PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Minimizing the biases in the observational study of resuscitative endovascular balloon occlusion of the aorta: A research protocol for a prospective study analyzed with propensity score matching with time-varying covariates
AUTHORS	Matsumura, Yosuke; Shiraishi, Atsushi; Kushimoto, Shigeki

VERSION 1 – REVIEW

REVIEWER	Stein, Deborah UCSF
REVIEW RETURNED	28-Jul-2021

GENERAL COMMENTS	A few points that would strengthen the manuscript significantly. 1. The entire manuscript should under go an editorial review for English grammar 2. Some clarification of the methods is needed 3. In the article summary, the terms "mimics" with respect to the propensity score match analysis is too strong. Perhaps "approximates" is a much better term. 4. In the article summary, the patients didn't "require" REBOA, they "received" treatment with a REBOA. 5. In the article summary, it is not just a matter of "adjusting perfectly" but rather equalizing the patients as much as could be done in an observational trial. 6. Please define RT. I assume you mean resuscitative thoracotomy, but this is not defined. 7. I realize that different countries do things differently, but are "emergency physicians" really making decisions about operative interventions? 8. Are tertiary centers not trauma centers? 9. I do not understand why a real power analysis can not be done. 10. What is "hemostasis decision"? Is this the decision to place a REBOA or not or the decision for IR/OR? 11. Is baseline information at "the time of hemostasis" or" hemostasis decision"? Please clarify

REVIEWER	Borger van der Burg, BLS Alrijne Hospital, Surgery
REVIEW RETURNED	13-Jan-2022

GENERAL COMMENTS	Thank you for the opportunity to review this paper. The question the authors try to answer is very important. In the field of advanced bleeding control there is a strong debate on the effectiveness of REBOA, primarily based on papers using propensity matching. The RCT's are including slowly. This prospective design tries to mimic a RCT and adresses possible confounding factors. I think

	this article can strenghten the evidence base for the use of REBOA. Some minor comments and suggestions on the writing are below, I would like the authors to check and if agreed change. Abstract P2, Line 14. as a bridge to definitive bleeding control of subdiafragmatic injury. P2, Line 17. Have poorly adjusted for confounding factors P2, Line 41. Who require bleeding control P2, Line 46. After the data set is fixed, missing values will be MULTIPLY; please correct Introduction P7, Line 22 definitive bleeding control P9, Line 25 to undergo surgical or endovascular bleeding control. P9, Line 54 from trauma or tertiary (insert space) P9, line 57 torso or truncal? Requiring surgical or endovascular bleeding control P10, Line 9 how is this number estimated? P11, Line 12 hemostasis is a confusing term, I suggest bleeding control throughout the paper Statistical Analysis P12, Line 17 increase the apparent mortality rate P12, line 33 after the data set … is fixed

REVIEWER	Norii, Tatsuya University of New Mexico - Albuquerque, Emergency Medicine
REVIEW RETURNED	20-Jan-2022

GENERAL COMMENTS	Summary: Authors plan to conduct a multicenter observation trial to investigate whether resuscitative endovascular balloon occlusion of the aorta (REBOA) plus standard trauma care results in better survival compared to standard trauma care alone for hemodynamically unstable torso trauma patients. The paper is well written overall, and the methods described in the paper technically sound. Specific comments: A potential suggestion would be to mention age cutoff (if there is any) in the study protocol. Although there are several studies that have described use of REBOA in pediatric trauma patients, the efficacy and safety of REBOA use in pediatric patients are largely unknown and it might be beneficial if the study can include pediatric patients.1,2 An international multi-disciplinary group recently published a core outcome set for REBOA.3 Although it might not be feasible for this present study to measure all outcomes, authors might want to consider adding some of the outcome measures that were listed in the article, such as cardiac arrest after ED arrival and neurological outcomes at discharge. Although the methods section is generally well written, I have several minor questions and potential suggestions. Authors might want to describe who will enter the data and how to confirm that all cases that meet the inclusion criteria are captured in the REDCap

	database, particularly cases that did not receive REBOA (if there is any plan to monitor compliance.) Regarding the statistical analysis plan, authors state that the baseline time point is defined as the moment of hemostasis decision. The type of decision is often made when CT scan or FAST exam are performed. It might be beneficial if authors could comment on how they plan to handle cases that receive REBOA before those imaging studies are performed or even in the prehospital setting. Minor comments: Page 9, line 54: “traumaor” should be “trauma or” Page 12, line 54: I guess it is “time of decision to perform hemostasis” instead of “time of hemostasis”. References: Norii T, Miyata S, Terasaka Y, Guliani S, Lu SW, Crandall C. Resuscitative endovascular balloon occlusion of the aorta in trauma patients in youth. J Trauma Acute Care Surg. 2017 May;82(5):915-920. doi: 10.1097/TA.0000000000001347. PMID: 28030495. Theodorou CM, Brenner M, Morrison JJ, Scalea TM, Moore LJ, Cannon J, Seamon M, DuBose JJ, Galante JM; AAST AORTA Study Group. Nationwide use of REBOA in adolescent trauma patients: An analysis of the AAST AORTA registry. Injury. 2020 Nov;51(11):2512-2516. doi: 10.1016/j.injury.2020.08.009. Epub 2020 Aug 8. PMID: 32798039; PMCID: PMC7609470. Nahmias J, Byerly S, Stein D, Haut ER, Smith JW, Gelbard R, Ziesmann M, Boltz M, Zarzaur B, Biffl WL, Brenner M, DuBose J, Fox C, Galante J, Martin M, Moore EE, Moore L, Morrison J, Norii T, Scalea T, Yeh DD. A core outcome set for resuscitative endovascular balloon occlusion of the aorta: A consensus based approach using a modified Delphi method. J Trauma Acute Care Surg. 2022 Jan 1;92(1):144-151. doi: 10.1097/TA.0000000000003405. PMID: 34554137.

REVIEWER	Bekdache, Omar McGill University Health Centre, Surgery
REVIEW RETURNED	24-Jan-2022

GENERAL COMMENTS	Dear Editor – BMJ Open Review of the Manuscript : Minimizing the biases in the observational study of Resuscitative endovascular balloon occlusion of the aorta: A research protocol for a prospective study analyzed with propensity score matching with time-varying covariates Manuscript ID: bmjopen-2021-053743 Review Date: January 24, 2022 Nice study protocol addressing a relevant research question that was clearly defined.

	Meanwhile, couple of issues need revision and worth considering before accepting the work. Conducting RCTs is trauma especially in life-threatening conditions like the one in question is always faced with ethical limitations. That's why researchers tend to substitute for these gold standard evidence based medical platforms with observational studies. In order to limit the bias and reduce the impact of confounding factors, we refer to adjusted propensity score matching studies. Nevertheless, these studies will never replace or mimic RCTs. So, I advise to refrain from using the term 'Mimic' while describing those studies and rather use either the term "Replace" or "Substitute" when describing the strengths and limitations of the study. We tend to define a specific time interval when describing study protocols. The starting date of the study is well defined while the ending date is not defined. I can understand that the researchers have linked the study to a defined number of cases (100-500) that will automatically stop the study once the number of cases is achieved, but I think the range is very big (400), I would rather be more specific and close the study once a certain number (preferably 200) is reached. An important limitation to this study that is worth mentioning – and perhaps trying to address – is that the REBOA use group was defined as the cases that had a decision only to use REBOA. We would never know the exact number of cases that effectively ended up using REBOA and hence, changed the outcome. I don't know if the methodology of the study can still be fine-tuned to define that 'Real' REBOA users and compare it to the control group. Among exclusion criteria – while intracranial traumatic bleeding injuries can constitute a relative limitation to the use of REBOA by some clinicians due to the increased intravascular pressure induced to the upper part of the body during the deployment of the balloon - I think it's wise to exclude exsanguinating thoracic injuries, as these are by almost all REBOA users considered contraindications for REBOA. Other minor suggestions / corrections – Page #7 – Line 54: Define what you mean by traumaor ? or is this a typo ?! Page #9 – Line 22: I would say: 'surgical repair ' instead of ' repair surgery'. Page #9 – Line 38: I would use: 'will be' instead of 'is' as we are referring to a future study. Page #11 – Line 49: Not all readers would know what an 'Immortal time bias' is, preferable to have an explanatory sentence that can briefly define what it's referring to. Page #13 – Line 38: 'Occlusion' instead of 'Obstruction'. Page #14 – Line 19: Mentioned 'Table 1' after participating hospital – although participating hospitals don't appear in the table.

	Warm Regards Omar Bekdache MD, MSc, FRCS, FACS, EBSQ Chief of Trauma Service and Chair of Trauma Committee – Tawam Hospital / Former Johns Hopkins affiliate. Clinical Associate Professor of Surgery – UAE University Trauma & Acute Care Surgery fellowship – McGill University Former President – ACS UAE Chapter

VERSION 1 – AUTHOR RESPONSE

Authors' Reply to the Reviewer 1
Reviewer: 1
Dr. Deborah Stein, UCSF
Comments to the Author:
A few points that would strengthen the manuscript significantly.
Thank you for comments and your time in reviewing our revised manuscript. The red font indicates revised text. We have made revisions as requested and include point-by-point responses.

1. The entire manuscript should under go an editorial review for English grammar
Response:
The revised manuscript underwent an editorial review for English grammer. We attached the CERTIFICATE OF ENGLISH PROOFREADING.

2. Some clarification of the methods is needed
Response:
We clarified some parts of the method section as follows.

3. In the article summary, the terms "mimics" with respect to the propensity score match analysis is too strong. Perhaps "approximates" is a much better term.
Response:
We agree that the term “mimic” is not appropriate to explain our study design. Other reviewer recommended to use “substitute” for the same reason. It was a very difficult choice, but we would like to use "substitute" instead of "mimic".

Previous:
Propensity score match analysis mimics the randomized controlled trials in critically ill patients requiring REBOA
Revised (P5L6):
Propensity score matching substitutes the randomized controlled trials conducted in critically ill patients who have undergone REBOA by equalizing the patients similar to that performed in an observational trial.

Previous:

To minimize observational study biases and mimic a randomized controlled trial, the JAST-REBOA study prospectively registered traumatic shock patients, wherein their data will be collected from traumaor tertiary care centers.
Revised (P9L1):
To minimize the biases inherent in observational studies and to substitute a randomized controlled trial, the JAST-REBOA study prospectively registered patients; their data will be collected from trauma or tertiary care centers. .

4. In the article summary, the patients didn't "require" REBOA, they "received" treatment with a REBOA.
Response:
We have corrected the term to “receive” according to your suggestion.
Previous:
Propensity score match analysis mimics the randomized controlled trials in critically ill patients requiring REBOA
Revised (P5L6):
Propensity score matching substitutes the randomized controlled trials conducted in critically ill patients who have undergone REBOA by equalizing the patients similar to that performed in an observational trial.

5. In the article summary, it is not just a matter of "adjusting perfectly" but rather equalizing the patients as much as could be done in an observational trial.
Response:
We have deleted the expression “adjusting perfectly” and added “equalizing the patients as much as could be done in an observational trial” according to your suggestion.
Previous:
The significant heterogeneity of the trauma patients might not be able to equalize the groups.
Revised ():
The significant heterogeneity of the trauma patients might not be able to equalize the groups.

6. Please define RT. I assume you mean resuscitative thoracotomy, but this is not defined.
Response:
The American Association for the Surgery of Trauma (AAST) prospective Aortic Occlusion for Resuscitation in Trauma and Acute Care Surgery (AAST-AORTA) registry demonstrated a possible survival benefit of REBOA compared with resuscitative thoracotomy (RT) in hypotensive patients who did not experience cardiac arrest.

7. I realize that different countries do things differently, but are "emergency physicians" really making decisions about operative interventions?
Response:
Emergency physicoans and surgeons discuss and decide the strategy. We added “surgeons”.
Previous:
The objective of this study is to compare standard trauma care alone (non-REBOA group) with standard trauma care plus REBOA (REBOA group) for hemodynamically unstable torso trauma patients whom emergency physicians have decided to undergo hemostatic surgery or interventional radiology.
Revised (P8L7):

This study aims to compare the standard trauma care alone (non-REBOA group) with standard trauma care plus REBOA (REBOA group) for hemodynamically unstable torso trauma patients who require hemostatic surgical or endovascular bleeding control based on the evaluation of the emergency physicians and surgeons.

8. Are tertiary centers not trauma centers?
Response:
Most “trauma center” is not designated by the national government or Japan Surgical Society. Only several trauma centers are designated by the local government. Most tertiary care center practically work as trauma center.

9. I do not understand why a real power analysis can not be done.
Response:
We added power analysis of this study and revised the manuscript accordingly.
Previous:
This research project plans an adaptive design with interim analyses since it is difficult to determine a priori the final sample size estimated from prespecified mortalities in the REBOA and control groups. When the REBOA group registration reaches 100 and 200 cases, the study sample size will be recalculated using absolute differences in the primary outcome incidence, with a significance level of 0.05 and a power of 0.8. The assumed increase in the required sample number due to missing data and propensity score matching was 1.5. In this study, we plan to register 100-500 REBOA enforcement cases, with the maximum registered number capped at 500.
Revised (P14L9):
Assuming a 50% mortality rate in the control group and a 35% mortality rate in the REBOA group, a total of 140 patients are required per group, as the required sample size has increased 1.5 times compared with that calculated in the matching. A more specific number of cases will be presented using an adaptive design with interim analyses. When the REBOA group registration reaches 100 and 200 cases, the study sample size will be recalculated using absolute differences in the primary outcome incidence, with a significance level of 0.05 and a power of 0.8. The assumed increase in the required sample number due to missing data and propensity score matching was 1.5, with the maximum registered number capped at 500.

10. What is "hemostasis decision"? Is this the decision to place a REBOA or not or the decision for IR/OR?
Response:
Firstly, we replaced the term “hemostasis” to “bleeding control” through out the manuscript according to the other reviewer’s suggestion.
The time of “decision of surgery” and “actual start of surgery” differ. This period is the “immortal time”. We used the timepoint of “bleeding control decision” as the baseline to reduce the immortal time bias (resuscitation time bias, survivorship bias). We added further explanation in the manuscript.
Added (P13L19):
Immortal time is the period of follow-up during which, by design, death or the study outcome cannot occur. In this study, the patients who “underwent” bleeding control surgery should not die prior to surgery. Thus, we chose the timing of decision as the baseline timepoint.

11. Is baseline information at "the time of hemostasis" or" hemostasis decision"? Please clarify
Response:
The baseline is the time of hemostasis decision. We clarified and revised sentence.

Previous:
The data analysis will employ propensity score matching with time-varying covariates, wherein the baseline timepoint is defined as the moment of hemostasis decision.
Revised (P11L6):
The data analysis will involve propensity score matching with time-varying covariates, wherein the baseline timepoint is defined as the moment of bleeding control decision. The baseline timepoint can be the patients' arrival (determined based on the prehospital information or physiological instability), the moment of imaging diagnosis (X-ray, focused assessment with sonography for trauma, or computed tomography scan), or recognition of the physiological deterioration. In patients who are expectedto require bleeding control in the prehospital setting, the arrival time was used as the baseline timepoint as the prehospital diagnosis is not definite.

Authors' Reply to the Reviewer 2
Reviewer: 2
Dr. BLS Borger van der Burg, Alrijne Hospital
Comments to the Author:
Thank you for the opportunity to review this paper. The question the authors try to answer is very important. In the field of advanced bleeding control there is a strong debate on the effectiveness of REBOA, primarily based on papers using propensity matching. The RCT's are including slowly. This prospective design tries to mimic a RCT and adresses possible confounding factors. I think this article can strenghten the evidence base for the use of REBOA.
Response:
Thank you for comments and your time in reviewing our revised manuscript.

Some minor comments and suggestions on the writing are below, I would like the authors to check and if agreed change.
Response:
The red font indicates revised text. We have made revisions as requested and include point-by-point responses.

Abstract
P2, Line 14. as a bridge to definitive bleeding control of subdiafragmatic injury.
Response:
We revised accoeding to your suggestion.

Previous:
Resuscitative endovascular balloon occlusion of the aorta (REBOA) has been used as a bridge for the definitive hemostasis of subdiaphragmatic injury.
Revised (P3L3):
Resuscitative endovascular balloon occlusion of the aorta (REBOA) has been used as a bridge to definitive bleeding control of subdiaphragmatic injury.

P2, Line 17. Have poorly adjusted for confounding factors
Response:
We added "for" according to your suggestion.
Added ():
Since previous observational studies have poorly adjusted for confounding factors, it is necessary to incorporate REBOA-specific and time-varying covariates in the model.

P2, Line 41. Who require bleeding control
Response:
We replaced “hemostasis” to “bleeding control”

Previous:
The present study will prospectively register traumatic shock patients who require hemostasis within 60 minutes of arrival at the emergency department,
Revised (P3L13):
To minimize observational study biases, this study will prospectively register traumatic shock patients who require bleeding control within 60 min upon arrival at the emergency department, with in-hospital mortality as the primary outcome.

P2, Line 46. After the data set is fixed, missing values will be MULTIPLY; please correct
Response:
We corrected this sentence as follows.

Previous:
After the data sets are fixed, missing values will be multiply imputed for all variables.
Revised (P3L15):
After the data set is fixed, the missing values for all variables will be imputed using the multiple imputation technique.

Introduction
P7, Line 22 definitive bleeding control
Response:
We replaced “hemostasis” to “bleeding control”

Previous:
Recently, resuscitative endovascular balloon occlusion of the aorta (REBOA) 2, which temporarily regulates aortic flow via balloon occlusion, has been used for a bridge to the definitive hemostasis of subdiaphragmatic injury.
Revised (P6L5):
Recently, resuscitative endovascular balloon occlusion of the aorta (REBOA),[2] which temporarily regulates the aortic flow via balloon occlusion, has been used as a bridge to definitive bleeding control of subdiaphragmatic injury.

P9, Line 25 to undergo surgical or endovascular bleeding control.
Response:
We revised the sentence accordingly.

Previous:
The objective of this study is to compare standard trauma care alone (non-REBOA group) with standard trauma care plus REBOA (REBOA group) for hemodynamically unstable torso trauma patients whom emergency physicians have decided to undergo hemostatic surgery or interventional radiology.
Revised (P8L7):
This study aims to compare the standard trauma care alone (non-REBOA group) with standard trauma care plus REBOA (REBOA group) for hemodynamically unstable torso trauma patients who

require hemostatic surgical or endovascular bleeding control based on the evaluation of the emergency physicians and surgeons.

P9, Line 54 from trauma or tertiary (insert space)
Response:
Thank you for pointing out this typo.

Previous:
To minimize observational study biases and mimic a randomized controlled trial, the JAST-REBOA study prospectively registered traumatic shock patients, wherein their data will be collected from traumaor tertiary care centers.
Revised (P9L1):
To minimize the biases inherent in observational studies and to substitute a randomized controlled trial, the JAST-REBOA study prospectively registered traumatic shock patients; their data will be collected from trauma or tertiary care centers.

P9, line 57 torso or truncal? Requiring surgical or endovascular bleeding control
Response:
We revised this sentence according to your suggestion.

Previous:
The present study will then enroll patients with torso hemorrhage requiring hemostasis (surgery and interventional radiology) within 60 minutes of arrival.
Revised (P9L3):
This study will then enroll patients with truncal hemorrhage requiring surgical or endovascular bleeding control within 60 min upon arrival at the center.

P10, Line 9 how is this number estimated?
Response:
We estimated this number from the registered cases of Japan Trauma Data Bank (JTDB). The total registered number of patients from 2004 to 2019 was 338,744, and that of REBOA cases was 1947.
Added (P9L5):
The establishment of a prospective registration system will allow the smooth enrollment of study patients, and approximately 100 patients who underwent REBOA are likely to be registered every year, which was estimated from the registered cases of JTDB.

P11, Line 12 hemostasis is a confusing term, I suggest bleeding control throughout the paper
Response:
We replaced “hemostasis” to “bleeding control” throughout the manuscript, including Table 1.

Previous:
The following patient data will be collected: demographics, mechanism of injury, vital signs on arrival, hemostasis decision, past medical history, trauma severity, blood examination, diagnostic imaging, trauma care time course, site of hemostasis, hemostasis method, blood transfusion requirement, information of arterial access for REBOA placement, initial aortic occlusion method, hospital course, and complications (Table 1).
Revised (P10L10):

The following patient data will be collected: demographics, mechanism of injury, vital signs on arrival, bleeding control decision, past medical history, trauma severity, blood examination results, diagnostic imaging results, trauma care time course, site of bleeding control, bleeding control method, blood transfusion requirement, information of arterial access for REBOA placement, initial aortic occlusion method, hospital course, and complications (Table 1).

Previous:
Access-related complications will also include dissection, pseudoaneurysm (requiring repair surgery or endovascular therapy), puncture hematoma, retroperitoneal hematoma (requiring hemostasis procedure rather than compression),
Revised (P10L15):
The access-related complications will also include dissection, pseudoaneurysm (requiring surgical repair or endovascular therapy), puncture hematoma, retroperitoneal hematoma (requiring bleeding control procedure rather than compression),

Previous:
The data analysis will employ propensity score matching with time-varying covariates, wherein the baseline timepoint is defined as the moment of hemostasis decision. To minimize survivorship biases, the patients whom the treating physician has decided to attempt hemostasis will be enrolled, regardless of whether hemostasis will actually occur or not. In fact, elderly patients, or those taking anti-thrombotic drugs, may present with delayed shock and can even be enrolled. Thus, we will enroll patients judged by a physician to require hemostasis within 60 min of arrival, which may decrease apparent mortality in the REBOA group due to survivorship biases (resuscitation time bias).7 In certain cases, the physiological derangement in REBOA cases might even increase apparent mortality rate.
Revised (P11L6)
The data analysis will involve propensity score matching with time-varying covariates, wherein the baseline timepoint is defined as the moment of bleeding control decision. The baseline timepoint can be the patients' arrival (determined based on the prehospital information or physiological instability), the moment of imaging diagnosis (X-ray, focused assessment with sonography for trauma, or computed tomography scan), or recognition of the physiological deterioration. In patients who are expected to require bleeding control in the prehospital setting, the arrival time was used as the baseline timepoint as the prehospital diagnosis is not definite. To minimize survivorship biases, the patients in whom the treating physician has decided to attempt bleeding control will be enrolled, regardless of whether bleeding control will actually occur or not. In fact, older patients or those taking anti-thrombotic drugs may present with delayed shock and can even be enrolled. Thus, patients judged by a physician to require bleeding control within 60 min upon arrival at the emergency room will be enrolled, which may decrease apparent mortality in the REBOA group due to survivorship biases (immortal time bias or resuscitation time bias).[14] In certain cases, the physiological derangement in REBOA cases might even increase the apparent mortality rate.

Previous:
In the primary analysis of this study, propensity scores for the probability of REBOA decision (regardless of the actual REBOA deployment) will be calculated using baseline information at the time of hemostasis, not the time of arrival at the emergency room.
Revised (P12L19):
In the primary analysis of this study, propensity scores for the probability of REBOA decision (regardless of the actual REBOA deployment) will be calculated using baseline information at the time that bleeding control was decided, not the time of arrival at the emergency room.

Previous:

Vital signs on arrival and at the decision of hemostasis
Revised (Table 1)
Vital signs on arrival and at the decision of bleeding control

Previous:
Chest X-ray (Chest injury requiring bleeding control)
Pelvis X-ray (Pelvic fracture requiring bleeding control)
Revised (Table 1):
Chest X-ray (Chest injury requiring bleeding control)
Pelvis X-ray (Pelvic fracture requiring bleeding control)

Statistical Analysis
P12, Line 17 increase the apparent mortality rate
Response:
We added “the” accordingly.
Added (P11L20)
In certain cases, the physiological derangement in REBOA cases might even increase the apparent mortality rate.

P12, line 33 after the data set … is fixed
Response:
Thank you for your correction.
Previous:
After the data sets in the analysis are fixed,
Added (P12L13)
After the data set in the analysis is fixed,

Authors' Reply to the Reviewer 3
Reviewer: 3
Dr. Tatsuya Norii, University of New Mexico - Albuquerque
Comments to the Author:
Summary:
Authors plan to conduct a multicenter observation trial to investigate whether resuscitative endovascular balloon occlusion of the aorta (REBOA) plus standard trauma care results in better survival compared to standard trauma care alone for hemodynamically unstable torso trauma patients. The paper is well written overall, and the methods described in the paper technically sound.
Response:
Thank you for comments and your time in reviewing our revised manuscript. The red font indicates revised text. We have made revisions as requested and include point-by-point responses.

Specific comments:
A potential suggestion would be to mention age cutoff (if there is any) in the study protocol. Although there are several studies that have described use of REBOA in pediatric trauma patients, the efficacy and safety of REBOA use in pediatric patients are largely unknown and it might be beneficial if the study can include pediatric patients.1,2
An international multi-disciplinary group recently published a core outcome set for REBOA.3
Response:
Thank you for your fruitful suggestion. The authors recognized the previous studies including referece 1 and 2 that reported adolocent population. The original research protocol of AAST-

AORTA study is approved by University of Maryland, which is officially available on the website of AAST (https://www.aast.org/Research/Multi-Institutional-Studies). The protocol only includes adult, middle age, and elderly. The author never understand the reason adolocent population were included in the AORTA database.
Reference 1, the analysis of JTDB included 15 young children (<16) and 39 adolecents (16-18) among 12-year JTDB population. Reference 2, the AORTA analysis both only include adolescent. Majority is seventeen.
Our protocol includes 16 years old, which will enroll most population.
Recently small profile REBOA catheters are available (Rescue Balloon, ER-REBOA, REBOA balloon kit, and COBRA-OS). These novel devices will bring the opportunity of REBOA in young children in near future. However, we gave up including young children because such population are not officially recognized the appropriate target of REBOA due to the risk of leg ischemia.
We really appreciate the suggestion and hopefully the population should be evaluated international survey first, then will be included in the clinical study.
Added (P9L11):
We will enroll patients aged 16 years and older based on the previous studies that included children.[10 11]

Although it might not be feasible for this present study to measure all outcomes, authors might want to consider adding some of the outcome measures that were listed in the article, such as cardiac arrest after ED arrival and neurological outcomes at discharge.
Response:
We appreciate your suggestion. The neurogolical outcome was measured as the complication of hypoxic enceplalopathy. We consider adding cardiac arrest after ED arrival.

Although the methods section is generally well written, I have several minor questions and potential suggestions. Authors might want to describe who will enter the data and how to confirm that all cases that meet the inclusion criteria are captured in the REDCap database, particularly cases that did not receive REBOA (if there is any plan to monitor compliance.)
Response:
We added the description explaining who enter the data in the database.
As you pointed out the severity of the patients who did not receive REBOA may differ by the insttutions. However, we accept the differences in severitybetween sites because we compare two groups adjusted for severity after matching.
Added (P10L5):
One or two persons (a physician, a research nurse, or a medical clerk) in charge of inputting information at each facility will register the patient information in the database.

Regarding the statistical analysis plan, authors state that the baseline time point is defined as the moment of hemostasis decision. The type of decision is often made when CT scan or FAST exam are performed. It might be beneficial if authors could comment on how they plan to handle cases that receive REBOA before those imaging studies are performed or even in the prehospital setting.
Response:
We added more detail explanation on how they plan to handle cases that receive REBOA before those imaging studies are performed or even in the prehospital setting.
Added (P11L8):
The baseline timepoint can be the patients' arrival (determined based on the prehospital information or physiological instability), the moment of imaging diagnosis (X-ray, focused assessment with sonography for trauma, or computed tomography scan), or recognition of the physiological

deterioration. In patients who are expected to require bleeding control in the prehospital setting, the arrival time was used as the baseline timepoint as the prehospital diagnosis is not definite.

Minor comments:
Page 9, line 54: “traumaor” should be “trauma or”
Response:
Thank you for pointing out this typo.
Previous:
To minimize observational study biases and mimic a randomized controlled trial, the JAST-REBOA study prospectively registered traumatic shock patients, wherein their data will be collected from traumaor tertiary care centers.
Revised (P9L1):
To minimize the biases inherent in observational studies and to substitute a randomized controlled trial, the JAST-REBOA study prospectively registered traumatic shock patients; their data will be collected from trauma or tertiary care centers.

Page 12, line 54: I guess it is “time of decision to perform hemostasis” instead of “time of hemostasis”.
Response:
Thank you for pointing out. We corrected the sentence. Since another reviewer recommended to replace “hemostasis” to “bleeding control”, we modified the term accordingly.
Previous:
In the primary analysis of this study, propensity scores for the probability of REBOA decision (regardless of the actual REBOA deployment) will be calculated using baseline information at the time of hemostasis, not the time of arrival at the emergency room.
Revised (P12L19):
In the primary analysis of this study, propensity scores for the probability of REBOA decision (regardless of the actual REBOA deployment) will be calculated using baseline information at the time that bleeding control was decided, not the time of arrival at the emergency room.

Authors' Reply to the Reviewer 4
Reviewer: 4
Dr. Omar Bekdache, McGill University Health Centre
Comments to the Author:

Nice study protocol addressing a relevant research question that was clearly defined.
Meanwhile, couple of issues need revision and worth considering before accepting the work.
Thank you for comments and your time in reviewing our revised manuscript. The red font indicates revised text. We have made revisions as requested and include point-by-point responses.

Conducting RCTs is trauma especially in life-threatening conditions like the one in question is always faced with ethical limitations. That’s why researchers tend to substitute for these gold standard evidence based medical platforms with observational studies. In order to limit the bias and reduce the impact of confounding factors, we refer to adjusted propensity score matching studies. Nevertheless, these studies will never replace or mimic RCTs. So, I advise to refrain from using the term ‘Mimic’ while describing those studies and rather use either the term “Replace” or “Substitute” when describing the strengths and limitations of the study.
Response:
Thank you for pointing out. We agree that the term “mimic” is not an appropriate to explain the present study.

Previous:
Propensity score match analysis mimics the randomized controlled trials in critically ill patients requiring REBOA
Revised (P5L6):
Propensity score matching substitutes the randomized controlled trials conducted in critically ill patients who have undergone REBOA by equalizing the patients similar to that performed in an observational trial.

Previous:
To minimize observational study biases and mimic a randomized controlled trial, the JAST-REBOA study prospectively registered traumatic shock patients, wherein their data will be collected from traumaor tertiary care centers.
Revised (P9L1):
To minimize the biases inherent in observational studies and to substitute a randomized controlled trial, the JAST-REBOA study prospectively registered traumatic shock patients; their data will be collected from trauma or tertiary care centers.

We tend to define a specific time interval when describing study protocols. The starting date of the study is well defined while the ending date is not defined. I can understand that the researchers have linked the study to a defined number of cases (100-500) that will automatically stop the study once the number of cases is achieved, but I think the range is very big (400), I would rather be more specific and close the study once a certain number (preferably 200) is reached.
Response:
We appreciate your thoughtful comments on the number of cases. We described the wide range number at present, but we will perform the interim analysis as the nature of adaptive design. Then we will be able to suggest more specific number.
Previous:
This research project plans an adaptive design with interim analyses since it is difficult to determine a priori the final sample size estimated from prespecified mortalities in the REBOA and control groups. When the REBOA group registration reaches 100 and 200 cases, the study sample size will be recalculated using absolute differences in the primary outcome incidence, with a significance level of 0.05 and a power of 0.8. The assumed increase in the required sample number due to missing data and propensity score matching was 1.5. In this study, we plan to register 100-500 REBOA enforcement cases, with the maximum registered number capped at 500.
Revised (P14L9):
Assuming a 50% mortality rate in the control group and a 35% mortality rate in the REBOA group, a total of 140 patients are required per group, as the required sample size has increased 1.5 times compared with that calculated in the matching. A more specific number of cases will be presented using an adaptive design with interim analyses. When the REBOA group registration reaches 100 and 200 cases, the study sample size will be recalculated using absolute differences in the primary outcome incidence, with a significance level of 0.05 and a power of 0.8. The assumed increase in the required sample number due to missing data and propensity score matching was 1.5, with the maximum registered number capped at 500.

An important limitation to this study that is worth mentioning – and perhaps trying to address – is that the REBOA use group was defined as the cases that had a decision only to use REBOA. We would never know the exact number of cases that effectively ended up using REBOA and hence, changed the outcome. I don't know if the methodology of the study can still be fine-tuned to define that 'Real' REBOA users and compare it to the control group.
Response:

Thank you for your suggestion. We added the limitation section.
Added (P17L13):
Limitations
There are some potential limitations of this study. The REBOA use group was defined as the cases that were required to undergo REBOA. The exact number of cases that underwent REBOA and whose outcome will likely change will remain unclear. In addition, significant heterogeneity was observed in the study population, which may have an effect on the matching process.

Among exclusion criteria – while intracranial traumatic bleeding injuries can constitute a relative limitation to the use of REBOA by some clinicians due to the increased intravascular pressure induced to the upper part of the body during the deployment of the balloon - I think it's wise to exclude exsanguinating thoracic injuries, as these are by almost all REBOA users considered contraindications for REBOA.
Response:
We added exclusion criteria reagarding exsanguinating thoracic injuries.
Previous:
In contrast, we will exclude patients who presented with cardiac arrest before initial presentation, regardless of spontaneous circulation return.
Revised (P9L13):
By contrast, we will exclude patients who presented with cardiac arrest before the initial presentation, regardless of return of spontaneous circulation, and apparent contraindication to REBOA such as exsanguinating thoracic injuries.

Other minor suggestions / corrections –
Page #7 – Line 54: Define what you mean by traumaor ? or is this a typo ?!
Response:
Thank you for pointing out.
Previous:
To minimize observational study biases and mimic a randomized controlled trial, the JAST-REBOA study prospectively registered traumatic shock patients, wherein their data will be collected from traumaor tertiary care centers.
Revised (P9L1):
To minimize the biases inherent in observational studies and to substitute a randomized controlled trial, the JAST-REBOA study prospectively registered traumatic shock patients; their data will be collected from trauma or tertiary care centers.

Page #9 – Line 22: I would say: 'surgical repair ' instead of ' repair surgery'.
Response:
We revised the sentence accordingly.
Previous:
Access-related complications will also include dissection, pseudoaneurysm (requiring repair surgery or endovascular therapy)
Revised (P10L15):
The access-related complications will also include dissection, pseudoaneurysm (requiring surgical repair or endovascular therapy),

Page #9 – Line 38: I would use: 'will be' instead of 'is' as we are referring to a future study.
Response:

We revised the sentence accordingly.
Previous:
The primary outcome of this study is in-hospital mortality.
Revised (P11L2):
The primary outcome of this study will be in-hospital mortality.

Page #11 – Line 49: Not all readers would know what an 'Immortal time bias' is, preferable to have an explanatory sentence that can briefly define what it's referring to.
Response:
We revised and added the sentence regarding immortal time bias.

Previous:
Thus, we will enroll patients judged by a physician to require hemostasis within 60 min of arrival, which may decrease apparent mortality in the REBOA group due to survivorship biases (resuscitation time bias).
Revised (P11L17):
Thus, patients judged by a physician to require bleeding control within 60 min upon arrival at the emergency room will be enrolled, which may decrease apparent mortality in the REBOA group due to survivorship biases (immortal time bias or resuscitation time bias).

Added (P13L19):
Immortal time is the period of follow-up during which, by design, death or the study outcome cannot occur. In this study, the patients who "underwent" bleeding control surgery should not die prior to surgery. Thus, we chose the timing of decision as the baseline timepoint.

Page #13 – Line 38: 'Occlusion' instead of 'Obstruction'.
Response:
We revised the sentence.
Previous:
Analysis limited to REBOA vs. non-aortic obstruction will be performed for the subgroup without cardiac arrest at arrival using an analysis method similar to that of primary analysis.
Revised (P15L19):
Analysis comparing REBOA and non-aortic occlusion will be performed for the subgroup that did not experience cardiac arrest upon arrival at the emergency room using an analysis method similar to that of primary analysis.

Page #14 – Line 19: Mentioned 'Table 1' after participating hospital – although participating hospitals don't appear in the table.
Response:
We deleted "Table 1" from the sentence.
Deleted:
This observational study was registered in the UMIN Clinical Trials Registry (UMIN000035458) and was approved by the Ethics Committee of each participating hospital (Table 1) and Ethics Committee of the JAST.

VERSION 2 – REVIEW

REVIEWER	Norii, Tatsuya University of New Mexico - Albuquerque, Emergency Medicine
REVIEW RETURNED	10-Mar-2022

GENERAL COMMENTS	The manuscript significantly improved and I have no further suggestions.

REVIEWER	Bekdache, Omar McGill University Health Centre, Surgery
REVIEW RETURNED	03-Mar-2022

GENERAL COMMENTS	Revision file reviewed carefully. All concerns / recommendations were addressed appropriately. No additional revision is needed from my side at this point and manuscript can proceed to publication