Predicting severe outcomes in COVID-19

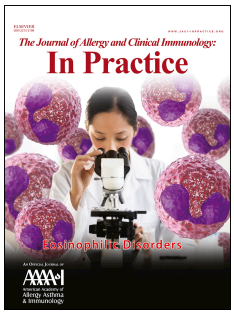
Lipworth, Brian; Chan, Rory; Kuo, Chris

Published in:
The Journal of Allergy and Clinical Immunology: In Practice

DOI:
10.1016/j.jaip.2020.06.039

Publication date:
2020

Document Version
Peer reviewed version



Predicting severe outcomes in COVID-19

Brian Lipworth, MD, Professor of Allergy and Pulmonology, Rory Chan, MBChB, Clinical research fellow, Chris RuiWen Kuo, MBChB, Clinical research fellow

PII: S2213-2198(20)30674-7

DOI: https://doi.org/10.1016/j.jaip.2020.06.039

Reference: JAIP 2959

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 22 June 2020

Accepted Date: 22 June 2020

Please cite this article as: Lipworth B, Chan R, RuiWen Kuo C, Predicting severe outcomes in COVID-19, *The Journal of Allergy and Clinical Immunology: In Practice* (2020), doi: https://doi.org/10.1016/j.jaip.2020.06.039.

Title: Predicting severe outcomes in COVID-19

(Invited Editorial RE 20-00530)

Authors: Brian Lipworth MD, Professor of Allergy and Pulmonology
Rory Chan MBChB, Clinical research fellow
Chris RuiWen Kuo MBChB, Clinical research fellow

Affiliation: Scottish Centre for Respiratory Research
Ninewells Hospital and Medical School
University of Dundee
Scotland, UK

Corresponding Author: Brian Lipworth
Scottish Centre for Respiratory Research
Ninewells Hospital and Medical School
University of Dundee
Scotland, UK, DD1 9SY
b.j.lipworth@dundee.ac.uk

Word count: 1201

Key Words: COVID-19, SARS-CoV-2, Interleukin-6, C reactive protein, Oxygenation, Cytokine, Inflammation, Ventilation

Contributors statement:
BJL had the idea and is responsible for the overall content as guarantor. BJL, RC, and CRK all performed the literature search and contributed to the writing of the article. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Conflicts of interest:

Dr. BJ Lipworth reports grants and personal fees from Sanofi, grants and personal fees from AstraZeneca, grants and personal fees from Teva, personal fees from Cipla, personal fees from Glenmark, Cipla, Dr Reddys, Cricassia, Vectura, Thorasys, Nowus, Mylan and Lupin, grants, personal fees and other from Chiesi, outside the submitted work; and Son of BJL is employee of AstraZeneca.

Dr. Chan has no relevant conflicts of interest.

Dr. Kuo reports personal fees from AstraZeneca, personal fees and other from Chiesi, personal fees from Circassia, outside the submitted work.

SARS-CoV2 infection enters via the nose, and, following aspiration to the lower respiratory tract, may then rapidly involve the lungs, resulting in severe hypoxic pneumonia. In the later stage of COVID-19 there is also a cytokine-mediated hyper-inflammatory response and coagulopathy, which in many respects simulates a viral induced multi-organ autoimmune response [1] (Figure). Patients who tend to fare worse with more severe outcomes are males, elderly, smokers, Black and Asian people, those with obesity, along with the presence of comorbidities such as diabetes, hypertension, chronic heart, lung and kidney disease, dementia, neoplasia, and immunosuppression[2].

Along with these various risk factors, much interest has centred around trying to identify biomarkers to predict which patients admitted to hospital with severe COVID-19 are most likely to rapidly deteriorate and require intensive care with invasive ventilation. A ratio for arterial oxygen tension (PaO2) or oxygen saturation (SaO2) to the fraction of inspired oxygen (FiO2), referred to as the P/F or S/F ratio respectively, of less than 300 is used to define the presence of respiratory failure, while a ratio of less than 100 is indicative of severe acute respiratory distress syndrome (ARDS). Some cases of ARDS with COVID-19 may be accompanied by the development of secondary *hemophagocytic lymphohistiocytosis (Figure).*

Biomarkers of hyperinflammation in COVID-19 include C reactive protein (CRP), interleukin-6 (IL6), ferritin, D-dimers, lactate dehydrogenase (LDH), procalcitonin, lymphopenia, and thrombocytopenia[1]. Since IL6 induces hepatic synthesis of CRP, it would be expected that they would track together as makers of systemic inflammation [3]. This in turn begs the question as to whether circulating levels of IL6 and CRP are associated with worse outcomes in severe COVID-19. A retrospective cohort evaluation among 140 patients with COVID-19 reported IL6 levels greater than 32.1 pg/ml and CRP greater than 41.8 mg/l were more likely to be related to severe disease, with respective hazard ratios of 2.4 (95%CI 1.06-5.3) and 4.4 (95%CI 1.9-10.3) [4]. Another study of 127 patients with COVID-19 found that IL6 was superior to other inflammatory markers in identifying severe disease in terms of the area under the receiver operating curve (AUC) being 0.84 with a sensitivity of 88% and specificity of 75%[5]. Furthermore, when IL-6 was combined with CRP and hypertension, the AUC improved to 0.90 with sensitivity of 100% and specificity of 66%. However, relatively few of the patients in either of these studies had severe disease, in particular with regard to patients requiring invasive ventilation A more informative study from Germany in a single University-based hospital setting studied two separate cohorts comprising 89 patients with severe hypoxic COVID-19 pneumonia, evaluating biomarkers on admission and during the course of the illness, with 36% requiring invasive ventilation[6]. A cut off value for IL6 of 49

pg/ml on admission had an AUC of 0.89, while a cut off of 65 pg/ml for maximal levels had an AUC of 0.93, in regard to predicting the need for invasive ventilation. Corresponding cut-off and AUC values for CRP were 32 mg/ml and 0.83 on admission and 97mg/ml and 0.85 for maximal levels. The cut offs for maximal IL-6 and CRP levels in the validation cohort of 49 patients both correctly classified 80% of patients regarding their risk of respiratory failure, whereas corresponding values at presentation were 71% and 76%. Moreover, in the combined cohort, patients reached the cut-off for IL6 greater than 65 pg/ml and CRP greater than 97 mg/L at a median of 23.2 and 15.7 hours prior to intubation.

In this issue of the journal, Vultaggio and coworkers from Italy have taken the biomarker analysis a step further in a cohort of 208 patients with severe COVID-19 in a single University-based hospital setting, with clinical deterioration occurring in 63 cases, of whom 39 were intubated and 16 died[7]. Notably 45 patients worsened within 3 days of admission. The highest AUC values for predicting 3 day worsening were observed for S/F ratio (0.81) followed by IL6 (0.78), CRP and LDH (both 0.76) and ferritin (0.70). Combining IL6, CRP, and S/F ratio in a composite score resulted in an improved AUC value of 0.88. Moreover, the composite score also exhibited good performance for predicting deterioration over 21 days or death, with AUC values of 0.83 and 0.82 respectively. The authors duly acknowledged the limitations of the study due to the relatively small sample size as well as the need for further validation of the composite score outside of a University-based hospital setting.

Taken together, these findings may have some important potential implications in the management of patients with severe COVID-19. Firstly, raised IL6 or CRP on initial presentation or rising levels during the course of the illness in conjunction with falling S/F or P/F ratio clearly indicates a need to escalate treatment. One such therapeutic intervention might be the use of systemic corticosteroids, which non-selectively suppress pro-inflammatory cytokines. The preliminary results from the United Kingdom RECOVERY trial in severe COVID-19 showed that, compared to 4321 patients receiving usual care, treatment with dexamethasone 6mg for 10 days in 2014 patients was associated with a 35% relative reduction in deaths after 28 days in ventilated patients and a 20% relative reduction in patients requiring oxygenation alone [8]. For patients being ventilated or oxygenated, this translated into treating 8 or 25 cases respectively with dexamethasone in order to prevent one death. It will be pertinent to know if reductions in mortality with dexamethasone were more pronounced in patients who had raised levels of CRP or IL6 or a reduced P/F ratio, either alone or combination.

We propose that a tailored biomarker approach towards endotype-guided pharmacotherapy might in turn result in improved outcomes in patients with severe COVID-19. For example, one strategy in such patients might be to escalate therapy in terms of selectively inhibiting pro-inflammatory cytokines. In this regard, we await to see the full results from randomised controlled trials with anti-IL6 agents, as preliminary data with sarilumab versus placebo reported marked reductions in CRP, which appeared to be disconnected from improvements in clinical outcomes in severe COVID-19[9]. Another approach involved selectively inhibiting IL1β with the IL1 antagonist anakinra, which in a small cohort study reduced the need for invasive ventilation and death in patients with severe COVID-19 [10]. Perhaps, as is the case with dexamethasone, one might expect to see the biggest improvements with selective cytokine blockers in those patients with more critical disease where hyperinflammation and coagulopathy are most prominent.

References

1. Lipworth B, Chan R, Lipworth S, RuiWen Kuo C. Weathering the Cytokine Storm in Susceptible Patients with Severe SARS-CoV-2 Infection. J Allergy Clin Immunol Pract 2020; 8:1798-801.
2. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020; 369:m1985.
3. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020; 8:420-2.
4. Liu F, Li L, Xu M, Wu J, Luo D, Zhu Y, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol 2020; 127:104370.
5. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis 2020; 95:332-9.
6. Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, Bergwelt-Baildon MV, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol 2020.
7. Vultaggio A, Vivarelli E, Virgili G, Lucenteforte E, Bartoloni A, Nozzoli C, et al. Prompt predicting of early clinical deterioration of moderate-to-severe COVID-19 patients: usefulness of a combined score using IL-6 in a preliminary study. The Journal of Allergy and Clinical Immunology: In Practice.
8. Horby P, Lim WS, Emberson J, Mafham M, Bell J, Linsell L, et al. Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. medRxiv 2020:2020.06.22.20137273.
9. https://investor.regeneron.com/news-releases/news-release-details/regeneron-and-sanofi-provide-update-us-phase-23-adaptive (accessed 18th June 2020)
10. Huet T, Beaussier H, Voisin O, Jouveshomme S, Dauriat G, Lazareth I, et al. Anakinra for severe forms of COVID-19: a cohort study. The Lancet Rheumatology.

Figure Legend

SARS-CoV-2 infection enters the respiratory tract via the nose, which, in susceptible individuals, is followed by development of COVID-19 pneumonia with hypoxaemia and need for oxygenation. This may be accompanied by a profound cytokine cascade involving IL6 stimulating hepatic synthesis of CRP. Cytokine activation in turn results in ARDS and coagulopathy with release of D-dimers and, in some cases, secondary *hemophagocytic lymphohistiocytosis.*