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

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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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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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hospital admission in their patients. We checked these data in the first 170 consecutive COVID-19 patients admitted in our wards with evidence of SARS-CoV-2 pneumonia necessitating oxygen therapy of at least 2 L per minute from March 8 through April 20. Their main characteristics on admission were the following: sex ratio male:female 116:54, age—median value, interquartile range value, (range)—69-18 (33-97), C-reactive protein (mg/L): 67-126 (1.3-480), platelet count (Giga/L): 291-180 (47-1266), PT ratio: 1.06-0.17 (0.82-9.85), fibrinogen (g/L): 6.85-2.14 (1.24-12.0), and D-dimer (µg/L): 2.182-2.626 (0.104-100.10). We unfortunately could not prevent the death of 25 patients (14.7%): 13 from day 1 to day 7 after admission, 9 from day 8 to day 14, and 3 after day 14. As our hospital was not at saturation at this point and thus normal care was provided, we believe that the patients observed by Zhang et al were not initially affected by major severity criteria. This may be the consequence either of a systematic local organization of care directing patients to different hospitals according to their perceived severity, or of the non-representativeness of the patients analyzed by comparison with all the COVID-19 patients hospitalized into the recruiting medical structures. This affects the possibility of generalizing their results to all COVID-19 patients.

Zhang et al used a cutoff value of D-dimers as a predictor for in-hospital mortality of 2.0 µg/mL. Among their 343 analyzed patients, only 19.5% had D-dimer values at least equal to this cutoff value and 77.8% lower than the cutoff value. By comparison, considering our first consecutive 170 patients, all studied on admission (Vidas D-dimer Exclusion II, Biomérieux, Craponne, France; threshold normal value: 0.5 µg/mL fibrinogen-equivalent units), 77 (45.1%) had D-dimers lower that the 2.0 µg/mL cutoff and 93 (54.9%) at least equal to the cutoff. Because D-dimers are increasingly considered to indicate severity in COVID-19 patients,[4] the patients described by Zhang and colleagues appear to be selected to be less severe than those ordinarily observed.

Moving to mortality rates among patients classified according to their D-dimer levels, Zhang and colleagues found only 1 of 267 when D-dimer values were lower than 2.0 µg/mL (0.37%) and 12 of 67 (17.9%) when D-dimer values are at least equal to 2.0 µg/mL, showing a striking difference. By comparison, applying the same cutoff to our patients, it was 8 of 77 (10.4%) under the cutoff and 17 of 93 (18.3%) for the highest category of D-dimer values, which is less impressive. Mortality rates for the highest values are quite similar, but are different for the lowest values. This must be understood. Among our 25 patients who died, 13 were deceased within 8 days after admission (52%), whereas extrapolating from the survival curve given in the initial paper[5] shows that half of the rare cases who died occurred before day 16. The paper thus appears to have included initially less severe cases with a less acute or sudden deterioration during hospitalization. It is likely that the numerous cofactors leading to patient's frailty are not similar between the group of patients managed by Zhang et al and the group of patients we managed. They are probably less prevalent in the studied Chinese population. This could explain a more frequent and earlier unfavorable evolution in our patients who presented with COVID-19, which might have been predicted to be less severe on the basis of D-dimers below the cutoff (frailty indicators do not systematically impact on D-dimer levels). Here also, the precise nature of the population included is the major component of the possible generalization of the results. This is not fully assuaged using a methodology based on a Cox proportional hazard analysis adjusted on the predicted interacting factors, which takes into account only the relationships within the population studied and not those in the general population.

To conclude, although the increasing volume of, mainly retrospective, heterogeneous data on the value of using D-dimers to manage COVID-19 might be attractive, it remains beset with uncertainties[6] and is strongly dependent on the true clinical representativeness and characteristics of the studied patients. The general impression is that elevated D-dimers are worrying, but the thresholds are variable and the clinical interpretation of this potential range is still very uncertain since no treatment exists that elevated D-dimers alone can legitimize. Outside of treatment of acute thrombotic complications, it is not even clear whether the levels of D-dimers in COVID-19 patients react to the type and intensity of antithrombotic and anticoagulant treatments, or whether a potential sensitivity, if it showed a dose effect, would modify the clinical prognosis. We know that Sars-CoV-2 globally activates the hemostatic system and has thrombotic consequences. We do not know much more that has a real practical medical value. We currently cannot use D-dimers to improve management and prognosis.

CONFLICT OF INTEREST

All the authors declare that they have no relevant conflict of interest with this work.

AUTHOR CONTRIBUTIONS

J.-C.G. designed the research, analyzed data, and wrote the paper. E.M., E.C.-N., and S.B. acquired the laboratory data. P.L., J.-M.M., D.L., A.S., C.R., L.M., S.D.B., and J.-Y.L. managed the patients. All authors discussed the results and approved the final version of the manuscript.

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Response to 'The association between D-dimer in COVID-19 patients and mortality remains beset of uncertainties'

We appreciate the opportunity to respond Dr Gris and colleagues who still have doubts about the predictive value of D-dimer in COVID-19.[1,2] We totally understand the concerns from Dr Gris and colleagues who just want to manage their patients better. We are trying to explain the potential influence factors here, hoping to provide any useful information for managing the COVID-19 patients.

The mortalities differed greatly among studies, hospitals, or even countries. Up to 8 June 2020, the overall mortality of COVID-19 in China was 5.5% (4638/84191),[3] which was 6.6% for Hubei (containing Wuhan, 4512/68135), China.[3] During the outbreak, our hospital was designated to admit the laboratory-confirmed COVID-19 patients who were moderate type (84.0%, 288/343), severe type (11.7%, 40/343), or critical severe type (4.4%, 15/343) according to the Chinese clinical guidance for COVID-19 pneumonia diagnosis and treatment.[4] Mild cases who had no or mild clinical symptoms, and no sign of pneumonia on chest imaging, were mainly admitted to mobile cabin hospitals.[5] As a whole, the distribution of patients existing in our study was basically consistent with the epidemiological characteristics of COVID-19 in Hubei, China. Thus, due to small sample sizes (191 cases, 99 cases, respectively) of the two retrospective studies,[6,7] the mortalities from the two studies should be unrepresentative, and comparison of the mortalities might be inappropriate.

Meanwhile, according to the distribution of C-reactive protein (CRP; 67-126, 1.3-480) provided by Dr Gris et al and CRP (median: 3.22 mg/L, IQR: 0.34-22.5 mg/L) in our original article,[8] it could be roughly inferred that the study populations were significantly different between the two studies. It is certain that the severe/critical cases suffered much higher mortalities compared to those mild or moderate cases. Thus, these might contribute to the difference of mortalities.

Another unignorable point we have mentioned as a limitation was the difference of length from symptom onset to admission.[8] Due to differences in patient number and medical resources in different areas, the lengths from illness onset to admission might be hugely varying. For example, the median of length from illness onset to admission in our study was 10 days (interquartile range [IQR]: 7-15 days), which might also contribute to the difference between the data from Dr Gris and ours. This was why we suggested that dynamic measurement of D-dimer could provide more information.

Actually, when we first analyzed the data, we were surprised by the striking difference of mortalities between two group (12 deaths versus 1 deaths). Then we cross-checked the original data several times and it was true. There were unexpectedly no significant differences observed in Dr Gris's data (8/77 versus 17/93),[2] which might

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