Original Article

Association between vasopressor use and mortality in patients with severe traumatic brain injury: a nationwide retrospective cohort study in Japan

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Aim: Vasopressors are frequently incorporated into severe traumatic brain injury management algorithms. However, evidence regarding their clinical effectiveness is lacking. We undertook a nationwide retrospective cohort study to determine the association between vasopressor use and mortality in patients with severe traumatic brain injury.

Methods: Data were collected between January 2004 and December 2018 from the Japanese Trauma Data Bank, which includes data from 272 emergency hospitals in Japan. Adults aged 16 years and over with severe traumatic brain injury but without major extracranial injuries were examined. A severe traumatic brain injury was defined based on a Glasgow Coma Scale score of 3–8 on admission. Multivariable analysis and propensity score matching were carried out. Statistical significance was assessed using 95% confidence intervals.

Results: In total, 10,295 patients were eligible for analysis, with 654 included in the vasopressor group and 9,641 included in the nonvasopressor group. The proportion of deaths at hospital discharge was higher in the vasopressor group than in the nonvasopressor group (81.80% [535/654] versus 40.24% [3,880/9,641]). This finding was confirmed in a multivariable logistic regression analysis (adjusted odds ratio, 5.37; 95% confidence interval, 4.23–6.81). Among propensity score-matched patients adjusted for severity, the proportion of deaths at hospital discharge remained higher in the vasopressor group than in the nonvasopressor group (81.87% [533/651] versus 56.22% [366/651]) (odds ratio, 3.52; 95% confidence interval, 2.73–4.53).

Conclusion: The study results suggest that vasopressor use in patients with severe isolated traumatic brain injury is associated with a higher mortality at hospital discharge.

Key words: Brain injury, mortality, resuscitation, trauma, vasoconstrictor agent

INTRODUCTION

SEVERE TRAUMATIC BRAIN injury (TBI) is a leading cause of death and disability in people of all ages worldwide[1–3] and is associated with high economic and social costs.[4] Although little can be done to reverse the primary brain damage, secondary brain injury due to dysregulation of cerebral blood flow is potentially preventable. As the penumbra (the brain tissue surrounding the impacted core of the TBI) becomes particularly vulnerable to cell death, the preservation of this area is an important objective in the acute management of patients with severe TBI.[5–8]

Hypotension in the acute phase of severe TBI is a key factor associated with poor clinical outcomes.[7–9] Indeed, the most recent international guidelines on the management of severe TBI recommend the maintenance of systolic blood pressure (BP) to improve clinical outcomes and decrease mortality.[5] Previous studies have suggested that vasopressor use is associated with increased mortality in trauma patients with hemorrhagic shock.[10] Although vasopressors are empirically used in patients with TBI, there is a lack of evidence pertaining to their clinical effectiveness. Therefore, the aim of this study was to assess the possible association between vasopressor use and mortality in patients with severe TBI using data from the Japanese Trauma Data Bank (JTDB) registry, which is the largest trauma databank in Japan.[11]

METHODS

Study design, population, and setting

THIS WAS A nationwide retrospective cohort study undertaken using the JTDB (Doc. S1). Basically, the use of vasopressor for emergency life-saving procedures was recorded in JTDB. We included TBI patients (≥16 years of age) who were transported to a JTDB-participating hospital and registered in the database between January 2004 and December 2018. We defined a TBI as any injury (parenchymal or vascular) to the internal contents of the skull, including the brainstem, cerebellum, and cerebrum, using the Abbreviated Injury Scale (AIS) code. We segregated patients with severe TBI based on a Glasgow Coma Scale score of 3–8 on admission. Exclusion criteria comprised the following: maximum head AIS score of 6 (lethal injury) or 9 (unspecified injury), severe extracranial injuries (AIS score ≥3: 3, serious; 4, severe; and 5, critical), cardiopulmonary arrest on or before hospital arrival, cardiopulmonary resuscitation (i.e., use of adrenaline during cardiopulmonary resuscitation), and requirement for interhospital transport.[12,13] We also excluded cases involving missing outcome data or variables required for propensity score (PS) matching. Cardiopulmonary arrest was defined as a systolic BP of 0 mmHg and/or heart rate of 0 b.p.m. on or before hospital arrival.[14] Traumatic brain injury patients transported to JTDB-participating hospitals were treated based on the guidelines for the management of severe TBI, which recommend the use of vasopressors for the maintenance of the systolic BP at more than 110 mmHg after enough volume resuscitation.[15]

Study outcomes

The primary outcome of this investigation was mortality at hospital discharge. The secondary outcome was emergency department (ED) mortality and acute respiratory distress syndrome (ARDS).

Propensity score matching

In this study, we utilized a PS matching analysis, as the use of vasopressors was not randomly assigned. A PS matching analysis was undertaken as described in Document S1.

Statistical analyses

We divided patients into two groups (vasopressor and non-vasopressor). Descriptive data are presented as counts and percentages (categorical variables) or means and standard deviations (SDs) (continuous variables). Outcomes were evaluated using univariable and multivariable logistic regression analyses for all cohorts to assess the robustness of the results. Based on these analyses, we calculated the odds ratios (ORs) and 95% confidence intervals (CIs). In the multivariable logistic regression model, we adjusted for the 14 variables used in the PS calculation, based on previous reports.[9,10,16–19] In addition, subgroup analyses, in terms of the type of TBI, were carried out to identify the potential benefits and drawbacks of the use of vasopressors. In each subgroup, multivariable logistic regression analysis, adjusted for the aforementioned variables (except the type of TBI), was carried out to assess the independent effect of vasopressor use on mortality at hospital discharge.

All statistical analyses were undertaken using STATA (version 16; StataCorp LP). Statistical significance was assessed using 95% CIs. This study was reported in accordance with the STROBE statement for cohort and cross-sectional studies.[20]

RESULTS

A TOTAL OF 10,295 patients were included in the study; 654 (6.35%) received vasopressors and 9,641 (93.65%) did not. Figure 1 depicts the flow of patients included in this study.

Patient characteristics are summarized in Table 1. There were no significant differences in age, sex, type of TBI, medical history (stroke or the use of anticoagulant or antiplatelet therapy), or Injury Severity Score between the two groups. In the vasopressor group, traffic accidents (46.8% [306/654]) were the leading cause of brain injury, followed by falls (42.0% [275/654]); in contrast, falls (50.3% [4,853/9,641]) were the primary cause of brain injuries in the nonvasopressor group. Glasgow Coma Scale scores on admission to the ED were lower in the vasopressor group (4.33 [SD, 1.60]) than in the nonvasopressor group (5.22 [SD, 1.84]). The proportions of patients with hypotension on admission to the ED and a maximum head AIS score of 5 were higher in the vasopressor group than in the nonvasopressor group (17.7% [116/654] versus 4.5% [436/9,641] and 70.8% [463/654] versus 56.1% [5,412/9,641], respectively). The vasopressor group received treatments more commonly than the nonvasopressor group, including prehospital intravenous infusion (8.6% [56/654] versus 4.4% [429/9,641], respectively) and blood transfusion in the first 24 h (45.1% [295/654] versus 24.3% [2,347/9,641], respectively).

Table 1 also shows the baseline characteristics of the PS-matched patients. Following PS matching, 651 patients in each group were included. The characteristics of PS-
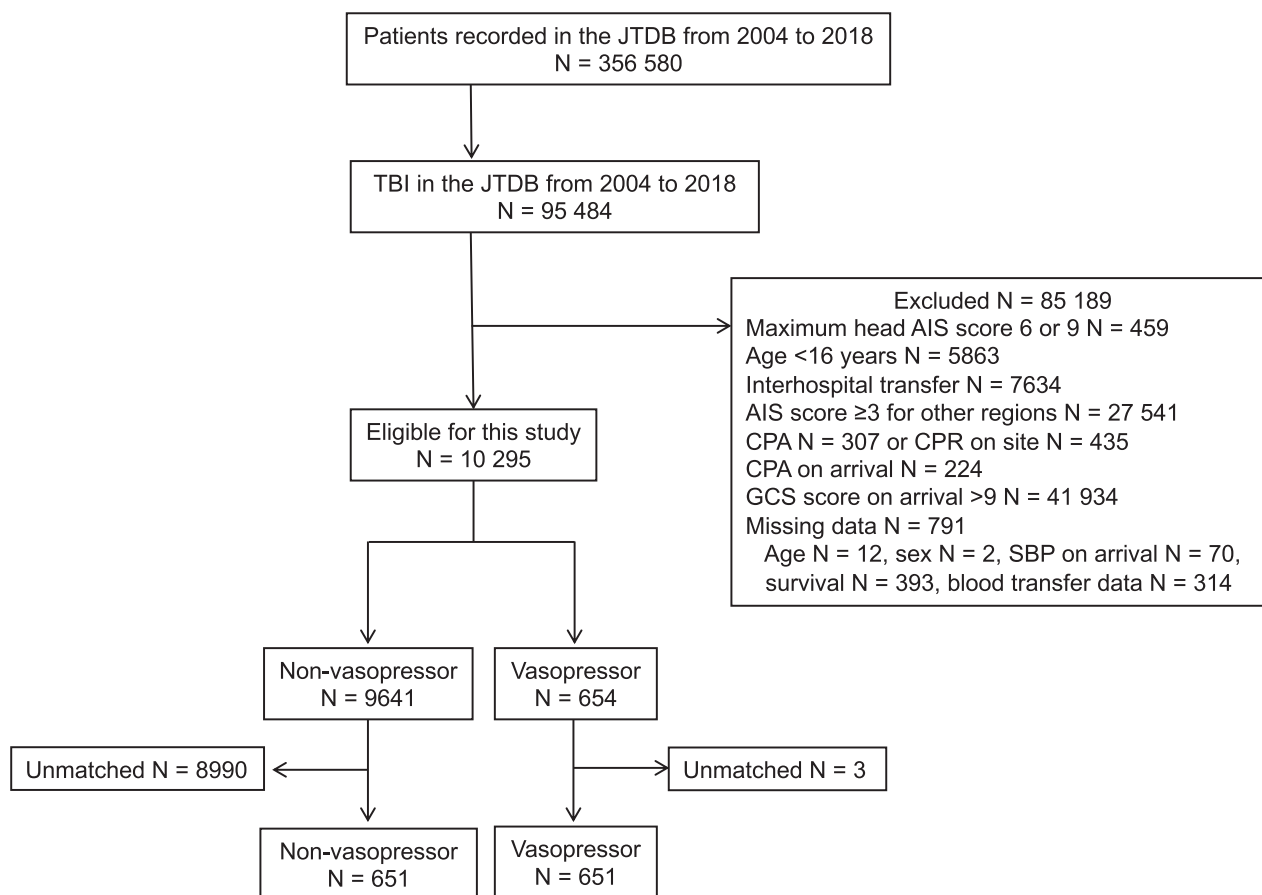
Fig. 1. Flowchart of the patients included in this study. AIS, Abbreviated Injury Scale; CPA, cardiopulmonary arrest; CPR, cardiopulmonary resuscitation; GCS, Glasgow Coma Scale; JTDB, Japan Trauma Data Bank; SBP, systolic blood pressure; TBI, traumatic brain injury.

matched patients were finely balanced in terms of absolute standardized mean differences.

The results of the multivariable logistic regression analysis and PS matching for the primary outcome are presented in Table 2. Mortality at hospital discharge was higher in the vasopressor group than in the nonvasopressor group (adjusted OR, 5.37; 95% CI, 4.23–6.81). For PS-matched patients, mortality at hospital discharge was 81.87% (533/651) in the vasopressor group and 56.22% (366/651) in the nonvasopressor group. The PS matching analysis indicated that mortality at hospital discharge was higher in the vasopressor group than in the nonvasopressor group (OR, 3.52; 95% CI, 2.73–4.53).

Table 2 also shows the results of the multivariable logistic regression analysis and PS matching for the secondary outcomes. For PS-matched patients, ED mortality in the vasopressor group was higher than that in the non-vasopressor group (2.15% [14/651] versus 8.14% [53/651], respectively) (OR, 4.03; 95% CI, 2.21–7.34). Acute respiratory distress syndrome in the vasopressor group tended to increase, compared with the nonvasopressor group (0.77% [5/651] versus 1.23% [8/651], respectively) (OR, 1.60; 95% CI, 0.52–4.94). Subgroup analysis suggested that the use of vasopressors for severe TBI was associated with higher mortality at hospital discharge for each type of TBI (Table 3).

DISCUSSION

IN THIS RETROSPECTIVE cohort study, we evaluated the effect of vasopressor use on mortality in patients with severe TBI, using a nationwide trauma database in Japan. Using robust analyses to adjust for TBI severity, we found that the use of vasopressors was significantly associated with higher mortality, not only at hospital discharge but also in the ED. Subgroup analysis confirmed these results and also indicated that the use of vasopressors for severe TBI was

Table 1. Characteristics of patients with severe traumatic brain injury (TBI) with and without vasopressor use (all patients and propensity score [PS]-matched patients)

		All patients			PS matched patients		
		Nonvasopressor N = 9,641	Vasopressor N = 654	SMD	Nonvasopressor N = 651	Vasopressor N = 651	SMD
Age, years; mean (SD)		62.82 (20.45)	64.42 (18.81)	0.081	64.75 (18.62)	64.50 (18.76)	0.014
Gender (male)		6,736 (69.90)	430 (65.70)	0.088	428 (65.70)	429 (65.90)	0.003
Year of onset	2004–2006	478 (5.00)	45 (6.90)	0.159	63 (9.70)	45 (6.90)	0.007
	2007–2009	1,252 (13.00)	118 (18.00)	–	89 (13.70)	115 (17.70)	–
	2010–2012	2,265 (23.50)	154 (23.50)	–	150 (23.00)	154 (23.70)	–
	2013–2015	3,059 (31.70)	181 (27.70)	–	201 (30.90)	181 (27.80)	–
	2016–2018	2,587 (26.80)	156 (23.90)	–	148 (22.70)	156 (24.00)	–
Type of trauma (blunt)		9,205 (95.50)	625 (95.60)	0.004	622 (95.50)	622 (95.50)	0.000
Cause of trauma	Motor accident	3,421 (35.50)	306 (46.80)	0.213	293 (45.00)	303 (46.50)	0.005
	Fall	4,853 (50.30)	275 (42.00)	–	293 (45.00)	275 (42.20)	–
	Other	1,367 (14.20)	73 (11.20)	–	65 (10.00)	73 (11.20)	–
Type of TBI	Contusion	3,807 (39.50)	228 (34.90)	0.096	226 (34.70)	228 (35.00)	0.006
	Acute epidural hematoma	704 (7.30)	43 (6.60)	0.111	36 (5.50)	43 (6.60)	0.030
	Acute subdural hematoma	121 (1.30)	17 (2.60)	0.006	10 (1.50)	17 (2.60)	0.054
	Intracerebral hemorrhage	1,320 (13.70)	66 (10.10)	0.052	72 (11.10)	66 (10.10)	0.052
	Other focal hematoma	795 (8.20)	45 (6.90)	0.098	54 (8.30)	45 (6.90)	0.075
	Diffuse axonal injury	3,466 (36.00)	237 (36.20)	0.029	252 (38.70)	235 (36.10)	0.045
	Diffuse brain swelling	500 (5.20)	95 (14.50)	0.317	88 (13.50)	93 (14.30)	0.022
	Subarachnoid hemorrhage	4,506 (46.70)	344 (52.60)	0.117	337 (51.80)	342 (52.50)	0.015
	Other injury	1,614 (16.70)	92 (14.10)	0.074	92 (14.10)	92 (14.10)	0.000
Hypotension on arrival		436 (4.50)	116 (17.70)	0.43	107 (16.40)	113 (17.40)	0.025
GCS on arrival, mean (SD)		5.22 (1.84)	4.33 (1.60)	0.517	4.37 (1.65)	4.33 (1.61)	0.023
Prehospital IV		429 (4.40)	56 (8.60)	0.167	57 (8.80)	56 (8.60)	0.005
Blood transfusion		2,347 (24.30)	295 (45.10)	0.447	313 (48.10)	292 (44.90)	0.065
Operation for elevated ICP		3,331 (34.60)	240 (36.70)	0.045	269 (41.30)	240 (36.90)	0.091
PMH stroke		275 (2.90)	17 (2.60)	0.016	14 (2.20)	17 (2.60)	0.030
Anticoagulant/ antiplatelet		633 (6.60)	32 (4.90)	0.072	33 (5.10)	32 (4.90)	0.007
Max head AIS	3	1,295 (13.40)	46 (7.00)	0.316	38 (5.80)	46 (7.10)	0.046
	4	2,934 (30.40)	145 (22.20)	–	143 (22.00)	145 (22.30)	–
	5	5,412 (56.10)	463 (70.80)	–	470 (72.20)	460 (70.70)	–
ISS, mean (SD)		21.46 (6.08)	23.38 (5.39)	0.333			
Systolic BP on arrival, mmHg; mean (SD)		153.50 (38.90)	140.57 (48.58)	0.279			
HR on arrival, b.p.m.; mean (SD)		89.17 (24.16)	92.35 (26.96)	0.121			
PMH coronary artery disease		473 (4.90)	24 (3.70)	0.058			

Table 1. (Continued)

	All patients			PS matched patients		
	Nonvasopressor N = 9,641	Vasopressor N = 654	SMD	Nonvasopressor N = 651	Vasopressor N = 651	SMD
PMH heart failure	237 (2.50)	14 (2.10)	0.031			
PMH hypertension	1,890 (19.60)	102 (15.60)	0.096			

Note: Data are shown as *n* (%) unless otherwise indicated.
Abbreviations: AIS, Abbreviated Injury Scale; BP, blood pressure; GCS, Glasgow Coma Scale; HR, heart rate; ICP, intracranial pressure; ISS, Injury Severity Score; IV, intravenous injection; PMH, past medical history; SD, standard deviation; SMD, standardized mean difference.

Table 2. Outcome comparisons between patients with severe traumatic brain injury with and without vasopressor use before and after propensity score (PS) matching

	Total	Nonvasopressor	Vasopressor	Crude OR (95% CI)	Adjusted OR (95% CI)
All patients	10,295	9,641	654	–	–
Death at hospital discharge	4,415 (42.88%)	3,880 (40.24%)	535 (81.80%)	6.68 (5.45–8.18)	5.37 (4.23–6.81)
Death in the emergency department	200 (1.94%)	147 (1.52%)	53 (8.10%)	5.7 (4.12–7.88)	3.16 (2.19–4.56)
Acute respiratory distress syndrome	76 (0.74%)	67 (0.69%)	9 (1.38%)	1.99 (0.99–4.02)	2.15 (1.03–4.49)
PS matched patients	1,302	651	651	–	–
Death at hospital discharge	899 (69.05%)	366 (56.22%)	533 (81.87%)	3.52 (2.73–4.53)	–
Death in the emergency department	67 (5.15%)	14 (2.15%)	53 (8.14%)	4.03 (2.21–7.34)	–
Acute respiratory distress syndrome	13 (1.00%)	5 (0.77%)	8 (1.23%)	1.60 (0.52–4.94)	–

–, not applicable.
Abbreviations: CI, confidence interval; OR, odds ratio.

Table 3. Subgroup analysis of patients with severe traumatic brain injury (TBI) with and without vasopressor use

Type of TBI	Death at hospital discharge		Adjusted OR (95% CI)
	Nonvasopressor, *n/N* (%)	Vasopressor, *n/N* (%)	
Contusion	1,377/3,807 (36.17)	187/228 (82.02)	5.59 (3.81–8.19)
Acute epidural hematoma	363/1,320 (27.50)	40/66 (60.61)	2.75 (1.53–4.96)
Acute subdural hematoma	1,372/3,466 (39.58)	189/237 (79.75)	4.76 (3.31–6.85)
Intracerebral hemorrhage	286/795 (35.97)	35/45(77.78)	4.56 (2.03–10.26)
Other focal hematoma	69/121 (57.02)	15/17 (88.24)	8.62 (1.42–52.25)
Diffuse axonal injury	128/704(18.18)	28/43(65.12)	6.27 (2.89–13.61)
Diffuse brain swelling	365/500 (73.00)	91/95 (95.79)	7.06 (2.37–21.01)
Subarachnoid hemorrhage	1,677/4,506 (37.22)	291/344 (84.59)	6.37 (4.55–8.91)
Other injury	914/1,614 (56.63)	74/92 (80.43)	4.68 (2.55–8.58)

Abbreviations: CI, confidence interval; OR, odds ratio.

associated with higher mortality at hospital discharge in all types of TBI.

In our study, blood pressure on arrival was lower and heart rate was higher in the vasopressor group than in the nonvasopressor group. Hypotension is a well-known risk factor for the occurrence of secondary cerebral damage and poor outcomes, especially after TBI.[7–9] Indeed, analyses based on the large IMPACT prospective database indicated that even a systolic BP less than 120 mmHg is a strong predictor of unfavorable neurological recovery.[21] Therefore, vasopressor use is frequently incorporated into severe TBI management algorithms aimed at preventing or treating cerebral ischemia caused by reduced cerebral perfusion pressure.[5,15] However, controversies and challenges still remain regarding the use of vasopressors in the treatment of TBI. For instance, noradrenalin is associated with a greater risk of brain edema, as it increases cerebral perfusion pressure.[22]

In the abnormal state of autoregulation after severe TBI, an excessive elevation of intracranial pressure favors edema formation by increasing capillary hydrostatic pressure across the blood–brain barrier, thereby causing brain herniation.[23] This could also result in unwanted hemodynamic effects, such as intracranial hemorrhage, leading to increased mortality.[24,25] Our study also showed that not only traumatic hemorrhage but also diffuse brain swelling were associated with higher mortality. These would be caused by promoted bleeding or edema following excessive cerebral perfusion pressure. Additionally, vasopressors cause an array of adverse effects on other organs.[26] A catecholamine surge after TBI can lead to peripheral insults (induced by the release of proinflammatory substances) and result in increased vascular permeability, which could trigger the development of ARDS.[26,27] In response to these findings, the latest Brain Trauma Foundation guidelines recommend that vasopressors should be used more conservatively.[5] Grände suggested that vasopressors should be avoided in all cases of severe TBI.[28]

Although most guidelines target systolic BP, there are some problems. In this study, which focused on isolated TBI, hypotension in the emergent phase would be caused by transcapillary leakage-induced hypovolemia in the hyperadrenergic state after TBI, following removal of the potential confounding variable of non-brain injury-related fatal conditions.[29] Arterial BP could be conversely increased in the hyperadrenergic state, where the BP value would be an unreliable parameter for the evaluation of hypovolemia. In both situations, unless there is adequate fluid resuscitation, the use of vasopressors would exacerbate cerebral ischemia caused by reduced cerebral perfusion flow, due to the contraction of arterial vessels.[30]

The authors acknowledge several limitations of this observational study. First, PS matching analysis has the risk of residual selection bias. Some differences between the two groups could still exist, even after PS matching, particularly if data on important confounding factors are not included in the analysis. Second, although the use of vasopressors (mainly catecholamine) not for life-prolonging treatment but for as emergency life-saving procedures was recorded in the JTDB, detailed information on the following parameters was not available: vasopressor type and dose, timing of vasopressor administration, patient's vital signs, intracranial pressure or fluid volume before vasopressor administration, and purpose of vasopressor use. Thus, we could not accurately determine whether vasopressors were used for resuscitation or the maintenance of cerebral perfusion pressure. In cases of TBI, vasopressors are used in many clinical situations, such as low cerebral perfusion pressure with hypotension, or brain stem injury including with herniated brain. The use of vasopressors for more fatal conditions may affect the association between vasopressor use and high mortality. Nevertheless, to avoid this issue as much as possible, this study excluded patients with severe extracranial injuries and adjusted for severity between the two groups using PS matching. In addition, the data included in this study primarily involved cases of blunt trauma, which cannot be extended to penetrating TBI. Furthermore, the cause of mortality (e.g., TBI origin) was not documented in the JTDB. Finally, this was an observational study, and there may have been other unknown confounding factors. The results of this investigation could not establish causality and remain limited to associations. Ideally, the results should be validated in other cohorts and randomized trials.

CONCLUSIONS

A MONG PATIENTS WITH severe isolated TBI admitted to JTDB-participating trauma centers, the use of vasopressors was associated with increased mortality at hospital discharge, even after controlling for multiple known confounders by PS matching.

ACKNOWLEDGMENTS

DISCLOSURE

APPROVAL OF THE research protocol: The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Committee of Osaka University Graduate School of Medicine (Osaka, Japan), Approval No. 16260.

Informed consent: The requirement for written informed consent was waived due to the retrospective nature of the study. Personal identifiers were removed from the Japanese Trauma Data Bank registry before data extraction in this study.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None.

DATA AVAILABILITY STATEMENT

THE DATA THAT support the findings of this study are available from the JTDB; however, the availability of these data is restricted.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Doc. S1. Japanese Trauma Data Bank (JTDB) and propensity score (PS) matching.