Author’s response to reviews

Title: Proenkephalin A 119-159 (penKid) – a novel biomarker for acute kidney injury in sepsis: An observational study.

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Version: 1 Date: 11 Oct 2019

Author’s response to reviews:

Point-by-point response to reviewer comments
Changes in the revised manuscript are highlighted in yellow.

If troublesome formatting, please see exact copy of responses below included in the cover letter.

Reviewer #1 Dr. Corey B. Bills

Abstract

Briefly specify: How were patients enrolled? Randomly, consecutively?
Author response: Patients were enrolled consecutively. Specified in abstract. (Page 2, line 1)

Briefly explain exclusion criteria, and over what time period, so that the author has a better sense of what proportion of patients this represents
Author response: Exclusion criterion was age under 18 years. Patients were enrolled consecutively during office hours (6AM-6PM) between Dec 1st 2013 and Feb 1st 2015.

Page 3, line 1: What does "income level of penKid mean"? Please clarify and again on line 17
Author response: Clarified in manuscript. We mean ‘at presentation’.

Page 3, line 22: The use of the term "unselected" is unclear to me.
Author response: We understand the use of the term ‘unselected’ might be unclear to the reader. We mean there is no selection of patients (given they are 18 years or older).

Introduction
Page 4, line 37: please provide citation for reliability.
Author response: Due to shortening of Introduction references have been renumbered. Ref #11 is now Ref #9 (Denning, 2008) and covers the full paragraph.

Regarding the AKI definitions. What proportion of patients presented with AKI (rather than developed AKI during presentation throughout to the follow-up 7 days)?
Author response: As AKI requires dynamic changes of creatinine, it is difficult to assess if AKI is present at presentation when only one measurement is available. Diuresis was unfortunately not recorded. We have added this as a weakness. (p 16, lines 17-20)

Page 9 line 25: if not already done previously can you define severe sepsis for the reader?
Author response: We agree that the severe sepsis definition can be clarified and have added information accordingly (p. 5, lines 15-18): ‘The criteria for organ dysfunction were adopted from the consensus criteria and, at the time, current SSC guidelines i.e. severe sepsis was defined as suspected or confirmed infectious disease in combination with at least two SIRS criteria and presence or development of hypotension, hypoperfusion or organ failure within 48 hours after presentation at the ED.’

METHODS/RESULTS/DISCUSSION/LIMITATIONS
Recognizing that eGFR is a component of sCr, but was wondering if sCr was at all predictive of renal function/aki, MOF or mortality at 48 or 7 days, especially given the current definitions/standard by KDIGO and RIFLE use sCR and not eGFR?
Author response: Please see Supplemental Material containing supplementary tables and figures describing correlation with serum Creatinine and specified outcomes (AKI 48h, 7d, MOF and 28d Mortality). Description of supplementary materials added at the end of the manuscript (pp 21, lines 6-20).

Secondarily given the standard practice of ED physicians is the use of Scr as a measure (in some even more than eGFR) it might be helpful to include this info. In other words, given the conclusion that penKid is an effective predictor of AKI even in normal Cr is there a way to strengthen this in the results section to make it more clear.
Author response: Tried to clarify argument regarding clinical challenge in identifying patients at risk of developing AKI and presenting with normal or slightly elevated serum Creatinine which can provide false sense of renal function reserve to the treating ED physician. (page 10, lines 12-16).

Reviewer #2 Dr. Federico Franchi, M.D
Major Concerns
“In particular, there are no data and information regarding the treatments of patients after admission to the emergency department that may have influenced the outcomes analyzed. As a consequence, it is difficult to argue that penKid at ED admission can actually be a good predictor of bad outcome.”
Author response: We certainly agree that there are huge influences on outcomes depending on treatment and care during the entire hospitalization and after discharge. However, the aim of this study was to test if the ED physician can be guided by one initial measurement of penKid sampled at presentation to the ED. Such a biomarker must be “immune” to differences in treatment and surveillance that occurs after the initial management. We thus agree that e.g. serial
penKid measurements during the entire hospital stay might have a substantially stronger relationship with renal outcome and mortality, but this information is not available to the ED physician at the bedside. We have commented upon this in the discussion (page 17, lines 21-26).

Introduction
The introduction should be reduced by around 30-40%, especially the paragraph 1.1.
Author response: Introduction has been shortened. From 493 to 352 words.

Method
Statistical analysis: The logistic regression analysis used should be better described.
Author response: Description of the statistical analysis and measures has been clarified. (page 6, lines 15-18)

Please address why the study was not registered, approved by the Ethic Committee in 2013 and only submitted now. Why such a long delay?
Author response: We would like to reiterate that the study conducted is observational, not interventional which is why we haven’t seen trial registration as a prerequisite. The reason for the discrepancy between Ethic Committee approval and manuscript submission is that plasma was analyzed for PenKid first, June 2018. We have clarified this in the data collection section in the manuscript (page 4, lines 21-23)

The number of patients enrolled should be reported only in the results.
Author response: Patients enrolled is now only specified in the results section. (page 6, line 24).

Results
Please provide the ROC curve of penKid, sCr, and eGFR.
Author response: We have added data on ROC curves in results section (p9, lines 17-20) and provide ROC-curves as figures in the supplementary files (supplementary figures 1-4).
Please also provide a similar analysis used to test penKid also for sCr. It might be interesting for readers to understand how much penKid is superior to sCr to predict bad outcome.
Author response: As expected creatinine had strong association with creatinine-based outcomes (AKI after 48 hours and 7 days). Contrary, penKid was stronger in predicting mortality. We comment upon this in the revised version results section and have added the data on creatinine in supplementary tables 1 and 2.
A logistic regression analysis to predict each outcome considered in the study including all variables collected, should be performed.
Author response: Logistic regression analyses containing all variables not already presented in the main manuscript are presented in Supplementary Table 3.

Minor Concern
Please add the number to the pages.
Author response: Pages have been numbered.