Peer Review File
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First Round Peer Review

Reviewer A

The Author must be complimented for this interesting study, which was retrospectively conducted, nevertheless giving input for new prospective studies. The methodic is well described and the results are exhaustively displayed.
Reply 1: Thank you for your comments.

Reviewer B

Since 76% of the rapid group had surgery, that alone would account for shorter ICU stays and rapid transition to PO. Conservative management of aortic dissection may account for the increased LOS due to caution of the treating team to avoid hypertensive spikes while transitioning to enteral.
Reply 2: We have added text to this effect, addressing the potential impact of a larger proportion of the rapid group having undergone operational repair (see Page 12, line 271).

Reviewer C

As a frank impression, I think that the rapid group, which the transition from IV to PO antihypertensives was able to be performed quickly, was the result of the patient's condition being better than the slow group.
Reply 3: We agree that the patient's condition likely greatly impacted length of ICU admission. We elaborated on this in our limitations (Page 12, line 283).

As the authors stated in their limitations, the greatest shortcoming of this paper is the lack of an institutional workflow or protocol of transition from IV to PO antihypertensives. In addition, the reason why the transition from IV to PO antihypertensives was delayed in the slow group has not been explained.
Reply 4: We agree that this would be a valuable insight to add. Unfortunately, the rationale for these decisions was not described in the progress notes and was likely case-specific. Text to that effect has been added (see Page 10, line 255)

Reviewer D

Introduction
- Authors described “as a result, patients can remain in the intensive care unit (ICU) for extended durations for close hemodynamic monitoring required for continuous IV medications.” How did author defined “extended”? If patients require monitoring, it would not be extended. Please provide scientific data to support the idea that patients have been monitored inappropriately.
Reply 5: Our interest in this research question was based on pharmacists’ experience at our institution where some of these patients remain on stable rates of IV antihypertensive infusions with enteral access but primary teams do not uptitrate PO regimens to facilitate weaning the IV drips. We have observed that some of these patients would be ready for ICU discharge but the ongoing IV drips delay floor transfer. We have removed this description for clarity since we were not referencing any specific threshold (see Page 4, line 73)
- The requirement of hemodynamic monitoring would be related to the clinical importance of monitoring itself (e.g., strict blood pressure control for aortic dissection) rather than IV drip. Therefore, patients would need to stay in ICU even after IV is replaced with PO. Please differentiate monitoring requirement from type of medication.
Reply 6: We have modified this paragraph to better illustrate this point, clarifying that we were interested in patients who are on stable infusion rates, where more aggressive titration would facilitate weaning drips and possibly expedite ICU discharge (see Page 4, line 74). This clarification was also added to the abstract.
- Please provide the hypothesis tested in this study.
Reply 7: We have added this text as advised (see Page 5, line 92)

Methods
- Retrospective nature of the study cannot be a reason for waiving informed consent.
Reply 8: We have modified this text as advised (see Page 5, line 91)
- Please describe more about how to conduct screening of patients. Did author conduct medical chart review in each patient?
Reply 9: We conducted a medical chart review on each patient that met inclusion/exclusion criteria. This is addressed in the text (see Page 6, line 116)
What does “The Vizient Clinical Database was used to generate a report that identified patients” mean?
Reply 10: We have added text to elaborate on this, as advised (see Page 5, line 107)
- What was a rationale for >6h use of IV antihypertensive medication for the inclusion?
Reply 11: We have added this text as advised (see Page 6, line 122)
- What was a rationale of 72 hours for the definition for the rapid group?

Reply 12: We initially opted to describe this in the Discussion (see Page 10, line 228). We have also added this text to the Methods (see Page 6, line 136)
- Why did authors use the timing of full transition from IV to PO? As duration of transition highly depends on patient condition, the initiation of transition would be more clinically important. This definition would cause selection biases.
Reply 13: We sought to evaluate the utility of PO meds as a means to wean IV infusions since hemodynamic stability no longer requiring IV drips may help tee up a patient for ICU discharge. Text has been added for clarity (Page 6, line 117). We did take the time point when patients gained enteral access into consideration as well. (Page 7, line 134).
We agree that initiation of transition would be important to evaluate, and included this as a potential investigation for future studies (see Page 14, line 325)
- As rapid initiation PO medications instead of IV ones would potentially introduce inappropriate blood pressure control, so adverse events would happen in such population. ICU-free days is appropriate rather than ICU-length of stay.
Reply 14: Thank you for your comment. We hoped to capture adverse events by citing incidences of hypotension requiring medication dose reductions. The incidences reported all occurred during ICU admission since we intended to evaluate the utility/role of PO meds in helping to wean IV drips. ICU-free days may be a more sensitive outcome to evaluate, but our calculations were based on a prior study evaluating admission length.
- The term "delay to initiation of PO" would be inappropriate because some patients should be placed under IV medication for more strict blood pressure control.
Reply 15: We agree, and all the patients selected for this study were deemed to require IV medications to reach strict hemodynamic goals. We used the term moreso to indicate a later timepoint of initiation of PO, not necessarily to indicate that appropriate care was postponed. This has been reworded for clarity (see Page 6, line 142)
- Incidence of hypotension cannot be evaluated with Wilcoxon rank-sum test nor independent t-test.
Reply 16: This omission has been corrected (see Page 7, line 154)
- As this study is an observational study and significant selection bias would exist, any statistical analysis considering confounding factor must be conducted. Sensitivity analyses and subgroup analyses are also recommended to interpret results appropriately.
Reply 17: There were many different variables to consider, and we felt it would be challenging to analyze that the complexities of these patients' conditions and care using quantifiable measures that were able to be easily compared based on the available data that was collected. Although we opted not to perform sensitivity analyses and subgroup analyses, we added more text to describe appropriateness of results (see Page 13, line 297).
- Even based on previous studies, a 7-day difference in ICU length of stay by rapid transition of medication would be overestimated.
Reply 18: Since the study by Michaud et al was the only investigation that we found

evaluating a similar study question as our research, this was the timeline we used to calculate the required sample. We felt deviating from this would have been an arbitrary estimation.

Results
- Please avoid to state “not statistical significance” in patient characteristics because too small sample size is obviously lacking a power to detect differences in patient background. In addition, multiple hypothesis testing introduced the overestimation p-values.
Reply 19: We have modified this text as advised (see Page 8, line 166)
- Regarding ICU LOS, difference between the groups was only 4.1 days. However, $p<0.0001$ was obtained only in 54 patients although the power analyses identified the study needed 62 patients for examining 7-day differences. This is obviously strange and statistical appropriateness cannot be provided. The appropriateness of results should be explained.
- As explained in practice patterns, there are significant differences in practice between the groups. Authors should consider adjusting these confounding factors before discussion and conclusions.
Reply 20: for the above 2 bullets, please refer to Reply 17

Discussion
- “rapid transition to PO vasoactive agents within 72 hours of IV infusion initiation was associated with a shorter median ICU length of stay.” This is not true because authors did not adjust confounding factors.
- Discussion is too redundant. Authors should focus on how to interpret their results after providing adjusted analyses and avoid conducting literature review in discussion.
Reply 21: Although we opted not to perform sensitivity analyses and subgroup analyses, we added more text to describe appropriateness of results (see Page 13, line 296). More text dedicated to interpretation of findings has been added throughout the Discussion.

Reviewer E

Overall, this is a well written paper. My major criticism is that there is a distinct lack of clinically relevant or patient centred outcomes considered in this study. If the data is available, I would recommend adding 30-day mortality at a minimum. However, in its absence I do not think that this should necessarily preclude publication. The paper serves to contribute to a currently lacking body of research and helps to answer an important clinical question that may ultimately improve outcomes for patients with acute aortic dissection in the future. I support the publication of this paper given the authors take the time to duly consider the specific suggestions made in the structured appraisal provided.

Reply 22: We agree mortality would have been valuable information to present, however we did not collect data after hospital discharge. We will consider this in future endeavors with this research.

Structured Appraisal:

Introduction (including aims):

- **57:** I would avoid using the word 'injury' as it reads to infer trauma of some description.
  Reply 23: We have modified this text as advised (see Page 4, line 60)
- **66:** the referenced paper (5) looks pretty similar to the present study with respect to sample size, methods and outcomes. I think it is probably important to acknowledge the fact that the authors are looking at a different patient demographic who are being managed in a different health care system in order to prove consistency as opposed to just repeating a study that has already been done.
  Reply 24: We have added this text, as advised, in the Discussion section (see Page 10, line 229)

- Overall, a well written introduction which clearly explains the outstanding questions in the literature and how the present study aims to help answer them.

Methods:

- **83-95:** Well defined methods with ethics, recruitment and data gathering procedures clearly outlined.
- **96-107:** Well defined study and group inclusion/exclusion criteria, however reasons for choosing these cut off values are not mentioned until the discussion (**i.e.** used in previous study). Figure 1 and 2 are very helpful and well set out.
  Reply 25: With regard to cut off values, we initially opted to describe this in the Discussion (see Page 10, line 228). We have also added this text to the Methods (see Page 6, line 122 and line 136)
    - ***101-102:*** I am not sure why it was necessary to exclude all 'vulnerable populations'. I think it was a good idea to exclude pregnant patients as they represent a physiologically complex and unique patient population but I don't think that being a prisoner should impact any of the study outcomes aside from hospital length of stay perhaps.
      Reply 26: While no patients in this study comprised these populations, we agree that exclusion of vulnerable groups may not always be necessary and may impact the generalizability of scientific findings. This statement has been deleted.
- **108-110:** Whilst the present study looks at a number of important endpoints I would like to have seen more of a focus on clinically relevant or patient centred outcomes. At the very least I don't think you can have a study looking

at the management of aortic dissection without mentioning mortality. Additional endpoints might include sequale of 'impaired perfusion to vital organs' (**e.g.** stroke, renal failure etc..). Instead of 'hypotension' I would probably be more interested to see whether patients experienced tachycardia or hypertension following early transition to an oral antihypertensive regimen. The authors do mention 'subsequent aortic events' as a secondary outcome in the methods but this is not revisited.
Reply 27: We agree this would have been interesting information to present. However the additional depth of chart review was not able to be completed to include these variables. We have observed that patients who were maintained on only IV infusions have also experienced these effects, and any comparisons between the patients who did and did not experience tachycardia/hypertension would have been more patient-/case-specific evaluations. Regarding the secondary outcome, we have modified the text to this effect (see Page 9, line 201)

- **117-119:** Overall an underpowered study – the sample was smaller than required to detect a large effect size (with only 80% power) that was not observed.
  Reply 28: We have added text to elaborate on this point (see Page 13, line 296)

- Overall, a very well structured and clearly explained methodology supported by figures 1 and 2. Whilst lacking in clinically significant endpoints I can appreciate the utility of those which have been studied. The study is underpowered.

Results:

- **Table 1:**
  - Ethnicity and past medical history are also commonly included demographic features within the 'aortic dissection' literature. However, I can appreciate the space limitations.
  - In row 7, the authors attempt to provide information on 'Type of aortic dissection' but do not actually mention which type – is this a typo?
    Reply 29: We have corrected the text as advised (see Table 1, row 7). This should read "Type A aortic dissection", not 'Type of'.

- ***Baseline information:***
  - I think more attention needs to afforded to the dissection type. Type A and B dissections are extremely different entities with distinct management approaches, clinical courses and prognoses. Whilst the authors mention that dissection types are 'balanced between the groups' I would prefer to see this for myself represented in table 1.
    Reply 30: see above Reply 29
  - The authors mention multiple 'differences' between the groups (**i.e.** age, gender, surgical repair) however proceed to state that statistical

significance was not met – if we do not know if these are 'true differences' then are they worth mentioning? Admittedly, age and gender do come quite close to meeting significance though.
Reply 31: Noted. First paragraph of Results has been revised. Further discussion of comparison between groups has been added (see Page 12, line 231)

- Pertinent similarities between the groups have been well selected and mentioned appropriately.

- ***Inpatient haemodynamic management;***
  - 74.1% (slow) 'vs' 48.3% (rapid) used esmolol – seems like a notable difference probably worth mentioning.
    Reply 32: We have added text to describe this as advised (see Page 8, line 182)
- ***Outcomes;***
  - Discussion points as mentioned above.
- ***Practice patterns;***
  - The authors state that 'data on vasoactive patterns and timeline of events are depicted in Table 4 and Table 5, respectively' – I think that this may be a typo as table 4 contains the timeline of events and table 5 contains vasoactive practice patterns.
    Reply 33: We have corrected this as advised (see Page 9, line 203)

- Overall, good presentation of pertinent results relevant to study aims.

Discussion:

- **192:** I would probably like to have seen the delay to initiation of PO medications discussed as a potential modifiable variable (**i.e.** patients in the 'slow group' had increased delays to starting PO medications so maybe future studies should be looking at the effect of early initiation of PO medications on ICU LOS). This reference to Zhu et al.'s paper may be a good opportunity to bring it up.
  Reply 34: We have added this as advised (see Page 14, line 325)
- **197:** I agree that a lack of 'established clinical conversions' makes for a challenging process when trying transition patients onto PO medications in the ICU. Good point.

- **199:** It might be worth clarifying who the 'treating team' is. In an Australian context (and throughout many other countries) titration of antihypertensive infusions and transition to PO agents is exclusively managed by intensivists.
  Reply 35: We have added this as advised (see Page 10, line 237 and line 243)
- **228:** How does the small sample size limit the study?
  Reply 36: We have elaborated on this as advised (see Page 13, lines 297)
- 230-231: I don't think that variations in practice is necessarily a limitation. If everyone was doing the same thing then there wouldn't be anything to study.

Reply 37: We appreciate the comment. We simply want to acknowledge that inconsistencies in practice make this challenging to study

- **231-232:** Whilst cardiothoracic and vascular surgery practices were not compared, similar numbers of patients from each group were admitted under each team so I think this is OK.

- Overall, a well written discussion with humble considerations of the study limitations.

Conclusion:

- **242:** If IV infusions of vasoactive agents are often the only indication for ICU admission, then isn't the research question essentially answered before even conducting the study (**i.e.** the longer patients are on IV antihypertensives the longer their ICU LOS will be as this is the only reason that they are there).
  Reply 38: We have modified the text to emphasize that role of PO medications as a means to wean IV infusions and prep for ICU discharge (see Page 13, lines 307)
- **245:** I don't think that the authors can deduce that early transition to PO medications will reduce long term CVC complications from the present study. I would probably advise leaving this comment out.
  Reply 39: This has been deleted per suggestion
- **251-252:** the authors cannot conclude that early transition to PO antihypertensives does not increase risk of adverse events as, aside from 'hypotension', this was not studied.
  Reply 40: This has been revised (see Page 13, line 317)
- 253-255: do the authors have any more specific suggestions for future studies would be welcome here (e.g. RCT – however I think more retrospective data suggesting that early transition to PO antihypertensives does not confer any harm to patients would be required in the first instance)?
  Reply 41: We have added additional suggestions as advised (see Page 14, line 328)

- Overall, a concise conclusion that addresses the study aims.

Figures:

- Well set out.
- Figures 1 and 2 particularly helpful in following study design.
- ?Typo in table 1, row 7 as mentioned.
  Reply 42: Corrected. See Reply 29.

References:

- Appropriately structured.
- Would probably have expected more citations however I can appreciate the paucity of the research body on this topic.

Search engine optimization (title, abstract, key words):

Title - Concise and accurately reflects study aims.

Abstract – Again, in the conclusion I would not definitively state that reduced ICU LOS either rapid transition occurred 'without an increase in adverse events' as only 'hypotension' was looked at in the present study. Otherwise, no specific criticisms.
Reply 43: This has been revised (see Page 3, line 54)
Key words – Well chosen to maximise impact.

Reviewer F

The authors investigated the impact of delayed transition from intravenous agents to oral agents on the intensive care unit length of stay (ICU LOS) in patients with acute aortic dissection. Although the relationship between the transitional time of administration route between ICU LOS is an interesting topic, this reviewer has some concerns about the manuscript.

Major points
1. There are many factors that affect ICU LOS other than the transitional time of the administration route of antihypertensive agents. In this study, sources of bias such as patient background, surgical procedures, and the patient condition at ICU admission or after surgery were not considered in the analysis of outcomes.
Reply 44: We have added more specific text to this point to our limitations (see Page 12, line 283).
2. The rationale for grouping the patients using 72 hours as the threshold between the rapid and short groups should be described.
Reply 45: We initially opted to describe this in the Discussion (see Page 10, line 228). We have also added this text to the Methods (see Page 6, line 122 and line 136)

3. Even though there are few previous studies, the literature review is insufficient in the Discussion section.

Minor points
1. The total number of patients per group does not match the number of enrolled patients (the Result section and Figure 2).
Reply 46: Thank you. We have corrected this as advised (see Page 7, line 141; Figure 2)
2. The evaluation of normality and presentation of values should be described in the statistical analysis section.
Reply 47: This has been added as suggested (see Page 7, line 154). We opted to

describe this in the respective tables.

Reviewer G

Thank you very much for the opportunity to review the manuscript entitled "Impact of delayed transition off intravenous vasoactive agents for aortic dissection on intensive care unit length of stay". The objective the study is to compare the impact of rapid vs slow transition from IV to enteral vasoactive medications on ICU length of stay (LOS).

In my opinion, the publication's major concern is the flawed reasoning: "Deferred conversion to PO agents may lead to extended ICU LOS additional costs and inefficient resource utilization." The question is whether it is the TIME of inclusion of oral medications that affect LOS and complications or the DECISION to include them based on hemodynamic monitoring and assessment of the patient's clinical condition. Retrospectively, patients who were "fit" for such conversion might result a different LOS and complications - perhaps they were healthier, tolerated the surgical trauma better, had different surgical techniques, different pain treatments (regional blocks, adjuvants, etc.), and different physiotherapy. Following this logic, I would be extremely cautious about whether EVERY patient we initiate IV->PO conversion <72h will have a shorter LOS, fewer complications, and better BP/HR control. The only way to demonstrate this relationship is to do a prospective, randomized, blinded study. Thus, I'm afraid I have to disagree with the statement that "This study supports that patients with acute aortic dissection can be transitioned from vasoactive infusions to PO antihypertensive agents within 72 hours." Imagine an unstable patient on urapidil and NTG infusion who is started on a postoperative day 1-3 to convert to PO drugs.
Reply 48: We sought to evaluate the utility of PO meds as a means to wean IV infusions since hemodynamic stability no longer requiring IV drips may help tee up a patient for ICU discharge. We have revised the wording to better clarify this throughout the manuscript
I believe that the rapid conversion from IV to PO is not the reason for the shortened ICU LOS, but is the consequence of other factors.

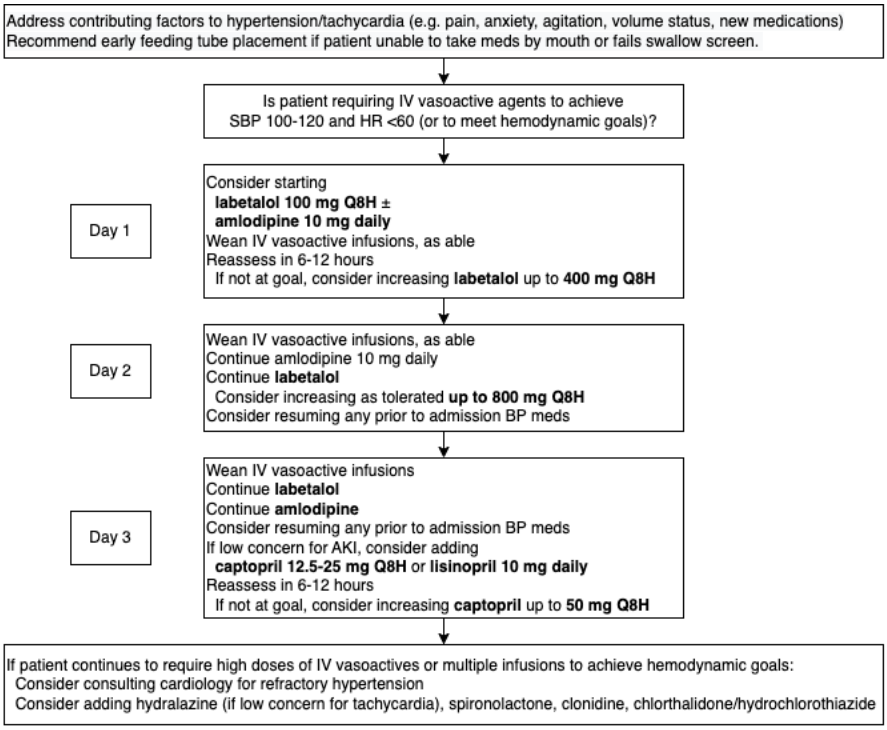
The primary question is, what was IV drug dose at which IV->PO conversion was initiated? Also, is it possible to gain insight into hemodynamic monitoring data (CO/CI, SVRi, Lactates, SvO2), patient's neurological and pain status, atherosclerosis (walk distance), physical activity (MET), and blood pressure values before hospital stay? In addition, there is no information on the type of AA (Table 1), and involvement of renal and visceral arteries, which may also affect pressure control.
Reply 49: While we didn't note the IV rate at the time of PO initiation, Table 2 includes mean and max doses for reference. We agree the remaining variables would have been valuable information to our evaluation, but unfortunately this data was not

collected

It is worth analyzing subgroups because your population is extremely inhomogeneous (operated and non-operated patients - for what reason was the procedure not performed? Patients operated with different techniques, from endovascular to classical, including aortic arch replacement. Was the arch replacement procedure in deep hypothermia?
Reply 50: While we agree this would be valuable information to our evaluation, much of this data was not collected. We opted to forgo further analysis.

Demonstrating the authors' intentions in a retrospective study will require great caution and good planning of WHAT data to use. I am afraid that not all of them are accessible.

Also, are you able to propose a protocol for iv->po transition?
Reply 51: We initially opted to leave out since this was not the protocol used by our specific institution. Below is a draft of a protocol we presented to our vascular/CT surgery departments. Please advise if this would be worth including in the paper.



This guidance document is not intended to supersede clinical judgment while evaluating individual patient response to these medications. Routes for medications described are PO/per feeding tube unless otherwise specified

Enteral medications included in algorithm were selected for rapid onset and short-acting to facilitate titration and weaning of IV vasoactive infusions. Alternatively, may consider restarting patient's prior to admission antihypertensives, but if unable to achieve hemodynamic goals, consider switching to agents included in algorithm.

Minor issues:
- Line 59: aortic dissection is "often" -> "always" a medical emergency.
Reply 52: We have opted to remove the word “often” (see Page 4, line 59);
- Line 84: please provide bioethics committee approval number
Reply 53: We have added this to Methods as advised (see Page 5, line 101). Also

available in Footnote Ethical Statement

- Table 1: missing inf about the type of Ao dissection
Reply 53: We have modified the text as advised (see Table 1, row 7). This should read "Type A aortic dissection", not 'Type of'.

- Sources should be referenced according to the Vancouver reference style. In text references should be identified using numbers in round brackets. For reports with up to three authors, all the author names should be listed. However, if a report has more than three authors, the first three authors should be listed
Reply 54: References have been corrected (see Page 17), and in-text references corrected throughout manuscript

Second Round Peer Review

Reviewer A

Thank you for the opportunity to review this revised manuscript. Although authors responded to my comments, some of them are not appropriate explanation.

1. Hemodynamic stability is not equal to the state that can tolerate to consistent infusion. As author replied, patients who have been on stable rates of IV antihypertensive infusions with enteral access for certain duration of time would be ideal candidates who should take po antihypertensive medication. Therefore, "slow" transition should not be defined using predefined cut-off value (72h in this study). Authors should define slow as no-transition of medication even after stable rates of IV antihypertensive infusions with enteral access for certain duration of time (24h, 48h, or anything according to previous studies.
Reply 1: While we understand reviewer A's position, we believe that using the initiation of PO meds timepoint would speak more to the inherent vasoactive infusion requirements of the patient as opposed to the role and impact of the PO meds themselves of reducing infusion requirements. We sought to evaluate the utility of PO meds as a means to wean IV infusions since hemodynamic stability no longer requiring IV drips may help tee up a patient for ICU discharge. While we find the proposed situation interesting, we were more interested in assessing the role of the initiation and uptitration of PO medications to help wean IV infusion requirements.

2. "A waiver of informed consent was obtained since this study met the criteria for minimal risk" of what?
Reply 2: We have added text to elaborate on this, as advised (see Page 5, line 104)

3. The cut-off as 6h for inclusion needs reference. Patients with 72h, but it is obviously standard care.

Reply 3: There is no reference for the 6h cut-off as this was an arbitrary decision. We previously added text to explain this choice on Page 6, line 124

4. If authors aimed to evaluate the role of PO medications in helping to wean IV infusions, they should evaluate the timing of initiation of PO meds, rather than the timing of finishing IV meds.
Reply 4: Please refer to Reply 1 for response to Comments 1 and 5.

5. In the response letter, "ICU-free days may be a more sensitive outcome to evaluate, but our calculations were based on a prior study evaluating admission length." Does this mean ICU LOS is unavailable? If so, please clarify it in Methods and Limitations. However, if authors did medical chart review, it is strange why ICU LOS is unavailable.
Reply 5: ICU length of stay is available; this is what we chose as our primary outcome. We chose ICU admission length over ICU-free days since our referenced paper by Michaud evaluated this endpoint. We sought to perform this study on a different patient demographic who are being managed in a different health care system in order to prove consistency, thus chose the same outcome.

6. Authors chose not to conduct additional analyses such as sensitivity analyses because "it would be challenging to analyze that the complexities of these patients' conditions and care using quantifiable measures that were able to be easily compared based on the available data that was collected." This challenge is the same as interpreting results by simply comparing outcome data that was just available. This is the reason why we cannot interpret such outcomes with potential biases. Authors should try to adjust covariate as possible.
Reply 6: After further discussion, the authors chose not to perform sensitivity analysis. Given the sample size, sensitivity analyses would not be reliable since choosing an appropriate covariate would be challenging, with the many limitations we have outlined.