. Huang, F. Wang, G. Li, Y. Li, L. Xing, L. Peng, M. Yang, M. Cao, H. Zheng, W. Wu, R. Zou, D. Li, Z. Xu, H. Wang, M. Zhang, Z. Zhang, G.F. Gao, C. Jiang, L. Liu, Y. Liu, Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19, J. Allergy Clin. Immunol. (2020).

[6] N.H.a.H.C.o. China, Diagnosis and Treatment Plan for New Coronavirus Infected Pneumonia (Trial Seventh Edition). <http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml>, 2020 (accessed March 4.2020).

[7] C.K. Wong, C.W. Lam, A.K. Wu, W.K. Ip, N.L. Lee, I.H. Chan, L.C. Lit, D.S. Hui, M. H. Chan, S.S. Chung, J.J. Sung, Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome, Clin. Exp. Immunol. 136 (1) (2004) 95–103.

[8] Y. Jiang, J. Xu, C. Zhou, Z. Wu, S. Zhong, J. Liu, W. Luo, T. Chen, Q. Qin, P. Deng, Characterization of cytokine/chemokine profiles of severe acute respiratory syndrome, Am. J. Respir. Crit. Care Med. 171 (8) (2005) 850–857.

[9] J.Y. Chien, P.R. Hsueh, W.C. Cheng, C.J. Yu, P.C. Yang, Temporal changes in cytokine/chemokine profiles and pulmonary involvement in severe acute respiratory syndrome, Respirology 11 (6) (2006) 715–722.

[10] W.H. Mahallawi, O.F. Khabour, Q. Zhang, H.M. Makhdoum, B.A. Suliman, MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile, Cytokine 104 (2018) 8–13.

[11] H.S. Shin, Y. Kim, G. Kim, J.Y. Lee, I. Jeong, J.S. Joh, H. Kim, E. Chang, S.Y. Sim, J. S. Park, D.G. Lim, Immune Responses to Middle East Respiratory Syndrome Coronavirus During the Acute and Convalescent Phases of Human Infection, Clin. Infect. Dis. 68 (6) (2019) 984–992.

[12] Y. Chi, Y. Ge, B. Wu, W. Zhang, T. Wu, T. Wen, J. Liu, X. Guo, C. Huang, Y. Jiao, F. Zhu, B. Zhu, L. Cui, Serum Cytokine and Chemokine Profile in Relation to the Severity of Coronavirus Disease 2019 in China, (1537-6613 (Electronic)).

[13] Y. Jamilloux, T. Henry, A. Belot, S. Viel, M. Fauter, T. El Jammal, T. Walzer, B. François, P. Sève, Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions, (1873-0183 (Electronic)).

[14] R.A. Haroun, W.H. Osman, A.M. Eessa, Interferon-γ-induced protein 10 (IP-10) and serum amyloid A (SAA) are excellent biomarkers for the prediction of COVID-19 progression and severity, (1879-0631 (Electronic)).

[15] I. Thevarajan, T.H.O. Nguyen, M. Koutsakos, J. Druce, L. Caly, C.E. van de Sandt, X. Jia, S. Nicholson, M. Catton, B. Cowie, S.Y.C. Tong, S.R. Lewin, K. Kedzierska, Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19, Nat. Med. (2020).

[16] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, Clinical features of

patients infected with 2019 novel coronavirus in Wuhan, China, (1474-547X (Electronic)).
[17] P.F. Laterre, B. François, C. Collienne, P. Hantson, R. Jeannet, K.E. Remy, R.S. Hotchkiss, Association of Interleukin 7 Immunotherapy With Lymphocyte Counts Among Patients With Severe Coronavirus Disease 2019 (COVID-19), (2574-3805 (Electronic)).
[18] G.A.-O. Monneret, D. de Marignan, R. Coudereau, C. Bernet, F. Ader, E. Frobert, M. Gossez, S.A.-O.X. Viel, F. Venet, F. Wallet, Immune monitoring of interleukin-7 compassionate use in a critically ill COVID-19 patient, (2042-0226 (Electronic)).
[19] Y. Chen, J. Wang, C. Liu, L. Su, D. Zhang, J. Fan, Y. Yang, M. Xiao, J. Xie, Y. Xu, Y. A.-O. Li, S. Zhang, IP-10 and MCP-1 as biomarkers associated with disease severity of COVID-19, (1528-3658 (Electronic)).
[20] S. Lev, T. Gottesman, G. Sahaf Levin, D. Lederfein, E. Berkov, D. Diker, A. Zaidman, A. Nutman, T. Ilan Ber, A. Angel, L. Kellerman, E. Barash, R. Navon, O. Boico, Y. Israeli, M. Rosenberg, A. Gelman, R. Kalfon, E. Simon, N. Avni, M. Hainrichson, O. Zarchin, T.M. Gottlieb, K. Oved, E. Eden, B. Tadmor, Observational cohort study of IP-10's potential as a biomarker to aid in inflammation regulation within a clinical decision support protocol for patients with severe COVID-19, (1932-6203 (Electronic)).
[21] S.K. Dhar, V. K, S. Damodar, S. Gujar, M. Das, IL-6 and IL-10 as predictors of disease severity in COVID-19 patients: results from meta-analysis and regression, (2405-8440 (Print)).
[22] M.A.-O. Pereira, I.A.-O. Barros, A.A.-O. Jacob, M.A.-O. Assis, S.A.-O.X. Kanaan, H. A.-O.X. Kang, Laboratory findings in SARS-CoV-2 infections: State of the art, (1806-9282 (Electronic)).
[23] Z. Liu, J. Li, D. Chen, R. Gao, W. Zeng, S. Chen, Y. Huang, J. Huang, W. Long, M. Li, L. Guo, X. Wang, X. Wu, Dynamic Interleukin-6 Level Changes as a Prognostic Indicator in Patients With COVID-19, (1663-9812 (Print)).