Survival of severe blunt trauma patients treated with resuscitative endovascular balloon occlusion of the aorta compared with propensity score-adjusted untreated patients

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BACKGROUND: Despite a growing call for use of resuscitative endovascular balloon occlusion of the aorta (REBOA) for critically uncontrolled hemorrhagic shock, there is limited evidence of treatment efficacy. We compared the mortality between patients who received a REBOA with those who did not, adjusting for the likelihood of treatment and injury severity, to measure efficacy.

METHODS: We analyzed observational prospective data from the Japan Trauma Data Bank (2004–2011) to compare the mortality between adult patients who received a REBOA with those who did not. To adjust for potential treatment bias, we calculated the likelihood of REBOA treatment via a propensity score (PS) using available pretreatment variables (vital signs, age, sex, as well as anatomic and physiologic injury severity) and matched treated patients to up to five similar PS untreated patients. We compared survival to discharge between treated and untreated groups using conditional logistic regression and Cox proportional hazards regression.

RESULTS: Of 45,153 patients who met inclusion, 452 patients (1.0%) received REBOA placement. These patients were seriously injured (median Injury Severity Score [ISS], 35) and had high mortality (76%). Patients who did not receive a REBOA had significantly lower injury severity (median ISS, 13; $p < 0.0001$) and lower mortality (16%). After matching REBOA patients with controls with similar PSs for treatment, the crude conditional odds ratio of survival by REBOA treatment was 0.30 (95% confidence interval, 0.23–0.40).

CONCLUSION: REBOA treatment is associated with higher mortality compared with similarly ill trauma patients who did not receive a REBOA. The higher observed mortality among REBOA-treated patients may signal "last ditch" efforts for severity not otherwise identified in the trauma registry. (*J Trauma Acute Care Surg*. 2015;78: 721–728. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Epidemiologic study, level III; therapeutic study, level IV.

KEY WORDS: Balloon occlusion; resuscitation/method; trauma centers; blunt trauma; aortic diseases/therapy.

Trauma is among the leading causes of death in the world. Almost 1 of 10 deaths in the world is caused by injury. The rates are even higher in developing countries.[1] Despite the recent technologic advances in medicine and trauma care, the mortality from the blunt thoracoabdominal injury remains high, with hemorrhage as the leading cause of death.[2]

Patients who are most critically ill with blunt trauma need emergent definitive care such as surgery or interventional angiography. However, these patients are often too unstable to go to the operative or angiography suite even after aggressive resuscitation such as massive transfusion.

One rational approach is early stabilization of the patient's bleeding in the emergency department. Iatrogenic aortic occlusion is a traditional way to control life-threatening bleeding. Two major techniques have been invented to occlude the aorta. Resuscitative thoracotomy with aortic clamping was first reported in 1976 for trauma.[3] It has been widely used in many countries including the United States and has been documented in trauma treatment guidelines.[4] The other method uses resuscitative endovascular balloon occlusion of the aorta (REBOA)[5] or sometimes called intra-aortic balloon occlusion to control hemorrhage distal to the occlusion.

Reported use of REBOA to stabilize patients with hemorrhagic shock from severe trauma cases exists since 1954.[6] A REBOA is placed in five steps.[5] The first step is to obtain femoral arterial access using a Seldinger technique. This maneuver can be performed percutaneously with "blind" technique but also by using ultrasound or cut-down approach. Balloon insertion and positioning in the aorta is the next step. The positioning of the balloon is guided by the location of the injuries and must be proximal to the injuries. Radiologic imaging (x-ray or fluoroscopy) is typically used to confirm the positioning of the balloon. The third step is to inflate the balloon with saline according to manufacturer guidelines. Increased central aortic pressure and diminished distal pulses are usually observed if the positioning and inflation of the balloon are adequately performed. Once definitive hemorrhagic control is achieved via surgery or intravascular embolization, the balloon can be gradually deflated in the fourth step. The final and fifth step is sheath removal. REBOA placement does not usually require advanced surgical skill. Although REBOA is less invasive and may be technically easier than resuscitative thoracotomy with aortic clamping for nontrauma surgeons, REBOA has not been used widely in most countries including the United States.

Although multiple recently published clinical and animal studies regarding REBOA use[7–11] for critically uncontrolled hemorrhagic shock have raised interest, there is still limited clinical evidence of REBOA treatment efficacy, and the available evidence is limited to case series, small sample size studies, and animal data.

To address these limitations, we analyzed prospectively collected data from the Japan Trauma Data Bank (JTDB) to compare the mortality between patients who received a REBOA to control life-threatening hemorrhage with those who did not receive a REBOA, adjusting for the likelihood of treatment and injury severity. We hypothesized that placement of a REBOA device would improve patient survival.

PATIENTS AND METHODS

Study Design and Participants

We analyzed observational prospective data from the JTDB to compare the mortality between patients who received a REBOA device with those who did not among a cohort of critically ill adult blunt trauma patients. The JTDB is a Japan-wide trauma registry, established in 2003, by the Japanese Association for the Surgery of Trauma and the Japanese Association for Acute Medicine, which consists of data from major emergency departments/trauma centers in Japan. Since the JTDB was established, multiple studies have used the JTDB data for a variety of reasons, for example, to develop a new trauma score and to measure the impact of preexisting medical conditions on in hospital mortality from injuries.[12–19] At the time of our analysis, 196 major emergency departments/trauma centers contributed to the registry. To be certified as a trauma-training program, the hospital has to participate in the JTDB. Japanese Joint

Commission also requires tertiary medical centers to participate in this trauma registry. Therefore, most major trauma centers currently contribute to JTDB. We restricted our analysis to patients 18 years and older who received care for blunt trauma of any body region at a facility where at least one REBOA device had been placed. We excluded patients with missing survival data. We obtained permission from the JTDB to use the data. The ethics committee of Kenwakai Ohtemachi Hospital and the University of New Mexico Health Sciences Center approved the study design.

Study Setting

In Japan, REBOA is usually placed by emergency physicians or trauma surgeons through the femoral artery with or without fluoroscopy in the setting of uncontrolled hemorrhagic shock. In contrast with the United States, where REBOA is not commonly used, REBOA is recognized as a standard procedure in Japan, and emergency physician competency in REBOA placement is required for board certification by the emergency physician with the Japanese Association for Acute Medicine.[20] Therefore, REBOA devices are stocked in nearly all tertiary emergency centers and many secondary emergency centers in Japan. Many secondary hospitals stock REBOA in the emergency department, while others maintain stock in the angiography or operative suite.

In Japan, trauma is somewhat less common, and trauma surgeons are not typically present in the hospital 24/7. As a result, delays to definitive care are more common in Japan than in the United States, and temporizing measures to gain hemorrhage control are often needed.

Data Collection

The JTDB has set up standardized data elements to capture clinical characteristics and outcome data for trauma patients admitted to the hospital. Data were collected prospectively from the participating institutions via a secure Web-based interface. Data were usually entered by the treating physicians who are typically familiar with Abbreviated Injury Scale (AIS) scoring[21,22] or who attended the AIS coding course operated by Japan Trauma Care and Research. Available data included age, sex, mechanism of injury, vital signs recorded by emergency medical service (EMS) and upon arrival, treatments, Injury Severity Score (ISS),[23,24] type and time of operative intervention, intensive care unit stay, and survival status at discharge. A series of times including call received by EMS, EMS arrival on the scene, arrival at the hospital, physician's first contact, first transfusion, computed tomography, and definitive care (i.e., surgery or interventional angiography) were also recorded. However, the timings of emergency procedures performed in the emergency department, including REBOA, are not recorded.

Outcome Measures

Our main outcome measure was survival to discharge.

Statistical Analysis

To compare baseline characteristics of the REBOA-treated and REBOA-untreated groups, we used χ^2 tests for categorical data and Wilcoxon rank-sum tests for continuous data.

To test our principal outcome, we compared survival differences in REBOA-treated and REBOA-untreated groups. Since decisions to place a REBOA depended solely on the clinical decision making of the treating physician, rather than by random treatment allocation (such as would be the case in a clinical trial), we had to adjust for the likelihood of treatment to account for unobserved treatment bias. One well accepted methodology to adjust for nonrandom treatment allocation in observational studies is propensity score (PS) matching.[25] This technique uses pretreatment characteristics to predict the likelihood of treatment. Subjects who did receive the treatment are matched to subjects who did not receive the treatment but whose PS (likelihood of treatment) were very similar. Once treated subjects are matched to similar untreated subjects, survival differences can be observed. Adjustment for confounding variables can still be considered during the analysis because residual confounding may persist.

In our analysis, we calculated the likelihood of REBOA device placement (PS) using unconditional logistic regression. We used available pretreatment variables including age, sex, calendar year, Revised Trauma Score (RTS), mechanism of injury (e.g., traffic crash, fall), maximum AIS for each of the nine body regions, and treating facility to calculate the PS.

Once the PS was calculated, we matched patients who received a REBOA to up to five patients who did not receive a REBOA but who had similar PS (±0.1%) using a greedy matching algorithm.[26] Most cases had five controls (n = 214, 61%). The remaining cases had fewer controls (4 controls, n = 18 [5%]; 3 controls, n = 33 [9%]; 2 controls, n = 27 [8%]; 1 control, n = 60 [17%]). Our PS-matched data set included 351 patients who had a REBOA placed and 1,456 propensity-matched patients who did not have a REBOA placed. We then used conditional logistic regression to calculate the odds of survival in patients who received a REBOA with those who did not while accounting for the matched design effect.

Among the patients who had a REBOA device placed, we compared patients who survived with those who did not survive to identify potential characteristics associated with survival.

We also performed several subgroup analyses. We restricted the analysis to clinical scenarios which might be physiologically optimal for REBOA treatment, such as isolated serious pelvic fractures, lower extremity injuries, and abdominal injury. We defined isolated serious pelvis or lower extremity injury as patients who had maximum AIS of 3 or greater in Region 8 (lower extremity and pelvis) and maximum AIS of 2 or lower in all other regions. We also performed similar analysis for isolated serious abdominal injury. We defined the isolated abdominal injury as patients who had maximum AIS of 3 or greater in Region 5 (abdomen) and maximum AIS of 2 or lower in all other regions.

We also compared REBOA-treated and REBOA-untreated PS-adjusted groups using a failure-time analysis, including Kaplan-Meier plots of survival over time. We used the log-rank method to compare survival curves. Finally, we used a Cox proportional hazards modeling approach to compare survival between the treated and untreated matched PS groups while simultaneously adjusting for additional confounders such as age, RTS, and ISS. This analysis adjusted for the clustering imposed by the matching of PS between treated and untreated patients. We used SAS statistical software (SAS version 9.3, The SAS Institute, Cary, NC) for analysis and the R statistical language[27] for graphing.

RESULTS

Study Participant Selection and Patient Demographics

The JTDB registry included 94,664 patients between 2004 and 2011. Figure 1 shows the flow of patient selection and the reasons and numbers of patients excluded. Of the remaining 45,153 patients, 452 patients (1.0%) received REBOA placement. Table 1 details the clinical characteristics of patients who received a REBOA device compared with those who did not. Patients who received a REBOA were mostly men (67%), had a median ISS of 35 (interquartile range [IQR], 25–45), and had a median age of 54 years (IQR, 32–69). The overall mortality for REBOA patients was 76%.

Patients who did not receive a REBOA were also mostly men (68%) but had significantly lower injury severity (median ISS, 13; IQR, 9–22; $p < 0.0001$) and were significantly older (median age, 60 years; IQR, 39–76; $p < 0.0001$) compared with the REBOA-treated group. The overall mortality for patients who did not have a REBOA placed was 16%.

Table 2 compares patients who survived after REBOA device placement compared with patients who did not survive despite REBOA placement. In the REBOA group, the patients who survived had significantly higher Glasgow Coma Scale (GCS) compared with those who did not survive (mean GCS, 11.6 vs. 7.2; $p < 0.0001$). The patients who survived also had significantly higher systolic blood pressure measurements upon hospital arrival compared with those who did not survive (mean, 89.7 mm Hg vs. 67.5 mm Hg; $p < 0.0001$). There were also statistically significant differences in sex, ISS, RTS, and Trauma and Injury Severity Score (TRISS) calculated probability of survival. There were no statistically significant differences in age, prehospital systolic blood pressure, and prehospital heart rate on arrival at hospital.

Propensity-Matched Group

Since patients who received a REBOA were considerably sicker than those who did not receive a REBOA, we used the PS to match patients who received a REBOA to patients who did not receive a REBOA but who had a similar likelihood of receiving one as measured by the PS. Incomplete pretreatment data (usually baseline vital signs) necessary to calculate the PS resulted in an additional 101 exclusions, resulting in a total number of REBOA-treated patients of 351.

The demographic characteristics of the propensity-matched groups are summarized in Table 3. Both groups had similar characteristics in terms of age, sex, and ISS. The probability of survival in the REBOA-treated group was significantly lower than the survival in the untreated group (26.2% vs. 51.3%, $p < 0.0001$).

The crude conditional odds ratio (OR) for survival by REBOA treatment was 0.30 (95% confidence interval [CI], 0.23–0.40). This OR means patients who received REBOA were three times more likely to die than patients with similar severity of injury but did not receive REBOA.

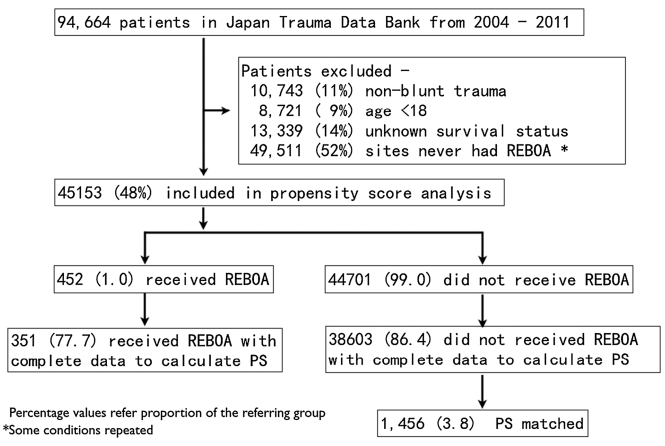

Figure 1. Study participant selection.

Isolated Trauma Subgroup Analysis

We looked at survival differences by REBOA treatment when patients had isolated serious injury in the abdominal or the pelvis/lower extremity regions (isolated injury defined as AIS score ≥ 3 in the indicated region with AIS scores < 3 in all other regions). In both of these cases, subgroup analyses restricted to abdominal injury (OR for survival, 0.32; 95% CI, 0.08–1.23) or isolated serious pelvis/lower extremity injury (OR, 0.27; 95% CI, 0.03–2.7) did not show any significant survival benefit from REBOA placement.

Survival Analysis

Figure 2 shows the overall Kaplan-Meier survival curves for the REBOA-treated and the PS-matched control group. Survival was significantly lower in the treated group ($p < 0.0001$). In a Cox proportional hazards model with only REBOA treatment in the model, the REBOA-treated group survived half as often as the PS-matched control group (hazard ratio, 0.52; 95% CI, 0.45–0.60). After adjustment for additional covariates, including age, RTS, ISS, and the interaction of REBOA and RTS, survival in the REBOA group was even lower (hazard ratio, 0.35; 95% CI, 0.30–0.42; at mean RTS value, 4.73).

DISCUSSION

REBOA treatment is associated with higher mortality compared with similarly ill blunt trauma patients who did not receive a REBOA. Adjustment for residual confounding in illness severity (RTS and ISS) further reduced the efficacy of REBOA.

Unlike previous clinical studies, we used large prospectively collected to obtain enough number of patients to measure the efficacy of REBOA. We believe that our study is the first clinical study to compare the mortality between patients who received a REBOA with those who did not, adjusting for the likelihood of treatment and injury severity. The observed association between the REBOA group and non-REBOA group was significant and persisted despite multiple adjustment of covariables.

The results of our study differ from previous studies about REBOA use. REBOA was first reported to control hemorrhage including severe trauma in the 1950s.[6] Since then, REBOA has been used in multiple settings including massive gastrointestinal bleeding,[28] gynecologic emergencies,[29] and ruptured aortic aneurysms.[30,31] Recent clinical studies suggest a potential benefit

TABLE 1. Characteristics of Patients Before Adjustment for Likelihood of REBOA Treatment

	Total		REBOA+		REBOA−		
	n	(%)	n	(%)	n	(%)	p*
Overall	45,153	—	452	(1.0)	44,701	(99.0)	
Survival to discharge	37,849	(83.8)	109	(24.1)	37,740	(84.4)	<0.0001
Male	30,459	(67.5)	301	(66.6)	30,158	(67.5)	0.6914
Female	14,690	(32.5)	151	(33.4)	14,539	(32.5)	
Mechanism of injury							
Traffic related	21,239	(47.0)	272	(60.2)	20,967	(46.9)	<0.0001
Fall	18,192	(40.3)	141	(31.2)	18,051	(40.4)	<0.0001
Industrial	586	(1.3)	2	(0.4)	584	(1.3)	0.1064
Falling object	456	(1.0)	3	(0.7)	453	(1.0)	0.4594
Crush	772	(1.7)	9	(2.0)	763	(1.7)	0.6428
Train	338	(0.7)	9	(2.0)	329	(0.7)	0.0021
Sports	364	(0.8)	0	(0.0)	364	(0.8)	0.0541
Other blunt	1,267	(2.8)	8	(1.8)	1,259	(2.8)	0.1801
Unknown	1,939	(4.3)	8	(1.8)	1,931	(4.3)	0.0078
ISS							
Mean (SD)	16.9	(12.8)	35.6	(15.5)	16.8	(12.6)	<0.0001
Median	13		35		13		
IQR	9–22		25–45		9–22		
n	64,333		441		63,892		
RTS							
Mean (SD)	6.89	(2.0)	4.57	(2.6)	6.90	(2.0)	<0.0001
Median	7.84		5.15		7.84		
IQR	6.90–7.84		2.69–6.82		6.94–7.84		
n	55,014		396		54,618		
Age, y							
Mean (SD)	57.2	(21.7)	51.5	(20.7)	57.2	(21.7)	<0.0001
Median	60		54		60		
IQR	38–76		32–69		39–76		
n	66,722		452		66,270		

*χ^2 for categorical data; Wilcoxon rank-sum test for continuous data.

of REBOA in the setting of critically uncontrolled hemorrhagic shock,[11,32] but these studies are relatively small and lack a control group to compare the efficacy of REBOA placement. However, our present study shows that REBOA treatment is associated with higher mortality compared with similarly ill trauma patients who did not receive a REBOA.

While overall, we did not find a treatment benefit for REBOA, our analysis of REBOA survivors compared with REBOA nonsurvivors may suggest which patients REBOA may potentially benefit. The REBOA survivors have lower ISS and higher TRISS calculated probability of survival, consistent with a previous study.[32] The indication for REBOA might be similar to the indication of emergency open thoracotomy. Although indications for emergency open thoracotomy and aortic cross clamping are now more specific and clear,[4,33,34] they were previously broad and performed as a "last ditch" effort to salvage dying trauma patients. Because REBOA placement is less invasive than emergency open thoracotomy but theoretically can be used as an alternative, REBOA might be used in Japan as a last ditch effort as the emergent thoracotomy had been performed in Japan and other countries. Further clinical studies will need to confirm if REBOA is beneficial in any subset of patients.

Some might hypothesize that the lack of evidence of treatment efficacy in our study is related to the training or technique of REBOA insertion, which might be different. As Stannard et al.[5] described in a recent article, REBOA devices are usually inserted with five steps. The described technique is almost identical in Japan. In Japan, REBOA has been incorporated into the practice guideline of emergency medicine,[20] and physicians have to be able to perform REBOA to be qualified as a board-certified emergency physician. Currently, the Japanese Association for Acute Medicine requires a minimum experience of three cases of REBOA insertion during residency training to be certified as an emergency physician in Japan. The experience of REBOA placement obtained during residency training does not seem to be different from the experience obtained through the current REBOA training in United States.[35]

We should acknowledge several limitations of our study. Because this is an observational study, a number of potential biases and confounders need to be considered as threats to internal validity. Perhaps, the greatest potential bias is the selection of patients for REBOA placement. To correct for this bias, we used a PS process to improve the comparability of the

TABLE 2. Comparison of Survivors to Nonsurvivors Among REBOA-Treated Patients

	Survivors (n = 109)	Nonsurvivors (n = 343)	*p**
Age, mean (SD), y	48.6 (19.4)	52.4 (21.0)	0.0985
Sex, male, %	79.4	62.7	0.0035
Prehospital systolic blood pressure, mean mm Hg	96.7	104.2	0.0511
Prehospital heart rate, mean, beats/min	95.1	97.0	0.2576
Prehospital respiratory rate, breaths/min	26.1	23.4	0.0756
Hospital initial systolic blood pressure, mean mm Hg	89.7	67.5	<0.0001
Hospital initial heart rate, mean beats/min	105.3	88.8	0.0339
Hospital initial respiratory rate, breaths/min	27.9	20.6	<0.0001
GCS	11.6	7.2	<0.0001
ISS, mean, (SD)	30.6 (15.6)	37.3 (15.1)	0.0001
Maximum AIS,* by region			
Region 1 (head)	1.1	1.9	0.0001
Region 4 (thorax)	2.1	2.5	0.0353
Region 5 (abdomen)	2.8	2.3	0.0229
Region 8 (pelvis and lower extremities)	2.0	2.4	0.0485
RTS	6.3	4.1	<0.0001
TRISS calculated Probability of survival, % (SD)	71% (31%)	35% (33%)	<0.0001
Time to transfusion, mean, min**	160.3 (127.4)	124.4 (93.5)	0.0019
Time to definitive care, mean (SD), min†	213.2 (163.5)	171.6 (134.2)	0.0027

*Wilcoxon rank-sum test, χ^2 test, where appropriate.
**A total of 243 patients received a transfusion (67 survived, 176 died).
†A total of 221 patients had an intraoperative procedure (71 survived, 150 died).

treated and untreated groups. Although we used all relevant pre-REBOA treatment variables provided in the registry, including age, sex, mechanism of injury, severity of injury, and facility, it is possible that some confounding factors not included in the study may have affected the outcome. We did not use the data of timing of definitive care including surgery or embolization to calculate the PS because they are posttreatment variables (i.e., performed after REBOA). However, even after adjustment of these posttreatment variables, REBOA placement is still associated with higher mortality.

TABLE 3. Characteristics of Patients After Adjustment for Likelihood of REBOA Treatment

	Total		REBOA+		REBOA−		
	n	(%)	n	(%)	n	(%)	*p**
Overall	1,807	—	351	(19.4)	1,456	(80.6)	
Survival to discharge	839	(46.4)	92	(26.2)	747	(51.3)	<0.0001
Male	1,208	(66.9)	234	(66.7)	974	(66.9)	0.9348
Female	599	(33.1)	117	(33.3)	482	(33.1)	
ISS							
Mean (SD)	32.4	(16.4)	34.0	(15.3)	32.0	(16.6)	0.0091
Median	30		34		29		
IQR	20–42		22–45		19–42		
n	1,800		351		1,453		
RTS							
Mean (SD)	4.72	(3.1)	4.70	(2.6)	4.73	(3.2)	0.0111
Median	5.97		5.35		6.08		
IQR	0.73–7.55		2.83–6.90		0.00–7.84		
n	1,807		351		1,456		
Age, y							
Mean (SD)	51.8	(20.3)	51.6	(20.6)	51.8	(20.2)	0.9443
Median	53		54		53		
IQR	34–68		32–69		34–68		
n	1,807		351		1,456		

*χ^2 for categorical data; Wilcoxon rank-sum test for continuous data.

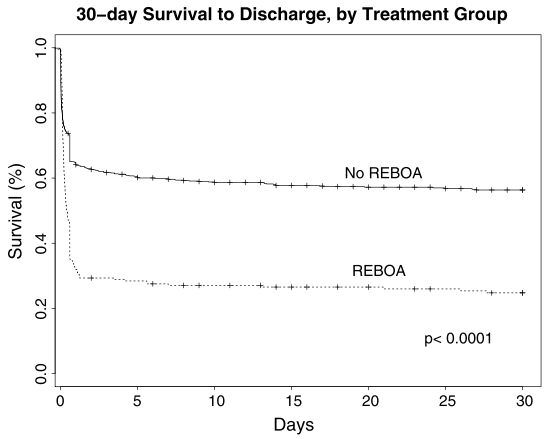

Figure 2. Kaplan-Meier 30-day survival curves of patients treated with either REBOA placement or no REBOA placement.

Since we used trauma registry data, we are limited by the data elements collected in the registry. Many details of the clinical care are not provided in the registry, including the timing of REBOA insertion as well as level of placement or inflation time of REBOA. The volume of fluid resuscitation is also not provided in the trauma registry. Thus, the responsiveness to fluid resuscitation is also unknown. These are important factors regarding REBOA treatment that limit our ability to tease out treatment effects.

Our analysis is limited to blunt trauma patients. Patients with blunt thoracoabdominal trauma may not benefit from aortic occlusion because of the potential of multiple sites of hemorrhage in the setting of critically ill patient. It remains to be seen if REBOA might be beneficial in penetrating trauma where the site of hemorrhage might be more specifically controlled.

Since we used the national trauma data bank in Japan, the result might be different in other countries. The demographic characteristics of trauma in Japan may differ compared with other developed countries. For example, one third (33%) of the patients in the JTDB are older than 65 years. This is significantly higher than the percentage in other national trauma registries, for example, 22% in US trauma registry, 28% in Canada, 30% in the United Kingdom.[12] The immediate access to definitive care (e.g., trauma surgeon or interventional radiologist) is different among countries. Theoretically, because REBOA is used to control bleeding temporarily when access to a definitive care is delayed, REBOA may be beneficial in developing countries, in the field, or under conditions where the access to definitive care is limited.

CONCLUSION

Our analysis of a large prospectively collected nationwide trauma registry data set shows that REBOA treatment is associated with higher mortality compared with similarly ill trauma patients who did not receive a REBOA. After adjusting for physiologic parameters (RTS), anatomic injury severity (ISS), and age, REBOA treatment remained significantly associated with a worsened outcome compared with patients who did not have a REBOA placed. The higher mortality among REBOA-treated patients may signal last ditch efforts for severity not otherwise identified in the trauma registry. Prospectively controlled study with randomized treatment allocation is needed to confirm our findings.

AUTHORSHIP

T.N. and C.C. conducted statistical analysis. All authors conceived, designed, analyzed, interpreted, wrote, and critically revised the manuscript.

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DISCLOSURE

The authors declare no conflicts of interest.

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