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# 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

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| | |

**Protocol**

**Complete manuscript title:**
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

**Running head**: Matching study to assess REBOA in torso trauma

**Authors:**
Yosuke Matsumura, MD, PhD[1, 2], Atsushi Shiraishi, MD, PhD[3], Shigeki Kushimoto MD, PhD[4]

**Affiliation**
1. Department of Emergency and Critical Care Medicine, Chiba University Graduate School of Medicine
2. Department of Intensive Care, Chiba Emergency Medical Center
3. Emergency and Trauma Center, Kameda Medical Center
4. Division of Emergency and Critical Care Medicine, Tohoku University School of Medicine

**Correspondence:**
Yosuke Matsumura
Department of Intensive Care, Chiba Emergency Medical Center
3-32-1 Isobe, Mihama, Chiba, 261-0012, Japan
Phone: +81-43-279-2211
E-mail: yousuke.jpn4035@gmail.com; matsumuray@chiba-u.jp

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Trauma management, vascular surgery, interventiomal radiology, resuscitative endovascular balloon occlusion of the aorta, REBOA

## ABSTRACT

### Introduction

Resuscitative endovascular balloon occlusion of the aorta (REBOA) has been used as a bridge for the definitive hemostasis of subdiaphragmatic injury. Since previous observational studies have poorly adjusted confounding factors, it is necessary to incorporate REBOA-specific and time-varying covariates into the model. We hypothesized that REBOA results in better survival in comparison between the REBOA group and a matched control group (non-REBOA group) for hemodynamically unstable torso trauma patients.

### Methods and analysis

The JAST-REBOA study is a prospective multicenter matched-cohort study organized by the Clinical Trial Committee of the Japanese Association for the Surgery of Trauma. To minimize observational study biases, the present study will prospectively register traumatic shock patients who require hemostasis within 60 minutes of arrival at the emergency department, with the primary outcome being in-hospital mortality.

After the data sets are fixed, missing values will be multiply imputed for all variables. In the primary analysis, propensity scores for the probability of REBOA decision (regardless of the actual REBOA deployment) will be calculated from baseline information using a logistic regression generalized linear mixed-effect model, which will be done for both REBOA use and non-REBOA use groups.

## Ethics and dissemination

The study was approved by the Ethics Committee of each participating hospital. The results will be disseminated to the participating hospitals, submitted to peer-reviewed journals for publication, and presented at congresses.

**Trial registration number** UMIN Clinical Trials Registry; UMIN000035458.

Registered January 6 2019.

## Article Summary

This prospective multicenter-matched cohort study compares the REBOA group and non-REBOA group using a research protocol minimizing biases.

*Strengths and limitations of this study*

- Propensity score match analysis mimics the randomized controlled trials in critically ill patients requiring REBOA.
- The data analysis, including time-varying covariates, can minimize the survivorship biases (resuscitation time bias) and physiological changes in the patients.
- The multiple imputation method substitutes missing or unmeasured values, often seen in severe cases, and minimizes selection biases.
- The observational study dealing with critically ill patients may not be able to adjust perfectly the background of two groups consisting of patients who have significant heterogeneity.

## Introduction

Hemorrhagic shock is the leading cause of preventable trauma death.[1] In response, immediate surgical and/or endovascular intervention is required for definitive control of non-compressible torso hemorrhages involving the thorax, abdomen, or pelvis. 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. Proximal aortic pressure from this injury is expected to be elevated by augmented afterload, increasing the risk of ischemic complications in the distal organ or lower extremities.

Observational studies using a multicenter database from Japan (Japan Trauma Data Bank, JTDB) [3,4] and the United States (Trauma Quality Improvement Program, TQIP)[5] suggested a possible negative effect on survival outcome. In contrast, another study using the JTDB recently reported better survival in patients undergoing REBOA,[6] concluding opposite results to those previously utilized in the same Japanese database. Although these reports analyzed a considerable number of patients from multiple centers, these results might be biased due to a lack of REBOA-specific information in the dataset.

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 as compared to resuscitative thoracotomy (RT) in hypotensive patients not in cardiac arrest.[8] Additionally,

ABOTrauma registry, a Swedish-based international registry, presented potential benefits in partial or intermittent REBOA as compared to complete REBOA.[9] The Diaganostic and Interventional Radiology in Emergency, Cririca l care and Trauma (DIRECT)-Intraaortic Balloon Occlusion (IABO) registry, a Japanese multicenter retrospective observational database, has also shown fewer access-related complications using a smaller profile REBOA device[10]. These registries included detailed REBOA-related information but did not have an appropriate control group (non-REBOA group). Thus, clinical questions regarding "REBOA vs RT," "partial/intermittent REBOA vs complete REBOA," and "Small vs Large profile" are not the ones that truly need to be clarified.

Notably, these previous researches have also poorly adjusted their confounding factors. Although the JTDB and TQIP analyses compared the REBOA group to a matched cohort (non-REBOA group), the database did not include REBOA-specific variables or time-varying covariates. In contrast, the AAST-AORTA study compared the REBOA group with the RT group, which is not the proper control group for comparison. Even the DIRECT-IABO and ABOtrauma registry only included REBOA cases, which did not make any comparison between REBOA and non-REBOA groups. Moreover, the results of these previous studies suggested high heterogeneity among the enrolled patients.

Therefore, it is necessary to incorporate REBOA-specific and time-varying covariates into the model. To overcome the limitations of previous studies, we propose a feasible prospective observational study to evaluate the risks and benefits of REBOA in

traumatic hemorrhagic shock patients. Our clinical question is to investigate whether there is a survival benefit of REBOA in traumatic patients with hemorrhagic shock. We then hypothesized that REBOA would result in better survival in comparison to a matched control group.

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.

## Methods and analysis

*Study setting of The Japanese Association for the Surgery of Trauma-Resuscitative Endovascular Balloon Occlusion of the Aorta (JAST-REBOA) study*

The JAST-REBOA is a prospective, observational, multi-institutional, matched-cohort study organized by the Clinical Trial Committee of the JAST.

*Patients enrollment and Eligibility criteria*

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. The present study will then enroll patients with torso hemorrhage requiring hemostasis (surgery and interventional

radiology) within 60 minutes of arrival. The establishment of a prospective registration system will encourage smooth enrollment of subject cases, and approximately 100 REBOA cases are likely to be registered every year.

Although head injury and multiple injuries are fatal exacerbation factors, these injuries are often accompanied by subdiaphragmatic injury. Thus, we will include patients with multiple injuries, regardless of head injury. In contrast, we will exclude patients who presented with cardiac arrest before initial presentation, regardless of spontaneous circulation return.

**The methodology of the study**

All data collected at each facility will be anonymized, wherein data will be collected and managed using the Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the Kameda Medical Center.[11 12] REDCap is a secure web-based software platform designed to support data capture for research studies, providing the following: 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads of common statistical packages; and 4) procedures for data integration and interoperability using external sources.

*Outcome measurements*

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**). Access-related complications will also include dissection, pseudoaneurysm (requiring repair surgery or endovascular therapy), puncture hematoma, retroperitoneal hematoma (requiring hemostasis procedure rather than compression), distal embolism, arteriovenous fistula, arterial stenosis (requiring thrombectomy, angioplasty, or surgical operation), arterial rupture, and finally, leg ischemia (requiring fasciotomy or lower limb amputation). Device-related complications will include catheter malposition (catheter indwelling in an unintended vessel), balloon migration (downstream movement of the balloon), and balloon rupture. The primary outcome of this study is in-hospital mortality.

**Statistical Analysis**

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.

Many variables which are to be used in this study will be collected in the resuscitation room during the initial trauma assessment. Therefore, many variables may have missing data, especially in severe cases, since excluding cases with missing data induces selection bias. Moreover, this study will query each facility about missing and erroneously entered values (inconsistencies between variables and statistical outliers) following the completion of registration. After the data sets in the analysis are fixed, missing values will be substituted for all variables using the multiple imputation method (multiple imputations by the chained equation, number of iterations: 20, number of data sets: 25).

*Primary analysis*

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. Baseline information would include demographics, past medical history,

mechanism of injury, prehospital treatment intervention, physiological parameters after hospital arrival, trauma severity score (Revised Trauma Score, Abbreviated Injury Scale, and Injury Severity Score), blood test findings, diagnostic imaging findings, and clusters from each facility using a logistic-regression generalized linear mixed-effect model. Following baseline information collection, propensity score matching for REBOA use and non-REBOA use groups will be performed.[13]

Furthermore, the absolute standardized difference in variables for propensity score estimation will be used to assess the match balance between the two groups, wherein an absolute standardized mean difference of <0.1 is generally considered an acceptable match balance. Intergroup comparisons will involve assessing risk differences (primary outcome), in-hospital mortality risk ratio, and survival time.

Moreover, the primary outcome will be analyzed using linear regression. Sensitivity analysis will be performed on three models in propensity score-matched subjects using propensity score matching on rolling entry interventions, inverse probability of treatment weighting, within-cluster matching, and a generalized estimating equation (GEE). Specifically, propensity score matching on rolling entry interventions using minutes from the decision on REBOA use can further eliminate immortal time bias.[14] Meanwhile, the inverse probability of treatment weighting will be used to compensate for the selection bias in cases with small overlapping propensity scores between the treatment and control groups, whereas within-cluster matching and GEE will consider facility differences in use

tendency, skill level, and outcome of REBOA cases. The significance level was set to $P < 0.05$ in the two-tailed test, and correction using multiple comparisons was not performed.

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.

*Secondary analysis*

Secondary endpoints will include hemorrhagic death, blood transfusion requirement within the first 24 hours, complications (systemic complications, device-related complications, and vascular access-related complications), ICU-free days, and ventilator-free days within 28 days after hospitalization.

*Subgroup analysis*

Based on the subgroup analysis in a previous study [4], we predefined the analysis of

interaction for REBOA use and primary outcome.

Sex (male vs female)

Age (<60 vs ≥60)

Type of trauma (blunt vs penetrating)

SBP on arrival (<80 mmHg vs ≥80 mmHg)

AIS chest (0-3 vs 4-5)

AIS abdomen (0-3 vs 4-5)

AIS pelvis and lower extremities (0-3 vs 4-5)

REBOA use per institute per year (≥2 vs <2)

Angioembolization (no vs yes)

*Other analysis*

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. On the other hand, analysis limited to REBOA vs. RT will be performed for the subgroup with cardiac arrest cases occurring within 60 minutes after arrival using the same aforementioned analysis method.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Ethical approval**

This observational study was registered with the UMIN Clinical Trials Registry (UMIN000035458), and it was approved by the Ethics Committee of each participating hospital (**Table 1**) and the Ethics Committee of the Japanese Association for the Surgery of Trauma (JAST).

Since this observational study will only record and collect clinical data in routine trauma care, no privacy invasion is associated with the subjects' participation, and individual consent will not be required. The patients' data will be anonymized and registered in the electric data capture system, and data obtained by the investigation shall not be used for purposes other than research. After withdrawal of consent, relevant data will be deleted, unless already published.

**Trial status**

The first edition of the trial protocol was approved on May 31, 2018, and the latest protocol was approved on July 9, 2020, at the Chiba University Graduate School of Medicine. The ethical committee of the Japanese Association for the Surgery of Trauma has approved this latest protocol. Exactly 19 hospitals participated in this study and were approved by the Institutional Ethical Committee. Patient enrollment was initiated on

October 1, 2019.

**Acknowledgment**

We would like to thank the Clinical Trial committee of the Japanese Association for the Surgery of Trauma.

*The Clinical Trial committee of the Japanese Association for the Surgery of Trauma*

Takashi Tagami (Committee chairman), Department of Emergency and Critical Care Medicine, Nippon Medical School Musashikosugi Hospital, Bunkyo-ku, Tokyo, Japan

Shigeki Kushimoto (Former chairman, Board director in charge), Division of Emergency and Critical Care Medicine, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

Kaori Ito, Department of Emergency Medicine, Teikyo University School of Medicine Itabashi-ku, Tokyo, Japan

Akira Endo, Trauma and Acute Critical Care Center, Tokyo Medical and Dental University Hospital of Medicine, Bunkyo-ku, Tokyo, Japan

Hiroyuki Ohbe, Division of Emergency and Critical Care Medicine, Tohoku University School of Medicine, Sendai, Miyagi, Japan

Takayuki Ogura, Tochigi Prefectural Emergency and Critical Care Center, Saiseikai Utsunomiya Hospital, Utsunomiya, Tochigi, Japan

Morihiro Katsura, Department of Surgery, Okinawa Chubu Hospital, Uruma, Okinawa, Japan

Daisuke Kudo, Division of Emergency and Critical Care Medicine, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

Yutaka Kondo, Department of Emergency and Critical Care Medicine, Juntendo University Urayasu Hospital, Urayasu, Chiba, Japan

Atsushi Shiraishi, Emergency and Trauma Center, Kameda Medica Center, Kamogawa, Chiba, Japan

Kazuhiko Sekine, Department of Emergency and Critical Care Medicine, Saiseikai Central Hospital, Minato-ku, Tokyo, Japan

Asuka Tsuchiya, Department of Emergency and Critical Care Medicine, Tokai University School of Medicine, Mito, Ibaraki, Japan

Shunichiro Nakao, Department of Traumatology and Acute Critical Medicine Osaka University Graduate School of Medicine, Suita, Osaka, Japan

Akiyoshi Hagiwara, Emergency Department, Niizashiki Chuo General Hospital, Niiza, Saitama, Japan

Mineji Hayakawa, "Department of Emergency Medicine, Hokkaido University Hospital, Sapporo, Hokkaido, Japan

Toru Hifumi, Department of Critical Care and Emergency Medicine, St. Luke's International Hospital, Chuo-ku, Tokyo, Japan

Yosuke Matsumura, Department of Intensive Care, Chiba Emergency Medical Center, Chiba, Chiba, Japan

Shokei Matsumoto, Department of Emergency and Critical Care, Saiseikai Yokohama-shi Tobu Hospital, Yokohama, Kanagawa, Japan

Hideto Yasuda, Department of Critical Care Medicine, Jichi Medical University, Saitama Medical Center, Omiya, Saitama, Japan

Kazuma Yamakawa, Department of Emergency Medicine, Osaka Medical University, Takatsuki, Osaka, Japan

Tetsuya Yumoto, Department of Emergency, Critical Care, and Disaster Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Okayama, Japan

Yuya Yoshimura, Department of Emergency and Critical Care Medicine, Hachinohe City Hospital, Hachinohe, Aomori, Japan



**Data statement**

The results will be disseminated to the participating hospitals and board-certified educational institutions of JAST, submitted to peer-reviewed journals for publication, and presented at congresses. Technical appendix, statistical code, and dataset will be available by the participating researchers after the publication of the main results.

## Author Contributions

YM, the principal investigator of the JAST-REBOA study, conceived research proposal. YM and AS designed the protocol and drafted the manuscript. AS drafted the statistical plan. SK supervised the planning of the JAST-REBOA in the Multi-institutional research committee of the Japanese Association for the Surgery of Trauma. All authors read and approved the final manuscript.

## Conflict of interest statement

Yosuke Matsumura was a Clinical Advisory Board Member of Tokai Medical Products (2015-2017).

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## Patient consent for publication

Not required.

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**Table 1** The patients' data collected in the present study

| | |
|---|---|
| Demographics | Age<br>Sex |
| Mechanism of injury | Driver of motor vehicle<br>Motorcycle<br>Bicycle<br>Pedestrian<br>Fall<br>Tumble (Fall on the ground)<br>Others |
| Vital signs on arrival and at the decision of hemostasis | Respiratory rate<br>$SpO_2$<br>Systolic blood pressure<br>Heart rate<br>Glasgow coma scale<br>Body temperature |
| Past medical history | Charlson comorbidity index [15] |
| Trauma severity | Abbreviated Injury Scale<br>Injury Severity Score |
| Blood examination | Hemoglobin (g/dL)<br>Hematocrit (%)<br>Platelet ($10^3$/μL)<br>PT-INR<br>APTT (sec)<br>Fibrinogen (mg/dL)<br>FDP (μg/mL)<br>D-dimer (μg/mL)<br>pH<br>$PaO_2$<br>$PaCO_2$<br>BE (mEq/L)<br>Lactate (mmol/L) |
| Diagnostic imaging | FAST (positive or negative)<br>Chest X-ray (Chest injury requiring hemostasis)<br>Pelvis X-ray (Pelvic fracture requiring hemostasis) |
| The time course of trauma care | Injury<br>Arrival<br>Thoracoabdominal CT |

| | |
|---|---|
| | Decision of hemostasis (Baseline)<br>Arterial access placed<br>Decision of REBOA<br>Inflation of REBOA<br>Deflation of REBOA<br>Decision of transfusion<br>Start of definitive hemostasis<br>ICU admission |
| The site of hemostasis | Chest, Abdomen, Pelvis, Retroperitoneum |
| Hemostasis method | Surgery or interventional radiology |
| Blood transfusion requirement within the first 24 hours | Packed red blood cell<br>Fresh frozen plasma<br>Platelet<br>Other blood products |
| Arterial access information | Location<br>Anatomical site (R/L, Femoral/ Brachial)<br>puncture method (Blind, US-guided, Cutdown)<br>Sheath size |
| Initial aortic occlusion method | Resuscitative thoracotomy, REBOA, None |
| Hospital course | Days on mechanical ventilation<br>ICU discharge<br>In-hospital mortality<br>Cause of death |
| Complications | Device-related complications<br>Access-related complications<br>Systemic complications |

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**Protocol**

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**Running head**: Matching study to assess REBOA in torso trauma

**Authors:**

Yosuke Matsumura, MD, PhD[1, 2], Atsushi Shiraishi, MD, PhD[3], Shigeki Kushimoto MD, PhD[4]

**Affiliation**

1. Department of Emergency and Critical Care Medicine, Chiba University Graduate School of Medicine
2. Department of Intensive Care, Chiba Emergency Medical Center
3. Emergency and Trauma Center, Kameda Medical Center
4. Division of Emergency and Critical Care Medicine, Tohoku University School of Medicine

**Corresponding author:**

Yosuke Matsumura

Department of Intensive Care, Chiba Emergency Medical Center, 3-32-1 Isobe, Mihama, Chiba, 261-0012, Japan

Phone: +81-43-279-2211

E-mail: yousuke.jpn4035@gmail.com; matsumuray@chiba-u.jp

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**Keywords**: trauma management, vascular surgery, interventional radiology, resuscitative endovascular balloon occlusion of the aorta, REBOA

## Abstract

*Introduction*

Resuscitative endovascular balloon occlusion of the aorta (REBOA) has been used as a bridge to definitive bleeding control of subdiaphragmatic injury. Since previous observational studies have poorly adjusted for confounding factors, it is necessary to incorporate REBOA-specific and time-varying covariates in the model. We hypothesized that REBOA improves the survival of hemodynamically unstable torso trauma patients after comparing the REBOA group with a matched control group (non-REBOA group).

*Methods and analysis*

The Japanese Association for the Surgery of Trauma-Resuscitative Endovascular Balloon Occlusion of the Aorta study is a prospective multicenter matched-cohort study organized by the Clinical Trial Committee of the Japanese Association for the Surgery of Trauma. 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. After the data set is fixed, the missing values for all variables will be imputed using the multiple imputation technique. In the primary analysis, propensity scores for the probability of REBOA decision (regardless of the actual REBOA deployment) will be calculated from the baseline information using a logistic regression generalized linear mixed-effect model, which will be performed for both the REBOA use and non-REBOA use groups.

*Ethics and dissemination*

This study was approved by the Ethics Committee of each participating hospital. The results will be disseminated to the participating hospitals, submitted to peer-reviewed journals for publication, and presented at congresses.

**Trial registration number:** UMIN Clinical Trials Registry; UMIN000035458. Registered in January 6, 2019

## Article summary

This prospective multicenter-matched cohort study compares the REBOA and non-REBOA groups using a research protocol minimizing biases.

*Strengths and limitations of this study*

- 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.
- Adjusting with time-varying covariates can minimize the survivorship biases (resuscitation time bias) and physiological changes in the patients.
- The multiple imputation method can substitute missing or unmeasured values and minimizes selection biases.
- Within-cluster matching may allow the adjustment of unobserved cluster-level variables to minimize the institutional biases.
- The significant heterogeneity of the trauma patients might not be able to equalize the groups.

## Introduction

Hemorrhagic shock is the leading cause of preventable trauma-related death.[1] Hence, immediate surgical and/or endovascular intervention is required for definitive control of non-compressible torso hemorrhages involving the thorax, abdomen, or pelvis. 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. The proximal aortic pressure from this injury can be elevated by augmenting the afterload, thus increasing the risk of ischemic complications in the distal organ or lower extremities.

Observational studies using a multicenter database from Japan (Japan Trauma Data Bank, JTDB)[3,4] and the United States (Trauma Quality Improvement Program, TQIP)[5] suggested a possible negative effect of REBOA on the survival outcome. By contrast, another study using the JTDB recently reported better survival in patients undergoing REBOA,[6] which is contradictory to the results of previous studies utilizing the same Japanese database. Although these studies analyzed a considerable number of patients from multiple centers, the results might be biased due to the lack of REBOA-specific information in the dataset.

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] Additionally, the ABOTrauma registry, a Swedish-based international registry, presented the potential benefits of partial or intermittent REBOA compared with those of complete REBOA.[8] The Diagnostic and Interventional Radiology in Emergency, Critical Care and Trauma (DIRECT)-Intraaortic Balloon Occlusion (IABO) registry, a Japanese multicenter retrospective observational database, has also shown fewer access-related complications associated with the use of a smaller profile REBOA device.[9] These registries included detailed REBOA-related information but did not have an appropriate control group (non-REBOA group). Thus, clinical questions comparing "REBOA and RT," "partial/intermittent REBOA and complete REBOA," and "small and large profile" do not need to be clarified.

Notably, these previous studies have also poorly adjusted their confounding factors. Although the JTDB and TQIP analyses compared the REBOA group with a matched cohort (non-REBOA group), the database did not include REBOA-specific variables or time-varying covariates. By contrast, the AAST-AORTA study compared the REBOA group with the RT group, which is not the proper control group for comparison. Even the DIRECT-IABO and ABOTrauma registry only included REBOA cases and did not make any comparison between the REBOA and non-REBOA groups. Moreover, the results of these previous studies suggested high heterogeneity among the enrolled patients.

Therefore, REBOA-specific and time-varying covariates must be incorporated

in the model. To overcome the limitations of previous studies, a feasible prospective observational study should be conducted to evaluate the risks and benefits of REBOA in traumatic hemorrhagic shock patients. Our clinical question aims to investigate whether REBOA has survival benefits in traumatic patients with hemorrhagic shock. We then hypothesized that REBOA would improve the survival of traumatic patients with hemorrhagic shock compared with that of a matched control group.

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.

## Methods and analysis

### *Study setting of the Japanese Association for the Surgery of Trauma-Resuscitative Endovascular Balloon Occlusion of the Aorta study*

The Japanese Association for the Surgery of Trauma-Resuscitative Endovascular Balloon Occlusion of the Aorta (JAST-REBOA) study is a prospective, observational, multi-institutional, matched-cohort study organized by the Clinical Trial Committee of the JAST.

### *Patient enrollment and eligibility criteria*

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. This study will then enroll patients with truncal hemorrhage requiring surgical or endovascular bleeding control within 60 min upon arrival at the center. 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.

Although head injury and multiple injuries are fatal exacerbation factors, these injuries are often accompanied by subdiaphragmatic injury. Thus, we will include patients with multiple injuries, regardless of the presence or absence of head injury. We will enroll patients aged 16 years and older based on the previous studies that included children.[10 11] 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.

**The methodology of the study**

All data collected in each facility will be anonymized; the data will be collected and managed using the Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the Kameda Medical Center.[12 13] REDCap is a secure web-based software

platform designed to collect data for studies; it 1) provides an intuitive interface for validated data capture, 2) has audit trails for tracking data manipulation and export procedures, 3) has automated export procedures for seamless data downloads of common statistical packages, and 4) has procedures for data integration and interoperability using external sources. 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.

*Outcome measurements*

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**). 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), distal embolism, arteriovenous fistula, arterial stenosis (requiring thrombectomy, angioplasty, or surgical operation), arterial rupture, and leg ischemia (requiring fasciotomy or lower limb amputation). The device-related complications will

include catheter malposition (catheter indwelling in an unintended vessel), balloon migration (downstream movement of the balloon), and balloon rupture. The primary outcome of this study will be in-hospital mortality.

**Statistical analyses**

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.

Data of several variables that will be used in this study will be collected in the resuscitation room during the initial trauma assessment. Therefore, many variables might have missing or incorrect data, especially in patients with severe cases, since excluding those with missing data induces selection bias. Moreover, this study will query each facility about missing and erroneously entered values following the completion of registration. This data cleaning process involves treatment of the missing values and outliers. Missing values include all missing values for all study variables within the observation period. The outliers of a nominal variable are any contradiction between two or more nominal variables (e.g., treatment performed after death). The outliers of numerical variables are statistically detected using robust regression analysis. A datasheet containing the detected missing values and outliers is returned to the participating sites for re-input. This process will be repeated twice. After the data set in the analysis is fixed, the missing values will be substituted for all variables using the multiple imputation method (multiple imputations by the chained equation, number of iterations: 20, number of data sets: 25).

*Primary analysis*

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. The baseline information would include demographics, past medical history, mechanism of injury, prehospital treatment intervention, physiological parameters after hospital arrival, trauma severity score (Revised Trauma Score, Abbreviated Injury Scale, and Injury Severity Score), blood test findings, diagnostic imaging findings, and clusters from each facility using a logistic-regression generalized linear mixed-effect model. After obtaining the baseline information, propensity score matching for the REBOA use and non-REBOA use groups will be performed.[15]

Furthermore, the absolute standardized difference in variables for propensity score estimation will be used to assess the match balance between the two groups; an absolute standardized mean difference of <0.1 is generally considered an acceptable match balance. Intergroup comparisons will involve assessment of the risk differences (primary outcome), in-hospital mortality risk ratio, and survival time.

Moreover, the primary outcome will be analyzed using linear regression. Sensitivity analysis of three models will be performed in propensity score-matched participants using propensity score matching on rolling entry interventions, inverse probability of treatment weighting, within-cluster matching, and a generalized estimating equation (GEE). Specifically, propensity score matching on rolling entry interventions using minutes from the decision to perform REBOA can further eliminate immortal time bias.[16] 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. Meanwhile, the inverse probability of treatment weighting will be used to compensate for the selection bias in cases where the propensity scores are overlapping between the treatment and control groups, while within-cluster matching and GEE will be used to determine the facility differences in terms of use tendency, skill level, and outcome of REBOA cases. The significance level was set to $P<0.05$ in the two-tailed test, and correction using multiple comparisons was not performed.

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.

*Secondary analysis*

Secondary endpoints will include hemorrhagic death, blood transfusion requirement

within the first 24 h, complications (systemic complications, device-related complications, and vascular access-related complications), intensive care unit-free days, and ventilator-free days within 28 days after hospitalization.

*Subgroup analysis*

Based on the subgroup analysis in a previous study,[4] the analysis of interaction for REBOA use and primary outcome were predefined.

Sex (male vs female)

Age (<60 vs ≥60)

Type of trauma (blunt vs penetrating)

Systolic blood pressure on arrival (<80 mmHg vs ≥80 mmHg)

Abbreviated Injury Scale (AIS) chest (0–3 vs 4–5)

AIS abdomen (0–3 vs 4–5)

AIS pelvis and lower extremities (0–3 vs 4–5)

REBOA use per institute per year (≥2 vs <2)

Angioembolization (no vs yes)

*Other analysis*

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. In contrast, analysis comparing REBOA and RT will be performed in the subgroup of patients who experienced cardiac arrest within 60 min after arrival at the emergency room using the same aforementioned analysis method.

## Ethics and dissemination

*Ethical approval and consent to participate*

This clinical trial will be conducted according to the principles of the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Ministry of Health, Labour and Welfare of Japan and Japanese Ministry of Education, Culture, Sports, Science and Technology. This observational study was registered in the UMIN Clinical Trials Registry (UMIN000035458) and was approved by the Ethics Committee of each participating hospital and Ethics Committee of the JAST (2018-1).

Since this observational study will only record and collect clinical data during routine trauma care, patient's privacy invasion will not be breached during their participation in the study, and individual consent will not be required. The patients' data will be anonymized and registered in the electric data capture system, and the data obtained during the investigation will not be used for purposes other than research. After withdrawal of consent, relevant data will be deleted, unless already published.

*Dissemination*

The results of this study will be submitted to peer-reviewed journals for publication and presented at congresses. The dataset of this study will be disseminated to the participating hospitals and board-certified educational institutions of the JAST. Technical appendix, statistical code, and dataset will be available from the participating researchers after the publication of the main results.

*Patient and public involvement*

The study patients and public were not involved in the study design, conduct, reporting, or dissemination plans of this study.

**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.

**Trial status**

The first edition of the trial protocol was approved on May 31, 2018, and the latest protocol was approved on July 9, 2020, at the Chiba University Graduate School of Medicine. The ethical committee of the Japanese Association for the Surgery of Trauma has approved this latest protocol. Exactly 19 hospitals participated in this study and were approved by the Institutional Ethical Committee. Patient enrollment was initiated on October 1, 2019. This study was initiated in May 31, 2018 (approved at the primary institute) and was planned to end in March 31, 2024.

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Department of Emergency Medicine, Osaka Medical University, Takatsuki, Osaka, Japan; Tetsuya Yumoto, Department of Emergency, Critical Care, and Disaster Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Okayama, Japan; and Yuya Yoshimura, Department of Emergency and Critical Care Medicine, Hachinohe City Hospital, Hachinohe, Aomori, Japan

**Authors' contributions**

YM, the principal investigator of the JAST-REBOA study, conceived the research proposal. YM and AS designed the protocol and drafted the manuscript. AS drafted the statistical plan. SK supervised the planning of the JAST-REBOA in the multi-institutional research committee of the Japanese Association for the Surgery of Trauma. All authors read and approved the final manuscript.

**Conflict of interest**

Yosuke Matsumura was a Clinical Advisory Board Member of Tokai Medical Products (2015-2017).

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## Patient consent for publication

Not required.

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**Table 1** Patients' data collected in this study

| | |
|---|---|
| Demographics | Age<br>Sex |
| Mechanism of injury | Driver of motor vehicle<br>Motorcycle<br>Bicycle<br>Pedestrian<br>Fall<br>Tumble (fall on the ground)<br>Others |
| Vital signs on arrival and at the decision of bleeding control | Respiratory rate<br>$SpO_2$<br>Systolic blood pressure<br>Heart rate<br>Glasgow coma scale<br>Body temperature |
| Past medical history | Charlson comorbidity index [17] |
| Trauma severity | Abbreviated Injury Scale<br>Injury Severity Score |
| Blood examination | Hemoglobin (g/dL)<br>Hematocrit (%)<br>Platelet ($10^3$/μL)<br>PT-INR<br>APTT (s)<br>Fibrinogen (mg/dL)<br>FDP (μg/mL)<br>D-dimer (μg/mL)<br>pH<br>$PaO_2$<br>$PaCO_2$<br>BE (mEq/L)<br>Lactate (mmol/L) |
| Diagnostic imaging | FAST (positive or negative)<br>Chest X-ray (Chest injury requiring bleeding control)<br>Pelvis X-ray (Pelvic fracture requiring bleeding control) |
| The time course of trauma care | Injury<br>Arrival<br>Thoracoabdominal CT |

| | |
|---|---|
| | Decision of hemostasis (baseline)<br>Arterial access placed<br>Decision of REBOA<br>Inflation of REBOA<br>Deflation of REBOA<br>Decision of transfusion<br>Start of definitive hemostasis<br>ICU admission |
| The site of hemostasis | Chest, abdomen, pelvis, retroperitoneum |
| Hemostasis method | Surgery or interventional radiology |
| Blood transfusion requirement within the first 24 h | Packed red blood cell<br>Fresh frozen plasma<br>Platelet<br>Other blood products |
| Arterial access information | Location<br>Anatomical site (R/L, femoral/brachial)<br>puncture method (blind, US-guided, cutdown)<br>Sheath size |
| Initial aortic occlusion method | Resuscitative thoracotomy, REBOA, none |
| Hospital course | Days on mechanical ventilation<br>ICU discharge<br>In-hospital mortality<br>Cause of death |
| Complications | Device-related complications<br>Access-related complications<br>Systemic complications |

1

**The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.**

| | Item No. | STROBE items | Location in manuscript where items are reported | RECORD items | Location in manuscript where items are reported |
|---|---|---|---|---|---|
| **Title and abstract** | | | | | |
| | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found | (a) P1L3<br>(b) P2 | RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.<br><br>RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.<br><br>RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | 1.1: P1L3<br>1.2: n/a<br>1.3: n.a |
| **Introduction** | | | | | |
| Background rationale | 2 | Explain the scientific background and rationale for the investigation being reported | P6L2 | | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | P8L7 | | |
| **Methods** | | | | | |
| Study Design | 4 | Present key elements of study design early in the paper | P8L13 | | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | P8L13 | | |

| | | | | | |
|---|---|---|---|---|---|
| Participants | 6 | *(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants<br><br>*(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study* - For matched studies, give matching criteria and the number of controls per case | (a) P8L20<br>(b) P12L18 | RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.<br><br>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.<br><br>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. | 6.1 P8L20<br><br>6.2 P8L20<br><br>6.3 n/a |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | P10L9 | RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. | P24 (Table1) |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement).<br>Describe comparability of assessment methods if there is more than one group | P10L9 | | |

| | | | | | |
|---|---|---|---|---|---|
| Bias | 9 | Describe any efforts to address potential sources of bias | P11L13 | | |
| Study size | 10 | Explain how the study size was arrived at | P14L9 | | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | P11L5 | | |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) *Cohort study* - If applicable, explain how loss to follow-up was addressed<br>*Case-control study* - If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses | (a)P12L18, P14L19, P15L18<br>(b)P15L5<br>(c)P12L2<br>(d)n/a<br>(e)P13L14 | | |
| Data access and cleaning methods | | .. | | RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. | 12.1 P17L2<br>12.2 P12L7 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | RECORD 12.2: Authors should provide information on the data cleaning methods used in the study. | |
| Linkage | | .. | | RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. | n/a |
| **Results** | | | | | |
| Participants | 13 | (a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)<br>(b) Give reasons for non-participation at each stage.<br>(c) Consider use of a flow diagram | n/a | RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram. | n/a |
| Descriptive data | 14 | (a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate the number of participants with missing data for each variable of interest<br>(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount) | n/a | | |
| Outcome data | 15 | *Cohort study* - Report numbers of outcome events or summary measures over time<br>*Case-control study* - Report numbers in each exposure | n/a | | |

| | | | | | |
|---|---|---|---|---|---|
| | | category, or summary measures of exposure<br>*Cross-sectional study* - Report numbers of outcome events or summary measures | | | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | n/a | | |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | n/a | | |
| **Discussion** | | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | n/a | | |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | P17L13 | RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported. | n/a |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, | n/a | | |

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| | | limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | | | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | n/a | | |
| **Other Information** | | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | P20L18 | | |
| Accessibility of protocol, raw data, and programming code | | .. | | RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. | n/a |

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.