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

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Sir Editor,

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 is not said why these peculiar patients had a 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 above, 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 on 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 later, for example depending on the week after admission. Many additional complications can arise in these patients which, 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 evoked by the authors, this is a purely univariate analysis, a multivariate analysis is strongly lacking, 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 prioritised. 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 DIC, which is probably true in the most severe patients and near fatal outcome but which is far 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 haemorrhagic risk. The mechanisms, determinants, roots and independent value of increased D-dimers in Covid-19 patients must be fully understood in order to propose the most pathophysiologically relevant treatments to test.

### References

1 Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, Zhang Z. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost.* 2020; Apr 19. doi: 10.1111/jth.14859.

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