

# **The usefulness of plasma levels of mature and total adrenomedullin as biomarkers indicating the magnitude of surgical stress responses: A single-center, prospective, observational study**

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Handling editor:

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The usefulness of plasma levels of mature and total adrenomedullin as biomarkers indicating the magnitude of surgical stress responses: a single-center, prospective, observational study  
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at <http://www.jctres.com/en/author-guidelines/> under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Apr 17, 2021.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission

record there.

Yours sincerely,

Michal Heger  
Editor-in-Chief  
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #2: In this paper Authors concluded that plasma levels of mature and total adrenomedullin is as biomarkers indicating the magnitude of surgical stress responses. This is an interesting paper but authors should better elucidate into the methods section what is the difference on the assay of ADM they used and the one cited in Reference n.16. Moreover into the discussion more space should be dedicated on the result into literature on the role of bioADM in Sepsis and Acute Heart failure; see papers from Di Somma S et al.

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Authors' response

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Japan, March 30, 2021

Re: revision JCTRes-S-20-00181

Dear Prof. Michal Heger:

Thank you for providing us with the opportunity to resubmit a revised version of our manuscript entitled "The usefulness of plasma levels of mature and total adrenomedullin as biomarkers indicating the magnitude of surgical stress responses: a single-center, prospective, observational study."

We have addressed all comments of the reviewers using the track changes function in Word (attached as supplementary material not for publication). Moreover, every modification or rebuttal of the reviewer's comments is detailed per comment below in red italics.

We are grateful for the useful comments of the reviewers, as a result of which the paper has been considerably improved.

On behalf of the authors, kindest regards,

Toyoaki Maruta

**REVI**

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## **EWER COMMENTS**

### Reviewer #2:

In this paper Authors concluded that plasma levels of mature and total adrenomedullin is as biomarkers indicating the magnitude of surgical stress responses. This is an interesting paper but authors should better elucidate into the methods section what is the difference on the assay of ADM they used and the one cited in Reference 16.

*We are grateful for your comments and suggestions, which we have addressed individually to the fullest extent as indicated below.*

*In the methods section, we have added our assay's antibodies binding portions:*

*P8, lines 120-125, "Plasma levels of both mAM and tAM were measured by a specific fluorescence immunoassay (Tosoh Corporation, Tokyo, Japan) with two independent antibodies: for the tAM assay, one that binds to the ringed structure (amino acid 12-25) and the other to the middle region (amino acid 25-36) between the ring and the C-terminal portions; and for the mAM assay, one that binds to the ringed structure (amino acid 12-25) and the other to the C-terminus (amino acid 46-52), as previously described [25, 26]."*

*In the discussion section, we have added the details of bio-ADM assay:*

*P20, lines 293-295, "This bio-ADM assay uses two monoclonal antibodies against amino acid 21–32 and 42–52. The limits of detection and quantitation were 3 and 11 pg/ml (= 0.50 and 1.83 pM), respectively."*

*The antibodies used in our mAM assay and in the bio-ADM assay recognize locations that are in close proximity to one another. Thus, we consider that our mAM assay is as reliable as the bio-ADM assay reported by Weber et al. (P20-21, lines 300-304)*

Moreover, into the discussion more space should be dedicated on the result into literature on the role of bio-ADM in Sepsis and Acute Heart failure; see papers from Di Somma S et al.

*We have added References 44 and 45:*

*44. Molvin J, Jujic A, Navarin S, et al. Bioactive adrenomedullin, proenkephalin A and clinical outcomes in an acute heart failure setting. Open Heart. 2019; 6: e001048.*

*45. Kim H, Hur M, Struck J, Bergmann A, Di Somma S. Circulating Biologically Active Adrenomedullin Predicts Organ Failure and Mortality in Sepsis. Ann Lab Med. 2019; 39: 454-463.*

*We have explained the role of bio-ADM in sepsis and in acute heart failure with reference to papers by Di Somma S et al:*

*P21, lines 305-323, "In acute heart failure, bio-ADM performs as a suitable biomarker for the severity of congestion and 1-year mortality [44]. Furthermore, the correlation of the bio-ADM plasma levels on ICU admission with the requirement and quantity of vasopressors and mortality in sepsis is well established [13, 14, 16, 45]. Kim et al. reported that bio-ADM concentration is significantly higher among patients with septic shock, vasopressor use, and in non-survivors than in patients with solitary sepsis, no vasopressor use, and in survivors. Further, bio-ADM concentration and SOFA score equally in predicting 30-day mortality [45]. Marino et al. reported that patients with sepsis who require vasopressors on admission have significantly higher bio-ADM levels on admission than those who do not, and that admission ADM levels are strongly associated with 28-day mortality [16]. Simon et al. reported that, during the hospital stays, patients on vasopressor therapy in the ICU exhibit significantly higher bio-ADM levels after 16 hours of sepsis than patients without any vasopressor therapy [14]. Caironi et al. reported that the inotropic score over the first 7 days of treatment for septic patients alive at that time is greater in those with higher levels of bio-ADM at day 1 compared with those with lower levels, and bio-ADM concentrations on day 1 are independently associated with 90-day mortality [13]. These findings suggest that the mature bioactive AM (tAM or bio-ADM) is recognized as a biomarker of organ failure, similar to the conventional total AM (tAM). Our present study findings also support evidence that mature AM reflects the degree of organ damage, even during the perioperative*

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2<sup>nd</sup> Editorial decision  
30-Mar-2021

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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger  
Editor-in-Chief  
Journal of Clinical and Translational Research

Comments from the editors and reviewers: