

July 13, 2022

Reviewer 2

Journal of Clinical Medicine

Dear Reviewer 2,

Please find attached a revised version of our manuscript, “Preoperative Inflammatory Markers and the Risk of Postoperative Delirium in Patients Undergoing Lumbar Spinal Fusion Surgery” (jcm- 1811184).

We thank you for your suggestions regarding the original version of our paper; most of the suggested changes have been incorporated into the revision.

All of the revisions are described in detail in the order mentioned in the review, following the reviewer’s comments in italics. We believe that the revisions have greatly improved the manuscript and hereby submit the revised version for consideration for publication.

Comments to author:

The authors determined the associations between preoperative blood inflammatory markers and POD in patients undergoing lumbar spinal fusion surgery. This is a retrospective study and of the 3,081 enrolled patients, 187 developed POD. A significant increase in the NLR, MLR and CAR was observed in the POD group. Multivariate analysis showed that the second, third and highest quartiles of the NLR were significantly associated with the development of POD. The ROC curve revealed that the discriminative ability of the NLR, MLR, and CAR for predicting POD development was low, but marginally acceptable. Some minor concerns were listed below:

[We thank the reviewer for these comments and suggestions, which have helped us to improve our manuscript.](#)

1. The prevalence of POD in the retrospective study was relatively low compared to previous studies. The authors explained that a retrospective assessment of POD may have led to underestimation of the incidence of POD. I suggest that the authors should compared the

prevalence of POD with the previous retrospective studies.

The incidence of POD varied depending on the type of surgery. The prevalence of POD after spinal surgery ranged from 3.8 to 40.4% and from 0.84 to 27.6% in two previous meta-analyses. The prevalence of POD after lumbar spinal fusion surgery was 7.4% in our study. This retrospective assessment of POD may have led to underestimate of its incidence. Additionally, the prevalence of POD in our study was relatively low compared to previous retrospective studies. Previous retrospective studies reported an incidence rate of 9.3–18% in patients who underwent lumbar decompression or lumbar fusion surgery. These differences in the incidence of POD were dependent on the diagnostic method used. In our study, patients were diagnosed via psychiatric consultations when symptoms developed, to provide a solid diagnosis. Some patients with milder symptoms may have been missed during this process.

We have revised the Discussion, as follows:

Additionally, the prevalence of POD in our study was relatively low compared to previous retrospective studies. Previous retrospective studies reported an incidence rate of 9.3 – 18% in patients who underwent lumbar decompression or lumbar fusion surgery [24-26]. These differences were dependent on the diagnostic method used. In our study, patients were diagnosed via psychiatric consultations when symptoms developed. Some patients with milder symptoms may have been missed during this process.

(page 9, lines 231– page 9, lines 237)

We have also added these citations.

24. Jiang, X.; Chen, D.; Lou, Y.; Li, Z. Risk factors for postoperative delirium after spine surgery in middle- and old-aged patients. *Aging Clin Exp Res.* 2017, 29(5):1039-44. doi: 10.1007/s40520-016-0640-4.

25. Susano, M.J.; Scheetz, S.D.; Grasfield, R.H.; Cheung, D.; Xu, X.; Kang, J.D.; Smith, T.R.; Lu, Y.; Groff, M.W.; Chi, J.H.; Crosby, G.; Culley, D.J.. Retrospective analysis of perioperative variables associated with postoperative delirium and other adverse outcomes in older patients after spine surgery. *J Neurosurg Anesthesiol.* 2019 Oct;31(4):385-391. doi: 10.1097/ANA.0000000000000566.

26. Fineberg, S.J.; Nandyala, S.V.; Marquez-Lara, A.; Oglesby, M.; Patel, A.A.; Singh, K. Incidence and risk factors for postoperative delirium after lumbar spine surgery (Phila Pa 1976). *Spine*

2. In this study, clinical information regarding the patients' preoperative cognitive function, as assessed using the Mini-Mental State Examination among other neuropsychology tests, was not collected. The authors should describe and discuss how the tests of preoperative cognitive function will affect the incidence of POD in the previous studies.

We agree. Preoperative cognitive impairment is associated with POD. The results of previous studies showed that the Mini-Mental State Examination score is significantly associated with POD. However, this study was retrospective and lacked information on preoperative cognitive function, such as the Mini-Mental State Examination or other neuropsychology tests that might indicate an increased risk of POD; this was a limitation of the study.

We have revised the Discussion as follows.

Additionally, preoperative cognitive impairment is associated with POD. Previous meta-analyses showed that Mini-Mental State Examination scores are significantly lower in the POD group than those in the non-POD group [22]. However, we lacked information on preoperative cognitive function, that might increase the risk of POD, which was a limitation of this study

(page 9, lines 246 – page 9, lines 250)

3. In the two groups, the use of corticosteroids was significantly different. The authors should discuss the role of corticosteroids in the development of POD.

Previous studies have reported that polypharmacy, medications with anticholinergic activity, and anti-psychotic medications are related to POD. The involvement of steroids and antihistamines in the development of POD is less clear. The preoperative use of anti-psychotics, corticosteroids, and antihistamines was significantly different between the POD and non-POD groups in our study. We identified the risk factors of POD in patients undergoing spinal fusion surgery through multivariate logistic regression analysis, and only anti-psychotics, among the medications used preoperatively, were significantly associated with POD (OR 3.52, 95% CI 2.08–5.97; $p < 0.001$). Our results were not different from those of previous studies.

Thus, we have revised the Discussion as follows.

Previous reports investigating the risk factors for POD after spinal surgery have been published. The number of medications, medications with anticholinergic activity, and anti-psychotic medications are related to POD [27-29]. Among the drug used preoperatively, the use of anti-psychotics, corticosteroids, and antihistamines was significantly different between the POD and non-POD groups. We identified the risk factors of POD through multivariate logistic regression analysis, and only anti-psychotic drug among the pre-operatively used medications, were significantly associated with POD. The relationship between the use of steroids, and antihistamines in the development of POD is unclear [29]. Our results were not different from those of previous studies.

(page 9, lines 238 – page 9, lines 246)

We have added these citations.

27. Kassie, G.M.; Nguyen, T.A.; Kalisch Ellett, L.M.; Pratt, N.L.; Roughead, E.E. Preoperative medication use and postoperative delirium: A systematic review. *BMC Geriatr.* 2017, 17, 298. [CrossRef]
28. Bilotta, F.; Lauretta, M.P.; Borozdina, A.; Mizikov, V.M.; Rosa, G. Postoperative delirium: Risk factors, diagnosis and perioperative care. *Minerva Anesthesiol.* 2013, 79, 1066–1076.
29. Clegg, A.; Young, J.B. Which medications to avoid in people at risk of delirium: A systematic review. *Age Ageing* 2011, 40, 23–29.

4. In patients with lumbar fusion surgery, most regularly received the oral pills of NSAIDs for the pain treatment. However, the author did not list the difference of use of NSAIDs in patients. The use of NSAIDs may affect the inflammatory levels.

We agree. Unfortunately, we did not include NSAID use data in our basic data. It is impossible to obtain data within a short time from an institution that manages a clinical data warehouse in a limited time. NSAID data cannot be included given the time limit of the revision. Thus, we describe this as a limitation, as follows:

We also lacked information regarding the use of NSAIDs, which could affect the inflammatory markers; this was a limitation of the study.

(page 11, lines 323 – page 11, lines 324)

We have addressed all of the issues raised by the reviewers. We are grateful for the constructive comments provided during the review process. We believe that our paper has been improved by these suggestions.

Yours faithfully,

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