Spontaneous Major Haemorrhage in COVID-19 Patients: a Proposal for a Pathophysiology-Based Angiographic Treatment

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To the Editor:

We read with great interest the letter, *Bleeding in COVID patients: what we have understood so far*, by Lucatelli and colleagues [1]. The authors share their experience as an Interventional Radiology (IR) department in the battleground of *Coronavirus Disease 2019* (COVID-19)-related spontaneous major haemorrhages (SMHs) and, notably, propose a sort of an algorithm for selecting those patients requiring angiographic treatment, irrespective of eventual active bleeding at CT imaging. They also provide some technical suggestions regarding which materials are to be preferred for an effective embolization in the specific setting of COVID-19 patients. In short, they conclude that a combination of embolic agents (specifically, gelfoam or glue) together with coils could be of great effectiveness, since it promotes clot formation. However, with regard to this last point, our experience as regional referral hub for cardiovascular emergencies does not fully corroborate the authors' conclusions.

Between 1st March 2020 and 1st March 2021, 27 consecutive COVID-19 patients were referred to our IR department for SMHs. Of these, 25(92.6%) were receiving

prophylactic antithrombotic treatment. Now, regardless of the vessels each time accountable for the individual bleeding episodes (lumbar/ileolumbar [16/27,59.2%], inferior epigastric [3/27,11.1%], deep circumflex iliac [2/27,7.4%], right bronchial [2/27,7.4%], inferior gluteal [1/27,3.7%], lateral circumflex femoral [1/27,3.7%], sigmoidal [1/27,3.7%], and internal thoracic artery [1/27,3.7%]), COVID-19-related SMHs have been proven to have a common angiographic pattern, consisting of multiple, tiny bleeding foci affecting distal vascular territories [2]. This finding is also consistent with the pathophysiology of SARS-CoV-2 (*Severe Acute Respiratory Syndrome infection Coronavirus 2*) [3], characterized by widespread endothelial cell injury, possibly resulting in diffuse microvascular damage, with both a substantial component of local thrombosis [4] and imbalances in platelet recruitment. The COVID-19 specific incidence of SMHs ($\approx 2\%$) is indeed higher than observed in general admission patients receiving low molecular weight heparin [2].

Considering this peculiar bleeding pattern, we usually performed superselective embolization of the entire arterial segment accounting for the haemorrhage with small sized polyvinyl alcohol particles (mostly ranging between 150 and 355 μm), to ensure proper deployment of embolic material as distal as possible. Conversely, Lucatelli and colleagues do not report information about the amount of ethiodol use to adjust the polymerization time of glue nor about the exact texture of gelfoam (powder, slurry or pledget). In our experience, technical success [5] was achieved in all patients (27/27,100%); one patient only experienced rebleeding (1/27 $\approx$ 3.7%). These data support a different, pathophysiology-based approach in the treatment of COVID-19-related SMHs, as compared to what Lucatelli and colleagues suggest. IR main goal should be

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not simply promoting clot formation, but rather provide a proper slowdown of the blood flow specifically in distal vascular territories (those primarily affected by viral injury) with very small sized embolic material. Furthermore, we suggest the use of permanent embolic agents, since we have to admit not knowing how much time virus-induced microvascular injury takes to fully reabsorb.

In conclusion, failure to recognize the pathophysiology underlying COVID-19-related SMHs could undermine the effectiveness of any IR intervention. Particular attention should be paid in the selection of embolic agents, both in terms of type and size.

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Declaration

Conflict of interest The authors declare that they have no conflict of interest.

Consent for Publication Consent for publication was obtained for every individual person's data included in the study.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Patients signed an informed consent for the collection of all data related to their hospitalization for COVID-19 infection and to eventual use for publication. The study was approved

by the Institutional Ethics Committee (Protocol Number: 34/int/2020).

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