

<Author response to reviewer 2>

The authors report the correlation of radiologically assessed psoas muscle area (PMA) and intraoperative hypotension (IOH) in elderly patients undergoing femur fracture surgery. The data presented are sound, and well worked up and the findings are interesting in various aspects. In the best-case scenario the data and conclusions drawn from the manuscript might lead to a somewhat personalized approach to preoperative patient preparation as well as personalized induction and fluid management of anesthesia for this kind of population and procedure. This might lead to an improved postoperative outcome if interpreted well.

However, my major concern with this paper is that the conclusions from the data analysis are not presented in an appropriate and clear form to guide the reader to clinically relevant conclusions. The authors themselves stated in their results that *"Multivariate logistic regression revealed that low PMA (OR 3.86; 95% CI, 2.82–5.29; $P < 0.001$) normalized by BSA, 250 high baseline systolic blood pressure (OR 1.03; 95% CI, 1.01–1.05; $P = 0.001$), and old age 251 (OR 1.06; 95% CI, 1.02–1.10; $P = 0.003$) were significant independent predictors of IOH, whereas the number of mFI variables was not a significant independent predictor of IOH 253 ($P = 0.870$)."* So why do we need PMA then if age itself and preoperative high baseline blood pressure are proper predictors for IOH? In clinical routine age and baseline blood pressure can be assessed easily whereas PMA normalized by BSA is by far a more time-consuming procedure.

Nevertheless, the data are extremely interesting. A conclusion that can really be drawn from the data is that PMA is superior in predicting IOH to mFI (Results: Figure 3). IOH has to be avoided since it is associated with negative perioperative outcomes. Could we avoid it with a different choice of drugs for induction of anesthesia and Hb and fluid management? Induction of anesthesia was standardized and propofol is known to have negative inotropic effects besides vasodilatation. Could we use other drugs for patients at risk to develop IOH? The authors state that the transfusion trigger was a Hb of 8 mg/dL. Should the transfusion trigger be higher in patients with low PMA normalized by BSA? Could this lead to reduced IOH? Should patients with preoperatively low PMA receive special care after surgery?

⇒ **Response:** We appreciated your thoughtful consideration. As you said, some patients' characteristics such as age and preoperative blood pressure have been shown to be associated with IOH. However, it does not often give enough clue to predict IOH (For example, from our results, age was a significant factor to predict IOH, however, the mean age of no-IOH group and IOH was 78.62, and 82.46, all of which represent old patients). Hence, lots of studies (e.g., using risk factors, technology like HPI, echocardiography of sonographic values, etc.) have been still conducted to get a better sense of prediction in intraoperative or postoperative outcomes.

In our institution, we have measured frailty using questionnaire-based methods before some major surgeries, while frailty has been spotlighted again for its usefulness as a preoperative risk evaluation tool in the recent decade. It is actually time-consuming for clinical use and limited to applicate to patients with femur fractures owing to their restricted physical conditions or inability to provide medical history as we mentioned in the text. However, PMA measurement obtained from existing CT images can be a feasible method like anesthesiologists checking chest x-rays before surgery. More interestingly, our data showed that PMA could predict IOH better than mFI score. We believe that simple measurement of PMA from CT images will help evaluate and understand patients preoperatively. I really appreciate your thoughtful comments.

Therefore, my suggestions are:

It is far-fetched to associate IOH with 3 months outcome because many other factors influence outcomes during this prolonged postoperative period. IOH can reasonably be associated with neurological and cardiological complications within the immediate postoperative period (7 days). Please change and clarify throughout.

⇒ **Response:** I agree with you that there might be various factors that can influence outcomes during this prolonged postoperative period. We have added references for using 3-month outcome data according to your valuable comment #2. Although we provided postoperative adverse outcomes as secondary endpoints, it is hard to conclude the relationship between IOH and postoperative outcomes from our results. Since our primary outcome was to investigate the association with IOH, it would be underpowered to conclude the association with postoperative outcomes which has much lower incidence compared to IOH.

#1. The title should be changed to "Predictability of Radiologically Measured Psoas Muscle Area for Intraoperative Hypotension and Adverse Outcome in Older Adult Patients Undergoing Femur Fracture Surgery".

⇒ **Response:** We appreciated your thoughtful consideration. However, this article provides the causal relationship between the PMA and the likelihood of IOH occurrence. Although we provided the relationship between PMA and postoperative 3-month adverse outcomes as secondary endpoints, it is hard to conclude that IOH is related to postoperative 3-month adverse outcomes from our results. Because the result in Table 4. showed that IOH was not a significant independent predictor of 3-month unfavorable outcomes after adjusting for confounders. ($P = 0.478$).

Therefore, in this study, we focused on IOH and investigated whether an easily measurable method, PMA, could predict IOH in older adult patients undergoing hip fracture surgery. We would like to revise the introduction and conclusion to improve validity rather than changing the title.

According to our hypothesis, we revised the sentences to clarify the introduction in line 58, and the conclusion in line 433.

⇒ Introduction, line 58: "IOH is associated with postoperative outcomes and frequently occurs in frail patients; they typically have a higher sympathetic drive and reduced baroreflex sensitivity, which leads to IOH [20-21]. The association between low PMA and adverse surgical outcomes in older adult patients with hip fractures has been described [5]. To the best of our knowledge, no study has demonstrated the association between sarcopenia, presented as low PMA, and IOH development."

⇒ Conclusion, line 433: "PMA normalized by BSA using pre-existing CT was a significant predictor of IOH occurrence and unfavorable surgical outcomes in older adult patients with hip fractures. Moreover, preoperative simple measurement of PMA was superior to mFI in predicting IOH. To discuss the relationship between IOH and adverse surgical outcomes, further prospective studies using the time weighted average IOH are warranted."

#2. Introduction: Why use 1-year mortality (line 35) in the introduction? Thereafter you refer to 3-month mortality which makes more sense. Please introduce a reference for 3-month mortality in the introduction.

⇒ **Response:** As you recommended, I changed 1-yr mortality to 3-month mortality rate and introduced the reference [2-4] as below.

⇒ Introduction, line 36: "Surgical outcomes of patients with hip fractures are associated with a high 3-month mortality rate (4.7–19.5 %) and physical morbidity [2-4]."

References were added as below.

2. Ove, T.; Fredrik, H.; Ola, E, D.; Are,H, P.; Olav, R. Clinical and biochemical prediction of early fatal outcome following hip fracture in the elderly. *Int Orthop* **2011**, 35, 903–907.
3. Istianah, U.; Nurjannah, I.; Magetsari, R. Post-discharge complications in postoperative patients with hip fracture. *J Clin Orthop Trauma* **2021**,14, 8–13.
4. Ha, Y.; Cha Y.; Yoo, J.; Lee, J.; Lee Y.; Koo K. Effect of dementia on postoperative mortality in elderly patients with hip fracture. *J Korean Med Sci* **2021**, 36, e238.

#3. Results: Is PMA normalized by BSA time-consuming to measure reliably? How long does it take to measure it? Can it be used easily in clinical routine? This would encourage clinicians to introduce PMA normalized by BSA in clinical routine, and thus, strengthen your manuscript. Please give a time estimate of the procedure in the results.

⇒ **Response:** Thank you for your thoughtful consideration. As I mentioned in the discussion, measuring PMA from CT images took just a few minutes. PACS provides a function to measure an area like PMA using region of interest (ROI) program, and we just need to draw an outline of the psoas muscle as shown in Fig 2, which can be easily done within a minute. Then, calculating by BSA ($\sqrt{[\text{height (cm)} * \text{weight (kg)}] / 3600}$) can be also readily done with a calculator within a minute. For us, it took less than one minute to get the result for one patient. According to your advice, we have added the estimation time in the results.

⇒ Results, Line 224: "The ICC between the two researchers for measuring PMA was excellent: 0.977 (95% CI, 0.95–0.99; P < 0.001), and measuring PMA from CT images took only less than 1min."

#4. Did patients with IOH suffer increased perioperative neurological complications (TIA, stroke, postoperative delirium)? This would be very interesting if you can assess these data. If there is no difference IOH cannot be a major factor for the 3-months outcome.

⇒ **Response:** As we described postoperative data in Table 2, postoperative neurologic complication (CVA) showed higher incidence in IOH group, but there was no significant difference between the groups. Also, CVA was not the significant factor after adjusting confounding factors (Table 3). From the previous studies [1,2], the incidence of stroke was reported as 0.004% to 0.09% within 10 days. They analyzed 48,241 [1] and 3387 patients [2] for assessing the relationship between IOH and stroke. Our study did not have enough sample size to compare and conclude the association with neurologic complications, because we need a much greater sample size to compare postoperative outcomes that have much lower incidence compared to that of IOH. Therefore, no firm conclusion on the

relationship between IOH exposure and neurologic complications or 3-month adverse outcomes can be drawn from this study. To conclude the relationship between IOH exposure and neurologic complications, further studies with a greater number of patients are warranted.

#5. In the Discussion, it has clearly to be stated that: mFI is inferior to PMA normalized to BSA in detecting patients with perioperative high risk to develop IOH in elderly patients undergoing surgery for femur fracture. Therefore, it might be a valuable parameter to draw attention to these patients who are at an increased risk and act accordingly (intraoperative monitoring, induction of anesthesia, fluid management, and transfusion trigger).

⇒ **Response:** Thank you for your thoughtful consideration. We tried to demonstrate the usefulness of PMA instead of mFI, but it seems that my intentions were not conveyed properly. Therefore, I revised the sentences according to your advice.

⇒ In Line 340: "In the present study, we found that PMA normalized by BSA was superior to mFI in predicting IOH. Measuring PMA from CT images before surgery could be a faster and more simple method than mFI for assessing the risks of IOH. Predicting IOH could improve individual anesthetic management, in terms of preparing for hypotensive situations: meticulous titration of anesthetic agents, preparation of additional peripheral intravenous lines, vasopressors, sufficient pre-induction fluid supplement, and continuous arterial blood pressure monitoring to prevent hypotensive events during the surgery."

#6. Sudfeld et al. found 34% of IOH, whereas your population revealed about 71% of IOH. This might be due to the definition of IOH or to the fact that Sudfeld et al. evaluated just 30 min after induction of anesthesia and your data refer to the entire period of the procedure. However, induction of anesthesia and the period till skin incision can be used for the optimization of hemodynamics since this period is not influenced by surgical interventions. Please discuss this accordingly.

⇒ **Response:** As you mentioned, IOH incidence differs by large variations in the definition of IOH and the characteristics of the study population. Nirav et al. [3] reported that 88% of the moderate to high-risk population had at least one hypotensive event as defined as MAP <65 mmHg for 1 min, which had a higher incidence than our results.

Even though the post-induction period is not influenced by surgical interventions, it can be also affected by other factors like patients' dehydration status, the amount, or kinds of induction agents, and whether or not taking antihypertensive medication. We considered that hypotensive events in the entire surgical process are more clinically important to our population because we believed that they reflected perioperative patients' overall condition more than post-induction hypotension (46.7% of our population, not presented in the manuscript).

Overall, the manuscript is well-written and the data analysis is sound. The findings are very interesting to various physicians treating this patient population.

⇒ **Response:** Thank you for your kind comments. I hope the revised manuscript would be acceptable. I appreciate your consideration.

References

- [1] Bijker, J.B.; Persoon, S.; Peelen, L.; et al. Intraoperative hypotension and perioperative ischemic stroke after general surgery. *Anesthesiology* **2012**; 116: 658e64.
- [2] Sabate', S.; Mases, A.; Guilera, N.; et al. Incidence and predictors of major perioperative adverse cardiac and cerebrovascular events in non-cardiac surgery. *Br J Anaesth* **2011**, 107(1), 879e90.
- [3] Nirav, J. S.; Graciela, M.; Sachin K. The incidence of intraoperative hypotension in moderate to high risk patients undergoing non-cardiac surgery: A retrospective multicenter observational analysis. *J Clin Anesth* **2020** Nov;66:109961