



Letter in response to: circulating von Willebrand factor and high molecular weight multimers as markers of endothelial injury predict COVID-19 in-hospital mortality

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Dear Editor

We would like to congratulate Philippe et al. [1] on the excellent work they have done to highlight the importance of von Willebrand Factor (VWF) and in particular the larger multimers, that are more biologically active, in the pathophysiology of COVID-19. The major strengths of this study are the large volume of patients enrolled ($n=208$), and the ability to predict mortality. The marked difference between the VWF:Ag levels between critical patients (507%) versus non-critical (288%) was highly significant ($p < 0.0001$). On further analysis, the ROC for VWF:Ag was the most predictive for mortality with an AUC of 0.92 (95% CI 0.88–0.96) with cut-off levels of VWF:Ag (423%) able to predict mortality in univariate, multivariate modelling, Kaplan–Meier estimator, and Cox proportional hazard. This study is also the first to demonstrate a clear relationship between the high molecular weight VWF multimers (HMWM) and critically ill patients which stands to reason given that ultra-large VWF polymers are more biologically active and play an extremely important role in clot formation under high stress. On univariate analysis, the odds ratio of association with mortality for HMWM ratio was 116 (95% CI 10.2–1943, $p < 0.001$).

The earliest report known to us that demonstrated very high levels of VWF was that of Escher et al. [2] with Goshua et al. [3] subsequently reporting marked elevations in plasma VWF concentrations in in-patients admitted with COVID-19. This group showed that increased levels were associated with disease severity—mean VWF antigen levels of $565 \pm 199\%$ vs 278 ± 133 for those admitted to ICU compared to those not admitted to ICU ($p < 0.0001$). Rauch et al. [4] looked at the progression of patients with COVID-19 in relationship to their admission VWF. Those with the highest VWF levels required greater levels of oxygen support, whereas those patients that had normal VWF levels on admission did not require admission to hospital nor supplementary oxygen ($n = 10$).

Shortly after this publication, Ladikou et al. [5] showed an increase in the VWF antigen levels of patients with COVID-19 and admitted to the ICU with a positive correlation seen in the VWF levels and the age of the patients. They reported a median VWF antigen level of 350% whilst also showing a markedly reduced level of ADAMTS13 (49.7%) suggesting loss of the VWF cleaving protease that ordinarily degrades large VWF multimers and reduces its activity. They speculated that excess release of VWF seen in COVID-19 patients leads to depletion of ADAMTS13 and contributes to the prothrombotic state. Further analysis of their data showed that median VWF levels were significantly higher in patients that died (477%) compared to the ones that remained alive (335%) ($p = 0.015$). In conjunction with these data showing huge elevations in VWF and reductions in ADAMTS13, there are further research to show that the VWF:ADAMTS13 ratio is greatly deranged. Huisman et al. [6] were the first to show a mean VWF:ADAMTS13 ratio of 8.5 (normal 0.5–2) from 12 patients admitted to the ICU. Subsequently, Mancini et al. [7] demonstrated similar findings with an elevated VWF:Ag to ADAMTS13 activity ratio that was strongly associated with disease severity with the worst ratio, 8.3, seen in those patients that required high

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intensity care (intubation and mechanical ventilation) compared to those requiring low intensity care, 3.42 ($p < 0.001$).

In response to the publication by Rauch, we proposed using agents targeting the GP1b receptor [8], caplacizumab or anfibatide, and we believe that these agents still represent viable treatment options for patients with COVID-19. We are delighted to see that others have also begun suggesting that these agents may represent a viable and logical treatment option in selected patients. We would, however, disagree with the suggestion that aspirin, at least at typical low doses of 75–100 mg, may prove beneficial, as binding of platelets to the VWF via the GP1b receptor results in activation of the GP2b3a receptor and therefore the optimal ‘standard’ anti-platelet agents to use would be antagonists to this receptor. Similarly, in a propensity score matched study of Tremblay et al. [9], there was no significant difference in the survival or time to mechanical ventilation in patients already receiving either anti-coagulation or anti-platelet agents prior to symptomatic infection compared to matched controls. Although the exact drugs being taken were not reported in the paper, it is likely that the majority of patients on anti-platelet agents were on aspirin.

Given the growing body of data that is now published and which confirms the marked abnormality within, with very high levels of VWF:Ag and markedly deranged VWF:ADAMTS13 ratio, we believe that the use of GP1b receptor antagonists would be feasible and should be considered for those patients with VWF:Ag levels of over 200% and VWF:ADAMTS13 ratios of ≥ 4 based on the existing literature. Alternatively, IV N-Acetyl Cysteine, which has been shown to reduce the size of VWF multimers could also be used and has a long history and familiarity amongst clinicians. The cheap nature of this drug and the ability to take the drug in its oral form as patients improve is also appealing. In patients with markedly deranged VWF:Ag and ADAMTS13 levels, as mentioned earlier, it could be used in conjunction with GPIIb/IIIa blockers as this combination has previously been shown to significantly impair clot formation [10]. When using these drugs it is important to note that high VWF levels may impede the effect of GPIIb/IIIa antagonists and Eptifibatide may offer advantages over Tirofiban in this regard [11]. Recombinant ADAMTS13 would represent a viable alternative and potentially in combination with IV NAC would allow a ‘normalisation’ of the abnormal VWF:ADAMTS13 ratio. We believe that the exploration of therapies aimed principally at targeting this imbalance is critical to the continued success against COVID-19. Although a single anti-platelet agent may reduce mortality, we believe that a combined approach, as outlined above, and likely involving NAC could allow a targeted approach to the underlying abnormality in the VWF:ADAMTS13 ratio as well as enable focussed intensive treatment for those patients at highest risk earlier in the disease course.

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Declarations

Conflict of interest PB has previously approached both Sanofi to trial Caplacizumab and Lees pharma to trial Anfibatide in COVID+ve patients. GC, GP, and OJ none relevant.

Ethical approval Ethical approval was not required for this letter.

Consent to Participate Consent to participate was not required.

Consent for publication Consent for publication is not required.

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