Author’s response to reviews

Title: The dating of thrombus organization in cases of pulmonary embolism: an autopsy study

Authors:

Celestino Sardu (drsarducele@gmail.com)
Gelsomina Mansueto (gelsomin.mansueto@unina.it)
Dario Costa (dario.costa@unicampania.it)
Emanuele Capasso (emanuele.capasso@unina.it)
Federica Varavallo (celestino.sardu@virgilio.it)
Giuseppina Brunitto (celestino.sardu@unicampania.it)
Rosanna Caserta (sarducelestino@libero.it)
Salvatore Esposito (drcelesardu@gmail.com)
Massimo Niola (massimo.niola@unina.it)
Celestino Sardu (drsraducele@gmail.com)
Raffaele Marfella (raffaele.marfella@unicampania.it)
Claudio Napoli (claudio.napoli@unicampania.it)
Mariano Paternoster (mariano.paternoster@unina.it)

Version: 3 Date: 05 Aug 2019

Reviewer reports:

Dionyssios Leftheriotis (Reviewer 1): My major comments on this interesting topic are the following:

1. comorbidities possibly related with prognosis and death are not presented in detail (hypertension, diabetes, peripheral angiopathy, atrial fibrillation etc)
We thank the reviewer for his/her comments. As You suggested, we did not present in detail the comorbidities possibly related with prognosis and death. Therefore, in the revised form of the manuscript we reported the lost informations. As first, in Results You might see that 5 patients did not have clinical history of pre-existing pathologies. “In 5 patients without clinical history of pre-existing pathologies the death occur in the first hour; thus they were considered cases of SUD. In these cases we do not observed cellular infiltration, fibrosis or neovascularization (Table 4). In the other cases, 10 patients have cardiomyopathy under pharmacological treatment, 11 were patients hospitalized for abdominal or fracture surgery and 4 patients with cardiomyopathy received surgery after head injury”. You might see it at page, line. However, in these 25 patients we had the following pathologies as You correctly suggested:

a. hypertension: 11 (44%)
b. diabetes: 3 (12%)
c. peripheral angiopathy: 6 (24%)
d. atrial fibrillation: 3 (12%)
e. cancers: 2 (8%)

You might see these informations in the Results, at page 6, line 18-24.

2. data from computed tomography, such as the size and location of thrombi, are not presented and discussed, although related with prognosis. If not performed, please explain the reasons.

We thank the reviewer for his/her comments. In the present studied we analyzed 30 autopsies of patients deaths for pulmonary embolism. As you suggested, we did not report data from computed tomography, such as the size and location of thrombi. On other hand, as You correctly suggested, these data are related with prognosis. Therefore, we reviewed for every patient the computed tomography exam executed before the fatal death event. However, we reported the thrombus location as Mediastinal pulmonary artery (n 7 (23.3%)), Lobar pulmonary artery (n 5 (16.7%), Segmental pulmonary artery (n 15 (50%)), Sugsegmental pulmonary artery (n 3 (10%)). To date, from computed tomography exam we reported a clot volume about 2863.11±853.08 mm3. You might see these data at page 6, line 20-24.

3. the relation between time of thrombus formation and death is not clear in the discussion and conclusions, although mentioned as of clinical importance in introduction.
We thank the reviewer for his/her comments. As You suggested, we clarified this point. You might see it in the Discussion at page 10, line 16-24, and at page 11, line 1-7, and in the Conclusions, at page 11, line 21-24, and page 12, line 1-14.

4. the clinical implication of histological findings in terms of prognosis and therapeutic suggestions would enforce the clinical impact of the study

We thank the reviewer for his/her comments. As You correctly suggested, we clarified this point. However, we revised this relevant study concept. You might see it in the Conclusions, at page 11, line 21-24, and page 12, line 1-14.

5. the clinical implication of the study is missing in general. The authors rise the question of whether thrombi were formed prior or following a traumatic event. Would this change clinical practice regarding prophylactic anticoagulation according to risk factors? Would time to thrombus formation and death lead to modification of the current antithrombotic strategy?

We thank the reviewer for his/her comments. As You suggested, we reported these relevant informations in the Conclusions, at page 11, line 21-24, and page 12, line 1-14.

Jae Yeong Cho (Reviewer 2): In the current manuscript, the authors investigated the difference of pathological findings according to time after thrombus was developed in deceased patients with PE. Lymphocyte infiltration was usually seen between 1hr and 24hr, fibroblast infiltration was seen in periphery between 48hr and 72hr, and central thereafter. It seems that this manuscript is the second revision and this reviewer think that some of the issues were appropriately addressed. However, the authors had better consider following issues:

1) The authors should clearly state what the real clinical implication of the current study.

We thank the reviewer for his/her comments. As You suggested, we have to state the real clinical implication of the current study. However, we discussed and clarified this relevant point in the Conclusions, at page 11, line 21-24, and page 12, line 1-14.
2) Also, the authors consider the scope of the journal. This type of study is associated with forensic medicine or pathology rather than cardiology journal.

We thank the reviewer for his/her comments. As You correctly suggested, we reported data about an autopsy and forensic study. On other hand, according to Your suggestions, we translated these informations and results in a possible clinical application for patients with EP and SUD. Therefore, because EP is a severe cardiovascular complication, and it is linked to a higher mortality and SUD rate, we speculate that this new research might open a new investigative and clinical scenario, and that it might be applied to ameliorate clinical prognosis in patients with EP in the current clinical practice. However, in this way our study might match with a Cardiology journal.

3) There is no statistical method to determine the difference between two or more different time group.

We thank the reviewer for his/her comments. As You suggested, we did not report a comparison between two groups of study. In the present study we evaluated the time of thrombus formation in order to determine the precise moment of death for patients with PE. However, by autopsy we identified death causes allowing the determination of discrepancies between clinical and autopsy diagnoses. Therefore, we verified the morphological and histological criteria of fatal cases of PE by the evaluation of the dating of thrombus formation considering 5 ranges of time. Moreover, we did not perform a study to compare two or more different time group, because this is not our study aim, and it is outside of the research interest of the present study. On other hand, if You retain necessary we can perform additional statistical analysis to compare two or more different time group of patients with EP.

4) How the previous inflammatory state can be effectively ruled out? If there is systemic infection or underlying vasculitis. The result would be influenced indeed.

We thank the reviewer for his/her comments. As You suggested, systemic infection or underlying vasculitis might influence study results. Therefore, because we did not enroll these patients in our study, and it might influence clinical outcomes of the study, to explain this important point we reported the following sentence, at page 5, line 15-16: “From the present study we excluded patients with diagnosis of systemic infection or underlying vasculitis”.

Javier E. Anaya-Ayala, MD, MSc. (Reviewer 3): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

We thank the reviewer for his/her comments. As You suggested, we included all comments for the authors in this box. However, we uploaded as attachments annotated versions of manuscripts, graphs, supporting materials.

Please overwrite this text when adding your comments to the authors.

We thank the reviewer for his/her comments. As You suggested, we overwrote this text to add the comments to the authors.