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Liberal vs. Restrictive Transfusion in Patients with Moderate and Severe Traumatic Brain Injury: A Secondary Analysis of the RESTRIC Trial, a multicenter, cluster-randomized crossover trial

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Abstract

Introduction

Traumatic brain injury (TBI) is a major cause of morbidity and mortality. However, the impact of transfusion strategy on patients with moderate to severe TBI remains unclear. Thus, we aimed to determine whether transfusion strategies in the acute phase of trauma care influence clinical outcomes in patients with severe trauma and TBI who are at risk for major bleeding.

Methods

To compare the effect of liberal versus restrictive red blood cell (RBC) transfusion strategies on clinical outcomes in TBI patients, we performed a secondary analysis of the RESTRIC trial, a multicenter, cluster-randomized crossover trial in Japan. We assessed liberal (10–12 g/dL) and restrictive (7–9 g/dL) RBC transfusion strategies in adult trauma patients at risk for major bleeding, focusing on patients with head abbreviated injury score (AIS) ≥ 2. Logistic regression analysis adjusted for age, sex, mechanism of trauma, injury severity score, shock on arrival (defined as systolic blood pressure under 90 mmHg), Glasgow Coma Scale score, and the use of antithrombotic agent was performed. The primary outcome was the proportion of favorable neurological outcomes at discharge, defined as Glasgow Outcome Scale (GOS) scores of 4 or 5. We conducted the same analysis in subgroups stratified by TBI severity (moderate: AIS 2–3; severe: AIS 4–5).

Results

After omitting patients according to exclusion criteria, 153 RESTRIC trial patients were included in this study (liberal group: 68; restrictive group 85). The proportion of favorable GOS scores was 26.5% (18/68) in the liberal group and 30.6% (26/85) in the restrictive group; adjusted logistic regression did not show a significant difference (OR 1.06, 95% CI 0.44–2.56, p = 0.90). We also observed this trend in our subgroup analysis (moderate; OR 1.39, 95% CI 0.47–4.09, p = 0.55; severe: OR 0.68, 95% CI 0.10–4.84, p = 0.70).

Conclusions

In this secondary analysis of the RESTRIC trial focusing on patients with severe trauma and TBI at risk for major bleeding, transfusion strategies in the acute phase of trauma care were not associated with favorable GOS at discharge.

Introduction

Trauma is one of the leading causes of death worldwide (1). Even when death is avoided, neurological dysfunction frequently occurs following severe trauma (2). Red blood cell (RBC) transfusion is a fundamental component of early trauma resuscitation, yet the optimal transfusion threshold for patients with traumatic injuries remains an area of ongoing debate. In particular, traumatic brain injury (TBI) presents unique physiological considerations, as cerebral hypoxia and secondary brain injury may be

exacerbated by anemia, raising concerns that low RBC transfusion thresholds could compromise cerebral oxygen delivery (3) (4). Furthermore, studies have shown that anemia and RBC transfusion are independent risk factors for unfavorable functional outcomes in TBI patients (5) (6). However, some studies show marginal benefits from RBC transfusion strategies when using high thresholds in selected subgroups (7) (8). The effectiveness of blood transfusion and maintaining higher hemoglobin levels for TBI patients is inconclusive.

Recently, two randomized trials focusing on RBC transfusion strategy for brain injury patients have been conducted. The TRAIN trial, which compared restrictive and liberal transfusion strategies in a broad trauma population with varying injury patterns and severities, was unable to clarify whether the effect of transfusion strategies differs according to head injury severity (9). In that study the median time from admission to randomization was three days (interquartile range [IQR] 2–5 day) in the liberal group and three days (IQR 2–6) in the restrictive group, and the proportion of salvage therapies for elevated intracranial pressure was 27.7% in the liberal group and 31.9% in the restrictive group. Meanwhile, the HEMOTION trial focused on moderate to severe TBI patients and evaluated Glasgow Outcome Scale-Extended scores at six months (10). However, in this trial, the median amount of RBC transfusion was three units (IQR 2–5) in the liberal group and zero units (IQR 0–1) in the restrictive group, indicating that both of the proportion of patients receiving RBC transfusion and the amount of RBCs administered were relatively low. As a result, only 38.4% of the patients in the restrictive strategy group received at least one RBC transfusion. In addition, randomization was performed when patients developed anemia with a hemoglobin level of ≤ 10 g/dL. Consequently, both large-scale studies lacked clinical data before randomization and did not adequately reflect the acute phase of trauma care for severe trauma patients. Therefore, the potential impact of transfusion strategies in patients with severe trauma and TBI at risk for major bleeding during the acute phase remains uncertain.

The RESTRIC trial, a multicenter, cluster-randomized crossover trial in Japan, compared liberal (target hemoglobin level: 10–12 g/dL) and restrictive (7–9 g/dL) RBC transfusion strategies in adult trauma patients at risk for major bleeding and requiring early transfusion just after arrival at the emergency department (11) (12). In this study, more than 80% of enrolled patients received RBC transfusions, and the median cumulative volume of RBCs administered was about 10 units within 28 days. While the primary analysis demonstrated comparable overall clinical outcomes between the two strategies, the effect of transfusion thresholds may differ in subgroups with specific injury patterns, particularly those with head trauma. Given the complex balance between minimizing transfusion-related complications and ensuring adequate cerebral perfusion, a focused evaluation in TBI patients stratified by severity is warranted.

Thus, we aimed to determine whether transfusion strategies in acute phase trauma care influence clinical outcomes in patients with severe trauma and TBI who are at risk for major bleeding.

Methods

Study Design and Data Collection from RESTRIC trial

RESTRIC trial was a cluster-randomized crossover, non-inferior, multicenter trial of patients with severe trauma and was registered with the UMIN Clinical Trial Registry (UMIN000034405) on October 8, 2018. Ethics Committee Tohoku University Graduate School of Medicine, and the Institutional Review Board of Hokkaido University Hospital approved. The protocol was initially approved on October 11, 2018. This study was supported in part by research grant from the General Insurance Association of Japan and the Marumo Emergency Medical Research Promotion Fund.

This study evaluated liberal (target hemoglobin level of 10–12 g/dL) versus restrictive (7–9 g/dL) RBC transfusion strategies with a 1:1 ratio in adult trauma patients. The RESTRIC trial included patients with trauma aged ≥ 20 who had one of the following complications or conditions based on physicians' judgement: severe bleeding that could result in circulatory shock; suspected severe bleeding after arrival at the emergency department; and potential for severe postoperative bleeding during the acute trauma phase. RBC transfusion is initiated before confirming a decrease in hemoglobin levels. Therefore, each RBC transfusion strategy was defined based on the target hemoglobin level rather than the threshold hemoglobin level. Either of the transfusion strategy was applied to the patients until following: seven days after admission to the hospital; discharge from the intensive care unit (ICU); decision to withdraw active treatment; and death. Patients were followed up for 28 days. The RESTRIC trial excluded patients based on the following criteria: cardiac arrest before or upon arrival at the emergency department; transfer from another hospital; physician's decision to withdraw active treatment at initial assessment; complications of severe burns (≥ 15% body surface area); pregnancy; chronic anemia, as determined by the attending physician based on medical history (hemoglobin level: ≤ 7g/dL); and objection to blood transfusion. The allocated transfusion strategy was posted at each center to provide opt-out opportunities to patients and their next-of-kin. The allocated transfusion strategy was applied to all patients during the initial trauma resuscitation phase and upon arrival at the emergency department. Written informed consent was obtained as soon as possible from the patients or their next-of-kin, after which the patients were enrolled in the trial; thereafter, the transfusion strategy was applied until a predefined initiation and follow-up period.

This study was a secondary analysis of the RESTRIC trial. The Hyogo Emergency Medical Center Ethics Committee approved the study (2024011) in accordance with the Helsinki Declaration and waived the requirement for written informed consent because anonymized data from a pre-existing database were used.

Eligibility Criteria

For the present analysis, after excluding patients according to the above RESTRIC trial criteria, we focused on patients with head injuries to assess whether transfusion thresholds differentially affected outcomes among those with TBI. From the original trial cohort, we identified patients with TBI, defined

according to head Abbreviated Injury Scale (AIS) score, and focused on the patients with head AIS scores over or equal to two. Patients with missing outcomes and protocol deviation were also excluded.

Outcomes

The primary outcome was favorable neurological outcomes at discharge, defined as Glasgow Outcome Scale (GOS) scores of 4 or 5. Secondary outcomes were as follows: 28-day survival, the proportion of complications during the first 28 days (transfusion-related acute lung injury, cerebral infarction, pulmonary embolism, acute myocardial infarction, bowel ischemia, deep venous thrombosis [DVT], sepsis), ventilator-free days, catecholamine-free days, and ICU-free days during the first 28 days after arrival at the emergency department. The number of event-free days for patients who died during the first 28 days after arrival at the emergency department was zero.

Statistical Analysis

We used descriptive statistics to characterize the study population. Discrete variables are described using median and IQR. Categorical variables are described using percentages.

To compare primary outcome between the two groups, we performed a logistic regression analysis adjusted for age, sex, mechanism of trauma (blunt or not), injury severity score (ISS), Glasgow Coma Scale (GCS) score, shock on arrival (defined as blood pressure less than 90mmHg), and the use of antithrombotic agent before injury. We used the same methods for our subgroup analysis, where patients were stratified by TBI severity for detailed investigation (moderate was defined as head AIS scores of 2 and 3, and severe was defined as head AIS scores of 4 and 5). Of secondary outcomes, categorical variables were compared with *Chi-square* test, and discrete variables including ICU length of stay, ventilator-free-days, and catecholamine-free days were evaluated by negative binomial distribution adjusted by the same variables.

Missing values in each variable were not replaced nor substituted. Statistical analysis was performed using STATA/IC 15 (StataCorp, Lakeway, TX, USA).

Results

Patient Flowchart

Of the 5,935 trauma patients ≥ 20 years old enrolled in the RESTRIC study, 1,045 were eligible for the original study after applying the exclusion criteria. Among these, 411 patients remained in the original study.

In the current study, those with missing GOS score (n = 1) or protocol deviations (n = 7), or those with head AIS scores less than or equal to one (n = 250) were then also excluded. Finally, 153 patients were included in this study (liberal group, 68 vs. restrictive group, 85) (Fig. 1).

Baseline Characteristics

In this cohort, background characteristics were similar in both groups (Table 1). Of enrolled patients, 76 cases were categorized as moderate and 77 cases were categorized as severe head trauma. Compared with patients in the liberal group, although ISS scores were similar (29 [24.5–39.5] vs. 29 [20–43], p = 0.73), the proportion of shock patients in the restrictive group was higher (16.2% [11/68] vs. 30.6% [26/85], p = 0.04). Although the number of patients who received RBC transfusion within 28 days were significantly different (92.6% [63/68] vs. 81.2% [69/85], p = 0.04), no differences were observed in the total amount of RBCs (10 [6–15] vs. 8 [2–16], p = 0.18), fresh frozen plasma [FFP] (10 [4–16] vs. 8 [4–20], p = 0.76), and platelets (0 [0–15] vs. 0 [0–20], p = 0.76) transfused within 28 days between groups.

Table 1
Patients' characteristics.

Age, median (IQR)		**Total cohort N = 153**	**Missing**	**Liberal Group N = 68**	**Restrictive Group N = 85**	**P value**
		61 (43–74)	**0**	**60 (42.5–74)**	**61 (44–74)**	**0.69**
Sex, male, n (%)		102 (66.7)	0	45 (66.2)	57 (66.1)	0.91
Mechanism of trauma, n %	Blunt	151 (98.7)	-	68 (100)	83 (97.6)	0.20
	Penetrating	1 (0.7)	-	0 (0)	1 (1.2)	0.37
	Other	1 (0.7)	-	0 (0)	1 (1.2)	-
ISS, median (IQR)	Total	29 (22–41)	0	29 (24.5–39.5)	29 (20–43)	0.73
AIS, median (IQR)	Head	4 (2–5)	0	4 (3–5)	3 (2–5)	0.37
	Face	0 (0–1)	0	0 (0–2)	0 (0–1)	0.25
	Chest	3 (0–3)	0	2 (0–3)	3 (0–4)	0.08
	Abdomen	0 (0–2)	0	0 (0–2)	1 (0–3)	0.07
	Pelvic or limb	2 (0–3)	0	2.5 (2–3)	2 (0–3)	0.04
	Surface	0 (0–1)	0	0 (0–1)	0 (0–1)	0.76
TBI severity, n (%)	Moderate AIS 2–3	76 (49.7)	0	32 (47.1)	44 (51.8)	0.56
	Severe AIS 4–5	77 (50.3)	0	36 (52.9)	41 (48.2)	-
Comorbidity, n (%)	Chronic heart failure	3 (2.0)	0	1 (1.5)	2 (2.4)	0.70
	Chronic renal failure	1 (0.7)	0	0 (0)	1 (1.2)	0.37
	Chronic liver failure	1 (0.7)	0	0 (0)	1 (1.2)	0.37

* IQR: interquartile range, ISS: Injury Severity Score, AIS: Abbreviated Injury Scale, TBI: traumatic brain injury, SBP: systolic blood pressure, RR: respiratory rate, HR: heart rate, GCS: Glasgow Coma Scale, PT-INR: prothrombin time–international normalized ratio

Age, median (IQR)		**Total cohort N = 153**	**Missing**	**Liberal Group N = 68**	**Restrictive Group N = 85**	**P value**
		61 (43–74)	**0**	**60 (42.5–74)**	**61 (44–74)**	**0.69**
	Chronic respiratory failure	0 (0)	0	0 (0)	0 (0)	-
	Immunosuppression	0 (0)	0	0 (0)	0 (0)	-
Antithrombotic agents prior to injury, n (%)	Antiplatelet	12 (7.8)	-	5 (7.4)	7 (8.2)	0.84
	Anticoagulant	3 (2.0)	-	1 (1.5)	2 (2.4)	0.70
	Both	2 (1.3)	-	0 (0)	2 (2.4)	0.20
	None	135 (88.2)	-	62 (91.2)	73 (85.9)	0.31
	Unknown	1 (0.7)	-	0 (0)	1 (1.2)	-
Vital signs on arrival, median (IQR)	SBP, mmHg	122 (90–145)	0	125 (105.5–147)	120 (85–143)	0.19
	SBP < 90, n (%)	37 (24.2)	0	11 (16.2)	26 (30.6)	0.04
	RR, bpm	23 (18–28)	0	20.5 (16.5–26)	24 (20–29)	0.05
	HR, bpm	97 (80–118)	0	95.5 (78–116)	100 (81–118)	0.59
GCS score, median (IQR)	Total	11 (6–13)	0	9.5 (6–13)	12 (6–14)	0.20
	Eye	3 (1–4)	0	2 (1–3)	3 (1–4)	0.07
	Verbal	3 (1–4)	0	2.5 (1–4)	4 (1–4)	0.11
	Motor	5 (4–6)	0	5 (4–6)	5 (4–6)	0.46

* IQR: interquartile range, ISS: Injury Severity Score, AIS: Abbreviated Injury Scale, TBI: traumatic brain injury, SBP: systolic blood pressure, RR: respiratory rate, HR: heart rate, GCS: Glasgow Coma Scale, PT-INR: prothrombin time–international normalized ratio

Age, median (IQR)	**Total cohort N = 153**	**Missing**	**Liberal Group N = 68**	**Restrictive Group N = 85**	**P value**
	61 (43–74)	**0**	**60 (42.5–74)**	**61 (44–74)**	**0.69**
Surgery within 6 hours, n (%)	71 (46.4)	0	34 (50.0)	37 (43.5)	0.43
Head	13 (8.5)	0	6 (8.8)	7 (8.2)	0.90
Chest	5 (3.3)	0	3 (4.4)	2 (2.4)	0.48
Abdomen	24 (15.7)	0	8 (11.8)	16 (18.8)	0.23
Pelvic	25 (16.3)	0	15 (22.1)	10 (11.8)	0.09
Limb or neck	8 (5.2)	0	4 (5.9)	4 (4.7)	0.75
Other	1 (0.7)	0	1(1.5)	0 (0)	0.26
Laboratory data on arrival, median (IQR)					
Hemoglobin, g/dL	12.3 (10.8–13.9)	0	12.1 (10.9–13.7)	12.4 (10.7–14)	0.81
Fibrinogen, mg/ml	200 (161–250)	0	202.5 (173–250.5)	197 (156–246)	0.72
Platelets, 10^3/µml	216 (167–270)	0	228.5 (180–268.5)	207 (160–271)	0.22
PT-INR	1.08 (1.01–1.19)	0	1.06 (1.00–1.17)	1.11 (1.02–1.22)	0.03
Lactate, mmol/L	3.2 (2.1–4.7)	3	3.15 (1.84–4.78)	3.28 (2.40–4.70)	0.21
Number of patients who received transfusion within 28 days, (%)					

* IQR: interquartile range, ISS: Injury Severity Score, AIS: Abbreviated Injury Scale, TBI: traumatic brain injury, SBP: systolic blood pressure, RR: respiratory rate, HR: heart rate, GCS: Glasgow Coma Scale, PT-INR: prothrombin time–international normalized ratio

Age, median (IQR)		**Total cohort N = 153**	**Missing**	**Liberal Group N = 68**	**Restrictive Group N = 85**	**P value**
		61 (43–74)	**0**	**60 (42.5–74)**	**61 (44–74)**	**0.69**
	Red blood cells	132 (86.3)	0	63 (92.6)	69 (81.2)	0.04
	Fresh frozen plasma	122 (79.7)	0	54 (79.4)	68 (80.0)	0.93
	Platelets	55 (35.9)	0	23 (33.8)	32 (37.6)	0.62
Transfusion amount within 28 days, units, median (IQR)						
	Red blood cells	10 (4–16)	0	10 (6–15)	8 (2–16)	0.18
	Fresh frozen plasma	10 (4–18)	0	10 (4–16)	8 (4–20)	0.76
	Platelets	0 (0–20)	0	0 (0–15)	0 (0–20)	0.76

* IQR: interquartile range, ISS: Injury Severity Score, AIS: Abbreviated Injury Scale, TBI: traumatic brain injury, SBP: systolic blood pressure, RR: respiratory rate, HR: heart rate, GCS: Glasgow Coma Scale, PT-INR: prothrombin time–international normalized ratio

Figure 2 and Fig. 3 show blood hemoglobin level trends in the acute phase within 168 hours after admission and the amount of RBCs and FFP administered within 28 days in both groups, respectively.

Outcomes

Primary and secondary outcomes are shown in Table 2. There was no difference in favorable GOS scores (26.5% [18/68] vs. 30.6% [26/85], OR 1.06, 95% CI 0.44–2.56, p = 0.90), and similar results were found in subgroup analysis based on TBI severity (moderate: 40.6% [13/32] vs. 47.7% [21/44], OR 1.39, 95% CI 0.47–4.09, p = 0.55, severe: 13.9% [5/36] vs. 12.2% [5/41], OR 0.68, 95% CI 0.10–4.84, p = 0.70).

Table 2
Primary and secondary outcomes.

Favorable GOS score, %		**Liberal Group N = 68**	**Restrictive Group N = 85**	**Adjusted Odds Ratio (95% CI)**	**P value**
	Total	**18/68 (26.5)**	**26/85 (30.6)**	**1.06 (0.44–2.56)**	**0.90**
	Head AIS score 2–3	13/32 (40.6)	21/44 (47.7)	1.39 (0.47–4.09)	0.55
	Head AIS score 4–5	5/36 (13.9)	5/41 (12.2)	0.68 (0.10–4.84)	0.70
28-day survival, %		58/68 (85.3)	73/85 (85.9)	0.91 (0.29–2.87)	0.88
Complication during the first 28 days, %					
	Transfusion-related acute lung injury	0/68 (0)	0/85 (0)	-	-
	Cerebral infarction	0/68 (0)	2/85 (2.4)	-	0.20
	Pulmonary embolism	0/68 (0)	4/85 (4.7)	-	0.07
	Acute myocardial infarction	0/68 (0)	0/85 (0)	-	-
	Bowel ischemia	0/68 (0)	0/85 (0)	-	-
	Deep venous thrombosis	2/68 (2.9)	12/85 (14.1)	-	0.02
	Sepsis	5/68 (7.3)	1/85 (1.2)	-	0.05
Event-free days during the first 28 days, days, IQR*					
	Ventilator-free days**	20 (10–26)	23 (12–28)	0.018 (-0.24–0.28)	0.89
	Catecholamine-free days**	28 (28–28)	28 (25–28)	-0.027 (-0.28–0.22)	0.84

* Negative binomial distribution was conducted, adjusted for age, sex, mechanism of trauma, injury severity score, shock on arrival (defined as systolic blood pressure under 90 mmHg), Glasgow Coma Scale score, and use of antithrombotic agent, GOS: Glasgow Outcome Scale, AIS: Abbreviated Injury Scale, IQR: interquartile range, ICU: intensive care unit, CI: confidence interval

** 1 patient missing data in liberal group.

Favorable GOS score, %		Liberal Group	Restrictive Group	Adjusted Odds Ratio	P value
		N = 68	N = 85	(95% CI)	
	Total	**18/68 (26.5)**	**26/85 (30.6)**	**1.06 (0.44–2.56)**	**0.90**
	ICU-free days**	15 (4–21)	16 (7–23)	0.036 (-0.28–0.35)	0.82

* Negative binomial distribution was conducted, adjusted for age, sex, mechanism of trauma, injury severity score, shock on arrival (defined as systolic blood pressure under 90 mmHg), Glasgow Coma Scale score, and use of antithrombotic agent, GOS: Glasgow Outcome Scale, AIS: Abbreviated Injury Scale, IQR: interquartile range, ICU: intensive care unit, CI: confidence interval

** 1 patient missing data in liberal group.

There was no significant difference in 28-day survival between the two groups (85.3% [58/68] vs. 85.9% [74/85], OR 0.91, 95% CI 0.29–2.87, p = 0.88). Although transfusion-related acute lung injury, acute myocardial infarction, and bowel ischemia were not found in either group, DVTs were frequently found in the restrictive group (2.9% [2/68] vs. 14.1% [12/85], p = 0.02). Negative binomial distribution showed no significant differences in ICU-free days (15 [4–21] vs. 16 [7–23], coefficient 0.034, 95% CI -0.27 to 0.34, p = 0.82), ventilator-free days (20 [10–26] vs. 23 [12–28], coefficient 0.018, 95% CI -0.24 to 0.28, p = 0.89), and catecholamine-free days (28 [28–28] vs. 28 [25–28], coefficient − 0.027, 95% CI -0.28 to 0.22, p = 0.84), respectively.

Discussion

Our study demonstrated that favorable neurological outcomes, evaluated using GOS scores, did not differ among adult patients with TBI and severe trauma at risk for major bleeding. This finding remained consistent, even after analysis of subgroups stratified by TBI severity. In addition, the total amount of transfused RBC, FFP, and platelet units within 28 days did not differ significantly between groups.

Although some randomized trials have been conducted, this topic remains controversial. Gobatto et al. demonstrated lower hospital mortality and more favorable neurological status at six months in the liberal group (< 9g/dL) compared to the restrictive group (< 7g/dL) (13). However, findings from recent large studies were not consistent with this previous study. Although the TRAIN trial, which included 850 patients with brain injury from internal and external causes with hemoglobin < 9 g/dL randomized to liberal (< 9 g/dL) vs. restrictive transfusion strategies (< 7 g/dL) for 28 days, showed that liberal strategy reduced unfavorable neurologic outcomes at 180 days, the study did not show outcomes among patients with only TBI (9). There were 742 patients in the HEMOTION trial, which compared moderate to severe TBI in patients with GCS scores of 12 or lower randomized to liberal (≤ 10 g/dL) vs. restrictive (≤ 7 g/dL) transfusion and showed that the liberal strategy did not significantly reduce unfavorable neurologic outcomes at six months, although survivors in the liberal arm had slightly better functional independence (10). In this study, the median time from injury to hospital admission exceeded 60 minutes, and

randomization was performed more than 50 hours after injury. Also, the median time between hemoglobin measurements and RBC transfusion was about two hours. Therefore, this setting neither reflected the immediate to acute phase of trauma care nor targeted patients requiring immediate hemostasis. The same trend was recognized even in the severe trauma group with ISS scores equal to 15 or over (14). We believe that our study provides further perspectives pertaining to transfusion strategy in the immediate to acute phase trauma care.

Complications can be influenced by transfusion strategy. Previous studies have reported that the incidence of acute respiratory distress syndrome was numerically higher, whereas cerebral ischemic events were lower in the liberal transfusion group, while the occurrence of DVT did not differ (9) (10). However, results from these randomized controlled trials were inconsistent, and the hemoglobin thresholds used to guide transfusion strategies differed across studies. Interestingly, the current study demonstrated a higher proportion of patients who developed DVT in the restrictive group. Venous thromboembolism is frequently observed in acutely ill medical patients with anemia, and chronic anemia has been reported to be potentially associated with DVT (15). DVT is also frequently observed in patients with severe trauma (16) (17). Unfortunately, routine screening for DVT was not mandated in this study, and diagnostic examinations were performed at the physician's discretion. Therefore, the timing of DVT development, the optimal frequency of screening, and the association between transfusion strategy and DVT development remain unknown.

Because of the brain's unique metabolism, transfusion strategies using different hemoglobin thresholds have been proposed to achieve better outcomes and have been applied in several brain disorders. A systematic review of acute brain injury, including injuries from external and internal causes, found no statistically significant difference in overall neurological outcomes, although sensitivity analyses suggested a possible benefit from liberal transfusion (18) (19). The results were consistent, even among patients with acute subarachnoid hemorrhage and spontaneous intracerebral hemorrhage (20) (21). A review including five randomized trials focused solely on TBI similarly reported no significant difference in mortality or unfavorable neurologic outcomes at six months between two different strategies, although restrictive thresholds reduced RBC exposure (22). However, the results of this review appear to have been disproportionately influenced by a single study, possibly because its sample size was substantially larger than that of the other included studies, thereby giving it greater weight in the overall analysis (10). Further large-scale research is warranted for robust evidence.

Hemoglobin levels primarily influence intracranial pressure (ICP) and brain oxygenation indirectly through changes in arterial oxygen content and cerebral blood flow (22). Raising hemoglobin level with RBC transfusion increases arterial oxygen content and often improves brain tissue oxygen tension ($PbtO_2$), especially when baseline $PbtO_2$ is low or there is a high risk of ischemia (23). $PbtO_2$-guided protocols that include transfusion as one of several interventions (along with FiO_2, cerebral perfusion pressure optimization, etc.) significantly reduce the burden of cerebral hypoxia compared with ICP-only management, though effects on long-term outcome are still being clarified (24). Since the effectiveness of high-level hemoglobin may differ depending on severity, our study focused on trauma patients with

TBI at risk for major bleeding and stratified moderate and severe head trauma cases. However, it did not show the efficacy of transfusion strategies, even in the subgroups. Identification of patients most likely to benefit from specific transfusion strategies remains unclear and should be considered in future studies. Ongoing assessment of the effect of bundled intervention, including the amount of RBC transfusion guided by invasive monitoring of brain-tissue oxygenation, may clarify these perspectives (25).

Limitations

Our study has several limitations. First, this is a secondary analysis of an original study (11); therefore, the number of enrolled patients is insufficient and underpowered, resulting in substantial uncertainty and a wide 95% CI. Second, we did not evaluate long-term outcomes. Since sufficient oxygen delivered by hemoglobin could be beneficial for damaged brain-tissue for the process of recovery, long-term outcomes, including neurological function, should be assessed. Third, the proportion of complications was fewer than that in other previous studies; therefore, we could not evaluate some of those variables using statistical analysis in the current study. Fourth, some residual confounders were unmeasured due to the lack of original data. However, we compared two groups using data from a prospective, multicenter, cluster-randomized trial and identified an association between transfusion strategy in the immediate to acute trauma phase and outcomes in patients with severe trauma and TBI at risk for major bleeding, which provided us additional robust evidence in this field.

Conclusions

In this secondary analysis of the RESTRIC trial focusing on patients with severe trauma and TBI at risk for major bleeding, transfusion strategies in the immediate to acute phase of trauma care were not associated with favorable GOS score at discharge when comparing the liberal and restrictive groups. Further studies evaluating long-term outcomes and different phases of trauma care are warranted to clarify the optimal transfusion strategy.

Declarations

Conflicts of interest:

None declared.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board Committee of Hyogo Emergency Medical Center (2014011).

There is no fund and grant to support this study.

Informed consent

was obtained from all individual participants included in the original study.

Author Contribution

T.N., D.K., and M.H., participated in the study design and data acquisition. T.N. analyzed the data. All authors were actively involved in the drafting and critical revision of the manuscript.

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Figures

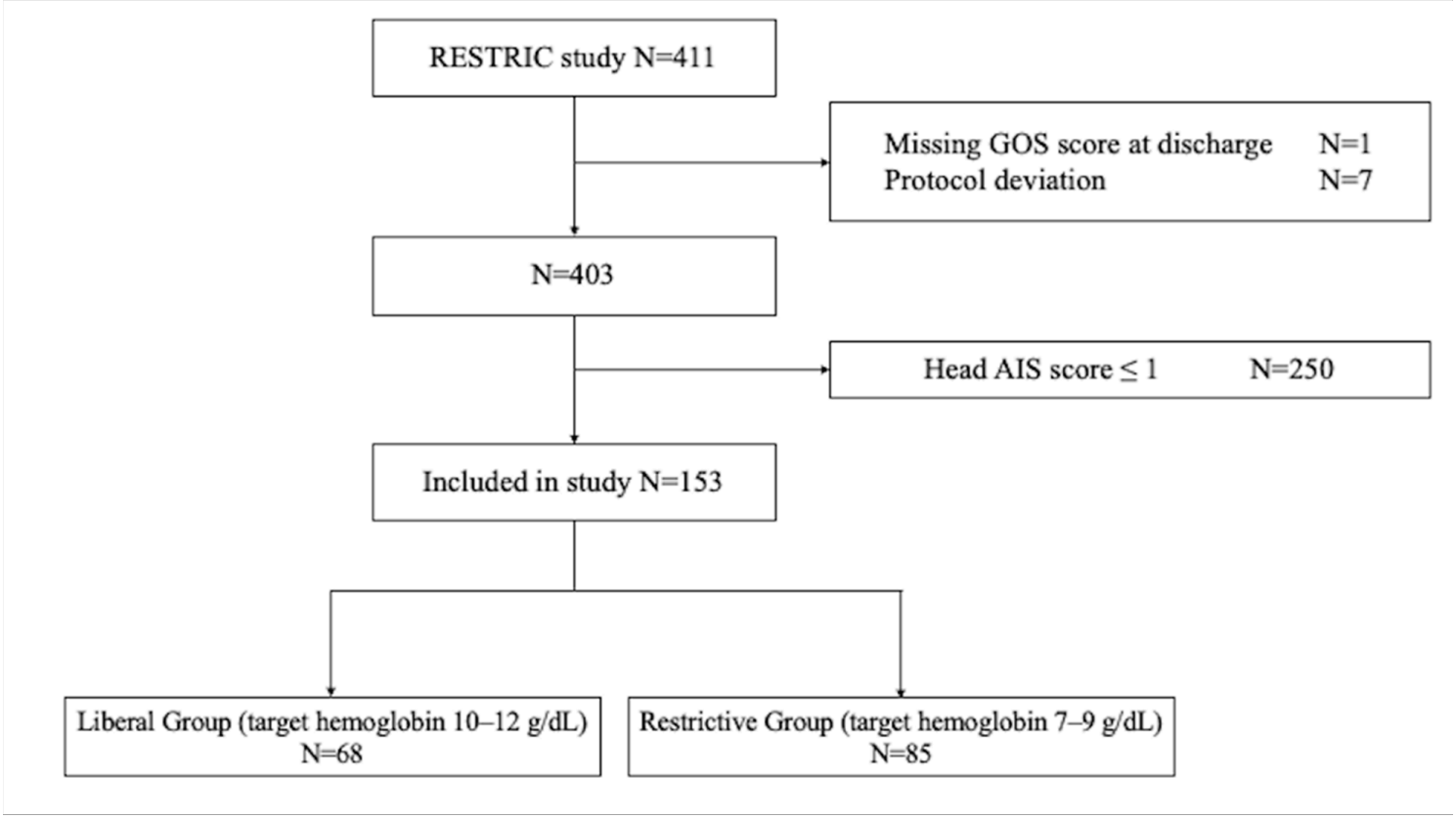


Figure 1

Flowchart of patients enrolled in this study.

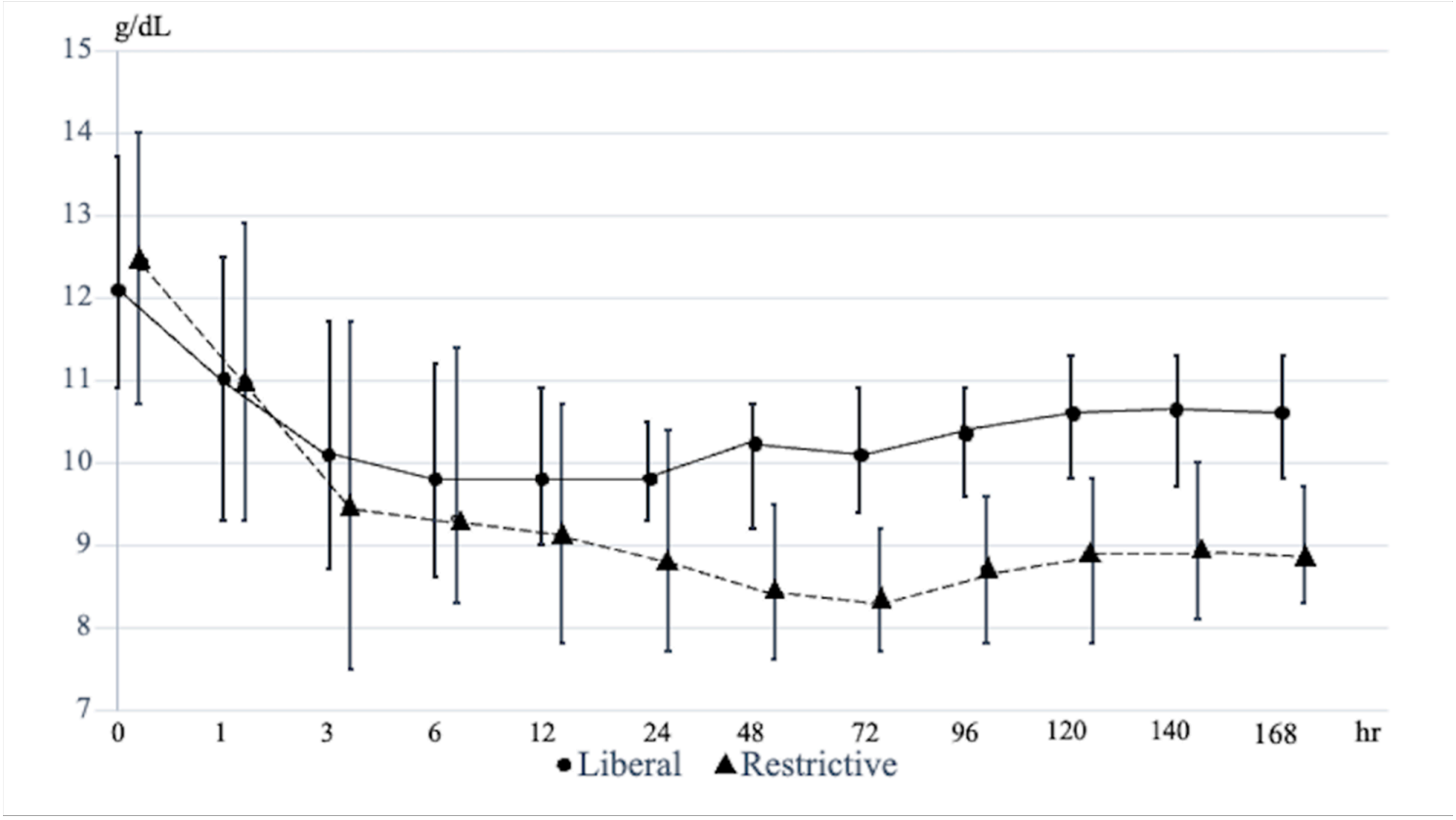


Figure 2

Hemoglobin trends in the liberal and restrictive groups within 168 hours after admission. Data are expressed as medians (interquartile range).

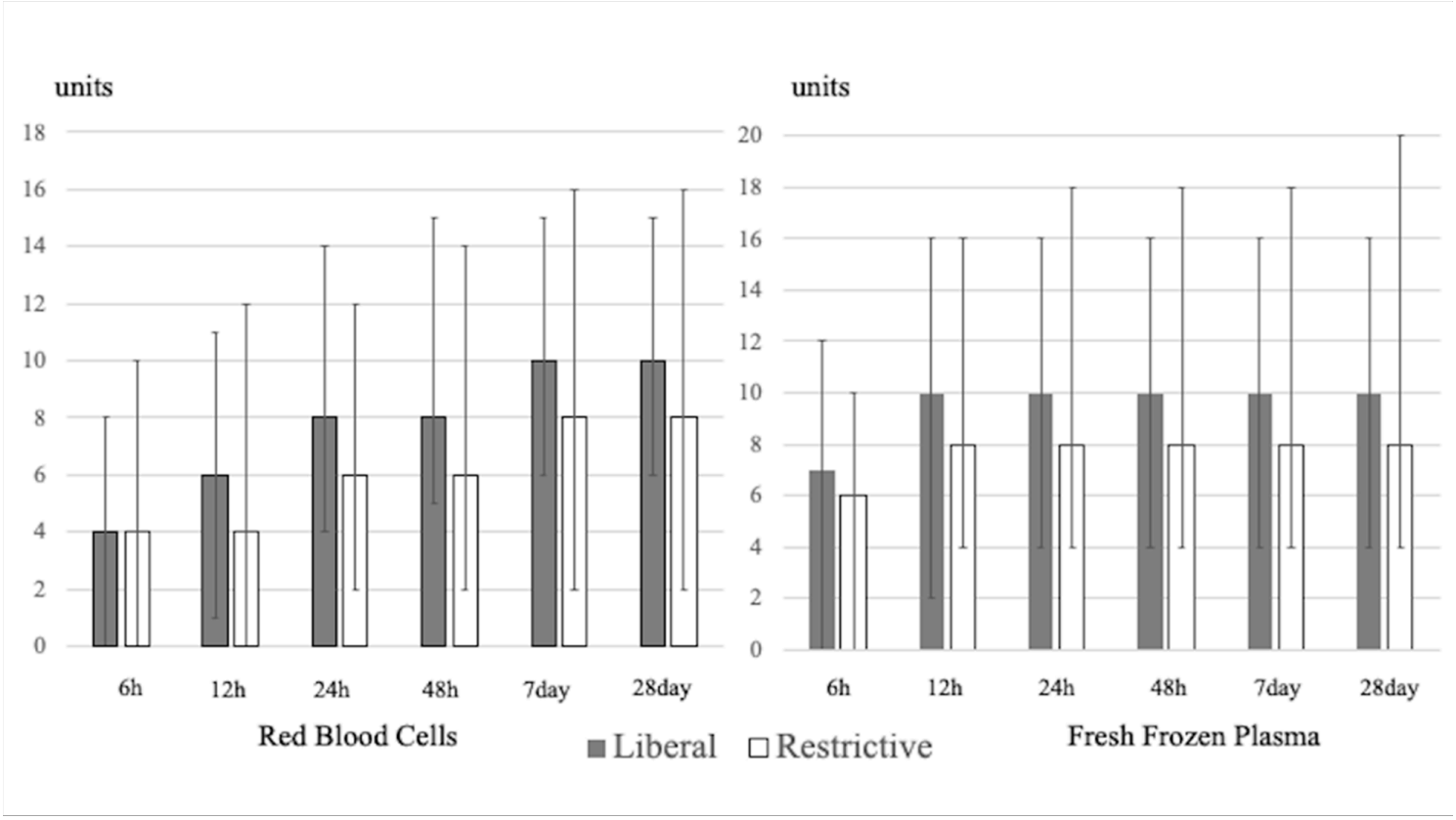


Figure 3

Red blood cell and fresh frozen plasma transfusion trends in the liberal and restrictive groups within 28 days after admission. Data are expressed as medians (interquartile range)