Transfusion Intensity, Not Balance, Drives Acute Kidney Injury in Hemorrhagic Shock Patients

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Conflict of Interest

No conflicts of interest to declare

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Transfusion Strategies and AKI in Hemorrhagic Shock

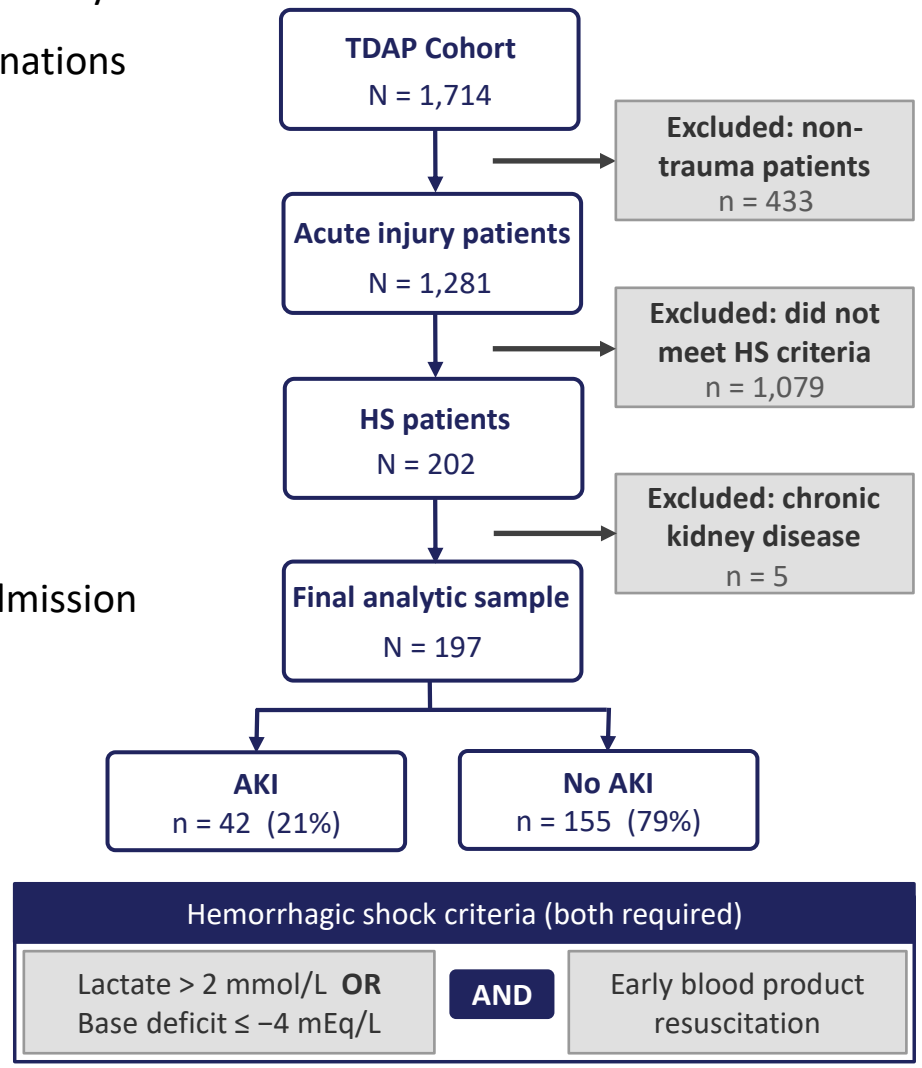
- **Background**
  - Acute kidney injury (AKI) is a common complication of hemorrhagic shock and carries high mortality
  - Damage control resuscitation emphasizes **balanced transfusion ratios**
    - Current guidelines favor a PRBC:FFP:PLT (red blood cells : plasma : platelets) ratio of 1:1:1 vs. 2:1:1 to decrease mortality[1]
    - Recent studies suggest ratios favoring plasma[2] and platelets[3] over red blood cells
  - It remains unclear whether **transfusion balance (composition) or transfusion intensity (volume of transfused blood products)** contributes more to AKI development

- **Objective**
  - Evaluate the association of transfusion composition and intensity during the first 24 hours of hospital admission with the development of AKI in hemorrhagic shock trauma patients

[1] *Holcomb et al, The PROPPR randomized clinical trial. JAMA. 2015*
[2] *Fujiwara et al, High FFP to RBC ratio and survival outcomes in blunt trauma. JAMA Surg. 2024*
[3] *Takiguchi et al, Transfusion ratios and survival in severe blunt trauma patients receiving massive transfusion. Nature Sci Rep. 2025*

Study Design

- The **Tissue and Data Acquisition Protocol** (TDAP) is a prospective multicenter cohort study
  - 3 medical centers (Walter Reed, Grady, Duke) with varying trauma center designations and both military and civilian patients
  - 1,714 patients enrolled between 2014 and 2023
- **Hemorrhagic shock (HS) definition**
  - Physiologic criteria: elevated lactate (> 2 mmol/L) **OR** base deficit (≤ -4 mEq/L)
  - Blood product resuscitation on hospital admission
- **Final analytic sample**
  - 197 trauma patients, all with hemorrhagic shock and without AKI at hospital admission
    - 42 (21%) with AKI, 155 (79%) without AKI
- **Exposures (measured as the final values over the first 24 hours from admission)**
  - Plasma fraction (FFP / total blood products volume)
  - Total blood products volume
- **Outcomes**
  - Primary: in-hospital AKI status
  - Secondary: hospital and ICU length of stay, ventilator-free days, 28-day mortality



Statistical Methods

- Between-group comparisons (Wilcoxon rank-sum test, Fisher's exact test, chi-squared test)
- Multivariable models adjusted for two prespecified confounders, age and injury severity score (ISS), chosen for their established association with both transfusion requirement and renal injury
  - Risk ratios with 95% confidence intervals (modified Poisson regression with HC3 robust standard errors)
  - Cox-proportional hazard ratios to incorporate the timing of AKI
- Exposures modeled per 1,000 mL (volume) and per 10% (plasma fraction); volume also examined across quintiles
- Dose-response relationships were visualized with logistic generalized additive models (GAMs) using thin-plate smoothing splines
- Sensitivity analyses
  - Winsorized exposure data at the 5^{th} and 95^{th} percentiles
  - Examined the PRBC:FFP ratio
  - Subgroup analysis by site

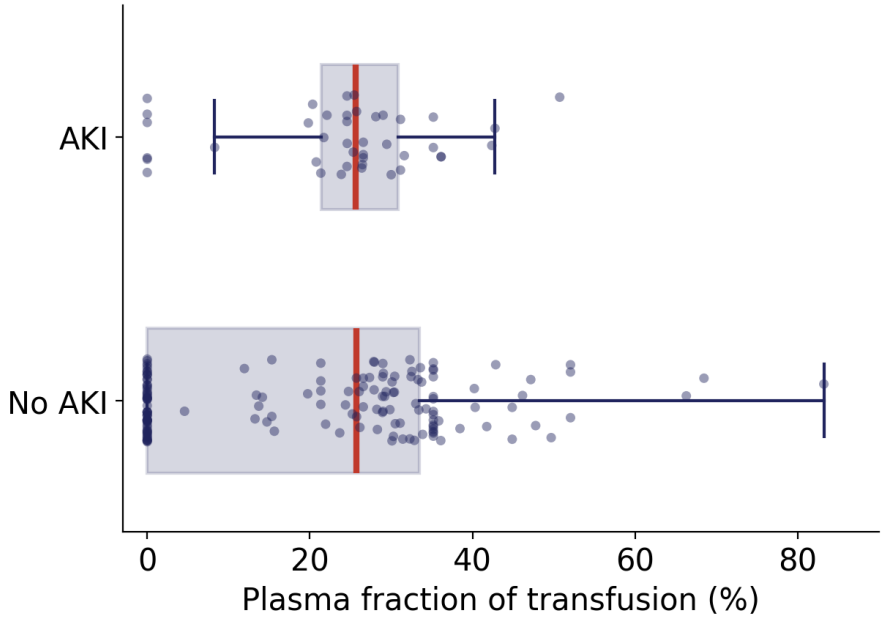
AKI is Associated with Worse Outcomes

- Demographics
  - Mostly similar
  - More comorbidities in AKI patients
- **Similar injury severity score and mechanism of injury**
- Labs and vitals
  - Higher initial creatinine in AKI patients
  - More tachycardic on arrival in AKI patients
- Resuscitation differences
  - **Greater transfusion volume in AKI patients**
  - **Similar plasma fraction in both patients**
- Secondary outcomes
  - Longer hospital and ICU length of stay in AKI patients
  - *Fewer* ventilator-free days (at 28 days) in AKI patients
  - Higher mortality in AKI patients

Demographics	HS with AKI (n=42)	HS without AKI (n=155)	p-value
Age, years	42 (26-59)	37 (25-48)	0.085
Male sex	34 (81%)	118 (76%)	0.679
White race	22 (52%)	48 (31%)	**0.017**
Comorbidities			
Hypertension	9 (21%)	8 (5%)	**0.003**
Diabetes mellitus	6 (14%)	5 (3%)	**0.013**
Mechanism of injury			
Blunt	13 (31%)	52 (34%)	0.854
Penetrating	15 (36%)	56 (36%)	1.000
Injury severity score	34 (21-43)	29 (20-38)	0.220
Physiology on arrival			
Systolic blood pressure, mmHg	111 (90-136)	117 (95-135)	0.484
Heart rate, bpm	110 (95-120)	100 (82-117)	**0.017**
Initial hemoglobin, mg/dL	12.1 (10.6-13.6)	12.1 (10.9-13.5)	0.905
Initial creatinine, mg/dL	1.4 (1.20-1.70)	1.1 (1.00-1.40)	**<0.001**
Transfusion volume and plasma fraction			
Total blood products (initial 24 h), L	3.79 (1.91-7.36)	1.53 (0.70-4.23)	**<0.001**
Plasma fraction (initial 24 h), %	26%	26%	0.36
Hospitalization metrics			
Time to AKI diagnosis, days	1 (0-8)	—	—
Hospital length of stay, days	41 (18-52)	18 (11-35)	**<0.001**
Intensive care unit length of stay, days	18 (6-36)	7 (3-14)	**<0.001**
Ventilator-free days at 28 days	17 (0-26)	26 (22-28)	**<0.001**
Mortality at 28 days	4 (9.5%)	0 (0%)	**0.002**

Medians (IQR) and N (%) are shown above

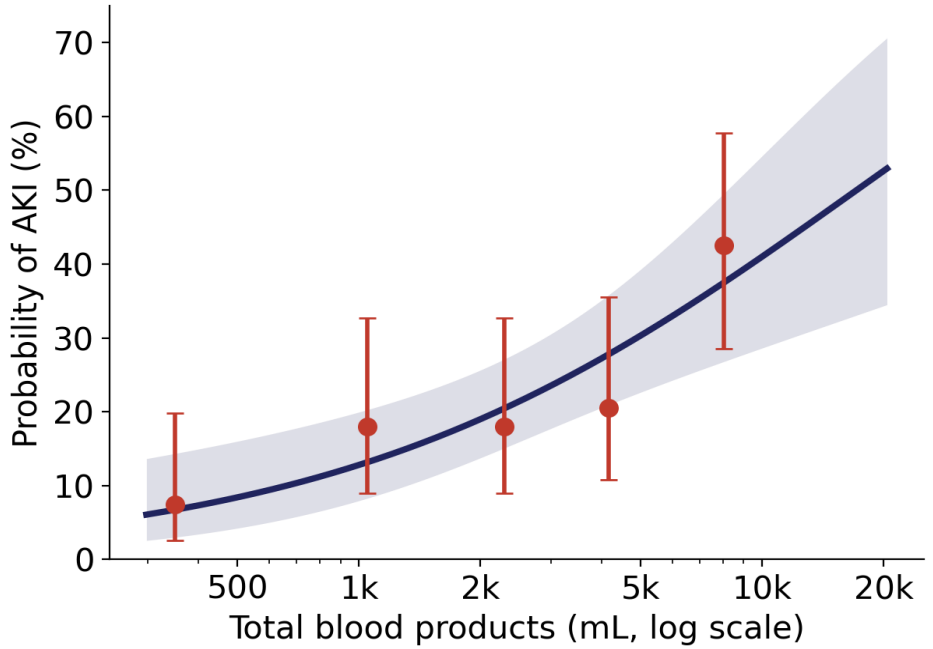
Plasma Fraction was Identical for Both Patient Groups



Resuscitation components in first 24 hours from admission	HS with AKI (n = 42)	HS without AKI (n = 155)	p-value
Plasma fraction, %	25.6 (21.4-30.9)	25.7 (0.0-33.5)	0.356
Packed red blood cells, mL	2,800 (1,138-5,250)	1,284 (675-2,800)	**<0.001**
Fresh frozen plasma, mL	950 (380-2,280)	380 (0-1,140)	**<0.001**
Platelets given, n (%)	20 (47.6)	52 (33.5)	0.106
Crystalloids, mL	2,900 (579-4,500)	1,800 (1,000-3,000)	0.063
Cryoprecipitate given, n (%)	13 (31.0)	34 (21.9)	0.227
Total blood products, mL	3,793 (1908-7,365)	1,553 (700-4,295)	**<0.001**
Tranexamic acid, n (%)	11 (26%)	52 (34%)	0.457
Medians (IQR) and N (%) are shown above			

- Patients who developed AKI **received more PRBC and FFP**, but similar amounts of platelets
- **Transfusion balance was identical**: The plasma fraction was 26% for both patient groups (p=0.356)
- Despite identical medians, the two distributions of plasma fractions significantly differ
  - Patients without AKI received transfusions with a broader range of plasma fractions, including a higher proportion of transfusions with 0% plasma (37% vs. 14%), than patients with AKI
- Similar proportions of crystalloids, cryoprecipitate, and tranexamic acid for both groups

Transfusion Volume Drives AKI Development, not Plasma Fraction



Points: observed AKI (%) by quintile with 95% CIs. Curves: GAM (thin-plate spline) fits with 95% CIs.

Risk increases multiplicatively with transfusion volume

Comparison	AKI risk
2,000 mL vs. 1,000 mL (1,000 mL increase)	1.10× higher
4,000 mL vs. 1,000 mL (3,000 mL increase)	1.33× higher
7,000 mL vs. 1,000 mL (6,000 mL increase)	1.78× higher

- Risk rises across the **full range** of volume
- Observed AKI: **9% → 42%** across volume quintiles

Adjusted RR 1.10

(95% CI 1.06–1.14, p<0.001) per 1,000 mL

- Winsorized (5^{th}/95^{th} percentiles) RR 1.17 (1.08–1.26, p<0.001)

- Because the model is multiplicative, risk compounds rather than increasing linearly
- A patient receiving 7,000 mL has **~1.8× the AKI risk** of one receiving 1,000 mL

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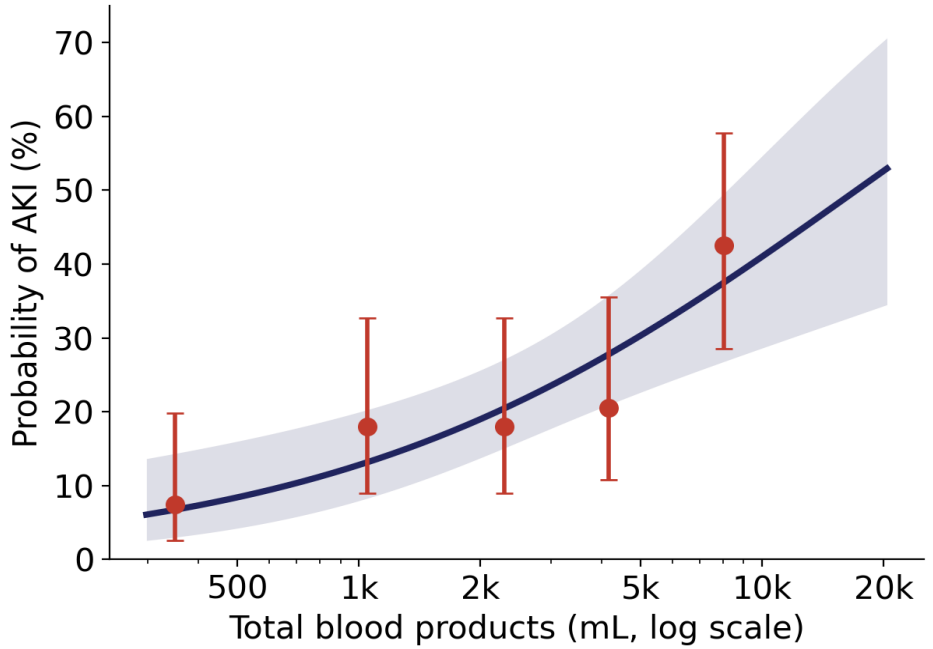

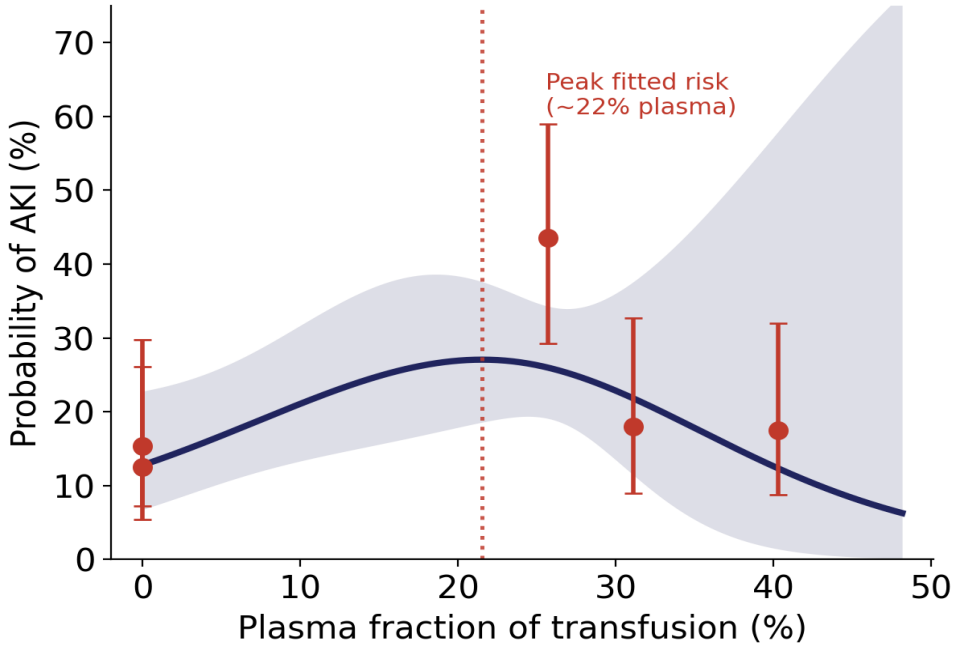

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- No consistent dose-response across its range
- Risk highest at ~22% plasma fraction
- Adjusted **RR 1.08** (0.91–1.27, p=0.38) per 10% change in plasma fraction
- Winsorized (5th/95th percentiles) RR 1.07 (0.88–1.29, p=0.51)
- Adjusted RR 0.97 (0.59–1.58, p=0.89) for the log PRBC:FFP ratio

Study Limitations

- Residual confounding remains possible – the injury severity score (ISS) incompletely captures severity, and other clinical factors (such as injury mechanism and prehospital treatment) were not fully accounted for
- AKI status ascertained from repository coding; its early onset argues against major misclassification
- Prehospital transfusion data were not available
- Chronic kidney disease excluded, strengthening internal validity at some cost to generalizability
- Single cohort of patients used, so external validation warranted

Clinical Reasoning Supports The Volume Effect

- Greater volume of blood product resuscitation was associated with a higher risk of AKI
  - Graded, dose-dependent fashion: Each additional liter of blood products was associated with 10% higher risk of AKI development after adjustment
  - The relationship held whether modeled as a risk ratio or as a hazard ratio (HR 1.12, 95% CI 1.06-1.19)
  - Consistent effect size across sites: adjusted RR 1.12 (Grady) and 1.05 (Duke); volume × site interaction p=0.31
- Plasma fraction showed an inconsistent risk profile

- Transfusion **volume** likely marks injury and hemorrhage severity — and may add direct renal insults
  - Direct renal effects: cell-free hemoglobin and heme-mediated tubular injury
  - Nitric-oxide scavenging with renal vasoconstriction
  - Immunomodulatory effects of stored components
- The **continuous** dose-response curve implies cumulative physiologic insult rather than there being a ‘massive-transfusion’ cutoff threshold
- Clinical impact: optimizing transfusion ratios alone is unlikely to reduce AKI — **hemorrhage control and perfusion** are the targets

Conclusion

- AKI was observed in 21% of hemorrhagic shock patients and associated with substantially worse clinical outcomes
- Patients with hemorrhagic shock constitute a particularly high-risk subgroup for AKI
- In traumatic hemorrhagic shock, AKI is driven by **transfusion volume (intensity)**, not balance (plasma fraction)
- Each additional 1,000 mL of blood products **multiplies AKI risk by 1.10**; composition had no consistent association
- To reduce post-injury renal injury, focus on **hemorrhage control and restoring perfusion**, not ratio optimization alone

Transfusion intensity, not balance, drives AKI risk in HS trauma patients