Assessing the comparative effectiveness of advances in pre-hospital trauma care: Lessons learned

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• There are no conflicts of interest to disclose.
Since the end of major combat operations in Iraq and Afghanistan, analysis of the lessons learned from those wars has focused largely on the wisdom of various foreign-policy decisions, the wars' financial and human costs, and their repercussions for U.S. national security. Although it's long been held that "the only victor in war is medicine," until recently there had been little consideration of the effect of war on military and civilian trauma care.

That changed with the June 2016 release of a report on the topic by the National Academies of Sciences, Engineering, and Medicine. The academies examined how the U.S. military pursued its goal of reducing morbidity and mortality after injury and the implications that its work might have for improving care in civilian settings. The report provides a blueprint for change in national health policy and calls for a National Trauma Care System aimed at eliminating preventable deaths and disabilities caused by accidents, intentional acts of violence, and natural disasters.1

The wars in Iraq and Afghanistan presented U.S. military medicine with its toughest challenge since the Vietnam War. In the wars' early phases, the military had no overarching system to collect actionable data on the causes and timing of death, much less to monitor care delivery and outcomes. As injuries and deaths mounted, it became clear that a better approach was needed. In 2004, the Army, Navy, and Air Force agreed to create the Joint Trauma System (JTS), an enterprise modeled on high-performing civilian trauma systems. The initial goals of the JTS included the creation of a trauma registry, modeled on the American College of Surgeons National Trauma Data Bank, to compile treatment and outcomes data, including information on the timing and causes of death and disability; the establishment of procedures to improve performance and the quality of care; and the formation and dissemination of clinical practice guidelines.

Data from the trauma registry illuminated the most pressing challenges, such as bleeding control, and identified aspects of care that were suboptimal or were associated with poor outcomes. The JTS also provided a mechanism for informing the military's trauma research program, evaluating new products and interventions, and integrating techniques developed in the civilian sector, such as damage-control surgery. Because it's not feasible to conduct randomized, controlled trials to assess new innovations or practice methods in a war zone, the JTS relied on retrospective and
1. Ignoring indication bias
2. Ignoring survival/immortal time bias
3. Ignoring time-varying treatment
4. Ignoring time-dependent confounding
5. Assuming uniform effects over time
6. Assuming missing values are missing at random
7. Selecting invalid covariates (collider bias)
37 unique studies identified, 1 prospective, 0 RCTs, 10 excluded for ambiguities

Significant heterogeneity precluded a valid summary relative risk (RR) from meta-analysis

25/27 studies rated very low quality

No survival benefit identified
Three Major Methodologic Flaws
noted in systematic review by Smith et al

1. **Study groups not equivalent, bias/confounding**
   a. Indications for PHT (bleeding severity)
   b. Interventions other than PHT (pre-post designs)
   c. Time (from injury to start of PHT, post-PHT survival time)
   d. Misclassification of PHT (transported from scene vs. transferred)

2. **Sample sizes too small, too few patients at high risk of hemorrhage-related mortality**

3. **Key data often missing**
Our MEDEVAC PHT Study

Methods

First to frame the issue in explicit terms of timing

✓ Minimized bias & confounding
✓ Included a large, representative sample of the highest-risk patients most likely to benefit
✓ Tracked down missing data

Identified 5 key lessons for future pre-hospital studies
Lesson 1: Select valid covariates (potential confounders) for matching or statistical adjustment
502 potential study candidates met 3 criteria:
1) U.S. military casualty in Afghanistan April 1, 2012 - August 7, 2015
2) Evacuated alive from the point of injury by MEDEVAC helicopter
3) Documented one of the established indications for PHT:
   a) Multiple traumatic amputations, at least one above knee or elbow
   b) Pre-hospital heart rate >120 beats/minute or systolic blood pressure <90 mmHg

55 PHT recipients were stratified based on 5 factors:
1) Mechanism of injury (gunshot vs. explosion)
2) Positive indicator of hemorrhagic shock (Yes/No)
3) Traumatic limb amputations
   a) 0=none
   b) 1=1 below knee/elbow
   c) 2=2 or more below knee/elbow or 1 above knee/elbow but below hip
   d) 3=2 or more above knee/elbow
4) Maximum severity of head injury by Abbreviated Injury Severity (AIS) score (0-1 vs. 2 vs. >3)
5) Significant torso hemorrhage by AIS score (Yes/No)

447 non-recipients were group-matched to recipients

345 matching non-recipients

102 unmatched non-recipients.
Pre-hospital hypertonic saline RCT stratified by the 24 hour sum of RBC transfusions (0, 1-9, 10 or more units) as a surrogate for bleeding severity
Options toward a Solution 1.

1a. Intervention: Prehospital HSD/control
Valid covariate: Pre-intervention injury and bleeding severity status
Outcome: 24 hour injury survival

1b. Intervention: Prehospital HSD/control
Collider covariate: 24 hour sum of RBC transfusions as surrogate for severity
Outcome: 24 hour injury survival

1c. Randomized intervention: Prehospital HSD/control
Valid covariate: Pre-intervention injury and bleeding severity status
Outcome: 24 hour injury survival
Collider covariate: 24 hour sum of RBC transfusions as surrogate for severity

Directed Acyclic Graph
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Lesson 2: Identify all highest-risk, PHT-eligible patients (especially pre-hospital deaths) and adjust for left truncation (immortal time/survival bias) given patients had to survive long enough to receive PHT.
Injury mortality rates precipitously decline reflecting the sequence of competing risks: early death from bleeding, later head injury, and finally, complications.

<table>
<thead>
<tr>
<th>Time interval after ED admission</th>
<th>Deaths</th>
<th>Hours at Risk</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 6 hours</td>
<td>88</td>
<td>3,590</td>
<td>0.0245</td>
</tr>
<tr>
<td>From &gt;6 hours to 24 hours</td>
<td>34</td>
<td>14,039</td>
<td>0.0024</td>
</tr>
<tr>
<td>From &gt;24 hours to 30 days</td>
<td>84</td>
<td>491,618</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

PROMMTT study after removal of deaths within 30 minutes of ED arrival
The Missing Dead: The Problem of Case Ascertainment in the Assessment of Trauma Center Performance

David Gomez, MD, Wei Xiong, MSc, Barbara Haas, MD, Sandra Goble, MS, Najma Ahmed, MD, PhD, FACS, and Avery B. Nathens, MD, PhD, FACS

**Background:** If there are systematic differences in the types of patients captured in registries, then differences in outcomes in centers might be related not to differences in the practice of care, but differences in registry inclusion criteria. We set out to evaluate the effect of variable case ascertainment of dead on arrivals on external benchmarking of risk-adjusted mortality using a form of sensitivity analysis.

**Methods:** We used data from the National Trauma Data Bank to look for indirect evidence of systematic differences in case ascertainment. We evaluated whether there was any relationship between fewer than expected early (≤24 hours) deaths and overall risk-adjusted mortality. Fewer than expected early deaths were estimated through the W statistic and through an adjusted ratio of early to late (E/L) deaths. E/L ratios were assessed due to the potential correlation between performance and absolute number of early deaths as assessed by the W statistic.

**Results:** We estimate that as many as 47% of all deaths might be missing due to problems with case ascertainment. Centers with unexpectedly few early deaths (W statistic) were consistently high performing centers with a lower than expected overall mortality. More importantly, there was no relationship between the E/L death ratio and overall risk-adjusted mortality.

**Conclusions:** Variable case ascertainment of dead on arrivals does not affect the ability to assess performance. Given that our approach has several assumptions, it is critically important that external validation of trauma registries be performed. If centers are to be judged through the quality of their data, then it is incumbent to first assure that data quality meets expectations.

**Key Words:** Trauma quality improvement, External benchmarking, Risk adjustment, Dead on arrival.

Pattern of Early Survival in Trauma After Injury
100% (Mock cohort, for example only)

Which individual ✭ is at greater risk?

75% Survival Analysis Time → Min 60
Options toward a Solution 2.

Conduct survival analysis using Cox proportional hazards modeling to adjust for covariates (potential confounders) and specify “delayed entry” to appropriately adjust for left truncation (survival long enough to receive PHT)
Delayed Entry in Survival Analysis

1. Non-recipient Patient 1 died at 32 min
2. Non-recipient Patient 2 died at 14 min
3. PHT-Recipient Patient 3 entered at min 17, survived min 60
4. PHT-Patient 4 entered at min 6 and died min 44
5. Non-recipient Patient 5 survived min 60

0 Survival Analysis Time → Min 60
Adjusted Cox Proportional Hazards Models

24 hour survival

a. 24 hour survival

HR = 0.26 (95% CI = 0.08 – 0.84, \(P=0.025\))

30 day survival

b. 30 day survival

HR = 0.39 (95% CI = 0.16 – 0.92, \(P=0.031\))

Conditional 30-day survival among 24-hour survivors

c. Conditional 30-day survival among 24-hour survivors

HR = 0.84 (95% CI = 0.18 – 4.00, \(P=0.831\))
Lesson 3: Some in-hospital transfusions may be initiated sooner after injury than some pre-hospital transfusions. Need to accurately define the intervention – its start-time (relative to injury occurrence) may be more important than the location or provider-type.
Early Transfusion, Pre- or In-Hospital Adjusted Cox Proportional Hazards Models for 24 hour Survival

Transfusion within 15 minutes vs. longer delays after MEDEVAC rescue from point of injury:

a. HR = 0.17 (95% CI = 0.04 – 0.73, \( P = 0.017 \))

Conditional survival among 16-minute survivors: Transfusion within 16-20 minutes vs. longer delays:

b. HR = 0.94 (95% CI = 0.41 – 2.17, \( P = 0.887 \))
Options toward a Solution 3.
Redefine the intervention in explicit terms of timing and perform appropriately adjusted survival analyses to determine whether there is a critical time window for initiation or administration.
Lesson 4: Early death precludes longer-term outcomes. If the intervention affects early death, the assessment of longer-term outcomes must be adjusted for the competing risk of early death.
Key Requisite: Study Groups are at Equal Risk of Death at Start of Treatment

As time progresses, only survivors can experience subsequent events.
Suppose we want to test the hypothesis that PHT reduces total 24 hour blood product consumption? Need SACE for any hope of an interpretable result.
Lesson 5: Cautiously interpret findings in light of other evidence available and evaluate robustness to alternative assumptions and analysis strategies
History of the $P$ value as an index of significant between-group difference

- **~1770**: Pierre-Simon Laplace first calculated it to compare male vs. female births

- **1839**: The American Statistical Association founded

- **~1900**: Karl Pearson formally introduced it for $\chi^2$

The ASA's Statement on p-Values: Context, Process, and Purpose

Ronald L. Wasserstein & Nicole A. Lazar

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Key Take-home Points from the ASA’s 2016 Statement on P value:

1. Does **not** measure the size of an effect or the importance of a result.
2. Does **not** measure the probability that the hypothesis is true or that the data were produced by random chance alone.
3. Does **not** provide a good measure of evidence regarding a model or hypothesis.
4. Should **not** form the basis of scientific conclusions or policy decisions.
So, what does the $P$ value actually mean?

Assuming the null hypothesis is true (i.e., between-group difference=0), the sample was drawn randomly, and the observed data are unbiased, it measures only the probability that the results could have been produced by random chance alone.
“describe in detail the full sequence of events that led to the statistics presented, including 1) the motivation for the study, 2) its design, 3) the original analysis plan, 4) criteria used to include and exclude subjects and data, and 5) a thorough description of all the analyses that were conducted.”

Test for alternative assumptions using sensitivity analysis!
Recent Prospective PHT Studies/Trials

1. **PAMPer RCT** – plasma vs. standard of care – **multi-site**
   a. ClinicalTrials.gov NCT01818427, 03/2013 – 03/2017
   b. Currently enrolling

2. **COMBAT RCT** – fresh frozen plasma vs. crystalloid – **single site**
   a. ClinicalTrials.gov NCT01838863, 04/2013 – 04/2017
   b. Terminated due to futility

3. **PROHS observational study** – RBCs/plasma vs. crystalloid – **multi-site**
   b. Inconclusive results due to between-group imbalance

4. **PUPTH RCT** – thawed plasma vs. normal saline – **single site**
   b. Withdrawn due to low enrollment

5. **RePHILL RCT** – RBCs/lyophilized plasma vs. normal saline – **multi-site**
   a. EU Clinical Trials EudraCT2015-001401, 13 12/2015 – 06/2017
   b. Currently enrolling

6. **PREHO-PLYO RCT** – lyophilized plasma vs. normal saline – **multi-site**
   a. ClinicalTrials.gov NCT02736812, 03/2016 – 04/2017 (EU)
   b. Currently enrolling
Challenges for Recent PHT Studies/Trials

- Enroll sufficient numbers of high-risk patients
- Deliver PHT soon enough after injury occurrence to prevent hemorrhagic mortality
- Completely ascertain mortality (pre-hospital, in-hospital and 30-day) and other outcomes
Questions:

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