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The American Journal of Pathology, Vol. 192, No. 9, September 2022

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The American Journal of
PATHOLOGY
ajp.amjpathol.org

CORRESPONDENCE

Dynamic Angiopoietin-2 Serum Level as Endothelial Damage Marker and Potential Therapeutic Target

To the Editor-in-Chief:

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We read with great attention the study of Price et al.[1] The authors identified an interesting low vascular injury signature, which was significantly associated with lower platelet count and higher mortality. The data also suggested that this signature could help in identifying coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome patients in whom vascular targeted therapies may be useful. The signature includes 22 proteins associated with vascular injury, platelet levels, and vascular function. Tie2 was also added, being an angiopoietin-1 and angiopoietin-2 (ANGPT2) receptor. Interestingly, this signature has an inverse correlation with the severity of patients' condition, with these proteins constituting in a way a kind of normalcy signature when normally expressed. ANGPT2 predictive power for prognosis and mortality was not tested in the reported cohort; however, the data showed that the ANGPT2 levels were higher in the plasma of patients with the low mean protein abundance cluster. We previously reported a large cohort of hospitalized patients with COVID-19.[2] A three-day ANGPT2 increase of at least twofold from baseline was strongly associated with in-hospital mortality, whereas 10-day angiopoietin-2 increase of at least twofold from baseline was significantly associated with nonresolving pulmonary condition by multivariate analysis in our study. Interestingly, the pathologic picture in the lungs from nine autopsies in our study was similar to that reported in the present article. In our study, we stained the lung samples for ANGPT2, Tie2, CD68, and CD34, whereas in the present study, lungs were stained for ANGPT2, CD61, phosphorylated mixed lineage kinase domain-like protein (pMLKL), and CD31. In both of the studies, diffuse alveolar damage in COVID-19, interstitial inflammation, dilated capillaries, and microthrombi were seen. A marked ANGPT2 staining was present in the areas of higher damage, in newly formed vessels in the alveolar walls, in pericytes, and in macrophages inside alveolar spaces. In our study, ANGPT2 colocalized with Tie2, which was similarly overexpressed, likely powerfully induced by elevated ANGPT2.

On the whole, these two studies[1,2] address an extremely relevant topic (ie, the role of the angiogenic factor ANGPT2 in the pathogenesis of the inflammatory and vascular disruptive syndrome occurring in COVID-19). ANGPT2 is released from endothelial granules Weber Palade bodies in case of vascular inflammation. The endothelium can be activated by circulating inflammatory mediators, such as polymorphonuclear leukocyte or monocyte-derived enzymes. The aberrant dysregulation of ANGPT2 influences and promotes vascular hyperpermeability. ANGPT2 modulates the function of angiopoietin-1 (that promotes instead the stabilization of nascent blood vessels). ANGPT2 is able to disrupt this action and become predominant in the pathogenic mechanism. Furthermore, abnormally high ANGPT2 levels can promote vascular leakage, such as in acute respiratory distress syndrome conditions.[3,4] Interestingly, in this study,[1] the authors indicated a novel feature in the ANGPT2-associated vascular injury (ie, induction of vascular cell death). It is possible that the low vascular signature may be associated with worse prognosis, as it highlights a condition

DOI of original article: https://doi.org/10.1016/j.ajpath.2022.04.002
Supported by a Regione Emilia-Romagna−Bankitalia grant (E.V.).
Disclosures: None declared.

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of down-regulated control mechanisms. ANGPT2, both as circulating factor and at the lung level, represents a much more direct indicator for the pathogenic mechanism underlying COVID-19 acute respiratory distress syndrome and therefore is, in our view, a more powerful candidate prognostic factor. Not less important, two tests 3 days apart may be simpler and more affordable than the complex low vascular signature proposed.

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https://doi.org/10.1016/j.ajpath.2022.05.011

Authors' Reply

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DOI of original article: https://doi.org/10.1016/j.ajpath.2022.05.011

Supported by NIH National Institute on Aging under award 1U19AG063744 (J.K.); NIH National Heart, Lung, and Blood Institute grant T32HL134629-01A1 (D.R.P.); and Stony Wold-Herbert Fellowship Fund (D.R.P.).

Disclosures: None declared.

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We thank Melegari et al for their letter and their interest in our article. Our study derived a 22-protein vascular injury signature based on blood proteins' association with both mortality and platelet level and showed that this signature correlated with clinical (eg, mortality and recovery) as well as pathophysiological [eg, platelets, angiopoietin 2 (ANGPT2), and necrotic vascular cell death] readouts throughout the time course of coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome (ARDS).[1] Notably, the data demonstrated that this association held even when non−COVID-19 ARDS subjects were included in the analysis.

Melegari et al suggest that serial measurements of ANGPT2 separated by 3 days are a more feasible prognostic biomarker for COVID-19 than the baseline measurement of the 22-protein signature derived in the mentioned article.[1] After a multivariable adjustment, a twofold increase in ANGPT2 over 3 days accurately predicted mortality in a mixed disease severity cohort of COVID-19 subjects.[2] These findings fit nicely with the robust literature linking ANGPT2 and prognosis in sepsis/acute lung injury: ANGPT2 has been linked to prognosis in sepsis[3,4] and ARDS,[5] including a large meta-analysis.[6] Serial ANGPT2 measurements have similarly been linked to ARDS prognosis in non−COVID-19 infection−related acute lung injury,[7] further supporting ANGPT2 as a robust prognostic biomarker. Although the reported protein signature is in part defined by its association with patient mortality, it was not primarily intended for clinical prognosis applications.

Instead, these findings better fit within a growing body of evidence linking the Tie2/angiopoietin axis with platelet activation in systemic inflammation and acute lung injury. Disruption of the endothelial Tie2 axis has been shown to be a sentinel event in septic disseminated intravascular coagulation, with loss of Tie2 signaling preceding signs of overt platelet consumption and Tie2 activation working to normalize prothrombotic responses.[8] More recently, alterations in the Tie2/angiopoietin axis have been linked to the procoagulant endothelial dysfunction in severe COVID-19.[9] Our article offers a relevant complement to these findings in several ways. First, it links the dysregulated Tie2/angiopoietin axis to platelet level and blood markers of coagulopathy in a diverse ARDS cohort (COVID-19 as well as bacterial and influenza ARDS), demonstrating the clinical relevance of aberrant vascular activation and coagulopathy to a general ARDS population. And second, by including ARDS subjects with diverse etiologies of low platelet levels (eg, lack of platelet production in patients with malignancy), the link between the Tie2/angiopoietin axis and platelet level can be generalized to non−platelet-consumptive ARDS processes. As platelets are essential sources of angiocrine factors, including the endothelial-stabilizing angiopoietin-1 and angiogenic factors platelet-derived growth factor-A and platelet-derived growth factor-B, deficiency in these factors may reflect an inherent vascular