COVID-ARDS: A Vascular Endotype

Andrew E. Vaughan^{1,5,6}, John P. Reilly^{2,3,5}, Douglas B. Cines^{3,4}, Nuala J. Meyer^{2,3,5}, Nilam S. Mangalmurti^{2,3,5*}

¹Department of Biomedical Sciences, University of Pennsylvania School of Veterinary Medicine

²Division of Pulmonary, Allergy and Critical Care, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA

³Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia PA 19104, USA

⁴Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia PA 19104, USA

⁵Lung Biology Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

⁶ Institute for Regenerative Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.

*To whom correspondence should be addressed:

Nilam S. Mangalmurti, MD

Perelman School of Medicine

University of Pennsylvania

Stemmler Hall

3450 Hamilton Walk

Philadelphia, PA 19104

nspatel@pennmedicine.upenn.edu

215-573-9918 (phone)

215-573-4469 (fax)

Conflict of interest statement: All authors have declared no conflict of interest

Key Words: COVID-19, SARS-CoV-2, ARDS, Lung Injury

Abstract

COVID-19, the pandemic caused by the SARS-CoV-2 coronavirus can progress to pneumonia and Acute Respiratory Distress Syndrome (ARDS), resulting in an extraordinary level of ICU utilization and considerable mortality. Several pathophysiological features of COVID-19 associated ARDS are strikingly atypical, leading to the hypothesis that COVID-19 related ARDS represents a unique endotype of ARDS (*1*). With the caveat that studies are ongoing, and observations are preliminary, there appear to be striking differences in the pulmonary physiology of COVID-19 patients compared to the features of ARDS precipitated by other respiratory pathogens and viruses (e.g. influenza). These observations suggest that dysfunction of the pulmonary vasculature contributes to the pathogenesis of COVID-19-induced ARDS. We will highlight observations that implicate the lung microvasculature as a critical mediator of COVID-ARDS.

Clinical Risk Factors for COVID-19 and non-COVID-19 ARDS

Early reports of COVID-19 patient cohorts from China and Italy have identified several risk factors for severe illness and death (*2-4*). Most of these risk factors are unsurprising as they are also risk factors for non-COVID-19 ARDS, including age, cardiovascular disease, chronic lung disease, cancer, and chronic kidney disease. Alternatively, several risk factors appear unique to severe COVID-19 disease, suggesting a distinct ARDS phenotype. First, male sex has been reported to be strongly associated with mortality in multiple COVID-19 cohorts (*2, 5*). Sex-based biological differences may influence the development and outcome of ARDS, but sex has not been consistently established with mortality in non-COVID-19 ARDS (*6*). Additionally, diabetes appears to be another risk factor for severe COVID-19 disease (*3, 4*). In contrast,

diabetes is associated with a reduced risk of ARDS and is included in the Lung Injury Prediction Score as a negative predictor (7-9).

Most recently, ABO blood type has been reported to be associated with COVID-19 susceptibility in pre-printed articles that have not yet undergone peer review. Specifically, in a multicenter cohort from Wuhan and Shenzhen, China and another cohort from New York City, ABO blood type A was over-represented and blood type O underrepresented in COVID-19 patients relative to the general public (10, 11). This is consistent with reports of an association between ABO blood type A and increased risk of infection with the previous SARS-CoV reported in 2005 by a group from Hong Kong (12). In an *in vitro* model of SARS-CoV infection, anti-histo blood group antibodies inhibited the viruses' spike protein from interacting with its cellular receptor, ACE2, suggesting a possible underlying mechanism(13). In undifferentiated ARDS, ABO blood type A has also been reported to be associated with an approximately 14% higher risk of ARDS relative to blood type O in sepsis and severe trauma (14). ABO blood type A is also associated with risk of multiple thrombotic diseases including myocardial infarction, stroke, and venous thromboembolism (15), as well as plasma concentrations of endothelial derived proteins important in microvascular coagulation and cell adhesion including von Willebrand Factor, intracellular adhesion molecule-1, and E-selectin (16-19) It is therefore also possible that the mechanisms that underlie these associations may also impact an association between SARS-CoV2 infection and the development of severe COVID-19 disease by blood type.

Unique Clinical Features of COVID-19 ARDS

Although increased physiologic dead space and decreased lung compliance are expected in ARDS, ARDS related to COVID-19 often presents with relatively preserved compliance. In

our experience, the static compliance has been 35 – 40 despite $\text{FiO}_2 > 70\%$ and $\text{PEEP} > 15 \text{ cm H}_2\text{O}$. Thus, although the compliance is abnormal, and would be consistent with the ARDS conceptual model articulated in the Berlin definition (20), compliance is less impacted than oxygenation and dead space. It is worth noting that the 2012 ARDS Definition Task Force considered a requirement for static compliance $\leq 40 \text{ ml/cm H}_2\text{O}$ or minute ventilation $\geq 10 \text{ L./min}$ to be declared severe ARDS, and the inclusion of those variables did not change mortality risk compared to meeting hypoxia criteria alone, thus neither compliance nor minute ventilation was included in the ARDS definition (20).

Autopsy studies also highlight both similarities to and distinctions from undifferentiated ARDS. In one series, pathologic findings included diffuse alveolar damage (DAD), hyaline membranes (HM), and inflammatory exudates(21). In contrast, another series of 5 subjects highlighted the lack of DAD or HM while highlighting microvascular thrombi (22). This heterogeneity, even at the pathologic level, is consistent with larger autopsy series where even among cases with persistent and severe ARDS, the presence of HM was only 69% (23).

The Lung Endothelium during Homeostasis

The network of vessels surrounding the alveoli are lined with endothelial cells that play a vital role in lung homeostasis. The pulmonary endothelium is in intimate contact with alveolar epithelial cells and red bloods cells, forming a semi-permeable barrier essential for gas exchange (24, 25). In addition to facilitating gas exchange and performing critical barrier functions, the lung endothelium regulates leukocyte trafficking and coagulation. Furthermore, the pulmonary microvascular endothelium filters the entire systemic circulation and is routinely exposed to noxious stimuli including blood borne pathogens, toxins, and endogenous inflammatory

mediators. While most respiratory viruses do not infect endothelial cells directly, the robust inflammatory response induced by these pathogens causes significant injury to the pulmonary vasculature. Inflammation-induced disruption of homeostatic endothelial functions can result in impaired diffusion, disrupted barrier function, aberrant coagulation, and increased permeability, many of the hallmarks of ARDS. Restoration of vascular integrity is thus vital for return of lung function.

Potential Mechanisms for Vascular Injury

One of the more intriguing possibilities contributing to this vascular ARDS phenotype is the involvement of the SARS-CoV-2 receptor, ACE2. ACE2 is a key player in the renin-angiotensin system responsible for regulation of blood pressure and electrolyte balance. Angiotensin II acts on a variety of target cells to produce acute and long-term physiological effects including vasoconstriction, sympathetic nervous stimulation, smooth muscle and fibroblast proliferation, and inflammation. ACE2 counteracts angiotensin II activity by catalyzing its proteolytic cleavage into Angiotensin (1-7).

As the primary cellular receptor for SARS-CoV-2, it might be expected that higher levels of ACE2 would result in more severe disease. However, some preliminary studies find the opposite, as women exhibit higher ACE2 expression but are less prone to severe COVID-19 disease than men(26). A series of reports after the original SARS outbreak sheds some mechanistic light on these observations. ACE2 knockout mice exhibit much more severe lung injury after acid aspiration, while administration of recombinant ACE2 is protective(27). Another report demonstrated that binding of SARS-CoV Spike protein to ACE2 resulted in a loss of ACE2 protein, and administration of recombinant Spike-Fc protein worsened lung injury by

increasing angiotensin II activity(28), though it remains unclear *how* this occurs. It is important to note that these studies were performed with the original SARS-CoV Spike protein, so it is not certain whether CoV-2 Spike would have similar effects. Nonetheless, they provide significant rationale for some of the pathophysiological differences observed with COVID-19 ARDS. Loss of ACE2 repression of angiotensin II activity promotes microvascular thrombosis through direct and indirect means(29-31), and prolonged vasoconstriction and hypertension are well known to induce endothelial injury. Moreover, angiotensin II can directly induce endothelial apoptosis (32, 33) and inhibit endothelial cell proliferation, thus preventing angiogenic repair / regeneration, worsening lung injury, and preventing recovery(34).

Another potential mechanism of vascular injury contributing to ARDS involves dysregulated complement activation. One of the oldest evolutionary defenses, the complement system serves as a first line defense against pathogens and is essential for the removal of dead cells and maintenance of organismal homeostasis. While the effector functions of opsonization, inflammation, chemotaxis and cytolysis promote pathogen clearance, dysregulated or excessive complement activation can lead to tissue injury and organ failure.(35) Perhaps one of the best examples of this is the prothrombotic and anaphylotoxic effects of activated complement component 5 (C5a)(36).

It is not immediately obvious why SARS-CoV-2 would activate complement more so than other etiologies of ARDS. Intriguingly, preliminary studies suggest a specific SARS-CoV-2 protein might directly interface with the complement system to increase the risk of thrombosis(37). The nucleocapsid (N) protein of several coronaviruses, including SARS-CoV-2, was shown to bind directly and activate a key protease in the complement activation cascade, MASP-2, resulting in complement activation(37). *In vivo* administration of adenoviral vectors

expressing SARS nucleocapsid strongly enhanced LPS-induced lung injury in mice, which was prevented by co-administration of MASP-2 neutralizing antibodies (37). In earlier, pre-clinical studies of SARS-CoV-induced lung injury, mice deficient in C3 were relatively protected from lung injury following SARS-CoV infection and exhibited less lung neutrophil recruitment and lower levels of cytokines in the lungs and circulation (38). Further evidence for both alternative and classical pathway activation in COVID-ARDS is presented in recent autopsy studies where C4d and C5b-9 complex deposition was detected in the lung vasculature (22, 37).

Interestingly the alternate pathway of complement activation is considered always “on”, requiring tight regulation by soluble and membraned bound complement regulatory proteins which serve to protect the endothelium and maintain quiescence. Medical conditions such as diabetes among others identified as risk factors for SARS-CoV-2 mortality, lead to dysfunctional complement regulatory proteins (e.g. in the case of CD55 and CD59 due to glycation), thereby increasing susceptibility to complement induced tissue damage.(39-41) Given the atypical risk factors for COVID ARDS it is plausible that complement activation and wide-spread endothelial dysfunction contribute to the pathogenesis of COVID-ARDS.

Conclusions

Despite the best care and implementation of lung protective strategies , the mortality for COVID-ARDS remains high(42). Given the many indications of vascular involvement, vascular-centric, endothelial protective therapies should be considered as adjuncts in the treatment of patients with COVID-ARDS. Indeed, we believe that these unique vascular manifestations involved in COVID-ARDS justify its consideration as a distinct ARDS endotype. In view of the potential for targeted therapies of the complement pathway, anti-coagulation, and other

endothelial protective therapies such as nitric oxide, it is urgent that researchers from all backgrounds generate a comprehensive molecular model through which to frame vascular endothelial dysfunction in COVID-ARDS. While much ongoing COVID-19 research focuses on the epithelium and the inflammatory / immune response, therapeutic successes are unlikely without significant attention on the vascular endothelium as well, as the lung only properly functions through the synergistic interactions of all these cells types. Clinicians, epidemiologists, translational and bench researchers must come together to define the disease, identify biomarkers for disease progression and test therapies for this devastating disease.

Funding: NHLBI 126788 (NSM)

References

1. J. P. Reilly, C. S. Calfee, J. D. Christie, Acute Respiratory Distress Syndrome Phenotypes. *Semin Respir Crit Care Med* **40**, 19-30 (2019).
2. G. Onder, G. Rezza, S. Brusaferro, Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA*, (2020).
3. Z. Wu, J. M. McGoogan, Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*, (2020).
4. F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, J. Xiang, Y. Wang, B. Song, X. Gu, L. Guan, Y. Wei, H. Li, X. Wu, J. Xu, S. Tu, Y. Zhang, H. Chen, B. Cao, Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* **395**, 1054-1062 (2020).
5. T. Chen, D. Wu, H. Chen, W. Yan, D. Yang, G. Chen, K. Ma, D. Xu, H. Yu, H. Wang, T. Wang, W. Guo, J. Chen, C. Ding, X. Zhang, J. Huang, M. Han, S. Li, X. Luo, J. Zhao, Q. Ning, Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* **368**, m1091 (2020).
6. B. A. McNicholas, F. Madotto, T. Pham, E. Rezoagli, C. H. Masterson, S. Horie, G. Bellani, L. Brochard, J. G. Laffey, L. S. Investigators, E. T. G. the, Demographics, management and outcome of females and males with acute respiratory distress syndrome in the LUNG SAFE prospective cohort study. *Eur Respir J* **54**, (2019).
7. S. Yu, D. C. Christiani, B. T. Thompson, E. K. Bajwa, M. N. Gong, Role of diabetes in the development of acute respiratory distress syndrome. *Crit Care Med* **41**, 2720-2732 (2013).
8. S. Honiden, M. N. Gong, Diabetes, insulin, and development of acute lung injury. *Crit Care Med* **37**, 2455-2464 (2009).
9. G. J. Soto, D. J. Kor, P. K. Park, P. C. Hou, D. A. Kaufman, M. Kim, H. Yadav, N. Teman, M. C. Hsu, T. Shvilkina, Y. Grewal, M. De Aguirre, S. Gunda, O. Gajic, M. N. Gong, Lung Injury Prediction Score in Hospitalized Patients at Risk of Acute Respiratory Distress Syndrome. *Crit Care Med* **44**, 2182-2191 (2016).
10. M. Zietz, N. P. Tatonetti, Testing the association between blood type and COVID-19 infection, intubation, and death. *medRxiv*, 2020.2004.2008.20058073 (2020).
11. J. Zhao, Y. Yang, H. Huang, D. Li, D. Gu, X. Lu, Z. Zhang, L. Liu, T. Liu, Y. Liu, Y. He, B. Sun, M. Wei, G. Yang, X. Wang, L. Zhang, X. Zhou, M. Xing, P. G. Wang, Relationship between the ABO Blood Group and the COVID-19 Susceptibility. *medRxiv*, 2020.2003.2011.20031096 (2020).
12. Y. Cheng, G. Cheng, C. H. Chui, F. Y. Lau, P. K. Chan, M. H. Ng, J. J. Sung, R. S. Wong, ABO blood group and susceptibility to severe acute respiratory syndrome. *Jama* **293**, 1450-1451 (2005).
13. P. Guillon, M. Clement, V. Seville, J. G. Rivain, C. F. Chou, N. Ruvoen-Clouet, J. Le Pendu, Inhibition of the interaction between the SARS-CoV spike protein and its cellular receptor by anti-histo-blood group antibodies. *Glycobiology* **18**, 1085-1093 (2008).
14. J. P. Reilly, N. J. Meyer, M. G. S. Shashaty, R. Feng, P. N. Lanken, R. Gallop, S. Kaplan, M. Herlim, N. L. Oz, I. Hiciano, A. Campbell, D. N. Holena, M. P. Reilly, J. D. Christie,

- ABO blood type A is associated with increased risk of ARDS in whites following both major trauma and severe sepsis. *Chest* **145**, 753-761 (2014).
15. S. R. Stowell, C. P. Stowell, Biologic roles of the ABH and Lewis histo-blood group antigens part II: thrombosis, cardiovascular disease and metabolism. *Vox Sanguinis* **114**, 535-552 (2019).
 16. V. Emilsson, M. Ilkov, J. R. Lamb, N. Finkel, E. F. Gudmundsson, R. Pitts, H. Hoover, V. Gudmundsdottir, S. R. Horman, T. Aspelund, L. Shu, V. Trifonov, S. Sigurdsson, A. Manolescu, J. Zhu, Ö. Olafsson, J. Jakobsdottir, S. A. Lesley, J. To, J. Zhang, T. B. Harris, L. J. Launer, B. Zhang, G. Eiriksdottir, X. Yang, A. P. Orth, L. L. Jennings, V. Gudnason, Co-regulatory networks of human serum proteins link genetics to disease. *Science* **361**, 769-773 (2018).
 17. M. Franchini, F. Capra, G. Targher, M. Montagnana, G. Lippi, Relationship between ABO blood group and von Willebrand factor levels: from biology to clinical implications. *Thrombosis Journal* **5**, 14 (2007).
 18. M. Barbalic, J. Dupuis, A. Dehghan, J. C. Bis, R. C. Hoogeveen, R. B. Schnabel, V. Nambi, M. Bretler, N. L. Smith, A. Peters, C. Lu, R. P. Tracy, N. Aleksic, J. Heeriga, J. F. Keaney, Jr, K. Rice, G. Y. H. Lip, R. S. Vasan, N. L. Glazer, M. G. Larson, A. G. Uitterlinden, J. Yamamoto, P. Durda, T. Haritunians, B. M. Psaty, E. Boerwinkle, A. Hofman, W. Koenig, N. S. Jenny, J. C. Witteman, C. Ballantyne, E. J. Benjamin, Large-scale genomic studies reveal central role of ABO in sP-selectin and sICAM-1 levels. *Human Molecular Genetics* **19**, 1863-1872 (2010).
 19. S. Kiechl, G. Pare, M. Barbalic, L. Qi, J. Dupuis, A. Dehghan, J. C. Bis, R. C. Laxton, Q. Xiao, E. Bonora, J. Willeit, Q. Xu, J. C. Witteman, D. Chasman, R. P. Tracy, C. M. Ballantyne, P. M. Ridker, E. J. Benjamin, S. Ye, Association of variation at the ABO locus with circulating levels of soluble intercellular adhesion molecule-1, soluble P-selectin, and soluble E-selectin: a meta-analysis. *Circulation. Cardiovascular genetics* **4**, 681-686 (2011).
 20. V. M. Ranieri, G. D. Rubenfeld, B. T. Thompson, N. D. Ferguson, E. Caldwell, E. Fan, L. Camporota, A. S. Slutsky, Acute respiratory distress syndrome: the Berlin Definition. *Jama* **307**, 2526-2533 (2012).
 21. S. E. Fox, A. Akmatbekov, J. L. Harbert, G. Li, J. Q. Brown, R. S. Vander Heide, Pulmonary and Cardiac Pathology in Covid-19: The First Autopsy Series from New Orleans. *medRxiv*, 2020.2004.2006.20050575 (2020).
 22. C. Magro, J. J. Mulvey, D. Berlin, G. Nuovo, S. Salvatore, J. Harp, A. Baxter-Stoltzfus, J. Laurence, Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. *Translational Research*, (2020).
 23. A. W. Thille, A. Esteban, P. Fernández-Segoviano, J.-M. Rodriguez, J.-A. Aramburu, O. Peñuelas, I. Cortés-Puch, P. Cardinal-Fernández, J. A. Lorente, F. Frutos-Vivar, Comparison of the Berlin Definition for Acute Respiratory Distress Syndrome with Autopsy. *American Journal of Respiratory and Critical Care Medicine* **187**, 761-767 (2013).
 24. J. B. West, Blood flow to the lung and gas exchange. *Anesthesiology* **41**, 124-138 (1974).
 25. W. C. Aird, Phenotypic heterogeneity of the endothelium: II. Representative vascular beds. *Circ Res* **100**, 174-190 (2007).

26. J. J. Chen, Q.; Xia, X.; Liu, K.; Yu, Z.; Tao, W.; Gong, W.; Han, J.J., Individual Variation of the SARS-CoV2 Receptor ACE2 Gene Expression and Regulation. *Preprints*, 2020030191.
27. Y. Imai, K. Kuba, S. Rao, Y. Huan, F. Guo, B. Guan, P. Yang, R. Sarao, T. Wada, H. Leong-Poi, M. A. Crackower, A. Fukamizu, C.-C. Hui, L. Hein, S. Uhlig, A. S. Slutsky, C. Jiang, J. M. Penninger, Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* **436**, 112-116 (2005).
28. K. Kuba, Y. Imai, S. Rao, H. Gao, F. Guo, B. Guan, Y. Huan, P. Yang, Y. Zhang, W. Deng, L. Bao, B. Zhang, G. Liu, Z. Wang, M. Chappell, Y. Liu, D. Zheng, A. Leibbrandt, T. Wada, A. S. Slutsky, D. Liu, C. Qin, C. Jiang, J. M. Penninger, A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nature medicine* **11**, 875-879 (2005).
29. E. Y. Senchenkova, J. Russell, L. D. Almeida-Paula, J. W. Harding, D. N. Granger, Angiotensin II-mediated microvascular thrombosis. *Hypertension* **56**, 1089-1095 (2010).
30. N. J. Brown, D. E. Vaughan, Role of Angiotensin II in Coagulation and Fibrinolysis. *Heart Failure Reviews* **3**, 193-198 (1999).
31. A. Celi, S. Cianchetti, G. Dell’Omo, R. Pedrinelli, Angiotensin II, tissue factor and the thrombotic paradox of hypertension. *Expert Review of Cardiovascular Therapy* **8**, 1723-1729 (2010).
32. S. Dimmeler, V. Rippmann, U. Weiland, J. Haendeler, A. M. Zeiher, Angiotensin II Induces Apoptosis of Human Endothelial Cells. *Circulation Research* **81**, 970-976 (1997).
33. T. Watanabe, T. A. Barker, B. C. Berk, Angiotensin II and the Endothelium. *Hypertension* **45**, 163-169 (2005).
34. M. E. Pueyo, J.-B. Michel, Angiotensin II receptors in endothelial cells. *General Pharmacology: The Vascular System* **29**, 691-696 (1997).
35. R. Xu, F. Lin, C. Bao, F.-S. Wang, Mechanism of C5a-induced immunologic derangement in sepsis. *Cellular & Molecular Immunology* **14**, 792-793 (2017).
36. P. A. Ward, The dark side of C5a in sepsis. *Nature Reviews Immunology* **4**, 133-142 (2004).
37. T. Gao, M. Hu, X. Zhang, H. Li, L. Zhu, H. Liu, Q. Dong, Z. Zhang, Z. Wang, Y. Hu, Y. Fu, Y. Jin, K. Li, S. Zhao, Y. Xiao, S. Luo, L. Li, L. Zhao, J. Liu, H. Zhao, Y. Liu, W. Yang, J. Peng, X. Chen, P. Li, Y. Liu, Y. Xie, J. Song, L. Zhang, Q. Ma, X. Bian, W. Chen, X. Liu, Q. Mao, C. Cao, Highly pathogenic coronavirus N protein aggravates lung injury by MASP-2-mediated complement over-activation. *medRxiv*, 2020.2003.2029.20041962 (2020).
38. L. E. Gralinski, T. P. Sheahan, T. E. Morrison, V. D. Menachery, K. Jensen, S. R. Leist, A. Whitmore, M. T. Heise, R. S. Baric, Complement Activation Contributes to Severe Acute Respiratory Syndrome Coronavirus Pathogenesis. *mBio* **9**, (2018).
39. X. Qin, A. Goldfine, N. Krumrei, L. Grubissich, J. Acosta, M. Chorev, A. P. Hays, J. A. Halperin, Glycation Inactivation of the Complement Regulatory Protein CD59. *A Possible Role in the Pathogenesis of the Vascular Complications of Human Diabetes* **53**, 2653-2661 (2004).
40. J. Acosta, J. Hettinga, R. Fluckiger, N. Krumrei, A. Goldfine, L. Angarita, J. Halperin, Molecular basis for a link between complement and the vascular complications of diabetes. *Proc Natl Acad Sci U S A* **97**, 5450-5455 (2000).

41. R. Flückiger, E. Cocuzzi, R. H. Nagaraj, M. Shoham, T. S. Kern, M. E. Medof, DAF in diabetic patients is subject to glycation/inactivation at its active site residues. *Mol Immunol* **93**, 246-252 (2018).
42. P. K. Bhatraju, B. J. Ghassemieh, M. Nichols, R. Kim, K. R. Jerome, A. K. Nalla, A. L. Greninger, S. Pipavath, M. M. Wurfel, L. Evans, P. A. Kritek, T. E. West, A. Luks, A. Gerbino, C. R. Dale, J. D. Goldman, S. O'Mahony, C. Mikacenic, Covid-19 in Critically Ill Patients in the Seattle Region — Case Series. *New England Journal of Medicine*, (2020).