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Correspondence
Ning Tang, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China.
Email: tonyjesus@126.com

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Uncertainties on the prognostic value of D-dimers in COVID-19 patients

We read with great interest the paper by Zhang and colleagues[1] describing the predictive value of D-dimers tested on admission on in-hospital mortality in patients with Covid-19. These interesting results may supply an easy-to practice laboratory marker to clinical teams managing the patients. However, a number of uncertainties must be mentioned.

First, this is a purely retrospective study, focused on patients who had a D-dimer testing at admission. It was not stated why these peculiar patients had D-dimer testing. The total number of patients from which this studied subgroup was selected is not given. A selection bias is thus likely.

Second, if we consider, despite the methodological limitations mentioned, that the available data constitute a kind of derivation cohort, a prospective validation cohort, systematically including all patients entering hospital, is lacking.

Third, the impact of the modalities and intensities of the antithrombotic/anticoagulant treatments given to the patients on the D-dimer predictive value is not studied.

Fourth, nothing is said about the putative predictive value of the variations, day after day, of the D-dimer levels during hospital stay on the vital prognosis. We also do not know if the area under the D-dimer level curve obtained day after day is by itself a prognostic marker.

Fifth, the accuracy of the D-dimer predictive value capacity on mortality is not clearly studied according to the time of death, whether very early, early, or late; for example, depending on the week after admission. Many additional complications can arise in these patients that, over time, make the plausibility of an initial short half-life marker to predict death less likely. In the same way, computed positive predictive and negative predictive values of the proposed D-dimer threshold level would have added some interesting information.

Sixth, as suggested by the authors, this is a purely univariate analysis, a multivariate analysis is strongly lacking, and we do not know the impact of confounders (some laboratory markers being also strongly associated with prognosis in the paper) on the claimed strong predictive value of D-dimers.

The authors have to be congratulated for their very initial data, which now have to be consolidated using strong methodological approaches. This has been difficult in the emergency of such an outbreak situation, but must now be prioritized. The underlying meaning of increased D-dimer levels in Covid-19 patients must be clearly understood, the prevailing interpretation has been coagulation activation finally leading to disseminated intravascular coagulation, which is probably true in the most severe patients and near-fatal outcome but that have yet to be demonstrated in the initial disease despite striking high D-dimer levels. This has strong clinical consequences, as the observed high D-dimer levels have induced spontaneous therapeutic interventions and experts' recommendations increasing the antithrombotic/anticoagulant dosages, thus increasing the hemorrhagic risk. The mechanisms, determinants, roots, and independent value of increased D-dimers in Covid-19 patients must be fully understood to propose the most pathophysiologically relevant treatments to test.

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CONFLICT OF INTEREST

All authors declare having no competing conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing of this letter and approved its final version.

Jean-Christophe Gris[1,2,3]
Isabelle Quéré[4]
Antonia Pérez-Martin[5]
Jean-Yves Lefrant[6]
Albert Sotto[7]

[1]*Department of Haematology, Nîmes University Hospital, Nîmes, France*
[2]*University of Montpellier, Montpellier, France*
[3]*I.M. Sechenov First Moscow State Medical University, Moscow, Russia*
[4]*Department of Vascular Medicine, Montpellier University Hospital, Montpellier, France*
[5]*Department of Vascular Investigations and Vascular Medicine, Nîmes University Hospital, Nîmes, France*
[6]*Department of Intensive Care, Nîmes University Hospital, Nîmes, France*
[7]*Department of Infectious and Tropical Diseases, Nîmes University Hospital, Nîmes, France*

Correspondence
Jean-Christophe Gris, Consultations et Laboratoire d'Hématologie, Centre Hospitalier Universitaire, GHU Caremeau, Place du Pr. Robert Debré, F-30029 Nîmes cédex 9, France.
Email: jean.christophe.gris@chu-nimes.fr

ORCID

Jean-Christophe Gris https://orcid.org/0000-0002-9899-9910
Isabelle Quéré https://orcid.org/0000-0002-1492-9764

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Response to "Uncertainties on the prognostic value of D-dimers in COVID-19 patients"

We appreciate the opportunity to respond to the letter from Dr Gris and colleagues. It is true there were several limitations in our study. However, we still believe that D-dimer level at admission could be an effective and easily available predictor in patients with coronavirus disease 2019 (COVID-19).

First, selection bias was the first limitation we mentioned in the Discussion section.[1] Selection bias was mainly attributed to the fact that it was a single center, and the limits of retrospective study and the conditions during the early outbreak of COVID-19 in Wuhan, China. A total of 712 patients with COVID-19 were admitted to our hospital during the outbreak; we had enrolled all 343 eligible patients who had D-dimer levels and definite outcomes (death or survival). Generally, D-dimer, as one aspect of a coagulation profile, should be ordered on admission for every patient with COVID-19. Our clinicians had realized that D-dimer could be a good marker in management of COVID-19 patients, which was supported by Wang and colleagues at the early outbreak.[2] However, due to limits in the number of medical staff, many patients had not had D-dimer tests on admission, especially in those with mild cases.

Second, a well-designed prospective cohort study could provide higher-level evidence to confirm the prognosis value of D-dimer in patients with COVID-19. However, the number of new diagnosed COVID-19 cases is too rare to conduct a prospective study in China now. So, a standardized, pooled, multi-center retrospective study might have more operability, which is also our expectation.

Third, we did not think anticoagulation or antithrombotic medication before admission would have observable impact on the predictive value of D-dimer in COVID-19 patients. Because oral anticoagulation use before admission usually was a long-term state, which would generate a relatively stable level of D-dimer. Furthermore, in a previous review, elevated D-dimer can also be well used to predict unfavorable outcomes in patients during oral anticoagulation use.[3]

The main purpose of our study was to provide a simple and easy-to-use marker to distinguish those who might have high mortality risks on admission. Anticoagulation therapy in hospital might

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