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Predicting Futility in Severely Injured Patients: Using Arrival Lab Values and Physiology to Support Evidence-Based Resource Stewardship

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Short title: Futility Cut Points after Trauma

ABSTRACT

Background: The recent pandemic exposed a largely unrecognized threat to medical resources, including daily available blood products. Some of the most severely injured patients who arrive in extremis consume tremendous resources yet succumb shortly after arrival. We sought to identify cut-points available early in the patient's resuscitation that predicted 100% mortality.

Study Design: Cut-points were developed from a previously collected dataset of all level-1 trauma patients admitted 01/10-12/16. Objective values available on or shortly after arrival were evaluated. Once generated, we then validated these variables against (1) a prospective dataset 11/17-10/21 of severely injured patients and (2) a multicenter, randomized trial of hemorrhagic shock patients. Analyses were conducted using STATA 17.0 (College Station, TX), generating positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity.

Results: The development dataset consisted of 9,509 patients (17% mortality), with 2,137 (24%) and 680 (24%) in the two validation datasets. Several combinations of arrival vitals and labs had 100% PPV. Patients undergoing CPR in the field or on arrival (with subsequent ROSC) required lower fibrinolysis LY-30 (30%) than those with systolic pressures (SBP) of ≤50 (30-50%), ≤70 (80-90%), and ≤90 mmHg (90%). Using a combination of these validated variables, the Suspension of Transfusions and Other Procedures (STOP) criteria were developed, with each element predicting 100% mortality, allowing physicians to cease further resuscitative efforts.

Conclusion: The use of evidence-based STOP criteria provides cut-points of futility to help guide early decisions for discontinuing aggressive treatment of severely injured patients arriving in extremis.

Keywords: trauma, futility, fibrinolysis, coagulopathy, thrombelastography

INTRODUCTION

Major improvements in transport times, prehospital capabilities, initiation of balanced resuscitation, and rapid access to surgical intervention over the last decade have improved survival rates in those traumatically injured.(1–4) The unintended consequence of these triumphs, however, has led to the presentation of patients with non-survivable injuries in a time-frame in which intervention is considered and often employed due to prognostic uncertainty. Discerning survivability in these patients remains problematic. Several studies have attempted to predict survivability based on variables such as injury severity, pre-hospital arrest, arrival pH, blood transfusion volume, and coagulation parameters.(5–13) Many of these studies either failed to predict mortality or did so late into a massive resuscitation. Additionally, many of these studies predate the adoption of damage control resuscitation principles, improved prehospital capabilities including blood product administration, and the use of whole blood during massive transfusions.(3)

The COVID-19 pandemic exposed the precarious blood storage and supply chain issues, and US trauma centers were not immune to this.(14) Adding to this, surgeons are now faced with patients who previously would have been declared dead shortly after arrival, now making it to the trauma center alive and often even to the operating room and ICU, exhausting even more resources, only to die shortly after.(14, 15) Constructing a prognostication model for reliably determining futility early in the course of resuscitation would help direct precious resources to salvageable patients. Using arrival labs and hemodynamics, we sought to identify cut-points available early in the patient's resuscitation that could be used as reproducible and objective criteria to predict 100% mortality.

METHODS

The University of Texas Health Science Center-Houston and the Memorial Hermann Hospital Institutional Review Boards approved this study. The Red Duke Trauma Institute (RDTI) at Memorial Hermann Hospital is an American College of Surgeons–verified level-1 trauma center and the primary teaching hospital for the McGovern Medical School–University of Texas Health Science Center. Memorial Hermann is one of only two level-1 trauma centers in Houston, Texas, and operates LifeFlight (LF), our helicopter transport service. The trauma center annually evaluates more than 11,000 trauma patients.

Development dataset

We began by evaluating a previously maintained database which collected data on all adult trauma patients (>15 years of age) who met highest-level trauma team activation and were admitted to our Level-1 trauma center between January 2010 and December 2016.(16) From this cohort, information including patient demographic characteristics, laboratory values, Injury Severity Score (ISS), management interventions, and outcomes were extracted. To allow us to focus on (1) those patients in whom futility was in question and where tremendous efforts might be expended, and (2) to adequately evaluate early physiological and laboratory variables (many of which were missing in patients who died early), we chose to exclude those patients who were dead on arrival or who died in the first 30 minutes of arrival. Patients with >20% total body surface area burns were also excluded.

Extreme arrival laboratory data were based on published cut points and were evaluated independently and in conjunction with other variables. For coagulation parameters, we evaluated rapid thrombelastography (r-TEG) values on admission, including: activated clotting time (ACT) which reflects initial fibrin formation and is increased with factor deficiency; alpha angle which

represents the rate of clot formation; maximal amplitude (mA) which is the greatest amplitude of the tracing and reflects platelet contribution to clot strength; and LY-30 which represents the percent amplitude reduction of the clot at 30 minutes after mA and reflects the degree of fibrinolysis.(17) The *return of spontaneous circulation (ROSC)* was defined as return of a perfusing cardiac rhythm after initial traumatic arrest, in prehospital, emergency (ED), or operating room (OR) settings.

Validation datasets

These results were then taken and validated against two separate datasets with known outcomes and previous publications. We validated the initial results against a dataset from a randomized controlled trial from twelve level-1 trauma centers in North America, conducted from August 2012- December 2013. The Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial randomized trauma patients predicted to receive a massive transfusion to a plasma:platelet:red blood cell ratio of 1:1:1 or 1:1:2.(3) Next, we evaluated these cut-points against a more recent set of patients managed with a more consistent application of damage control resuscitation principles (balanced ratios consistent with whole blood, limited crystalloids, and permissive hypotension) and a more robust prehospital transfusion program. This was a prospectively maintained dataset of all level-1 adult trauma patients (>15 years and older) transported to Memorial Hermann Hospital from November 2017 to October 2021 who received emergency-release, uncrossmatched products in the prehospital or emergency department setting.(18)

Once a set of validated variables were identified that could predict 100% mortality across several patient populations, we planned to summarize those into a simple list to allow clinicians and surgeons to potentially cease interventions, including transfusions and other life-sustaining

therapies. The Suspension of Transfusions and Other Procedures (STOP) criteria were developed from those physiological and laboratory data available within minutes to the first hour of arrival.

Statistical analyses

Predictive analyses included positive predictive value (PPV), negative predictive value, sensitivity, and specificity. All analyses were performed using STATA Statistical Software, version 17.0 (Stata Corp). Continuous data are presented with the 25th and 75th percentile interquartile range with comparisons between groups performed using Wilcoxon rank sum test. Categorical data are reported as proportions and, where appropriate, tested for significance using chi-square or Fisher's exact tests. All statistical tests were 2-tailed at the 0.05 level.

RESULTS

Developmental dataset

A total of 9,509 patients were included in the initial dataset. The median age was 36 (24, 53). 75% were male and 47% were white. The majority of patients (74%) sustained a blunt mechanism of injury. The median ISS for group was 17 (9, 27), with an overall mortality of 17%.

Extreme physiology in the field carried high mortality, but were, by themselves, not universally fatal. Field systolic blood pressures (SBP) of less than 70 mmHg and less than 50 mmHg had a mortality of 38% and 45%, respectively. Field Glasgow coma scale (GCS) of 3, 4, and 5 carried mortality rates of 41%, 27%, and 30%. Extreme arrival physiology carried higher mortality rates than field, but were, again, not uniformly fatal. Arrival SBP of less than 70 mmHg and less than 50 mmHg had a mortality of 57% and 85%, respectively. Arrival GCS of 3, 4, and 5 carried mortality rates of 33%, 38%, and 32%.

Extreme disturbances in ED laboratory values carried high mortality but were not uniformly fatal as a single cut-point. Worsening lactate levels demonstrated increased mortality; lactate >10 (68%), lactate >12 (72%), lactate >16 (78%), and lactate >20 (85%). Initial base deficit and pH values were also associated with mortality, but not as strongly as lactate. Further analysis with these values were dropped. Rapid TEG values extremes were evaluated and found to have poor discrimination for mortality. However, the only variable of note was r-TEG LY-30 where increasing levels of lysis were associated with increased mortality; >30% (81%), >50% (86%), >70% (87%), >80% (92%), and >90% (95%).

When field and ED physiological values were combined, lactate and LY-30 values were able to achieve 100% PPV (**Table 1**). Lactate values as low as 10, when associated with lysis of 90% or greater, were able to predict 100% mortality rates. Higher lactates (16-20) were unable to improve on PPV or reach 100% with lower LY-30 values. In patients with traumatic arrest followed by ROSC, much lower lactate and lysis values were able to achieve 100% PPV (**Table 2**). With arrest and subsequent ROSC, lower values of other variables such as prehospital GCS and base deficit were also able to predict 100% lethality.

Validation datasets

The PROPPR dataset included 680 patients with median age of 34 (25, 51), of which 78% were male and 62% were white. The median ISS was 26, with 55% blunt mechanism and 37% with traumatic brain injury. Overall mortality was 24%. Profound hypotension with either lysis of 30% or greater or lactate of 15 or more resulted in 100% PPV for mortality (**Table 3**). When lactate and lysis were combined, a lower threshold of hypotension (70 mmHg or less) was able to achieve similar results.

The second validation dataset included 2,137 patients with a median age of 38 (26, 56). Approximately 72% were male and 38% were white. 68% of these patients sustained a blunt mechanism of injury with nearly 50% sustaining traumatic brain injury. The median ISS was 28 (17, 41) with an in-hospital mortality of 24%. In this validation dataset, similar cut-points for 100% mortality prediction were noted, with the addition of cut-points in the setting of ROSC (**Table 4**).

Of note, when we evaluated patients in the development and second validation dataset who met at least one of the criteria for 100% mortality, up to 10% were transfused >100 units of blood products prior to succumbing to their injuries and physiology. Building on these findings, the results from both the developmental and validation datasets were the summarized into the previously discussed STOP criteria. These are suggested as clean and clear criteria to facilitate their use and application in the clinical setting for patients presenting in extremis. This includes those patients presenting with cardiac arrest and ROSC (**Table 5**).

Phenotypic evaluation of less extreme values driving mortality

Based on the findings of higher levels of fibrinolysis (>70%) in the setting of less extreme shock values (lactate <12 mmol/L), we evaluated this population of patients compared to a cohort without these disparate values. There were no differences in age, race, sex, or mechanism of injury between patients with high lysis-low lactate and those without this combination. However, the patients with high lysis-low lactate values were more likely to have prehospital or ED arrest with ROSC (14 vs. 2%) and to have lower systolic blood pressures [median 88 (50, 117) vs. 110 mmHg (88, 134)] and GCS [3 (3, 11) vs. 13 (3, 15)] in the field; all $p<0.05$. This group also arrived to the ED more hypotensive [78 (66, 95) vs. 106 (88, 129); $p<0.001$.

The high lysis-lower lactate cohort had significantly higher head abbreviated injury scale AIS scores [4 (3,5) vs. 3 (0,4); p=0.002], with no differences in other regional AIS scores or overall ISS (all p>0.05). These patients also received more RBC [7 (3, 11) vs. 1 unit (0,5)], plasma [7 (3, 11) vs. 2 units (0,5)], and platelet [1 (0,2) vs. 0 units (0,1)] transfusions in the first four hours; all p<0.05. The high lysis-low lactate phenotype also presented with a significantly greater rate of hypofibrinogenemia by r-TEG alpha less than 60 degrees (57 vs. 8%; p<0.001). Overall mortality was significantly greater in the high lysis-low lactate group (81 vs 18%, p<0.001), with a shorter time to death [2.8 (1.5, 12.9) vs. 33.6 hours (12.5, 113); p<0.001] versus the comparison cohort.

DISCUSSION

In our analysis of three robust datasets of severely injured trauma patients, we found that several combinations of arrival vitals and laboratory values resulted in 100% PPV for mortality. Fibrinolysis and shock were the most predictive for futility. Moreover, in patients undergoing cardiopulmonary resuscitation (CPR) in the field or on arrival (with subsequent ROSC), futility was predicted at lower fibrinolysis values than those in profound shock. Furthermore, we found that among these datasets, up to 10% of patients with 100% predicted mortality consumed over 100 units of blood products during the early phase of resuscitation, consuming tremendous valuable resources and manpower, signaling the need for our proposed STOP criteria. Predicting futility early after patient arrival is critical for resource conservation and, most importantly, alleviating prolonged patient suffering. Having readily available datapoints for trauma surgeons to easily recognize futility markers would be universally advantageous. The first most apparent datapoints on patient arrival to the hospital would be a history of en-route CPR and presenting vitals. Martin et al. found more than 99% of patients died with a history of

pre-hospital pulseless electrical activity (PEA) arrest after blunt injury.(7) Moore et al, however, showed a survival rate of 14% in those with pre-hospital CPR after blunt and penetrating trauma.(8) Studies such as these have pushed our guidelines to deem resuscitative thoracotomy futile when prehospital CPR exceeds 10 minutes after blunt trauma and 15 minutes after penetrating trauma.(19) Additionally, patients with no cardiac motion in pulseless trauma patients have been found to be fatal with over 99% specificity.(20, 21) These investigations and subsequent guidelines have been extremely useful for identifying futility and are considered universally accepted, however, patients who do not present with the aforementioned degree of extremis are often more difficult to predict.

The next available datapoints the patient would theoretically provide are age and injury severity. Age has consistently shown us that the elderly fare poorly after trauma.(5, 6, 10) Several studies however, have shown that age and injury alone cannot consistently predict futility.(6, 22) In a geriatric trauma population, Newell et al showed that even in those over 55 years old receiving damage control laparotomy, over 50% survived.(22) Therefore, even futility in the frail elderly patients with severe injury can't be conclusively predicted by age alone.

The next subset of patients are those who survive long enough to attain laboratory testing and receive blood products. Several studies have shown that patients may still survive with extreme derangements. Two studies showed that despite a pH of <7.2 after traumatic injury, >40% of patients survived.(9, 10) Additionally, Ross et al found that no pH threshold predicted mortality.(9) One report showed that over 10% of patients with pH of <7.0 survived and over 30% survived with a lactate of 10 mmol/L.(10) Therefore, markers of global hypoperfusion are, at best, mediocre at futility prediction. Markers of coagulopathy using r-TEG have also been evaluated for futility prediction with more promising results. Farrell et al showed that patients

with the "death diamond" tracing on r-TEG (defined as mA≤14 minutes and time from mA to total lysis of <30 minutes) had a 94% mortality rate.(13) Cotton et al demonstrated that LY30 >7.5% was associated with mortality in three out of four patients.(17) Furthermore, previous work from our group combined hypoperfusion lab assessment and coagulopathy, showing 100% PPV for mortality in pediatric patients presenting with any of the following admission values: INR ≥ 3, pH ≤6.95, base excess ≤ -22, platelet count ≤ 30,000, hemoglobin ≤ 5.0 g/dL, r-TEG mA ≤ 30mm or LY-30 ≥ 50%.(16)

Adding to the "coagulopathy equals death" concept, many studies have evaluated transfusion rates and volumes. Numerous studies show higher mortality rates for high volume product transfusions ranging from 31-53 units.(5, 23) A recent ACS-TQIP study showed that no volume within 4 or 24 hours and a transfusion rate within 4 hours could predict futility, however, final 24 hour mean RBC transfusion rate of ≥7 units/hour experienced in-hospital death.(11) Therefore, using volume or transfusion velocity remains imprecise when attempting to predict futility. Interestingly, in our study, patients with high lysis (>70% by LY-30) and low lactates (<12 mmol/L) had 81% mortality (versus 18% in the comparison cohort). On examination of these patients, we noted that they were more likely to be transported by air, receive pre-hospital blood, and have severe head injury (AIS>3). These patients also present with a source of hemorrhage (receiving significantly more blood than the comparator group) but have a severe brain injury with associated hypofibrinogenemia. Following severe brain injury, previous research suggests an "uncoupling" of the autonomic and cardiovascular systems, as well as systemic endothelial dysfunction and uncoupling of the fibrinolytic pathway.(24–27) The authors feel that this is the population in which we can expeditiously apply our findings to and provide an opportunity for resource stewardship. Locally, these patients have been described by several of our faculty as

ones we are able to rescue on the macro level (with ROSC and often making it the OR), but fail to capture them on the micro level (with endothelial, coagulation, and electrophysiological uncoupling).

The above studies offer good data to suggest we should intermittently perform a "time-out" during resuscitations to ensure we are not exhausting valuable resources and prolonging suffering, but they do not assist with early prediction of futility and assist with early conservation of resources. The presented STOP criteria combine pre-hospital history, arrival physiology, and initial labs to help providers perform a "futility time-out" earlier in the throes of resuscitative efforts, providing more opportunity for resource conservation.

Our study has several limitations worth noting, besides being retrospective in nature. We opted to exclude all deaths within 30 minutes of arrival for several reasons. First, most patients who die within minutes of arrival don't get laboratory values before they ultimately expire. The authors felt that these patients tend to have a more obvious clinical trajectory and would likely falsely improve the predictive values of the cut points, but this choice almost certainly affected our findings. An additional limitation is that our initial analysis was performed on a single institution's experience prior to PROPPR, and thus, a uniformed practice of balanced transfusion and damage control resuscitation. However, to account for this, we validated our findings using our institution's dataset after PROPPR and additionally with a multi-institutional dataset. We felt this would be more generalizable using different injury and practice patterns around the country. Lastly, the majority of the patients were severely injured in trauma systems with extraordinary pre-hospital capabilities and immediate blood products, which may have affected the "rescue" potential of these patients.

CONCLUSION

Extreme admission physiology and laboratory values, with and without traumatic arrest and ROSC, are capable of early prediction of 100% mortality in severely injured adults. The STOP criteria are evidence-based cut-points of futility that can guide early decisions for discontinuing aggressive treatment and use of precious resources in severely injured patients arriving in extremis. Additional validation will be required prior to widespread adoption.

Precis

Futility has been difficult to predict in those traumatically injured. Using three large datasets, futility cut points with 100% PPV were found using arrival physiology and labs. The constructed Suspension of Transfusion and Other Procedures (STOP) criteria helps guide early decisions for discontinuing aggressive treatment.

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Table 1. Development Dataset Cut Points from 9,509 Patients (01/201-12/2016) for Arrival Laboratory Values Achieving Near-Fatal or Universally Fatal Outcomes

Variable	PPV, %	NPV, %	Sensitivity, %	Specificity, %
Lactate ≥10 and LY-30 ≥90%	100	88	6	100
Lactate ≥12 and LY-30 ≥30%	87	89	12	99.7
Lactate ≥12 and LY-30 ≥50%	92	88	10	99.9
Lactate ≥12 and LY-30 ≥70%	94	88	8	99.9
Lactate ≥12 and LY-30 ≥80%	98	88	7	100
Lactate ≥12 and LY-30 ≥90%	100	88	4	100
Lactate ≥16 and LY-30 ≥30%	86	89	11	99.8
Lactate ≥16 and LY-30 ≥50%	91	88	9	99.9
Lactate ≥16 and LY-30 ≥70%	93	88	7	99.9
Lactate ≥16 and LY-30 ≥80%	98	88	6	100
Lactate ≥20 and LY-30 ≥30%	86	89	11	99.8
Lactate ≥20 and LY-30 ≥50%	91	88	8	99.9
Lactate ≥20 and LY-30 ≥70%	93	88	7	99.9
Lactate ≥20 and LY-30 ≥80%	98	88	5	100

Lactate values are expressed in mmol/L

PPV, positive predictive value; NPV, negative predictive value; LY-30, percent amplitude reduction at 30 minutes after thrombelastography maximal amplitude achieved

Table 2. Development Dataset Cut Points from 9,509 Patients (01/2010-12/2016) for Near-Fatal or Universally Fatal Outcomes after Arrest and Return of Spontaneous Circulation

Variable	**PPV**	**NPV**	**Sensitivity**	**Specificity**
ROSC and LY-30 ≥30%	100	88	3	100
ROSC and lactate ≥12	97	88	4	99.9
ROSC and base deficit ≥ 10	100	87	2	100
ROSC and field GCS 3	100	87	2	100

Lactate values are expressed in mmol/L

PPV, positive predictive value; NPV, negative predictive value; ROSC, return of spontaneous circulation; LY-30, percent amplitude reduction at 30 minutes after thrombelastography maximal amplitude achieved; GCS, Glasgow coma scale

Table 3. First Validation Dataset Cut Points from 680 Patients Enrolled in a Randomized, Multicenter Trial (08/2012-12/2013) for Values Achieving Near-Fatal or Universally Fatal Outcomes with and Without Arrest and Return of Spontaneous Circulation

Variable	**PPV, %**	**NPV, %**	**Sensitivity, %**	**Specificity, %**
ED SBP≤50 and LY-30≥30%	100	80	8	100
ED SBP≤70 and LY-30≥70%	96	80	8	99.9
ED SBP≤70 and LY-30≥90%	100	81	7	100
ED SBP≤50 and lactate ≥15	99	79	6	99.9
ED SBP≤70, lactate>15, & lysis>30	100	80	7	100

Lactate values are expressed in mmol/L

PPV, positive predictive value; NPV, negative predictive value; ED; emergency department; SBP, systolic blood pressure; LY-30, percent amplitude reduction at 30 minutes after thrombelastography maximal amplitude achieved

Table 4. Second Validation Dataset Cut Points for Values Achieving Near-Fatal or Universally Fatal Outcomes With and Without Arrest and Return of Spontaneous Circulation

Variable	**PPV, %**	**NPV, %**	**Sensitivity, %**	**Specificity, %**
ED SBP≤50 and LY-30≥30%	100	78	33	100
ED SBP≤70 and LY-30≥90%	98	78	33	100
ED SBP≤50 and lactate ≥15	100	77	31	100
ED SBP≤70, lactate>15, & lysis>30	100	77	30	100
ROSC and LY-30 ≥30%	100	78	33	100
ROSC and lactate ≥12	100	76	29	100
ROSC and base deficit ≥12	98	72	4	100
ROSC and field GCS 3	99	77	27	100

Lactate values are expressed in mmol/L

PPV, positive predictive value; NPV, negative predictive value; ED; emergency department; SBP, systolic blood pressure; LY-30, percent amplitude reduction at 30 minutes after thrombelastography maximal amplitude achieved; ROSC, return of spontaneous circulation; GCS, Glasgow coma scale

Table 5. The proposed STOP (Suspension of Transfusion and Other Procedures) Criteria. Summary Recommendations Developed to Guide Clinicians and Surgeons in Cessation of Aggressive Resuscitation Strategies in Patients Arriving in Extremis

Variable	**PPV, %**	**NPV, %**	**Sensitivity, %**	**Specificity, %**
Arrival SBP≤50 and LY-30≥30%	100	78	33	100
Arrival SBP≤50 and lactate ≥15	100	77	31	100
Arrival SBP≤70, lactate ≥15, & LY≥30	100	77	30	100
ROSC and LY-30 ≥30%	100	78	33	100
ROSC and lactate ≥12	100	76	29	100
ROSC and field GCS 3	100	77	27	100

Lactate values are expressed in mmol/L

PPV, positive predictive value; NPV, negative predictive value; ED; emergency department; SBP, systolic blood pressure; LY-30, percent amplitude reduction at 30 minutes after thrombelastography maximal amplitude achieved; ROSC, return of spontaneous circulation; GCS, Glasgow coma scale