PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Interrogating a clinical database to study treatment of hypotension in the critically ill
AUTHORS	Joon Lee, Rishi Kothari, Joseph A. Ladapo, Daniel J. Scott and Leo A. Celi

VERSION 1 - REVIEW

REVIEWER	James A. Russell AB, MD Professor of Medicine, University of British Columbia, Vancouver, BC, Canada
REVIEW RETURNED	27/02/2012

THE STUDY	7. The discussion would be improved by comparing your study results to (1) sepsis management guidelines (Dellinger et al 2008) and (2) AHA guidelines for cardiogenic shock. 8. De Backer et al (NEJM 2010;362:779-789) compared norepinephrine to dopamine in shock and found no difference in mortality but more arrhythmias with dopamine. In the subgroup of cardiogenic shock this was especially important because dopamine was wassociated with a higher mortality than norepinephrine. Accordingly, it would be useful to compare association of the use of dopamine to the use of norepinephrine on mortality in your cohort.
RESULTS & CONCLUSIONS	1. Page 6, paragraph 2. The ICU LOS is calculated in survivors only, which creates a bias. In virtually all randomized controlled trials (RCTs) and cohort studies, ICU LOS is reported for all patients. Of course you could also add the results for ICU LOS of survivors only. 2. Page 7, paragraph 2. The use of a clear propensity score is to be admired. However, please clarify that the propensity score was developed while blinded to outcomes. 3. The use of vasopressors for hypotension is predicated on adequate fluid resuscitation, i.e. vasopressors are to be added if patients remain hypotensive despite adequate fluid resuscitation. It is not clear from the current report whether and how patients were assessed as to adequacy of fluid resuscitation. In septic shock RCTs some measures of adequacy of fluid resuscitation that have been used include (1) fluids of at least 20 ml/kg (e.g PROWESS SHOCK) and (2) persistently increased or rising arterial lactate (e.g. Rivers). It would be advantageous to report some such measure of adequacy of fluid resuscitation in the patients who received vasopressors. Furthermore, amount of fluid resuscitation should be added as a variable to the vasopressor propensity score model. 4. Terminology. Dobutamine is not really a vasopressors but is an inotropic agent. Perhaps the term vasoactive agents (including vasopressors and intropic support) would be more appropriate. Accordingly, dobutamine should be removed from the list of vasopressors and the vasopressors analyses.
GENERAL COMMENTS	SUMMARY

	This is a single center (Beth Israel Hospital, Boston USA), retrospective cohort study (n=3163) to determine the efficacy (hospital mortality, ICU length of stay (LOS) and other organ dysfunction measurements) and safety of interventions (fluids and vasopressors) in patients who are hypotensive. The authors sued unadjusted and adjusted analyses as well as propensity scoring and sensitivity analyses. Fluids were associated with improved markers of hypotension. Vasopressors were associated with several adverse outcomes (increased mortality, prolonged ICU LOS, and more renal dysfunction) MAJOR 1. Page 6, paragraph 2. The ICU LOS is calculated in survivors only, which creates a bias. In virtually all randomized controlled trials (RCTs) and cohort studies, ICU LOS is reported for all patients. Of course you could also add the results for ICU LOS of survivors only. 2. Page 7, paragraph 2. The use of a clear propensity score is to be admired. However, please clarify that the propensity score was developed while blinded to outcomes. 3. The use of vasopressors for hypotension is predicated on adequate fluid resuscitation, i.e. vasopressors are to be added if patients remain hypotensive despite adequate fluid resuscitation. It is not clear from the current report whether and how patients were assessed as to adequacy of fluid resuscitation. In septic shock RCTs some measures of adequacy of fluid resuscitation that have been used include (1) fluids of at least 20 ml/kg (e.g PROWESS SHOCK) and (2) persistently increased or rising arterial lactate (e.g. Rivers). It would be advantageous to report some such measure of adequacy of fluid resuscitation in the patients who received vasopressors. Furthermore, amount of fluid resuscitation should be added as a variable to the vasopressor propensity score model. 4. Terminology. Dobutamine is not really a vasopressors but is an inotropic agent. Perhaps the term vasoactive agents (including vasopressors and intropic support) would be more appropriate. Accordingly, dobutamine should be removed from the list of vasopressors and the vasopressors analyses. MINOR 1. I would add the sample size to the abstract (n =2332 who had complete data) because the sample size is a strength of your study. 2. Page 4, paragraph 1. Another strength of administrative, clinical databases is that they assess use of interventions in practice (i.e. efficiency) whereas RCTs often create a somewhat “artificial” population because of inclusion and exclusion criteria that may not reflect true practice. I note that there were very few exclusion criteria in the current study, which is another strength. 3. Page 5, paragraph 2. The study pools all types of hypotension (septic, cardiogenic, hypovolemic, and post-traumatic), which creates a very heterogeneous population in whom different approaches to treatment of hypotension may be appropriate. You later state that you separated the (1) septic and (2) CHF groups. I would also separate according to: (1) septic, (2) cardiogenic, (3) trauma-induced hypotension and redo analyses in these subgroups (i.e. evaluate the trauma subgroup). My concern is the use of vasopressors in the trauma patients could bias against the safety of vasopressors in the other groups when the subgroups are pooled. 4. Page 5, last paragraph. I would say the two primary “independent”

	variables of interest… 5. Page 6, paragraph 2. Why did you dichotomize the HIS variable for analyses? I would have thought the continuous variable would be more sensistive. How did you choose a cutoff of 150 mmHg.min.? 6. Page 6, paragraph 3. Explain how you chose the control variables. Some are new to me (e.g. MAP in the 3 hours prior to hypotension) and require literature validation or your rationales. 7. The discussion would be improved by comparing your study results to (1) sepsis management guidelines (Dellinger et al 2008) and (2) AHA guidelines for cardiogenic shock. 8. De Backer et al (NEJM 2010;362:779-789) compared norepinephrine to dopamine in shock and found no difference in mortality but more arrhythmias with dopamine. In the subgroup of cardiogenic shock this was especially important because dopamine was wassociated with a higher mortality than norepinephrine. Accordingly, it would be useful to compare association of the use of dopamine to the use of norepinephrine on mortality in your cohort.

REVIEWER	David Ray MBChB MD FRCA FFICM Consultant in Anaesthesia & Critical Care Royal Infirmary of Edinburgh Scotland I have no competing interests to declare.
REVIEW RETURNED	26/03/2012

THE STUDY	In this study a large electronic database has been interrogated to look for association of vasopressor treatment of hypotension in critically ill patients and their outcome. It is not clear whether the whole database from 2001 to 2008, or only part of it, was used - 3163 patients met the inclusion criteria but the whole database contains data from >30000 patients. Patients were admitted to one of four different critical care units, some of which deal with subspecialist areas such as cardiac surgery. These differing patient populations are not clearly described and there is no acknowledgement that management of hypotension should be directed to the underlying cause which may differ between these populations (although the authors have attempted to adjust for this to some degree). The authors state that some patients had non-invasive arterial pressure monitoring (usually measured every 10-15 minutes) but do not state how many patients had direct intra-artetrial pressure monitoring (where measurement occcurs beat-to-beat) or how they defined an episode of hypotension in patients with intra-arterial monitoring. The concept of a hypotension severity index is flawed where different measurement techniques and freqency of arterial pressure measurement are used within the overall study population. It is not clear to this reviewer exactly what separates the group of "treated patients" and "fluid resuscitated patients" - it appears that patients in either group could receive vasopressors and/or fluids.
RESULTS & CONCLUSIONS	The authors wish to study treatment of hypotension in critically ill patients and specifically study any relationship between vasopressor therapy and outcome. The main finding is that vasopressor therapy is associated with worse outcome even when adjusted using propensity analysis.

	A major problem is that the authors have included inotropes (epinephrine) and inodilator therapy (dobutamine) in their inclusion criteria for vasopressor therapy. Whilst epinephrine certainly has vasopressor activity at higher doses, dobutamine can certainly not be considered to be a vasopressor. The results are reported for the whole population in four different critical care units which will each have a different population of patients who may require differing approaches to the management of hypotension; for example patients with congestive cardiac failure are much more likely to require inotropic support rather than vasopressor therapy to manage hypotension which may well result from primary pump failure rather than vasodilatation - this contrasts with management of hypotension in septic patients where vasoconstriction is more likely to be required than inotropic support. The authors do not appear to have studied just the effect of vasoactive therapy on outcome as patients could be included if they were already receiving vasopressor therapy and the dosage was increased. There is no consideration given to duration or intensity/dosage of vasopressor therapy and effect on outcome. 831 (approx 25%) patients had missing data which led to logistic regression modelling being performed with data from from only 75% of those studied, resulting in a potential large source of bias. The patients included are not particularly representative of critically ill patients in the UK - the very low SAPS score and low overall mortality of 12.9% suggests that generally the patients studied were much less unwell than would usually be found in UK critical care units. Why was SAPS used to assess severity of critical illness? - either SAPS II or APACHE II or III would be expected to be used routinely. 63% of hypotensive episodes as defined by the authors were not treated with either administration of fluid or vasopressor therapy - does this suggest that the definition used by the authors was incorrect? Phenylephrine is often used in the management of hypotension associated with epidural analgesia - there is no mention of whether any patients included had this technique of postoperative pain relief.

VERSION 1 – AUTHOR RESPONSE

MAJOR

1. Page 6, paragraph 2. The ICU LOS is calculated in survivors only, which creates a bias. In virtually all randomized controlled trials (RCTs) and cohort studies, ICU LOS is reported for all patients. Of course you could also add the results for ICU LOS of survivors only.

Response: We built a new ICU LOS regression model for all patients including those who died and added the results to Table 4. Vasoactive agents are not significantly related to ICU LOS in the new results. The purpose of excluding those who died in the ICU is because of the opposite directions of the relationship between LOS and risk of death among those who survived and those who died. For survivors, the higher the risk of death, the longer the LOS, while for the non-survivors, the higher the risk of death, the shorter the LOS. This might explain why the association between vasoactive agents and ICU LOS was lost when both survivors and non-survivors were included in the analysis. It is for

this reason that the Society of Thoracic Surgeons (STS) risk models for cardiac surgery restrict the definition of “LOS < 6 days” to those who are discharged alive.

2. Page 7, paragraph 2. The use of a clear propensity score is to be admired. However, please clarify that the propensity score was developed while blinded to outcomes.

Response: Yes, the propensity scores were calculated while being blind to in-hospital mortality. This has been clarified in the paragraph which is now the third paragraph on page 7.

3. The use of vasopressors for hypotension is predicated on adequate fluid resuscitation, i.e. vasopressors are to be added if patients remain hypotensive despite adequate fluid resuscitation. It is not clear from the current report whether and how patients were assessed as to adequacy of fluid resuscitation. In septic shock RCTs some measures of adequacy of fluid resuscitation that have been used include (1) fluids of at least 20 ml/kg (e.g PROWESS SHOCK) and (2) persistently increased or rising arterial lactate (e.g. Rivers). It would be advantageous to report some such measure of adequacy of fluid resuscitation in the patients who received vasopressors. Furthermore, amount of fluid resuscitation should be added as a variable to the vasopressor propensity score model.

Response: In order to take into account the degree of fluid resuscitation prior to the HE, we added the total volume of fluids (normal saline and lactated ringer) given to the patient between ICU admission and HE onset, to all propensity score models. This new variable is now explained in the first paragraph on page 7. We updated the third paragraph on page 9, Table 3, and Appendix I with the new results. Interestingly, the total amount of fluid administered prior to the HE was not significant (after adjusting for other variables) in any of the propensity score models, yielding negligible changes in the model discrimination and calibration, as well as the p values.
It is challenging to capture adequacy of fluid resuscitation in a retrospective study, mainly due to the lack of a standard way of assessing fluid responsiveness. Traditional static measures such as central venous pressure were not consistently obtained among the patients, and have been shown to be poorly predictive of fluid responsiveness [Vincent JL, 2011]. Dynamic measures have not been sufficiently standardized and validated across critically ill patients, especially those who are spontaneously breathing, those who are mechanically ventilated but not deeply sedated or those who have cardiac arrhythmias. We made the assumption that vasoactive agents were initiated or their dose increased after clinician assessment that the patient will not benefit from additional fluid administration. This limitation has been added to the Discussion (page 13).
Vincent JL. "Let's Give Some Fluid and See What Happens" versus the "Mini-fluid Challenge". Anesthesiology 2011; 115(3): 455-6.

4. Terminology. Dobutamine is not really a vasopressors but is an inotropic agent. Perhaps the term vasoactive agents (including vasopressors and intropic support) would be more appropriate. Accordingly, dobutamine should be removed from the list of vasopressors and the vasopressors analyses.

Response: We agree that the term “vasopressors” is misleading. However, we are still interested in analyzing dobutamine since it is administered to raise blood pressure, although its working mechanism is different from how vasopressors work. Therefore, we changed “vasopressors” to “vasoactive agents” throughout the manuscript.

MINOR

1. I would add the sample size to the abstract (n =2332 who had complete data) because the sample size is a strength of your study.

Response: We added the sample size to the abstract.

2. Page 4, paragraph 1. Another strength of administrative, clinical databases is that they assess use of interventions in practice (i.e. efficiency) whereas RCTs often create a somewhat “artificial” population because of inclusion and exclusion criteria that may not reflect true practice. I note that there were very few exclusion criteria in the current study, which is another strength.

Response: This point has been added to the paragraph.

3. Page 5, paragraph 2. The study pools all types of hypotension (septic, cardiogenic, hypovolemic, and post-traumatic), which creates a very heterogeneous population in whom different approaches to treatment of hypotension may be appropriate. You later state that you separated the (1) septic and (2) CHF groups. I would also separate according to: (1) septic, (2) cardiogenic, (3) trauma-induced hypotension and redo analyses in these subgroups (i.e. evaluate the trauma subgroup). My concern is the use of vasopressors in the trauma patients could bias against the safety of vasopressors in the other groups when the subgroups are pooled.

Response: There is no easy way to identify trauma patients in MIMIC-II. However, in our response to one of the other reviewer’s comments, we conducted an ICU-service-specific analysis to further address the heterogeneity among the patients. Since almost all trauma patients are cared for in SICU, we request the reviewer to look at the SICU-specific analysis instead. The results from the ICU-service-specific analysis are shown in Appendix II; the major findings from the overall cohort still persist in the SICU subgroup. The second paragraph on page 8 and the first paragraph on page 10 were added/modified to discuss the methods and results associated with the new analysis. The Discussion was updated accordingly in the second paragraph on page 11. The Results section of the Abstract was also modified.

4. Page 5, last paragraph. I would say the two primary “independent” variables of interest…

Response: We added the word “independent” as suggested (now the second paragraph on page 6).

5. Page 6, paragraph 2. Why did you dichotomize the HIS variable for analyses? I would have thought the continuous variable would be more sensistive. How did you choose a cutoff of 150 mmHg.min.?

Response: HSI was dichotomized to enable logistic regression analysis. The cutoff of 150 mmHg·min was determined based on the fact that the median HSI in our cohort was 154 mmHg·min. This has been clarified in the paragraph (now the third paragraph on page 6).

6. Page 6, paragraph 3. Explain how you chose the control variables. Some are new to me (e.g. MAP in the 3 hours prior to hypotension) and require literature validation or your rationales.

Response: This paragraph (now the fourth paragraph on page 6) has been expanded to describe what the control variables represent in the models.

7. The discussion would be improved by comparing your study results to (1) sepsis management guidelines (Dellinger et al 2008) and (2) AHA guidelines for cardiogenic shock.

Response: We have added a paragraph in the Discussion (page 12) to reference the suggested clinical guidelines.

8. De Backer et al (NEJM 2010;362:779-789) compared norepinephrine to dopamine in shock and found no difference in mortality but more arrhythmias with dopamine. In the subgroup of cardiogenic

shock this was especially important because dopamine was wassociated with a higher mortality than norepinephrine. Accordingly, it would be useful to compare association of the use of dopamine to the use of norepinephrine on mortality in your cohort.

Response: Due to inadequate power and the difference in mortality type (28-day mortality by De Backer et al vs. in-hospital mortality in the present study), we are unable to conduct a formal, adjusted comparison. However, we computed the unadjusted mortality rates among the patients who received only dopamine or norepinephrine and added the results to the Discussion (page 12).

Reviewer: David Ray MBChB MD FRCA FFICM
Consultant in Anaesthesia & Critical Care
Royal Infirmary of Edinburgh
Scotland

Response: We would like to thank the reviewer for the constructive feedback. Please see our itemized response below. All changes in the manuscript are shown in red.

In this study a large electronic database has been interrogated to look for association of vasopressor treatment of hypotension in critically ill patients and their outcome. It is not clear whether the whole database from 2001 to 2008, or only part of it, was used - 3163 patients met the inclusion criteria but the whole database contains data from >30000 patients.

Response: We used the entire MIMIC-II to find the adult patients who met our inclusion criteria. Please note that there are ~8,000 neonates in MIMIC-II, implying that there are ~25,000 adult patients in MIMIC-II. The first paragraph on page 5 was revised to focus on the adult population size. Since there is no reason to believe that particular years were associated with a higher (or lower) prevalence of hypotension, we assume that our cohort was selected more or less evenly from 2001 to 2008.

Patients were admitted to one of four different critical care units, some of which deal with subspecialist areas such as cardiac surgery. These differing patient populations are not clearly described and there is no acknowledgement that management of hypotension should be directed to the underlying cause which may differ between these populations (although the authors have attempted to adjust for this to some degree).

Response: In order to properly account for differences among the four ICU service types (MICU, SICU, CCU and CSRU), we conducted an ICU-service-specific analysis by building a propensity model for each service type to investigate the primary outcome variable (in-hospital mortality). Please note that we also added an additional control variable in the propensity score models to address the other reviewer's comment: the total volume of fluids given to the patient between ICU admission and the beginning of the HE. We report the new results in Appendix II. Fluid resuscitation was not significantly associated with in-hospital mortality in any of the service types. Vasoactive therapy was significantly related to higher in-hospital mortality in all service types except CSRU. The fact that different control variables are associated with the propensity for vasoactive therapy in different service types reflects that there exist variations in hypotension treatment across service types. The second paragraph on page 8 and the first paragraph on page 10 were added/modified to discuss the methods and results associated with the new analysis. The Discussion was updated accordingly in the second paragraph on page 11. The Results section of the Abstract was also modified.

The authors state that some patients had non-invasive arterial pressure monitoring (usually measured every 10-15 minutes) but do not state how many patients had direct intra-artetrial pressure monitoring (where measurement occcurs beat-to-beat) or how they defined an episode of hypotension in patients

with intra-arterial monitoring. The concept of a hypotension severity index is flawed where different measurement techniques and freqency of arterial pressure measurement are used within the overall study population.

Response: While it is true that the invasive arterial blood pressure measurement technique yields beat-by-beat, high-resolution waveforms, we used nurse-verified invasive blood pressure measurements that are still recorded every 10-15 minutes. We added a sentence in the last paragraph on page 5 to clarify this. Also, 1,486 and 1,677 patients were monitored using invasive and non-invasive techniques, respectively, and these numbers have been reported in the second last paragraph on page 8.

It is not clear to this reviewer exactly what separates the group of "treated patients" and "fluid resuscitated patients" - it appears that patients in either group could receive vasopressors and/or fluids.

Response: “Treated” means administration of either fluids OR vasoactive agents. “Fluid resuscitated” means administration of fluids regardless of vasoactive therapy. Therefore, the fluid resuscitated group is a subset of the treated group. This has been clarified in the first paragraph on page 8.

A major problem is that the authors have included inotropes (epinephrine) and inodilator therapy (dobutamine) in their inclusion criteria for vasopressor therapy. Whilst epinephrine certainly has vasopressor activity at higher doses, dobutamine can certainly not be considered to be a vasopressor. The results are reported for the whole population in four different critical care units which will each have a different population of patients who may require differing approaches to the management of hypotension; for example patients with congestive cardiac failure are much more likely to require inotropic support rather than vasopressor therapy to manage hypotension which may well result from primary pump failure rather than vasodilatation - this contrasts with management of hypotension in septic patients where vasoconstriction is more likely to be required than inotropic support.

Response: We agree that dobutamine is not a vasopressor. As part of our response to the other reviewer’s comment, we replaced the term “vasopressor” with “vasoactive agent” throughout the manuscript. Since dobutamine is still given to raise blood pressure, despite the fact that its working mechanism is different from vasopressors, we feel that we must keep dobutamine in our study to avoid confounding the results.
As mentioned above in our response to an earlier comment, we conducted a new ICU-service-specific analysis to address differences across service types.

The authors do not appear to have studied just the effect of vasoactive therapy on outcome as patients could be included if they were already receiving vasopressor therapy and the dosage was increased. There is no consideration given to duration or intensity/dosage of vasopressor therapy and effect on outcome.

Response: This is a limitation of the study. Due to the limited sample size, especially in the sensitivity analyses, we could not investigate granular treatment features such as the duration or dosage of vasoactive therapy. Furthermore, please note that the focus of the study was to find out whether the identified HEs (according to our particular definition) were treated and whether the treatment was related to clinical outcomes. Hypotension treatments outside the HEs were out of the scope of this study. This limitation has been mentioned in the Discussion (page 12-13).

831 (approx 25%) patients had missing data which led to logistic regression modelling being performed with data from from only 75% of those studied, resulting in a potential large source of bias.

Response: This is another limitation of the study. We have disclosed potential bias arising from missing data in the Discussion (last paragraph on page 12).

The patients included are not particularly representative of critically ill patients in the UK - the very low SAPS score and low overall mortality of 12.9% suggests that generally the patients studied were much less unwell than would usually be found in UK critical care units. Why was SAPS used to assess severity of critical illness? - either SAPS II or APACHE II or III would be expected to be used routinely.

Response: Although SAPS II and APACHE II/III are more commonly used in research studies, they are not available in MIMIC-II mainly due to the difficulty associated with retrospectively extracting previous health status. We feel that complementing SAPS I with the Elixhauser comorbidities (chronic illness) should capture severity of illness in an acceptable manner. The lower than expected mortality rate is mainly due to the CSRU patients whose mortality was only 2.9%.

63% of hypotensive episodes as defined by the authors were not treated with either administration of fluid or vasopressor therapy - does this suggest that the definition used by the authors was incorrect?

Response: More than one half of the HEs were not treated with either fluids or vasoactive therapy. A survey of these episodes (data not shown) revealed that these HEs were either accompanied by evidence of adequate tissue perfusion, i.e., good urine output and/or mentation, or related to medications, e.g., sedatives, and managed by dose reduction of the medication. Furthermore, the analyses of all HEs and only those treated with either fluids or vasoactive therapy yielded the same findings, suggesting robustness of the association between vasoactive agents and mortality.

Phenylephrine is often used in the management of hypotension associated with epidural analgesia - there is no mention of whether any patients included had this technique of postoperative pain relief.

Response: There is no easy way to identify the patients who received epidural analgesia in MIMIC-II. However, given that only SICU and CSRU patients are candidates for receiving epidural analgesia, the new ICU-service-specific analysis (Appendix II) may give some insight in this regard.

VERSION 2 – REVIEW

REVIEWER	David Ray MBChB MD FRCA FFICM Consultant in Anaesthesia & Critical Care Royal Infirmary of Edinburgh Scotland
REVIEW RETURNED	23/04/2012

RESULTS & CONCLUSIONS	The manuscript is not easy to read in some places and the large number of tables with odds ratios and propensity scores are very detailed. If it was possible to display some of these results pictorially or graphically it would aid the understanding for many readers (though I accept that it may be difficult to display the results in such a format).
GENERAL COMMENTS	I thank the authors for their considered responses to my previous comments. The amendments they have made have addressed many of my concerns and they now better acknowledge the limitations of their study. Despite the improvements made I remain a little concerned that fluid resuscitation (or lack of it) may be the major factor here. The authors

	have understandably assumed that fluid was not given because the attending clinician considered further fluid optimisation was not required, but in reality there are other reasons why fluid may not have been given. If patients who received vasoactive therapy alone were also under-fluid resuscitated this might explain why their risk of death was higher (as indeed the authors suggest given that "the corresponding vasoactive ORs for in-hospital mortality decreased, most substantially in patients who recieved fluid resuscitation (from 2.30 to 1.03)". Since three times as many patients in the study population received vasoactive therapy alone compared to vasoactive therapy plus fluids this may have unmasked the deleterious effect of giving such drugs to patients without ensuring adequate fluid stauts. However the authors have already discussed this as a potential limitation and I am not sure that they can improve their analysis further.

REVIEWER	James A. Russell Professor of Medicine, University of British Columbia Vancouver, BA, Canada No competing interests with this study.
REVIEW RETURNED	30/04/2012

GENERAL COMMENTS	This submission is much improved and responds well to the questions and concerns I raised. The subgroup comparisons (different ICU types) are interesting and confirm the primary results. The inclusion of available fluid resuscitation data and aliases was also very helpful, thank you.