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Impact of resuscitative endovascular balloon occlusion of the aorta on gastrointestinal function with a matched cohort study

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ABSTRACT

Background Resuscitative endovascular balloon occlusion of the aorta (REBOA) can temporarily control arterial hemorrhage in torso trauma; however, the abdominal visceral blood flow is also blocked by REBOA. The aim of this study was to evaluate the influence of REBOA on gastrointestinal function.

Methods A retrospective review identified all trauma patients admitted to our trauma center between 2008 and 2019. We used propensity score matching analysis to compare the gastrointestinal function between subjects who underwent REBOA and those who did not. Data on demographics, feeding intolerance (FI), time to feeding goal achievement, and complications were retrieved.

Results During the study period, 55 patients underwent REBOA. A total of 1694 patients met the inclusion criteria, 27 of whom were a subset of those who underwent REBOA. After 1:1 propensity score matching, the REBOA and no-REBOA groups were assigned 22 patients each. Patients in the REBOA group had a significantly higher incidence of FI (77% vs. 27%; OR, 9.1; 95% CI, 2.31 to 35.7; p=0.002) and longer time to feeding goal achievement (8 vs. 6 days, p=0.022) than patients in the no-REBOA group. Patients in the REBOA group also showed significantly prolonged durations of ventilator use (8 vs. 4 days, p=0.023). Furthermore, there was no difference in the mortality rate between the groups (9% vs. 9%, p=1.000).

Conclusions REBOA was associated with gastrointestinal dysfunction. Our study findings can be useful in providing guidance on managing nutrition in trauma patients who undergo REBOA.

Level of evidence Level IV

Study type Care management

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The influence of resuscitative endovascular balloon occlusion of the aorta (REBOA) on abdominal organs has been poorly understood in clinical practice.

WHAT THIS STUDY ADDS

⇒ Feeding intolerance occurred at a high rate (77%) in patients with REBOA.

⇒ REBOA use was associated with feeding intolerance.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ The study holds the potential to provide valuable insights into the nutritional management of trauma patients undergoing REBOA.

INTRODUCTION

Resuscitative endovascular balloon occlusion of the aorta (REBOA) can temporarily control arterial hemorrhage and support coronary and cerebral circulation in torso trauma. However, REBOA carries a risk of several critical complications.[1 2] Particular caution should be exercised regarding distal ischemic complications occurring below the balloon deployment, including abdominal visceral ischemia, spinal cord ischemia, and limb ischemia.[3 4] An animal study demonstrated that REBOA causes significant histological damage to the gastrointestinal mucosa.[5] The influence of REBOA on abdominal organs, which is related to enteral nutrition (EN), has been poorly understood in clinical practice.

Early EN offers numerous advantages, such as reducing infectious and thrombotic complications and improving survival outcomes in the management of severe trauma patients.[6 7] Therefore, it is recommended to initiate EN as soon as possible after resuscitation from shock.[8] However, feeding intolerance (FI) frequently occurs and disrupts early EN in trauma patients. The use of REBOA, which can obstruct gastrointestinal blood flow (except with zone 3 placement), may significantly impact the feasibility of EN.

REBOA causes ischemia/reperfusion injury of the distal region due to the temporary (not permanent) occlusion of the aorta. This ischemia/reperfusion injury in the gastrointestinal tract can trigger a cytokine cascade and initiate a systemic inflammatory response, which can lead to multiple organ failure after trauma.[9–11] Animal models have demonstrated that aortic occlusion leads to the release of cytokines and an increased incidence of organ damage.[5 12 13] REBOA, except with zone 3 placement, carries a high risk because the gastrointestinal tract, which contains a significant amount of lymphoid tissue, plays a critical role in the immune system.

There is concern in clinical practice regarding the potential adverse effects of REBOA on gastrointestinal function and organ damage. However, these implications have not been thoroughly studied in clinical settings. Our hypothesis was that REBOA may have a negative impact on gastrointestinal function and contribute to a systemic inflammatory

response. The study objective was to assess the influence of REBOA on gastrointestinal function and other organ damages based on the experience of a single center.

METHODS

A retrospective review identified all trauma patients admitted to our trauma intensive care unit (ICU) between January 2008 and December 2019 from our prospectively maintained trauma registry at a Japanese major trauma center authorized by the Yokohama City Emergency Committee (Saiseikai Yokohamashi Tobu Hospital, Yokohama, Japan). Patients who underwent an aortic cross-clamping procedure, had zone 3 REBOA placement, early death less than 72 hours, or who were younger than 16 years were excluded. We used an existing proposed aortic zone classification for REBOA.[2] Also, early death (<72 hours) was excluded because it takes some days to analyze whether the FI or not. In fact, the target population is patients who survived at least 4 days after the injury.

Outcome and data collection

Patients were divided into two groups based on whether they underwent REBOA or not. Demographics and injury-specific factors were collected and compared between the two groups. The following data were collected: age, sex, body mass index (BMI), mechanism of injury, systolic blood pressure (SBP), heart rate, Glasgow Coma Scale, Injury Severity Score (ISS), and associated injury (Abbreviated Injury Scale (AIS) ≥3).

Gastrointestinal and other outcomes were assessed as follows. FI, time to achieve feeding goals, ileus, diarrhea, constipation, highest gastric residual volume (GRV) during ICU stays, acute kidney injury (AKI), pneumonia, and in-hospital mortality were recorded. Pneumonia was assessed based on clinical signs and symptoms. AKI was evaluated based on serum creatinine levels and urine output between day 2 and day 7 using the Kidney Disease: Improving Global Outcomes (KDIGO) classification.[14]

Inflammatory response was assessed by measuring C-reactive protein (CRP) levels and white blood cell (WBC) counts during the first week of admission. The primary outcome measure was FI, whereas secondary outcomes included inflammatory response and other complications.

Management and procedure of REBOA

All patients were managed according to the Advanced Trauma Life Support Course manual. The decision regarding REBOA placement, inflation time, and balloon size was made by the attending Japanese board-certified emergency physician based on overall condition. The REBOA catheter was inserted into the accessible femoral artery using the Seldinger technique. REBOA deployment was performed using the external measurement method.[15] Two commercial products were used for REBOA: Rescue Balloon (Tokai Medical Products, Aichi, Japan) with a 7-Fr sheath and IABO Block Balloon (MERA, Tokyo, Japan) with a 10-Fr sheath. The choice of device was made randomly depending on stock availability. The balloon was immediately inflated when necessary and kept inflated for the minimum required REBOA inflation time.

Management of EN

In accordance with our hospital clinical practice protocol, EN was started through nasogastric tube with intermittent infusion within 48 hours of admission unless there was refractory shock status and a specific contraindication. The head of the bed was elevated to 30 degrees during EN. The feeding goal was set with a standard formula by the hospital nutritionist who was exclusively assigned to the emergency and critical care unit. GRV was evaluated every 6 hours and the feeding rate was enhanced until 200 mL/h was reached, unless GRV was above 150 mL or there were any gastrointestinal complications. FI was defined as a delay (≥4 days after admittance) in reaching 30% of target goal energy with enteral feeding. There is no widely agreed upon definition for FI.[16] Therefore, FI was defined based on a consensus among the study authors by referencing other studies. The definitions of other gastrointestinal complications are shown in online supplemental table 1.

Statistical analysis

Continuous variables were reported as medians (IQR), whereas categorical variables were presented as counts and percentages. To facilitate practical interpretation, continuous variables were transformed into categorical variables. The χ^2 test and Mann-Whitney U test were used for comparisons.

In the propensity score-matched cohort, univariate analysis was conducted to evaluate the outcomes between the two groups. $P<0.05$ was considered statistically significant. ORs were calculated along with the corresponding 95% CIs.

To minimize selection bias, propensity score matching analysis was performed between the two groups. Propensity scores were generated for each patient using a logistic regression model that incorporated patient and injury characteristics as well as emergency procedures. The model included variables such as age, BMI, injury type (blunt/penetrating), SBP<80 mm Hg, AIS score ≥3 for each body part (head, chest, abdomen, and pelvis), bowel and mesenteric injury, and laparotomy. These covariates were selected considering clinical severity and factors that impact gastrointestinal function.

Patients were then matched in a 1:1 ratio using the nearest neighbor method without replacement, with a caliper distance of 0.01.[17] We assessed the balance of covariates in estimating propensity scores by calculating standardized differences.[18] An absolute standardized mean difference of less than 0.2 was considered indicative of an acceptable match balance between the groups. All statistical analyses were performed using IBM SPSS Statistics V.25.0 (SPSS).

RESULTS

Patient selection and matching

During the study period, a total of 12 060 trauma patients were transported to our emergency room. Out of these patients, 2290 were admitted to our trauma ICU and 55 of them underwent REBOA placement. Among the patients who underwent REBOA placement, 28 were excluded from this study for the following reasons: age younger than 16 years (n=2), early death within 72 hours (n=25, with 18 deaths occurring within 24 hours), and zone 3 placement (n=1). As a result, a final cohort of 1694 patients met the inclusion criteria for this study. After 1:1 propensity score matching, both the REBOA and the no-REBOA groups consisted of 22 patients each. Patient selection flow and exclusion criteria are depicted in online supplemental figure 1.

Patient characteristics

Before matching, the REBOA group showed significantly higher anatomic and physiologic severity compared with the no-REBOA group (online supplemental table 2). Table 1 presents the clinical characteristics of the propensity score-matched groups. Propensity score matching ensured that patient characteristics were similar between the REBOA and the no-REBOA group, with an

Table 1 Demographic characteristics of all patients after propensity score matching with or without REBOA

	REBOA (n=22)	No-REBOA (n=22)	P value	Standardized difference
Patient characteristics				
Male	18 (81.8)	15 (68.2)	0.296	0.319
Age (y)	45 (27–52)	44 (26–55)	0.897	0.088
Age≥65 (y)	3 (13.6)	4 (18.2)	0.680	0.125
BMI	20 (18–24)	20 (19–24)	0.938	0.032
Blunt mechanism, n (%)	19 (86.4)	20 (90.9)	0.635	−0.143
REBOA placement zone, n (%)				
Zone 1	17 (77.3)	–	–	–
Zone 2	5 (22.7)	–	–	–
ISS	33 (18–43)	26 (17–39)	0.444	0.284
ISS≥25, n (%)	15 (68.2)	12 (54.5)	0.537	0.283
SBP<80 mm Hg, n (%)	10 (45.5)	10 (45.5)	1.000	0.000
GCS<9, n (%)	10 (45.5)	7 (31.8)	0.537	0.283
Associated injury				
Head AIS score ≥3, n (%)	6 (27.3)	7 (31.8)	1.000	−0.100
Chest AIS score ≥3, n (%)	12 (54.5)	13 (59.1)	1.000	−0.092
Abdomen AIS score ≥3, n (%)	15 (68.2)	16 (72.7)	1.000	−0.100
Pelvis and lower extremity AIS score ≥3, n (%)	8 (36.4)	8 (36.4)	1.000	0.000
Bowel and mesenteric injury, n (%)	3 (13.6)	4 (18.2)	0.680	−0.125
Emergency surgery				
Craniotomy, n (%)	1 (4.5)	0 (0)	0.312	0.309
Thoracotomy, n (%)	1 (4.5)	2 (9.1)	0.550	
Celiotomy, n (%)	11 (50.0)	10 (45.5)	1.000	0.091
Angioembolization, n (%)	16 (72.7)	19 (86.4)	0.262	−0.343

Continuous variables are presented as median (IQR). Categorical variables are presented as number (%).
AIS, Abbreviated Injury Scale; BMI, body mass index; GCS, Glasgow Coma Scale; ISS, Injury Severe Score; REBOA, resuscitative endovascular balloon occlusion of the aorta; SBP, systolic blood pressure.

absolute standardized difference for propensity score variables of less than 0.2 (figure 1). In the matched cohort, the median REBOA inflation time was 55 (35–111) minutes with 7 missing values out of 22. The overall rate of laparotomy and angioembolization was 47.7% and 79.5%, respectively.

Outcomes

Before matching, overall, the incidence of FI was 21.1%, and the in-hospital mortality rate was 5.4% (online supplemental table 3). The outcomes in the matched cohort are summarized in table 2. Regarding the complications of REBOA, one case each of lower extremity compartment syndrome and mesenteric ischemia was observed, with an incidence rate of 4.5% each.

Patients in the REBOA group had a significantly higher incidence of FI (77% vs. 27%; OR, 9.1; 95% CI, 2.31 to 35.7; p=0.002) and a longer time to feeding goal achievement (7.5 (6.8–11.5) days vs. 5.5 (3.0–8.5) days, p=0.022) compared with patients in the no-REBOA group (figure 2). Furthermore, patients in the REBOA group also had significantly prolonged durations of ventilator use (8.0 (5.0–16.5) days vs. 4.0 (0.0–8.8) days, p=0.023) and longer ICU stays (20 (13.0–41.0) days vs. 11.0 (7.0–19.5) days, p=0.006). Furthermore, patients in the REBOA group tended to have higher rates of other gastrointestinal symptoms (ileus, diarrhea, and constipation), pneumonia, and AKI, but these were not statistically significant. There was no difference in the in-hospital mortality rate between the two groups (9% vs. 9%, p=1.000). Regarding the inflammatory response biomarkers, the mean CRP level and WBC count generally tended to be higher in the REBOA group than in the no-REBOA group; however, the differences were not statistically significant (figure 3).

DISCUSSION

This is the first study to specifically address gastrointestinal function after REBOA placement in clinical practice. In our single-center retrospective cohort study with propensity score matching analysis conducted at a Japanese urban trauma center, REBOA use was associated with FI and a longer time to achieve feeding goals.

Patients who underwent REBOA placement experienced prolonged durations of mechanical ventilation and longer ICU stays. No statistically significant differences in the incidence of pneumonia and AKI between the REBOA and non-REBOA group were observed. Although previous large-scale multi-institutional studies on REBOA have been conducted, our study contributes to the existing literature by providing a detailed exploration of the impact on gastrointestinal function. The development of FI is a critical concern, particularly in relation to timely initiation of EN, which offers numerous benefits for critically ill patients.

FI is a frequently observed complication in severe trauma patients. Although the definition of FI varies across studies, recent research has consistently shown a high incidence of FI ranging from 33% to 50% in this patient population.[6 7 19] The etiology of FI in trauma patients is likely multifactorial. Previous studies have highlighted the associations between gastrointestinal disorders and factors such as high ISS, head injury, and abdominal trauma.[7 20] In our study, the incidence of FI and ileus was found to be 52.3% and 18.2%, respectively, relatively high

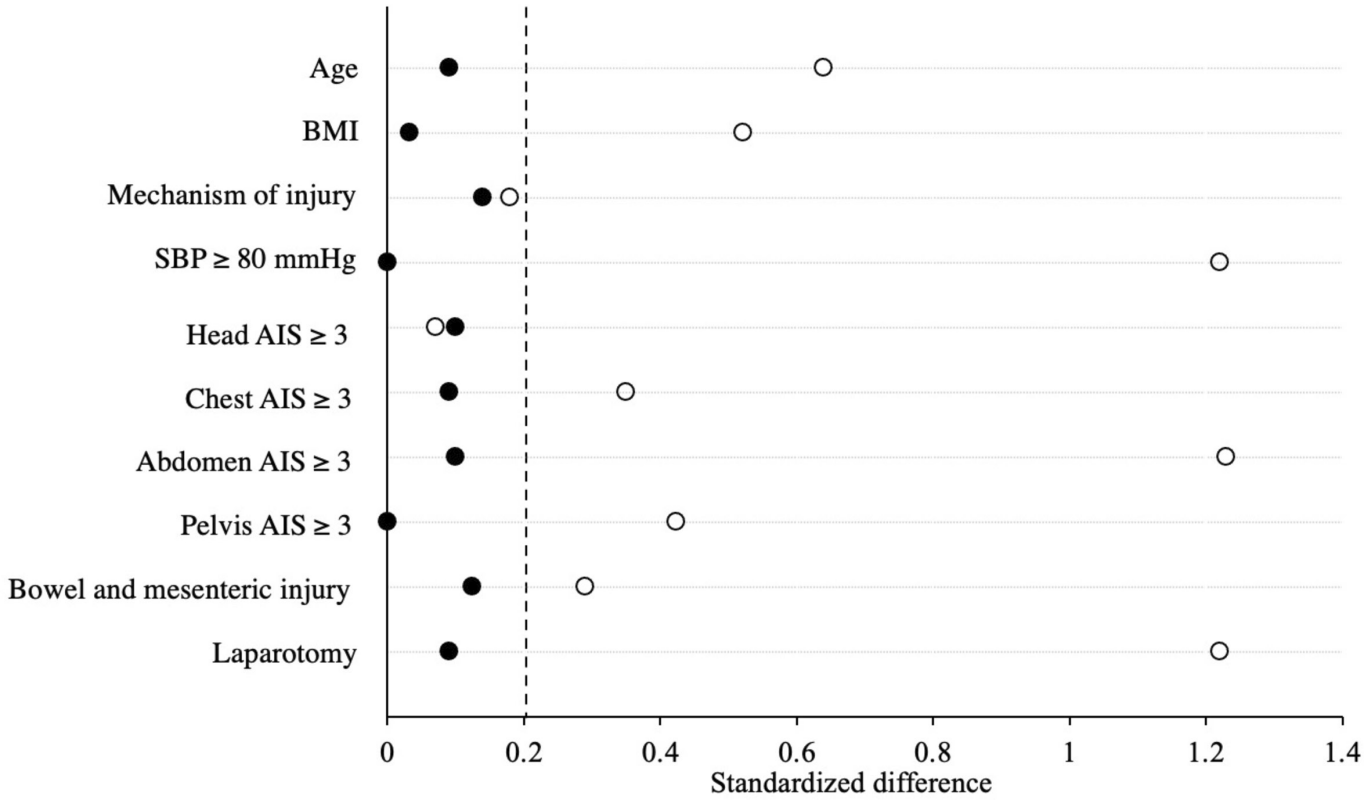

Figure 1 Standardized differences in propensity score variables between the REBOA and no-REBOA group before and after matching. AIS, Abbreviated Injury Scale; BMI, body mass index; REBOA, resuscitative endovascular balloon occlusion of the aorta; SBP, systolic blood pressure.

compared with previous reports. This elevated FI incidence can be attributed not only to the effects of REBOA but also to our patient population, which consisted of individuals with higher ISS and abdominal trauma. Furthermore, it is important to note that opioids, which were administered to all patients in our study, can impair gastrointestinal motility in critically ill patients.[21]

Table 2 Clinical outcomes of patients after propensity score matching with or without REBOA

	REBOA (n=22)	No-REBOA (n=22)	P value
Gastrointestinal outcome			
Feeding intolerance	17 (77.3)	6 (27.3)	0.002
Ileus	6 (27.3)	2 (9.1)	0.118
Diarrhea	5 (22.7)	2 (9.1)	0.216
Constipation	17 (77.3)	14 (63.6)	0.510
GRV (mL)	100.0 (55.0–180.0)	55.0 (0.0–135.0)	0.073
Time to feeding goal (days)	7.5 (6.8–11.5)	5.5 (3.0–8.5)	0.022
Parental nutrition	4 (18.2)	4 (18.2)	1.000
In-hospital mortality	2 (9.1)	2 (9.1)	1.000
Pneumonia	7 (31.8)	5 (22.7)	0.736
Acute kidney injury	7 (31.8)	5 (22.7)	0.736
KDIGO stage 1/2/3	0/4/3	0/2/3	
Ventilator days	8.0 (5.0–16.5)	4.0 (0.0–8.8)	0.023
ICU length of stay (days)	20.0 (13.0–41.0)	11.0 (7.0–19.5)	0.006
Length of stay (days)	49.0 (26.0–89.5)	30.5 (13.8–58.0)	0.106

Continuous variables are presented as median (IQR). Categorical variables are presented as number (%).
GRV, gastric residual volume; ICU, intensive care unit; KDIGO, the Kidney Disease Improving Global Outcomes; REBOA, resuscitative endovascular balloon occlusion of the aorta.

The present study demonstrated that REBOA was a risk factor of FI. FI is known to be associated with an increased risk of several complications, higher hospitalization costs, and prolonged hospital stays.[22 23] Furthermore, FI can contribute to the development of multiple organ failure in severe trauma patients.[24] A large study utilizing the US nationwide trauma registry reported that REBOA was associated with higher rates of AKI, although there was no significant difference in other complications.[25] In our study, we observed numerically higher rates of pneumonia, AKI, and longer hospital stays in patients who underwent REBOA placement compared with those without REBOA, although these differences did not reach statistical significance. Further studies with large sample size are needed to comprehensively explore the relationship between REBOA and complications or length of hospital stays.

REBOA has the potential to induce FI in trauma patients. First, REBOA can exacerbate intestinal ischemia in addition to hemorrhagic shock. Animal studies show that the mesenteric artery blood flow is significantly reduced during inflation[26] and histological evidence of intestinal mucosal damage has been observed.[5] Second, REBOA may promote gut edema. A study in an animal model of hemorrhagic shock reported a significant increase in fluid resuscitation volume after 90 minutes of REBOA.[27] Considering the inflammatory cytokine response and the potential for ischemic/reperfusion injury, it is likely that vascular permeability is increased in the intestine, leading to resuscitation-induced gut edema and subsequent intestinal dysfunction.[28] Intra-abdominal hypertension should be carefully monitored during REBOA. In our study, several gastrointestinal symptoms besides FI were

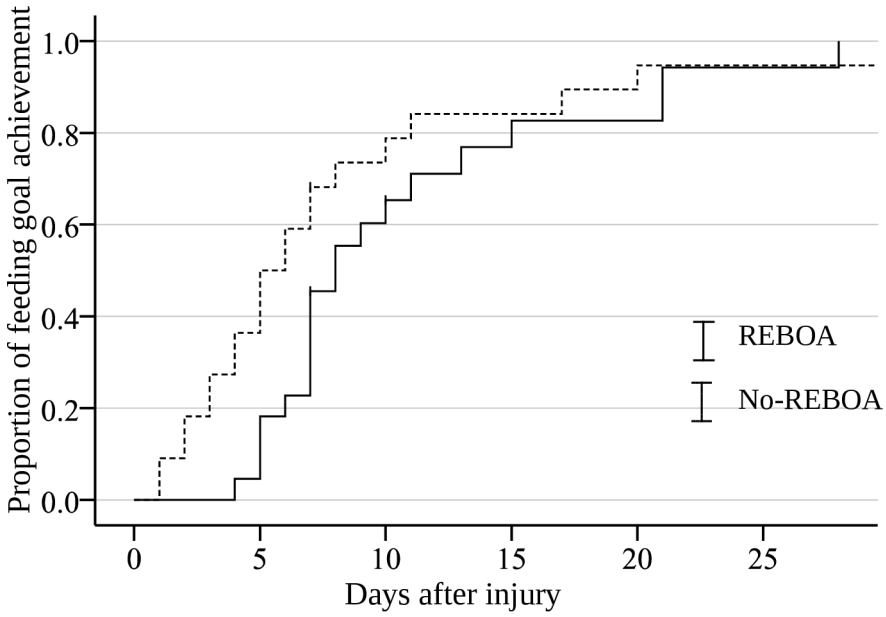

Figure 2 Patients in the no-REBOA group had a shorter time to reach the feeding goal than those in the REBOA group (p = 0.021). REBOA, resuscitative endovascular balloon occlusion of the aorta.

more common in patients with REBOA and there was one case of mesenteric ischemia necessitating bowel resection. Therefore, trauma surgeons should exercise caution in the deployment of REBOA, aiming to minimize the risk of ischemic complications. Appropriate partial REBOA techniques may also prove beneficial in mitigating the occurrence of ischemic complications.

Here, CRP was used as an indicator of inflammatory response and did not show a significant increase in patients with REBOA. This may be because CRP is a less sensitive marker of inflammation compared with the direct measurement of cytokines. CRP production in the liver is regulated by the inflammatory cytokines interleukin 6 (IL-6) and has a direct correlation with IL-6 levels.[29 30] Unfortunately, we did not have data on inflammatory cytokine levels. Another reason for this result could be that the cytokine levels induced by REBOA were relatively low compared with the excessive cytokine levels associated with severe traumatic insult.

The present study has several limitations. The small sample size and single-center retrospective design are the primary limitations. Although higher rates of gastrointestinal symptoms, AKI, and pneumonia were observed in the REBOA group, these differences were not statistically significant. A large nationwide study conducted in the USA reported similar findings, showing a higher rate of AKI in the REBOA group.[25] A post hoc power calculation revealed a power of 25% to detect differences in AKI and pneumonia between groups in our study. There is the possibility of underestimating the effect sizes of the observed differences between groups. Multi-institutional trials are necessary to confirm these findings. Second, we conducted propensity matching by using data to minimize selection bias. However, unmeasured confounding factors must remain. The selected variables only would be difficult to balance the characteristics of the two groups divided by whether or not REBOA was

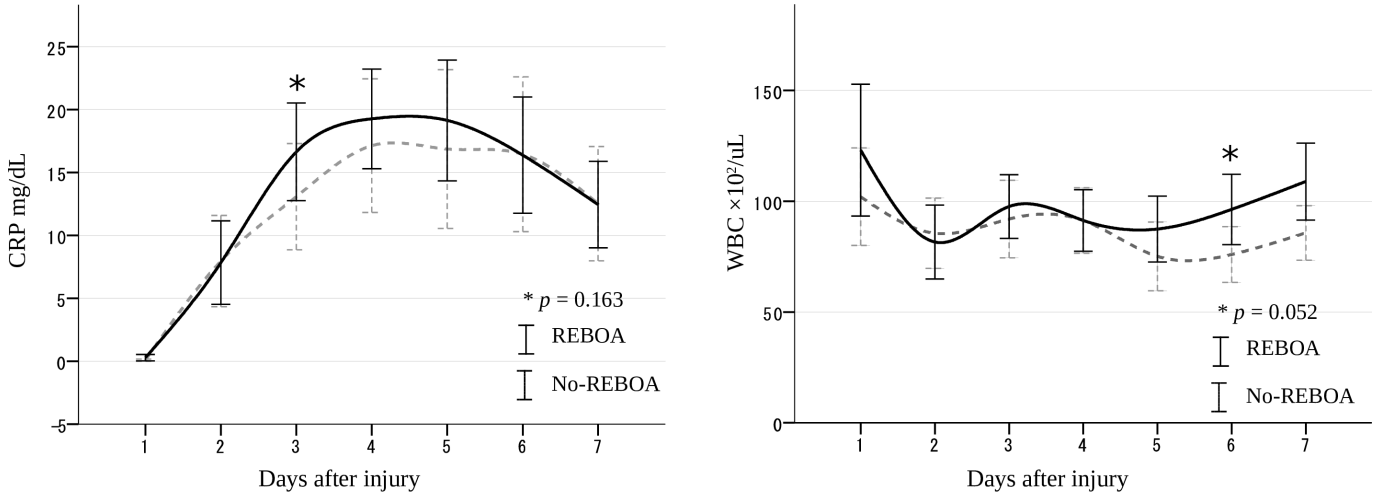

Figure 3 Comparison of CRP and WBC between the REBOA group and the no-REBOA group. *Day with the most difference of values. CRP, C-reactive protein; REBOA, resuscitative endovascular balloon occlusion of the aorta; WBC, white blood cell.

performed, as in a randomized controlled trial. Also, the upper limit of 0.2 for the absolute standardized mean difference is large. Although the limit of 0.1 is more appropriate, it does entail a trade-off as it restricts the number of eligible subjects. Third, this study did not consider REBOA balloon size and inflation duration, which could have a significant impact on intestinal mucosal damage. This is due to incomplete records regarding the REBOA balloon size and inflation time. Fourth, FI was defined by the study authors. The definition of FI should affect the result significantly. There is no universally accepted definition of FI. Instead, in this study, it has been defined using references from various studies.[16] Finally, the potential presence of survivorship bias may be caused because this study primarily focuses on patients who survived at least 4 days after the injury. This bias may result in an underestimation of the FI, as we may be analyzing a population that is inherently more resilient or responsive to interventions in terms of avoiding severe complications. These limitations highlight the need for large-scale studies that take into account additional factors to provide a more comprehensive understanding of the effects and potential complications associated with REBOA.

CONCLUSION

The present study demonstrated that REBOA was associated with gastrointestinal dysfunction, but it did not have a significant impact on the inflammatory response. A better understanding of the risk and mechanism would be useful in providing guidance on managing nutrition in trauma patients who undergo REBOA. Further studies are needed to validate the effects of REBOA on gastrointestinal function.

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Competing interests None declared.

Patient consent for publication Not applicable.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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