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Identification of Early Markers of Occult Tissue Hypoperfusion in Patients with Multiple Trauma Injuries

Kathryn M. Moore
University of Kentucky, kmmo222@uky.edu
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Kathryn M. Moore, Student

Dr. Debra Moser, Major Professor

Dr. Susan Frazier, Director of Graduate Studies
IDENTIFICATION OF EARLY MARKERS OF OCCULT TISSUE HYPOPERFUSION IN PATIENTS WITH MULTIPLE TRAUMA INJURIES

DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Nursing At the University of Kentucky

By
Kathryn M. Moore
Lexington, Kentucky

Director: Dr. Debra K. Moser, Professor of Nursing
Lexington, Kentucky

2016

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IDENTIFICATION OF EARLY MARKERS OF OCCULT TISSUE HYPOPERFUSION IN PATIENTS WITH MULTIPLE TRAUMA INJURIES

Injury is a global health problem and in the United States is the leading cause of death for persons aged 1 – 44 years. The primary causes of trauma related death are head injury and hemorrhage; hemorrhagic shock is difficult to recognize in the first hours after trauma. Identification of specific and optimal criteria upon which to base effective triage decisions for trauma patients has been an elusive goal for decades.

The purpose of this dissertation was to identify measures available in the prehospital phase of care and in the Emergency Department that should be included for a more comprehensive definition of the trauma patient who will require trauma center care to better allocate trauma care and resources available.

The first paper is a critical review of early physiologic markers of occult tissue hypoperfusion in which we examine markers of cardiovascular function and markers of tissue perfusion. In this review, we found surrogate measures of tissue perfusion include shock index as a measure of hemodynamic stability and acid-base indicators as measures of tissue oxygenation. This review guides the variable selection for the research study.

The second paper is a report of a study conducted to examine shock index calculated from the first available prehospital vital signs and first available emergency department vital signs as a predictor of mortality within 48-hours in trauma compared to the Injury Severity Score. Shock index can be calculated in real-time during the course of treatment and provides continuous input into the ever changing condition of the patient. Injury severity score is calculated once, at the time of hospital discharge and is used primarily as a marker for comparison of injury severity in research and quality measures of trauma care. The study consisted of 516,156 trauma patient data reported to the National Trauma Data Bank (NTDB) in 2009. The results revealed SI as calculated in both the pre-hospital phase of care by Emergency Medical Services and in the Emergency Department to be significant independent predictors of mortality within forty-eight hours from trauma injuries.

The third paper is a report of a study conducted to examine potential markers of occult tissue hypoperfusion within forty-eight hours of injury. The variables included four major variable categories, physiologic measures, anatomic measures, injury severity and presence of reported comorbid illness. The variable most predictive of death from trauma related injuries within forty-eight hours was the need for intubation.

The findings from this dissertation provide further evidence of the value of multiple physiologic markers in early recognition of occult tissue hypoperfusion. Data from neither the review of the literature nor the two data-based studies are sufficient to identify a brief, accurate,
easily used clinical instrument. Further work is needed to develop a clinically useful instrument to identify the occult tissue hypoperfusion in the trauma patient.

KEYWORDS: Trauma, Injury severity, Shock, Tissue hypoperfusion
Kathryn Marie Moore
Student’s Signature

07/28/2016
Date
IDENTIFICATION OF EARLY MARKERS OF OCCULT TISSUE HYPOPERFUSION IN PATIENTS WITH MULTIPLE TRAUMA INJURIES

By

Kathryn M. Moore

Dr. Debra Moser
Director of Dissertation

Dr. Susan Frazier
Director of Graduate Studies

July 28, 2016
Date
DEDICATION

For Lois
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CHAPTER ONE

Introduction

Injury is a global health problem and in the United States, it is the leading cause of death for persons aged 1-44 years.\(^1\) In 2014, unintentional injuries were responsible for 136,053 deaths in the United States and an additional 29 million injuries were severe enough to involve an Emergency Department (ED) visit.\(^1\) The primary results of unintentional injury death are head injury and hemorrhage.\(^2,{}^3\) These injuries result in death at the scene in approximately 60\% of all unintentional injury cases.\(^3,{}^4\) The remainder of deaths occur once the patient has reached the hospital. Of the approximately 40\% who survive the initial insult of trauma, 75\% of those individuals will die within the first 48 hours after sustaining injuries.\(^4,{}^5\) Those trauma deaths within the first 48 hours after sustaining traumatic injury that are related to occult tissue hypoperfusion as a result of unrecognized hemorrhagic shock.\(^3,{}^6,{}^7\) Hemorrhagic shock is difficult to recognize during that initial 48 hours after injury as it is often masked by compensatory mechanisms.\(^8\)

The purposes of the research presented in this dissertation was to identify a group of measures or conditions, available on admission to the Emergency Department (ED), that are early markers of occult tissue hypoperfusion in a population of patients with multiple trauma injuries, and to develop a clinical instrument using those markers to identify occult tissue hypoperfusion. The chapters of this dissertation represent the development of an initial program of research related to occult tissue perfusion. A critical review of the literature was conducted to determine potential markers of occult tissue hypoperfusion from the literature about the physiology of tissue hypoperfusion. Prior to evaluating potential markers of occult tissue hypoperfusion, a preliminary study was performed to compare shock index (SI) calculated from
data obtained by pre-hospital providers and data collected on arrival to the Emergency Department (ED) with the Injury Severity Score (ISS) reported in the National Trauma Data Bank (NTDB) in their ability to predict death from trauma within 48 hours of injury. The main focus of the dissertation work was to determine early markers of mortality from among 1) pulse; 2) systolic blood pressure; 3) shock index; 4) need for mechanical ventilation; 5) arterial base deficit; 6) serum lactate; 7) serum bicarbonate; 8) serum pH; 9) blood glucose; 10) mechanism of injury (blunt trauma, penetrating trauma or a combination of both); and 11) the presence of comorbid conditions among patients admitted to the Emergency Department with injuries from multiple trauma. Once those markers were identified, we sought to develop a clinical instrument using those markers to identify high risk patients within the first two hours in the course of treatment and evaluation.

**Hemorrhagic Shock**

Hemorrhage accounts for 80% of trauma deaths within the first hour of trauma center care, and almost 50% of deaths in the first 24 hours of trauma care.\(^2\)\(^-\)\(^11\) Hemorrhage leading to hemorrhagic shock during this first 24 to 48 hours post traumatic injury is often masked by physiologic compensatory mechanisms, making recognition difficult.\(^6\) Current intervention relies on detection of hemorrhage that has the potential to lead to occult tissue hypoperfusion as a result of decreased circulating volume. Once recognized, the patient must be managed with rapid resuscitation with crystalloid infusion, colloid infusion, administration of blood products using a massive transfusion protocol and damage control surgery.\(^12\) Left unrecognized and untreated, occult tissue hypoperfusion is associated with metabolic acidosis and death.\(^13\)
Shock was described by Samuel V. Gross in 1862 as “the rude unhinging of the machinery of life”\textsuperscript{14}. The machinery rudely unhinged in hemorrhagic shock begins with damage to cell mitochondria caused by blood loss and decreased tissue oxygenation, which ultimately leads to hypoperfusion; if left untreated, hypoperfusion leads to organ dysfunction, organ failure, and subsequent death.\textsuperscript{15} The mitochondria are the front-line, cellular-level consumers of oxygen and they initiate the physiologic and pathophysiologic response to hemorrhagic shock.\textsuperscript{16}

**Stages of Shock**

Four classes or stages of hemorrhagic shock have been described and are primarily based on the amount of blood lost at each stage.\textsuperscript{17} While the stages are described by the amount of blood loss, there are no clear demarcations between each stage and the physiologic response depends on individual patient characteristics. Hemorrhagic shock is an insidious process and often escapes clinical recognition until the patient is in an advanced stage.\textsuperscript{17}

Stage one shock is defined as an estimated blood loss of 0\% to 15\% of the total circulating volume, or about 750 mL of blood.\textsuperscript{14} Even this small volume stimulates the compensatory mechanisms of the body to maintain blood pressure and cardiac output. These compensatory responses that include negative circulatory feedback control mechanisms that attempt to return cardiac output and circulation to normal. The baroreceptor reflexes provide the initial compensatory response in response to augmented sympathetic stimulation; this leads to peripheral vasoconstriction to maintain blood pressure and heart rate at near normal levels.\textsuperscript{17}

Stage two shock is defined as hemorrhagic loss of circulating volume, from 750 mL up to about 1,500 mL, or a 15\% to 30\% blood loss.\textsuperscript{17} In stage two, sympathetic vasoconstriction occurs in vital organs, such as the liver and kidney, however due to the compensatory mechanisms, the blood pressure, respiratory rate and pulse remain within normal limits or at the worst show mild
deviations of normal. In both stage one and stage two, shock remains a reversible condition with control of hemorrhage and replacement of volume. During these stages of shock, the physiologic response includes stimulation of the release of antidiuretic hormone in an effort to conserve fluid by the kidney. As these renal changes occur, the vascular system is attempting to maintain adequate venous return to the cardiovascular system by vasoconstriction.

Stage three shock occurs with an estimated loss of 1,500 mL to 2,000 mL of circulating volume or 30% to 40% of the blood volume. An altered clinical presentation emerges as there are measurable decreases in cardiac output, blood pressure, heart rate, and perfusion as a result of hemorrhage. At this stage, the compensatory mechanisms are operating at full capacity, with failing homeostasis, but the condition remains reversible with identification and treatment. It is in stage three shock that the cells begin to produce lactic acid in response to cellular hypoxia. As a result of lactic acidosis, the mitochondria are unable to continue adenosine triphosphate synthesis and the cells must change to an anaerobic pathway to metabolize glucose. At this point, the organs are functioning in an anaerobic metabolic state, leading to the destruction and death of cells. Even here, the shock state may remain compensated to a degree that the patient may be in a state of normotensive or “cryptic” shock.

Left unrecognized and untreated in stage three shock, the organs will now suffer failure and acidosis, will become rapidly more severe. If bleeding continues, shock will progress to stage four. Stage four shock is described as blood loss greater than 2 liters and is generally referred to as refractory or irreversible decompensated shock. This systemic destruction at the cellular level and the ensuing vicious cycle of progressive shock leads to catastrophic microvascular damage, disseminated intravascular coagulopathy and systemic inflammatory response syndrome.
It is clear that earlier recognition of hemorrhagic shock is key to reducing mortality associated with occult hypoperfusion in the context of trauma. Hemorrhagic shock is an insidious killer, creating a great deal of physiologic damage and destruction before the shock state is recognized. The traditional markers of systolic blood pressure, pulse rate, lactic acid levels, and serum bicarbonate levels can remain relatively within normal limits until the compensatory mechanisms are overwhelmed. Thus, these markers, particularly in isolation, are insufficient to alert the clinician of the need for intervention. One marker explored as an alternative to either systolic blood pressure or pulse alone is shock index. Shock index is an indicator of hemodynamic instability, a mathematical quotient derived from heart rate (HR) divided by the systolic blood pressure (SBP). The SI is normally 0.5 to 0.7. Individually, HR and SBP are common variables in all current trauma triage scores and have been found to be less predictive than SI, which is calculated solely from these two variables. As a result, there is a great opportunity for research to identify more sensitive physiologic markers to identify early hemorrhagic shock and occult tissue hypoperfusion in order to prevent death after trauma.

**Mortality Consequences of Hemorrhagic Shock**

Hemorrhagic shock consistently represents the second-leading cause of trauma deaths within the first 48 hours after trauma. The leading cause of trauma death within 48 hours is central nervous system injury (CNS), and CNS injury has a high rate of pre-hospital mortality. Hemorrhagic shock accounts for 30% to 40% of trauma deaths within 48 hours and responds to intervention when detected and appropriately treated. Hemorrhage accounts for almost 50% of deaths from trauma within the first 24 hours of care and after 48 hours, less than 10% of trauma deaths are attributed to hemorrhagic shock.

**Conceptual Framework**
The conceptual framework used in this dissertation (Figure 1) was based on the physiologic description of trauma in this chapter. Traumatic injuries, whether blunt or penetrating, lead to hemorrhage, which left unrecognized and/or untreated leads to hypovolemia. As hypovolemia progresses through the stages of shock without intervention, occult tissue hypoperfusion occurs. It is during this period of occult tissue hypoperfusion that there may be specific abnormal markers available to recognize cryptic shock.

Metabolic derangements associated with shock lead to acidosis, as a result of poor delivery of oxygen to the tissues. This tissue hypoxia leads to anaerobic metabolism and glycolysis, leading to excess lactic acid in the blood. Tissue hypoxia is the result of occult tissue hypoperfusion. Abnormal markers of occult tissue hypoperfusion include acidosis, reflected by increase in base deficit, a reduction in blood pH, serum lactate elevation, potentially serum bicarbonate elevation, and elevated serum glucose.

Loss of circulating volume leading to hemorrhagic shock influences hemodynamic status with decreased blood pressure, which produces tissue perfusion and is associated with the development of anaerobic metabolism. The initial physiologic response to blood loss is an attempt to compensate for the loss with the response of catecholamines, antidiuretic hormone, and atrial natriuretic receptors respond to increase cardiac output and maintain perfusion pressure. Initially, these compensatory mechanisms maintain systolic blood pressure and heart rate at near normal levels. Due to the compensatory response, SI will be explored as a hemodynamic marker potentially more sensitive that either pulse rate or systolic blood pressure alone.

Respiratory rate increases as tissue oxygen demand increases and is used as a marker in trauma triage decisions. The Eastern Association for the Surgery trauma guidelines propose
that the first priority in the care of trauma patients is a patent airway to ensure adequate oxygenation and ventilation.\textsuperscript{27} Trauma care begins with the airway evaluation, and effective airway management is critical in the care of a patient with traumatic injuries.\textsuperscript{27} Trauma patients may require emergency tracheal intubation for various reasons following injury including hypoxia, hypoventilation, or failure to maintain or protect the airway owing to altered mental status, making respiratory rate an inconsistent marker.\textsuperscript{27} Therefore endotracheal intubation before or at the time of arrival to the ED will be used as a marker for respiratory status.

If occult tissue hypoperfusion is recognized early and treated appropriately, the shock state can be reversed.\textsuperscript{25} Left unrecognized, occult tissue hypoperfusion results in irreversible shock states leading to death within 48 hours of admission\textsuperscript{3,5,22}

**Research and Practice Gaps**

Hemorrhagic shock is the leading cause of trauma death and occult hypoperfusion leading to hemorrhagic shock is often unrecognized during the first 24 to 48 hours of trauma care.\textsuperscript{3} The work presented in this dissertation will add to our understanding about markers of occult tissue hypoperfusion in trauma. Early identification of occult hypoperfusion will provide opportunities for early interventions already accepted in the trauma community, such as initiation of massive transfusion protocols at admission to the ED and damage control surgery after admission to the ED to find and control hemorrhage before the need for imaging such as CT or MRI which may be delayed due to patient condition.

**Summary of Chapters in the Dissertation**

**Chapter 2: Early surrogate markers of tissue perfusion in trauma injuries: Critical review**

Chapter 2 is review of literature from 1994 to 2016 using the keywords “trauma and shock”, “hemorrhage and triage and injury” and “trauma markers of mortality”. The articles were
screened and reviewed and the physiologic variables of interest based on the literature were subdivided into: 1) shock index as a surrogate marker of tissue perfusion in trauma; 2) acid-base markers of tissue perfusion (i.e., serum base deficit, serum lactate, serum bicarbonate, serum glucose and serum pH); and 3) combination of SI and acid-base markers together to evaluate tissue perfusion.

Our findings suggested that the combination of SI and acid-base markers might provide dynamic information about occult tissue hypoperfusion that can be measured in the prehospital phase of care and the early period of ED treatment of trauma. Shock index and acid-base markers demonstrated promise as continued longitudinal measures during transport and in the ED in these reviewed studies, and may be useful until initiation of damage control surgery or definitive treatment of tissue hypoperfusion.

**Chapter 3: Shock index and injury severity score: Predictors of mortality after multi-system trauma**

This secondary analysis of data from the 2009 National Trauma Data Bank was performed to compare SI to ISS as predictors of trauma mortality within 48 hours of injury. The SI was compared to ISS because SI has been shown to be a predictor of both morbidity and mortality but has not been previously compared to ISS. The ISS is a score ranging from 1 to 75 measuring injury severity, which may be used to predict morbidity and mortality in trauma; this scoring system is the accepted standard in trauma research. Shock Index was calculated using the first available SBP and HR recorded by pre-hospital providers as the EMS shock index and the first available SBP and HR recorded in the ED as the ED shock index. These two calculations were first compared to ISS alone, then together to determine the ability of each to predict death within 48 hours from trauma.
This retrospective review found both EMS and ED SI to be more predictive of trauma mortality than ISS. The best measure based on the findings of this study is SI calculated in the ED. For each unit increase in the calculated ED SI, the odds of death within 48 hours of traumatic injury increased by 17%.

**Chapter 4: Identification of occult tissue hypoperfusion in patients with multiple trauma injuries**

Chapter 4 reports a retrospective analysis of 588 the medical records of trauma patients treated by the University of Kentucky Medical Center trauma team. In this study, we evaluated physiologic variables, anatomic variables and the presence of comorbid conditions as predictors of death from trauma within 48 hours. The physiologic variables were further subdivided into cardiovascular markers, respiratory marker and tissue perfusion markers. The cardiovascular markers were identified as SBP, HR, and SI. The respiratory marker was identified as need for intubation before or at the time of arrival to the ED. The tissue perfusion markers were selected from the literature review and those markers expected to be available in the patient chart and included arterial base deficit, lactate, bicarbonate, pH, and glucose. The anatomic variables included the mechanism of injury (blunt trauma, penetrating trauma, or both). The presence of comorbidities was documented in the record by category and for the purposes of this study was limited to only presence or absence of documented comorbidity.

**Chapter 5: Conclusions**

The final chapter is an integrated discussion in which the prior chapters are synthesized to advance the state of the science and provide a further examination of the work and identification of future studies.

**Summary**
This dissertation is the foundation for a program of research that seeks a comprehensive understanding of markers of occult tissue hypoperfusion. Earlier recognition of occult tissue hypoperfusion will provide opportunities for earlier treatment and prevention of deteriorating shock states, thus, patient outcomes will be improved.
Figure 1.1 Conceptual Framework

TRAUMA

HEMORRHAGE, HYPOVOLEMIA, OCCULT TISSUE HYPOPERFUSION

MEASURES OF OCCULT TISSUE HYPOPERFUSION

ACID-BASE AND SEROLOGIC MARKERS
- Base deficit elevation
- Acidotic pH
- Serum lactate elevation
- Serum bicarbonate elevation
- Serum glucose elevation

HEMODYNAMIC MARKERS
- Increasing pulse
- Decreasing systolic blood pressure
- Increasing shock index

RESPIRATORY MARKERS
- Worsening respiratory status as indicated by need for intubation

RECOGNIZED, OCCULT TISSUE HYPOPERFUSION IS TREATED AND SHOCK STATE IS REVERSED

LEFT UNRECOGNIZED, OCCULT TISSUE HYPOPERFUSION RESULTS IN IRREVERSIBLE SHOCK STATES AS MEASURED BY MORTALITY WITHIN 48 HOURS OF ADMISSION
CHAPTER TWO

Early Surrogate Markers of Tissue Perfusion in Trauma Injuries: Critical review

ABSTRACT

Background:

Failure to recognize occult tissue hypoperfusion as a result of hemorrhage is the primary cause of trauma mortality in the first 48 hours after injury. With the acceptance of permissive hypotension in managing trauma patients, restoration of adequate tissue oxygenation became the ‘gold standard’ for assessing the adequacy of resuscitation. A review of literature was performed to identify potential surrogate markers of adequacy of resuscitation.

Methods:

The literature review included articles from 1994 to 2016 using the keywords “trauma and shock”, “hemorrhage and triage and injury” and “trauma markers of mortality” The articles were screened and reviewed and the physiologic variables of interest based on the literature were subdivided into: 1) shock index as a surrogate marker of tissue perfusion in trauma; 2) acid-base markers of tissue perfusion (i.e., serum base deficit, serum lactate, serum bicarbonate, serum glucose and serum pH); and 3) combination of SI and acid-base markers together to evaluate tissue perfusion.

Results:

Twenty-seven articles were selected that described potential markers of occult tissue hypoperfusion. The review included potential markers of occult tissue hypoperfusion that assess hemodynamic stability, potential markers of occult tissue hypoperfusion that assess acid-base
status as a tissue oxygenation monitor, and potential markers of occult tissue hypoperfusion that assess both hemodynamic status and acid-base status.

**Conclusion:**

The findings suggested that the combination of SI and acid-base markers might provide dynamic information about occult tissue hypoperfusion that can be measured in the prehospital phase of care and the early period of ED treatment of trauma. Shock index and acid-base markers demonstrated promise as continued longitudinal measures during transport and in the ED in these reviewed studies, and may be useful until initiation of damage control surgery or definitive treatment of tissue hypoperfusion.
Early Surrogate Markers of Tissue Perfusion in Trauma Injuries: Critical review

Introduction and Background:

Trauma is the fifth leading cause of death in the United States overall. The economic impact of trauma is significant, at an estimated cost of $625.5 billion each year. According to 2010 statistics, death from unintentional injury accounts for 2,202,441 years of potential life lost before age 65.

Hemorrhage and hemorrhagic shock are responsible for up to 40% of trauma-related deaths. Trauma related hemorrhage can be managed with interventions, such as identification of hemorrhage within the first hours of trauma injuries and rapid transport for damage control surgery, as well as initiation of infusion of crystalloid and colloids to replace the lost volume to minimize the impact on mortality. Resuscitation alone will not ensure patient survival unless definitive treatment for the primary cause of the circulatory failure is delivered in a timely manner. The most common presentation of cardiovascular instability is because the hemorrhage has advanced to shock.

Shock is characterized by inadequate tissue perfusion with an imbalance between tissue oxygen delivery and oxygen utilization, with a cumulative build-up of tissue hypoxia or oxygen debt. Oxygen debt is indicted by extracellular release of anaerobic metabolism products such as lactic acid, leading to lactic acidosis in the patient.

Failure to recognize occult tissue hypoperfusion as a result of hemorrhage is the primary cause of mortality in the first 48 hours after injury due to trauma. Detection of occult tissue hypoperfusion within the first hours after trauma and rapid resuscitation with blood products or other oxygen carrying products as well as the use of definitive intervention for hemorrhagic
shock like damage control surgery, improve outcomes in critically injured and bleeding trauma patients.\textsuperscript{12}

The year 1994 was a turning point in trauma care with the publication of the sentinel research study by Bickell et al. ushering in the age of permissive hypotension in trauma management.\textsuperscript{30} This manuscript reported their work on the concept of permissive hypotension, allowing patients actively bleeding to maintain a lower systolic blood pressure (SBP) during transport with the elimination of the practice of aggressive volume resuscitation in the early phases of trauma resuscitation.\textsuperscript{30}

The Bickell et al. study was a prospective trial comparing immediate and delayed fluid resuscitation in adult trauma patients with penetrating torso injuries. The standard of care at the time of the study was aggressive fluid resuscitation in both the pre-hospital phase of care and in the Emergency Department (ED) to attain SBP greater than 100 mm Hg. For the purposes of the study, aggressive fluid resuscitation was defined as greater than 500 mL of crystalloid fluid administered intravenously during a thirty minute transport to the ED.\textsuperscript{30} The impetus for the study was previous research examining aggressive volume resuscitation in trauma with the finding it was potentially harmful.\textsuperscript{31-36} The two outcomes of interest for the study were survival to hospital discharge and complications to include adult respiratory distress syndrome, sepsis, acute renal failure, coagulopathy, wound infection, and pneumonia. The delayed resuscitation group experienced a 70\% survival rate as compared with a 62\% survival rate (8\% improvement in survival) for the immediate fluid resuscitation group (p = 0.04).\textsuperscript{30} Of the patients in the delayed resuscitation group, 23\% had one or more complications, compared with a 30\% complication rate (7\% reduction in complications) for the immediate fluid resuscitation group (p
With the acceptance of permissive hypotension, the focus moved from monitoring SBP as a resuscitation and mortality marker to assessing markers of tissue perfusion.

Restoration of adequate global and tissue oxygenation is the ‘gold standard’ for assessing the adequacy of resuscitation. A variety of strategies exist to assess circulatory status, including hemodynamic markers such as SI, and use of anaerobic metabolism serum markers pH, lactate, base deficit, and other serum marker of lactic acidosis. Metabolic acidosis and lactic acidosis are byproducts of anaerobic metabolism, and when measured with serum markers, they can be useful markers of persistent tissue hypoxia or oxygen debt.

The purpose of this critical review is to evaluate the predictive powers of potential markers of occult tissue hypoperfusion in trauma to include surrogates for hemodynamic status and measures of acid-bases status from the literature on the physiology of tissue hypoperfusion in trauma.

**Methods:**

An electronic literature search covering articles published from January 1994 to March 2016 was conducted using the Cumulative Index of Nursing and Allied Health (CINAHL), MEDLINE and PubMed. Keywords included ‘trauma and shock’, ‘hemorrhage and triage and injury’, ‘tissue perfusion’ and ‘trauma markers of mortality’. The time frame was selected to include research performed since the time the concept of permissive hypotension was accepted in practice. The search was limited to English language papers. The search resulted in forty-four articles of which the titles and abstracts were screened for inclusion criteria. Reference lists of relevant articles were screened for additional studies.
Studies were included in the review if they were in the English language, and reported either prospective observation comparisons of markers of tissue perfusion or retrospective analysis of physiologic markers of trauma mortality. Studies were excluded when the sample included patients with isolated head injuries. Twenty-seven articles were included in the final analysis for this review paper.

The focus of this review was to evaluate existing literature that identified physiologic markers of compensated and uncompensated hemorrhagic shock. The physiologic variables reviewed included surrogate markers of tissue perfusion and then further limited to those markers available at the time of arrival to the ED. The studies found were retrospective or prospective observation studies and were evaluated for quality using the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.45

Results:

Of the twenty-seven articles selected that described potential markers of occult tissue hypoperfusion, the review was structured by potential markers of occult tissue hypoperfusion that assessed hemodynamic stability, potential markers of occult tissue hypoperfusion that assessed acid-base status as a tissue oxygenation monitor, and potential markers of occult tissue hypoperfusion that assess both hemodynamic status and acid-base status.

Potential markers of occult tissue hypoperfusion that assessed hemodynamic stability

Six studies examined the value of SI as a hemodynamic marker in predicting trauma outcomes.18,40,46–49 Shock index is an indicator of hemodynamic instability, a mathematical quotient derived from heart rate (HR) divided by the SBP.19 The SI is normally 0.5 to 0.7.19 Individually, HR and SBP are common variables in all current trauma triage scores and have
been found to conceal deficiencies in systemic oxygenation, cardiac function, and increased likelihood of death.\textsuperscript{50-52} SI is calculated from these two variables, providing the necessary information to calculate SI when HR and SBP are available.\textsuperscript{19-21} As an indicator of hemodynamic instability, SI is an indicator of systemic oxygenation, cardiac function, and increased likelihood of death.\textsuperscript{50-52}

The physiological significance of SI has been evaluated in both experimental and clinical studies.\textsuperscript{19} These studies have shown SI to have an inverse linear relationship with left ventricular stroke work in acute circulatory failure.\textsuperscript{19} Therefore, when left ventricular stroke work, as induced by hemorrhage, trauma, or sepsis is reduced, it is associated with an elevation of SI and a deterioration in left ventricular mechanical performance or lack of recruitable preload in the form of volume.\textsuperscript{19}

Shock index has been evaluated in a number of retrospective studies to examine its utility in predicting unplanned transfer to the ICU, trauma mortality, ruptured ectopic pregnancy and risk for massive transfusion, all the result of hypovolemia and tissue hypoperfusion.\textsuperscript{18,21,40,48,53,54} In every retrospective study reviewed, SI was found to be an accurate predictor of mortality (Table 2-1).\textsuperscript{18,40,47-49} A limited number of prospective analyses have been performed using SI. A 2005 study by Birkhahn and colleagues using healthy volunteers to simulate a model of early acute hypovolemia by removing 450 mL of blood, assessing the HR, SBP, and SI immediately and at five minutes after the blood loss. They found a significant elevation in SI (mean elevation 0.75, \(p < 0.001\)) after a blood donation of 450 mL.\textsuperscript{46} They found SI to be more useful in detecting hypoperfusion than either HR or SBP alone since both HR and SBP remained within normal ranges while the SI elevated above normal.\textsuperscript{46} The initial HR was 74 beats per minute (bpm) (71, 77) and at five minutes after blood loss, the HR was 83 bpm (79, 88) with a \(p\) value of
< 0.001. The initial SBP was 123 mm Hg (118, 127) and at 5 minutes after blood loss, the SBP was 114 mm Hg (108, 119) with a p value of < 0.001. The initial SI was 0.61 (0.58, 0.64) and at 5 minutes after blood loss, a surrogate for occult hypovolemia and occult hypoperfusion, was 0.75 (0.70, 0.80) with a p value of < 0.001.46

**Potential markers of occult tissue hypoperfusion that assessed acid-base status as a tissue oxygenation monitor**

There are a variety of acid-base and laboratory markers, to include, but not limited to base deficit, serum lactate, serum bicarbonate, and serum glucose. These were the only laboratory markers available in the ED available to monitor metabolic acidosis as a surrogate for tissue oxygenation and tissue perfusion. Of the twelve articles reviewed using acid-base and serological markers of tissue perfusion, seven articles used base deficit or lactate as a marker of acidosis as a surrogate of tissue perfusion (Table 2.2).55-60 Of those articles, two used base deficit alone as a marker of acidosis as a surrogate of tissue perfusion.56,57

Another equally powerful indicator of acidosis as a surrogate marker for tissue oxygenation and shock severity is serum lactate. Lactate was used as a measure of tissue perfusion in six articles, generally in combination with base deficit (Table 2.2).55,58,59,61-63 Only one study examined lactate as a single measure of tissue perfusion.61 Four studies combined base deficit and lactate and both found lactate a better predictor of tissue hypoperfusion and mortality.55,58-60 Kincaid et al, identified the association of increased BD with risk of both multiple organ failure as a result of hypoperfusion and death (AUC = 0.71).55 Husain et al. reported similar findings of a correlation of elevated BD and lactate with twenty-four hour mortality (R² = 0.92).58 In a retrospective analysis, Kaplan et al. examined several acid-base variables, to
include both BD and lactate as well as pH and reported those acid-base variables (BD AUC = 0.989, Lactate AUC = 0.981) to be strong predictors of 28-day trauma survival.\textsuperscript{59} Martin et al. reported a similar correlation between BD and lactate with mortality (Lactate AUC = 0.70, BD AUC – 0.66).\textsuperscript{60} (Table 2-2).\textsuperscript{55,58-60}

Since 1971, there has been discussion of a relationship between elevated blood glucose and elevated serum lactate, as lactate is a byproduct of glycolysis.\textsuperscript{64} Duane et al. evaluated the relationship between glucose and serum lactate in the ability to predict tissue hypoperfusion, given that elevated lactate is a marker of tissue hypoperfusion.\textsuperscript{63} Five of the studies examined include glucose as a marker of tissue perfusion as compared serum lactate (Table 2.3).\textsuperscript{63,65-68} All studies examined found elevated glucose to be a marker of tissue perfusion in trauma associated with impaired tissue perfusion and mortality (Table 2.3).\textsuperscript{63,65-68}

Potential markers of occult tissue hypoperfusion that assessed both hemodynamic status and acid-base status

The remaining nine studies reviewed included markers of both hemodynamics and acid-base and serological markers (lactate, BD, pH).\textsuperscript{41,53,69-75} Of the studies reviewed, all except one found markers of acid-base to be more predictive of mortality from trauma than the markers of hemodynamics (Table 2.4).\textsuperscript{41,53,69-75} Morrison et al. found SI to better correlate than BD with the need for surgical torso hemorrhage control in a small retrospective analysis of 103 trauma patients (HR AUC = 0.80, SBP AUC = 0.75, SI AUC = 0.85, BD AUC = 0.79).\textsuperscript{69} In more broad examinations of trauma patients, Mutschler and colleagues examined records from 21,853 trauma patients in Germany and found worsening BD and SI (SI AUC = 0.719, BD AUC = 0.711) to both be associated with worsening injury severity score (ISS) and increased
transfusion requirements in trauma patients. Paladino and colleagues reviewed 1435 trauma records to compare the sensitivity of HR and SBP alone to the addition of lactate and BD. They found HR and SBP alone had a sensitivity of 40.9% to identify major injury, while the addition of lactate and BD increased major injury detection to 76.4%, as measured by the need for blood transfusion related to hemorrhagic hypovolemia or an ISS greater than fifteen. In a later study they examined SI as a measure of cardiovascular function, as measured by the need for blood transfusion or an ISS greater than fifteen, and found SI (SI AUC = 0.63), Lactate (Lactate AUC = 0.69), and BD (BD AUC = 0.72) to be predictive of the need for blood transfusion or an ISS greater than fifteen. Guyette et al. conducted a retrospective observational study with 387 trauma patients and found prehospital lactate superior (SBP AUC =0.59, SI AUC = 0.66, Lactate AUC = 0.78) to SBP in predicting the need for resuscitative care as measured by the need for blood transfusion > 5 units, immediate damage control surgery, and hospital mortality in trauma patients with a reported prehospital SBP between 90 mmHg and 100 mmHg. In research reported by Vandromme et al. and Caputo et al., both found an elevated lactate to be more predictive of mortality in trauma than SBP. In a retrospective analysis of 2413 trauma patients, Vandromme et al. reported lactate more predictive than SBP for need for transfusion and mortality (SBP AUC = 0.60, Lactate AUC = 0.74). Caputo et al. reported triage vital signs have no correlation to lactate or BD, as the odds of operative intervention were significantly greater in patients with elevated lactate (4.17 P = 0.003) than abnormal triage vital signs or BD. In a small (n=31) observational pilot study, Thom et al. reported BD to be the better detection method as compared to SI for occult tissue hypoperfusion and was associated with increased hospital LOS (Z=-2.63, P = 0.008). Additionally, a 2006 retrospective analysis by Parks et al. reported SBP correlated poorly with BD (r = 0.28). In the analysis, the mean SBP did not
decrease to 90 mm Hg or lower until the BD was worse than 20, a BD level associated with 65% mortality.75

Discussion:

Twenty-seven studies were reviewed in which investigators examined and compared potential early surrogate markers of tissue perfusion in trauma injuries. Shock index was reported as a significant marker of occult tissue hypoperfusion as a measure of hemodynamic stability in six studies as compared to SBP or HR alone. Twelve studies examined potential markers of occult tissue hypoperfusion that assess acid-base status as a tissue oxygenation monitor and all twelve reported either lactate, BD, or both measures to be significant markers of acid-base status as a marker of occult tissue hypoperfusion. The remaining nine studies examined a combination of hemodynamic stability and acid-base status as potential markers of occult tissue hypoperfusion. No single marker or combination of markers emerged in this review as a potential marker to place into clinical practice. From that information, the authors conclude the literature does not identify specific markers of occult tissue hypoperfusion. Shock index did emerge as a more significant marker of occult tissue hypoperfusion as a measure of hemodynamic stability than either SBP or HR alone.18,40,46-49 The probable reasons SBP and HR have been shown to be less reliable as a marker of occult tissue hypoperfusion is likely due to confounding factors to include pain, catecholamine response, medications, and early resuscitation efforts. The retrospective studies used either outcome measures of mortality (28-day mortality, survival to the ED, death in 24 hours, or 48-hour mortality) or transfusion of between two and ten units of blood. These differences in outcome measures make it more difficult to compare the findings.
Of the six studies reviewed, Vandromme et al. examined the relationship of incremental increases in SI with the relative risk for requiring transfusion of more than ten units of packed red blood cells, an indicator of occult tissue hypoperfusion in the prehospital setting. This study provides some guidance related to using SI as a guide to treating occult tissue hypoperfusion. The consistent finding across all studies was that SI may be most useful for the identification of patients in the compensatory phases of hemorrhagic shock and that further investigation is warranted. Unfortunately, SI has not been widely accepted in practice, therefore continued work will be done.

Lactate, BD, or both measures were shown to be significant markers of acid-base status as a tissue oxygenation monitor and marker of occult tissue hypoperfusion. Neither measure emerged as the most reliable marker of acid-base status as a tissue oxygenation monitor and marker of occult tissue hypoperfusion. All seven studies reviewed included mortality (death within 96-hours of trauma, increased mortality rate, survival to hospital discharge, death within 24-hours of trauma, and 28-day survival) as an outcome measure rather than the decrease in tissue perfusion leading to that mortality. Two of the seven stratified BD in increments as compared to mortality. The results differed since each study had a different range for BD to compare to mortality. Both studies showed worsening mortality as BD increased. One other study, Blow et al., described a mean lactate of 9.4 as correlating with death within 24-hour of injury. The rest of the studies reviewed lactate and BD as predictors of mortality, but did not provide specific values for either lactate or BD. Work remains to better quantify lactate and BD as a marker of acid-base status as a tissue oxygenation monitor and marker of occult tissue hypoperfusion.
Five of the twelve studies evaluating acid-base status examined glucose as a marker of acid-base status as a tissue oxygenation monitor and marker of occult tissue hypoperfusion. Four of the five studies were conducted by the same research group at University of Maryland and described infection as the most common outcome. It remains unclear whether hyperglycemia is a marker of a more critically ill patient or the cause of a worse outcome.

The nine remaining studies examined a combination of hemodynamic stability and acid-base status as potential markers of occult tissue hypoperfusion. The outcome measures for these studies included immediate need for damage control surgery, worsening ISS, need for blood transfusion, and mortality. Given the findings, the potential for a combination of markers to create a predictive model exists.

Despite the consistent finding across all reviewed studies that SI may be most useful for the identification of patients in the compensatory phases of hemorrhagic shock, only five of the nine studies examined SI as a measure of hemodynamic stability as a marker for tissue perfusion. The remaining four studies used SBP as a measure of hemodynamic stability as a marker for tissue perfusion. This offers an opportunity to first examine SI as a comparison with the acid-base measures and, more importantly, an opportunity to combine markers to create a predictive model for occult tissue hypoperfusion.

**Implications for nursing research:**

Each of the individual measures have been evaluated as markers of death from trauma injuries through retrospective analysis as a comparison against a variety of outcome measures consistent with occult tissue hypoperfusion. While it appears clear that acid-base measures (lactate, BD, pH) are dynamic measures of occult tissue perfusion, there has not been an effort to
combine markers to create a predictive model for occult tissue hypoperfusion with these measures or with the addition of SI as a marker of hemodynamic stability. Opportunities exist first to examine which markers might constitute a predictive model, then test the model in prospective observational studies. Once a predictive model has been identified, that model could be used to assess the outcomes of therapeutic interventions in prospective observational studies.

**Conclusion:**

Surrogate markers for tissue hypoperfusion such as SI, lactate and BD may well be the true dynamic variables that provide opportunities for early identification of occult tissue hypoperfusion that we can begin to measure in both the prehospital phase of care and the ED. Combining these markers has the potential to create a predictive model for identification of occult tissue hypoperfusion during transport and in the ED until initiation of damage control surgery or definitive treatment of tissue hypoperfusion. Further research is warranted to earlier and more accurately identify occult tissue hypoperfusion.
Figure 2.1 Search strategy and eligibility criteria

- **MeSH terms:** included ‘trauma and shock’, ‘hemorrhage and triage and injury’ and ‘trauma markers of mortality’.

- **Databases searched (1994-2016):** CINAHL, MEDLINE and PubMed

- **Search results:** 44 articles

- **Inclusion criteria:** the English language, a data analysis, either randomized control trial or retrospective analysis of physiologic markers of trauma mortality

- **Exclusion criteria:** isolated head injuries or review paper

- **Studies using shock index:** 6
- **Studies using acid-base variables:** 12
- **Studies using both SI and acid-base variables:** 9
<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Design and Sample</th>
<th>Statistical method</th>
<th>Marker for Tissue Perfusion</th>
<th>Outcome measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birkhahn (2005)</td>
<td>Prospective observational with healthy volunteers N = 46 Healthy volunteers</td>
<td>Paired t test</td>
<td>HR, SBP, SI</td>
<td>Change in SI five minutes after blood loss (mean elevation 0.75, p &lt; 0.001)</td>
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</tr>
<tr>
<td>Sloan (2014)</td>
<td>Retrospective data analysis N = 219 Trauma patients</td>
<td>AUC</td>
<td>SI</td>
<td>28-day mortality</td>
<td>Higher SI values in patients with hemorrhagic shock correlates with 28-day mortality (AUC = 0.71)</td>
</tr>
<tr>
<td>Cannon (2009)</td>
<td>Retrospective data analysis N = 2445 Trauma patients</td>
<td>Pearson’s Chi square</td>
<td>Change in SI from prehospital to ED</td>
<td>Survival from prehospital care to ED</td>
<td>Increasing SI is predictive of higher mortality Prehospital SI &gt; 0.9 SI ≤ 0.9 8.9% 5.8% P 0.05 ED arrival SI &gt; 0.9 SI ≤ 0.9 15.9% 6.3% P &lt; 0.001</td>
</tr>
<tr>
<td>King (1996)</td>
<td>Retrospective data analysis N = 1101 Trauma patients</td>
<td>AUC</td>
<td>SI</td>
<td>Death in 24 hours, ISS, ICU stay &gt; 1 day, blood transfusion &gt; 2 units</td>
<td>SI &gt;1 predicted death &lt; 24 hours (AUC = 0.75 ± 0.10) SI &gt; 0.71 predictive of ISS &gt;16 (AUC = 0.62) SI &gt; 0.77 predictive of ICU LOS &gt; 1 day (AUC = 0.58) SI &gt; 0.85 predictive of blood transfusion &gt; 2 units (AUC = 0.70)</td>
</tr>
<tr>
<td>Zarzaur (2008)</td>
<td>Retrospective data analysis N = 16,077 Trauma patients</td>
<td>AUC</td>
<td>HR, SBP, SI</td>
<td>48-hour mortality</td>
<td>SI predicts 48-hour mortality (AUC = 0.831)</td>
</tr>
<tr>
<td>Vandromme (2011)</td>
<td>Retrospective data analysis N = 8111 Trauma patients</td>
<td>Pearson’s Chi square</td>
<td>Prehospital SI</td>
<td>Risk of requiring massive transfusion (&gt;10 units)</td>
<td>Prehospital SI &gt; 0.9 identifies risk for massive transfusion SI RR ≤5 1.41 &gt;0.5-0.7 Ref</td>
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<tr>
<td>RBC in 24 hours</td>
<td>Value</td>
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<tr>
<td>&gt;0.7-0.9</td>
<td>1.06</td>
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<tr>
<td>&gt;0.9-1.1</td>
<td>1.61</td>
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<tr>
<td>&gt;1.1-1.3</td>
<td>5.57</td>
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<tr>
<td>&gt;1.3</td>
<td>8.13</td>
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</tbody>
</table>
Table 2.2 Acid-Base Marker Study Summary

<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Design and Sample</th>
<th>Statistical method</th>
<th>Marker for Tissue Perfusion</th>
<th>Outcome measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kincaid (1998)</td>
<td>Retrospective data analysis N = 100 Trauma patients</td>
<td>AUC</td>
<td>Lactate BD</td>
<td>Multi organ failure or death within 96 hours</td>
<td>Persistently elevated BD is associated with increased risk of multi organ failure and death within 96 hours (AUC = 0.71)</td>
</tr>
<tr>
<td>Mutschler (2013a)</td>
<td>Retrospective data analysis N = 16,305 Trauma patients</td>
<td>Kruskal-Wallis test</td>
<td>BD</td>
<td>Worsening ISS, massive transfusions (&gt;10 units in 24 hours), increased mortality</td>
<td>Worsening BD associated with worsening ISS and increased transfusion requirement</td>
</tr>
<tr>
<td>Hodgman (2012)</td>
<td>Retrospective data analysis N = 6767 Trauma patients</td>
<td>Multivariate logistic regression</td>
<td>BD</td>
<td>Survival to discharge</td>
<td>BD predicts survival to discharge</td>
</tr>
<tr>
<td>Blow (1999)</td>
<td>Pilot retrospective data analysis N=31 trauma patients</td>
<td>Correlation</td>
<td>Lactate</td>
<td>Respiratory compromise, multi-system organ failure, death within 24 hours after injury</td>
<td>Lactate of 9.4 ± 3.7 correlated with death P &lt; 0.05 Lactate of 3.6 ± 2.4 did not significantly correlate with death</td>
</tr>
<tr>
<td>Husain (2003)</td>
<td>Retrospective data analysis N = 137 SICU patients (trauma and major abdominal surgery patients)</td>
<td>Pearson’s correlation coefficient (r), coefficient of determination (R²)</td>
<td>Initial lactate, 24-hour lactate, initial BD, 24-hour BD</td>
<td>Mortality at the time of discharge</td>
<td>Initial lactate and 24-hour lactate significant predictor of mortality Initial BD not a significant predictor, 24-hour BD significant predictor of mortality Lactate and BD correlation r = -0.96 R² = 0.92</td>
</tr>
<tr>
<td>Study</td>
<td>Study Type</td>
<td>N</td>
<td>Acid-base Variables</td>
<td>28-day Survival</td>
<td>Acid-base variables are strong predictors of survival</td>
</tr>
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<td>-----------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>Kaplan^59</td>
<td>Retrospective data</td>
<td>282</td>
<td>pH, lactate and BD</td>
<td></td>
<td>(Lactate AUC = 0.981) (BD AUC = 0.989)</td>
</tr>
<tr>
<td>(2004)</td>
<td>analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin^62</td>
<td>Retrospective data</td>
<td>1298</td>
<td>Lactate, BD at</td>
<td>Mortality at</td>
<td>Both BD and lactate are useful markers at admission, elevated lactate is predictive even with normal BD</td>
</tr>
<tr>
<td>(2006)</td>
<td>analysis</td>
<td></td>
<td>admission</td>
<td>the time of</td>
<td>(Lactate AUC = 0.70) (BD AUC = 0.66)</td>
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<tr>
<td></td>
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<td></td>
<td>discharge</td>
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<tr>
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<tr>
<td>Duane (2006)</td>
<td>Prospective observational study N = 226 Trauma patients</td>
<td>Regression analysis</td>
<td>Lactate Glucose</td>
<td>ISS, mortality at discharge</td>
<td>Glucose and lactate correlate with increased ISS and increased mortality (ISS-Glucose, ( r^2 = 0.11 ), ( p=0.001 ) (ISS-lactate, ( r^2 = 0.06 ), ( p=0.004 ))</td>
</tr>
<tr>
<td>Bochicchio (2005a)</td>
<td>Prospective data comparison N = 942 Trauma patients</td>
<td>Multiple linear regression</td>
<td>Glucose</td>
<td>Infection, LOS, ventilator days, hospital mortality</td>
<td>High glucose associated with increased ventilator days ( p=0.01 ) High glucose associated with increased LOS ( p=0.001 ) High glucose associated with increased mortality ( p=0.01 )</td>
</tr>
<tr>
<td>Bochicchio (2005b)</td>
<td>Prospective data comparison N = 252 Trauma patients</td>
<td>Multiple linear regression</td>
<td>Glucose</td>
<td>Infection, LOS, ventilator days, hospital mortality</td>
<td>Admission glucose &gt; 200 is associated with increased LOS ( p=0.05 )</td>
</tr>
<tr>
<td>Sung (2005)</td>
<td>Prospective data comparison N = 1003 Trauma patients</td>
<td>Multiple linear regression</td>
<td>Glucose</td>
<td>Infection, LOS, ventilator days, hospital mortality</td>
<td>Hyperglycemia is associated with an increased relative risk of mortality of 2.2 ( (p=0.001) ), increased relative risk of infection of 3.01 ( (p=0.001) )</td>
</tr>
<tr>
<td>Bochicchio (2010)</td>
<td>Prospective data comparison N = 2200 Trauma patients</td>
<td>Multiple linear regression</td>
<td>Glucose</td>
<td>Infection, LOS, ventilator days, hospital mortality</td>
<td>Increased glucose is associated with increased ventilator days ( p=0.001 ), increased LOS ( p=0.001 ). increased mortality ( p=0.001 )</td>
</tr>
</tbody>
</table>
Legend: ISS = injury severity score; LOS = length of stay
<table>
<thead>
<tr>
<th>First Author (Year)</th>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morrison²⁹ (2012)</td>
<td>Retrospective data analysis N = 103 Trauma patients</td>
<td>AUC</td>
<td>HR, SBP, pulse pressure, SI, BD</td>
<td>Need for immediate damage control surgery</td>
<td>SI best correlated with the need for surgical control of torso hemorrhage (HR AUC = 0.80) (SBP AUC = 0.75) (SI AUC = 0.85) (BD AUC = 0.79)</td>
</tr>
<tr>
<td>Mutschler⁵³ (2013b)</td>
<td>Retrospective data analysis N = 21,853 Trauma patients</td>
<td>AUC to compare SI classification (Mutschler 2013a) to BD</td>
<td>SI, BD</td>
<td>Worsening ISS, massive transfusions (&gt;10 units in 24 hours), increased mortality</td>
<td>Worsening SI and BD associated with worsening ISS and increased transfusion requirement (SI AUC = 0.719) (BD AUC = 0.711)</td>
</tr>
<tr>
<td>Paladino⁷⁰ (2008)</td>
<td>Retrospective data analysis N = 1435 Trauma patients</td>
<td>Logistic regression</td>
<td>HR, SBP, lactate, BD</td>
<td>Need for blood transfusion, ISS &gt;15</td>
<td>HR and SBP alone had a sensitivity of 40.9% to identify major injury; additional of lactate and BD increased major injury detection to 76.4% with a p value &lt;0.01</td>
</tr>
<tr>
<td>Paladino⁷¹ (2011)</td>
<td>Retrospective data analysis N = 1435 Trauma patients</td>
<td>AUC</td>
<td>SI, lactate, BD</td>
<td>Need for blood transfusion, ISS &gt;15</td>
<td>(SI AUC = 0.63) (Lactate AUC = 0.69) (BD AUC = 0.72)</td>
</tr>
<tr>
<td>Guyette²² (2011)</td>
<td>Prospective observational study N = 387 Trauma patients</td>
<td>AUC</td>
<td>SBP, SI, prehospital lactate</td>
<td>Blood transfusion &gt; 5 units, immediate damage control surgery, hospital mortality</td>
<td>Prehospital lactate is superior in predicting need for resuscitative care in trauma patients with SBP between 90 mmHg and 100 mm Hg (SBP AUC =0.59) (SI AUC = 0.66) (Lactate AUC = 0.78)</td>
</tr>
<tr>
<td>Study</td>
<td>Study Design</td>
<td>Sample Size</td>
<td>Methodology</td>
<td>Outcomes</td>
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<tr>
<td>Vandromme 41 (2010)</td>
<td>Retrospective data analysis</td>
<td>N = 2413 Trauma patients</td>
<td>AUC, SBP, lactate</td>
<td>Blood transfusion &gt; 6 units, hospital mortality</td>
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<tr>
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<td></td>
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<td>Lactate more predictive than SBP for need for transfusion and mortality</td>
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<td>(SBP AUC = 0.60)</td>
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<td></td>
<td></td>
<td></td>
<td>(Lactate AUC = 0.74)</td>
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</tr>
<tr>
<td>Caputo 73 (2013)</td>
<td>Prospective observational study</td>
<td>N = 75 Trauma patients</td>
<td>Logistic regression SBP, HR, RR, lactate, BD</td>
<td>Operative intervention Triage vital signs have no correlation to lactate or BD, Odds of operative intervention were significantly greater in patients with elevated lactate (4.17 (1.57-11) P 0.003) than abnormal triage vital signs or BD</td>
<td></td>
</tr>
<tr>
<td>Thom 74 (2010)</td>
<td>Prospective observational study</td>
<td>N = 64 Trauma patients</td>
<td>Multivariate analysis BD, SI</td>
<td>Occult hypoperfusion (hypoperfusion in the presence of normal VS) Hospital LOS</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BD best detection method for occult tissue hypoperfusion and is associated with increased hospital LOS Z=-2.63 P =0.008</td>
<td></td>
</tr>
<tr>
<td>Parks 75 (2006)</td>
<td>Retrospective data analysis</td>
<td>N = 115,830 Trauma patients</td>
<td>Pearson correlation coefficient SBP</td>
<td>BD (marker of circulatory shock), hospital mortality Systemic hypotension is a late marker of shock, BD &gt;20 is a significant marker of hospital mortality</td>
<td></td>
</tr>
</tbody>
</table>

Legend: AUC = Area under the curve; HR = heart rate; SBP = systolic blood pressure; SI = shock index; ISS = injury severity score; ED = emergency department; ICU = intensive care unit; LOS = length of stay
CHAPTER THREE

Shock Index and Injury Severity Score as Predictors of Mortality after Multi-System Trauma: An Analysis of the 2009 National Trauma Data Bank

Abstract:

Background:

Decisions in the field about triage and treatment of injuries must not be delayed. Trauma patients often have complex injuries that may not fully manifest until later in treatment. Currently, the two best options are the Revised Trauma Score and pre-hospital provider judgment. The injury severity score (ISS), calculated at the time of discharge, provides the most information, but is only available as a measure for comparison in research and quality improvement.

Objectives:

The purpose of this study was to compare the ability of shock index (SI) calculated from data obtained by pre-hospital providers and data collected on arrival to the Emergency Department (ED) with the ISS reported in the National Trauma Data Bank (NTDB) in their ability to predict death from trauma within 48 hours of injury.

Methods:

A secondary analysis was done using data from the 2009 NTDB. The data were analyzed for descriptive information and logistic regression was done to evaluate the predictive ability of pre-hospital and ED SI as compared to the predictive ability of the reported ISS. Random samples of the larger database were used to run an initial and 5 replication models.
Results:

The sample consisted of 516,156 trauma patients reported to the NTDB. The SI value calculated in the ED was found to be the best measure for predicting death within 48 hours of admission to the hospital after traumatic injuries. For each unit increase of the EMS SI, the odds of death within 48 hours of traumatic injury increased by 3%, while for each unit increase in ISS, the odds of death within 48 hours of traumatic injury increased by 7%. Each of the 5 replication models produced virtually identical results.

Conclusion:

Shock Index is an independent predictor of mortality in trauma patients and may be useful as an early marker of hemodynamic instability, which merits further investigation. Routine use of the SI in clinical practice may provide a key opportunity to improve outcomes in trauma.
Shock Index and Injury Severity Score as Predictors of Mortality after Multi-System Trauma: An Analysis of the 2009 National Trauma Data Bank

Introduction:

Trauma patients often have multiple complex injuries that may not fully manifest until late in the course of treatment. This late manifestation does not lessen the urgency with which the nature of the injuries must be identified and properly treated. In order to fully assess the severity of injuries sustained in trauma and the potential effects on the injuries on patient outcomes, the full extent of the injuries must be known. In the pre-hospital setting, time and resources significantly limit providers in determining the full extent of the injuries sustained in trauma. Once the patient reaches the Emergency Department (ED), additional measures can be made, but the final results may not be available for hours to days. Triage and treatment of traumatic injuries must not be delayed due to information limitations.

The most frequently used measure for reporting injury severity is the Injury Severity Score (ISS).\textsuperscript{76-78} The ISS is an anatomic scoring system calculated at the time of hospital discharge that provides a composite score for the severity of injury patients with multiple injuries.\textsuperscript{76-78} The ISS is an anatomical scoring system that evaluates injuries using body regions and accounts for multiple injuries to multiple regions.\textsuperscript{76} Each region is assigned an Abbreviated Injury Scale (AIS) score and those scores are allocated to one of six body regions (head, face, chest, abdomen, extremities including pelvis, and external). The three most severely injured body regions have their score squared and added together to produce the ISS score.\textsuperscript{76} The ISS is an accurate instrument for comparison of injury severity, it is not useful for immediate triage decisions. The primary weakness of the ISS is that the score is derived an Abbreviated Injury
Scale (AIS), relying on an estimation of injury severity of each body regions, with a potential for error in any body region and only accounts for the most severe injury to the body region. Another weakness of the ISS is that many injury patterns can produce similar scores in different body regions and the injuries are not weighted by body region. The ISS was never intended as a triage instrument, rather as an instrument for research and quality improvement data comparison. This final ISS is not calculated until the entire injury picture is complete and may require operative intervention to have complete injury information and evaluation.\textsuperscript{78}

**Review of Literature**

The ISS is frequently used to compare the injury severity of patient populations and is used in evaluating care and measures of quality.\textsuperscript{79} The score values range from 0 to 75 and are based on an evaluation of the injuries identified in each of six body regions scaled by the severity of those injuries described as ranging from minor to un-survivable.\textsuperscript{76,78,80} The ISS is limited in usefulness as it only assesses anatomic injuries without consideration of the physiologic ramifications of injury. The information reported in the ISS is generally not fully available until the time of discharge.\textsuperscript{79} As such, the ISS is primarily used as a research instrument and for measures of quality and provides little useful information during either pre-hospital care or ED care. For the purposes of this study, ISS will be used as the standard measure of injury severity at the time of discharge as compared to an early marker of injury severity. The ISS is the gold standard for measuring injury severity at the time of discharge for research comparison and trauma system quality measures comparison.\textsuperscript{80,81}

The Revised Trauma Score (RTS) which is calculated in the field by pre-hospital providers and is a scale composed solely of physiologic variables. The RTS includes three
physiologic variables available at the scene of the injuries. They are the Glasgow Coma Score (GCS) to assess neurologic response; systolic blood pressure (SBP) to assess hemodynamic status; and respiratory rate to assess ventilation. The original Trauma Score was first published in 1981 and revised in 1989 by the same authors.\textsuperscript{82} The RTS is the most widely used pre-hospital field triage tool.\textsuperscript{81,83} While it is more useful in predicting trauma outcomes than any of the component physiologic parameters alone, it remains limited in its usefulness in making triage decisions in the field.\textsuperscript{83-85}

The component variables of the RTS (i.e., the GCS, SBP and respiratory rate) each have inherent shortcomings. The GCS may be altered by pre-existing alcohol or drugs in the patient’s system or by administration of sedative drugs by Emergency Medical Services (EMS). The SBP is influenced by compensatory mechanisms in response to the shock state associated with blood loss and traumatic injury and may remain within near normal ranges until the patient experiences later stages of shock. The respiratory rate is only accurate as long as the patient is able to protect their airway and breathe spontaneously. If the patient requires intubation, the respiratory rate is no longer an accurate measure.

The time most critical to making decisions related to care of the severely injured patient is the time immediately post injury, during transport and in the ED. The Shock Index (SI) has the potential for providing information needed to make immediate triage decisions.\textsuperscript{18,40,46-49,69,71} Shock Index is a calculation of heart rate (HR) divided by SBP, and normal is 0.5 to 0.7.\textsuperscript{46}

Shock Index can be calculated in the field or in the ED and was first described in 1967 by Allgower and Burri and has been studied in trauma and other hemorrhagic shock states.\textsuperscript{18,46,48} Shock Index was found to be more sensitive than either HR or SBP alone in the recognition of
the hemodynamic response to early acute blood loss of less than 450 mL in a 2004 study of healthy volunteers.\textsuperscript{46} Shock Index has been shown to be an early predictor of shock in states of uncontrolled hemorrhage, ruptured ectopic pregnancy, gastrointestinal bleeding, sepsis and trauma as well as a marker of both acute hypovolemia and left ventricular dysfunction.\textsuperscript{18-20,40,46-49,54,69,71,86-88}

In 2009, SI was examined as a predictor of mortality in traumatically injured patients.\textsuperscript{48} The investigators performed a retrospective analysis of a trauma registry of a single urban level I trauma center and examined the increase in SI from the pre-hospital setting to the ED. They found that an increase in SI to greater than 0.9 during transport to the ED predicted 8.9\% mortality in trauma patients (p = 0.05) and an increase in SI in the ED of greater than 0.9 predicted 15.9\% mortality (p < 0.001).\textsuperscript{48} A 2008 study found SI to be a better predictor of mortality in 48 hours than either HR or SBP alone, with SI predicting forty-eight hour mortality with an AUC of 0.831.\textsuperscript{49} The intent of the study investigators was to identify a reliable early post-injury mortality indicator to assist with accurate triage and appropriate and timely intervention to prevent mortality.\textsuperscript{49}

Subsequent retrospective studies published in 2010 and 2013 also evaluated the efficacy of SI as an early marker of shock states.\textsuperscript{21,53} Keller and colleagues examined the association of SI with unplanned transfers to the Intensive Care Unit, finding SI to be more accurate than vital signs alone as an indicator of clinical decline.\textsuperscript{21} Mutschler et al. performed a retrospective analysis of data recorded on more than 20,000 trauma patients in the German trauma registry.\textsuperscript{53} Shock Index was found to be a clinical indicator of worsening hypovolemic shock in this German population.\textsuperscript{53}
Specific Aims

The specific aims of this study were to: (1) compare the ability of SI as calculated by HR and SBP recorded by Emergency Medical Services (EMS) personnel at the scene of injury with the ISS as recorded in the National Trauma Data Bank (NTDB) to predict death within 48 hours of sustaining traumatic injuries; (2) compare the ability of SI as calculated by HR and SBP recorded in the ED with the ISS as recorded in the National Trauma Data Bank (NTDB) to predict death within 48 hours of sustaining traumatic injuries; and (3) compare the ability of SI as calculated by HR and SBP recorded by Emergency Medical Services (EMS) personnel at the scene of injury, and SI as calculated by HR and SBP recorded in the ED, with the ISS as recorded in the National Trauma Data Bank (NTDB) to predict death within 48 hours of sustaining traumatic injuries.

Methods

Design and Sample

This was a secondary analysis of data from the 2009 NTDB. The NTDB includes patients treated at trauma centers and hospitals across the United States. The study population consisted of de-identified patient data from the NTDB – 2009 (N = 627,664) from patients aged 16 to 80 with complete data recorded for the variables of interest (age, gender, race, death within 48 hours of injury, ISS, SBP, and HR) and a reported ISS of 16 or greater. The initial data set included 627,664 cases. The data were first filtered for missing variables of interest, leaving 516,156 cases.

The NTDB contains detailed date from over 900 registered US trauma centers. 89 Trained data coders at each hospital enter data into the registry at the time of discharge. The data files
received from contributing hospitals are screened by an edit check program upon submission for improved quality. The data from the NTDB used in this study only accounts for patients alive at the time of arrival to the ED. The data was reported from all facilities receiving trauma patients and reporting to the NTDB.

Variables

The demographic data used from the NTDB included a unique file identification number, age, gender, and race. Additional variables of interest included death (occurring anywhere) within 48 hours of injuries, length of hospital stay and whether the stay included time in the intensive care unit for those who were hospitalized after their ED stay, ISSAIS, and HR and SBP recorded by EMS and ED personnel. The latter two data elements were used to calculate the SI from HR divided by SBP. The EMS SI was calculated using the first recorded HR and SBP reported by EMS and recorded in the record. The ED SI was calculated using the first recorded HR and SBP reported and recorded in the ED.

The reported ISS used for the data analysis was the ISSAIS, the ISS calculated by the NTDB from AIS scores submitted directly by the reporting hospitals. The variable death within 48 hours of injury was obtained from the hospital discharge disposition data field.

Procedures

Institutional Review Board (IRB) approval was obtained from the University of Kentucky for the use of de-identified data in the NTDB. The data were analyzed with descriptive, comparative and analytical statistical measures using PASW Statistics 19, Version 19.0
From the full sample of 516,156 trauma patients, six samples were drawn that consisted of 10% random samples each. The first sample was used to test the proposed models and the remaining five were used to replicate the results of the first tests. In order to determine predictors of death within 48 hours, three separate logistic regression models were developed to test each of the specific aims. The main predictor variables included were EMS SI, ED SI and ISS. The follow additional predictors were included as covariates: age, gender, and race. The assumptions of logistic regression (i.e., linear relationship exists between the continuous level independent variables and the logit transformation of the dependent variable, no multicollinearity and no significant outliers or influential points) were tested. There were no influential outliers and there were no multicollinearity problems.

Results

The full sample consisted of 516,156 trauma patients injured in 2009 in the United Stated who were transported to a hospital reporting to the NTDB. Population demographics (Table 1) indicate the sample was relatively young (mean age 43, ± 19 years old), predominately white (70%) and male (68%). For those who survived their ED visit (98.7%) to be hospitalized, the mean hospital length of stay was 6.2 ± 9.1 days with a very large range from 1 day to 357 days.

Specific Aim 1.

A 10% random sample was determined (n = 51,552) and analysis performed. In the analysis addressing Specific Aim 1, to compare the ability of SI as calculated by HR and SBP recorded by EMS personnel at the scene of injury and ISS as recorded in the NTDB to predict death within 48 hours of sustaining traumatic injuries, both variables were significant predictors of death within 48 hours. For each unit increase of the EMS SI, the odds of death within 48 hours
of traumatic injury increased by 3%, while for each unit increase in ISS, the odds of death within 48 hours of traumatic injury increased by 7% (Table 2). Increasing age was also a predictor of increased risk of death within 48 hours of traumatic injury, while race and gender were not significant predictors (Table 2). Each of the 5 replication models produced virtually identical results.

Specific Aim 2.

In the analysis addressing Specific Aim 2, to compare the ability of SI as calculated by HR and SBP recorded in the ED and ISS as recorded in the NTDB to predict death within 48 hours of sustaining traumatic injuries, both variables were significant predictors of death. For each unit increase in the calculated ED SI, the odds of death within 48 hours of traumatic injury increased by 7% and for each unit increase in ISS, the odds of death within 48 hours of traumatic injury increased by 11% (Table 3). Increasing age was also a predictor of increased risk of death within 48 hours of traumatic injury, as was male gender and African American race (Table 3). Each of the 5 replication models produced virtually identical results.

Specific Aim 3.

In the analysis of Specific Aim 3, ED SI, EMS SI, and ISS were entered as predictors of the outcome of death within 48 hours from trauma injuries. Of the measures, ED SI was found to be the most sensitive measure for predicting death within 48 hours of admission to the hospital after traumatic injuries. For each unit increase in the calculated ED SI, the odds of death within 48 hours increased by 17%. For each unit increase in the calculated EMS SI, the odds of death within 48 hours increased by 2% and for each unit increase in the reported ISS, the odds of death
within 48 hours increased by 10%. (Table 4). Of the control variables, only increasing age was associated with increased risk of death.

**Discussion:**

The most important finding from this study was the determination that SI calculated in the ED was the strongest predictor of death within 48 hours of ED admission after trauma. This finding has important implications for clinical practice. Currently, both EMS and ED triage decisions in trauma are made based on variables that are easily masked by interventions or physiologic compensatory mechanisms triggered by a catecholamine response.

The findings from this study show SI to be an independent predictor of mortality within 48 hours as compared to ISS in trauma patients and may be useful as a marker of hemodynamic instability within the first 48-hours after injury, which merits further investigation. In the reported studies, SI of greater than 0.6 was described as mild shock and values greater than 0.85 to 0.90 indicated the lowest SI associated with mortality.\textsuperscript{21,40,48,49,53}

Previous studies have found SI to be an accurate indicator of injury and illness severity and as a triage tool. The 2009 study by Cannon et al. evaluating SI as a predictor of mortality in trauma examined both prehospital SI and ED SI and had similar findings.\textsuperscript{48} Key differences between the studies were the calculation of change in SI from prehospital to ED and the difference in the time from injury to death. Cannon et al. defined mortality as all death from traumatic injuries, whereas this study defined mortality as death from traumatic injuries within 48 hours of injury. Both studies found SI to be a significant predictor of mortality in trauma and this study compared SI to ISS calculated at the time of discharge.
Shock Index provides an easily calculated variable, using readily available information from vital signs to make real-time decisions. Clinical decisions regarding transport and interventions can be made with more meaningful data. Shock Index can be easily calculated in the field, in the ED or at the point of care. It is possible to easily include SI as a longitudinal variable calculated throughout the course of care of the trauma patient or in managing patients with early hemodynamic instability. Despite literature to support the use of SI, it remains an underused instrument.

**Limitations**

This study is a secondary analysis of a large data base and as such is limited by the accuracy and completeness of the data available. The large sample size may inflate the statistical significance of the variables due to the volume of patient data evaluated. The convenience sample of data obtained from the NTDB is also subject to various forms of bias. The variables selected for this study were described by the NTDB 2009 user manual to have selection or population bias.89

**Conclusions**

Findings from this secondary data analysis indicated that both EMS SI and ED SI are significant predictors of death from trauma injuries within 48 hours. Shock Index could be useful to both EMS and ED providers in making rapid triage and treatment decisions about critically injured patients with. With further study, this measure may be useful in triage and improving trauma systems. Shock Index may provide a key opportunity to improve outcomes in trauma care.
Additional work is needed to further examine the predictive value of SI in traumatic injuries and whether SI has potential to be used as a triage tool in the pre-hospital and ED for trauma evaluation. Shock index, in combination with other variables may well serve as a predictive model for triage and indicator of worsening conditions in patients with other conditions manifesting as hemodynamic instability. Shock index has been shown to be a more accurate measure of hemodynamic instability than either HR or SBP alone and may well be useful as a detector of occult tissue hypo-perfusion in patients experiencing hemodynamic instability.\textsuperscript{18,46,47}

We are missing an opportunity to recognize a large percentage of trauma population who could be helped by using more accurate methods to earlier identify occult tissue hypoperfusion. To better realize that opportunity, there is a need for real time analysis of SI as a predictor of worsening tissue hypo-perfusion in shock states.
Table 3.1 Characteristics of the entire available sample (n = 516,156)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>N (%)</th>
<th>Median (25&lt;sup&gt;th&lt;/sup&gt;, 75&lt;sup&gt;th&lt;/sup&gt; percentile)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>43 (19)</td>
<td></td>
<td>42 (26, 57)</td>
<td>16 – 80</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>351,674 (68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>164,482 (32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>339,600 (70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td></td>
<td>80,416 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td>8342 (1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian</td>
<td></td>
<td>4971 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native Hawaiian</td>
<td></td>
<td>1224 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>49851 (9.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td></td>
<td>31752 (6.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Died in the emergency department</strong></td>
<td></td>
<td>6411 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Length of hospital stay, days</strong></td>
<td>6.2 (9.1)</td>
<td></td>
<td>4 (2, 7)</td>
<td>1 - 357</td>
</tr>
<tr>
<td><strong>Intensive care unit stay</strong></td>
<td></td>
<td>140961 (34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hospital disposition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td></td>
<td>13787 (3.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left against medical advice</td>
<td>4218 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged or transferred with other care</td>
<td>107531 (24.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged home without additional services</td>
<td>31478 (71.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Survived emergency department but died within 48 hours</strong></td>
<td><strong>6704 (1.6)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3.2: Results of regression analysis to predict death within 48 hours from Emergency Medical Services Shock Index and Injury Severity Scores, n = 51,552 (10% random sample)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>Lower Confidence Interval</th>
<th>Upper Confidence Interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.014</td>
<td>1.008</td>
<td>1.021</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male versus female</td>
<td>1.128</td>
<td>0.875</td>
<td>1.453</td>
<td>0.352</td>
</tr>
<tr>
<td>African-American race compared to Caucasian</td>
<td>0.963</td>
<td>0.686</td>
<td>1.350</td>
<td>0.826</td>
</tr>
<tr>
<td>Race other than African-American compared to Caucasian</td>
<td>0.948</td>
<td>0.654</td>
<td>1.375</td>
<td>0.778</td>
</tr>
<tr>
<td>Emergency Medical Services Shock Index</td>
<td>1.03</td>
<td>1.028</td>
<td>1.032</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Injury Severity Score</td>
<td>1.07</td>
<td>1.043</td>
<td>1.094</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Legend: omnibus test of model, $\chi^2 = 790.9$, df 6, p = <0.001
Table 3.3: Results of regression analysis to predict death within 48 hours from Emergency Department Shock Index and Injury Severity Scores, \( n = 51,465 \) (10% random sample)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>Lower Confidence Interval</th>
<th>Upper Confidence Interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.015</td>
<td>1.010</td>
<td>1.020</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male versus female</td>
<td>1.238</td>
<td>1.003</td>
<td>1.528</td>
<td>0.047</td>
</tr>
<tr>
<td>African-American race compared to Caucasian</td>
<td>1.571</td>
<td>1.223</td>
<td>2.018</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race other than African-American compared to Caucasian</td>
<td>1.092</td>
<td>0.807</td>
<td>1.476</td>
<td>0.570</td>
</tr>
<tr>
<td>Emergency Department Shock Index</td>
<td>1.068</td>
<td>1.035</td>
<td>1.103</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Injury Severity Score</td>
<td>1.068</td>
<td>1.035</td>
<td>1.103</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Legend: omnibus test of model, \( \chi^2 = 1287.2, \) df 6, \( p = <0.001 \)
Table 3.4: Results of regression analysis to predict death within 48 hours from Emergency Department Shock Index, Emergency Medical System Shock Index and Injury Severity Scores, n = 52,550 (10% random sample)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>Lower Confidence Interval</th>
<th>Upper Confidence Interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.017</td>
<td>1.010</td>
<td>1.024</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male versus female</td>
<td>1.256</td>
<td>0.943</td>
<td>1.673</td>
<td>0.119</td>
</tr>
<tr>
<td>African-American race compared to Caucasian</td>
<td>1.321</td>
<td>.900</td>
<td>2.043</td>
<td>0.089</td>
</tr>
<tr>
<td>Race other than African-American compared to Caucasian</td>
<td>1.090</td>
<td>0.736</td>
<td>1.615</td>
<td>0.668</td>
</tr>
<tr>
<td>Emergency Department Shock Index</td>
<td>1.171</td>
<td>1.074</td>
<td>1.276</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emergency Medical System Shock Index</td>
<td>1.020</td>
<td>1.010</td>
<td>1.030</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Injury Severity Score</td>
<td>1.104</td>
<td>1.095</td>
<td>1.112</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Legend: omnibus test of model, $\chi^2 = 771.0$, df 7, $p = <0.001$
CHAPTER FOUR

Identification of Early Markers of Mortality in Patients with Multiple Trauma Injuries

Abstract:

Background:

Up to 30% of trauma deaths may show improved outcomes from earlier recognition of occult tissue hypoperfusion and earlier appropriate intervention. That early recognition has been elusive. In an effort to identify early markers of mortality in patients with multiple trauma injuries, this study evaluated physiologic variables, anatomic variables and the presence of comorbid conditions as predictors of death from trauma within 48 hours.

Objectives:

The purpose of the study was to determine early markers of morbidity and mortality from among 1) pulse; 2) systolic blood pressure; 3) shock index; 4) need for mechanical ventilation; 5) arterial base deficit; 6) serum lactate; 7) serum bicarbonate; 8) serum pH; 9) blood glucose; 10) mechanism of injury (blunt trauma, penetrating trauma or a combination of both); and 11) the presence of co-morbid conditions among patients admitted to the Emergency Department with injuries from multiple trauma.

Methods:

A retrospective analysis of 588 medical records of trauma patients treated by the University of Kentucky Medical Center trauma team was performed. Physiologic variables, anatomic variables and the presence of comorbid conditions as predictors of death from trauma within 48 hours were evaluated. The physiologic variables were further subdivided into cardiovascular markers, respiratory marker and tissue perfusion markers. The cardiovascular markers were identified as SBP, HR, and SI. The respiratory marker was identified as need for intubation before or at the
time of arrival to the ED. The tissue perfusion markers were selected from the literature review and those markers expected to be available in the patient chart and included arterial base deficit, lactate, bicarbonate, pH, and glucose. The anatomic variables included the mechanism of injury (blunt trauma, penetrating trauma, or both). The presence of comorbidities was documented in the record by category and for the purposes of this study was limited to only presence or absence of documented comorbidity.

Results:

In the final model containing all variables of interest, only endotracheal intubation, the respiratory variable, was predictive of the outcome. Patients who required endotracheal intubation has 6.5 times greater risk of dying within 24 hours of ED admission than those who were not intubated. The need for intubation overshadowed any other potential variable.

Conclusion:

We found only need for intubation as a predictor of 48-hour mortality when placed in a predictive model using multiple variables. The bivariate analyses support existing literature, but a comprehensive predictive model using multiple variables remains elusive. Additional work will continue to be done.
Identification of Early Markers of Mortality in Patients with Multiple Trauma Injuries

Introduction:

Every 5 minutes there is a death from a traumatic injury, which is the fifth leading cause of death overall after heart disease, cancer, stroke and chronic lower respiratory diseases.\textsuperscript{91} Because trauma is a condition of the young and carries the potential for permanent disability, it is responsible for significant loss in productive work years.\textsuperscript{91} The economic impact of trauma is significant at an estimated cost of $625.5 billion each year.\textsuperscript{28}

The primary causes of trauma related death are head injury and hemorrhage.\textsuperscript{2,3,23} Hemorrhage and hemorrhagic shock are responsible for up to 40\% of trauma-related deaths.\textsuperscript{11} Approximately 60\% of these trauma related deaths occur at the scene of injury and thus are best managed with prevention of the accident.\textsuperscript{3,4} The 40\% who survive the initial insult of trauma require ongoing triage and treatment of the injuries they sustain to improve chances of survival.\textsuperscript{92} Of that 40\% who survive the initial insult and are transported to appropriate care, 30\% will die within the first 48 hours after sustaining injuries.\textsuperscript{4,93,94} It is that 30\% of trauma deaths that may show improved outcomes from earlier recognition of occult tissue hypoperfusion and earlier appropriate intervention.

Failure to recognize occult hypoperfusion as a result of hemorrhage is linked to increased morbidity and mortality in early trauma.\textsuperscript{3,6} Early detection of occult hypoperfusion followed by rapid resuscitation with blood products and definitive intervention for hemorrhagic shock hold great promise in improving outcomes in critically injured and bleeding trauma patients.\textsuperscript{12} The remaining 10\% of trauma related death occurs after days or weeks as a result of infection and multiple organ dysfunction.\textsuperscript{13} Even this 10\% has a relationship to unrecognized and untreated hypo-perfusion from hemorrhage because delayed or inadequate resuscitation plays a major role
in multiple organ dysfunction. Since occult hypoperfusion is associated with increased mortality in trauma, the focus of this study was to identify early markers of occult tissue hypoperfusion leading to mortality in patients with multiple trauma.

**Review of Literature:**

In order to develop a comprehensive, accurate model with high sensitivity and specificity, we included a large number of potential predictors in order to arrive at the most efficient model. Variables were chosen as potential predictors for this study based on prior evidence from the literature that they were predictive of mortality. Variables were grouped into three broad categories of physiologic variables, anatomic variables, and presence of identified co-morbidity. The physiologic variables were further subdivided into cardiovascular variables, respiratory variables, and tissue perfusion.

*Physiologic Variables.

**Cardiovascular.** The following three variables were selected to measure the cardiovascular response to injury: heart rate HR), systolic blood pressure (SBP) and shock index (SI). Heart rate and SBP are common variables in all current trauma triage scores and thus are included, despite the consistent finding that they are less predictive than the calculated shock index (SI), which consists of both variables.  

Shock index was selected as an indicator of hemodynamic instability. Allgower and Burri (1967) first explored a mathematical quotient derived from HR divided by SBP as a more sensitive indicator than either HR or SBP alone of hemodynamic instability. Shock index is normally 0.5 to 0.7. Shock index has been evaluated in a number of retrospective studies to examine its utility in predicting unplanned transfer to the ICU, trauma mortality, ruptured ectopic...
pregnancy and risk for massive transfusion.\textsuperscript{18,21,40,48,53,54,71} Shock index was found consistently to be an accurate predictor of occult hypo-perfusion across settings.

A limited number of prospective analyses have been performed using SI. In 2005, investigators used healthy volunteers to simulate a model of early acute hypovolemia and found a significant elevation in SI after a blood donation of 450 mL. These investigators also found SI to be more useful in detecting hypo-perfusion than either HR or SBP alone.\textsuperscript{46} In another prospective study, investigators examined SI as a predictor of mortality among severely injured hemorrhagic shock patients and found SI to be predictive of mortality at the time of ED disposition.\textsuperscript{95} Despite the introduction of the SI in 1967 and repeated retrospective analysis and a few prospective studies, SI remains significantly underused in the United States and in a 2013 commentary published in Critical Care was described as “a potentially helpful decision aid”.\textsuperscript{96}

**Respiratory.** The variable selected to measure respiratory function was the need for intubation. Existing scales use respiratory rate as a variable for calculating trauma severity. The actual respiratory effort of the patient has the potential to be altered by several factors to include the need of EMS or ED personnel to protect the airway.\textsuperscript{97} If an endotracheal tube is inserted to protect the airway, the respiratory rate falls into a range of normal. Therefore, the need for intubation was selected as the variable to measure respiration.

**Tissue Perfusion.** Tissue perfusion variables included in this study were base deficit, serum lactate, serum bicarbonate, serum pH (arterial or venous, obtained at the time of admission to the ED) and serum glucose. Base deficit was first described as a guide to volume resuscitation in trauma by Davis and colleagues in a 1988 retrospective analysis of trauma patients.\textsuperscript{98} Additional retrospective studies done between 1990 and 1999 found base deficit to be a sensitive indicator of compensated shock and a marker of early mortality in trauma.\textsuperscript{55,99,100} In the first
decade of the twenty-first century, base deficit continued to demonstrate a significant contribution to predicting mortality in trauma patients.\textsuperscript{59,101-103} Since 2010, additional studies have shown base deficit to be strong indicator of shock in trauma.\textsuperscript{56,57} Base deficit as a predictor is limited to the first 24 hours under care. If the base deficit can be normalized during the first 24 hours of care, the mortality rate drops to only 9%.\textsuperscript{104}

Another equally powerful indicator of trauma mortality and shock severity is serum lactate. Several investigators have combined serum lactate and base deficit to predict trauma mortality and both have been found to be significant predictors of trauma mortality.\textsuperscript{58,62,70,105} Martin et al. found that while both base deficit and serum lactate were useful in identifying lactic acidosis and predicting mortality, increased lactate is more predictive than base deficit.\textsuperscript{62}

Serum lactate alone has long been used as a measure of lactic acidosis and has been associated with mortality related to hemorrhagic shock.\textsuperscript{22,106,107} More recently, investigators have begun looking at the possibility of obtaining serum lactate measures during the pre-hospital phase of care to earlier identify patients with occult hypo-perfusion. The existing studies have shown that the pre-hospital lactate is an important measure in identifying patients requiring earlier resuscitation.\textsuperscript{41,72}

Another marker of acidosis included in this analysis is pH. Kaplan et al. found pH to be a strong predictor of survivors and non-survivors in trauma.\textsuperscript{59} Serum bicarbonate was added as a variable as it does not require arterial blood gas and is a marker for acid-base status. Martin et al. found in a retrospective analysis comparing serum bicarbonate and arterial base deficit that serum bicarbonate provides equivalent information and may be substituted for base deficit as a predictive marker or guide for resuscitation.\textsuperscript{60,108} Glucose was selected as a variable because studies have shown glucose correlates well with lactate.\textsuperscript{63,66,109}
Anatomic Variables.

The anatomic variables chosen differentiate between blunt and penetrating injuries. Mechanism of injury has been established as an important predictive factor in trauma mortality. The EAST guidelines have listed both mechanism of injury and co-morbidities as important components of trauma triage. Mechanism of injury will be measured in this study by defining the injury as blunt, penetrating or both.

Specific aims

Specific Aim 1: To determine early markers of morbidity and mortality from among 1) pulse; 2) systolic blood pressure; 3) shock index; 4) need for intubation; 5) arterial base deficit; 6) serum lactate; 7) serum bicarbonate; 8) serum pH (arterial or venous); 9) blood glucose; 10) mechanism of injury (blunt trauma, penetrating trauma or a combination of both); and 11) the presence of comorbid conditions as reported in data to the National Trauma Data Bank among patients admitted to the Emergency Department with injuries from multiple trauma.

Methods

Design:

This study was a predictive retrospective patient record analysis carried out at the University of Kentucky Chandler Medical Center. The data were obtained from medical records of trauma patients meeting the inclusion and exclusion criteria.

Sample and setting:

The UK Chandler Medical Center is a Level I trauma center which serves as the regional resource center for the geographic area of northern and eastern Kentucky. To qualify as a Level I trauma center, UK must have at least 240 admissions each year with an Injury Severity Core of more than 15 treated by a panel of trauma surgeons.110
Inclusion criteria: The inclusion criteria for the study were that subjects be trauma patients aged 16 to 60 years of age seen at UK Chandler Medical Center from May 2011 to June 2013 with an Injury Severity Score of 16 or greater and with injuries consistent with potential for hemorrhagic shock. Injuries consistent with potential for hemorrhagic shock included long bone fractures, open fractures, penetrating trauma, blunt abdominal trauma, blunt chest trauma, and/or pelvic fractures. Patients presenting with a positive Focused Assessment with Sonography for Trauma (FAST) examination in the ED were included as were those patients admitted to the OR from the ED for hemorrhage control.

Patients age 16 to 60 were selected to encompass the range of adolescent and adult trauma patients that present while controlling for the physiologic variation seen in extremes of age in the very young and the older (greater than age 60 years) adult. The rationale for beginning the study in May of 2011 and ending in June of 2013 is to include two full years of trauma data that has been entered into the trauma data base at the University of Kentucky. The criteria of an injury severity score of 16 or greater is selected to ensure the sample will include those patients with the most severe injuries.111

The selection of injuries consistent with the potential for hemorrhagic shock includes long bone fractures open fractures, penetrating trauma, blunt abdominal trauma, blunt chest trauma, and/or pelvic fractures. Long bone fractures and pelvic fractures are associated with large amounts of blood loss.112,113 Patients presenting with a positive FAST examination in the ED were included because a positive FAST is suggestive of blood in the abdomen and is criteria for surgical exploration of the abdomen.
Exclusion criteria: Patients were excluded from the study if they presented to the ED with isolated head trauma or CPR in progress. Isolated head injuries are excluded because isolated head injury mortality is not associated with substantial hemorrhage.\textsuperscript{114}

A random list of patient records from the trauma registry for the selected time frame meeting the inclusion and exclusion criteria was provided by the UK Trauma Service Trauma Registrar and was filtered for those containing complete data. The trauma registry is a disease-specific collection of data elements describing the injury event, demographics, pre-hospital information, diagnosis, care, outcomes and cost of treatment for trauma patients.\textsuperscript{110}

We used a power analysis to determine the sample size of 500 for this study. With an alpha level of .05 and approximately 500 subjects, the power of the logistic regression model to detect an odds ratio as small as 1.8 was at least 85%. One way to obtain an odds ratio of this magnitude would be if the rate of mortality were 5% in one group and 9% in the other (e.g., groups defined by gender or age categories). Power analysis was done using nQuery Advisor (Elashoff, 1995-2005; Statistical Solutions Software).

A random list of 872 subjects was generated and after filtering for complete data, charts with complete data were be reviewed to achieve the final total sample size of 588. The data were entered by the Primary Investigator from the records by hand or where possible by electronic data transfer into a data spread sheet for evaluation.

**Measures:**

Predictor variables:

The physiologic variables included cardiovascular, respiratory and tissue perfusion variables. The cardiovascular variables of first recorded ED SBP, and HR were recorded. These measures are generally recorded with an automated blood pressure cuff and cardiac monitor. The
SBP and HR information were used to calculate the SI. Shock Index was calculated for each patient by dividing the recorded HR by the recorded SBP using a calculation function of SPSS.

The respiratory variable measured was indication for need for airway management and was recorded as a yes or no if the patient received endotracheal intubation prior to arrival in the ED or received endotracheal intubation in the ED.

The data used to measure tissue perfusion were base deficit, serum lactate, serum bicarbonate, serum pH and serum glucose. The initial laboratory data obtained on admission to the ED were used. The laboratory data recorded included the first arterial blood gas to obtain the arterial base deficit and pH. The first documented serum chemistry laboratory data were used to obtain the other labs.

The mechanism of injury was recorded as blunt injury or penetrating injury reported in the documentation. Co-morbidities were recorded as a yes if present and no if absent as documented in the record.

Outcome Variable. Mortality was the outcome for this study. Mortality was defined as death within 48 hours of admission to the ED as documented in the record.

Descriptive Variables. Demographic information: Patient age was recorded based on the date of birth of the patient and reflected the age of the patient at the time of injury. The patient’s gender was recorded based on the documentation in the medical record.

Procedures:

Institutional review board (IRB) approval was obtained by submission of the proposal to the UK IRB after approval by the doctoral committee. This study was deemed exempt by the IRB because the research involves no risk to the subject as it is a retrospective chart review and the information was recorded in such a manner that the subjects could not be identified directly.
or through identifiers linked to the subjects. After IRB approval was obtained, a random sample of medical records was obtained from the trauma coordinator at University of Kentucky Chandler Medical Center to select records for patients meeting inclusion criteria. A list of patient records for the selected time frame who met the inclusion and exclusion criteria were provided by the UK Trauma Service Trauma Registrar. A random list was generated and medical records with complete data for the measured variables were included in the analysis. The data were entered by the Primary Investigator from the records by hand or where possible by electronic data transfer into a data spread sheet.

**Data management and analysis:**

Sample characteristics were analyzed using descriptive statistics. Independent t tests were performed for continuous normally distributed measures and chi-square tests were performed for categorical measures as appropriate to describe the two groups and to compare differences between the two groups. Fisher’s exact test was used to compare differences between mechanisms of injury since the numbers of subjects with penetrating injuries was small resulting in more than 20% of the cells in the cross-tabulation table with expected counts less than five.

We used logistic regression to test the following variable sets, entered as successive blocks: 1) age and gender; 2) cardiovascular variables; 3) respiratory variable; 4) tissue perfusion variables; 5) mechanism of injury; and 6) comorbidity variables as predictors of mortality within 48 hours of ED admission. Forced variable entry was used in order to provide simultaneous control for all variables. The assumptions of logistic regression were tested and none were violated. An alpha of 0.05 was set a priori to determine significance, and all analyses were performed using SPSS, release 23.0.115

**Results:**
Characteristics of Participants

Participants (n = 560) surviving more than 48 hours were primarily female (68%) with a mean age of 36.8 ± 12.6 years. Participants (n = 28) surviving 48 hours or less were also primarily female (64.3%) with a mean age of 41.1 ± 12.4 years and an ISS of 32.3 ± 14.7. There was no significant difference between age and gender in the two groups (Table 4.1).

Physiologic Variables

The physiologic variables for each group were compared and several were found to be significantly different between the two groups (Table 4.2). The physiologic variables measuring tissue perfusion that were significantly different between the two groups included base deficit (alive at 48 hours, -3.8 ± 4.5; dead at 48 hours, -11.1 ± 8.3; P < 0.001), serum bicarbonate (alive at 48 hours, 21.8 ± 3.9; dead at 48 hours, 17.8 ± 5.6; P = 0.001), serum glucose (alive at 48 hours, 151.8 ± 55.5; dead at 48 hours, 207.1 ± 89.2; P = 0.003), and serum pH (alive at 48 hours, 7.3 ± 0.1; dead at 48 hours, 7.1 ± 0.2; P < 0.001).

The physiologic variables measuring cardiovascular function that were significantly different between the two groups were SBP (alive at 48 hours, 130.5 ± 22.5; dead at 48 hours, 108.0 ± 48.5; P = 0.021) and SI (alive at 48 hours, 0.8 ± 0.2; dead at 48 hours, 1.0 ± 0.4; P = 0.031). Heart rate was not different between the groups.

The physiologic variable measuring respiratory function was need for intubation and it was significantly different between the groups (alive at 48 hours, 97 intubated (17.3%); dead at 48 hours 21 intubated (75.0%; p < 0.001).

Mechanism of Injury and Comorbidity Variables

The remaining two variables, mechanism of injury and presence of comorbidity were compared as well (Table 4.3). Mechanism of injury was compared using Fisher’s Exact Test and
was not significantly different between the groups. Interestingly, comorbidity was significantly more common in the group alive at 48 hours (alive at 48 hours, 483 (86.3%); dead at 48 hours, 19 (67.9%); \( P = 0.007 \)).

**Predictors of Mortality within 48 Hours.**

We used logistic regression to determine independent predictors of mortality (Table 4). The model fit was evaluated using the Omnibus Tests of Model Coefficients (final step p value < 0.001) and the Hosmer-Lemeshow test (final step p value = 0.715). In the final model, 96.3% of all patients were correctly classified, but while 99.6% of patients who lived were classified correctly, only 24% of patients who died were correctly classified (6 of 24 who died were correctly classified and 19 of 24 who died were incorrectly classified).

As can be seen in the final model, which contains all variables, only endotracheal intubation, the respiratory variable, was predictive of the outcome. Patients who required endotracheal intubation had 6.5 times greater risk of dying within 48 hours of ED admission than those who were not intubated.

**Discussion:**

In this analysis, the only predictor for 48-hour mortality was need for intubation. With that finding, a subsequent literature review was conducted and we found Hannan et al. published a 2000 study that examined intubation as a predictor of mortality in trauma patients.\(^{116}\) The authors reported that the observed and predicted mortality rates for intubated patients (30.98%) were identical to two decimal places.\(^{116}\) The conclusion from the Hannan at al. study was similar to the findings in this analysis, that the need for intubation is predictive of worse injury/illness than in non-intubated patients.\(^{116}\) In clinical practice, the need for intubation indicates a worsening condition and may well initiate transfer to the Intensive Care Unit, if the patient is not
already there for care. The impetus for the Hannan et al. study was the desire to more accurately predict mortality for intubated patients without using verbal response and respiratory rate. In reviewing potential variables for this study, the issue of accounting for the variable of respiratory rate was addressed by using need for intubation as a surrogate marker. Another study examining mortality after emergency department intubation reported that mortality after ED intubation was relatively high (27%). Since the need for intubation encompasses a number of issues potentially associated with mortality, the need for intubation alone is a poor marker to broadly predict mortality. In this study, almost every living patient was correctly classified, while only 24% of those who died were correctly classified, so the usefulness of the model is limited.

There were a number of physiologic variables associated with alive or dead in the bivariate analysis, pH, BD, bicarbonate, glucose, SBP, and SI. These findings are consistent with the findings of other studies performing bivariate analysis of these variables reported in the literature review. The independently predictive ability of each variable diminished when considered in the company of other variables. It is difficult to predict negative outcomes with multiple variables, opening the opportunity for future research exploring other possible outcome measures.

The results of this study were first compared with national averages (NTDB) over the same time (May 2011 to June 2013) period in terms of mortality (3.43%) and gender (about 63% male). The most interesting finding in the comparison was gender of the subjects. According to all trauma demographics reviewed, trauma predominately affects males. Females were the predominant trauma patients in this study.

Limitations:
All scientific studies are subject to limitations and retrospective analysis has specific limitations. This specific study has limitation associated with retrospective analysis such as variations in treatment, variations in assessment instruments and reporting, and variables assessed by multiple individuals in non-standard ways. The findings of this study are also limited in that it was a single site study.

**Conclusion:**

We found only need for intubation as a predictor of 48-hour mortality when placed in a predictive model using multiple variables. The bivariate analyses support existing literature, but a comprehensive predictive model using multiple variables remains elusive.
Table 4.1 Characteristics of Participants (n = 588)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alive at 48 hours</th>
<th>Dead at 48 hours</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 560 (95.2%)</td>
<td>n = 28 (4.8%)</td>
<td></td>
</tr>
<tr>
<td>Age – years</td>
<td>36.8 ± 12.6</td>
<td>41.1 ± 12.4</td>
<td>P = 0.081</td>
</tr>
<tr>
<td>Gender – Male</td>
<td>179 (32.0%)</td>
<td>10 (35.7%)</td>
<td>P = 0.678</td>
</tr>
</tbody>
</table>
Table 4.2 Physiologic variables (n = 588)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alive at 48 hours n = 560 (95.2%)</th>
<th>Dead at 48 hours n = 28 (4.8%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue Perfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum base deficit</td>
<td>-3.8 ± 4.5</td>
<td>-11.1 ± 8.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum bicarbonate</td>
<td>21.8 ± 3.9</td>
<td>17.8 ± 5.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum glucose</td>
<td>151.8 ± 55.5</td>
<td>207.1 ± 89.2</td>
<td>0.003</td>
</tr>
<tr>
<td>pH</td>
<td>7.3 ± 0.1</td>
<td>7.1 ± 0.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiovascular Function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse</td>
<td>99.5 ± 23.0</td>
<td>101.1 ± 38.1</td>
<td>0.833</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>130.5 ± 22.5</td>
<td>108.0 ± 48.5</td>
<td>0.021</td>
</tr>
<tr>
<td>Shock index</td>
<td>0.8 ± 0.2</td>
<td>1.0 ± 0.4</td>
<td>0.031</td>
</tr>
<tr>
<td>Respiratory Function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endotracheal intubation</td>
<td>97 (17.3%) yes</td>
<td>21 (75.0%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Table 4.3 Mechanism of injury and comorbidity variables (n = 588)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alive at 48 hours</th>
<th>Dead at 48 hours</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 560 (95.2%)</td>
<td>n = 28 (4.8%)</td>
<td></td>
</tr>
<tr>
<td>Mechanism of injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blunt</td>
<td>511 (91.3%)</td>
<td>24 (85.7%)</td>
<td>0.306</td>
</tr>
<tr>
<td>Comorbidity – yes</td>
<td>483 (86.3%)</td>
<td>19 (67.9%)</td>
<td>0.007</td>
</tr>
</tbody>
</table>
Table 4.4 Logistic Regression Model for Predictors of Mortality within 48 hours of Admission to the Emergency Department

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>Exp B</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block 1, model p = 0.41, Hosmer-Lemeshow p = .357</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.021</td>
<td>1.021</td>
<td>0.989 – 10.54</td>
<td>0.203</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.456</td>
<td>1.164</td>
<td>0.477 - 2.844</td>
<td>0.391</td>
</tr>
<tr>
<td>Block 2, model p = 0.015, Hosmer-Lemeshow p = 0.550</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.027</td>
<td>1.028</td>
<td>0.994 – 1.063</td>
<td>0.112</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.412</td>
<td>1.510</td>
<td>0.589 – 3.875</td>
<td>0.391</td>
</tr>
<tr>
<td>Shock Index</td>
<td>4.242</td>
<td>66.575</td>
<td>0.992 – 4879.009</td>
<td>0.050</td>
</tr>
<tr>
<td>Heart rate</td>
<td>-0.016</td>
<td>0.984</td>
<td>0.945 – 1.024</td>
<td>0.420</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.017</td>
<td>1.017</td>
<td>0.977 – 1.059</td>
<td>0.415</td>
</tr>
<tr>
<td>Block 3, model p &lt; 0.001, Hosmer-Lemeshow p = 0.479</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.015</td>
<td>1.015</td>
<td>0.980 – 1.052</td>
<td>0.408</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.095</td>
<td>1.099</td>
<td>0.406 – 2.979</td>
<td>0.853</td>
</tr>
<tr>
<td>Shock Index</td>
<td>3.172</td>
<td>23.853</td>
<td>0.274 – 2072.734</td>
<td>0.164</td>
</tr>
<tr>
<td>Heart rate</td>
<td>-0.013</td>
<td>0.987</td>
<td>0.947 – 1.028</td>
<td>0.518</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.010</td>
<td>1.010</td>
<td>1.010 – 0.970</td>
<td>0.622</td>
</tr>
<tr>
<td>Endotracheal intubation</td>
<td>2.385</td>
<td>10.859</td>
<td>4.287 – 27.508</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Block 4, model p &lt; 0.001, Hosmer-Lemeshow p = 0.744</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.011</td>
<td>1.011</td>
<td>0.973 – 1.051</td>
<td>0.580</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.080</td>
<td>1.084</td>
<td>0.353 – 3.329</td>
<td>0.888</td>
</tr>
<tr>
<td>Predictor</td>
<td>Coefficient</td>
<td>Standard Error</td>
<td>Lower 95% CI</td>
<td>Upper 95% CI</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------</td>
<td>----------------</td>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Shock Index</td>
<td>2.861</td>
<td>17.476</td>
<td>0.097 – 3136.332</td>
<td>0.280</td>
</tr>
<tr>
<td>Heart rate</td>
<td>-0.019</td>
<td>0.981</td>
<td>0.937 – 1.029</td>
<td>0.434</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
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<td>1.011</td>
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*Block 5, model p < 0.001, Hosmer-Lemeshow p = 0.711*

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### Block 6, model p < 0.001, Hosmer-Lemeshow p = 0.715

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<td>Presence of comorbidities</td>
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CHAPTER FIVE

Conclusions

Background and purpose:

The overall purpose of this dissertation was to identify early markers of occult tissue hypoperfusion in patients with multiple trauma injuries. The following manuscripts were completed prior to testing for early markers of mortality in patients with multiple trauma injuries: 1) a review of the literature was to identify early surrogate markers of tissue perfusion in trauma injuries and 2) a retrospective analysis to compare SI to ISS as a predictor of mortality within 48 hours of trauma injuries. Based on these findings, a retrospective analysis was conducted to identify early markers of mortality within 48-hours in patients with multiple trauma injuries.

Advancing knowledge in trauma care is important because trauma injuries are the fifth leading cause of death in the US and one of the primary causes of injury related death is shock resulting from hemorrhage.\textsuperscript{23,120} Hemorrhagic shock is difficult to recognize in early stages, early shock is often masked by compensatory mechanisms such as catecholamine release or confounded by pain, medications, or resuscitation efforts. Evaluation of the patient for injuries is conducted while compensatory mechanisms are at work, masking early compensated shock.\textsuperscript{2}

The search for a multi-variable model to earlier predict occult tissue hypoperfusion to guide care has long been elusive.\textsuperscript{121} The goal of this dissertation was to identify markers to create that model, but after including the proposed variables, only the need for intubation remained as a significant predictor of 48-hour mortality.

The goal of the main study in this dissertation was to identify the markers of trauma mortality related to occult tissue hypoperfusion that should be included in a multi-variable model. The assumptions included the relationship between unrecognized occult tissue
hypoperfusion and trauma mortality. It is important to take into consideration the fact that trauma patients will often have multiple, complex injuries that may not fully manifest until later in the course of treatment. Hemorrhage due to penetrating trauma injuries may be obvious, while more insidious internal hemorrhage caused by blunt trauma may be masked by compensatory mechanisms, making triage difficult.

**Summary of findings**

Chapter two was a review of the available trauma literature examining early surrogate markers of tissue perfusion in trauma injuries. The articles reviewed combining hemodynamic measures and acid-base measures associated worsening SI and increasing BD and serum lactate to need for transfusion and need for damage control surgery.\(^{53,69,71,72}\) No clear picture emerged to identify one specific measure of acid-base status, particularly metabolic acidosis.

The measure of hemodynamic stability that emerged across all the studies evaluated was SI. Since 1967, SI has been examined as an instrument to identify shock states and is consistently more accurate than either HR or SBP alone.\(^{122}\) None of the English language articles reviewed provided a satisfactory pathophysiologic explanation of SI. Shock index has not been widely adopted for use in trauma or other specialties evaluating patients for hypovolemic shock or distributive shock, despite a strong record of retrospective data analyses finding SI to be superior to either HR or SBP alone in early identification of shock states. While recent studies like the ProCESS study examined SI as a guide to fluid resuscitation, SI as a guide failed to improve mortality.\(^{123}\) In the Berger et al. study, SI was found to be as sensitive as the systemic inflammatory response syndrome (SIRS) criteria in identifying sepsis risk in ED patients.\(^ {124}\) Despite this work, SI remains underused as a guide to resuscitative interventions. This underuse
opens the opportunity for well-designed, prospective studies that validate the use of SI to guide resuscitation.

Chapter three was a pilot study performed examining the NTDB to compare SI to ISS as a predictor of mortality. While SI has been found to be an easily calculated clinical marker for early shock, it has not been compared to ISS as a predictor of mortality. Mortality was conceptually linked to shock as progressive shock leads to organ dysfunction, progressive tissue death at the cellular level, leading ultimately to multiple organ failure and death. In that study, SI was found to be a stronger predictor of mortality than ISS. Injury Severity Score has traditionally been the gold standard for measuring and comparing injury severity for research and quality measures, but is not calculated until hospital discharge. Shock index can be easily calculated in real time along the injury or illness continuum.

While this study confirmed the value of SI in recognition of shock states, it did not evaluate resuscitative interventions associated with the worsening shock state. The study merely examined SI as a measure of shock leading to death within 48 hours of trauma injuries. Future work should include evaluation of the response to interventions while measuring shock state severity using SI. This study was also a retrospective analysis of a large data base and could be done as an observational study to evaluate response to interventions as measured by SI.

Chapter four was a retrospective analysis to first identify early markers of 48 hour mortality in trauma, then from those markers, identify a model using multiple variables to identify 48-hour mortality in trauma. We found SI, SBP, pH, BD, and serum bicarbonate were all associated with alive or dead within 48 hours. These findings are consistent with findings in the literature review in Chapter Two. No studies have been published to identify a gold standard to measure worsening metabolic acidosis, providing an opportunity for further research to
determine if there is indeed a gold standard or if any of the several acid-base measures available will provide adequate information to guide resuscitation. Again, a well-designed, prospective study to validate the use of acid-base measures to guide resuscitation interventions is needed.

In the study, respiratory rate was not evaluated, rather the need for intubation was a surrogate for abnormal respiratory rate. The rationale was that if the respiratory rate is abnormal, either high or low, intubation is indicated to protect the airway and facilitate ventilation. However, in the logistic regression examining multiple variables, only need for intubation was a predictor of death within 48 hours. This finding provides the opportunity to return to the use of counted respiratory rate as the respiratory variable or to remove the respiratory variable all together. Additional work should be done to further examine this finding.

There remain many questions to be answered, many that can only be answered with real-time, longitudinal studies as well as clinical trials exploring potential early interventions. These findings may well have application to other shock states and the future work will be done to continue the effort to identify a model to earlier identify occult tissue hypoperfusion in trauma.
References:


89. Surgeons ACo. National Trauma Data Bank NTDB Research Data Set Admission Year 2009. Chicago, IL: American College of Surgeons; 2009.
94. Trunkey DD. Trauma. Accidental and intentional injuries account for more years of life lost in the U.S. than cancer and heart disease. Among the prescribed remedies are improved preventive efforts, speedier surgery and further research. Scientific American 1983;249:28-35.


Vita

Kathryn Marie Moore, DNP, PhD candidate, APRN-BC, CNE, FCCM

Place of Birth: Lawrenceburg, TN

Address: 2349 Crestcliff Drive
Tucker, GA 30084

Education:

<table>
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<td>University of Kentucky</td>
<td>Certificate</td>
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<td>Clinical &amp; Translational Science</td>
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<tr>
<td>Case Western Reserve Univ.</td>
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Professional Experience:

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<td>2014 – 2016</td>
<td>Acute Care Nurse Practitioner</td>
<td>Northeast Georgia Medical Center, Gainesville, GA</td>
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2012 – Present  Associate Professor – Clinical
Marcus Stroke and Neuroscience Center, Grady Memorial Hospital, Atlanta, GA
Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, GA
Emory Center for Critical Care NP/PA Residency Program Atlanta, GA

2012 – 2015  Education and Simulation Coordinator

2011-2013  Chief Nurse
332nd Medical Brigade, US Army Reserve, Nashville, TN

2006-20011  Assistant Chief Nurse
4203rd US Army Hospital, US Army Reserve, Nashville, TN

2008–2012  Assistant Professor
University of Kentucky, College of Nursing, Lexington, KY

2008–2012  Acute Care Nurse Practitioner
University of Kentucky Chandler Medical Center, Lexington, KY

2008–2012  Adult Nurse Practitioner
Mission Lexington Medical Clinic, Lexington, KY

2007-2008  Assistant Professor
Austin Peay State University, School of Nursing, Clarksville, TN

2006-2008  Adult Nurse Practitioner
Middle Tennessee Hematology & Oncology, Nashville, TN

2003-2008  Clinical Research Specialist & Flight Nurse
Air Evac EMS, Inc., West Plains, MO

2005-2006  Assistant Chief Nurse & Acute Care Nurse Practitioner
10th Combat Support Hospital, Baghdad, Iraq

2005-2006  Assistant Chief Nurse & Acute Care Nurse Practitioner
10th Combat Support Hospital, US Army, Baghdad, Iraq

2004-2005  Clinical Head Nurse ICU
801st Combat Support Hospital, US Army Reserve, Chicago, IL

1997-2005  Adjunct Faculty
Vanderbilt University, School of Nursing, Nashville, TN
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<td>Clinical Head Nurse ICU</td>
<td>330th Combat Support Hospital, US Army Reserve, Millington, TN</td>
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<td>2003</td>
<td>Acute Care Nurse Practitioner &amp; Chief Nurse</td>
<td>330th Combat Support Hospital, US Army Reserve, Operation New Horizon, Base Camp Clinic, Belize, CA</td>
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<td>2002-2003</td>
<td>Director of Education and Research</td>
<td>330th Combat Support Hospital, Army Trauma Training Center, US Army, Ryder Trauma Center, Miami, FL</td>
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<td>2000-2003</td>
<td>Assistant Professor</td>
<td>Middle Tennessee State University, School of Nursing, Murfreesboro, TN</td>
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<td>2000-2003</td>
<td>Acute Care Nurse Practitioner &amp; Staff RN</td>
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<td>2002</td>
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<td>Alvin C. York Veteran’s Administration Medical Center, Emergency Department, Murfreesboro, TN</td>
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<td>Comprehensive Care Center, Regional HIV &amp; AIDS Clinic, Nashville, TN</td>
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1987-1989 Nursing Supervisor Life Care Center, Skilled Nursing Facility, Nashville, TN
1985-1987 Staff Nurse West Side Hospital, Surgical ICU, Nashville, TN
1984-1987 Staff Nurse Baptist Hospital, Medical ICU, Nashville, TN

Award and Honors:
Year Name of Award
2016 National Center for Emerging and Zoonotic Infectious Diseases Award for Partnering – Domestic, Centers for Disease Control
2015 Alumni Award for Excellence, Frances Payne Bolton School of Nursing Case Western Reserve University
2014 Health Care Heroes – Military Service Award, Atlanta Business Chronicle
2014 Finalist March of Dimes Nurse of the Year – Academic Education
2014 Fellow of the American Academy of Critical Care Medicine
2013-14 Fellow, Leadership for Academic Nursing Program, American Association of Colleges of Nursing, Washington, DC
2012-2015 Society of Critical Care Medicine Presidential Citation
2011 Vanderbilt University School of Nursing, Alumni Award for Clinical Achievement in Nursing
2011 Inducted into the Greek Alumni Hall of Fame, University of Kentucky
1999 Graduate Nursing Educator of the Year, Tennessee State University, College of Nursing

Publications:
Original Articles in Peer-Reviewed Journals


**Book Chapter**


**Presentations:**

**International Presentations (as APA citations, in reverse chronological order)**


**National Presentations**


Moore, K.M. (2015, September). *Deadly Triad of Trauma*, Podium presentation at the 2015 Region 6 Conference of the American Association of Critical Care Nurses, Atlanta, GA.


Moore, K.M., (2015, April). *Moving beyond silos to the next frontier: Simulation in inter-professional education.* Keynote address for the National Simulation Users Network Meeting, Atlanta, GA.


**Local, State, and Regional Presentations (as APA citations, in reverse chronological order)**

Moore, K.M. (2015, February). *Dare to innovate.* End note address for the 2015 Georgia Association of Nursing Education Annual Conference, Buford, GA.
Jessie M. Clark Middle School, Lexington KY.

Moore, K.M. (2010, October). *Ballistic injuries in trauma*. Presentation sponsored by UK Health Care Physician Liaison Group to Harrison Memorial Hospital, Cynthiana, KY.