Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

AUTHOR CONTRIBUTIONS

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

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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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decrease D-dimer level, but actually it is just one of several clinical interventions; there were also many other similar factors that might impact predictive value of D-dimer, such as hormone therapy, antibiotic therapy, and so on. Furthermore, the number of events was too small to perform full-adjusted analysis, which we also mentioned in our study.[1] Thus, the impact of clinical intervention, including but not limited to anticoagulation on predictive value of D-dimer should be assessed by future studies with bigger sample sizes.

Fourth, due to a 7- to 8-hour half-life in-vivo, D-dimer is quite suitable to be a dynamic monitor of COVID-19 progression. Two retrospective studies had reported that D-dimer showed a marked and continuous rise in non-survivors.[2,4] However, we don't think that the area under the D-dimer level curve obtained day after day could be a good prognostic marker, due to the fact that: the water-line of D-dimer differed greatly among patients, it is too difficult to ensure D-dimer testing would be performed day after day in every patient, and it is not easy to use for clinicians.

Fifth, as shown in Figure 2 in our study,[1] statistical significance of separation between patients with D-dimer ≥ 2.0 μg/mL and those with D-dimer < 2.0 μg/mL was achieved at 7 days after admission. Dynamic monitoring might provide more information to predict death. It can be said that the higher D-dimer level, the higher the mortality risk.

Sixth, we did not provide multivariate analysis of confounders. Instead, we performed a Cox proportional hazard analysis with adjustment of age, gender, and underlying diseases in our study to evaluate the independent predictive value of D-dimer. Given the limited number of events, there might be not enough reliability to perform multivariate analysis. Furthermore, the pure multivariate analysis might add nothing in management of COVID-19 patients. The optimum approach to use these confounders may be to establish a multiple-parameter prediction model.

D-dimer, as one of the key markers of severe coagulopathy, has been observed to be common in non-survivors of COVID-19. Up to now, the use of D-dimer in management of COVID-19 is attracting more and more attention. We are expecting further studies to describe more details.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest regarding this article.

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The association between D-dimers in COVID-19 patients and mortality remains beset of uncertainties

Dear Editor,

We appreciated the response to our letter from Dr Zhang and colleagues who actively support D-dimer level at admission as an effective and easy-to-perform laboratory predictor in patients with coronavirus disease 2019 (COVID-19).[1] We congratulate them for the work and thank them for the arguments they have provided. However, we still have many doubts, which observation of the cases we have managed in our university hospital do not dispel.

We still think that selection bias is a main confusion factor affecting their results. We were very surprised to read that only 13 deaths occurred during hospitalization in the 343 patients they included in their study, among the 712 patients admitted in their hospital during the outbreak: the mortality rate is thus only 3.8%. As a comparison, the mortality rates described in two other retrospective works from Wuhan City were 11%[2] and 28.3%.[3] They do not clearly define the precise minimal clinical criteria that induced

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