May 10th, 2021

Dr. Emmanuel Andrès and Prof. Dr. Michael G. Hennerici,
Editors-in-Chief
Journal of Clinical Medicine

Dear doctors,

Attached please find a copy of our revised manuscript entitled "Elderly Suffering from ST-Segment Elevation Myocardial Infarction- Results from a Database Analysis from Two Mediterranean Medical Centers", which we now submit following major revision for publication in *Journal of Clinical Medicine*. We have addressed all comments, and fulfilled the requirements by the reviewers. Below you will find a point-by-point response to the reviewers' comments.

Reviewer 1:

Thank you for the opportunity to review this manuscript. The manuscript addresses an important topic. However, I recommend to take the following suggestions into consideration.

We appreciate the reviewer's kind acknowledgment, and have implemented all changes suggested by the reviewer.

General points:

1. In order to conclude that octogenarians do not suffer increased risk of ischemic cardiac events after PCI (line 39) a competing risk analysis should be added since it would be possible that some octogenarians already died before another PCI would be necessary. As it is shown they have a higher all-cause mortality.

Thank you for that comment. We have now added a competing risk analysis for mortality for the two causes of death figure 3, with a cumulative incidence function for measure- all cause mortality, cardiovascular and non-cardiovascular death (figure 2). Interesting to see that the principle remained the same- all cause death is significantly higher for the elderly, but not CV death (albeit a non-significant trend towards a higher rate of CV death as well). Please also note I have added two new authors- Noa and Amos, who were kind enough to assist me with this specific analysis using R Version 4.0.0 software. The wording in the results is:
"A competing risk analysis for the causes of death also showed differences in non-cardiovascular and all-cause death, but not cardiovascular death (figure 3)." (lines 253-255)

2. In addition, I would recommend not including "death" (line 100) in the MACE as it has already been analyzed as the primary endpoint.

We have removed the all-cause death rate from the MACE. It now includes only myocardial infarction (MI), target vessel revascularization (TVR) and coronary artery bypass surgery (CABG). We therefore updated the endpoints description in the methods section (now lines 116-118), as well as modifying figure 2.

3. Please also explain in more detail if "other endpoints" such as vascular complications (line 102) were also included in MACE. I would suggest to include them and also include these endpoints in table 2 (e.g. bleeding is missing).

MACE includes cardiac events, now includes only MI, TVR and CABG, as detailed above. Bleeding indeed is missing and should have been included – this was now added to table 2 as directed, demonstrating similar 30-day bleeding rates between the groups, according to the TIMI major and minor definitions.

4. "renal failure" in Line 103: Is it postprocedural renal failure? Please explain in more detail and also explain how renal failure was defined in patients with a chronic kidney disease and an eGFR<50ml/min at admission.

Absolutely. Thank you for this important distinction. It is actually acute kidney injury post-PCI. We have therefore now added an explanation in the methods section: acute kidney injury was defined as a serum creatinine elevation ≥50% or ≥0.3 mg/dL from baseline in the first 72 h (lines 122-123), a definition which was proven to predict population attributable risk best. A separate explanation was added for renal failure at baseline (lines 126-128). It was also modified in table 2 to "Acute kidney injury".*

**Lei L, Xue Y, Guo Z, Liu B, He Y, Song F, Liu J, Sun G, Chen L, Chen K, Huang Z, Ying M, Zhang L, Su Z, Pan L, Chen S, Chen J, Liu Y. A comparison between different definitions of contrast-induced acute kidney injury for long-term mortality in patients with acute myocardial infarction. Int J Cardiol Heart Vasc. 2020 Apr 30;28:100522. doi: 10.1016/j.ijcha.2020.100522.*

5. "vascular complications": is it perforation of a coronary artery? Please describe this in more detail (line 102).

In this category we have included periprocedural hematomas, retroperitoneal bleeding, pseudoaneurysms, arteriovenous fistula, arterial thrombosis, distal embolism, dissection and transient limb ischemia. This was now added to the methods section (lines 119-121).

6. How was "cardiac death" (line 105) defined?

Cardiac death was defined as death occurring due to cardiovascular causes or cerebrovascular causes and any death without another known cause. This explanation was added to the methods section (lines 124-125):

"defined as death occurring due to cardiovascular causes or cerebrovascular causes and any death without another known cause".

7. Please describe inclusion criteria and endpoints in more detail: e.g. what is the institutional clinical events adjudication committee? Is the adjudication performed by physicians? (line 97).

Well, this is an all-comer registry, comprising of consecutive STEMI patients. The only exclusion criteria were detailed in the patient and setting paragraph:
"Exclusion criteria were presentation with cardiogenic shock, treatment by thrombolysis, and ineligibility for a year-long dual antiplatelet regimen." (lines 92-93)

Regarding the adjudication committee, it was indeed performed by physicians, and we now improved the phrasing:
"All events were further confirmed and adjudicated by the institutional clinical events adjudication committees comprising of three independent physicians." (line 114).

8. I would recommend to add a cox regression analysis for MACE at 30 days and 1-month.

A cox regression was added to the newly defined MACE at 30 days (table 4). The following was also added to the results: "30-day MACE was also assessed in regression analysis, demonstrating an increase in risk for events for patients with previous PCI (HR 1.42; 1.01-2.67, p=0.042), diabetes mellitus (HR 2.45; 1.43-4.37, p=0.021) and renal failure at baseline (HR 2.21; 1.23-4.98, p=0.008). Age was not an independent predictor of 30-day MACE." (lines 290-294)

9. Baseline table: I would recommend to add laboratory parameters such as hemoglobin, electrolytes, hs-cTnT, NTproBNP, creatinine, BUN etc. at admission. In addition, I would also add data on medication at admission and discharge and data of the "culprit lesion" and if the patient suffers a more vessel disease. Additionally, I would also include some of these variables in the cox regression analysis.

Thank you for this comment, we have added the available laboratory information to table 1, and have seen significant differences in GFR and hemoglobin. As requested, we also added information on medication at admission (table 1) as well as data on medications at discharge and on the culprit vessel (table 2).

10. How was obesity in the baseline table defined? would suggest to replace it by BMI.

Obesity is BMI>30 kg/m^2. Per your instructions, we've changed to mean BMI. This was added to table 1.

11. It would be interesting to see data on the lengths of hospitalization of the different age groups. In addition, are there data on possible hospital acquired infections and frailty of patients?

Thank you for this comment. The length of admission is available for the patients, and we have calculated these results and added to table 2. Unfortunately, we do not have information on the rate of hospital-acquired infections and frailty of these patients.

Statistics:

1. Several times is written p<0.01, but several p-values also have 3 decimal places. I would strongly recommend to show p-values in a uniform manner with 3 decimal places.

We have now corrected all such events.

2. Please explain the rational of p<0.1 for selection of univariate predictors (line 117) instead of using p<0.01.

The method of selection of predictors using univariate stepwise regression is well accepted but at the same time controversial, as many advocate the adoption of predictor selection mostly on expert, or in our case- clinical, judgement[1]. As for the cut-off of 0.1, again I believe there are no clear guidelines. Some even recommend choosing 0.25 for the initial selection of variables[2,3]. Others use 0.05. If the reviewer feels we should change to 0.01, please guide us in doing so.

1. *Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J 2014;35:1925–31.*
2. *Hosmer DW, Lemeshow S, Sturdivant RX. Applied logistic regression. New York: John Wiley & Sons, Incorporated, 2013*
3. *Chowdhury MZI, Turin TC. Fam Med Com Health 2020;8:e000262.*

3. Please also show the univariable analyses of your Cox regression.

We have added information on the univariate analysis, both in the text and two additional tables (3a and 3b- but we can also add as supplementary material, if more appropriate). Here is the written addition:
"Univariate analysis identified the following predictors of 30-day and 3-year mortality after STEMI: age over 80, previous PCI, previous MI, previous CABG surgery, diabetes mellitus, hypertension, hyperlipidemia, renal failure, LVEF, the implantation of DES, and intra-aortic balloon pump (tables 3a and 3b). We used these factors, including age, gender and the administration of Prasugrel as opposed to clopidogrel, for the multivariate analysis" (lines 276-280).

4. Please review normal distribution of continuous variables in the baseline table: e.g. in door to ballon times the standard deviation is nearly the mean. Therefore some variables might not be normally distributed and a presentation as median would be preferable.

As requested, we have changed the presentation of both door to balloon time and admission length to median and interquartile range in the baseline table.

Minor points:

1. Please state in the introduction to which of the both remaining group octogenarians are compared to (especially the order): Line 28-31.

These changes were made, including a few other, to maintain a word count below 200:
"More octogenarian patients were female (40.8 vs. 31.9 septuagenarians and 26.5% under 70y, p<0.01), had hypertension (79.5 vs. 69.5 and 45.9%, p<0.01), and renal failure (32.5 vs. 20.1 and 5.2%, p<0.01), and a lower left-ventricular ejection fraction (42.0 vs. 44.9 and 47.6%, p=0.012)"

2. Please correct bifurcation to bifurcation lesions in table 2.

Done, thank you.

We hope you find our manuscript suitable for publication in *Journal of Clinical Medicine.* Thank you for your consideration.

Sincerely yours,

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