EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Editorial

Confronting the controversy: Interleukin-6 and the COVID-19 cytokine storm syndrome

Luke Y.C. Chen, Ryan L. Hoiland, Sophie Stukas, Cheryl L. Wellington, Mypinder S. Sekhon

Please cite this article as: Chen LYC, Hoiland RL, Stukas S, *et al*. Confronting the controversy: Interleukin-6 and the COVID-19 cytokine storm syndrome. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.03006-2020).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Copyright ©ERS 2020. This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0.

Confronting the controversy: Interleukin-6 and the COVID-19 cytokine storm syndrome

Luke Y.C. Chen[1,2*], Ryan L. Hoiland PhD[3,4], Sophie Stukas PhD[5], Cheryl L. Wellington PhD[5], Mypinder S. Sekhon MD[6]

[1]*Division of Hematology, Department of Medicine, University of British Columbia, Vancouver, BC, Canada.*
[2]*Centre for Health Education Scholarship, University of British Columbia, Vancouver, BC, Canada*
[3]*Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, BC, Canada.*
[4]*Department of Cellular and Physiological Sciences, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada*
[5]*Department of Pathology and Laboratory Medicine, International Collaboration on Repair Discoveries, School of Biomedical Engineering, Djavad Mowafaghian Centre for Brain Health, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada.*
[6]*Division of Critical Care Medicine, Department of Medicine, University of British Columbia, Vancouver, BC, Canada.*

**Correspondence to: Dr. Luke Y.C. Chen, 2775 Laurel St, 10th Floor, Vancouver, BC, V5Z1M9, tel: 6048755270; fax: 6048754763; email: lchen2@bccancer.bc.ca*

Competing interests: the authors have no competing interests to declare.

Contributorship: All authors contributed to the conception and drafting of the article and provided critical revision for important intellectual content and final approval.
Acknowledgements: not applicable
Funding information: Dr. Chen is supported by the UBC Hematology Research Program. Dr. Sekhon is supported by the Vancouver Coastal Health Research Institute Clinician Scientist Award. Dr. Wellington is supported by grants from Canadian Institutes for Health Research, National Institutes of Health, Weston Brain Institute and Cure Alzheimer Fund.

Take home message (243/256 characters): Hypercytokinemic immune dysregulation in COVID-19 is known as cytokine storm syndrome. Interleukin-6 levels ≥ 80 pg/mL predict an increased risk of respiratory failure and death, and immunomodulatory therapy is an area of urgent investigation

The concept of COVID-19 related cytokine storm syndrome (COVID-CSS) emerged early in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic to explain why some patients exposed to this virus become critically ill with acute respiratory distress syndrome, multi-organ failure, and death. A seminal study from Wuhan, China reported higher serum concentrations of inflammatory cytokines in patients requiring critical care compared to those with milder disease, and the authors postulated that "cytokine storm was associated with disease severity".[1] COVID-19 hypercytokinemia initially invited comparisons to other respiratory viral infections that cause a dysregulated immune response, namely severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Subsequently, similarities between COVID-CSS and other cytokine storm syndromes such as hemophagocytic lymphohistiocytosis (HLH),[2] autoinflammatory syndromes, and chimeric antigen T-cell therapy cytokine release syndrome (CAR T-cell CRS) became apparent.[3-5] The proposition that hypercytokinemia is pathological in some patients with COVID-19 catalyzed numerous clinical trials of immunomodulatory and cytokine-inhibitor therapy. However, critics contend that CSS is a misleading conceptual framework in COVID-19 and two prominent editorials have raised significant doubt about COVID-CSS.[6, 7] In brief, these authors contend that:

1) there is no definition of cytokine storm syndrome;
2) median IL-6 levels are relatively low in COVID-19;
3) COVID-19 should be characterized as a hypoinflammatory vasculopathy rather than a hyperinflammatory hypercytokinemia syndrome;
4) therefore, immunomodulatory therapy may play little or no role in the treatment of COVID-19.

In this editorial, we address these controversies and demonstrate that cytokine storm syndrome may play an important role in severe respiratory failure and mortality caused by COVID-19.

1. Definition of cytokine storm syndrome

Critics of the COVID-CSS concept have claimed that “cytokine storm has no definition”,[6] and that there is “no evidence that COVID patients develop a cytokine storm”.[7] In fact, experts define cytokine storm syndrome as a clinical phenotype of:[8]

- immune dysregulation characterized by perpetuated activation of lymphocytes and macrophages
- resulting in secretion of large quantities of cytokines
- leading to overwhelming systemic inflammation and multi-organ failure with high mortality.

The term CSS was first coined to describe the hypercytokinemia in graft versus host disease after allogeneic stem cell transplant.[9] More recently, CAR T-cell CRS, which exhibits markedly elevated interleukin(IL)-6 levels often in excess of 1000 pg/mL (normal < 7 pg/mL), and responds to IL-6 blockade, has been included in the umbrella term CSS.[3] Many viral, bacterial and parasitic infections can cause CSS. Infectious pathogens such as Epstein-Barr virus (EBV) and *Mycobacterium tuberculosis* cause pathological immune activation characterized by markedly elevated cytokines and cytokine receptors such as interferon-γ (IFN-γ) and soluble interleukin-2 receptor (sIL-2r) in patients with inherited and acquired immune defects, leading to the clinical syndrome of hemophagocytic lymphohistiocytosis (HLH).[10, 11]

Detailed immunological studies have clearly established that some patients with severe COVID-19 indeed meet the general criteria for cytokine storm syndrome in a manner which is unique from other infectious CSS. A recent longitudinal comparison in patients with moderate versus severe COVID-19 demonstrated 3 distinct signatures of “immunological misfiring” in those with severe disease.[5] Patients with moderate disease (patients admitted to hospital who survived and did not require ICU admission) had low expression of inflammatory cytokines and increased tissue reparative growth factors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) (Figure 1A). In contrast, patients with severe disease (those who died or required ICU admission) had highly elevated pro-inflammatory cytokines including IL-1α, IL-1β, IL-6, IL-18 and TNF-α (Figure 1B).[5] Another study found that, whereas bacterial sepsis-induced

immunoparalysis is characterized by monocyte deficiency and inability to produce cytokines, in severe COVID-19, peripheral blood mononuclear cells (PBMCs) exhibit sustained TNF-α and IL-6 production with LPS stimulation *ex-vivo* and markedly elevated IL-6 and CRP concentrations *in-vivo*.[4] When compared to other respiratory viruses such as SARS-CoV-1, MERS-CoV and human parainfluenza virus and respiratory syncytial virus, the transcriptional hyperinflammatory response in SARS-CoV-2 is uniquely imbalanced, with low IFN-I and-III levels accompanied by very high expression of inflammatory chemokines and cytokines (IL-1, IL-6) and severe lymphopenia, resulting in a "high pro-inflammatory, low innate antiviral defense" state. [12]

Although there are not yet standard diagnostic criteria for COVID-CSS, the term is generally used to denote the subset of patients who demonstrate excessive immune activation characterized by markedly elevated inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6) and ferritin, as well as lymphopenia and a spectrum of end organ damage from isolated respiratory dysfunction to multi-organ failure. Clinical measurement of IL-6 is not widely available at present but is a relatively simple and inexpensive assay for many clinical laboratories to implement. In the early days of COVID-19 in our own center, when IL-6 was being measured for research purposes rather than clinical care, we used the following criteria for COVID-CSS: 1) COVID-19 pneumonia requiring mechanical ventilation; 2) fever (maximum temperature > 38°C); 3) CRP > 100 mg/L; and 4) peak serum ferritin > 1000 µg/L.[13] Patients meeting these criteria had markedly elevated research serum IL-6 levels, median 91 pg/mL, interquartile range (IQR) 54-696 pg/mL (n=15). However, IL-6 does not always correspond to CRP (which is produced by hepatocytes in response to IL-6) or ferritin (which is a marker of macrophage activity).[14] Recently, at least two large studies have shown that serum IL-6 is superior to CRP, ferritin, liver enzymes, and other simple clinical laboratory markers for predicting clinical outcomes such as respiratory failure and death, with an optimal cutoff of 80 and 86 pg/L, respectively.[15, 16] Taken together, these data imply that an IL-6 threshold ≥ 80 pg/mL carries prognostic value in future definitions COVID-CSS. Ultimately, multivariate prognostic models incorporating simple, widely available parameters such as SpO_2/FiO_2, neutrophil/lymphocyte ratio, CRP and ferritin along with cytokines/chemokines such as IL-1, IL-6, Interferon gamma-induced protein(IP)-10

and IL-10 may lead to prognostic scoring systems rather than the binary “yes/no” diagnostic model employed in HLH.[16, 17]

2. *Interleukin-6 and COVID-CSS*

The modest serum IL-6 elevations reported in early studies of COVID-19 have been cited as an argument against the relevance of CSS in this disease.[6, 7] For example, the median (7-45 pg/mL) and IQR for serum IL-6 levels were relatively low in four large studies of patients with mild to severe COVID-19.[6] However, median and IQR are estimates of central tendency, and in cytokine storm, the population of interest resides within the top quartile of patients. Further, the temporal heterogeneity of cytokine analysis in these studies may have missed rapid increases in cytokine levels in some patients. Importantly, cytokine storm pertains not to the majority of patients who exhibit a *physiological* response to a given exposure, but to the minority who suffer from *pathological* immune activation or dysfunction. To provide some analogies, only a minute proportion of those exposed to EBV develop HLH, and less than 15% of patients undergoing CAR T-cell therapy develop severe grade 3-4 CRS requiring IL-6 blockade. Likewise, a small but highly relevant proportion of those exposed to COVID-19 develop CSS.

In COVID-CSS, many inflammatory cytokines such as IL-1, IL-10 and tumor necrosis factor(TNF)-α are elevated approximately 2-100 fold above normative values, whereas IL-6 demonstrates much larger increases, in some cases more than 1000 fold above normal. Figure 2 illustrates levels of inflammatory cytokines IL-1β, IL-6 and TNF-α in 24 patients with severe COVID-19 requiring ICU admission in our center, both in absolute quantities and as a “fold elevation” above normative values. Several other large studies have reported markedly elevated serum IL-6 levels in the 100-10,000 pg/mL range in patients with severe disease.[12, 15, 17, 18] These markedly elevated IL-6 levels in COVID-CSS are similar in magnitude to severe CAR T-cell CRS,[19] and higher than other hyper-IL-6 syndromes such as multicentric Castleman disease, where IL-6 is elevated but typically < 100 pg/mL.[3, 20] HLH is said to encompass a diverse spectrum of “hyperferritinemic hyperinflammatory syndromes with a common terminal pathway but with different pathogenetic roots”.[21] Likewise in COVID-CSS, it appears increasingly likely that diverse “root”

signatures of immune dysregulation lead to a common terminal hyperinflammatory pathway characterized by markedly elevated IL-6, severe T-cell lymphopenia, and respiratory failure.[4, 5, 17]

3. Hypercytokinemia, vasculopathy, and endothelialitis

Some authors have proposed that the markedly elevated D-dimer levels and high rates of micro and macrovascular thrombosis, in contrast to modestly elevated median IL-6 levels, signify that COVID-19 pathophysiologic sequelae are related to hypoinflammatory vasculopathy rather than inflammatory cytokine storm.[7] The central role of the receptor angiotensin-converting enzyme-2 (ACE2) in viral cell entry and the complex vascular changes including intussusceptive angiogenesis and diffuse endothelial membrane disruption seen in autopsy studies indeed support a central role for vasculopathy in COVID related morbidity.[22] However, recent studies have demonstrated that hypercytokinemia and vasculopathy are not an either-or proposition. The pulmonary vasculature is a key site of intravascular coagulopathy and thrombotic complications of COVID-19.[23, 24] Earlier studies of the SARS-CoV spike (S) protein to angiotensin-converting enzyme (ACE) 2 demonstrated that binding of the S protein to ACE2 results in production of inflammatory cytokines including IL-1 and IL-6.[25, 26]

This hyperinflammatory response results in disruption of the endothelial barrier and hypercoagulability. Diffuse occlusion in the microcirculation of the pulmonary vascular bed may cause pulmonary hypertension, increased dead space ventilation and ultimately right heart failure. Serum endothelial factors such as soluble thrombomodulin, soluble P-selectin (sP-sel) and von Willebrand factor (vWF) play a major role in disease progression to acute respiratory distress syndrome (ARDS).[27] Taken together, these findings suggest a model in which COVID-19 is best viewed as an inflammatory endothelialitis, with direct viral infection of pneumocytes, endothelial and epithelial cells producing inflammatory cytokines and immune-mediated damage to the vasculature and surrounding tissue.[25, 27] (Figure 1B)

4. Cytokines, respiratory failure, and immunomodulatory therapy in COVID-19

Critics of CSS contend that hypercytokinemia seen in COVID-19 may be a necessary physiological response for viral clearance and warn against the use of immunomodulatory therapy in this context.[6, 7] In the more established CSS, the central role of particular cytokines is determined not only by studies linking cytokine elevation to characteristic organ damage, but also clinical trials demonstrating that cytokine blockade results in clinical benefit. Primary HLH is perhaps the paradigm for this model, in that the interferon-γ/chemokine ligand(CXCL)-9 axis is central to the pathophysiology of the disease,[28] and blocking this axis with emapalumab produces deep and sustained remissions.[29] Likewise, IL-1 has been shown to play a similar role in autoinflammatory syndromes and secondary HLH, and blockade with anakinra or canakinumab results in clinical benefit.[30, 31]

Evidence that IL-6 drives immune dysregulation and respiratory failure in COVID-CSS is rapidly accumulating. Elevated serum IL-6 is associated with lymphopenia, impaired lymphocyte cytotoxicity, and endothelial activation (Figure 1B). These immune defects can be partially restored by treatment with IL-6 blockade with tocilizumab.[4, 32] A German study demonstrated that IL-6 > 80 pg/mL in combination with C-reactive protein > 97 mg/L is highly predictive of respiratory failure.[15] In our own center IL-6 was found to be inversely related to the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO2/FiO2) and static lung compliance.[33] Moreover, a multivariate model generated from a large prospective cohort (n=501) showed that early systemic inflammation predicts mortality. Among 15 variables measured at hospital admission, CRP at a cutoff of 87.5 mg/L was the most sensitive (0.97) and IL-6 at a cutoff of 86 pg/mL was the most specific (0.89) for predicting death.[16]

The RECOVERY trial demonstrating mortality benefit from treatment with dexamethasone 6 mg daily, particularly in patients with severe disease, is the first randomized controlled trial (RCT) to definitively show benefit for immunomodulatory therapy.[34] Although numerous retrospective studies of cytokine blockade such as anakinra and tocilizumab and JAK inhibition such as baricitinib have shown promise, ultimately RCTs are needed. Several of these studies are underway or recently completed, and the results are eagerly anticipated.[3] COVID-19 patients demonstrating the CSS phenotype are certainly on the severe end of the disease spectrum. Therefore, trials should aim to target patients with a dysregulated immune

response to ascertain the true efficacy of immunomodulatory therapies. On Jul 29, 2020, a press release for the COVACTA RCT (NCT04320615) comparing tocilizumab and placebo in COVID-19 reported no difference in the primary outcomes (clinical status and mortality). However, there were positive trends in duration of hospital stay and ventilator free days, not considered significant because of the failure to meet the primary endpoints. The inclusion criteria for the COVACTA trial were quite broad, requiring only a definite diagnosis of COVID-19 pneumonia with an oxygen saturation of 93% or lower or SpO_2/FiO_2 < 300 mm Hg, with no mention of markers of systemic inflammation such as CRP or IL-6. Given the gradient seen towards more benefit in severely ill patients with dexamethasone treatment in the RECOVERY trial, subgroup analysis in the COVACTA trial as well as ongoing immunomodulatory RCTs will be of great interest.

Acknowledgement: The authors thank Dr. Catherine Biggs for her critical review of the manuscript.

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020: 395(10223): 497-506.
2. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, Hlh Across Speciality Collaboration UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020: 395(10229): 1033-1034.
3. England JT, Abdulla A, Biggs CM, Lee AYY, Hay KA, Hoiland RL, Wellington CL, Sekhon M, Jamal S, Shojania K, Chen LYC. Weathering the COVID-19 storm: Lessons from hematologic cytokine syndromes. *Blood Rev* 2020: 100707.
4. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, Damoraki G, Gkavogianni T, Adami ME, Katsaounou P, Ntaganou M, Kyriakopoulou M, Dimopoulos G, Koutsodimitropoulos I, Velissaris D, Koufargyris P, Karageorgos A, Katrini K, Lekakis V, Lupse M, Kotsaki A, Renieris G, Theodoulou D, Panou V, Koukaki E, Koulouris N, Gogos C, Koutsoukou A. Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure. *Cell Host Microbe* 2020: 27(6): 992-1000 e1003.
5. Lucas C, Wong P, Klein J, Castro TBR, Silva J, Sundaram M, Ellingson MK, Mao T, Oh JE, Israelow B, Takahashi T, Tokuyama M, Lu P, Venkataraman A, Park A, Mohanty S, Wang H, Wyllie AL, Vogels CBF, Earnest R, Lapidus S, Ott IM, Moore AJ, Muenker MC, Fournier JB, Campbell M, Odio CD, Casanovas-Massana A, Yale IT, Herbst R, Shaw AC, Medzhitov R, Schulz WL, Grubaugh ND, Dela Cruz C, Farhadian S, Ko AI, Omer SB, Iwasaki A. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature* 2020.
6. Sinha P, Matthay MA, Calfee CS. Is a "Cytokine Storm" Relevant to COVID-19? *JAMA Intern Med* 2020.
7. Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. *Intensive Care Med* 2020: 46(6): 1105-1108.
8. Shimizu M. Clinical Features of Cytokine Storm Syndrome. *In:* Cron RQ, Behrens EM, eds. Cytokine Storm Syndrome. Springer International Publishing, Cham, 2019; pp. 31-41.
9. Clark IA. The advent of the cytokine storm. *Immunol Cell Biol* 2007: 85(4): 271-273.

10. Hayden A, Park S, Giustini D, Lee AY, Chen LY. Hemophagocytic syndromes (HPSs) including hemophagocytic lymphohistiocytosis (HLH) in adults: A systematic scoping review. *Blood Rev* 2016: 30(6): 411-420.
11. Hayden A, Lin M, Park S, Pudek M, Schneider M, Jordan MB, Mattman A, Chen LYC. Soluble interleukin-2 receptor is a sensitive diagnostic test in adult HLH. *Blood advances* 2017: 1(26): 2529-2534.
12. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Moller R, Jordan TX, Oishi K, Panis M, Sachs D, Wang TT, Schwartz RE, Lim JK, Albrecht RA, tenOever BR. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. *Cell* 2020: 181(5): 1036-1045 e1039.
13. Hoiland RL, Stukas S, Cooper J, Thiara S, Chen LYC, Biggs CM, Hay K, Lee AYY, Shojania K, Abdulla A, Wellington CL, Sekhon MS. Amelioration of COVID-19 related cytokine storm syndrome: Parallels to chimeric antigen receptor-T cell cytokine release syndrome. *Br J Haematol* 2020.
14. Chen LYC, Hayden A, Mattman A. Extreme hyperferritinaemia, soluble interleukin-2 receptor, and haemophagocytic lymphohistiocytosis. *Br J Haematol* 2019: 185(3): 605-606.
15. Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, Bergwelt-Baildon MV, Klein M, Weinberger T. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol* 2020.
16. Laguna-Goya R, Utrero-Rico A, Talayero P, Lasa-Lazaro M, Ramirez-Fernandez A, Naranjo L, Segura-Tudela A, Cabrera-Marante O, Rodriguez de Frias E, Garcia-Garcia R, Fernandez-Ruiz M, Aguado JM, Martinez-Lopez J, Lopez EA, Catalan M, Serrano A, Paz-Artal E. IL-6-based mortality risk model for hospitalized patients with COVID-19. *J Allergy Clin Immunol* 2020.
17. Laing AG, Lorenc A, del Molino del Barrio I, Das A, Fish M, Monin L, Muñoz-Ruiz M, McKenzie DR, Hayday TS, Francos-Quijorna I, Kamdar S, Joseph M, Davies D, Davis R, Jennings A, Zlatareva I, Vantourout P, Wu Y, Sofra V, Cano F, Greco M, Theodoridis E, Freedman J, Gee S, Chan JNE, Ryan S, Bugallo-Blanco E, Peterson P, Kisand K, Haljasmägi L, Chadli L, Moingeon P, Martinez L, Merrick B, Bisnauthsing K, Brooks K, Ibrahim MAA, Mason J, Lopez Gomez F, Babalola K, Abdul-Jawad S, Cason J, Mant C, Seow J, Graham C, Doores KJ, Di Rosa F, Edgeworth J, Shankar-Hari M, Hayday AC. A dynamic COVID-19 immune signature includes associations with poor prognosis. *Nature Medicine* 2020.
18. Price CC, Altice FL, Shyr Y, Koff A, Pischel L, Goshua G, Azar MM, McManus D, Chen SC, Gleeson SE, Britto CJ, Azmy V, Kaman K, Gaston DC, Davis M, Burrello T, Harris Z, Villanueva MS, Aoun-Barakat L, Kang I, Seropian S, Chupp G, Bucala R, Kaminski N, Lee AI, LoRusso PM, Topal JE, Dela Cruz C, Malinis M. Tocilizumab Treatment for Cytokine Release Syndrome in Hospitalized COVID-19 Patients: Survival and Clinical Outcomes. *Chest* 2020.
19. Hay KA, Hanafi LA, Li D, Gust J, Liles WC, Wurfel MM, Lopez JA, Chen J, Chung D, Harju-Baker S, Cherian S, Chen X, Riddell SR, Maloney DG, Turtle CJ. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. *Blood* 2017: 130(21): 2295-2306.
20. van Rhee F, Wong RS, Munshi N, Rossi JF, Ke XY, Fossa A, Simpson D, Capra M, Liu T, Hsieh RK, Goh YT, Zhu J, Cho SG, Ren H, Cavet J, Bandekar R, Rothman M, Puchalski TA, Reddy M, van de Velde H, Vermeulen J, Casper C. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2014: 15(9): 966-974.
21. La Rosee P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, Birndt S, Gil-Herrera J, Girschikofsky M, Jordan MB, Kumar A, van Laar JAM, Lachmann G, Nichols KE, Ramanan AV, Wang Y, Wang Z, Janka G, Henter JI. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood* 2019: 133(23): 2465-2477.
22. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med* 2020.
23. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *The Lancet Rheumatology* 2020.

24. Huertas A, Montani D, Savale L, Pichon J, Tu L, Parent F, Guignabert C, Humbert M. Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19)? *European Respiratory Journal* 2020: 56(1): 2001634.
25. Colling ME, Kanthi Y. COVID-19-associated coagulopathy: An exploration of mechanisms. *Vasc Med* 2020: 1358863X20932640.
26. He L, Ding Y, Zhang Q, Che X, He Y, Shen H, Wang H, Li Z, Zhao L, Geng J, Deng Y, Yang L, Li J, Cai J, Qiu L, Wen K, Xu X, Jiang S. Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2+ cells in SARS patients: relation to the acute lung injury and pathogenesis of SARS. *J Pathol* 2006: 210(3): 288-297.
27. Goshua G, Pine AB, Meizlish ML, Chang C-H, Zhang H, Bahel P, Baluha A, Bar N, Bona RD, Burns AJ. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. *The Lancet Haematology* 2020.
28. Zoller EE, Lykens JE, Terrell CE, Aliberti J, Filipovich AH, Henson PM, Jordan MB. Hemophagocytosis causes a consumptive anemia of inflammation. *The Journal of experimental medicine* 2011: 208(6): 1203-1214.
29. Locatelli F, Jordan MB, Allen C, Cesaro S, Rizzari C, Rao A, Degar B, Garrington TP, Sevilla J, Putti MC, Fagioli F, Ahlmann M, Dapena Diaz JL, Henry M, De Benedetti F, Grom A, Lapeyre G, Jacqmin P, Ballabio M, de Min C. Emapalumab in Children with Primary Hemophagocytic Lymphohistiocytosis. *N Engl J Med* 2020: 382(19): 1811-1822.
30. de Koning HD, Schalkwijk J, van der Ven-Jongekrijg J, Stoffels M, van der Meer JW, Simon A. Sustained efficacy of the monoclonal anti-interleukin-1 beta antibody canakinumab in a 9-month trial in Schnitzler's syndrome. *Ann Rheum Dis* 2013: 72(10): 1634-1638.
31. Mehta P, Cron RQ, Hartwell J, Manson JJ, Tattersall RS. Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome. *Lancet Rheumatol* 2020.
32. Mazzoni A, Salvati L, Maggi L, Capone M, Vanni A, Spinicci M, Mencarini J, Caporale R, Peruzzi B, Antonelli A, Trotta M, Zammarchi L, Ciani L, Gori L, Lazzeri C, Matucci A, Vultaggio A, Rossi O, Almerigogna F, Parronchi P, Fontanari P, Lavorini F, Peris A, Rossolini GM, Bartoloni A, Romagnani S, Liotta F, Annunziato F, Cosmi L. Impaired immune cell cytotoxicity in severe COVID-19 is IL-6 dependent. *J Clin Invest* 2020.
33. Stukas S, Hoiland RL, Cooper J, Thiara S, Griesdale DE, Thomas AD, Orde MM, English JC, Chen LYC, Foster D, Mitra AR, Romano K, Sweet DD, Ronco JJ, Kanji HD, Chen Y-WR, Wong SL, Wellington CL, Sekhon MS. The association of inflammatory cytokines in the pulmonary pathophysiology of respiratory failure in critically ill patients with COVID-19. *Critical Care Explorations* 2020 (accepted manuscript, in press).
34. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med* 2020.

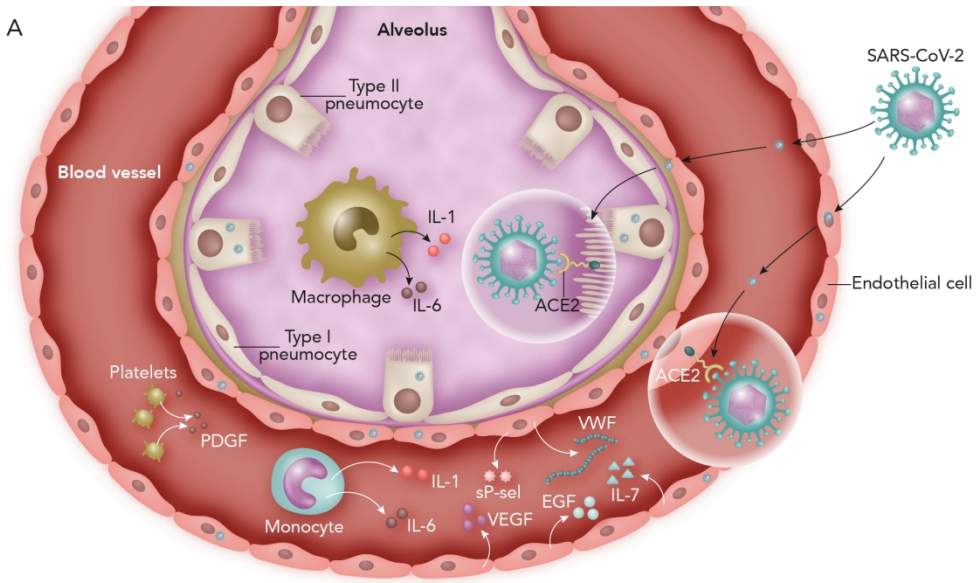
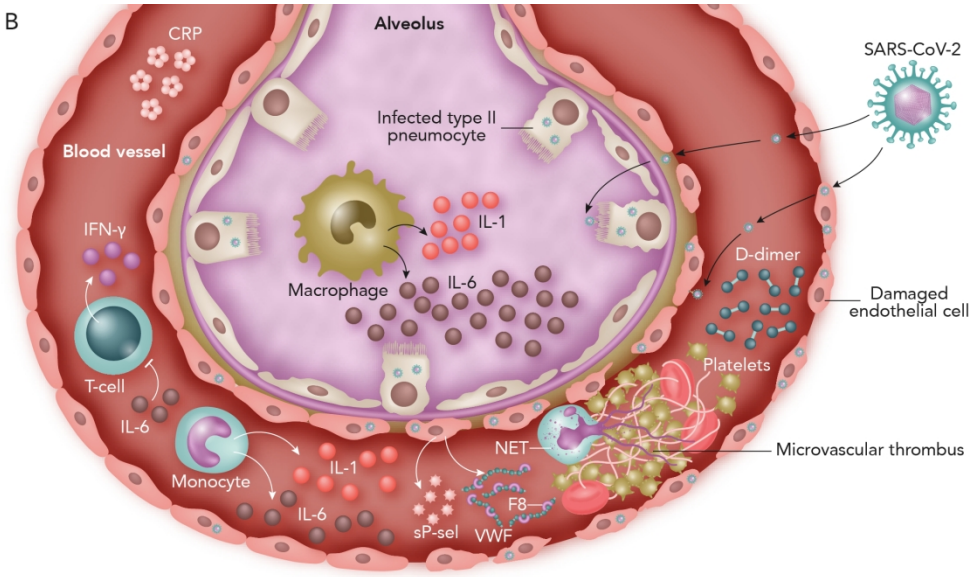


Figure 1. Schematic representation of mechanisms by which the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes mild disease in some patients and severe disease in others. In both cases, the virus enters human cells via binding to angiotensin-converting enzyme 2 (ACE2), a transmembrane receptor widely expressed in type II pneumocytes, macrophages, endothelial, and other pulmonary cells.[24,25] A. Mild disease (low incidence of coagulopathy and thrombosis, shorter hospital stay, low critical illness and mortality): These patients have low serum inflammatory cytokines and high tissue reparative growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), and interleukin(IL)-7.[5]B. Severe disease (high incidence of micro and macrovascular thrombosis, longer hospital stay, high critical illness, and mortality): Many of these patients have cytokine storm, with high serum inflammatory cytokines (such as IL-6, IL-1, IFN-γ) and markers of endothelial activation such as von Willebrand factor (vWF), factor 8 coagulant (F8) and soluble P-selectin (sP-sel) resulting in endothelialitis and microvascular thrombosis.[5,15,27] Markedly elevated IL-6 leads to lymphopenia and immunoparalysis which is partially restored by IL-6 blockade.[4,32] Abbreviations: NET: neutrophil extracellular trap; IFN-γ: interferon-γ


B
CRP
Alveolus
SARS-CoV-2
Infected type II pneumocyte
Blood vessel
IL-1
IFN-γ
D-dimer
Macrophage
IL-6
Damaged endothelial cell
Platelets
T-cell
IL-6
NET
Microvascular thrombus
Monocyte
IL-1
F8
IL-6
sP-sel
VWF

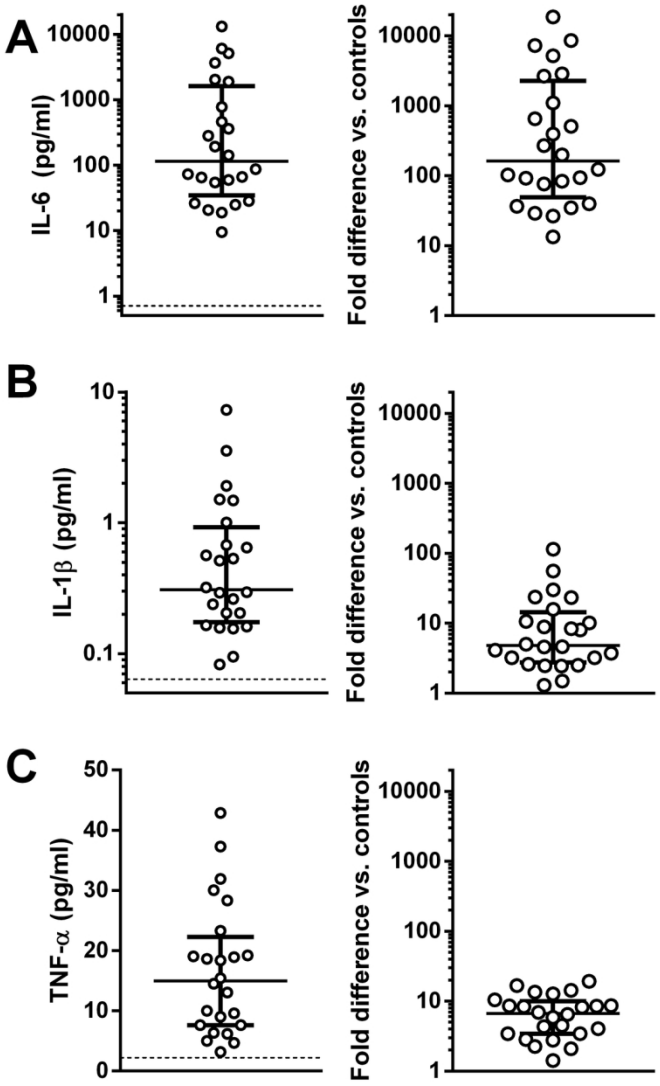


Figure 2. Absolute cytokine levels and their elevation compared to normative values. Depicted are the peak levels for interleukin(IL)-6 (panel A), IL-1β (panel B), and tumor necrosis factor(TNF)-α (panel C) from a Vancouver cohort of 24 critically ill COVID-19 patients. Further, we have represented the corresponding fold difference between cytokine levels observed in the COVID patients and those of healthy controls (i.e. normative values) on the right sided figure for each cytokine. These normative values can be seen as a horizontal dashed line for IL-6 (value: 0.71pg/mL), IL-1b (value: 0.064 pg/mL), and TNF-a (value: 2.23 pg/mL). All values were derived from the Simoa HD-1 analyzer.[13,33]