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# Association between whole blood versus balanced component therapy and survival in isolated severe traumatic brain injury

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## ABSTRACT

**Background** Whole blood transfusion (WBT) is associated with improved hemostasis and possibly mortality in patients with hemorrhagic shock after injury but there are no studies in patients with isolated severe traumatic brain injury (TBI). The objective of this investigation was to compare outcomes of balanced component therapy (BCT) versus WBT in patients with an isolated severe TBI.

**Methods** Adult patients (≥18 years) registered in the Trauma Quality Improvement Program (2016–2019) who suffered a blunt isolated severe TBI (head Abbreviated Injury Score ≥3 in the head and ≤1 in the remaining body regions) and who received a BCT (1–2:1 packed red blood cell (PRBC):fresh frozen plasma and 1–2:1 PRBC:platelets) or WBT were eligible for inclusion. Patients were matched, based on the transfusion received, using propensity score matching. The primary outcome of interest was in-hospital mortality.

**Results** A total of 217 patients received either WBT (n=82) or BCT (n=135). After propensity score matching, 50 matched pairs were analyzed. The rate of in-hospital mortality was significantly lower in the WBT compared with BCT group (43.1% vs 66.7%, p=0.025) corresponding to a relative risk (RR) reduction of 35% in in-hospital mortality (RR (CI 95%): 0.65 (0.43 to 0.97)). However, in subgroup analyses comparing those who were managed surgically and conservatively, this association only remained significant among patients who underwent neurosurgical intervention.

**Conclusions** WBT in patients with severe isolated TBI is associated with better survival compared with BCT in patients who require neurosurgical intervention. Further investigation into this finding using an appropriately powered, prospective study design is warranted.

**Level of evidence** Level III, therapeutic.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

⇒ The data is mounting in favor of whole blood transfusion (WBT) resuscitation in multi-injured trauma patients. However, there is a paucity of data in patients suffering isolated severe traumatic brain injury (TBI) who have received WBT compared with component therapy.

**WHAT THIS STUDY ADDS**

⇒ In the current retrospective investigation using the Trauma Quality Improvement Program, WBT was associated with better overall outcomes in patients who suffered an isolated severe TBI.

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

⇒ This finding highlights the need for further investigation of using robust prospective studies to validate this finding.

## BACKGROUND

Traumatic brain injury (TBI) remains one of the most common causes of mortality after trauma worldwide.[1] Management of TBI is mainly focused on preventing and treating secondary brain injury.[2 3] It has already been well established that hypotension and hypoxia, both of which contribute to cerebral ischemia, result in the development of secondary insults that lead to worse outcomes.[4–6] The presence of a concomitant hemorrhage further exacerbates this risk by impeding oxygen delivery and promoting pathological cascades in adjacent brain parenchyma which add to secondary brain injury.[7]

The use of balanced component therapy (BCT), with packed red blood cells (PRBCs), plasma, and platelets being transfused at a 1:1:1 ratio to mimic whole blood (WB), has previously been strongly associated with improved survival in polytraumatized patients who require transfusion.[8] During the last decade, after initial successes in military applications, the use of WB transfusion (WBT) in the resuscitation of hemorrhagic trauma patients has also gained popularity in civilian trauma centers.[9–12] WB provides all the components of blood, but has more coagulation factor and platelet bioactivity than BCT. Single-center and retrospective studies suggest that use of WB in massively bleeding patients is associated with improved hemostasis, which presumably results in improved oxygen-carrying capacity and oxygen delivery, as well as mortality.[8 9 13–15]

Furthermore, there are promising results from animal models of TBI that observed an improvement in the immunomodulatory response and overall outcomes after administration of WB[4 16]; nevertheless, the clinical utility of WB in patients who have suffered TBI has yet to be defined. If the mechanisms by which WB improves morbidity and mortality after injury are improved hemostasis, enhanced oxygen delivery, and favorable

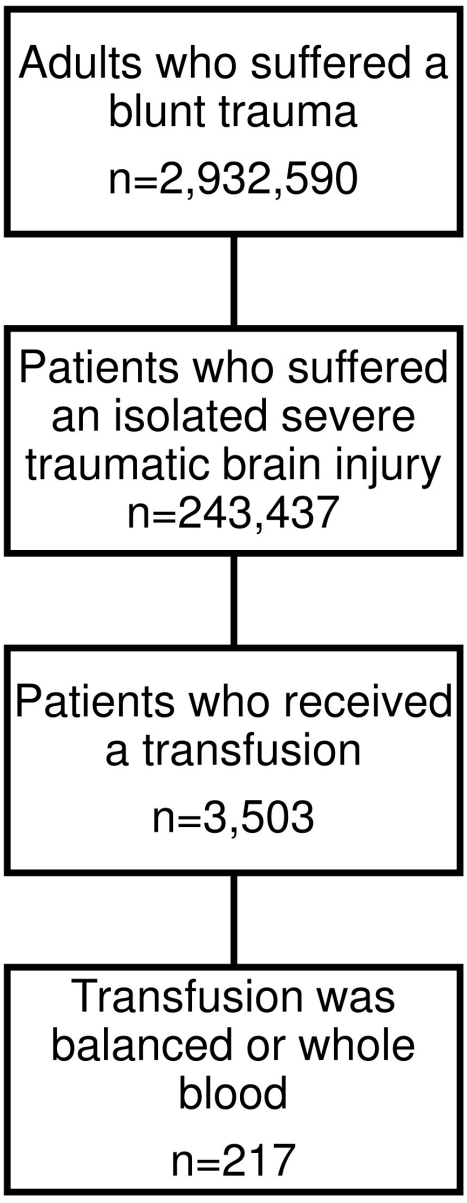


**Figure 1** Flow chart describing the selection of the sample population.

immunomodulation, it stands to reason that the use of WB in patients with TBI may also be associated with improved clinical outcomes. In the current study, an investigation was undertaken to compare how WB and BCT transfusions are associated with outcomes in patients with severe isolated TBI. The authors hypothesized that WBT is associated with improved overall outcomes.

## METHODS

Data were obtained from The American College of Surgeons Trauma Quality Improvement Program (TQIP) database. All adult patients (18 years or older) registered in TQIP between 2016 and 2019 who suffered an isolated severe TBI as a result of blunt trauma and received either WBT or BCT within the first 24 hours of admission were included. An isolated severe TBI was defined as Abbreviated Injury Scale (AIS) ≥3 in the head and ≤1 in the remaining regions. A balanced component transfusion was defined as a ratio of 1–2:1 PRBC:fresh frozen plasma as well as 1–2:1 PRBC:platelets, administered within the first 24 hours. The presence of a WBT was identified based on the presence of any of the following International Classification of Diseases (ICD)-10 procedure codes: 30230H0, 30230H1, 30233H0, 30233H1, 30240H0, 30240H1, 30243H0, 30243H1, 30250H0, 30250H1, 30253H0, 30253H1, 30260H0, 30260H1, 30263H0, 30263H1, 30273H1. Patients were excluded if they had a head AIS of 6 since these injuries are generally not considered survivable. Data retrieved included: age, sex, race, the AIS for each body region, comorbidities, presence of an advanced directive limiting care, administered transfusion, timing of the transfusion, discharge disposition, and complications.

The need for ethical approval by an institutional review board was waived for the current investigation as all analyses were performed using an anonymized, retrospective dataset. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines and Declaration of Helsinki were adhered to throughout the completion of the investigation.[17]

### Statistical analysis

All patients were grouped based on the type of transfusion they received, BCT or WBT. Patients who received a WBT were included in this cohort regardless of what blood component therapy they received (in the current analysis five of the patients in the WBT cohort prior to matching also received a BCT, after matching only one patient in the WBT cohort had also received a BCT). Continuous variables were tabulated using the median and IQR, as they were non-normally distributed, and categorical variables were instead presented as counts and percentages. Prior to matching, the statistical significance of differences between the groups was analyzed using the Mann-Whitney U-test for continuous variables and either the $\chi^2$ test or Fisher's exact test for categorical variables. The primary outcome of interest was in-hospital mortality.

Adjustment for potential confounders was accomplished using propensity score matching. Matching was performed based on patients' age, sex, race, highest AIS in each region, Glasgow Coma Scale (GCS), hypotension at admission (systolic blood pressure <90 mm Hg), comorbidities (hypertension, history of myocardial infarction, congestive heart failure, history of peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, smoking status, chronic renal failure, diabetes mellitus, cirrhosis, coagulopathy, currently receiving chemotherapy for cancer, disseminated cancer, drug use disorder, alcohol use disorder, major psychiatric illness), advanced directives limiting care, neurological surgery, as well as intracranial injuries (cerebral contusion, epidural hematoma, traumatic subdural hematoma, traumatic subarachnoid hemorrhage, diffuse axonal injury, other intracranial injury). Propensity scores were calculated using logistic regression, and patients were matched at a 1:1 ratio with a caliper of 0.2 using a nearest neighbor matching algorithm. After matching, balance was evaluated using the Wilcoxon signed rank test for continuous variables and McNemar's test with Bonferroni correction for categorical variables. When matching, missing values were counted as their own category when calculating propensity scores.

As an alternative analysis, the propensity scores were also used for inverse probability of treatment weighting (IPTW). In this analysis propensity scores were converted into weights.

The weights for those who received a WBT were calculated as $\frac{1}{propensity\ score}$ and the weights for those who received a BCT were calculated as $\frac{1}{1-\ propensity\ score}$. Balance after weighting was evaluated using absolute standardized differences (ASD).

**Table 1** Demographics of patients with severe TBI who received a transfusion

| | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | Balanced component transfusion (n=135) | Whole blood transfusion (n=82) | P value | Balanced component transfusion (n=50) | Whole blood transfusion (n=50) | P value |
| Age, median (IQR) | 67 (54–75) | 62 (52–77) | 0.677 | 68 (54–76) | 64 (56–77) | 0.892 |
| Sex, n (%) | | | 0.246 | | | 1.00 |
| Female | 53 (39.3) | 25 (30.5) | | 17 (34.0) | 16 (32.0) | |
| Male | 82 (60.7) | 57 (69.5) | | 33 (66.0) | 34 (68.0) | |
| Race, n (%) | | | | | | |
| White | 98 (72.6) | 59 (72.0) | 0.979 | 36 (72.0) | 35 (70.0) | 1.00 |
| Black | 14 (10.4) | 11 (13.4) | 0.598 | 7 (14.0) | 9 (18.0) | 0.789 |
| Asian | 4 (3.0) | 3 (3.7) | 0.713 | 1 (2.0) | 2 (4.0) | 1.00 |
| Pacific islander | 1 (0.7) | 0 (0.0) | 1.00 | 0 (0.0) | 0 (0.0) | NA |
| Other | 15 (11.1) | 5 (6.1) | 0.346 | 4 (8.0) | 2 (4.0) | 0.683 |
| Missing | 0 (0.0) | 2 (2.4) | | 0 (0.0) | 0 (0.0) | |
| Hypertension, n (%) | 52 (38.5) | 27 (32.9) | 0.494 | 19 (38.0) | 16 (32.0) | 0.677 |
| History of myocardial infarction, n (%) | 4 (3.0) | 0 (0.0) | 0.300 | 0 (0.0) | 0 (0.0) | NA |
| Congestive heart failure, n (%) | 7 (5.2) | 7 (8.5) | 0.491 | 4 (8.0) | 5 (10.0) | 1.00 |
| History of peripheral vascular disease, n (%) | 2 (1.5) | 0 (0.0) | 0.528 | 0 (0.0) | 0 (0.0) | NA |
| Cerebrovascular disease, n (%) | 6 (4.4) | 1 (1.2) | 0.258 | 2 (4.0) | 1 (2.0) | 1.00 |
| Dementia, n (%) | 6 (4.4) | 1 (1.2) | 0.258 | 0 (0.0) | 0 (0.0) | NA |
| COPD, n (%) | 11 (8.1) | 5 (6.1) | 0.770 | 6 (12.0) | 5 (10.0) | 1.00 |
| Current smoker, n (%) | 17 (12.6) | 9 (11.0) | 0.889 | 5 (10.0) | 5 (10.0) | 1.00 |
| Chronic renal failure, n (%) | 5 (3.7) | 1 (1.2) | 0.413 | 2 (4.0) | 1 (2.0) | 1.00 |
| Diabetes mellitus, n (%) | 31 (23.0) | 14 (17.1) | 0.387 | 11 (22.0) | 10 (20.0) | 1.00 |
| Cirrhosis, n (%) | 24 (17.8) | 2 (2.4) | 0.002 | 3 (6.0) | 2 (4.0) | 1.00 |
| Coagulopathy, n (%) | 10 (7.4) | 11 (13.4) | 0.225 | 5 (10.0) | 7 (14.0) | 0.752 |
| Anticoagulant therapy, n (%) | 29 (21.5) | 6 (7.3) | 0.134 | 9 (18.0) | 4 (8.0) | 0.505 |
| Missing | 30 (22.2) | 40 (48.8) | | 15 (30.0) | 25 (50.0) | |
| Currently receiving chemotherapy for cancer, n (%) | 5 (3.7) | 2 (2.4) | 0.713 | 3 (6.0) | 2 (4.0) | 1.00 |
| Disseminated cancer, n (%) | 7 (5.2) | 3 (3.7) | 0.746 | 3 (6.0) | 2 (4.0) | 1.00 |
| Drug use disorder, n (%) | 9 (6.7) | 5 (6.1) | 1.00 | 2 (4.0) | 3 (6.0) | 1.00 |
| Alcohol use disorder, n (%) | 30 (22.2) | 9 (11.0) | 0.056 | 7 (14.0) | 5 (10.0) | 0.752 |
| Major psychiatric illness, n (%) | 16 (11.9) | 9 (11.0) | 1.00 | 7 (14.0) | 6 (12.0) | 1.00 |
| Advanced directive limiting care, n (%) | 10 (7.4) | 3 (3.7) | 0.379 | 3 (6.0) | 3 (6.0) | 1.00 |
| Withdrawal of life supporting treatment, n (%) | 63 (46.7) | 16 (19.5) | 0.043 | 22 (44.0) | 13 (26.0) | 0.267 |
| Missing | 16 (11.9) | 35 (42.7) | 16 (11.9) | 10 (20.0) | 17 (34.0) | |

Age is measured in years. A patient may have had more than one race.
COPD, chronic obstructive pulmonary disease; TBI, traumatic brain injury.

An ASD <0.1 was considered balanced. After IPTW, a Poisson regression model with robust SEs was used to adjust for any covariates that remained unbalanced. Results were presented as an incidence rate ratio (IRR) and 95% confidence interval (CI). In this sensitivity analysis, missing data was managed using multiple imputation by chained equations. Subgroup analyses on patients who underwent neurosurgical intervention and those who were managed conservatively were also performed using this methodology.

A two-tailed p value of less than 0.05 was considered statistically significant in all analyses. Analyses were performed with the statistical programming language R (R Foundation for Statistical Computing, Vienna, Austria) using the *readxl*, *tidyverse*, *mice*, *sandwich*, and *MatchIt* packages.[18]

## RESULTS

During the inclusion period, 217 patients with an isolated severe TBI received a WBT or BCT (figure 1). Of these 82 (37.8%) received a WBT and 135 (62.2%) received a BCT. Before matching, age, sex, race, and comorbidity distributions were relatively similar between patients who received WBT and BCT with both cohorts consisting mostly of Caucasian male patients who were approximately 65 years old. Most patients in each cohort presented with a subdural bleed and/or subarachnoid hemorrhage and had an initial GCS of 3–8. However, the rate of liver cirrhosis was significantly lower among patients who received a WBT compared with those who received a BCT (2.4% vs 17.8%, p=0.002) (table 1). Those who received a WBT were also less severely injured based on their AIS (head AIS 5: 37.8% vs 75.6%, p<0.001). Consequently, patients who received a WBT were less likely to undergo neurological surgery (39.0% vs 68.9%, p<0.001) or to have a subdural hematoma (69.5% vs 90.4%, p<0.001) compared with patients who received a BCT (table 2). Similarly, patients who received a WBT demonstrated a significantly lower rate of in-hospital mortality (41.5% vs 61.5%, p=0.006) (table 3).

After matching, 50 pairs could be analyzed. All matched variables were balanced between the two groups (tables 1 and 2). There was no longer a significant difference in the need for operative intervention. The rate of in-hospital mortality remained

**Table 2** Clinical characteristics of patients with severe TBI who received a transfusion

| | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | Balanced component transfusion (n=135) | Whole blood transfusion (n=82) | P value | Balanced component transfusion (n=50) | Whole blood transfusion (n=50) | P value |
| Head AIS, n (%) | | | <0.001 | | | 1.00 |
| 3 | 15 (11.1) | 30 (36.6) | | 12 (24.0) | 10 (20.0) | |
| 4 | 18 (13.3) | 21 (25.6) | | 11 (22.0) | 14 (28.0) | |
| 5 | 102 (75.6) | 31 (37.8) | | 27 (54.0) | 26 (52.0) | |
| Face AIS, n (%) | | | 0.982 | | | 1.00 |
| Injury not present | 97 (71.9) | 58 (70.7) | | 35 (70.0) | 36 (72.0) | |
| 1 | 38 (28.1) | 24 (29.3) | | 15 (30.0) | 14 (28.0) | |
| Neck AIS, n (%) | | | 0.378 | | | NA |
| Injury not present | 135 (100.0) | 81 (98.8) | | 50 (100) | 50 (100) | |
| 1 | 0 (0.0) | 1 (1.2) | | 0 (0.0) | 0 (0.0) | |
| Spine AIS, n (%) | | | 1.00 | | | 1.00 |
| Injury not present | 133 (98.5) | 81 (98.8) | | 49 (98.0) | 49 (98.0) | |
| 1 | 2 (1.5) | 1 (1.2) | | 1 (2.0) | 1 (2.0) | |
| Thorax AIS, n (%) | | | 0.081 | | | 1.00 |
| Injury not present | 130 (96.3) | 74 (90.2) | | 48 (96.0) | 48 (96.0) | |
| 1 | 5 (3.7) | 8 (9.8) | | 2 (4.0) | 2 (4.0) | |
| Abdomen AIS, n (%) | | | 1.000 | | | 1.00 |
| Injury not present | 126 (93.3) | 76 (92.7) | | 48 (96.0) | 47 (94.0) | |
| 1 | 9 (6.7) | 6 (7.3) | | 2 (4.0) | 3 (6.0) | |
| Upper extremity AIS, n (%) | | | 0.824 | | | 0.789 |
| Injury not present | 118 (87.4) | 70 (85.4) | | 44 (88.0) | 42 (84.0) | |
| 1 | 17 (12.6) | 12 (14.6) | | 6 (12.0) | 8 (16.0) | |
| Lower extremity AIS, n (%) | | | 0.223 | | | 1.00 |
| Injury not present | 121 (89.6) | 68 (82.9) | | 44 (88.0) | 45 (90.0) | |
| 1 | 14 (10.4) | 14 (17.1) | | 6 (12.0) | 5 (10.0) | |
| External/other AIS, n (%) | | | 0.575 | | | 1.00 |
| Injury not present | 126 (93.3) | 74 (90.2) | | 45 (90.0) | 45 (90.0) | |
| 1 | 9 (6.7) | 8 (9.8) | | 5 (10.0) | 5 (10.0) | |
| Intracranial injury, n (%) | | | | | | |
| Cerebral contusion, n (%) | 51 (37.8) | 35 (42.7) | 0.567 | 20 (40.0) | 20 (40.0) | 1.00 |
| Epidural hematoma, n (%) | 11 (8.1) | 5 (6.1) | 0.770 | 4 (8.0) | 3 (6.0) | 1.00 |
| Traumatic subdural hematoma, n (%) | 122 (90.4) | 57 (69.5) | <0.001 | 41 (82.0) | 42 (84.0) | 1.00 |
| Traumatic subarachnoid hemorrhage, n (%) | 69 (51.1) | 38 (46.3) | 0.588 | 20 (40.0) | 23 (46.0) | 0.700 |
| Diffuse axonal injury, n (%) | 3 (2.2) | 6 (7.3) | 0.085 | 2 (4.0) | 3 (6.0) | 1.00 |
| Other intracranial injury, n (%) | 7 (5.2) | 9 (11.0) | 0.189 | 4 (8.0) | 2 (4.0) | 0.683 |
| GCS at admission, n (%) | | | 0.223 | | | 1.00 |
| Mild (GCS 14–15) | 31 (23.0) | 27 (32.9) | | 15 (30.0) | 15 (30.0) | |
| Moderate (GCS 9–13) | 23 (17.0) | 9 (11.0) | | 8 (16.0) | 8 (16.0) | |
| Severe (GCS 3–8) | 74 (54.8) | 46 (56.1) | | 27 (54.0) | 27 (54.0) | |
| Missing | 7 (5.2) | 0 (0.0) | | 0 (0.0) | 0 (0.0) | |
| Hypotension at admission, n (%) | 13 (9.6) | 13 (15.9) | 0.237 | 6 (12.0) | 6 (12.0) | 1.00 |
| Missing | 2 (1.5) | 2 (2.4) | | 0 (0.0) | 0 (0.0) | |
| Neurological surgery, n (%) | 93 (68.9) | 32 (39.0) | <0.001 | 27 (54.0) | 26 (52.0) | 1.00 |
| Transfusion volume (units), median (IQR) | | | | | | |
| Packed red blood cells | 2.8 (1.4–4.0) | 0.0 (0.0–2.8) | <0.001 | 2.8 (1.0–3.8) | 0.0 (0.0–2.7) | 0.082 |
| Fresh frozen plasma | 2.0 (1.1–2.6) | 0.0 (0.0–1.2) | <0.001 | 2.0 (1.0–2.7) | 0.0 (0.0–0.0) | <0.001 |
| Platelets | 1.9 (1.0–2.4) | 0.0 (0.0–0.4) | <0.001 | 1.9 (0.8–2.4) | 0.0 (0.0–0.4) | <0.001 |

AIS, Abbreviated Injury Score; GCS, Glasgow Coma Scale; TBI, traumatic brain injury.

significantly lower among patients who received a WBT (40.0% vs 62.0%, p=0.037). This corresponded to a 35% reduction in the risk of in-hospital mortality among patients who received a WBT, compared with those who received a BCT (relative risk (95% CI): 0.65 (0.43 to 0.97)). No differences were detected in complications in the matched cohort (table 3).

In the sensitivity analysis, after IPTW, most variables were balanced with an ASD <0.1 (online supplemental table 1). The remaining variables were included in the Poisson regression model. After this adjustment, receiving a WBT was associated with a 30% lower risk of in-hospital mortality, compared with

Table 3 Outcomes in patients with severe TBI who received a transfusion

| | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | Balanced component transfusion (n=135) | Whole blood transfusion (n=82) | P value | Balanced component transfusion (n=50) | Whole blood transfusion (n=50) | P value |
| In-hospital mortality, n (%) | 83 (61.5) | 34 (41.5) | 0.006 | 31 (62.0) | 20 (40.0) | 0.037 |
| Myocardial infarction, n (%) | 4 (3.0) | 0 (0.0) | 0.300 | 0 (0.0) | 0 (0.0) | NA |
| Cardiac arrest, n (%) | 7 (5.2) | 13 (15.9) | 0.017 | 4 (8.0) | 7 (14.0) | 0.505 |
| Stroke, n (%) | 1 (0.7) | 3 (3.7) | 0.153 | 0 (0.0) | 0 (0.0) | NA |
| DVT, n (%) | 2 (1.5) | 0 (0.0) | 0.528 | 0 (0.0) | 0 (0.0) | NA |
| Pulmonary embolism, n (%) | 1 (0.7) | 0 (0.0) | 1.00 | 0 (0.0) | 0 (0.0) | NA |
| ARDS, n (%) | 2 (1.5) | 0 (0.0) | 0.528 | 0 (0.0) | 0 (0.0) | NA |

ARDS, acute respiratory distress syndrome; DVT, deep vein thrombosis; TBI, traumatic brain injury.

those who received a BCT (IRR (95% CI): 0.70 (0.51 to 0.95), p=0.021).

In the subgroup analyses, fewer variables were balanced due to the smaller sample sizes (online supplemental tables 2 and 3). After adjusting for the remaining unbalanced variables using Poisson regression, receiving a WBT was associated with a 39% lower risk of in-hospital mortality in surgically managed patients, compared with those who received a BCT (IRR (95% CI): 0.61 (0.43 to 0.86), p=0.005). Among conservatively managed patients, however, receiving a WBT was not significantly associated with a lower risk of in-hospital mortality, compared with those who received a BCT (IRR (95% CI): 0.77 (0.54 to 1.09), p=0.143).

## DISCUSSION

Early and balanced transfusion has become the standard of care in treating trauma patients with significant hemorrhage.[8 9 14 19] In patients with TBI, restoration of adequate cerebral perfusion, oxygen delivery, and addressing coagulopathy is of paramount importance in mitigating secondary insults and improving overall outcomes.[6 20 21] In the current retrospective study, which makes use of a matched cohort of patients who sustained an isolated severe TBI, patients who received WB had a significantly higher chance of survival compared with patients who received a balanced component transfusion.

Within the evidence base, there are contradictory results regarding the survival benefit associated with WBT compared with BCT in trauma patients with hemorrhagic shock. In a 2009 analysis using the National Trauma Data Bank to study 1,745 severely injured patients (Injury Severity Score >25) who received a transfusion, patients who received component therapy were found to have a three times higher risk of death than those who received WBT.[22] A recent analysis of 2,785 trauma patients with severe hemorrhage revealed an early survival benefit (24 hours) in the cohort that received WBT as part of massive transfusion protocol (HR, 0.63; 95% CI, 0.41 to 0.96; p=0.03).[15] However, a systematic review, that identified 27 studies between 2006 and 2020 that collectively included >3,000 patients who had received >10,000 units of fresh WB found survival rates and complications to be equivalent when comparing patients who received a fresh WB transfusion with those who instead received component therapy.[23] Yet, using the TQIP database, Hanna *et al* found an association between patients who received cold-stored low-titer group O WB and a significant reduction in complications (including acute kidney injury, acute respiratory distress syndrome, deep venous thrombosis, pulmonary embolism, myocardial infarction, cardiac arrest, unplanned intubation, pneumonia, sepsis, and cerebrovascular accident) compared with those who received conventional component therapy. This relationship persisted even in a subgroup analysis based on the mechanism of injury.[13] To the authors' knowledge, there are no studies that specifically compare WBT to BCT in patients with TBI.

WB confers several advantages over conventional component therapy. For one, WB provides a balanced resuscitation in one bag with less additives and preservatives than an equivalent volume of conventional components. It has also a higher concentration of coagulation factors than stored or thawed plasma. Furthermore, it is easier and faster to transfuse than multiple components and avoids the risk of confusing the ratio of blood products administered in a stressful clinical setting. In the civilian setting, WB can be stored in refrigerators for a maximum of 21–35 days depending on the solution that is used.[12 24] Cold-stored group O WB does contain low titers of anti-A and anti-B antibodies; however, in practice the serological safety in regard to hemolysis when transfused to non-group O recipients is comparable to component therapy.[25]

Up to 26% of patients with TBI present to the emergency department with hypotension.[4] Several fluids have been used in the acute management of hypotension in TBI in an attempt to normalize the blood pressure and mitigate secondary brain injury. These include hypertonic saline, albumin, normal saline, and blood components.[26 27] TBI causes a global reduction in cerebral blood flow,[28 29] yet the deleterious effects of this may be reduced by elevating serum hemoglobin levels above 9 g/dL,[30] as this leads to improved oxygen delivery to the brain. Thus, early PRBC transfusion for restoring blood loss and oxygen-carrying capacity is an important component in the management of patients with TBI with concomitant hemorrhage.

Severe TBI in itself leads to a coagulopathic state that is strongly associated with poor outcomes.[20 21 31] It has been established that the cortical parenchyma and the adventitia layer of the vessels of the brain contain a particularly high amount of tissue factor, which is extensively released after injury.[32 33] This can result in a coagulopathic state and recurrent/ongoing intracranial hemorrhage. TBI-associated coagulopathy, defined as thrombocytopenia and/or an elevated international normalized ratio and/or a prolonged activated partial thromboplastin time, develops early but may also ensue several days after the initial trauma.[20 21] Early reversal by plasma or platelet transfusion might assuage the consequences of TBI-associated coagulopathy. In the randomized PAMPer (Prehospital Air Medical Plasma) trial, patients with GCS <8 and head AIS ≥3 displayed a significant improvement in 30-day survival after administration of plasma as compared with those who did not receive plasma.[34] The intracranial injury also activates a systemic stress response that leads

to a proinflammatory physiological response which in turn may affect the coagulation pathway. In an animal study of mice who were subjected to a combination of hemorrhagic shock and TBI, WBT was associated with a reduction in systemic and acute cerebral inflammation, measured by IL-2, MIP-1α, IL-1β, and serum neuron-specific enolase compared with hypertonic saline.[16]

In the current study, only patients who had isolated severe TBI and received transfusions were included to have a more homogeneous cohort. Interestingly, we found that both before and after matching, patients who had received a WBT were more likely to survive than those who received a BCT. After matching for available relevant confounding variables, there was a 22% (62.0% vs 40.0%, p=0.037) absolute decrease in the mortality rate in patients who were transfused with WB compared with BCT. This finding could be interpreted as proof of concept; however, further studies are needed to validate these results and to describe their physiologic basis.

Despite a well-balanced matched cohort, the current study has several limitations that need to be highlighted. As with all retrospective studies there are inherent confounders that cannot be fully accounted for or controlled for, which results in a risk of residual confounding. These missing variables included the indication for transfusion (though it may be hypothesized to be due to a combination of intraoperative blood loss as well as blood loss resulting from head lesions), the threshold for such therapy to be started, the reason underlying use of WBT as compared with BCT, the amount of WBT transfused, secondary insults (eg, hypoxia, recurrent hypotension, fever, and hypoglycemia), the use of other medications or fluids, and the ultimate cause of death. Furthermore, the coagulation status (based on thromboelastography/rotational thromboelastometry) and fibrinogen administration, if any, could not be accounted for in the TQIP dataset. The number of patients in each cohort after matching is low, which limits the potential external validity of the results. The dataset available does not contain hospital identifiers, which limits the ability to adjust for clustering of patients within hospitals. Whereas it was possible for patients in the WBT cohort to receive other blood components, only one patient in the WBT cohort after matching had received a BCT. Finally, 43% of patients in the BCT group lacked an associated ICD-10 corresponding to a blood transfusion. Consequently, there is a risk that patients who received a WBT were not included due to missing ICD-10 codes, which might have biased the results.

## Conclusion

WBT in patients with severe isolated TBI is associated with better survival compared with BCT in patients who require neurosurgical intervention. Further investigation into this finding using an appropriately powered, prospective study design is warranted.

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