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Courtney H. Meyer

Ultra-Massive Transfusion: Can a Machine Learning Model Predict Outcomes and Survivability in Adult Trauma Patients?

By

Courtney H. Meyer
MPH, Hubert Department of Global Health

Deborah McFarland, PhD, MPH
Committee Chair

Randi N. Smith, MD, MPH
Committee Member

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Courtney H. Meyer

B.S. Lehigh University, Bethlehem, PA, 2014
MD, Albany Medical College, Albany, NY, 2019

Co-Advisor: Deborah McFarland, PhD, MPH
Co-Advisor: Randi N. Smith, MD, MPH

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Abstract

Ultra-Massive Transfusion: Can a Machine Learning Model Predict Outcomes and Survivability in Adult Trauma Patients?

By: Courtney H. Meyer

Background: Despite the widespread use of ultra-massive transfusion (UMT) in the resuscitation of trauma patients, mortality remain high. There is scarce evidence determining the clinical and physiologic parameters in which this intervention is most effective. Simultaneously, the US faces a critical blood product shortage and appropriate allocation of resources remains an important public health issue. Therefore, this study sought to investigate the efficacy of UMT for trauma patients at a single institution and utilize machine learning modeling to predict outcomes and survivability.

Methods: A retrospective cohort study of adult trauma patients undergoing UMT (defined as ≥20 units of red cell products within 24 hours) was conducted at a Level I trauma center from May 2018-Nov 2021. Data was triangulated from the blood bank, electronic medical record, and institutional trauma registry. The outcome of interest was mortality at 24 hours and discharge. Demographics, injury characteristics, clinical presentation, and total products transfused were compared between those who survived and those who died. A statistical analysis and hour-by-hour time series analysis were conducted and machine learning (ML) predictive models were generated and validated using R (version 4.1.1).

Results: There were 1,164 patients with MTP activations and 193 (16.6%) were adult trauma patients meeting criteria for UMT. The in-hospital mortality rate was 38.8% at 24 hours and 54% at discharge. Those who died were more hemodynamically unstable and in a more advanced state of shock at the time of presentation. The deceased cohort received more total blood products at each time interval studied, with significantly higher rates of packed red blood cell and fresh frozen plasma transfusion. Ten distinct ML models were generated successfully identified clinical and physiologic parameters most strongly associated with mortality.

Conclusions: This study demonstrates that mortality rates for UMT remain high and increased blood product transfusion is not associated with improved outcomes. Analysis of physiologic and clinical parameters further supports that early hemorrhage control and achievement of hemodynamic stability are critical to survivability. With blood as a limited resource, it is imperative to continue research in this field in order to identify which patients will benefit most from this aggressive therapy.

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Chapter 1: Introduction

1.1 Overview & Significance

Hemorrhage is the leading cause of preventable death in trauma (Park et al, 2016). It accounts for over one-third of trauma mortality within the first 24 hours of injury, making early hemorrhage control and adequate resuscitation critical (Park et al, 2016; Rossaint et al, 2016). Over the last 30 years, damage control resuscitation (DCR), or blood-based resuscitation, has become the gold standard for trauma patients with hemorrhagic shock (Holcomb et al, 2013; Holcomb et al, 2015; McQuilten et al, 2021; Thompson, 2020). DCR has been shown to improve morbidity and mortality and decrease the incidence of traumatic coagulopathy, acidosis and hypothermia (Thompson, 2020).

With the rise of DCR as a leading resuscitation strategy for trauma patients has come the development of the principles of massive transfusion protocols (MTP) and ultra-massive transfusion (UMT). UMT, specifically, describes the administration of 20 or more red blood cell products within 24 hours of admission (Dzik et al, 2016; Matthay et al, 2021).

Despite the widespread use of UMT in the resuscitation of trauma patients with hemorrhagic shock, the mortality rate for this intervention remains quite high. Studies have estimated mortality rates ranging from 50-80% for this patient population (Dzik et al, 2016; Johnson et al, 2016; Matthay et al, 2021, Velmahos, 1998; Yu, 2018). However, to date, there is scarce literature determining the physiologic and clinical parameters in which this intervention is most effective.

Simultaneously, the United States continues to face a critical blood product shortage and appropriate allocation of medical resources remains an important public health issue (American Red Cross, 2022). The American Red Cross (ARC) estimates that 16 million blood product

transfusions are required, annually, but that demand outweighs supply (American Red Cross, 2022). Amidst the existing donation shortage, ARC report an additional 10% decrease, nationally, in donation rates during the most recent Omicron surge of the COVID-19 pandemic in January 2022 (American Red Cross, 2022; Comenzo, 2022). Furthermore, McQuilten et al. estimate that approximately 10% of all in-hospital blood transfusions are related to massive transfusion and trauma patients (McQuilten, 2021).

1.2 Purpose Statement

The purpose of this project is to investigate the efficacy of UMT for adult trauma patients with hemorrhagic shock at a single high volume trauma center and utilize machine learning modeling to predict outcomes and survivability.

1.3 Specific Aims

- **Aim 1:** To perform a retrospective review of adult trauma patients undergoing ultra-massive transfusion at a single institution by triangulating data from three institutional databases – trauma registry, blood bank and electronic medical records
- **Aim 2:** To determine the institutional efficacy of ultra-massive transfusion for adult trauma patients at a single institution and identify factors associated with outcomes and survivability
- **Aim 3:** To design and test a machine learning model to predict outcomes and survivability for adult trauma patients undergoing ultra-massive transfusion

1.4 Definition of Terms

- **Damage control resuscitation:** the use of early blood product transfusions and temporization of ongoing hemorrhage in trauma resuscitation
- **Exploratory laparotomy:** a systematic and thorough exploration of the abdominal cavity in the setting of traumatic injury to control hemorrhage, control contamination from the gastrointestinal tract and identify all injuries followed by definitive repair or damage control
- **Machine learning:** the use and development of computer systems that are able to learn and adapt without following explicit instructions, by using algorithms and statistical models to analyze and draw inferences from patterns in data
- **Massive transfusion**: transfusion of 10 or more red blood cell products over a 24-hour period
- **Massive transfusion protocol:** rapid administration of large amounts of blood products (at least 6 units) in fixed ratios for the management of hemorrhagic shock
- **Resuscitative thoracotomy:** thoracotomy performed in emergency department intended to temporize wounds and stabilize a patient via direct control of intrathoracic injuries, decompression of pericardial tamponade, and control of the aorta to prevent exsanguination
- **Ultra-massive transfusion**: transfusion of 20 or more red blood cell products over a 24-hour period

1.5 Abbreviations

- **ARDS:** acute respiratory distress syndrome
- **ATLS** American Trauma Life Support
- **CPR:** cardiopulmonary resuscitation
- **Cryo:** cryoprecipitate
- **FFP:** fresh frozen plasma
- **GSW** gunshot wound(s)
- **ICU:** intensive care unit
- **ISS:** injury severity score
- **LOS:** length of stay
- **MARS:** multivariate adaptive regression splines
- **MT:** massive transfusion
- **MTP:** massive transfusion protocol
- **OR:** operating room
- **pRBC:** packed red blood cells
- **UMT:** ultra-massive transfusion
- **WB:** whole blood
- **XGBoost:** extreme gradient boosting

Chapter 2: Comprehensive Review of the Literature

2.1 History of trauma resuscitation

Traumatic injury is an epidemic in the United States affecting individuals of all demographic backgrounds (CDC, 2021). It accounts for over 41 million emergency department visits, 2.3 million hospital admissions and over 200,000 deaths, annually (CDC, 2021). Hemorrhage is the leading cause of preventable death following traumatic injury (Park et al, 2016). It constitutes over one-third of all trauma mortality in the first 24 hours, making early hemorrhage control and adequate resuscitation critical in the management of this patient populations (Park et al, 2016; Rossaint et al, 2016)..

The principle of resuscitation in trauma dates back to the 1600s, with English physician Dr. William Harvey's discovery of the circulatory system (Thompson, 2020). This understanding that blood existed in systemic circulation set the stage for the concept of being able to control excessive bleeding (Thompson, 2020). Two centuries later, Dr. John Henry Leacock proved that blood was species-specific and in 1818, Dr. James Blundell performed the first human to human blood transfusion (Thompson, 2020). The first documented use of transfusion for resuscitation was done for women with postpartum hemorrhage and published in *The Lancet* in 1829 (Thompson, 2020).

Much of our subsequent understanding of resuscitation in trauma has been from combat medicine and military fieldwork and research. For centuries, wounded soldiers have provided an unparalleled patient population in which to study and test the most ground breaking strategies for hemorrhage control and resuscitation.

During World War I, the concept of blood types and cross matching was refined and strategies to prevent transfusion reactions were developed (Loughlin, 2020; Thompson, 2020).

The demand for whole blood during the war also led to significant strides in blood storage, banking and donation. During World War II, the technology to separate plasma into its constitutes was developed and component therapy became a key area of experimental research (Loughlin, 2020; Thompson, 2020). Recognizing the importance of early intervention and whole blood as a limited resource, resuscitation with crystalloid fluids prior to blood transfusion became a leading strategy during the Vietnam War (Thompson, 2020).

This notion was further supported by research in the early 1970s, which acknowledged the need to not only replace intravascular volume with blood, but to also replete the extracellular fluid deficit (Holcomb et al, 2007; Krausz, 2006; Thompson, 2020). This led to the development of the "3 to 1" dogma, a resuscitation strategy adopted by the American Trauma Life Support (ATLS) guidelines recommending 3mL crystalloid for every 1mL of blood loss (Holcomb et al, 2007; Krausz, 2006; Thompson, 2020). This was later revised in the 1980s to rapid infusion of 2L crystalloid fluid followed by blood product transfusion if bleeding persisted (Thompson, 2020)..

However, these tactics led to the overuse of crystalloid fluids and a myriad of complications for patients with hemorrhagic shock (Cotton et al, 2020; Holcomb et al, 2007; Krausz, 2006; Thompson, 2020). Studies demonstrated that aggressive resuscitation with crystalloid fluids causes increased inflammation and vascular permeability, leading to increased incidence of tissue damage, reperfusion injury, abdominal compartment syndrome, multi-organ failure, acute respiratory distress syndrome (ARDS) and mortality (Cotton et al, 2020; Holcomb et al, 2007; Krausz, 2006; Thompson, 2020).

Therefore, over the last 30 years, there has been a paradigm shift back to the use of damage control resuscitation (DCR) or blood-based resuscitation (Holcomb et al, 2013; Holcomb

et al, 2015; McQuilten et al, 2021; Thompson, 2020). This strategy is rooted in concepts developed during World War II and has since been refined during the conflicts in Somalia, Afghanistan and Iraq in recent years (Thompson, 2020). It has become the gold standard of care in the current trauma literature, demonstrating improved morbidity and mortality and decreased incidence of traumatic coagulopathy, acidosis and hypothermia, the deadly triad of pathophysiologic changes that occur after trauma (Cotton et al, 2020; Holcomb et al, 2013; Holcomb et al; 2015; Thompson, 2020).

2.2 Blood products and principles of balanced transfusion

Damage control resuscitation (DCR) is defined as the use of early blood product transfusions and temporization of ongoing hemorrhage in trauma resuscitation (Leibner, et al, 2020). It does not, however, specify which blood products and in which order. Therefore, optimizing the sequence and ratio of products transfused has become a key area of research.

The blood products available for transfusion include; whole blood (WB), packed red blood cells (pRBC), fresh frozen plasma (FFP), platelets and cryoprecipitate (Cryo). WB is composed of red blood cells, white blood cells and platelets, all suspended in plasma, which contains proteins and clotting factors. PRBCs, FFP and platelets, respectively, contain their individual constituents. Cryo is plasma that has been centrifuged and re-suspended in a smaller volume of plasma to contain concentrated doses of key clotting factors and proteins.

In 2013, Holcomb et al conducted the PROMMTT (Prospective, Observational, Multicenter, Trauma Transfusion) Study, a landmark, multi-center trial investigating transfusion ratios (Holcomb et al, 2013). They found that in the first 6 hours, 1:1 transfusion ratios of either

plasma: pRBC or platelets: pRBC compared 1:2 transfusion ratios had a survival benefit (Holcomb et al, 2013).

In 2015, Holcomb et al expanded on these findings with the PROPPR (Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients with Severe Trauma) Randomized Clinical Trial (Holcomb et al, 2015). This study found no difference in 24 hour or 30-day mortality, but did find significantly lower rates of exsanguination and earlier achievement of hemostasis in the group receiving 1:1:1 transfusion ratios (Holcomb et al, 2013). This work established component therapy with 1:1:1 transfusion ratios of pRBC: plasma: platelets as the gold standard in the current trauma literature (Holcomb et al, 2013).

In recent years, there has also been a resurgence on the importance of whole blood in civilian resuscitation (Cotton et al, 2020; Crowe et al, 2020; Leibner et al, 2020; Thompson, 2020). Rapid and early transfusion of whole blood has been used in combat for centuries and has proven efficacious and safe in that setting. However, the challenge of adapting such into the practice of resuscitation for civilian trauma patients has been the logistics of ABO compatibility and potential for hemolytic transfusion reactions as well as Rh alloimmunization in females of child bearing age (Cotton et al, 2020). While Rh-low-titer group 0 whole blood can mitigate these issues, it remains in limited supply. Current research is focused on streamlining access to this product and integration of whole blood into our trauma resuscitation standards of care, in particular in the prehospital phase (Crowe et al, 2020; Leibner et al, 2020).

2.3 Principles of massive transfusion and ultra-massive transfusion

With the rise of DCR as a leading resuscitation strategy for has come the development of the principles of massive transfusion protocols (MTP), massive transfusion (MT) and ultra-

massive transfusion (UMT). MTP refers to the rapid administration of large amounts of blood products (at least 6 units of pRBC) in fixed ratios for the management of hemorrhagic shock. Most modern day trauma centers are equipped with the processes and resources to rapidly activate MTP and begin transfusion of products for an acutely injured patient.

In the current literature, MT has been defined as 10 or more red cell units within 24 hours, 6 or more units in 6 hours or 5 or more units in 4 hours (Mitra et al, 2011). A consensus definition for UMT has not been well established in the literature. However, the definition most commonly used and the one employed for this research defines UMT as 20 or more units of red blood cell products within 24 hours of admission (Dzik et al, 2016; Matthay et al, 2021)

2.4 Current state of ultra-massive transfusion in trauma

Despite the widespread use of UMT in the resuscitation of trauma patients with hemorrhagic shock, the mortality rate for this intervention remains quite high. Studies have estimated in-hospital mortality rates ranging from 50-80% for this patient population (Dzik et al, 2016;Matthay et al, 2021; Velmahos, 1998; Yu, 2018). However, to date, there is scarce literature determining the patient and injury characteristics in which this intervention is most beneficial.

For example, Dzik et al in 2015 and Johnson et al in 2016 found correlational evidence to support increasing mortality with increasing transfusion requirements (Dzik et al, 2016; Johnson et al, 2016). In 2020, Morris et al demonstrated that transfusion "ceilings" were dependent on age and mortality rates were higher in older patients who received more pRBCs (Morris et al, 2020). In 2021, Matthay et al published one of the first studies investigating the interplay of these factors (Matthay et al, 2021). Using regression analysis, they determined older age, lower

GCS, thrombocytopenia and the presence of resuscitative thoracotomy were associated with lower survival in trauma patients undergoing UMT (Matthay et al, 2021).

While these studies all provide important advances in the literature, there is still a need for consensus guidelines regarding the physiologic and clinical parameters in which this aggressive and resource-demanding therapy is most effective.

2.5 Current state of national blood shortage

Blood products are a limited resource and the United States continues to face a critical shortage (American Red Cross, 2022). The American Red Cross estimates that 16 million blood product transfusions are required, annually, but that demand greatly outweighs the supply (American Red Cross, 2022). This public health crisis has been exacerbated by the ongoing COVID-19 pandemic. In January 2022, during the most recent Omicron surge, donation rates deceased an additional 10%, nationally (American Red Cross, 2022; McQuilten et al, 2021).

In a 2021 study, McQuilten et al. estimated that approximately 10% of all in-hospital blood transfusions are related to massive transfusion and trauma patients (McQuilten et al, 2022). With a mortality rate of 50-80%, establishing which patients may benefit from this resource-demanding therapy is an important area of public health research (Dzik et al, 2016; Johnson et al, 2016; Matthay et al, 2021, Velmahos, 1998; Yu, 2018).

Chapter 3: Manuscript

***Note**: This abstract has been accepted for presentation at the 81st Annual Meeting of the AAST (American Association for the Surgery of Trauma) and Clinical Congress for Acute Care Surgery. *September, 2022.* This manuscript has been submitted for peer review publication to the Journal of Trauma. *July, 2022.*

3.1 Title page

Title: Outcomes and survivability in adult trauma patients undergoing ultra-massive transfusion

Authors: [A-C]CH Meyer, MD, [D]A ElHabr [A,B]C Ward, MD, [A,B]J Gichoya, MD, MS, [A,B]Craig Coopersmith, MD, [A,B]J Sciaretta, MD, [A,B]C Dente, MD, [A,B]J Lyons, MD, [A-C]RN Smith, MD, MPH

Affiliations:
A: Grady Health System, Atlanta, GA
B: Emory University School of Medicine, Atlanta, GA
C: Rollins School of Public Health, Emory University, Atlanta, GA
D: Georgia Institute of Technology, Atlanta, GA

Corresponding Author:
Randi N. Smith, MD, MPH
Emory University School of Medicine
Glen Memorial Building
69 Jesse Hill Jr. Drive SE, Suite 102
Atlanta, GA 30303
P: 404-251-8916
randi.smith@emory.edu
ORCID: 0000-0002-2720-5917

Co-Author Contact Information
Courtney H. Meyer, MD, courtney.meyer@emory.edu, ORCID: 0000-0002-1594-4157
Andrew ElHabr, andrewelhabr@gatech.edu
Carson Ward, MD, carsonward@gmail.com
Morgan Sanders, RN, BSN, morgan.sanders@emory.edu
Alexis Thompson, MPH, Thompson.alexisn@gmail.com
Vignesh Majaraman Muralidharan, MS, ME, vignesh.jayaraman.muralidharan@emory.edu
Judy Gichoya, MD, judywawira@emory.edu
Craig Coopersmith, MD, cmcoop3@emory.edu
Christopher Dente, MD, cdente@emory.edu
John Lyons, MD, jdlyons@emory.edu

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3.2 Abstract

Background: Despite the widespread use of ultra-massive transfusion (UMT) in the resuscitation of trauma patients, mortality remains high. A recent published multicenter trial revealed unbalanced ratios contributes to these rates. Still, there is scarce evidence regarding the clinical and physiologic parameters in which this resource-demanding intervention is most effective. This study investigated our institutional efficacy of UMT and identified specific factors, beyond blood product ratios, associated with outcomes and survivability.

Methods: A retrospective cohort study of adult trauma patients undergoing UMT (defined as ≥ 20 units of red cell products within 24 hours) was conducted at a Level I trauma center from May 2018-Nov 2021. Data was triangulated from the blood bank, electronic medical records, and institutional trauma registry. The outcome of interest was mortality at 24 hours and discharge. Demographics, injury characteristics, clinical presentation, operative interventions and total products transfused were compared between survivors and deceased.

Results: There were 1,164 patients with MTP activations and 193 (16.6%) were adult trauma patients meeting criteria for UMT. The mortality rate was 38.8% at 24 hours and 54% at discharge. Those who died were more hemodynamically unstable and in a more advanced state of shock at the time of presentation. The deceased cohort received more total blood products, with significantly higher rates of pRBC (39 [26-53] vs 24 [19-32], p<0.001) and FFP (32 [18-47] vs 18 [14-26], p<0.001) transfusion. In multivariate analysis, independent predictors of mortality included a lower heart rate (OR=1.02 [95%CI 1.01,1.03], p<0.001) and lower GCS (OR=1.16

[95%CI 1.08,1.25], p<0.001) at the time of admission as well a higher total number of blood products transfused (OR=0.98 [95%CI 0.96-0.99], p<0.001).

Conclusions: This study demonstrates that mortality rates for UMT remain high and increased blood product transfusion is not associated with improved outcomes. Analysis of physiologic and clinical parameters further supports that early hemorrhage control and achievement of hemodynamic stability are critical to survivability.

Level of Evidence: III

3.3 Background

Hemorrhage is the leading cause of preventable death in trauma [1]. It accounts for over one-third of trauma mortality within the first 24 hours, making early hemorrhage control and adequate resuscitation critical [1, 2]. Over the last 30 years, damage control resuscitation (DCR) has become the gold standard for resuscitation of trauma patients with hemorrhagic shock [3-6].

DCR has been shown to improve morbidity and mortality and decrease the incidence of traumatic coagulopathy, acidosis and hypothermia. Specifically, the use of empiric 1:1:1 ratios of packed red blood cells (pRBCs), fresh frozen plasma (FFP) and platelets (PLT) has been shown to significantly decrease rates of exsanguination within the first 24 hours [5].

With the rise of DCR as a leading resuscitation strategy for trauma patients has come the development of the principles of massive transfusion protocols (MTP) and ultra-massive transfusion (UMT). UMT, specifically, describes the administration of 20 or more red blood cell products within 24 hours of admission [7, 8].

Despite the widespread use of UMT in the resuscitation of trauma patients with hemorrhagic shock, the mortality rate for this intervention remains quite high. Studies have estimated mortality rates ranging from 50-80% for this patient population [7-10]. A number of recent studies have provided correlational evidence between increasing blood product requirements and increasing mortality rates [7,8,10,11]. Furthermore, a 2021 multicenter study investigated the impact of transfusion ratios physiologic and laboratory characteristics of patients undergoing UMT as well as the impact of transfusion ratios on mortality [8]. Their findings demonstrated that pRBC/FFP and pRBC/platelet ratios greater than 1.5:1 were significantly and independently associated with increased mortality [8].

While all of these studies have contributed significantly to our current understanding of best practices for UMT in trauma resuscitation, there is still scarce literature determining the physiologic and clinical parameters in which this resource-demanding intervention is most effective.

With UMT as an aggressive therapy and blood in limited supply, this is a critical area for further research. Therefore, this study sought to investigate our own institutional efficacy of UMT for adult trauma patients with hemorrhagic shock and identify factors associated with improved outcomes and survivability.

3.4 Methods

Study Design & Inclusion Criteria

A retrospective cohort study was conducted at a large, academic, ACS verified Level I trauma center in Atlanta, GA. Data was obtained from May 2018-November 2021 (42 months)

and triangulated from the blood bank registry, electronic medical record (EMR) and institutional trauma registry.

First, the institutional blood bank registry was reviewed for all patients with a massive transfusion protocol (MTP) activation. This included all patients, hospital-wide, with an order placed by a physician or mid-level provider for MTP. This data was then cross referenced with the electronic medical record to determine if the patients were (1) adults over 18 years of age, (2) had a traumatic mechanism of injury and (3) met criteria for ultra-massive transfusion (UMT). UMT was defined as 20 or greater units of red cell products (packed red blood cells and/or whole blood) within the first 24 hours of admission. Data on the number of blood products transfused within 24hrs from admission was reported in the blood bank registry and cross referenced with the EMR charting and operative reports.

For those patients meeting inclusion criteria for the study, data pertaining to demographics, clinical presentation, injury classification, hospital course and outcomes was then obtained from the institutional trauma registry. The institutional trauma registry includes all hospitalized trauma patients.

Variables of Interest

The exposure of interest was UMT and the primary outcome of interest was in-hospital mortality at 24 hours and discharge. Secondary outcomes of interest included total number of units of all products transfusion, pRBC:FFP transfusion ratios, operative interventions, intensive care unit and hospital lengths of stay and complications. The blood products analyzed in this study included pRBC, FFP, platelets and cryoprecipitate. Transfusion ratios were analyzed as rates of pRBC: FFP within the first 24 hours of admission. Injuries were classified as blunt or

penetrating and then the mechanisms of injury (MOI) were grouped into the following categories; gunshot wounds (GSWs), motor vehicle collisions (MVCs), motorcycle collisions (MCC), pedestrian vs auto (peds vs auto), other blunt, and other penetrating.

Statistical Analysis

We compared all of the above metrics in patients who survived their UMT and those who did not using Chi-square (Fisher exact test) and two-sample t-tests. A subgroup analysis was also performed in the deceased cohort of patients between those who survived beyond 24 hours and those who did not.

Multivariate analysis was also conducted to determine independent risk factors for mortality and for total blood products transfused in adult trauma patients undergoing ultra-massive transfusion. All statistical analyses were performed using R version 4.1.1 (R Foundation for Statistical Computing). Significance was set at $\alpha=0.05$. IRB approval was obtained for this study.

3.5 Results

Over the study period, there were 1,164 patients with MTP activations and 193 (16.6%) were adult trauma patients meeting criteria for UMT. The overall in-hospital mortality rate for trauma patients undergoing UMT was 38.8% (n = 75) at 24 hours and 54% (n= 105) at discharge.

Demographics

The study population was comprised of predominately black (n = 156, 81%) males (n=150, 78%) with a median age of 29 years [IQR 24,-44]. There were no significant differences in demographic factors between those who survived UMT and those who did not (Table 1).

Injury Classification

The cohort of UMT patients who died presented with equal proportions of blunt to penetrating injury (50% blunt, 50% penetrating) while the surviving group had a slightly higher incidence of penetrating injury (39% blunt, 61% penetrating, $p = 0.13$). There were no significant differences in MOI, with both the deceased and surviving cohort presenting with predominantly GSWs, followed by MVCs and then peds vs auto. The median Injury Severity Score for the deceased cohort was 38 [IQR 26-50] compared to 34 [IQR 25-49] in those who survived ($p = 0.21$) (Table 1).

Clinical Presentation

On presentation to the ED, the group who did not survive had a lower median systolic (80 [IQR 58-116] vs. 90 [IQR 71-114], $p = 0.076$) and diastolic blood pressure (40 [IQR 0-78] vs 57 [IQR 0-80] $p = 0.15$). The deceased cohort also had a significantly lower heart rate (89 [IQR 39-128] vs 124 [IQR 103-140], $p < 0.001$), respiratory rate (0 [IQR 0-24] vs 22 [IQR 14-29], $p < 0.001$) and Glasgow Coma Score (3 [IQR 3-9] vs 14 [IQR 6-15], $p < 0.001$) at the time of admission (Table 2).

On initial trauma labs, both groups had similar median hematocrits while those who did not survive had a greater base deficit (-13 [IQR -21 to -9] vs -7 [IQR -13 to -2], $p < 0.001$). A

greater proportion of the deceased cohort required CPR in the ED (17% vs 2.3%, $p < 0.001$) and 38% (n= 40) underwent an ED thoracotomy compared to 2.3% (n = 2) in the surviving cohort ($p < 0.001$) (Table 2).

Blood Products Transfused

The median number of blood products transfused for the entire study population of patients undergoing UMT was 59 [IRQ 43-97]. The deceased cohort received more blood product overall, with a with a median of 80 units [IQR 50-110] compared to 50 units [IQR 39-62] in the surviving cohort ($p < 0.001$). This trend was consistent for the total numbers of pRBC, FFP and platelets transfused (Table 3).

Overall, less than 1/3 of the cohort received pRBC: FFP transfusion ratios greater than 1.5:1. The median ratio for the deceased cohort was 1.2 compared to 1.3 in the surviving cohort but this was not significant.

In a subgroup analysis of the deceased cohort, those who survived beyond the 24 hour period had a median pRBC to FFP ratio of 1.1 compared to 1.2 in the group who prior to that mark ($p = 0.010$). The deceased within 24 hours cohort had 31% of patients receiving greater than 1.5:1 pRBC: FFP transfusion ratios compared to 20% in the cohort that survived beyond 24 hours (Table 4).

Operative Intervention

Nearly the entire study population (98%) went immediately to the operating room (OR) from the ED. Both the surviving and deceased groups underwent similar rates of exploratory laparotomies and thoracotomies, for those who had not undergone one in the ED. Intra-

operatively, both cohorts also had similar rates of solid organ and vascular injury. Vascular injury included those intra-thoracic, intra-abdominal or extremity (Table 5).

Multivariate Analysis

In multivariate analysis, independent predictors of increased mortality included a lower heart rate (OR = 1.02 [95% CI 1.01,1.03], $p < 0.001$) and lower GCS (OR = 1.16 [95% CI 1.08,1.25], $p < 0.001$) at the time of admission as well a higher total number of blood products transfused (OR = 0.98 [95% CI 0.96-0.99], $p < 0.001$) (Table 6).

In an additional multivariate analysis, a lower heart rate (OR = -0.17 [95% CI -0.33,-0.02], $p = 0.030$) and lower base deficit (OR = -0.73 [95% CI -1.5, -0.01], $p < 0.049$) at the time of presentation were independent predictors of requiring greater total blood products (Table 7).

3.6 Discussion

It is well established that UMT is a potentially lifesaving intervention for adult trauma patients with hemorrhagic shock. However, given the associated high mortality rate and resource-demanding nature of UMT, it is critical to determine which patients will benefit most from this therapy. To the best of our knowledge, alongside the recent multicenter study, this is one of the first to investigate specific physiologic and clinical parameters which may be associated with mortality. It is critical to understand the specific details that contribute to survivability in order to develop decision-making tools that aid in the management of these complex patients requiring UMT. Therefore, the authors have some key findings from this study to discuss.

First, increased blood product transfusion was not associated with increased survival. Conversely, we found the deceased cohort received an average of 30 more total blood product units than the surviving cohort with higher rates of individual pRBC, FFP and platelet transfusion. This was also supported by our multivariate analysis, which found total blood products transfused to be an independent predictor of mortality. The authors interpret this trend not as a correlation between lower transfusion rate and survival, but rather as a proxy for delayed or inadequate hemorrhage control. While 98% of the study population did go for emergent operative intervention, it is reasonable to speculate that those requiring more blood product transfusions likely had more complex or challenging injuries to temporize.

Further contributing to demise of the deceased cohort was the fact that they presented with more hemodynamic instability and in a advanced state of hemorrhagic shock. Upon arrival to the ED, those who did not survive had similar blood pressures to the survivors but a lower median heart rate and greater base deficit. These findings represent progression into stage IV shock at the start of their resuscitation. While it is logical that those who presented sicker are more likely to die, identification of these clinical parameters early in resuscitation efforts may serve as a target for more aggressive intervention.

With the PROPPR trial in 2015, Holcomb et al established component therapy with 1:1:1 transfusion ratios as the gold standard for trauma patients. We found that our institution achieved transfusion ratios of pRBC to FFP less than 1.5:1 in 71% of patients. There were no significant differences in transfusion ratios between those who survived, those who died within 24 hours and those who died prior to discharge. However, it is important to note the small sample size of this subgroup analysis and the fact that these ratios were calculated from total blood products transfused over 24 hours and do not account for the order of products transfused. Furthermore,

our institution did not transfuse platelets at a high enough rate to be included in our ratio analysis. This was likely due to their limited supply and significant differences were not noted between the surviving and deceased cohorts.

Interestingly, our study demonstrated a mortality rate of 54% at discharge, which is at the lower end of the 50-80% mortality rate range estimated in the current literature. Another way of looking at this, is that 46% of individuals survive trauma requiring ultramassive blood product transfusion. The authors speculate this is due to the high volume of trauma patients we care for and our trauma team's familiarity with initiating and executing our institutional massive transfusion protocols.

Limitations

There are several limitations to this study the authors would like to acknowledge. First, it was retrospective in nature, leading to certain confounding variables that were not controlled for in study design. Additionally, UMT is a rare occurrence and while our institutional rates were significant, the authors recognize that 193 patients is a small sample size from which to draw practice changing conclusions. This study was also performed at a single institution. This may lead to internal biases in our practices and may limit the extent to which these results are externally valid.

Conclusions and Future Directions

Overall, this study demonstrates that mortality rates for UMT remain high and that increased blood product transfusion is not associated with improved outcomes. Analysis of physiologic and clinical parameters further supports that early hemorrhage control and

achievement of hemodynamic stability are critical to survivability. However, resuscitation is a dynamic process and further research is required to better understand how these factors change in real time and impact mortality. Understanding these parameters on a more granular scale may help elucidate the time points at which UMT transitions from a necessary and life-saving intervention to a resource-consuming and futile one. It will also be important to validate such work on a multi-center scale.

Chapter 4: Extended Methodology and Results

4.1 Extended methodology

4.1.1 Introduction

In addition to the data collection and analysis conducted for the manuscript, two additional analyses were conducted. The first was the machine learning predictive modeling component of this study and the second was an extended data collection and hour-by-hour time series analysis.

4.1.2 Machine learning predictive modeling overview

The machine learning component of this project was done using the institutional UMT data set. These data were collected via a retrospective cohort review at a large, academic, ACS verified Level I trauma center in Atlanta, GA from May 2018-November 2021 (42 months). Data was triangulated from the blood bank registry, electronic medical record (EMR) and institutional trauma registry (see section 3.4 for detailed methodology). The analysis was conducted using R version 4.1.1.

Machine learning, broadly, refers to a type of artificial intelligence which allows a computer system to learn and adapt algorithms in order to predict outcomes without explicit programming. Specifically, supervised learning, a subfield of machine learning, is done by introducing a given data set with a series of known inputs and outcomes and allowing the computer to "learn" the rule connecting them. In supervised machine learning, the model is trained, tested and then validated with different segments of the data set. There are an innumerable number of models that can be employed by machine learning models. Determining

the appropriateness of models is done based on the size of the data set, components within the data set and the outcome or question of interest.

Machine learning provides a novel context in which to study outcomes and survivability in trauma patients undergoing UMT. While traditional statistics allows for analysis of the physiologic and clinical factors impacting mortality, machine learning helps us to understand the interaction between these entities.

4.1.3 Machine learning predictive modeling methods

The following 10 models, discussed in detail below, were generated for this analysis; (1) Full Logistic Regression, (2) Small Logistic Regression, (3) LASSO, (4) Ridge Regression, (5), Elastic Net, (6) Multi-adaptive Regression Spline (MARS), (7) K-Nearest Neighbors, (8) Decision Tree, (9) Random Forest, and (10) Extreme Gradient Boosted Trees (XGBoost). For models 1 and 3-10, the following variables were used: age, gender, mechanism of injury, ISS, SBP, HR, GCS, total blood products and pRBC/FFP ratio. For model 2, an abbreviated list of those variables was selected and included: ISS, SBP, HR, GCS, Total Blood Product and pRBC/FFP ratio.

The decision was made to test 10 different models as UMT is a novel research area for machine learning. The purpose was to determine which type of model may be most well suited for this type of data and research question in the future. The discriminative ability of these models to separately predict survival versus mortality were assessed using area under the curve (AUC) values on a receiver operator characteristic (ROC) curve (see Table 1 Appendix 7.3.1 and Figure 1 Appendix 7.4.1). The calibration of each model, i.e. the model's ability to generate a

predicted risk of survival that agrees with the true observed risk of survival, was assessed as well. (see Figure 2 Appendix 7.4.1).

With large data, a single split of the data into training, validation, and testing sets is usually sufficient for both developing a strong predictive model and assessing this model's performance with a large amount of certainty. Due to the smaller size of the UMT data, this same exact approach would yield a large amount of uncertainty in the model's performance. Thus, a nested validation procedure, in which every data point is faithfully used in training and testing the model, is used to reduce the amount of uncertainty as much as possible. In this framework, the data is split into 10 subsets. In one run of this procedure, nine of the 10 subsets of the data are used for training/validation with a standard cross-validation procedure to select the best hyperparameters of the model of interest and then train this model with these hyperparameters. Then, this model makes predictions on the tenth held-out subset of the data. This process is repeated for all 10 subsets of the data to obtain predictions for every person in the data. Because the same exact hyperparameters of a model may not be used to generate predictions for the whole data set, histograms of the selected model hyperparameters in this process are observed to ensure that no serious "model drift" has occurred.

Logistic regression modeling (1 and 2) is equivalent to the multivariate analysis generated previously, but now within this nested validation framework, and the models are used to generate probability predictions instead of focusing on inference with odds ratios. LASSO and Ridge regression (3 and 4) are both types of regression analysis that use regularization to generate a more accurate prediction. They use 'shrinkage' to shrink data values towards a central mean. This is done when significant co-linearity exists in the data set and help avoid overfitting the model. LASSO regression will set values to zero while ridge regression will set coefficients

to be lower and minimize the impact of irrelevant features but not fully remove them. Elastic net (5) is a type of regression model that combines both the LASSO and ridge regression. It uses the penalties from both for regularization. MARS (6) is an algorithm that combines a series of simple linear regression functions using hinges. It generates multiple candidate models in the forward stage and then employs a backwards stage to remove those that do not reduce the overall error of the model.

K-nearest neighbor (7) model uses the assumption that similar data points are near one another. It then categorizes data based on a given k value or distance, independent of the actual data set entered.

Decision tree modeling (8) uses a stepwise algorithm which is able to predict the classification of a given variable. It does so via a series of stepwise, pragmatic decision at decision nodes until the outcome of interest is reached. A random forest (9) model uses a series of decision tree algorithms to generate a predictive model. It can help reduce overfitting of the model and increase precision.

XGBoost is a modeling strategy similar to random forest which creates a regression modeling using a series of decision trees. However, while random forest plot combines the decision trees in parallel, XGBoost allows progressive addition of the decision trees based on the weights of different variables. This can help improve accuracy and precision, particularly for tabular data, as the trees are added sequentially based on the weighted error of the prior tree.

4.1.4 Hour-by-hour time series analysis methods

The objective of this extended methodology was to obtain more detailed and granular time point data in order to enhance the ongoing analysis. In order to complete this portion of the

project, an additional data set was obtained. This dataset was obtained retrospectively via Epic (the institutional EMR) over the same time period from May 2018 through November 2021. It contained additional data points on the same 193 patients used in the original UMT institutional data set.

The data points included in this dataset were divided into 5 categories; transfusion data, lab data, vital signs and ventilator parameters, medications and intra-operative events. Data for each category was captured for the entire duration of hospitalization.

Transfusion data captured all blood products transfused, including matched and unmatched pRBCs, FFP, platelets, and cryoprecipitate. It also captured the start and stop time of each transfusion. Lab data captured all lab drawn, the time of the lab draw, the resulting value and the time of the result. Vital signs and ventilator parameters captured all recorded values of the following parameters with time stamps; temperature, blood pressure (manual and invasive), pulse, respiratory rate, oxygen saturation, PEEP, respiratory rate, ventilator mode, peak airway pressure, plateau pressure, FiO2 and exhaled tidal volume.

Medications captured all infusions and medications administered with time stamps, doses and concentrations. Intra-operative events captured anesthesia start and stop time, intubation, extubation, CPR start and stop and transport to ICU.

This data was inputted to R version 4.1.1 and a univariate and hour-by-hour time series analysis was conducted.

4.2 Extended results

4.2.1 Machine learning predictive modeling results

The machine learning analysis generated 10 distinct models for predicting mortality in adult trauma patients undergoing UMT. AUC values ranged from 0.702 [95% CI 0.627, 0.778] for the decision tree model to 0.792 [95% CI 0.730, 0.855] for the random forest model The additional top 3 performing models based on AUC were the MARS model (0.784 [95% CI 0.720, 0.850], K-nearest neighbor model (0.770 [95% CI 0.703, 0.837] and the small logistic regression model (0.767 [95% CI 0.700, 0.833] (see Table 1 Appendix 7.3.1 and Figure 1 Appendix 7.4.1).

The calibration plot demonstrates that generally all of the models are calibrated moderately well since most of the dots are fairly close to the dividing line (see Figure 2 Appendix 7.4.1). Focusing on just the three highest performing models, the calibration of the MARS model indicates that it slightly underpredicts the probability of survival in the higher risk range (0-50% chance of survival), and slightly overpredicts the probability of survival in the low risk range (50-100% change of survival), while the exact opposite observations can be made for the random forest and K-nearest neighbor models. This indicates that, in practice, if yielding a probability prediction of the true risk of a patient is desired, potentially as input for some king of sequential clinical decision, averaging the predictions from these individual models may be best.

Nested variable selection cross-validation was used for each model. As illustrated in Figures 3 and 4 in Appendix 7.4.1, this strategy demonstrated consistency in the variables selected for each model each time it was run. This consistency ensures that the predictions generated from using all of the data for both training and testing in the nested manner are reliable

and valid. For the LASSO model variable selection, HR and GCS were selected for each time the model was run, while the other variables were also consistently selected at a slightly lower rate. Similarly, for the decision tree model, ISS, SBP, HR, GCS, total blood products and pRBC: FFP ratio were all selected over 50% of the time.

4.2.2 Hour-by-hour time series analysis results

Overall, the results of the hour-by-hour analysis support and strengthen the findings of the univariate and multivariate analysis in Chapter 3. This data provides a more granular illustration of the dynamic patterns of vital signs, lab values and blood products transfusions over the first 24 hours for the study population. The following results are stratified by mortality. At time point 0, there were 192 total patients, with 104 (54%) in the deceased cohort and 88 (46%) in the surviving cohort.

4.2.2.1 Vital signs and laboratory values

When analyzing systolic blood pressure, both the surviving and deceased cohorts presented with a similar degree of hemodynamic stability (102 [86, 144] vs 98 [81, 111], p = 0.15). However, by the 4-8 hour window, the surviving cohort had a median systolic blood pressure within normal range while the deceased cohort's remained low [125 [111, 145] vs 110 [94, 131], p = 0.010). This trend continued in the 8-12 hour and 12-16 hour time periods. In hours 16-20 and 20-24, both groups had systolic blood pressures in the 110s with no statistically significant differences (see Table 1 Appendix 7.3.2 and Figure 1 Appendix 7.4.2).

In terms of median heart, both cohorts presented with tachycardia to the 120s. However, they began to show statistically significant differences by hours 12-16, where the deceased

cohort remained tachycardic at 120 [103, 129] and the surviving cohort had a down-trending median HR of 109 [96, 122] ($p = 0.014$). This pattern continued over the next 8 hours, with the deceased cohort remaining tachycardic to 114 [110, 130] at 20- 24 hours compared to the survivors who had a lower median HR of 107 [90, 119] by this point ($p = 0.006$) (see Table 2 Appendix 7.3.2 and Figure 1 Appendix 7.4.2).

Lactate, an important marker of severity of shock, showed significant differences between the two cohorts at each time point analyzed. In the initial 8 hours, the deceased group had a median lactate of 10.4 [8.1, 13.6] compared to 5.4 [3.9, 7.5] in the surviving group ($p < 0.001$). This trend persisted with the deceased cohort having a lactate of 8.4 [4.7, 12.1] at 24-48 hours compared to only 3.0 [2.0, 3.8] ($p <0.001$) in the surviving cohort (see Table 3 Appendix 7.3.2 and Figure 1 Appendix 7.4.2).

4.2.2.2 Blood products

During the initial 24 hours of admission, the deceased cohort received significantly higher median rates of total blood product transfusion at each time interval. This difference was more pronounced in the 0-1, 1-2, 2-4, 4-6 and 6-10 time intervals (see Table 4 Appendix 7.3.2 and Figure 2 Appendix 7.4.2). Cumulative median total blood product transfusion rates followed a similar trend, with significantly higher rates of product for the deceased cohort at each time period (see Table 5 Appendix 7.3.2 and Figure 3 Appendix 7.4.2).

Furthermore, when analyzed individually, the median units of each blood product transfused over time also demonstrated similar findings. In terms of pRBCs, the deceased cohort received a median of 12.5 [9.0, 16.8] units during the first hour compared to 10.0 [6.8, 14.0] units in the surviving cohort ($p = 0.011$). Over the next 14 hours, the deceased cohort continued

to receive an average of 1.5 to 2 units greater per 2-hour period than the survivors (see Table 6 Appendix 7.3.2 and Figures 4 and 5 Appendix 7.4.2). Similarly, the deceased received a median of 9.0 [5.0, 12.0] units of FFP during the first hour compared to 7.0 [4.0, 10.0] in the survivors ($p = 0.029$). FFP transfusions remained higher in the deceased cohort over the next 14 hours and reached a rate of less than 1 unit by the 14 to 24-hour period (see Table 7 Appendix 7.3.2 and Figures 4 and 5 Appendix 7.4.2).

The rate of platelet transfusions was greatest at 0-1 hours and 1-2 hours for each cohort and tapered to less than 1 unit per hour for the remaining time intervals (see Table 8 Appendix 7.3.2 and Figures 4 and 5 Appendix 7.4.2). Cryoprecipitate rates were highest for both groups at 2.0 units per hour in the 1 to 2-hour time period. The deceased cohort received a significantly higher median total units per time period in the 6-10 and 14-24 hour intervals (see Table 9 Appendix 7.3.2 and Figures 4 and 5 Appendix 7.4.2)

Lastly, both cohorts received an average of 4 units of whole blood in the first hour ($p = 0.92$). There were no significant differences in rates of whole blood transfusion over the remaining time periods (see Table 10 Appendix 7.3.2 and Figures 4 and 5 Appendix 7.4.2)

Chapter 5: Limitations, Conclusions, Public Health and Ethical Implications

5.1 Limitations

There are a number of limitations the authors of this project would like to acknowledge. First, this study was performed retrospectively. This design does not allow for the ability to control for certain confounding variables, which is recognized in the subsequent analysis. Additionally, the authors recognize that even at our large, urban, ACS Verified Level I trauma center with some of the highest rates of UMT in the country, it is still a relatively rare event. This yielded a small sample size, constricting the generalizability of the study findings. Furthermore, this data set was obtained from a single institution. The authors acknowledge this can lead to certain internal biases in practice and limit the external validity of the study findings.

Lastly, machine learning is an imperfect science and cannot replace 'the art of medicine.' The authors recognize the potential for machine learning to change the way we practice clinical medicine is vast, but that the human perspective remains of equal importance. Therefore, any conclusions drawn from this project should be used as an adjunct to clinical judgement.

5.2 Conclusions, public health and ethical implications

It is well established that UMT is a potentially lifesaving intervention for adult trauma patients with hemorrhagic shock (Dzik et al, 2016; Johnson et al, 2016; Matthay et al, 2021, Velmahos, 1998; Yu, 2018). However, given the associated high mortality rate and resource-demanding nature of UMT, it is critical to determine which patients will benefit most from this

aggressive therapy and patients in which UMT may be futile. To the best of our knowledge, this is one of the first studies to investigate specific physiologic and clinical parameters which may be associated with survival. The results have important clinical, research, public health and ethical implications.

From a clinical perspective, all 3 analyses conducted demonstrated that increased blood product transfusion was not associated with increased survival. Conversely, the deceased cohort received significantly higher blood products at each time interval studied and the total number of blood products proved to be an independent predictor of mortality. This trend is interpreted not as a correlation between lower transfusion rate and survival, but rather as a proxy for delayed or inadequate hemorrhage control. Further contributing to demise of the deceased cohort was the fact that they presented with more hemodynamic instability and in a more advanced state of hemorrhagic shock. These findings are relevant as identification of these clinical parameters early in resuscitation efforts may serve as a target for patients requiring more aggressive intervention.

This leads into the research implications of this work. While the predictive capability of the current models is limited by the size of the data set, machine learning provides an exciting and novel context with which to study this question. IRB approval has been obtained for the next phase of this project, which entails expansion to a multi-center study. This will generate a more robust dataset and ability to further train and validate a model with the goal of clinical application in the future.

It is important to continue in this field of research as the public health implications are vast. There is a critical blood shortage in the United States and the recent COVID-19 pandemic has highlighted the devastating reality that appropriate allocation of medical resources is an area

of great importance in public health (American Red Cross, 2022). This project demonstrated that a significant proportion of in-hospital blood product stores are utilized by adult trauma patients undergoing UMT. However, despite resource consumption, mortality rates for these patients remained high. With blood as a limited resource, in demand by many other patient populations, it is imperative to determine when use in extraordinary quantities for trauma patients is most appropriate and beneficial.

However, this question does not come without profound ethical considerations. It challenges the principles of justice and nonmaleficence in ways our healthcare system has struggled with, historically. How do we determine just allocation of a limited medical resource? How do we ensure this is done in a manner that does not marginalize certain populations or exacerbate existing health care inequities? How do we explain to patients that simply because we have the capacity to do something does not mean it is the right thing to do? How do we communicate the concept of futility?

While these questions do not come with a simple answer, they are at the forefront of our research on this topic. An overarching objective of utilizing machine learning to determine a "transfusion ceiling" and the parameters in which this therapy is most effective is to optimize just distribution of a finite resource. Furthermore, it is intended to equip providers with an evidence based algorithm of when UMT transitions from a necessary and lifesaving intervention to futile so as to maximize non-maleficence.

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Appendices

7.1 Manuscript tables

Table 1: Demographics and injury classification of adult trauma patients undergoing UMT

	Overall n = 193[1]	**Deceased** n = 105 (54%)[1]	**Alive** n = 88 (46%)[1]	**p-value**[2]
Age (median)	29 [24,44]	30 [25,44]	29 [24,40]	0.40
Percent male	150 (78%)	79 (75%)	71 (81%)	0.37
Race/Ethnicity				0.18
White	22 (11%)	14 (13%)	8 (9.1%)	
Black	156 (81%)	83 (79%)	73 (83%)	
Hispanic/Latino	3 (1.6%)	0 (0%)	3 (3.4%)	
Other/unknown	12 (6.2%)	8 (7.6%)	4 (4.5%)	
Injury Type				0.13
Blunt	86 (45%)	52 (50%)	34 (39%)	
Penetrating	107 (55%)	53 (50%)	54 (61%)	
Mechanism of Injury				0.71
GSW	103 (53%)	51 (49%)	52 (59%)	
MVC	39 (20%)	25 (24%)	14 (16%)	
MCC	17 (8.8%)	9 (8.6%)	8 (9.1%)	
Peds vs auto	22 (11%)	13 (12%)	9 (10%)	
Blunt other	8 (4.1%)	5 (4.8%)	3 (3.4%)	
Penetrating other	4 (2.1%)	2 (1.9%)	2 (2.3%)	
Injury Severity Score	34 [25,50]	38 [26,50]	34 [25,49]	0.24

[1] Median [IQR]; n (%)

[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 2: Clinical presentation data for adult trauma patients undergoing UMT

	Overall n = 193[1]	**Deceased** n = 105 (54%)[1]	**Alive** n = 88 (46%)[1]	**p-value**[2]
Systolic Blood Pressure	84 [60,116]	80 [58,116]	90 [70,114]	0.076
Diastolic Blood Pressure	45 [0,79]	40 [0,78]	57 [0,80]	0.15
MAP	59 [0,92]	47 [0,91]	67 [0,92]	0.18
Heart Rate	112 [71,134]	89 [39,128]	125 [103,140]	<0.001*
Shock Index	1.1 [0.6,1.5]	1.0 [0.0, 1.3]	1.2 [0.9,1.6]	<0.001*
Respiratory Rate	17 [0,26]	0 [0,24]	22 [14,29]	<0.001*
Glasgow Coma Score	7 [3,14]	3 [3,9]	14 [6,15]	<0.001*
Mode of Arrival				0.19
Ground Ambulance	171 (90%)	90 (87%)	81 (93%)	
Helicopter	19 (10%)	13 (13%)	6 (6.9%)	
Hematocrit	34 [31,40]	35 [28,40]	34 [32,40]	0.34
INR	1.2 [1.1,1.3]	1.2 [1.1,1.3]	1.1 [1.1,1.3]	0.085
Base Deficit	-10 [-17, -4]	-13 [-21, -9]	-7 [-13, -2]	<0.001*

Time in ED (Minutes)	25 [15,44]	22 [16,38]	31 [13,56]	0.44
ED CPR	20 (10%)	18 (17%)	2 (2.3%)	<0.001*
ED Thoracotomy	42 (22%)	40 (38%)	2 (2.3%)	<0.001*

[1] Median [IQR]; n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 3: Transfusion data for adult trauma patients undergoing UMT

	Overall n = 193[1]	**Deceased** n = 105 (54%)[1]	**Alive** n = 88 (46%)[1]	**p-value[2]**
Whole Blood	2 [0,4]	2 [0,4]	4 [0,4]	0.41
pRBC	30 [21,48]	39 [26,53]	24 [19,32]	<0.001*
FFP	23 [15,39]	32 [18,47]	18 [14,26]	<0.001*
Platelets	2 [2,4]	3 [2,4]	2 [2,3]	0.078
Cryoprecipitate	2 [1,4]	2 [1,6]	2 [0,3]	0.030*
Total Blood Products	59 [43,97]	80 [50,110]	50 [39,62]	<0.001*
TXA	167 (87%)	92 (88%)	75 (85%)	0.63
pRBC/FFP Ratio	1.2 [1.1,1.5]	1.2 [1.1,1.5]	1.3 [1.1,1.5]	0.10
pRBC/FFP Ratio ≥ 1.5:1	56 (29%)	29 (28%)	27 (31%)	0.64

[1] Median [IQR]; n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 4: Transfusion data for deceased adult trauma patients undergoing UMT

	Deceased within 24 hours n = 75 (71%)[1]	**Deceased beyond 24 hours** n = 30 (29%)[1]	**p-value[2]**
Whole Blood	2 [0,4]	4 [0,5]	0.31
pRBC	37 [26,51]	42 [26,56]	0.31
FFP	30 [18,44]	36 [19,50]	0.19
Platelets	2 [2,4]	4 [2,5]	0.016*
Cryoprecipitate	2 [0,4]	4 [1,6]	0.27
Total Blood	74 [50,104]	89 [53,120]	0.21
pRBC/FFP Ratio	1.2 [1.1,1.6]	1.1 [1.0,1.4]	0.10
pRBC/FFP Ratio ≥ 1.5:1	23 (31%)	6 (20%)	0.27

[1] Median [IQR]; n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 5: Operative intervention data for adult trauma patients undergoing UMT

	Overall n = 193[1]	**Deceased** n = 105 (54%)[1]	**Alive** n = 88 (46%)[1]	**p-value[2]**
Operative Intervention?	189 (98%)	102 (97%)	87 (99%)	0.63
Thoracotomy*	37 (25%)	17 (26%)	20 (23%)	0.68
Clamshell	26 (14%)	13 (12%)	13 (15%)	0.65
Exploratory Laparotomy	168 (87%)	92 (88%)	76 (86%)	0.80
Solid Organ Injury	113 (59%)	60 (57%)	53 (60%)	0.66

Vascular Injury	157 (81%)	86 (82%)	71 (81%)	0.83

* Excluding those who had an ED thoracotomy
[1] Median [IQR]; n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 6: Mortality Multivariate Regression

	Odds Ratio	**95% CI**	**p-value**
Age	0.98	(0.95,1.01)	0.2
Female	0.62	(0.19,1.96)	0.4
Mechanism of Injury			
GSW	-	-	
MVC/MCC	0.47	(0.14,1.56)	0.2
Peds vs. Auto	0.38	(0.08,1.68)	0.2
Other	0.54	(0.09,3.22)	0.5
Injury Severity Score	0.97	(0.94,1.00)	0.084
Systolic Blood Pressure	0.99	(0.98,1.00)	0.2
Heart Rate	1.02	(1.10,1.03)	0.003*
Base Deficit	1.05	(1.00,1.11)	0.051
Glasgow Coma Score	1.14	(1.04,1.26)	0.006*
Total Blood Products	0.97	(0.96,0.99)	<0.001*
pRBC/FFP Ratio	1.42	(0.45,4.94)	0.6

Table 7: Total Blood Products Multivariate Regression

	Odds Ratio	**95% CI**	**p-value**
Injury Severity Score	-0.04	(-0.43, 0.35)	0.8
Systolic Blood Pressure	0.13	(-0.03,0.29)	0.12
Heart Rate	-0.17	(-0.33,-0.02)	0.030*
Base Deficit	-0.73	(-1.5, 0.00)	0.049*
Glasgow Coma Score	-0.07	(-1.4, 1.3)	> 0.9

7.2 Manuscript figures

Figure 1: Clinical presentation of adult trauma patients undergoing UMT stratified by mortality

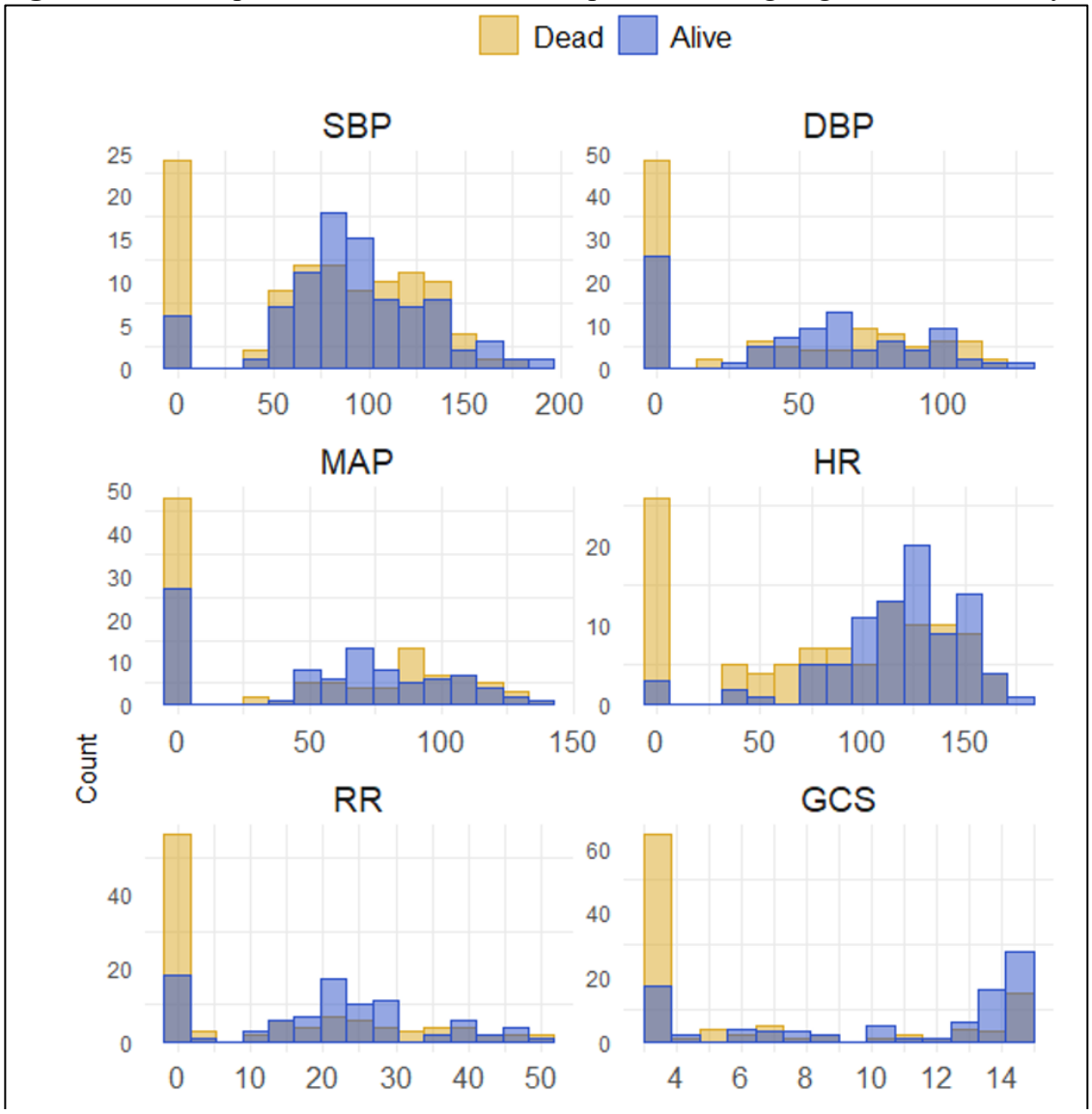


Figure 2: Transfusion data for adult trauma patients undergoing UMT stratified by mortality

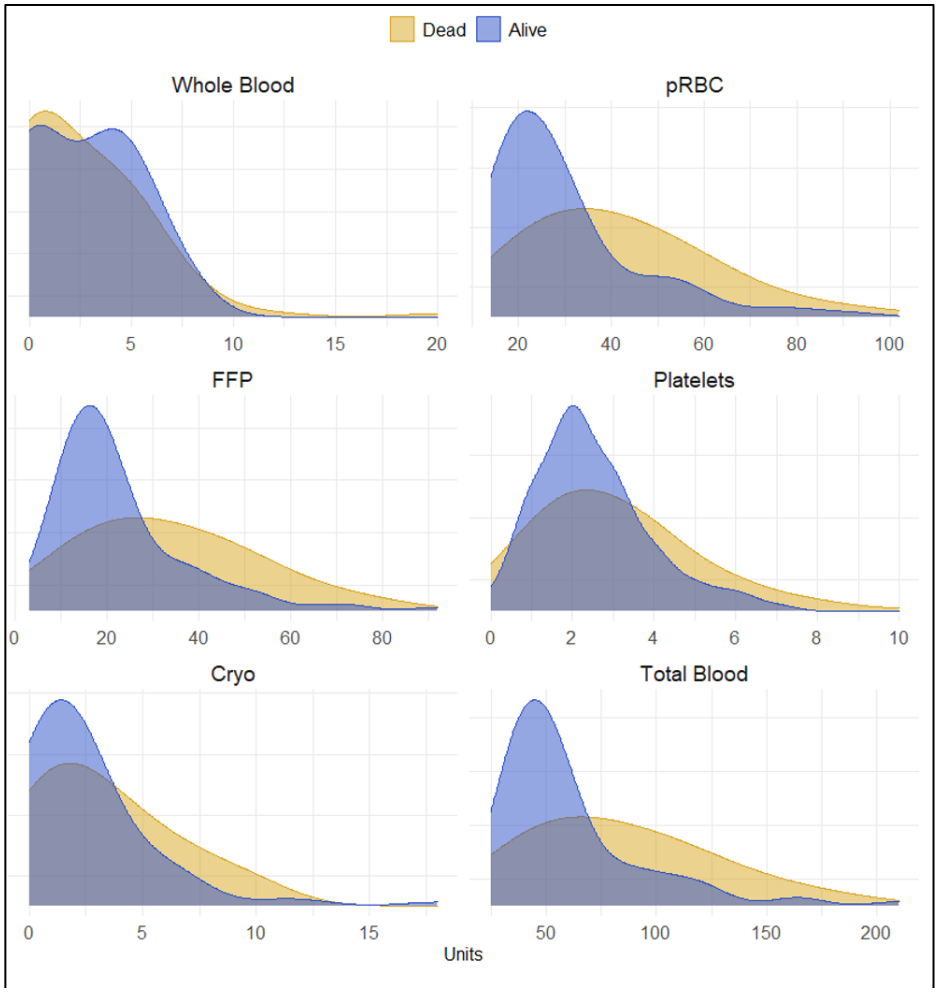


Figure 3: Kaplan Meir Curve for adult trauma patients undergoing UMT stratified by MOI

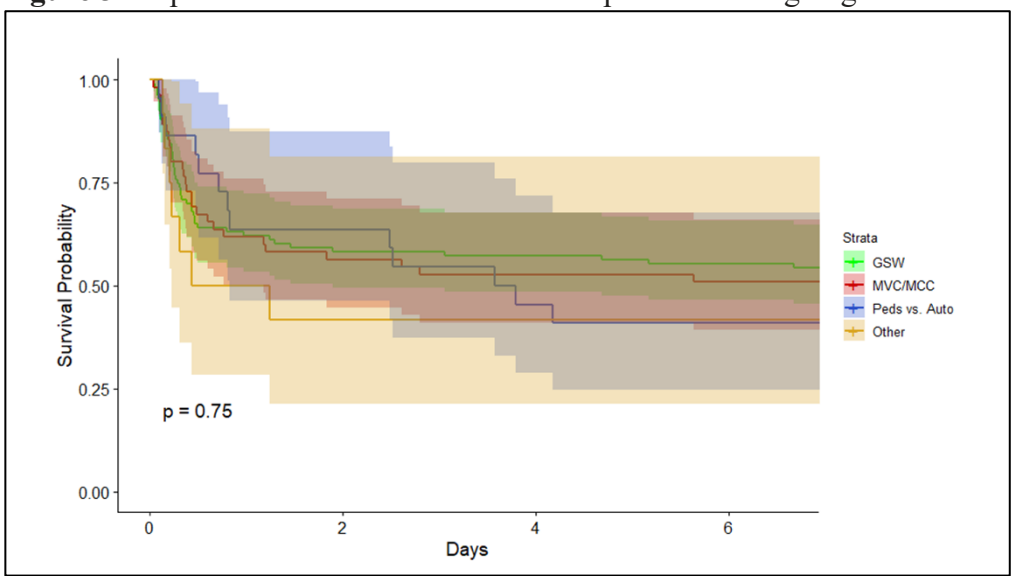
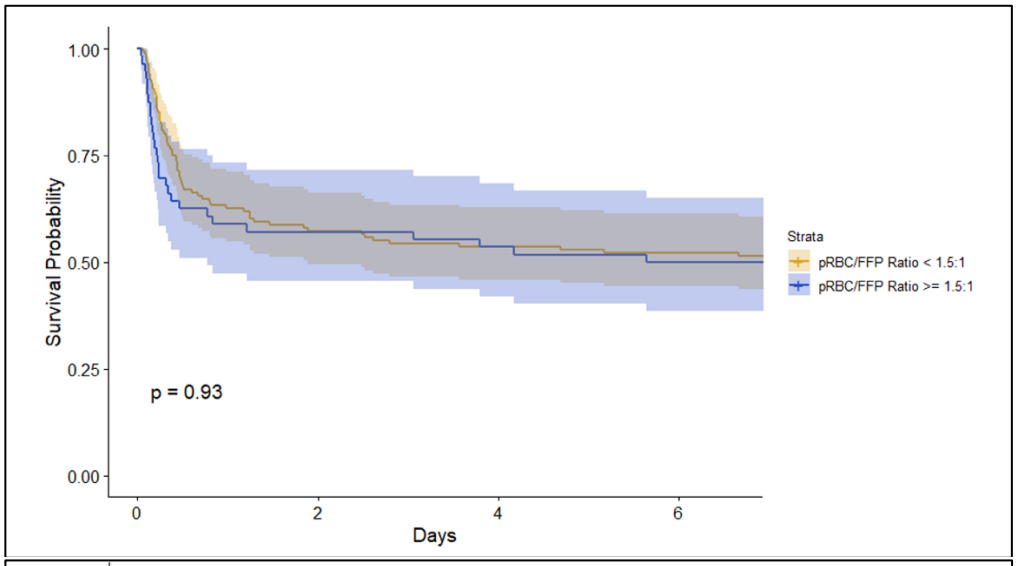
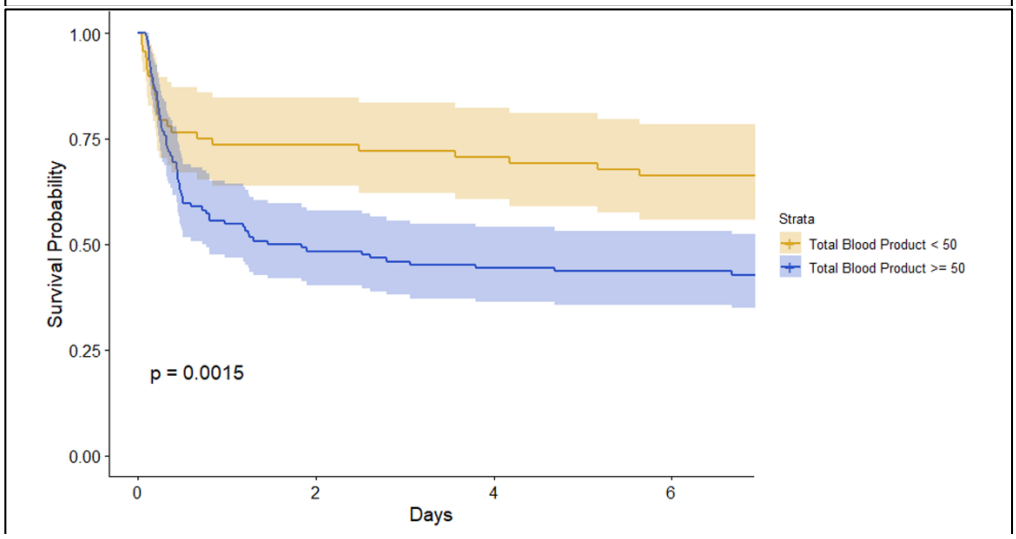


Figure 4: Kaplan Meir Curve for adult trauma patients undergoing UMT stratified by pRBC/FFP ratio





7.3 Extended results

7.3.1 Machine learning predictive modeling tables

Table 1: Model validation for 10 machine learning models predicting mortality for adult trauma patients undergoing UMT

Model Number	Model Name	Area under the Curve, (95% CI)
1	Full Logistic Regression	0.748 (0.679-0.817)
2	Small Logistic Regression	0.767 (0.700-0.833)
3	LASSO	0.737 (0.667-0.807)
4	Ridge Regression	0.746 (0.677-0.815)
5	Elastic Net	0.744 (0.675-0.813)
6	MARS	0.784 (0.720-0.850)
7	K-Nearest Neighbors	0.770 (0.703-0.837)
8	Decision Tree	0.702 (0.627-0.778)
9	Random Forest	0.792 (0.730-0.855)
10	XGBoost	0.745 (0.676-0.813)

7.3.2 Hour-by-hour time series analysis tables

Table 1: Median systolic blood pressure per hour for adult trauma patients undergoing UMT stratified by mortality

Time Period	Overall n = 131[1]	Deceased n = 46 (35%)[1]	Alive n = 85 (65%)[1]	p-value[2]
0-4 hours	101 [84, 112]	98 [81, 111]	102 [86, 114]	0.15
4-8 hours *Missing*	122 [106, 140] *32*	110 [94, 131] *10*	125 [111, 145] *22*	0.010*
8-12 hours *Missing*	118 [106, 134] *23*	108 [102, 128] *14*	125 [109, 135] *9*	0.011*
12-16 hours *Missing*	116 [102, 126] *26*	110 [98, 121] *19*	117 [104, 129] *7*	0.021*
16-20 hours *Missing*	114 [104, 124] *29*	112 [99, 127] *20*	114 [106, 124] *9*	0.44
20-24 hours *Missing*	114 [105, 128] *31*	114 [99, 128] *24*	114 [116, 128] *7*	0.58

[1] Median [IQR]; n (%)
[2] Wilcoxon rank sum test

Table 2: Median heart rate per hour for adult trauma patients undergoing UMT stratified by mortality

Time Period	Overall n = 154[1]	Deceased n = 66 (43%)[1]	Alive n = 88 (57%)[1]	p-value[2]
0-4 hours	123 [103, 135]	121 [96, 134]	123 [104, 136]	0.86
4-8 hours	104 [89,119]	101 [91, 118]	104 [85 120]	0.66

Missing	*69*	*31*	*38*	
8-12 hours	110 [95, 125]	115 [100, 128]	109 [95, 122]	0.23
Missing	*33*	*23*	*10*	
12-16 hours	111 [100, 125]	120 [103, 129]	109 [96, 122]	0.014*
Missing	*41*	*34*	*7*	
16-20 hours	111 [99, 123]	116 [108, 132]	108 [96, 120]	0.013*
Missing	*47*	*36*	*11*	
20-24 hours	111 [96, 120]	114 [110, 130]	107 [90, 119]	0.006*
Missing	*42*	*37*	*5*	

[1] Median [IQR]; n (%)
[2] Wilcoxon rank sum test

Table 3: Median lactate value per hour for adult trauma patients undergoing UMT stratified by mortality

Time Period	**Overall** n = 185[1]	**Deceased** n = 98 (53%)[1]	**Alive** n = 87 (47%)[1]	**p-value**[2]
0-8 hours	7.0 [4.4, 10.3]	10.4 [8.1, 13.6]	5.4 [3.9, 7.5]	<0.001*
8-16 hours	4.8 [3.0, 8.2]	9.3 [5.7, 13.2]	3.5 [2.6, 5.5]	<0.001*
Missing	*14*	*7*	*7*	
16-24 hours	4.5 [3.1, 6.9]	9.3 [5.7, 13.2]	**3.7** [2.3, 4.6]	<0.001*
Missing	*24*	*11*	**3.8** *13*	
24-48 hours	3.3 [2.1, 6.0]	8.4 [4.7, 12.1]	3.0 [2.0, 3.8]	<0.001*
Missing	*22*	*12*	*10*	

[1] Median [IQR]; n (%)
[2] Wilcoxon rank sum test

Table 4: Median total blood product per hour for adult trauma patients undergoing UMT stratified by mortality

Time Period	**Overall** n = 192[1]	**Deceased** n = 104 (54%)[1]	**Alive** n = 88 (46%)[1]	**p-value**[2]
0-1 hours	20 [14, 28]	23 [15, 31]	18 [12, 23]	0.010*
1-2 hours	14 [8, 21]	17 [11, 25]	12 [6, 16]	<0.001*
Missing	*11*	*6*	*5*	
2-4 hours	6 [3, 12]	9 [5, 16]	4 [2, 7]	<0.001*
Missing	*42*	*26*	*16*	
4-6 hours	3.5 [1.0, 7.6]	6.0 [2.8, 10.0]	1.5 [1.0, 3.5]	<0.001*
Missing	*124*	*69*	*55*	
6-10 hours	1.5 [0.5, 4.5]	3.2 [1.6, 7.2]	0.8 [0.2, 2.5]	<0.001*
Missing	*128*	*77*	*51*	
10-14 hours	0.50 [0.25, 1.44]	1.00 [0.25, 6.00]	0.50 [0.25, 1.00]	0.042*
Missing	*130*	*83*	*47*	
14-24 hours	0.30 [0.20, 0.80]	0.50 [0.20, 1.10]	0.30 [0.10, 0.50]	0.059
Missing	*126*	*83*	*43*	

[1] Median [IQR]; n (%)
[2] Wilcoxon rank sum test

Table 5: Cumulative median total blood product per hour for adult trauma patients undergoing UMT stratified by mortality

Time Period	Overall n = 192[1]	Deceased n = 104 (54%)[1]	Alive n = 88 (46%)[1]	p-value[2]
0-1 hours	20 [14, 28]	23 [15, 31]	18 [12, 23]	0.01
1-2 hours	17 [13, 24]	20 [15, 26]	15 [11, 20]	<0.001*
Missing	*11*	*6*	*5*	
2-4 hours	12 [9, 18]	16 [11, 19]	10 [8, 13]	<0.001*
Missing	*42*	*26*	*16*	
4-6 hours	9.3 [7.0, 14.1]	12.7 [9.2, 17.2]	7.0 [5.2, 9.3]	<0.001*
Missing	*124*	*69*	*55*	
6-10 hours	5.2 [3.4, 8.8]	8.9 [5.8, 10.6]	3.8 [3.0, 5.4	<0.001*
Missing	*128*	*77*	*51*	
10-14 hours	3.96 [2.46, 5.95]	6.14 [5.07, 8.14]	3.14 [2.14, 4.14]	<0.001*
Missing	*130*	*83*	*47*	
14-24 hours	2.56 [1.76, 3.73]	3.83 [3.29, 5.25]	1.96 [1.46, 2.67	<0.001*
Missing	*126*	*83*	*43*	

[1] Median [IQR]; n (%)
[2] Wilcoxon rank sum test

Table 6: Median pRBC units per hour for adult trauma patients undergoing UMT stratified by mortality

Time Period	Overall n = 191[1]	Deceased n = 104 (54%)[1]	Alive n = 87 (46%)[1]	p-value[2]
0-1 hours	12.0 [9.0, 16.8]	12.5 [9.0, 16.8]	10.0 [6.8, 14.0]	0.011*
Missing	*5*	*2*	*3*	
1-2 hours	7.0 [4.0, 11.0]	8.5 [5.2, 12.0]	6.0 [3.0, 8.0]	<0.001*
Missing	*19*	*10*	*9*	
2-4 hours	3.0 [1.5, 6.0]	4.0 [2.5, 7.8]	2.0 [1.0, 3.5]	<0.001*
Missing	*53*	*29*	*24*	
4-6 hours	2.0 [1.0, 4.25]	3.5 [1.50, 5.50]	1.5 [1.0, 2.38]	0.028*
Missing	*136*	*71*	*65*	
6-10 hours	1.25 [0.56, 2.7]	2.1 [0.75, 4.25]	0.88 [0.5, 1.25]	0.026*
Missing	*145*	*80*	*65*	
10-14 hours	0.50 [0.25, 1.5]	2.5 [0.5, 3.75]	0.25 [0.25, 1.0]	0.001*
Missing	*154*	*91*	*63*	
14-24 hours	0.2 [0.1, 0.55]	0.5 [0.3, 0.67]	0.2 [0.1, 0.4]	0.022*
Missing	*144*	*90*	*54*	

[1] Median [IQR]; n (%)
[2] Wilcoxon rank sum test

Table 7: Median FFP units per hour for adult trauma patients undergoing UMT stratified by mortality

Time Period	Overall n = 131[1]	Deceased n = 46 (35%)[1]	Alive n = 85 (65%)[1]	p-value[2]

0-1 hours *Missing*	8.0 [5.0, 11.0] *16*	9.0 [5.0, 12.0] *6*	7.0 [4.0, 10.0] *10*	0.029*
1-2 hours *Missing*	6.0 [3.0, 10.0] *19*	6.5 [4.0, 11.0] *7.0*	5.0 [3.0, 8.0] *12*	0.042*
2-4 hours *Missing*	3.0 [1.50, 6.0] *56*	4.0 [2.38, 7.50] *31*	1.50 [1.0, 3.5] *25*	<0.001*
4-6 hours *Missing*	2.50 [1.0, 4.0] *139*	3.0 [2.0, 5.0] *74*	1.0 [0.50, 3.0] *65*	0.005*
6-10 hours *Missing*	1.0 [0.50, 2.25] *144*	2.25 [0.81, 4.0] *81*	0.62 [0.25, 1.25] *63*	0.001*
10-14 hours *Missing*	1.0 [0.50, 2.25] *161*	2.62 [0.88, 4.06] *91*	0.50 [0.25, 1.00] *70*	0.003*
14-24 hours *Missing*	0.20 [0.20, 0.50] *149*	0.20 [0.20, 0.52] *87*	0.30 [0.20, 0.50] *62*	> 0.99

[1] Median [IQR]; n (%)
[2] Wilcoxon rank sum test

Table 8: Median platelet units per hour for adult trauma patients undergoing UMT stratified by mortality

Time Period	**Overall** n = 179[1]	**Deceased** n = 93 (52%)[1]	**Alive** n = 86 (48%)[1]	**p-value**[2]
0-1 hours *Missing*	1.0 [1.0, 1.0] *77*	1.0 [1.0, 1.0] *38*	1.0 [1.0, 1.0] *39*	0.007*
1-2 hours *Missing*	1.0 [1.0, 1.0] *90*	1.0 [1.0, 1.0] *33*	1.0 [1.0, 1.0] *57*	0.084
2-4 hours *Missing*	0.50 [0.50, 1.0] *103*	0.50 [0.50, 1.0] *52*	0.50 [0.5, 0.5] *51*	0.21
4-6 hours *Missing*	0.50 [0.5, 0.5] *149*	0.50 [0.5, 0.5] *75*	0.50 [0.5, 0.5] *74*	0.33
6-10 hours *Missing*	0.25 [0.25, 0.25] *146*	0.25 [0.25, 0.5] *79*	0.25 [0.25, 0.25] *67*	0.030*
10-14 hours *Missing*	0.25 [0.25, 0.25] *148*	0.25 [0.25, 0.38] *82*	0.25 [0.25, 0.25] *66*	0.088
14-24 hours *Missing*	0.1 [0.1, 0.1] *143*	0.1 [0.1, 0.1] *79*	0.1 [0.1, 0.1] *64*	0.70

[1] Median [IQR]; n (%)
2 Wilcoxon rank sum test

Table 9: Median cryoprecipitate units per hour for adult trauma patients undergoing UMT stratified by mortality

Time Period	**Overall** n = 141[1]	**Deceased** n = 73 (52%)[1]	**Alive** n = 68 (48%)[1]	**p-value**[2]
0-1 hours *Missing*	1.0 [1.0, 2.0] *117*	1.0 [1.0, 1.75] *59*	1.5 [1.0, 2.0] *58*	0.25
1-2 hours *Missing*	2.0 [1.0, 2.0] *69*	2.0 [1.0, 2.0] *32*	2.0 [2.0, 2.0] *37*	0.90

2-4 hours *Missing*	1.0 [1.0, 1.38] *75*	1.0 [1.0, 1.5] *34*	1.0 [0.75, 1.0] *41*	0.38
4-6 hours *Missing*	1.0 [0.50, 1.0] *124*	1.0 [1.0, 1.0] *63*	1.0 [0.5, 1.0] *61*	0.20
6-10 hours *Missing*	0.25 [0.25, 0.50] *116*	0.50 [0.25, 1.0] *59*	0.25 [0.25, 0.38] *57*	0.027*
10-14 hours *Missing*	0.38 [0.25, 0.50] *123*	0.38 [0.25, 0.56] *65*	0.38 [0.25, 0.50] *58*	0.66
14-24 hours *Missing*	0.15 [0.1, 0.2] *123*	0.25 [0.2, 0.3] *67*	0.1 [0.1, 0.2] *56*	0.016*

[1] Median [IQR]; n (%)
[2] Wilcoxon rank sum test

Table 10: Median whole blood units per hour for adult trauma patients undergoing UMT stratified by mortality

Time Period	**Overall** n = 57[1]	**Deceased** n = 27 (47%)[1]	**Alive** n = 30 (53%)[1]	**p-value**[2]
0-1 hours *Missing*	4.0 [3.0, 4.0] *7*	4.0 [3.0, 4.0] *6*	4.0 [3.0, 4.0] *1*	0.92
1-2 hours *Missing*	1.0 [1.0, 2.0] *46*	1.0 [1.0, 1.0] *22*	1.5 [1.0, 2.0] *24*	0.59
2-4 hours *Missing*	1.5 [1.0, 2.0] *52*	2.0 [1.5, 2.25] *24*	1.0 [0.75, 1.25] *28*	0.40
4-6 hours *Missing*	1.5 [1.5, 1.5] *56*	1.5 [1.5, 1.5] *26*	n/a *30*	n/a
6-10 hours *Missing*	1.0 [0.81, 1.25] *53*	1.0 [1.5, 1.5] *24*	0.25 [0.25, 0.25] *29*	0.35
10-14 hours *Missing*	1.0 [1.0, 1.0] *56*	n/a *27*	1.0 [1.0, 1.0] *29*	n/a
14-24 hours *Missing*	0.1 [0.1, 0.1] *56*	0.1 [0.1, 0.1] *26*	n/a *30*	n/a

[1] Median [IQR]; n (%)
[2] Wilcoxon rank sum test

7.3.3 Machine learning predictive modeling figures

Figure 1: Receiver operating characteristic curves and their respective areas under the curve for 10 machine learning models predicting mortality for adult trauma patients undergoing UMT

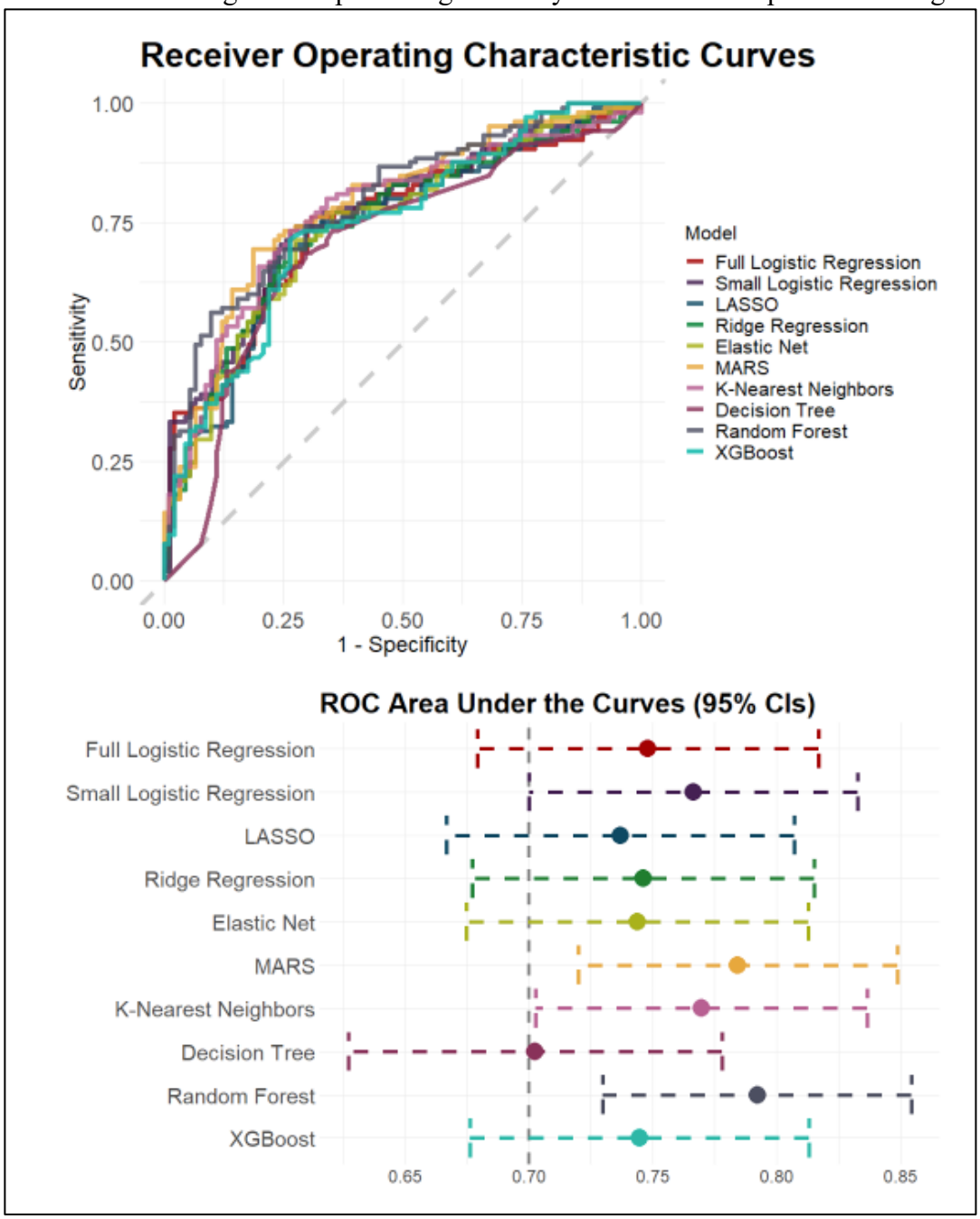


Figure 2: Calibration plot for 10 machine learning models predicting mortality for adult trauma patients undergoing UMT

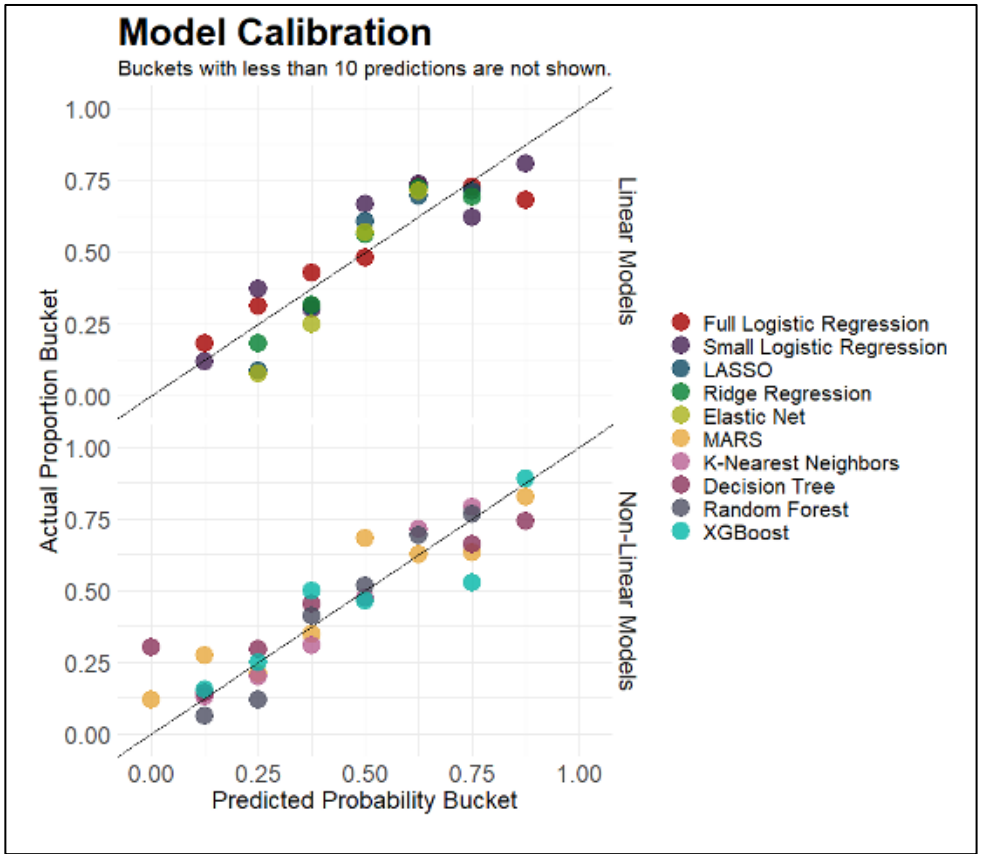


Figure 3: Nested LASSO variable selection for model (3) predicting mortality for adult trauma patients undergoing UMT

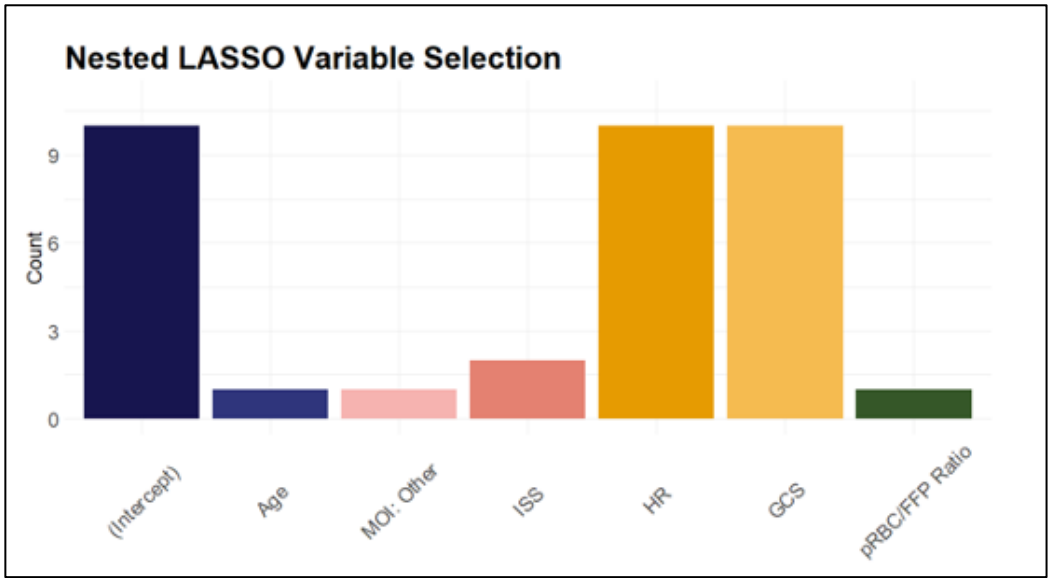


Figure 4: Nested decision tree splitting variable selection for model (8) predicting mortality for adult trauma patients undergoing UMT

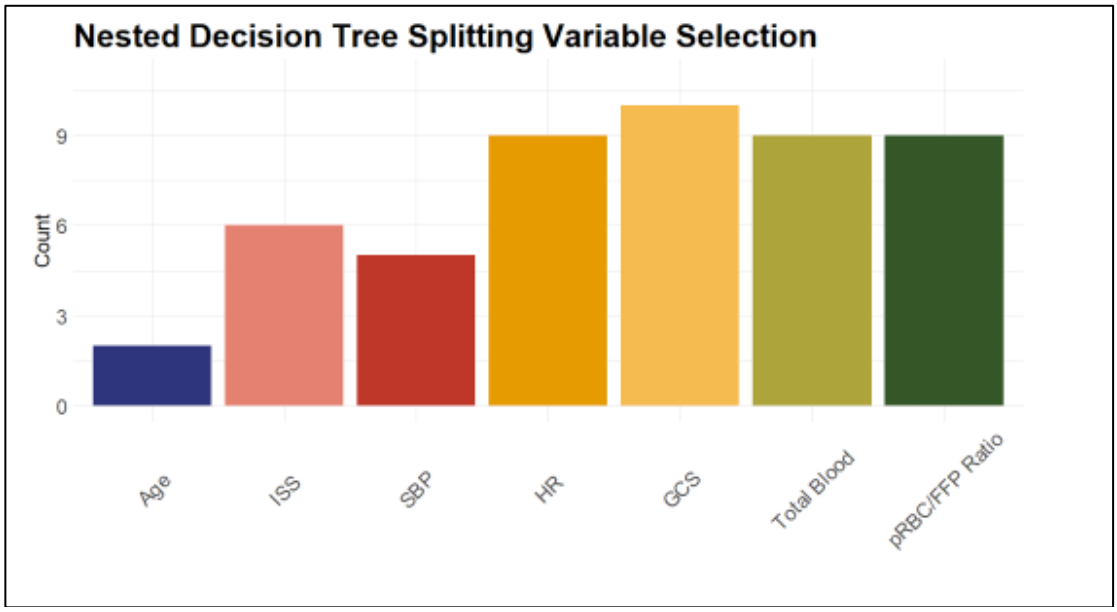
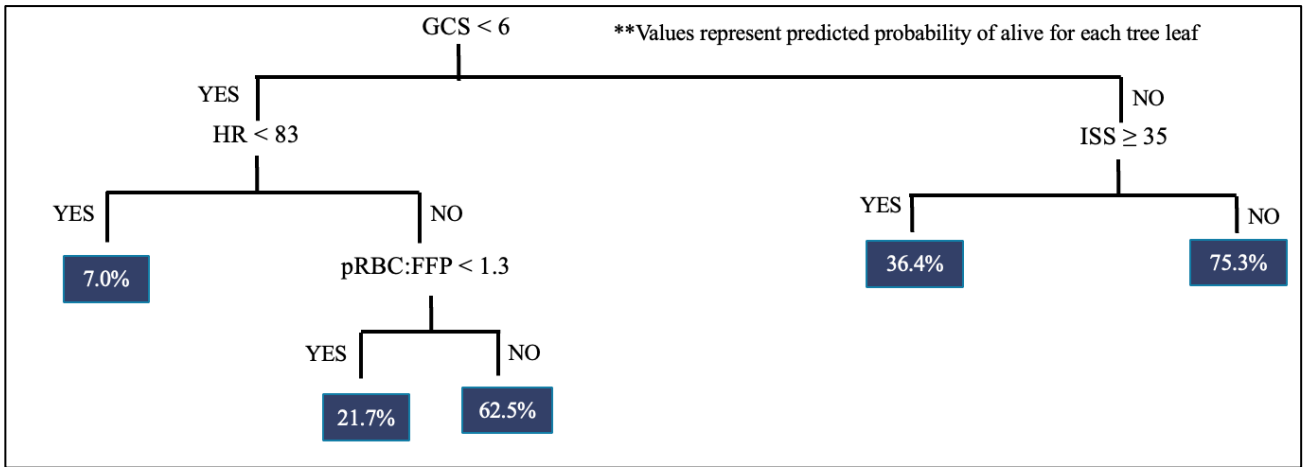


Figure 5: Decision tree model (8) predicting mortality for adult trauma patients undergoing UMT



7.3.4 Hour-by-hour time series analysis figures

Figure 1: Median 24 hour vital signs (A) and lactate values (B) for adult trauma patients undergoing UMT stratified by mortality

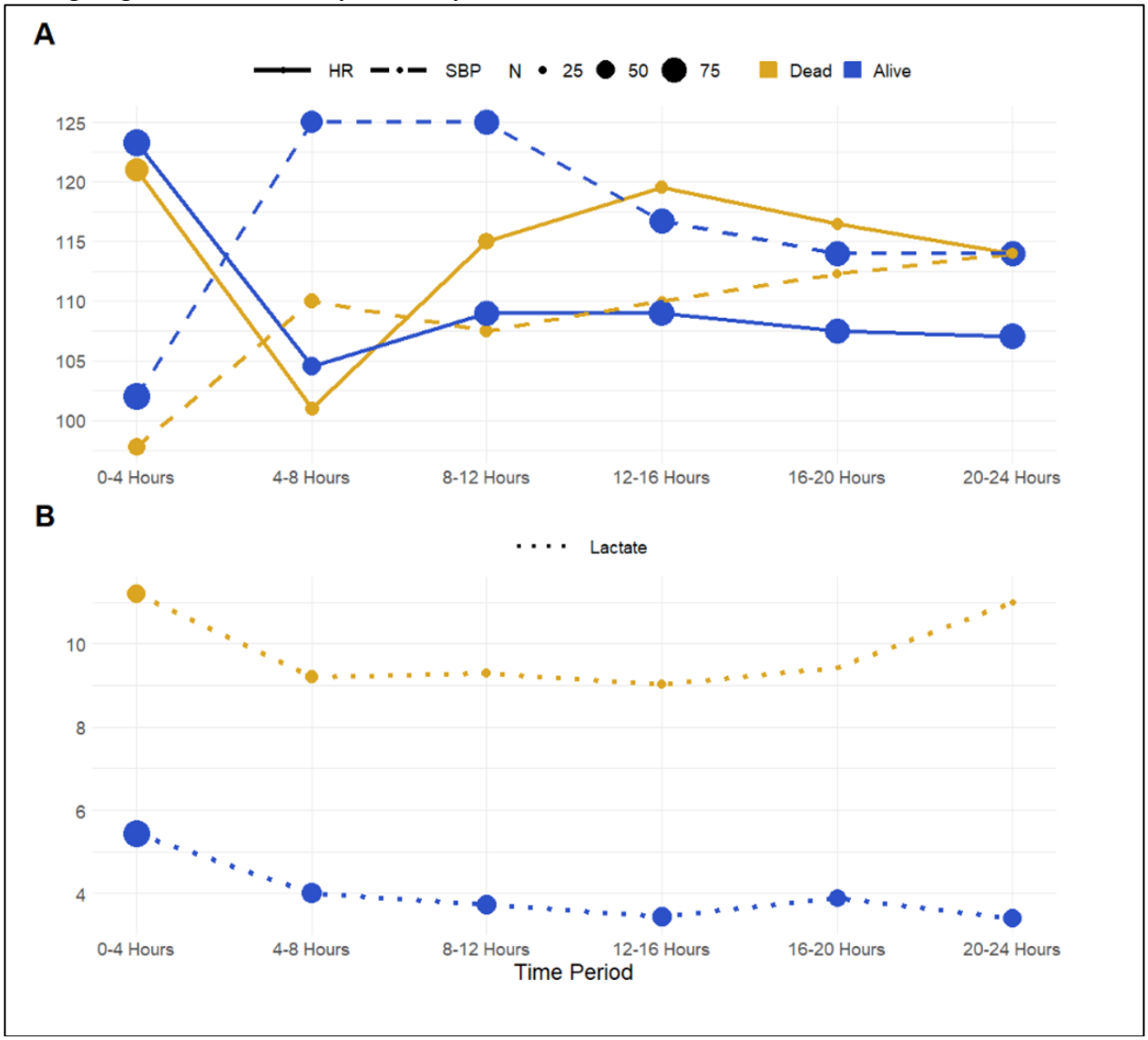


Figure 2: Median total blood products transfused per hour for adult trauma patients undergoing UMT stratified by mortality

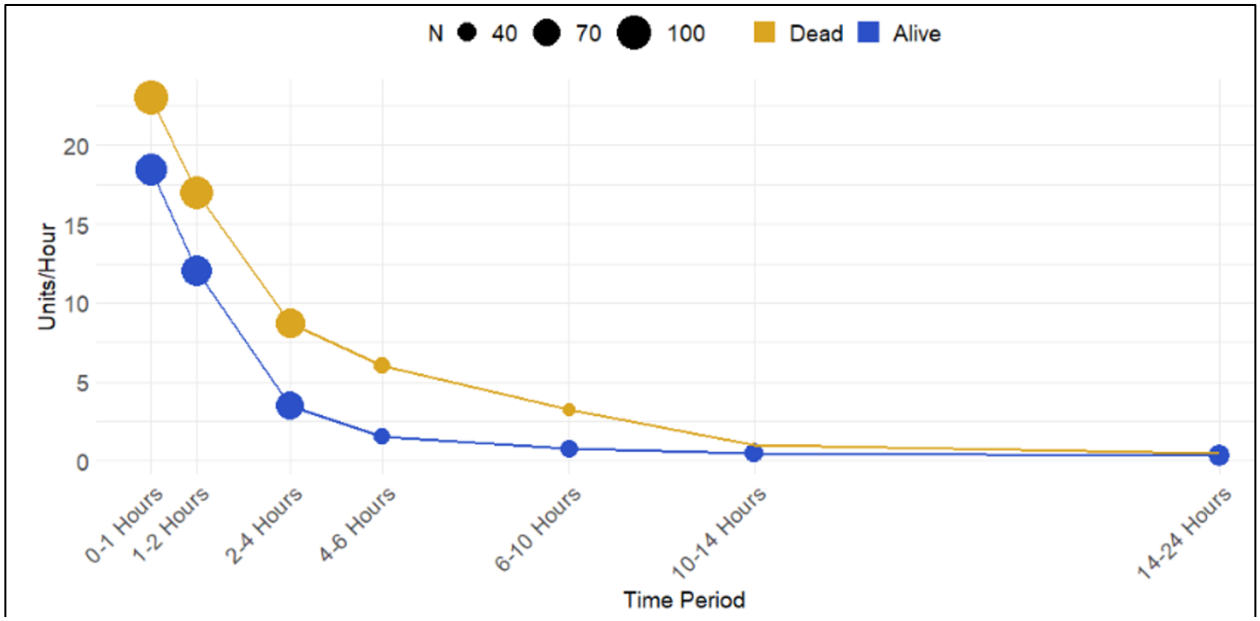


Figure 3: Cumulative median total blood products transfused per hour for adult trauma patients undergoing UMT stratified by mortality

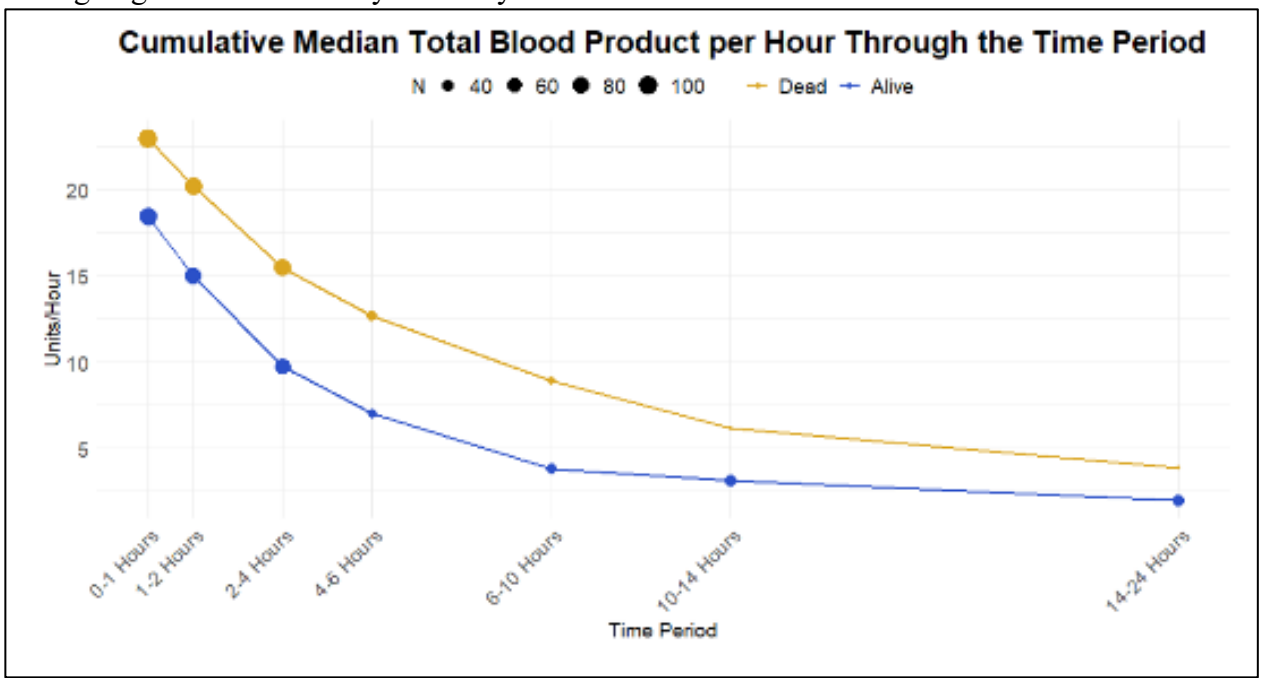


Figure 4: Median units of blood products per hour for adult trauma patients undergoing UMT stratified by mortality

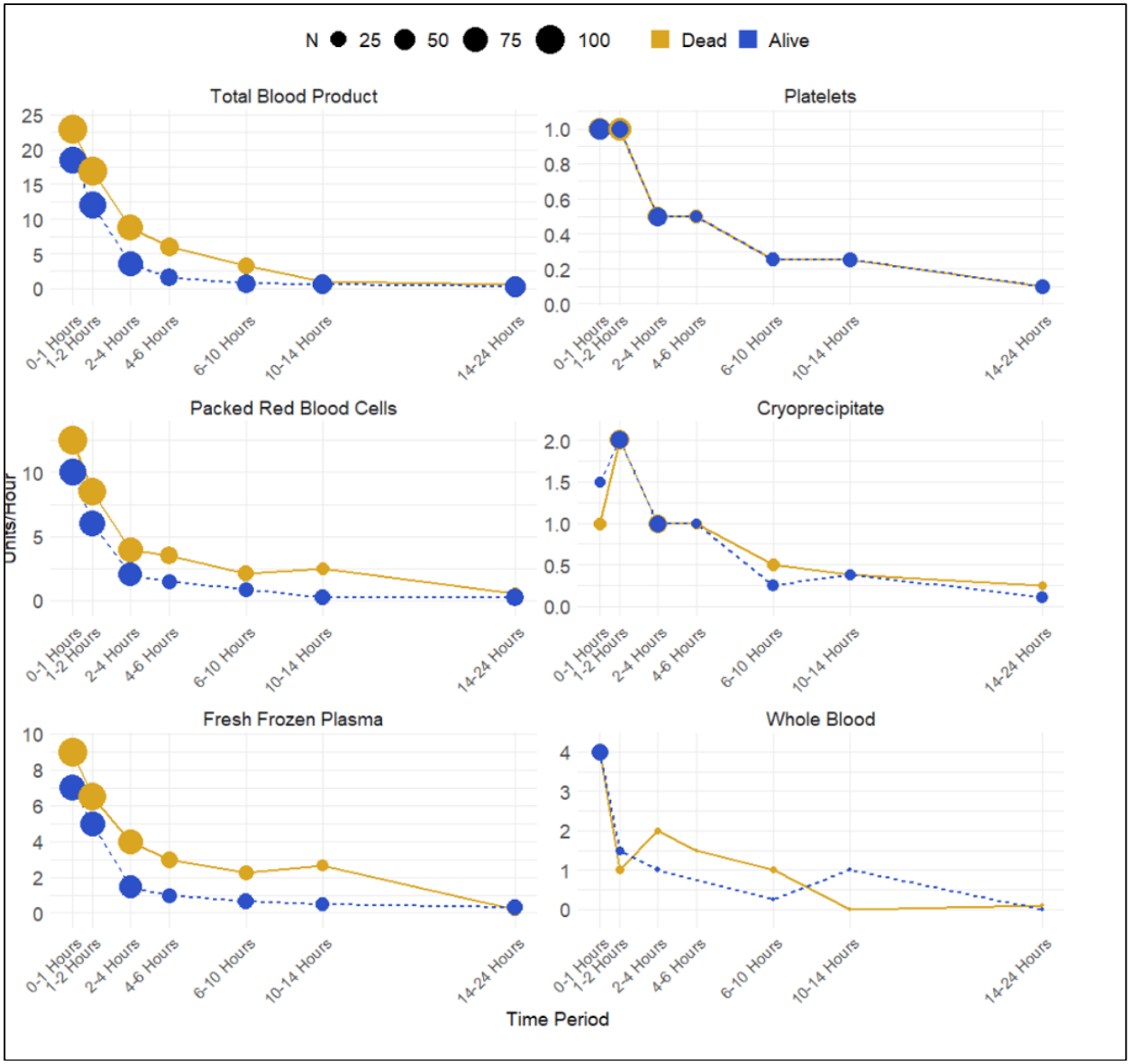


Figure 5: Graph of total product transfusion per hour data for adult trauma patients undergoing UMT stratified by mortality