

Peer Review File

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Reviewer Comments

The authors compare a cohort of COVID-19 patients who clinically had ARDS and received computed tomography pulmonary angiography (CTPA) with a (retrospectively analyzed) cohort of non-COVID-19 patients with ARDS and CTPA. They found a significantly higher incidence of pulmonary artery thromboembolism among COVID-19 patients than in the control group (59% vs. 10%), which is remarkable. The study is an important contribution to the ongoing COVID-19 research and therefore worthy of publication. However, it is necessary to take a close look at how this data was collected. I suggest to revise the following points:

Comment 1: It remains unclear according to which criteria the patients were subjected to CTPA and whether these criteria differ in the retrospective control cohort from the COVID-19 patients. Was CTPA only applied in patients with the clinical suspicion of pulmonary embolism (and only then)? Did COVID-19 patients already show clinical signs of pulmonary embolism more often (69% with CTPA) than the control group (33% with CTPA)?

Reply 1: You are right this is a major point that we did not detail enough. Indeed, we planned in advance to systematically perform CTPA approximately 7 days after intubation or earlier in case of respiratory or hemodynamic worsening in order to confirm or rule out pulmonary embolism in all patients with ARDS related to Covid-19. By contrast, CTPA was not systematic in the control group with pulmonary ARDS unrelated to Covid-19, and was performed only in patients who had suspected pulmonary embolism or infectious pulmonary complication (pulmonary abscess or pleural empyema). This is now detailed in the methods (see below).

Change in the text: As the pandemic occurred later in our region than in other parts of Europe, we were aware of a potential high risk of pulmonary embolism in patients with ARDS related to Covid-19. Consequently, we planned in advance to systematically perform CTPA approximately 7 days after intubation or earlier in case of respiratory or hemodynamic worsening, our objective being to confirm or rule out pulmonary embolism in all patients. By contrast, CTPA was not systematic in the control group with pulmonary ARDS unrelated to Covid-19, and was performed only in patients who had suspected pulmonary embolism or infectious pulmonary complication (pulmonary abscess or pleural empyema).

Comment 2: (pages 6 and 7 - primary outcome) In view of these uncertainties, it is not clear why the embolism cases were also related to the overall collective, i.e. patients with and without CTPA (17/42 in the COVID-19 cohort and 5/156 in the control cohort). These 17 and 5 cases, respectively, correspond to the number of cases also found in CTPA (17/29 and 5/51, respectively). The numbers therefore give little indication as to whether there were further pulmonary embolisms in the subcollectives without CTPA. More specifically, among the 105 patients in the control group who did not receive CTPA, a significant proportion may also have had (clinically unremarkable) pulmonary embolism or thrombosis in the pulmonary arteries.

Reply 2: We fully agree with you. However, we wanted to present the results exactly as in all previous studies that reported the proportion of pulmonary embolism in entire cohorts (minimal rate including patients who did not undergo CTPA) and then among all patients who underwent

CTPA (maximal rate). We are perfectly aware that the incidence of pulmonary embolism could be markedly underestimated especially in the control group since only one-third of patients underwent CTPA. To date, no study has systematically performed CTPA to confirm or rule out pulmonary embolism in ARDS unrelated to Covid-19, and consequently this is a major limitation. This point is now discussed (see change in the text).

Change in the text: Incidence of pulmonary embolism was 40% among all patients with ARDS related to Covid-19 and 59% among those who had CTPA, the actual incidence being between these 2 rates.

We also added: In the historical cohort, only one-third of patients with pulmonary ARDS unrelated to Covid-19 underwent CTPA, and it was performed much earlier after ICU admission than in patients with ARDS related to Covid-19. Consequently, the actual incidence of pulmonary embolism in patients with ARDS unrelated to Covid-19 could be markedly underestimated. To date, no study has prospectively assessed the incidence of pulmonary embolism in ARDS and we cannot exclude the eventuality that is necessary to perform CTPA later in the course of ARDS. Although we prospectively planned systematic CTPA to confirm or rule out pulmonary embolism after around one week of mechanical ventilation in all patients with ARDS related to Covid-19, CTPA was nonetheless performed in only 69% of patients, either because they were extubated earlier or because they were too severe to undergo scanner.

Comment 3: The authors discuss whether these are pulmonary artery thromboses or introduced thrombotic material, i.e. embolisms in the narrower sense. In this context, it would have been meritorious to look at the periphery even after the incidence of deep vein thrombosis (e.g. by ultrasound). The authors should justify why this was not possible or necessary.

Reply 3: It is a very good comment. We were aware of a potential high-risk of pulmonary embolism but not of deep venous thrombosis. In our organization, we had a specific dedicated time for CTPA. By contrast, for logistical reasons, radiologists did not want to perform ultrasound at bedside in patients with Covid-19. This limitation is stated in the discussion

Change in the text: Another limitation is that we did not perform routine ultrasound examination of the lower limb veins and consequently we cannot hypothesize the mechanism of pulmonary embolism. Whereas the incidence of deep venous thrombosis may also be particularly high in patients with Covid-19 reaching approximately 40 to 50% of cases, histological findings suggest that pulmonary embolism could be due to thrombosis of small pulmonary arteries rather than by thromboembolism.

Comment 4: In this context, the authors failed to refer to the study by Edler et. al (Int J Legal Med). Here, in a postmortem collective, deep vein thrombosis was found in 40% of cases in the legs and elsewhere.

Reply 4: We added this reference and discussed more extensively this point.

Change in the text: Whereas the incidence of deep venous thrombosis may also be particularly high in patients with Covid-19 reaching approximately 40 to 50% of cases...

Comment 5: The first sentence in the introduction must be put into perspective. COVID-19 is not synonymous with viral pneumonia. COVID-19 can lead to viral pneumonia - this is by no means obligatory.

Reply 5: You are right. We changed the first sentence (see below) to avoid confusion.

Change in the text: Covid-19 due to severe acute respiratory syndrome coronavirus (SARS-CoV-2) may be complicated by acute respiratory distress syndrome (ARDS)

Comment 6: It is remarkable how few of the COVID-19 patients with ARDS had comorbidities (no heart and lung diseases, no cancers! see Table 1), especially since these are actually known to be risk factors for severe courses. Was there a selection mechanism here? This is also remarkable insofar as these comorbidities themselves are already risk factors for pulmonary embolism, so that one could have expected an even lower incidence in the three COVID-19 groups. The authors should discuss this oddity carefully and critically!

Reply 6: We fully agree that the majority of our patients with Covid-19 had very few comorbidities. This is in keeping with the recent French cohort including more than 4000 patients with Covid-19 in ICUs and reporting that only 7% of patients had underlying immunodeficiency including solid cancer, solid transplant, hematological malignancies, or received immunosuppressant. This point was added in the discussion.

Change in the text: Lastly, patients with ARDS related to Covid-19 had surprisingly few underlying chronic diseases, especially few chronic cardiac or lung diseases, and few cancers whereas these are strong risk factors for pulmonary embolism. The explanation is unclear but could in part be due to strict lockdown of patients at risk for Covid-19. Regardless the reason, this is in keeping with the recent French cohort including more than 4000 patients with Covid-19 in ICUs and reporting that only 7% of patients had underlying immunodeficiency.

Comment 7: the bibliography sometimes lacks issues and page numbers (or, if not yet available, the doi).

Reply 7: It is true that numerous page numbers were lacking in several references online but not published yet. We updated the references.

Change in the text: see references