HYPOVOLEMIC SHOCK: QUANTIFYING THE RISK OF HYPOTENSION AND HYPOTHERMIA IN SEVERELY INJURED TRAUMA PATIENTS

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Submitted to the Graduate Faculty of

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2005

UNIVERSITY OF PITTSBURGH

Graduate School of Public Health

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August 2, 2005

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Abstract

Public Health Significance: Trauma represents the leading cause of mortality for young adults in their most productive years and incurs substantial short and long term disability. Death from trauma results in an annual loss of 492 years of productivity per 100,000 and costs $230 million a day. Most of these mortality and related medical expenses incurred early during the critical care unit stay. Improving the outcome during ICU phase will have substantial effects on trauma mortality and morbidity.

Subjective: Hypovolemic shock is a major consequence of trauma and usually represented with hypotension and hypothermia. Despite the documented risk of hypotension and hypothermia in increasing mortality and morbidity, that risk has not been practically quantified. In this study, we assessed the effect of hypotension and hypothermia severity on the outcome during first and second ICU days.

Methods: Trauma patients admitted to University of Pittsburgh trauma center during 1999-2000 were reviewed (n=783). Data on patients' demography, injury, vital signs, diagnosis, and outcome have been collected. The lowest recorded systolic blood pressure and duration in minutes of all episodes of SBP$\leq$ 90 mm Hg were collected. The lowest temperature and duration in minutes of all episodes of hypothermia ($\leq$36 °C) were also obtained. The outcome variable was death during hospitalization and length of ICU stay. Relative risk, Pearson Chi2, t-test, regression, and survival analysis were used.

Results: Patients with hypotension during the first 48 hours in ICU and hypothermia during the first 24 hours of ICU had an increased risk of mortality. The length of ICU stay increased upon the increase in the severity of hypotension and hypothermia. Each 5-degree reduction in SBP and 1°C reduction in temperature increased the risk of mortality by 1.37 and 1.51 respectively. Each 1-hour increase in SBP and temperature increased the mortality by 1.22 and 1.10 respectively.

Conclusion: A brief episode of hypotension during ICU day one was associated with increased mortality and mortality. For patients who survived ICU day one, hypotension in ICU day two predicts the outcome better than hypotension records of ICU day one. Hypothermia added significant information beside hypotension in quantifying the risk of shock. Hypotension and hypothermia should not only be treated promptly but also should be prevented.

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ACKNOWLEDGMENTS

I would like to thank all committee members for their support and cooperation during the dissertation preparation. Without their guidance, this work might not have been completed so thoroughly or as pleasantly. I would like to specially thank my advisor, Dr. Thomas Songer, for his availability and encouragement. I would like to thank my mentor Dr. Brian Harbrecht the director of University of Pittsburgh Trauma Center, for his kindness and excellent ability in training. My experience in research was directly related to his guidance and support. I also would like to thank the department of surgery at University of Pittsburgh headed by Dr. Timothy Biliar for providing an excellent academic environment that lead me for my scholarly accomplishment. I would like to thank all who supported the production of this work and all the technical related help. I also thank my family for their emotional support throughout the time preparing for this work.

1. INTRODUCTION

Trauma is a major public health burden globally and has emerged as a major public health problem since the early 1960s (1,2). Trauma in the USA represents the leading cause of death for young adults in their most productive years and incurs substantial short and long term disability. Death from trauma results in an annual loss of 492 years of productivity per 100,000 persons and costs $230 million a day. Most of these fatalities and related medical expenses are incurred early during stays in Critical Care Units (ICU). These severe injuries are among the most significant public health problems, not only in sheer magnitude, but also as compared with other problems. It has been documented by the Centers for Disease Control and Prevention (CDC) that injuries kill more American children, adolescents, and young adults than any other cause. In addition to the above described mortality, trauma is also the leading cause of disability in the United States where about 50 million injuries occur per year, almost 50% of which necessitate medical attention. In this regard, trauma might be considered an epidemic or perhaps a pandemic. The impact of trauma goes beyond mortality and morbidity to encompass the social and economic aspects of the society. Severe injuries and trauma are the leading cause of loss of working years and are responsible for more related loss than all cancers and heart diseases combined (3,4).

Trauma is defined as bodily injury severe enough to pose a threat to life or limb. Trauma results in significant physiological changes in nearly all body organs and systems. Many responses occur with traumatic injury such as fear, pain, hemorrhage, hypovolemia, hypoxemia, hypercarbia, acidosis, and other events related to tissue injury responses. Many other physiological reactions are also activated systematically and on multiple levels. Typically, reaction to trauma is proportional to the extent of injury and to related host factors. Trauma demands critical care attention and in many cases, multiple and serious surgical interventions on a large scale. Critical illness and death can result when the stress response is sustained after severe trauma.

2.1. Incidence of trauma

Many studies have attempted to examine the incidence and death rates of trauma in certain parts of the nation but have produced a various rates and percentages. Such variation was expected since trauma depends on the locale and demographic specifications. Trauma may reach 151 per 100,000 population. The related death rate averages 31 per 100,000 population, with variation according to race: 56% in Blacks, 34% in Hispanics, 26% in Caucasians, and 12% in Asians. (5). In another large study of 56,000 trauma patients, 73.5% survived and 26.5% died. Of those 26.5% who died, 60% died at the scene of injury and 40% at the hospital (6).

2.2. The emergence of trauma

Today, various events have been recognized as important factors leading to trauma, such as motor vehicle crashes, falls, injuries from firearms or from other acts of violence, and fire-related injuries. Trauma can be classified technically as injury that is blunt or penetrating. Motor vehicle crashes account for more than half of all deaths from non-intentional causes in the US. Injury increases in severity by 300% to 500% in crashes involving ejection. In the case of falls, victims are frequently elderly with co-morbidities affecting the outcome of the trauma.

Pedestrian trauma poses a high fatality risk since all energy related to vehicle speed, weight, and structures are absorbed by the victim's body. Penetrating trauma differs from the above blunt trauma since objects that penetrate the body cut, disrupt, damage, and bruise tissue. In general, all body parts are at risk of trauma and no trauma injury should be neglected.

2.3. From trauma to shock

Trauma causes shock. The American College of Surgeons defines shock as a circulatory system abnormality resulting in inadequate organ perfusion and inadequate tissue oxygen delivery (7). Shock has been recognized as an important pathophysiologic element in surgery and trauma. In this concern, shock is undoubtedly a pathologic condition rather than a disease unto itself. When the loss of blood is the main cause of shock it is expressed as hypovolemic shock. Shock is a complex event of various and combined etiologies involving not only reduction in tissue perfusion but also changes in the host's metabolic, inflammatory, and immune reactions.

The heart and blood vessels make up what is called the "Vascular Container." The body's blood is contained within this system. To function properly, this system must be filled with blood and pumped efficiently. In the normal condition prior to hypovolemic shock, venous blood returns to the heart adequately to maintain the cardiac output. Blood volume is maintained in the vascular system by the pumping action of the heart and the homeostatic function of the kidneys. In the event of acute hemorrhage, a decrease in intravascular volume will take place and quickly lead to a decrease in venous return to the heart. Such decrease will cause a decreased ventricular filling and a reduction in stroke volume (amount of blood pumped by the heart per minute). This decrease in cardiac output will cause a decrease in blood pressure and, if that decrease progressed further, will inevitably result in inadequate tissue perfusion (or hypoperfusion).

Hemorrhagic shock can be classified as non-progressive (or compensated) and progressive (or decompensated) shock. The first is adaptive and the second is a nonadaptive phase, ending in irreversible shock. In the compensated phase of shock, a redistribution of blood flow with microcirculatory response allows the body to adapt to the regional hypoperfusion with all related neuroendocrine responses. Among these early responses is the cardiovascular compensatory mechanism. In that mechanism, both heart rate and peripheral vascular resistance increase to maintain systemic blood pressure. If the blood loss continues beyond the early compensating mechanisms, blood pressure will continue to fall and will no longer sustain body demand.

In the decompensated phase, organ ischemia starts to take place, which will activate inflammatory and immune reactions, leading to capillary injury, irreversible cellular injury, and eventually, death. The decompensated stage can also initiate biochemical changes all over the body in the case of non-treatment. Due to decrease in tissue perfusion and oxygenation, body cells start to undergo many alterations in their functions. At the level of the Krebs cycle and due to shortage of substrate, pyruvate begins to shunt into the anaerobic pathway causing an increase in lactic acid production. The above process causes intracellular lactic acidosis and progress to a systemic level. The generalized metabolic acidosis causes further myocardial depression and alteration in vascular permeability, allowing fluid to leak from capillaries and causing as a result a further increase in the resistance to flow. Tissue hypoxia will deepen, causing a release of many vasoactive agents and myocardial depressants. At this stage, a severe shock is at a complete representation where disseminated intravascular coagulation is about to occur, causing further damage and hemorrhagic diasthesis. Cardiac output is further declining and irreversibly causing further endothelial damages. The circumstances at this point are very opportune for infection and septicemia. Organ failure starts to occur to most body systems (respiratory, renal, hepatic, gastrointestinal, etc) one after another and death might happen shortly at this point.

2.4. The incidence of hypovolemic shock

A study performed in Scotland by Ledingham McA. et al, 1974, looking for incidence of shock in a general hospital has found that that 21% of shock patients were related to hemorrhage due to trauma, with a 61% mortality rate (8). Those with hypovolemia due to causes other than hemorrhage comprised 65% of the total, with a 29% mortality rate. It is worthy of mention that some patients might fit into more than one category or might develop an additional kind of shock during hospitalization.

The prevalence of hypovolemic shock varies according to many factors, including the definition used for hypovolemic shock, underlying causes, and the population studied, as shown in the above examples. Those trauma patients who do not survive injuries due to shock may reach 56%. Such high mortality relates to severity of injury, underlying diseases, other co-morbidities, and the management of such cases in all related stages of medical care. From another prospective, the prevalence of hypovolemic shock depends on level of care and hospital locale. In general, trauma patients are predominantly at extreme risk of hypovolemic shock, especially with penetration injuries. Determining the prevalence and incidence of shock requires a precise description of the indicated population.

2.5. Incidence of hypotension and hypothermia

The incidence of hypotension and hypothermia in trauma patients is very significant and is often associated with high morbidity and mortality (9,10, 11). It has been shown that hypotension (systolic blood pressure, < 90 mm Hg) was among the admission variables associated with the highest relative risks of death in patients 65 years and older who had sustained blunt trauma (9). Hypothermia is associated with more severe injuries of the limbs and central hypoxia (12). It is well documented that the incidence of hypothermia in trauma patients is significantly high and independent of the month of admission (11). Many risk factors determine the severity of hypothermia in trauma, including extrication and transport time, severity of hemorrhage, extent of head injury, and the presence of drugs and alcohol in the trauma victim's blood. The incidence of hypothermia among injured patients on admission was 66% according to one study (13). That incidence was 57% from the time of injury until the end of primary operative procedures (14).

2.6. Significance of hypotension in shock morbidity and mortality

It has been proven that a hypotension or systolic blood pressure < 90 mm Hg is one of the variables closely associated with the highest relative risks of death in blunt trauma patients (9). Pre-hospital hypotension has been proven as a clinical predictor of outcome even in the face of normal ER SBP (15). That study showed mortality of 12% in the ER and 32% later when hypotension was present at both pre-hospital and ER settings. When the prehospital record showed the presence of hypotension even with normal SPB, mortality reached 2% in the ER, with 14% mortality later during hospital stay. When hypotension was detected only in the ER and was normal in prehospital records, mortality reached 12% in the ER and 15% later (10).

Although prolonged occult hypoperfusion has been associated with a worsened outcome (16), reperfusion after shock is also associated with production of endogenous oxidants that cause cytotoxicity and activate the inflammatory response (17). This process might take days after the initial traumatic injury and shock; during that period, a disseminated injury may occur due to release the of cytokines, proteases, and other additional oxidants. Death occurring more than 12 hours after injury relates primarily to occult hypoperfusion and multiple organ failure, which continue to pose a risk for days and weeks after the traumatic injury (18, 19). Such factors may suggest a great necessity to update the severity measures of shock to accurately predict outcome. Many studies connected the temporal physiological changes of shock and circulatory dysfunction with the outcomes through invasive and non-invasive methods of monitoring during the early hours and days of trauma and shock (20, 21, 22). One study showed that 84% of patient's mortality occurred during the first 48 hours after injury, 15% occurred between 2-7 days after injury, and only 11% thereafter (23). Many factors interact in the process of shock and related resuscitation. These factors can be grouped into three categories: injury severity and related injury mechanism, host-related factors, and resuscitation-related issues.

2.7. Significance of hypothermia in shock mortality and morbidity

Hypothermia is one of the major manifestations and frequent complications of hemorrhagic shock in trauma patients (24). Since hypothermia is associated with decreased cerebral blood flow and oxygen requirement, reduced cardiac output, and decreased arterial pressure, it can also affect the outcome of trauma and interfere with the course of treatment (25). One major concern in this regard is whether traumatic hypothermia relates to the shock itself or to the process of resuscitation. Animal experiments have shown that changes in systolic blood pressure are associated with changes in core temperature during hemorrhage and resuscitation, indicating that both hypotension and hypothermia are related to the pathophysiology of shock. (26). Many other experimental data indicate that hypothermia should be restored and maintained during resuscitation after trauma and hemorrhage (27). Hypothermia in injured trauma patients is usually underestimated. A study of a large cohort of 642 shows that patients with severe or even moderate injury are less likely to have their temperature measured (64%) than those with mild injury severity (79%) (28). The incidence of hypothermia (temperature <36C) among those with recorded temperature (77% of the above cohort) was 10 %.

In the above, we have highlighted the importance of trauma and how trauma leads to shock. We have described the importance of hypotension and hypothermia in the process of hypovolemic shock. In the following papers, an attempt has been made to quantify the risk of hypertension and hypothermia.

2.8. Three papers of this dissertation

Paper 1

- **Hypothesis**
  - An increase in the duration of hypotension during ICU day one would be associated with increased mortality & morbidity during the course of hospitalization in severely injured patients.

- **Background and rational**
    - Many previous studies have included a substantial number of moribund patients that died early from severe injuries despite sound and timely care.
    - Although noting the presence or absence of hypotension, these studies have failed to account for the magnitude of shock insult in the first and other subsequent days.

Paper 2

- **Hypothesis**
  - Hypotension (depth and duration) on ICU day 2 in severely injured patients is a predictor of adverse outcomes manifested in morbidity and mortality during the course of hospitalization.
- **Background and rational**
    - The critical first 24 hours of ICU care in severely injured patients has been emphasized, but subsequent days have been giving relatively less attention when attempting to predict ICU mortality.
    - Hypotension on ICU day 1 is associated with increased mortality rate but the effects of subsequent episodes of hypotension are unclear.

Paper 3

- **Hypothesis**
    - Hypothermia in consequence of severe injury can be predicted and can be factored in the related morbidity & mortality during the early stages of resuscitation.
- **Background and rational**

- Trauma patients frequently develop hypothermia during ICU stay and the prediction of such episodes have not been adequately investigated in previous studies.
- Hypothermia is a valuable indicator for shock outcome yet it has not been utilized efficiently as much as other shock indicators to predict the outcome of shock and to successfully resuscitate severely injured trauma patients.

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2. FIRST PAPER: A BRIEF EPISODE OF HYPOTENSION INCREASES MORTALITY IN CRITICALLY ILL TRAUMA PATIENTS

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Published in:

Journal of Trauma Injury, Infection, and Critical Care 2002; 53:232-236

2.1. Abstract

Objectives:

Hypotension is associated with increased mortality, however previous studies have failed to account for depth and duration of hypotension. We evaluated the effect of the duration of hypotension on outcome in injured patients.

Methods:

Trauma patients admitted to the Intensive Care Unit (ICU) from 1999 – 2000 were prospectively evaluated. Patients transferred to a ward $\leq$ 48 hours after admission were excluded. The lowest systolic blood pressure (SBP) and duration of all episodes of SBP below 90 mm/Hg were recorded along with the total ICU length of stay and discharge status. Kruskal-wallis test, Pearson X^2 and test for trend were used for analysis.

Results:

Patients with hypotension during the first 24 hours of ICU care had an increased mortality rate. A brief ($\leq$10 minutes) episode of hypotension was associated with increased mortality that increased with duration of hypotension (p=0.0001). ICU length of stay also increased with duration of hypotension (p=0.0001).

Conclusion:

Brief episodes of hypotension are associated with an increased risk of death in patients requiring admission to the ICU after injury and a longer ICU recovery for those who survive.

2.2. Introduction

Trauma represents the leading cause of death for adults in their most productive years (1,2) and incurs substantial short and long-term disability (3). The development of multiple organ dysfunction syndrome (MODS) contributes significantly to the morbidity and mortality of traumatic injury and is the leading cause of late deaths after injury.(4-6) A number of risk factors for the development of MODS and for trauma-related mortality have been identified. The presence of hypotension and shock are frequently implicated in the development of complications and MODS after injury. (5,7,8) Prehospital hypotension has been considered a clinical predictor of severe injury and a marker of substantial blood loss even in the face of normal emergency department (ED) systolic blood pressure (SBP). (9,10) Hypotension was one of the admission variables associated with highest relative risk of death in geriatric blunt trauma patients. (11) Patients with prehospital or emergency department hypotension had an early mortality rate of 12% and a late mortality rate of 32%, suggesting that prehospital hypotension is a valid criterion for trauma team activation (12).

It is intuitive that the presence of hypotension will be associated with increased mortality and morbidity. (5,9,13,14,15) However, many previous studies evaluating the effect of hypotension have included substantial numbers of moribund patients that died early from exsanguinating injuries despite sound and timely care. Furthermore, these studies have typically noted the presence or absence of hypotension but have failed to account for the magnitude of the shock insult, which may be reflected in the depth or duration of hypotension. Experimental studies in animal models of shock have demonstrated that magnitude of the physiologic insult after hemorrhage, the degree of tissue injury, the level of oxygen deficit, and the survival rate all correlate with the severity (degree and duration) of hypotension. (16-19) Conversely, no evaluation of the degree and duration of hypotension in injured patients has been performed.

We hypothesized that an increased duration of hypotension would be associated with increased mortality and morbidity in severely injured patients. Our data demonstrate that even brief periods of hypotension in the (ICU) are associated with significantly increased mortality and length of stay (LOS).

2.3. Patients and Methods

All injured patients admitted to the intensive care unit at the University of Pittsburgh Medical Center from 1999 to 2000 were prospectively reviewed. Patients who were transferred to a ward within 48 hours of admission were excluded. The medical records of all remaining eligible patients were examined for demographic information, emergency department data, information on vital signs, laboratory test results, and hemodynamic measurements. Injury severity, prehospital admission history, hospital course, and outcome were obtained from the computerized Trauma Registry. Hypotension was defined as a systolic blood pressure (SBP) $\leq$ 90 mm Hg. Duration was defined as the elapsed time in minutes (on the basis of data entry in the ICU records) from the initial SBP of $\leq$90 until the next recorded SBP >90 mm Hg. The lowest SBP and the duration in minutes of all episodes of SBP $\leq$ 90 mm Hg were retrieved from the computerized ICU record during the first 48 hours of ICU care. Preterminal episodes of SBP of $\leq$ 90 mm Hg were excluded. The total ICU LOS, total hospital LOS, and the death /discharge status for each patient were recorded.

Data are presented as the mean + STD. Categorical variables were analyzed by the X^2 test. A value of $p < 0.05$ was used to designate statistical significance. To characterize and comprehend the relation between hypotension duration during the initial 24 hours of ICU care and the outcome, we used the test for trend. To perform the test for trend, we ranked both death and ICU LOS along a time frame of early versus late in a manner that corresponded to previous work by other investigators. (20-23). The ranking used in this analysis was as follows: died early (< 2 days), died within 3 to 7 days, died late (>7 days), survived and was discharged from the ICU late (> 7 days), and survived and was discharged early (< 7 days). The Kruskal-Wallis test was used to determine the effect of depth and duration of hypotension on the ICU length of stay for both survivors and patients who died.

2.4. Results

From 1999 to 2000, there were 783 patients admitted to the ICU after injury. Of these patients, 247 patients were discharged from ICU less than 48 hours after admission and therefore excluded, leaving 536 patients for analysis. There were 370 men (69%) and 166 women (31%). We could not gather complete data for eight patients as a result of transfer to other facilities for insurance purposes. One patient was excluded when he was found to have an aortic dissection and no acute injury as the cause of admission. In the remaining 528 patients, 145 (28%) patients died during the course of hospitalization and 383 (72%) survived. The average age of all patients was 48.6 + 22.8 years. The average ICU and Hospital LOS for the entire group were 5.6

+ 8.6 days and 15.4 + 14.9 days, respectively. The average injury severity score (ISS) was 26 + 12. Examining the differences of the average age and average ISS, we found that those who died after 48 hours were older and more severely injured (age, 64 + 22.6 years; ISS, 30 + 17) than those who were discharged from the ICU alive after 48 hours, (age, 49 + 22; ISS, 25 +12).

In the initial 24 hours after ICU admission, 245 patients (46%) had at least one episode of hypotension and 288 (54%) did not. Of the 245 patients with SBP < 90 mm Hg, there were 85 patients (35%) whose lowest SBP was < 70 mm/Hg, 75 patients (30%) whose lowest SBP was between 71 and 80 mm Hg, and 85 patients (35%) whose lowest SBP was between 81 and 90 mm Hg. Of the remaining 288 patients, 75 of them (26%) had their lowest SBP between 91 and 100 mm Hg and 213 patients (74%) had their lowest SBP above 100 mm Hg. We tabulated the total duration of hypotension in minutes and categorized duration as brief (1-10 minutes), moderate (11-60 minutes), long (61-120 minutes), and prolonged (>120 minutes). The duration of hypotension in patients with SBP < 90 was as brief in 27 patients, moderate in 91 patients, long in 53 patients, and prolonged in 75 patients.

Figure 1 illustrates the overall mortality rate for patients who were and were not hypotensive during the first 24 hours of ICU care. Patients who had an episode of SBP ≤ 90 mm Hg had a significantly increased mortality compared with those that did not.

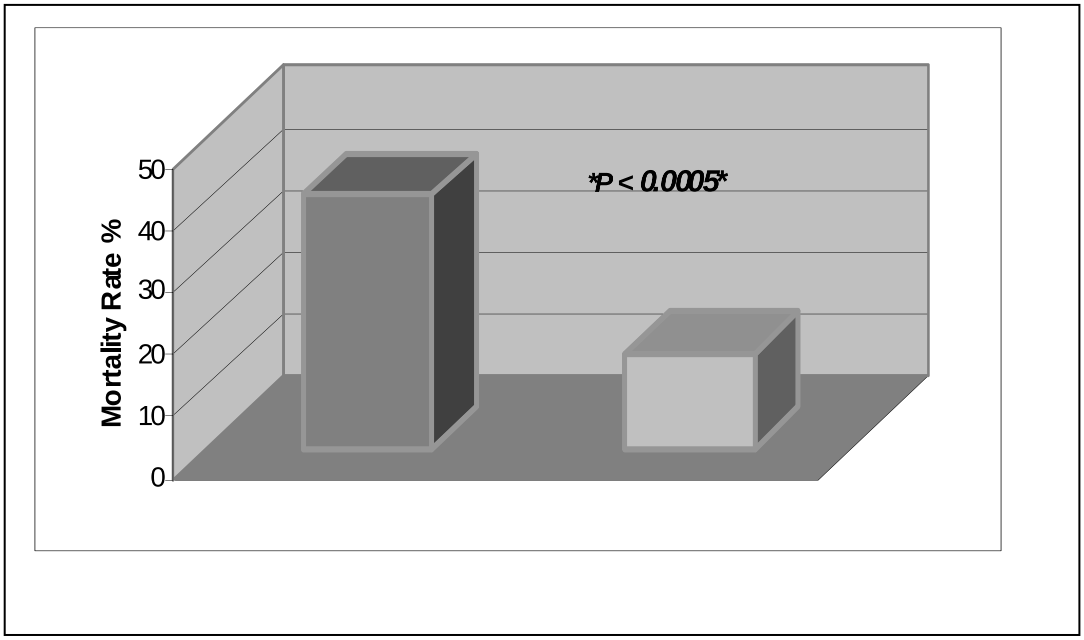

Figure 1. Mortality related to the lowest recorded SBP in the first ICU day.
The overall mortality rate for patients who were hypotensive (SBP ≤ 90 mm Hg) during the first 24 hours in the ICU is noted by the dark gray column. The mortality rate for patients who were not hypotensive (SBP >90 mm Hg) in the first 24 hours in the ICU is noted by the light gray column. A X^2 test was use to detect statistically significance differences (*p < 0.0005).

Figure 2 demonstrates the total LOS and survival of all patients according to their lowest measured SBP during the first 24 hours in ICU care. When the mortality rate was calculated after stratifying patients according to depth of hypotension, we found that mortality increased as the severity of hypotension increased, with statistically significant differences for all SBP categories ($p < 0.005$) (Fig. 3).

We next examined the duration of hypotension during the first 24 hours of ICU care. We found that mortality rate increased as the duration of hypotension increased (Fig 4).
When we examined ICU LOS in patients that were discharged from the ICU, we found that ICU LOS increased as the depth and duration of hypotension increased (Fig 5 and 6).

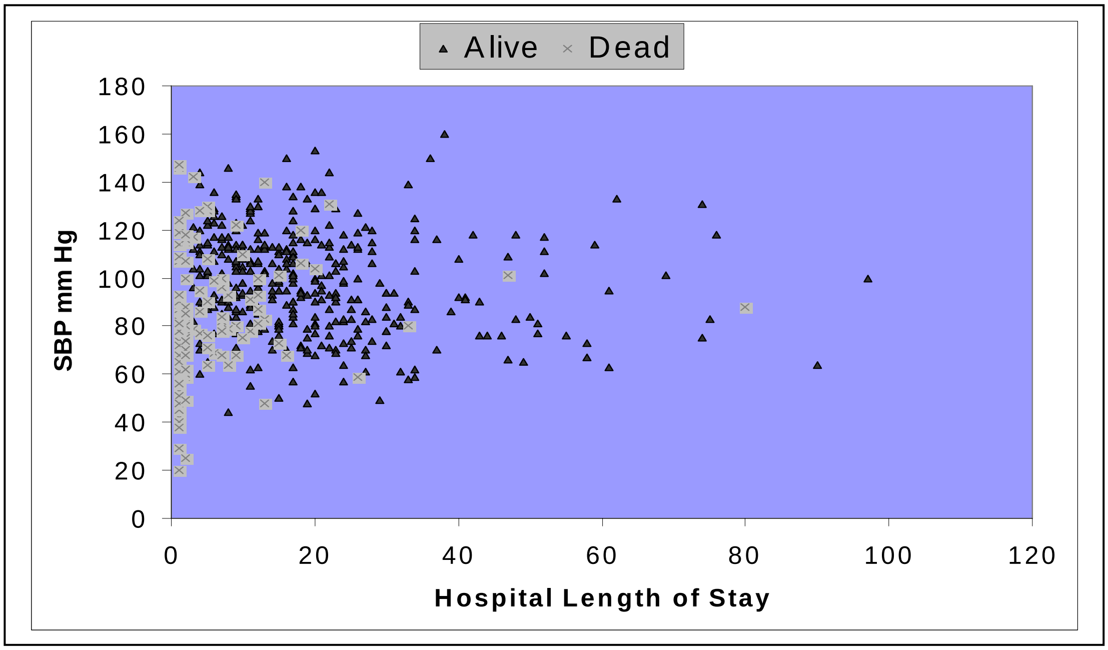

Figure 2. Illustration of lowest recorded SBP in the first ICU day in relation to length of stay and death. The total length of stay for all patients in relation to their lowest measured SBP in the first 24 hours in the ICU was stratified according to survival.

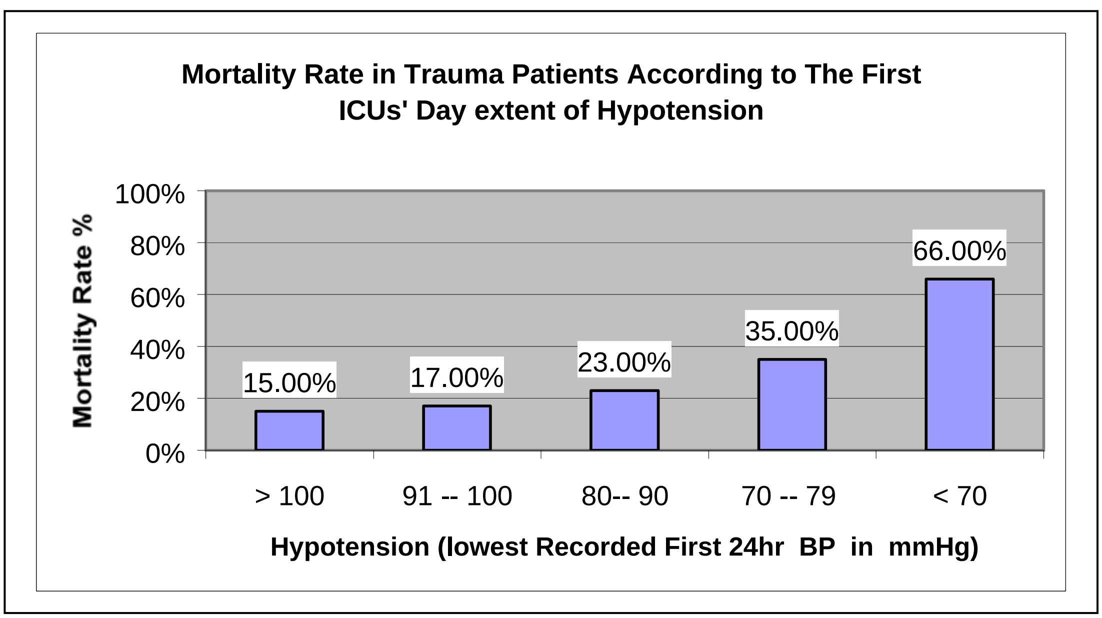

Figure 3. Morality rate in trauma patients in relation to depth of hypotension in the first ICU day. The morality rate was calculated after stratifying patients in groups according to their lowest SBP in the first ICU day. A statistically significance trend was noticeable (*p < 0.005).

In contrast, the length of stay for those who died in the ICU decreased as the depth and duration of hypotension increased (Fig 5 and 6). Using Kruskal-Wallis test to compare length of stay with duration and depth of hypotension, a statistically significant relationship was observed (p=0.0001).

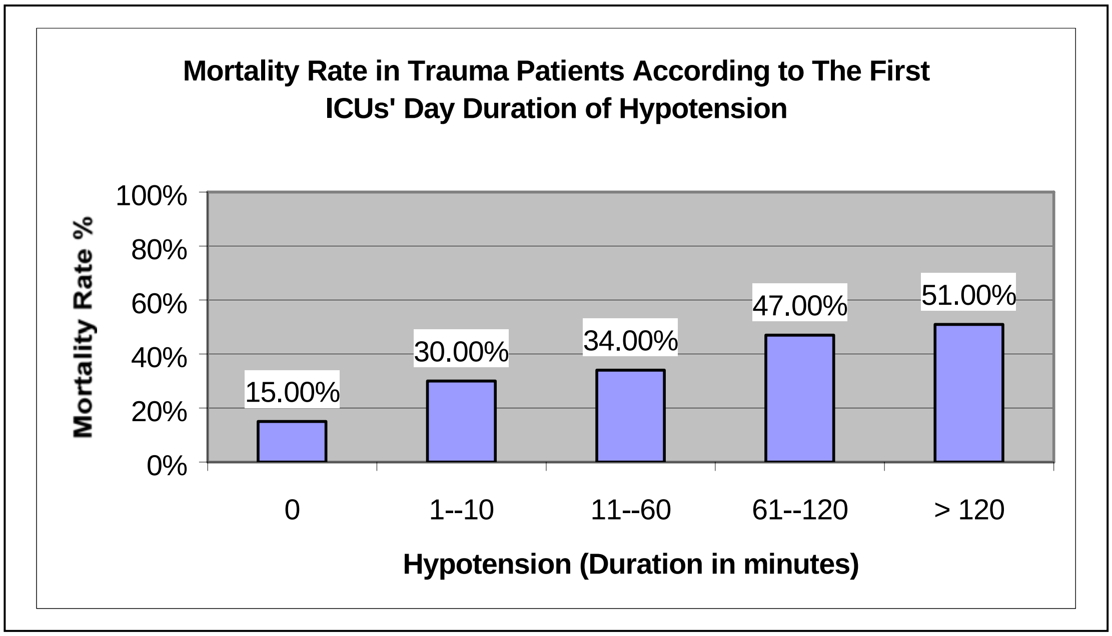

Figure 4. Mortality rate in trauma patients in relation to hypotension in the first ICU day.
The mortality rate was calculated after stratifying patients in groups according to their total duration in minutes of all episodes of SBP< 90 mm Hg in the first ICU day. A statistically significance trend was noticeable (*p < 0.005).

We stratified all patients who died according to time of death and examined these patients with reference to the duration of hypotension (Fig. 7). There were 96 patients who died early ($\leq$ 48 hours), 22 patients died within 3 to 7 days, and 27 patients who died late (> 7 days). As anticipated, patients who had prolonged and long periods of hypotension predominantly died early ($\leq$ 48 hours). However, a substantial group of patients with brief and moderate periods of hypotension also died early. Interestingly, in patients who died late (> 7 day), the largest group of deaths was present in those patients with brief (1-10 minutes) and moderate (11 – 60 minutes) periods of hypotension. When duration of hypotension was examined in patients who survived and were discharged from the ICU, patients who were discharged late (> 7 day) more frequently experienced episodes of hypotension than those discharged early ($\leq$ 7 days) (Fig. 8).

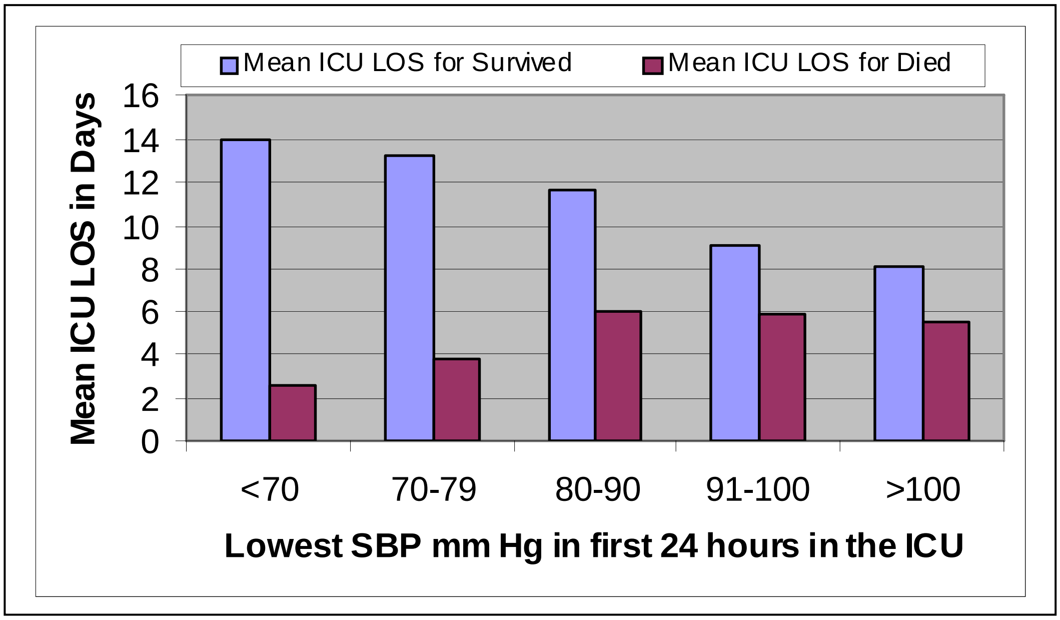

Figure 5. The effect of hypotension depth on ICU length of stay.
The means of ICU length of stay in days were plotted according to the lowest SBP for the first 24 hours in the ICU and according to whether the patient lived or died. A statistically significance differences using Kruskul-Wallis test were found in all SBP groups for those patients who survived (*p = 0.0001) and those who died (* p = 0.0001).

The test for trend (24) and Person X^2 using the duration of hypotension categories and the range of outcome described above demonstrated a statistically significant association between duration of hypotension and outcome (*p*=0.0001).

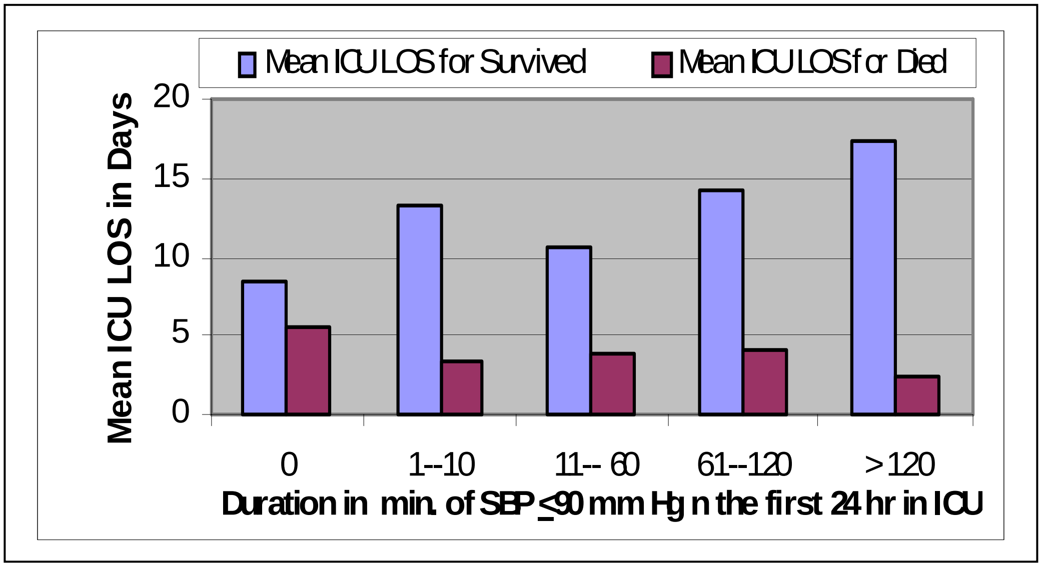

Figure 6. The effect of hypotension duration on ICU LOS.
The means of ICU length of stay in days were plotted according to the total duration in minutes of all episodes of SBP < 90 mm Hg in the first ICU day. Statistically significance differences using Kruskul-Wallis test were found in all groups for those patients who survived (*p = 0.0001) and those who died (* p = 0.0001).

2.5. Discussion

Hypotension was identified as a significant clinical event after injury in the early 20th century (25) and as a risk factor of early death and the development of MODS (14). It is intuitive that the presence of shock and hypotension may have significance adverse consequences. Franklin et al. demonstrated that patients who experience hypotension in the ED or in a prehospital setting frequently required operative treatment and had a high mortality rate (12). This high mortality rate associated with shock has been seen by other investigators as well (13). These studies, however, included many patients who were unsalvageable because of fatal exsanguinating injuries. Therefore, whether the effect of hypotension remains as profound in patients surviving their initial evaluation and resuscitation is less clear. Several authors have noted that the presence of hypotension is significantly associated with subsequent development of MODS (5). With fewer patients dying with MODS and with the outcome from MODS potentially improving (26,27), the effect of hypotension on mortality remains a viable question.

Most studies that have evaluated the contribution of hypotension to outcome after injury have examined hypotension as a categorical variable (i.e. it is present or not). Few studies have attempted to quantify the magnitude of the shock insult in trauma patients according to the degree and duration of shock. We know that duration of shock directly contributes to the pathphysiologic sequelae after hemorrhage and subsequent mortality in animal models of hemorrhage (16-19). Our data suggest that a similar relationship also exists in trauma victims.

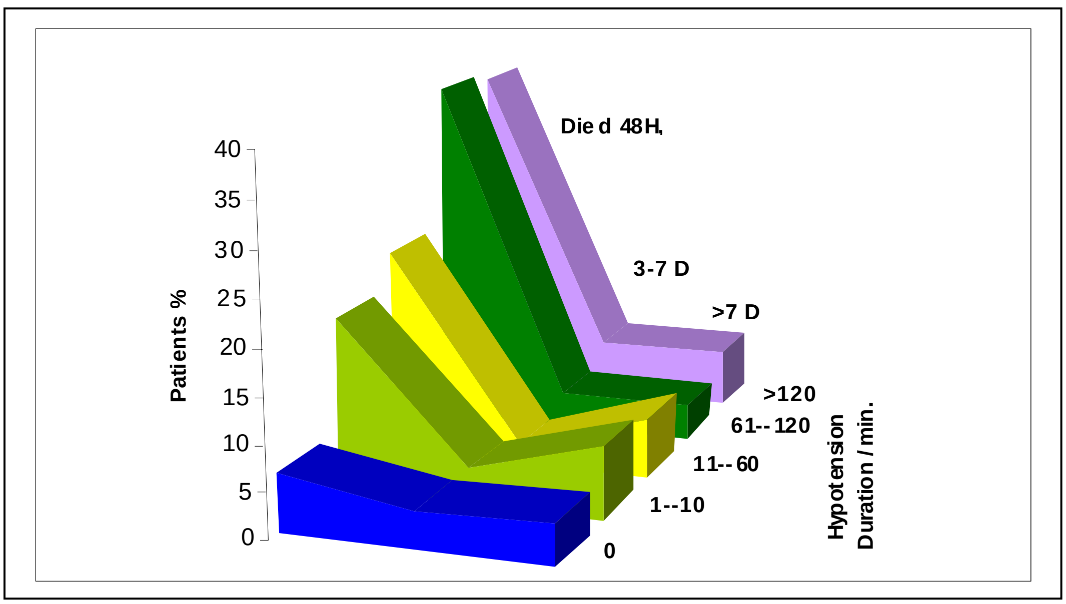

Figure 7. Duration of hypotension in patients who died.
The total duration of all episodes of hypotension (SBP < 90 mm Hg) for the first 24 hours in the ICU was tabulated according to whether the patient died: early (2 days), moderate (3 – 7 days), or late (> 7 days). The test for trend was statistically significant (*p = 0.0001).

In this study, we quantified the depth and duration of all episodes of SBP $\leq$ 90 mm Hg in a group of severely injured patients admitted to the ICU within a period of 2 years. Our data demonstrate significant increases in the mortality rate and morbidity (defined as ICU length of stay); even for brief episodes of SBP $\leq$ 90 mm Hg, mortality and morbidity increase as the depth and duration of hypotension increases.

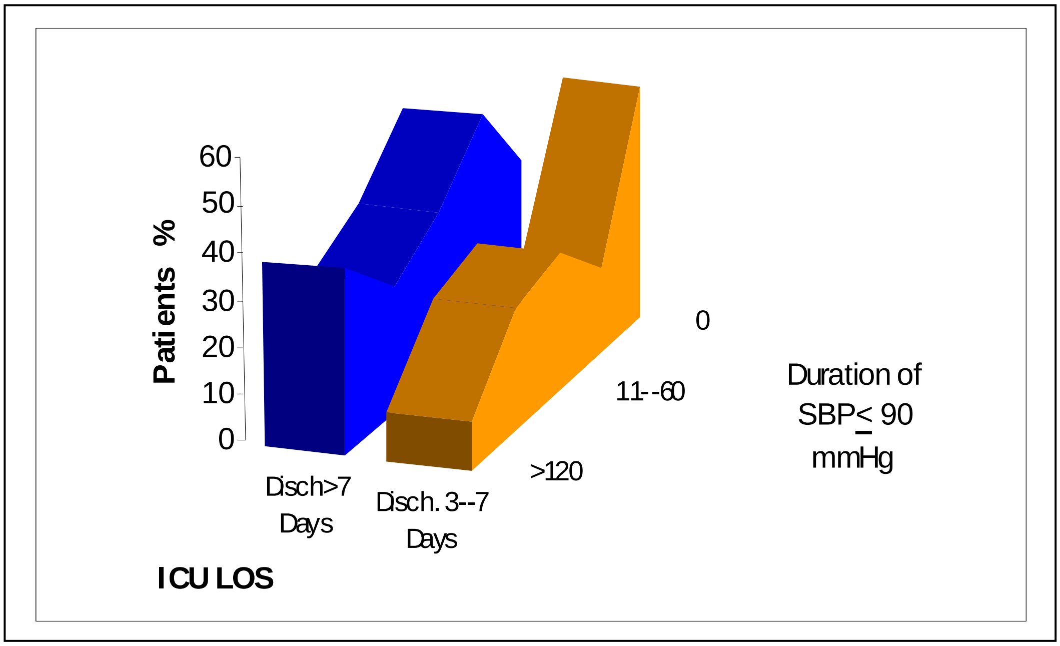

Figure 8. Duration of hypotension in patients who survived.
The total duration of all episodes of hypotension (SBP < 90 mm Hg) was tabulated and plotted according to whether the patient was discharged from the ICU early (<7 days) or late (>7 days). The test for trend was statistically significant (*p = 0.0001).

In this study, we excluded patients who died of exsanguinating injuries in the emergency department or in the operation room. We also excluded patients who were admitted to the ICU because of prehospital intubation, slow recovery from anesthesia, or other reasons, but were minimally injured and able to be transferred to a regular ward within 48 hours. The remaining patients represent a group of severely injured trauma victims (average ISS 26 $\pm$ 12) who were in the ICU from 5.6 $\pm$ 8.6 days and with an expectation of potential recovery from their injuries. Our data suggest that hypotension in the ICU in this group of patients has significant effects on morbidity and mortality.

Although the findings of this study are straight forward, our analysis does have limitations. We did not quantify the presence of hypotension in the emergency department resuscitation bay, operating room (OR), or before patients arrived to the ICU. It is not clear whether the results of this analysis can be extrapolated to hypotension that occurs in these areas before ICU admission. We did not evaluate how many patients may have had an episode of SBP $\leq$ 90 mm Hg in the ED and OR and were never admitted to an ICU. Whether duration of hypotension in the ED and OR has a similar relationship to outcome as that which occurs in the ICU, will require further study. In addition, SBP measurements of this study were obtained from the ICU record as documented by the ICU nursing staff. The accuracy of the SBP measurements and estimates of duration of hypotension therefore depend on the accuracy of the information entered into the medical record. Continuous real-time SBP measurements for patients with arterial lines that have a continuous read out included as part of the medical record is not yet available. Whether these limitations would substantially alter the results of current analysis is unclear.

Despite the limitations noted above, our results do have clinical relevance. These data suggest that any episode of hypotension may have significant clinical impact. These results emphasize the fact that hypotension not only should be aggressively treated in trauma patients but also should be aggressively prevented. This fact is particularly relevant as the nonoperative treatment of solid organ injuries continue to be refined. Development of hypotension is an indication of failure of nonoperative management for blunt abdominal injuries (28, 29, 30). Our data suggest that a consideration of the potential for a patient to become hypotensive, with its attendant contribution to mortality and morbidity should be weighed carefully when treatment options are considered.

In conclusion our data demonstrate that depth and duration of hypotension in the ICU correlate with morbidity and mortality after traumatic injury. They suggest that any episode of hypotension no matter how brief may have significant clinical impact.

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3. SECOND PAPER: HYPOTENSION ON THE SECOND ICU DAY PREDICTS MORBIDITY AND MORTALITY IN SEVERLY INJURED PATIENTS

Manuscript in preparation

3.1. Abstract

Introduction:

Hypotension is a predictor of mortality in injured patients but most studies include large numbers of moribund patients. We have shown that the occurrence of hypotension in the first 24 hours in the ICU is associated with increased morbidity and mortality. Subsequent days have been given less attention when attempting to predict ICU mortality. We hypothesized that the extent of hypotension on ICU day 2 in severely injured patients who survived day one would be a better predictor of mortality and morbidity than hypotension on ICU day 1.

Methods:

All Adult trauma patients admitted to the ICU at University of Pittsburgh Trauma Center from 1999-2000 were reviewed (n=783). Patients who had minimal injuries and were transferred to a ward less than 48 hours after admission (n=247), died during the first ICU day (n=62), or who had incomplete data (n=7) were excluded. Hypotension episodes just prior to death were excluded. The lowest systolic blood pressure (SBP) and the cumulative duration in minutes of all episodes of SBP ≥ 90 mm/Hg were recorded. The total ICU length of stay (ICU LOS) and the death/discharge status for each patient were recorded. Relative risk, Fisher's exact test, Wilcoxon rank sum test, linear regression, logistic regression, survival analysis, and Cox regression have been used in the analysis.

Results:

We studied 467 patients averaging 48 ± 22 (mean ± SD) years of age, 27.8 ± 12.6 on the ISS, 10.5 ± 9.9 days of ICU LOS, and 17.4 + 14.8 days of total hospital stay. Patients who had a hypotensive episode on ICU day 2 had a significant increase in their mortality rate. Patients who survived their first day in the

ICU, but experienced hypotension on day 2 in the ICU, had approximately 2.5 higher risk for mortality compared to those who had hypotension on ICU day one. Similarly, the occurrence of hypotension on ICU day two that lasted for four hours doubled the risk for mortality. Both the lowest reading of ICU day two SBP and hypotension duration were significant predictors of time for death in Cox regression model, ($P<0.001$).

Conclusion:

In severely injured patients, hypotension on ICU day 2 is associated with an overall higher hospital mortality and morbidity. For those who survived ICU day one, hypotension depth and duration on ICU day 2 predicts the risk of in hospital adverse outcomes better than hypotension depth and duration recorded on ICU day 1.

3.2. Introduction

Trauma injuries incur substantial mortality and disability (1). Injury is the leading cause of death and disability in young adults (2). Although improvements in critical care has improved survival of the critically injured or ill patients, the ability to predict which patients will recover from their illness and which patients will die is an imperfect process. Hypovolemic shock and hypotension are major consequences of trauma and affect the morbidity and mortality in severely injured patients. Hypotension is one of the admission variables associated with highest relative risk of mortality and morbidity (3,4). Moreover, hypotension is frequently implicated in the development of Multi-Organic Dysfunction Syndrome (MODS) after injury and associated with increased morbidity and mortality (5,6). In animal models, hypotension severity strongly associated with the degree of tissue injury, the magnitude of inflammatory response, and survival rate (7, 8). Previous animal studies from our institution have shown that prolonged hypotension duration increased severity of shock through intensifying the acidosis, increasing base deficit, and leading eventually to lacticacidemia (9). Reperfusion after shock is associated with production of endogenous oxidants that cause cytotoxicity and activate the inflammatory response (10). Many inflammatory response mediators, such as IL-6, do not begin their systemic anti-inflammatory effect until the postresuscitation phase of hemorrhagic shock (11). In addition, nitric oxide, which causes vasodilatation, hypotension and inhibition of platelet aggregation, appears not to increase its production significantly until prolonged hemorrhage take place and an irreversible hemorrhagic shock develops (12). Disseminated injury may also occur after hypovolemic shock due to the release of cytokines, proteases and other oxidants (13)

A number of assessment tools have been developed in an attempt to objectively quantify the severity of illness in critically ill patients, assess resource utilization, and stratify patients for mortality risk assessment. Most of the available scoring system were developed in medical ICUs or in mixed medical/surgical units and have less utility in surgical and trauma patients (14,15). These prediction tools can be expensive, labor intensive, and may be no better than the clinical judgment of experienced physicians or nurses (15)

Variation in mortality and length of stay in intensive care units is often attributed to patients' characteristics at admission (16). Age, gender, Injury Severity Score (ISS), and mechanism of injury have been associated with mortality and ICU Length of Stay (LOS). The presence of pre-hospital or emergency department hypotension has an impact on the outcome but the effects have been primarily reflected in the number of early deaths seen after injury (4,17). In trauma patients suffering hemorrhagic shock, 31% died within 2 hours of emergency department arrival, 12% died between 2 and 24 hours, 11% died after 24 hours, and 46% survived. Among those who survived > 24 hours, 39% developed infection and 24% developed organ failure (17). The multiple organ dysfunction score has been shown to correlate closely with duration of care. This may indicate that early identification and daily quantification of multiple organ dysfunction score may help identify patients at risk for prolonged illness and death (18).

The association of hypotension with increased mortality has been well established through several studies (19, 20). Hypotension is one of the risk factors for shock and organ failure. Its severity is related to the diverse outcomes in trauma (21). Hypotension on ICU day 1 is associated with increased mortality rate in critically ill ICU patients (6,17, 22, 23). We have shown in a previous study that any duration of hypotension in ICU day 1 should be prevented since a brief episode of hypotension can increase mortality in critically ill trauma patients (24). While hypotension on ICU day 1 has such significance, the effects of subsequent episodes of hypotension are unstudied and the use of hypotension duration as a predictor of outcome is unknown. We hypothesize that hypotension (depth and duration) on ICU day 2 in severely injured patients who survived ICU day one is a better predictor of adverse outcomes than that of ICU day one.

3.3. Patients and Methods

All trauma patients admitted to the ICU at The University of Pittsburgh Medical Center from 1999-2000 were reviewed (n=783). Patients who had minimal injuries and were transferred to a ward in less than 48 hours after admission (n=247) or died during the first ICU day (n=62) were excluded. The exclusion of the above 309 patients was fundamental since they did not complete the second ICU day due to discharge or death in the first ICU day. Therefore, they could not fulfill the criteria of this study. Many of the above described patients who remained less than 48 hours in ICU had minimal injuries and admitted intoxicated with Alcohol but soon recovered and transferred to general wards. We excluded seven patients as well since we could not gather complete data as a result of transfer to other facilities for insurance or other reasons. The remaining (n=467) patients entered the analysis of this study.

Hypotension was defined as a systolic blood pressure (SBP) $\leq$ 90 mm/Hg. Pre-terminal episodes of hypotension were excluded from the above criteria. Duration was defined as the elapsed time in minutes from initial SBP of $\leq$90 until the next recorded SBP >90 mm/Hg. The lowest SBP and the cumulative duration in minutes of all episodes of SBP $\leq$ 90 mm/Hg were recorded during ICU day one and two for all patients in this study. We did not count any terminal hypotension episodes just before death defined as a continuous decrease in SBP with out ever reverts towards normality and instead followed by eventual death. An ICU day for this study is defined as a complete 24 hours from the time of ICU admission. The total ICU length of stay (ICU LOS) and the death/discharge status for each patient were recorded. Vital signs, blood transfusion, vasopressers treatment, and other laboratory tests to evaluate organ functions were also collected. Demographic data, injury description, Injury Severity Score (ISS), and number of preexisting illnesses were also obtained. We collected data regarding Emergency Department (ED) disposition to Operating Room (OR) / Intensive Care Unit (ICU). We also gathered ICU data in reference to lowest base deficit, highest lactate, lowest ICU day one temperature, and blood and blood products transfused during ICU days one and two. Data in this paper are presented as mean $\pm$ SD. A Chi-squared and Fisher's exact test were used to test significance in categorical variables. T-tests and Wilcoxon rank sum tests were used to test significance differences in continuous variables. A p-value of < 0.05 was assigned to determine statistical significance. Survival analysis was used to test the effect of second day hypotension on the survival. Linear and logistic regression were used to look for pre ICU variable that may possibly predict hypothermia on the first ICU day. The outcome variable for the survival analysis was death during ICU stay. We also applied log-rank tests to show differences in survival estimates curves. We tabulated the risk of hypotension in the severely injured trauma patients. Cox regression was used to determine hypotension hazard ratio and related confidence intervals. We considered all deaths during hospitalization in quantifying the risk of hypotension after adjusting for age, ISS and other variables of significance effects.

Hypotension severity was expressed as depth (in mm Hg) and duration (in minutes). Hypotension duration for patients in this study was obtained from the available critical care records. Since there was no standard protocol for recording blood pressure in this study, blood pressure was recorded and followed by critical care nurses every 1-2 hours or as frequently as the patients' conditions required.

3.4. Results

In the remaining 467 patients who entered the analysis of this study, there were 322 men (69%) and 145 women (31%). The average age was 48 $\pm$ 22 years; (median age was 46 years) with an average Injury Severity Score (ISS) of 27.8 $\pm$ 12.6. Average ICU LOS was 10.5 $\pm$ 9.9 days (median ICU LOS was 7 days). Average total hospital LOS was 17.4 $\pm$ 14.8 days, (median Hospital LOS was13 days). Of the 467 patients who survived the first ICU day, 83 patients (18%) subsequently died after day 2 of ICU admission and 384 patients (82%) survived

Of the 467 patients who survived to the second ICU day, 194 patients (41.5%) had recorded a lowest SBP of $\leq$ 90 mm Hg with average mean of 76 $\pm$ 11 SD in ICU day one (first 24 hours after ICU admission) and 273 patients (52.5%) had recorded a lowest SBP of >90 mm Hg in ICU day 1 with average mean of 111 $\pm$ 14 SD. Likewise on ICU day 2 (24–48 hours after

ICU admission), the 467 patients who survived day one, 80 patients (17%) had recorded a lowest SBP of $\leq$ 90 mm Hg with average mean of 77.5 $\pm$ 12 SD and 387 patients (83%) had a recorded lowest SBP of >90 mm Hg in ICU with average mean of 166 $\pm$ 16 SD.

Testing gender and injury class (blunt vs. penetrating) against hypotension severity on ICU days one and two revealed no statistical significance between groups using Wilcoxon rank sum test. Additionally, there were no differences between patients with hypotension and patients with no hypotension in both ICU day one and two based on the average number of preexisting illness. Using the same test, we found that those who had been given more blood products, blood transfusion, and vasopressors on ICU days one and two had on average a much lower SBP on both ICU days 1 and 2. In addition, hypotensive patients of ICU days one and two had on average a more severe base deficit, higher lactate, and a lower ICU day one temperature than non-hypotensive patients.

Hypotension depth in mm Hg during ICU day 1 and day 2 for 467 patients of this study were ranked according to mm Hg readings and as follows: < 70, 71-90, and >90. Out of the 194 patients who had at least one episode of hypotension (blood pressure $\leq$ 90 mm Hg) in ICU day one, there were 137 patients (71%) whose average lowest SBP was 70 mm Hg and 57 patients (29%) whose lowest SBP was between 71 and 89 mm Hg. Hypotension duration for all total readings of SBP $\leq$ 90 during ICU days 1 and 2 were also ranked as short (1-120 minutes) and long (>120 minutes). The duration of hypotension in patients with SBP $\leq$ 90 mm Hg was short in 138 patients (71%) and long in 56 patients (29%).

Of the 80 patients who had at least one episode of hypotension (blood pressure $\leq$ 90 mm Hg) there were 16 patients (20%) whose average lowest SBP was 70 mm Hg and 64 patients (80%) whose lowest SBP was between 71 and 89 mm Hg. Hypotension duration for all the total readings of SBP $\leq$ 90 during ICU day 2 were also ranked as short (1-120 minutes) and long (>120 minutes). The duration of hypotension in patients with SBP $\leq$ 90 mm Hg was short in 54 patients (68%) and long in 26 patients (32%). Table 1 summarizes the above data. Figure 9 illustrates a tabulation of lowest recorded ICU days one and two according to hypotension duration groups. The differences in the means of lowest recorded SBP between the above hypotension duration groups is statistically significant in both ICU days one and two.

The overall mortality rates for patients both experiencing or not experiencing hypotension during the first and second ICU days were calculated and tested for statistical significance using Chi-squared test. Patients who had an episode of SBP $\leq$ 90 mm Hg in either day one or day two had a significantly increased mortality compared with those who did not (Figure 10). Hypotension has been shown as a significant risk factor for mortality in both ICU day 1 ($P < 0.01$) and ICU day 2 ($P < 0.001$). Hypotension in first and second ICU days has a relative risk of 2.03, 95% C.I. (1.37 –2.99) and 4.09, 95% C.I. (2.85 –5.86) respectively. The relative risk ratio of the second ICU day hypotension to the first ICU day hypotension is 2.01. We also have sorted the risk of mortality on the second ICU day hypotension adjusting for hypotension status of ICU day one. The relative risk was 3.52, (95% C.I. 2.2 - 5.6) in those who had also hypotension in day one and 3.89, (95% C.I. 3.89-7.75) for patients with no hypotension on day one in the ICU (Table 2).

Table 1. Hypotension status of ICU days one and two expressed in depth and duration and sorted according to the severity

ICU Day One: N=467					ICU Day two: N=467				
No hypotension n=273	**Hypotension n=194**				**No hypotension n=388**	**Hypotension n=80**			
	Depth *In mm Hg*		Duration *In minutes*			Depth *In mm Hg*		Duration *in minutes*	
>90 mm Hg zero duration	Light 71-90 mm hg	Heavy ≤70 mm hg	Short ≤120 minutes	Long >120 minutes	>90 mm Hg zero duration	Light 71-90 mm hg	Heavy ≤70 mm hg	Short ≤120 minutes	Long >120 minutes
n=273	137 *71%*	57 *29%*	138 *70%*	56 *29%*	n=388	64 *80%*	16 *20%*	54 *68%*	26 *32%*

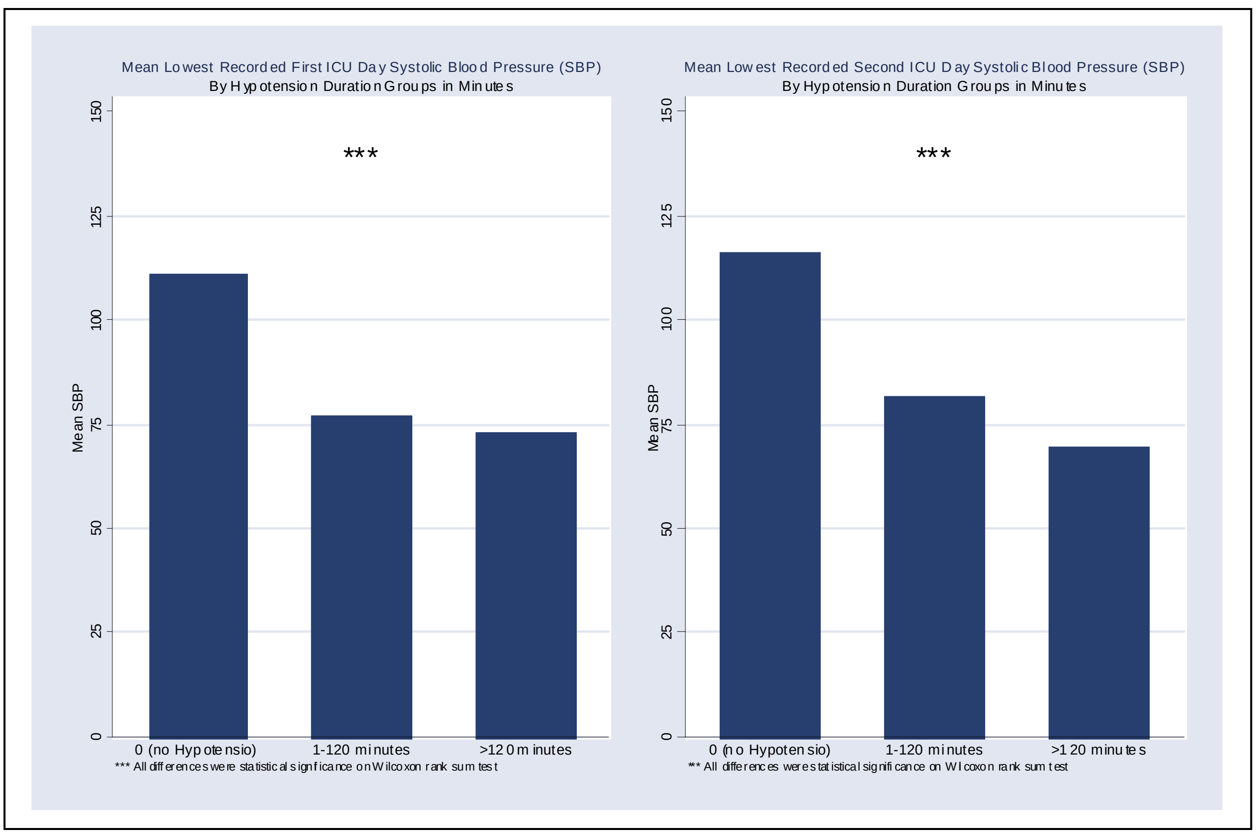

Figure 9. Illustration of means of the lowest SBP on days 1 and 2 in the ICU by hypotension duration groups

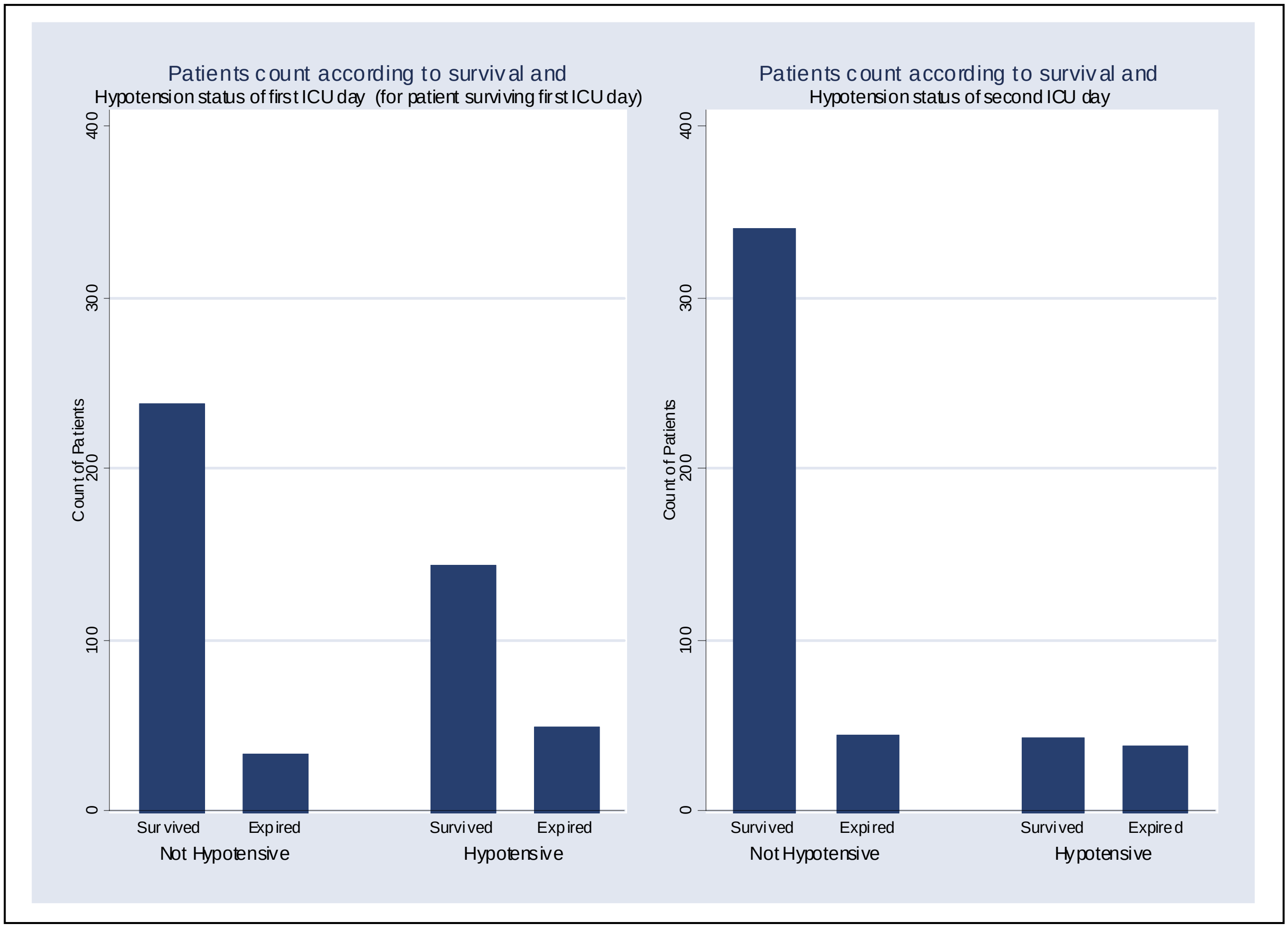

Figure 10. Illustration of means of the lowest SBP on days 1 and 2 in the ICU by hypotension duration groups

Table 2. 2X2 tabulations of hypotension status according to life/death status reporting risk ratio, confidence interval (C.I.), and p value for each.

****Tabulation According to**	**Hypotension Status and Related Outcome**			
	Outcome	**Hypotension** Patients #	**No Hypotension** Patients #	R.R. & (C.I.) "Chi-squared"
Hypotension in ICU day two Not adjusted to the status of hypotension in ICU day one (n=467)	Died	38	45	**4.09*** (2.9 – 5.9) p<0.001
	Survived	42	342	
Hypotension existed in both day one and day two (n=194)	died	30	19	**3.53*** (2.2 – 5.6) p<0.001
	survived	30	115	
Hypotension existed only in ICU day two but not in day one (n=273)	died	8	26	**3.89*** (2.0 – 7.8) p<0.01
	survived	12	227	
Hypotension in ICU day one Not adjusted to the status of hypotension in ICU day two (n=467)	died	49	34	**2.03*** (1.4 – 3.0) p<0.01
	survived	145	239	
Hypotension existed only in ICU day one but not in day two (n=387)	died	19	26	**1.38** (.79 – 2.4) P=0.255
	survived	115	227	

****The above tabulation is for trauma patients who survived ICU day One**

We looked at the differences in the means of ICU LOS according to hypotension status. These differences were statistically significant on Wilcoxon Rank-Sum Test in both groups of expired (p=0.01) and survived (p<0.002) patients. We also looked at the relation of lowest SBP and related hypotension duration measured on ICU days one and two. For those patients who survived ICU day one, we found that there were a positive correlation between the lowest SBP reading on ICU days one and two for the expired patients and negative correlation for the surviving patients. This is an indication that trauma patients with lower SBP stay longer in ICU if they survive or shorter since they expire more quickly. With longer duration of hypotension, we found a negative correlation with length of stay in the expired patients and a positive correlation in surviving patients. This is an indication that trauma patients with prolonged hypotension duration are staying longer in ICU upon survival or shorter due to quicker expiration.

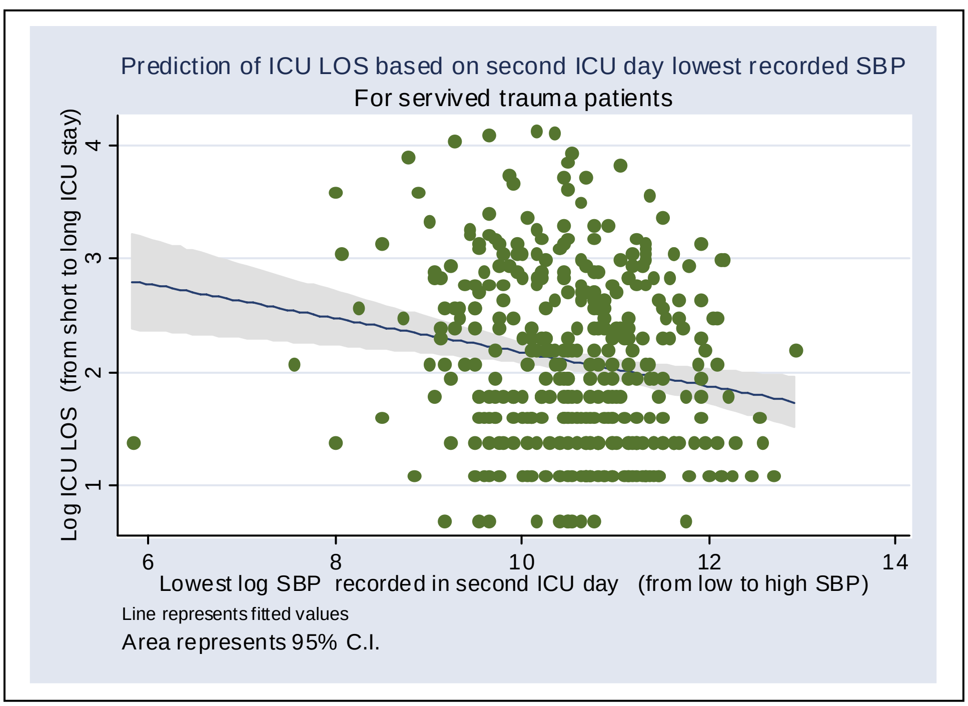

Figure 11. Lowest recorded SPB of ICU day two (in log transformation) in relation to ICU LOS in the survived trauma patients

This relationship is also depicted by linear regression (using log transformation) when we attempted to predict ICU LOS based on hypotension depth and duration in the first and second ICU days. Figure 11 shows the above-described relations between log ICU LOS and hypotension depth on ICU day two (log lowest recorded SBP in mm Hg). Figure 12 shows the above-described relations between log ICU LOS and hypotension duration on ICU day two (log duration of hypotension episodes in minutes).

Similarly, we compared the relationship between hypotension severity on second ICU day and injury severity score (ISS). We found a positive relation between hypotension duration on the second ICU day and ISS. A line expressing a positive relationship indicates that injury severity is a statistically significant factor in predicting hypotension severity in the survived, (P=0.03, R^2=0.13), Figure 13.

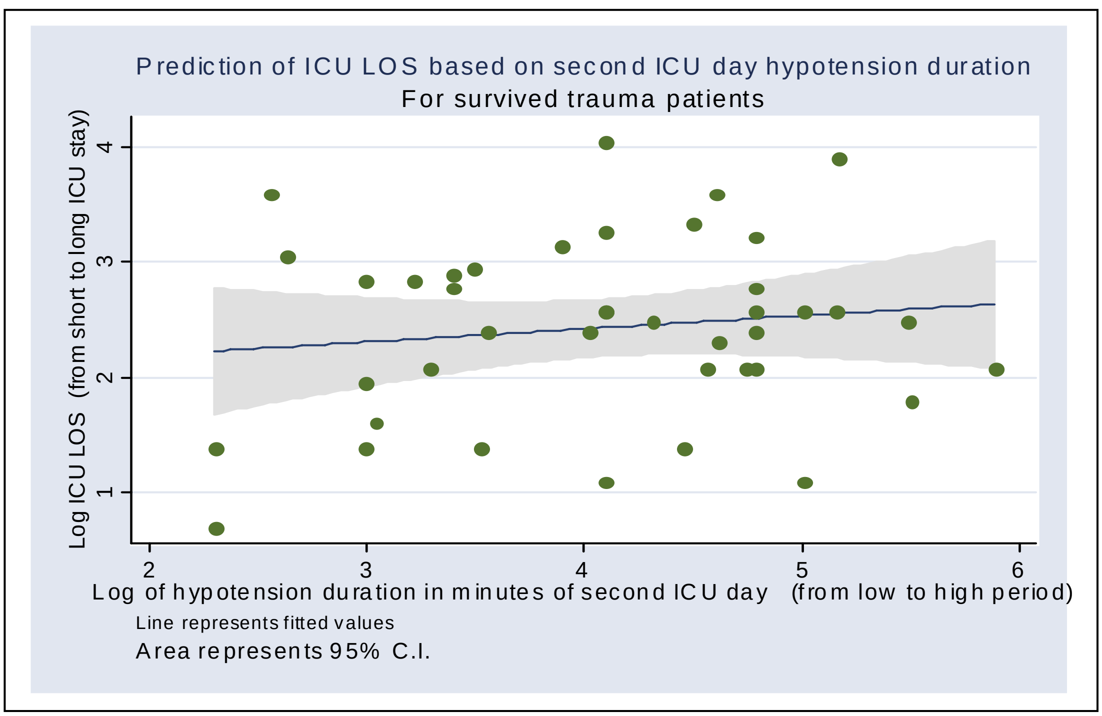

Figure 12. Log hypotension duration in minutes of ICU day two in relation to ICU LOS in the survived trauma patients

We did not depict any statistically significant relationship between the lowest recorded SBP of second ICU and ISS, even when we sorted by death/survival status and by SBP≤90 mm Hg (figure not shown).

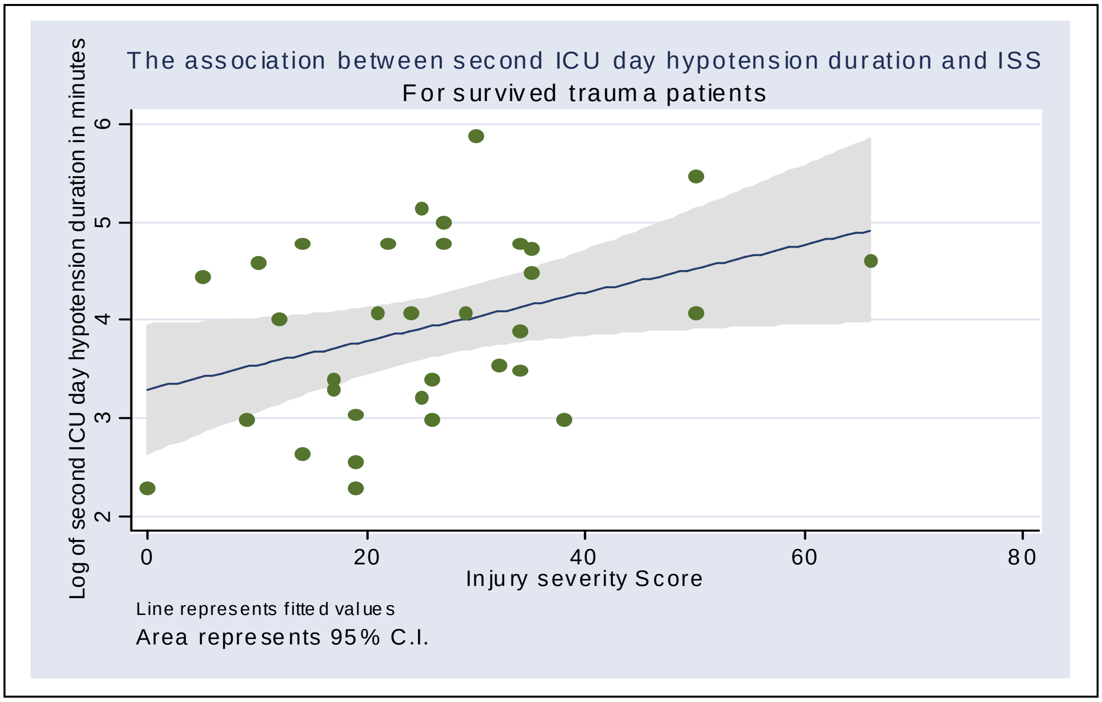

Figure 13. Injury Severity Score (ISS) to Log-hypotension duration in minutes of ICU day

Next, we applied survival analysis to check the relationship between hypotension and patients' outcome during ICU stay. Figures 14 and 15 show Kaplan-Meier Survival Estimates of survival curves of hypotension status of ICU day one and two with death as the failure variable and time to death in ICU as the analysis time. Patients would be censored as they were discharged from ICU. To test the equality of survivor functions, we used a Log-Rank Test. There were a strong statistically significant difference between the two groups with and without hypotension on ICU day two ($P < 0.001$) and to a lesser degree (but still significant) for ICU day one ($p<0.02$)

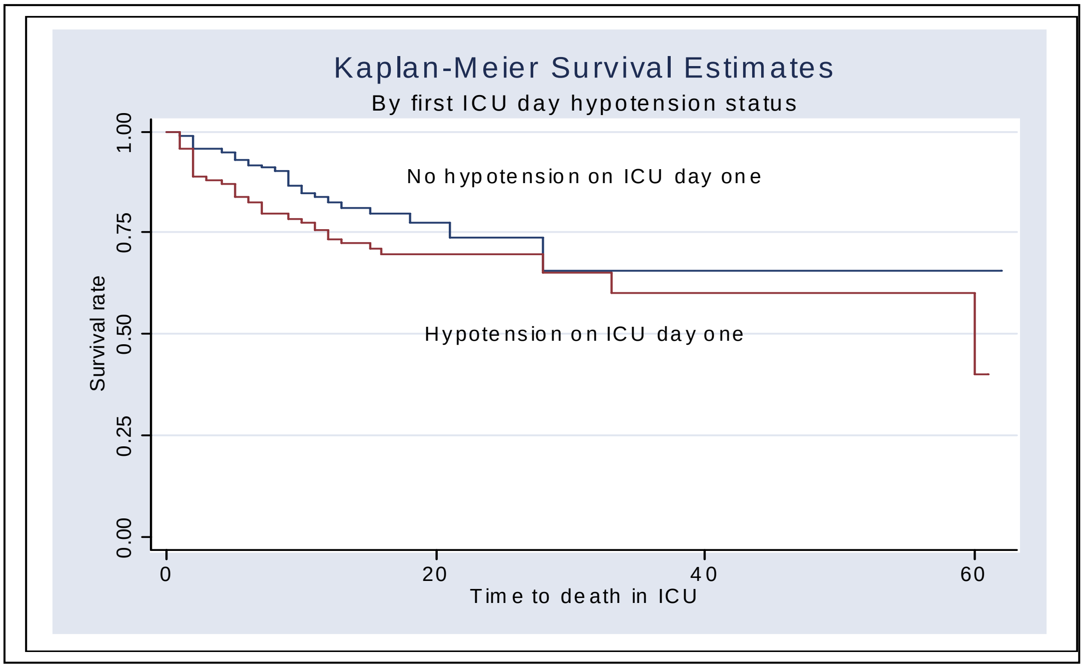

Figure 14. Kaplan-Meier Survival Estimates of two survival curves of ICU day one hypotension status

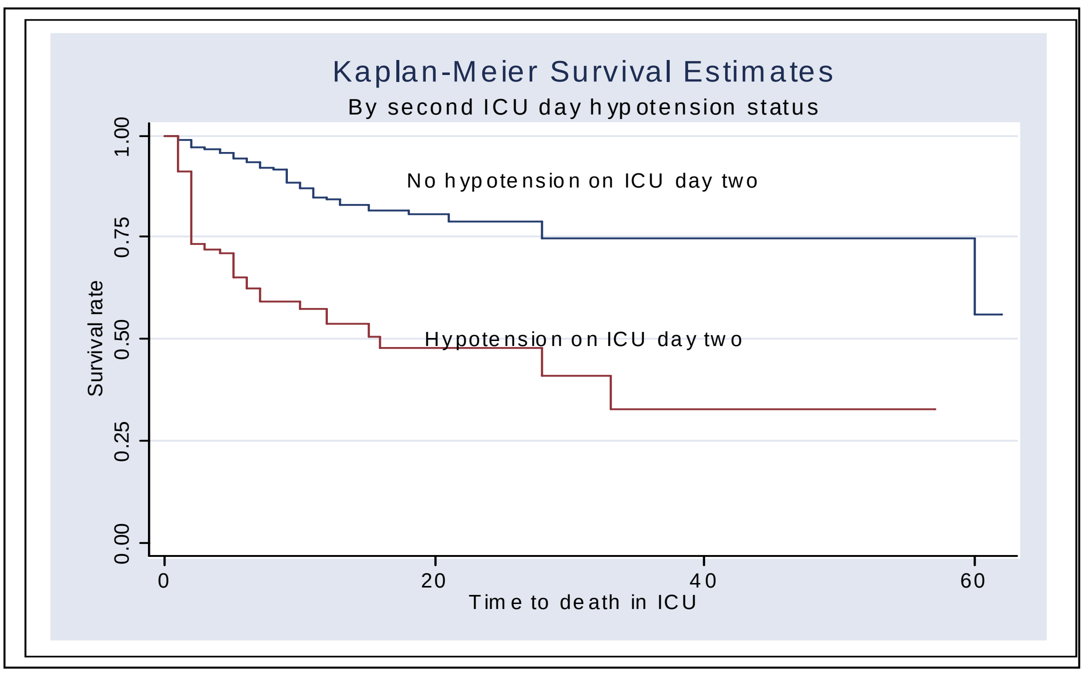

Figure 15. Kaplan-Meier Survival Estimates of two survival curves of ICU day two hypotension status

To further test for the severity effects of hypotension, we used the earlier described grouping (table 1) of hypotension severity in the above survival analysis model. We run the analysis on both hypotension depth and duration recorded in ICU day one and similarly on ICU day two. For hypotension in ICU day 2 (without adjusting for hypotension status of ICU day 1), we tested the equality of survival functions between the three curves of hypotension depth (lowest recorded SBP/mmHg) and the three curves of hypotension duration in minutes (separately). A highly statistically significant differences were found between all curves using log rank Test, P<0.001, (table 3 and figures 16 & 17). In comparison, using the same test on similar curves of ICU day one (without adjusting for hypotension status of ICU day 2), no statistically significant differences were shown, except between those with no hypotension compared to those presented with severe hypotension (SBP<70 mm Hg or hypotension lasted for longer than 2 hr); (Table 3 and Figures 18 & 19). We also applied the same survival analysis for those patients who had hypotension on ICU day one only, ICU day two only, and on both ICU days one and two. This is to control for the presence and absence of hypotension status in the other ICU day (day 1 vs. day 2). No ICU day two curves of lowest recorded systolic blood pressure show considerable alterations upon controlling for the presence and absence of ICU day one SBP. All related differences remained statistically significant (Figure 20A and 20B). In contrast, ICU day one curves of SBP were further intertwined when we took into consideration the presence and absence of hypotension in ICU day two (Figure 21A and 21B).

Similarly, No ICU day two curves of hypotension duration show considerable alterations upon controlling for the presence and absence of ICU day one SBP. All related differences remained statistically significant (Figure 22A and 22B). In contrast, ICU day one curves of hypotension duration were further intertwined when we took into consideration the presence and absence of hypotension in ICU day two (Figure 23A and 23B). Although it is noticeable, that ICU day one has significant effects on the outcome but upon surviving that day, hypotension of ICU day two stands by itself in outcome prediction better than ICU day two hypotension..

Table 3. Testing differences between Kaplan-Meier Survival Estimates of hypotension depth and duration

Hypotension	**Differences between Curves**	**ICU Day One** *p-value of Log-rank test*	**ICU Day Two** *p-value of Log-rank test*
Depth *SBP/mm HG*	>90 vs. 71-91	0.12	<0.001*
	71-90 vs. <70	0.10	<0.001*
	>90 vs. <70	<0.02*	<0.001*
Duration *In minutes*	Zero duration vs. 1-120	0.077	<0.001*
	1-120 vs. >120	0.41	<0.001*
	Zero duration Vs. > 120	<0.03*	<0.001*
The above testing were for the non adjusted for other ICU day hypotension status			

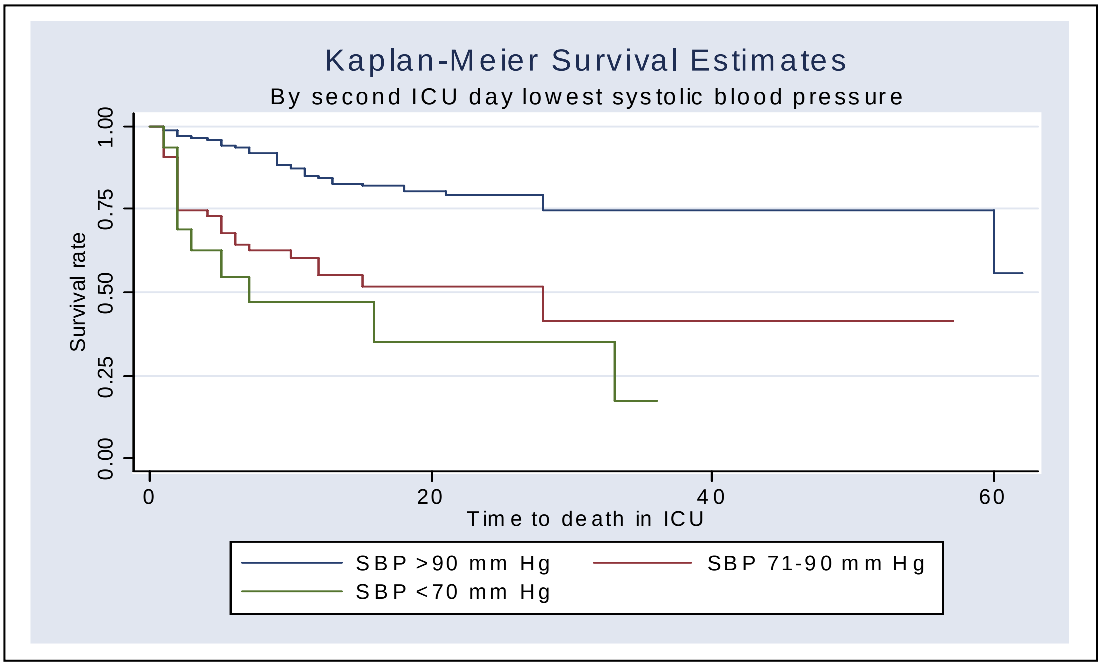

Figure 16. Kaplan-Meier Survival Estimates illustrate the differences in three groups of lowest recorded systolic blood pressure on ICU day two without consideration to ICU day one status of hypotension.

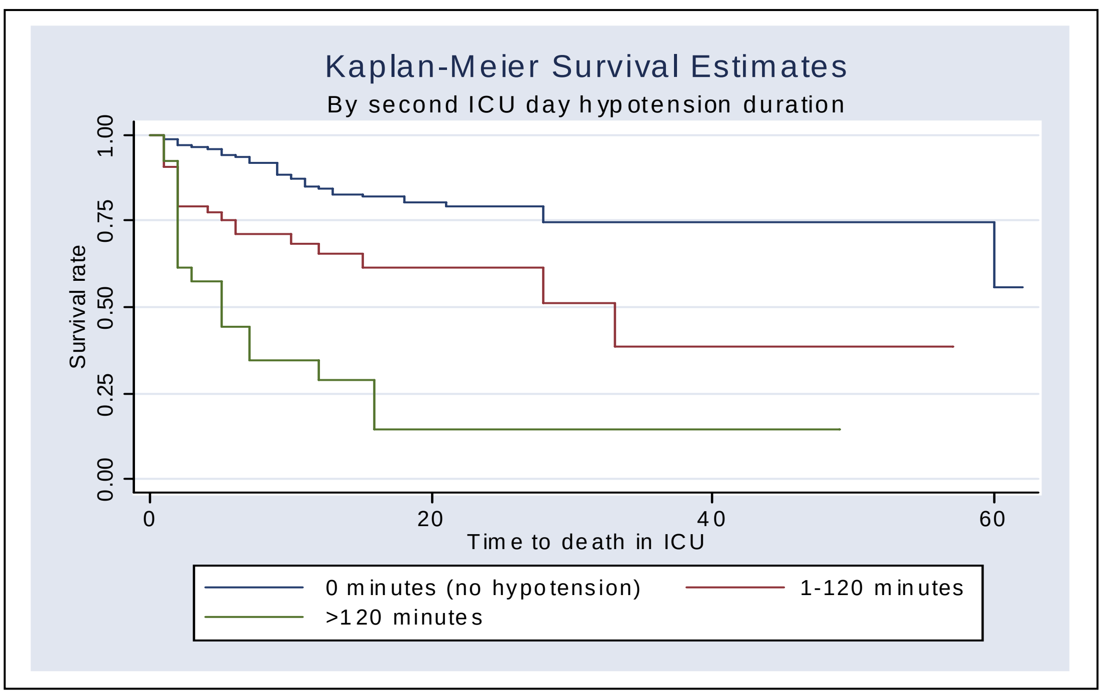

Figure 17. Kaplan-Meier Survival Estimates illustrate the differences in three groups of hypotension duration of ICU day two without consideration to ICU day one status of hypotension

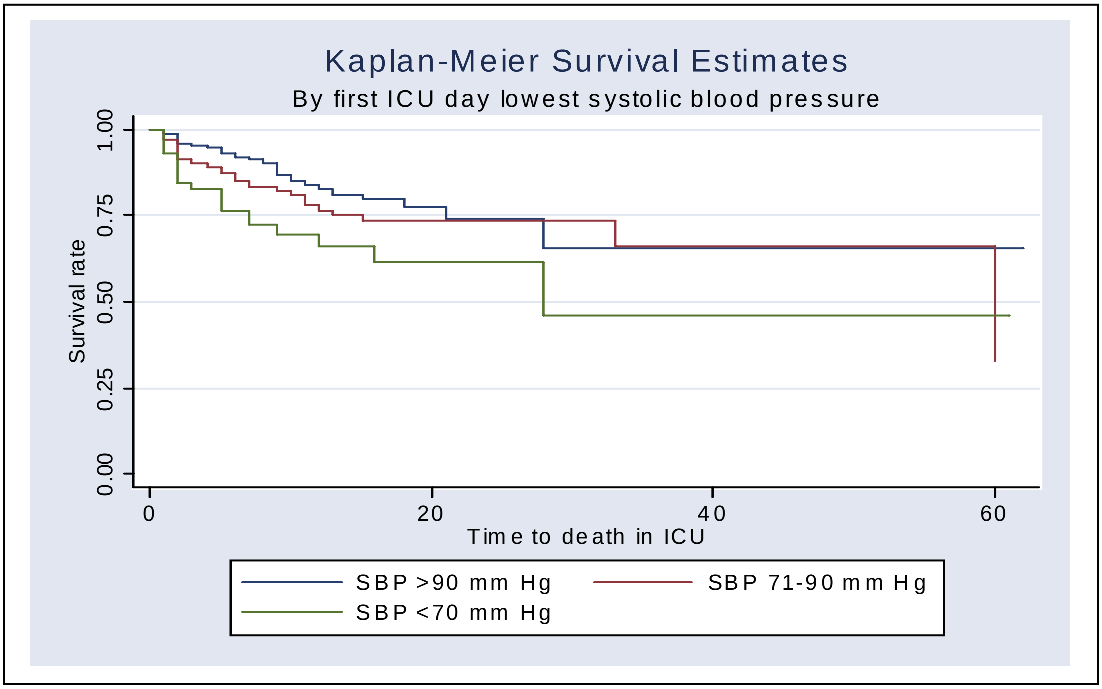

Figure 18. Kaplan-Meier Survival Estimates illustrate the differences in three groups of lowest recorded systolic blood pressure on ICU day one without consideration to ICU day two status of hypotension.

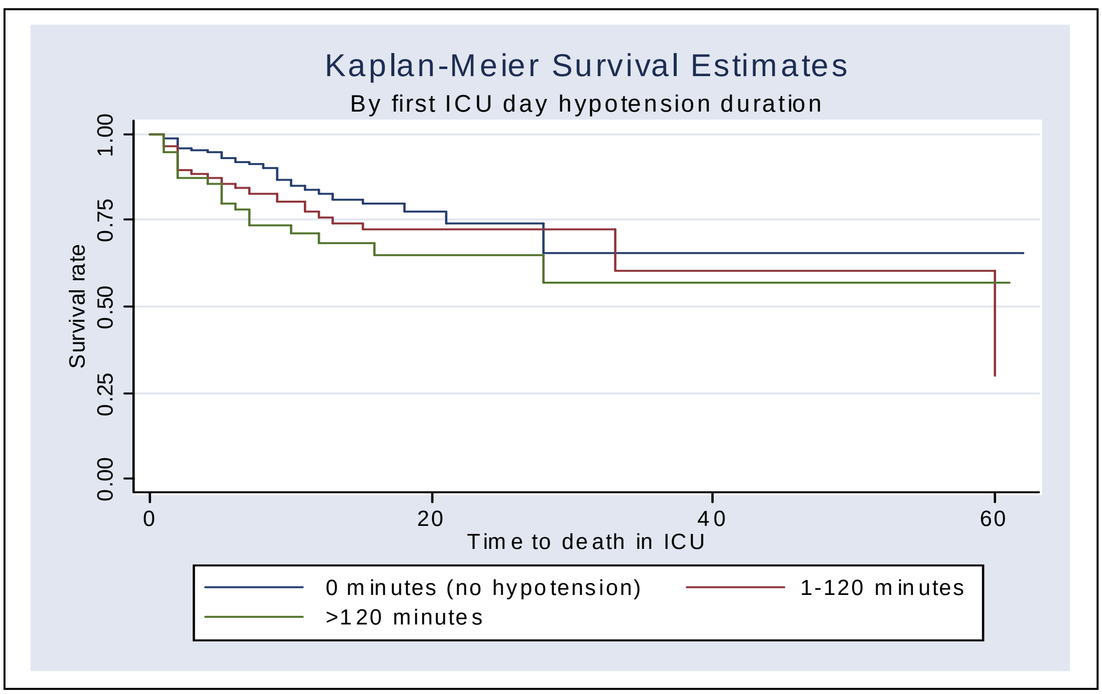

Figure 19. Kaplan-Meier Survival Estimates illustrate the differences in three groups of hypotension duration of ICU day one without consideration to ICU day two status of hypotension

(A) (B)

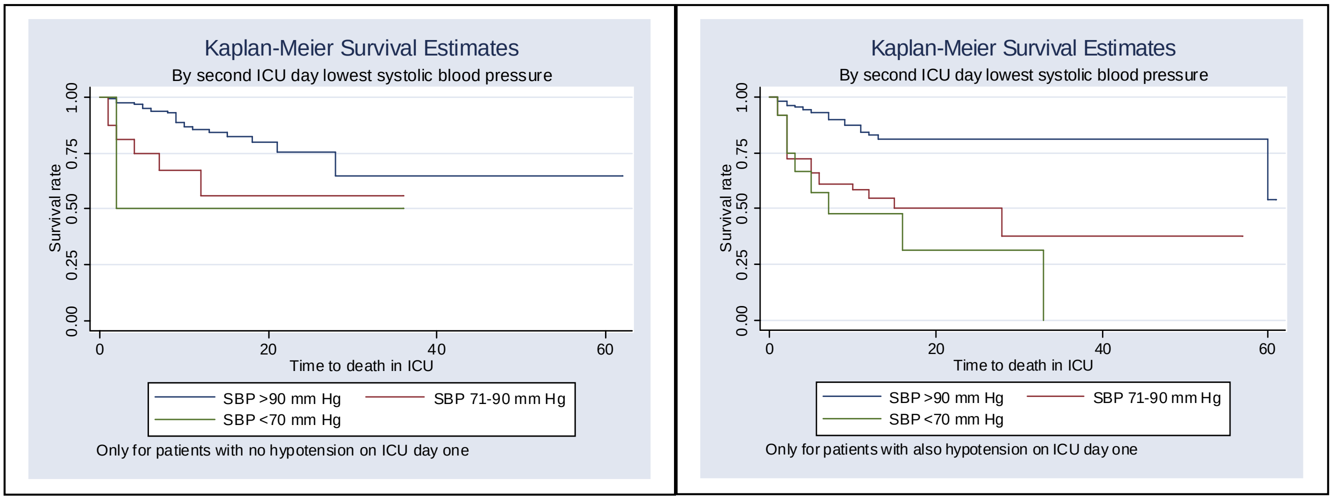

Figure 20. Kaplan-Meier Survival Estimates illustrate the differences in three groups of lowest recorded systolic blood pressure on ICU day two with consideration to ICU day one.
(A). Show the survival estimates when hypotension was present only on ICU day two.
(B). Show the survival estimates when hypotension was present on both ICU days one and two.

(A) (B)

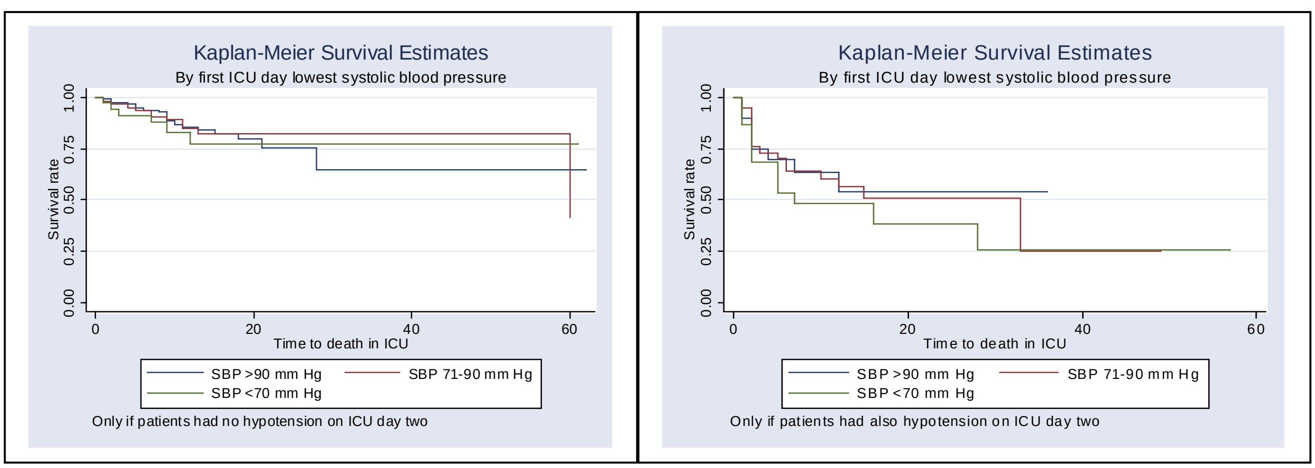

Figure 21. Kaplan-Meier Survival Estimates illustrate the differences in three groups of lowest recorded systolic blood pressure on ICU day one with consideration to ICU day two.
(A). Show the survival estimates when hypotension was present only on ICU day one.
(B). Show the survival estimates when hypotension was present on both ICU days one and two.

(A) (B)

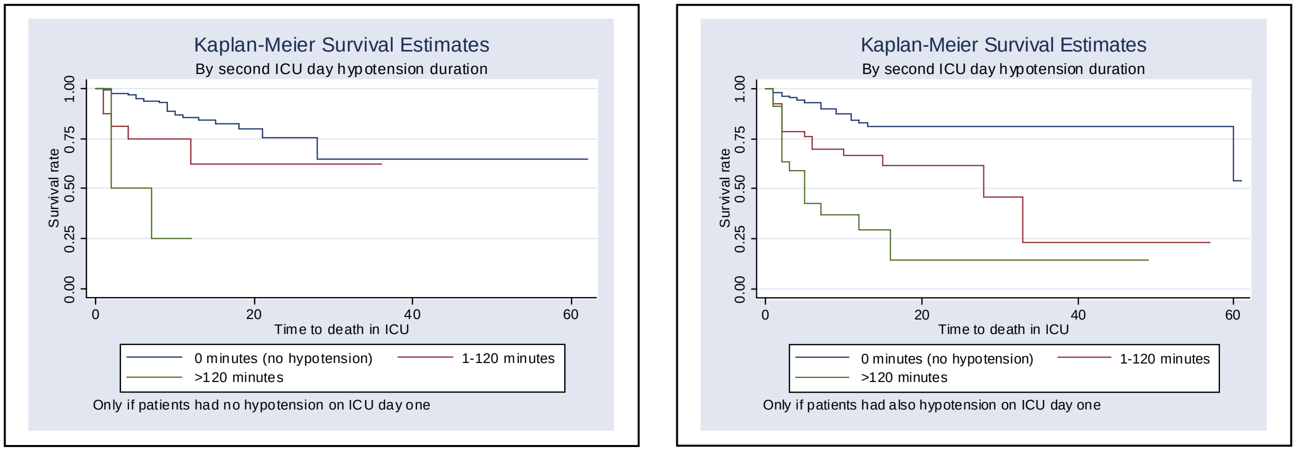

Figure 22. Kaplan-Meier Survival Estimates illustrate the differences in three groups of hypotension duration on ICU day two with consideration to ICU day one.

(A). Show the survival estimates when hypotension was present only on ICU day two.

(B). Show the survival estimates when hypotension was present on both ICU days one and two.

(A) (B)

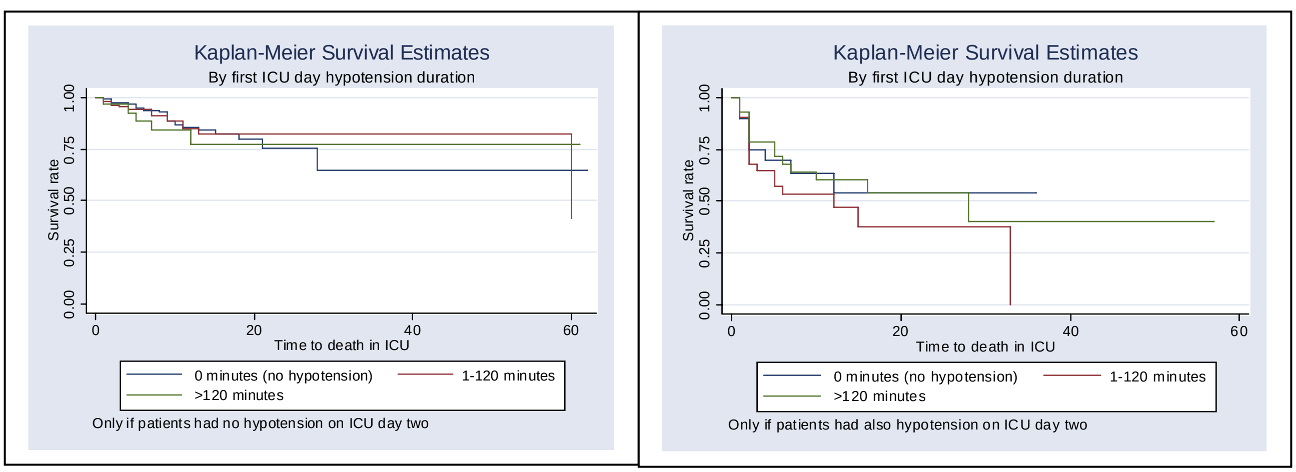

Figure 23. Kaplan-Meier Survival Estimates illustrate the differences in three groups of hypotension duration on ICU day one with consideration to ICU day two.

(A). Show the survival estimates when hypotension was present only on ICU day one.

(B). Show the survival estimates when hypotension was present on both ICU days one and two.

Finally, we applied Cox regression taking time to death in the ICU as the analysis time. We ware able to quantify the risk of hypotension on ICU days one and two for patients who survived ICU day one using Cox model adjusted for age and ISS. The hazard ratio for hypotension on ICU day one was 1.68 + 0.41 (Std. Err) p<0.04 (95% C.I. 1.03 – 2.71). The hazard ratio for hypotension on ICU day two was 4.09 + 0.98 (Std. Err) p<0.001 (95% C.I. 2.56 – 6.52). We also used Cox model to quantify the risk for each five degree drop in SBP and for each one hour increase in hypotension in both ICU days one and two adjusting also for age and ISS. For ICU day one, the relative risk for five mm Hg drop in SPB was 1.18 ± 0.05 (± Std. Err.), P<0.001 (95% C.I. 1.08 – 1.28) and for each 1 hour increase in duration of hypotension on ICU day one, the relative risk was 1.19 ± 0.06 (± Std. Err.), P<0.001, (95% C.I. 1.08 – 1.31). For ICU day two, the relative risk for five mm Hg drop in SPB was 1.36 ± 0.06 (± Std. Err.), P<0.001 (95% C.I. 1.24 – 1.50) and for each 1-hour increase in duration of hypotension on ICU day two, the relative risk was 1.22 ± 0.04 (± Std. Err.), P<0.001, (95% C.I. 1.15 – 1.29). (Table 4 summarize the above).

Table 4. Quantifying the risk of ICU days one and two hypotension for patients surviving ICU day one

Quantifying the risk of hypotension using Cox regression adjusting for age and ISS,					
ICU Day	**Hypotension**	**RR**	**Std. Err**	**P**	**95% C.I.**
One	Hypotension vs. no hypotension	1.67	0.41	<0.04	1.03 - 2.71
	Five degrees reduction in SBP (mm Hg)	1.18	0.05	<0.001	1.08 - 1.28
	On hour increase in hypotension	1.19	0.06	<0.001	1.08 - 1.31
Two	Hypotension vs. no hypotension	4.09	1.0	<0.001	2.56 - 6.52
	Five degrees reduction in SBP (mm Hg)	1.36	0.06	<0.001	1.24 - 1.50
	On hour increase in hypotension	1.22	0.04	<0.001	1.15 - 1.29

We also used Cox regression to look for other variables that also shared prognostic risk for death along with second ICU day hypotension. We fixed in the model the variable that indicated the reduction on lowest recorded ICU day two SBP sorted in five mm Hg increments. We were able to fit the following variables; one-hour increase in hypotension duration on ICU day two, hypothermia on ICU day one, one-decade increase in age and brain injury. The fitting improved even further upon including ED disposition to ICU vs. OR and ISS though these two variables were not statistically significant by themselves. The model indicated the variables that had the most effects on trauma mortality. The model included 411 patients with P<0.001. Table 5 showing the hazard ratio and related significance of Cox regression model.

Table 5. Cox regression with death as the failure and time to death in the ICU as the analysis time

Variables in the Model	**Haz. Ratio**	**Std. Err.**	**z**	**P>|z|**	**95% Cof. Interv.**
Reduction in lowest 2nd ICU day SBP by five degrees (mm Hg)	1.26	0.08	3.54	0.000	1.11 - 1.44
Increase in hypotension duration by 1 hr.	1.11	0.05	2.24	0.024	1.01 - 1.21
Age by decade	1.19	0.07	3.15	0.002	1.07 - 1.32
Hypothermia in 1st ICU day	2.20	0.60	2.86	0.004	1.28 - 3.77
Brain injury vs. multiple injury	1.96	0.49	2.71	0.007	1.2 – 3.19
Ed Disposition to ICU vs. OR	1.60	0.44	1.74	0.08	0.94 - 2.73
Injury Severity Score (ISS) by 10 points	1.02	0.09	0.17	0.86	0.85 – 1.21

3.5. Discussion

Hypotension on ICU day two has not been given enough attention compared to hypotension on ICU day one for critically ill trauma patients. We have shown in a previous analysis that a brief episode of hypotension on ICU day one increases mortality in critically ill trauma patients. In this study, we have attempted to quantify the risk of hypotension on ICU day 2 in critically ill trauma patients. We hypothesize that the risk of mortality and morbidity for those patients surviving ICU day two is better associated with hypotension severity measurement on day two than day one. In order to show the significant effect of ICU day two hypotension on mortality and morbidity, we compared most of our analysis with similar results related to ICU day one. We could not easily assess the relationship between mortality and severity of shock without accounting for length of ICU stay, ICU LOS explains many factors at the level of individual that could skew data. We combined the mortality and morbidity in relation to the severity of shock in this study by using survival analysis. We analyzed the severity of hypotension in two different ways: the depth of hypotension in mm Hg and the duration of hypotension in minutes. Based on our survival analysis model, we further quantified the risk of hypotension using Cox regression model.

Hypotension on ICU day two had a crude relative risk of mortality equal to 4.09 (C.I., 95% 2.9 – 5.9) compared to a relative risk of 2.03 (C.I., 95% 1.4 - 3.0) related to hypotension recorded on ICU day one. When we adjusted for time passed during ICU stay, the above differences became even wider. Upon grouping the patients in three groups (based upon the level of the depth and duration of the hypotension), The mean ICU stay was shorter for the expired patients and positively correlated with lowest recorded SBP of ICU day two. On the contrary, ICU length of stay was longer in the survived patients and positively correlated with lowest SBP of ICU day two. Injury severity score was positively associated with hypotension duration on ICU day two. For patients who survived ICU day one, the outcome of the group who experienced hypotension on ICU day two was significantly different than the group who did not experienced hypotension on ICU day two. Upon surviving ICU day one, hypotension on ICU day two yielded poorer outcome than hypotension on ICU day one.

For patients survived ICU day one, hypotension on ICU day two had a linear dose-response effect on trauma outcome after adjusting for the presence or absence of hypotension in ICU day one. The relative risk of mortality of hypotension on ICU day two decreased a little upon adjusting for the presence or absence of hypotension on ICU day one. This indicated that hypotension on ICU day one had some effect on the outcome. Hypotension on ICU day one for patients survived that day had a lesser effect on mortality upon adjusting for hypotension on ICU day two. This relative risk (R.R.) was 1.38, (95% C.I. 0.79 - 2.4), and not statistically significant.

We were able to quantify the relative risk of mortality related to patients survived ICU day one. The relative risk due to hypotension on ICU day two was 4.09 (95% C.I. 2.56 – 6.52), $p<0.001$. That risk is about 2.5 times greater than that of ICU day one hypotension controlling for age and ISS. We also managed to calculate the risk for each five mm Hg decrease on ICU day two and for one hour increase in hypotension duration. That risk was statistically significant and equal to 1.36 (95% C.I. 1.24-1.50), $P<0.001$ per each 5 mm Hg decrease in SBP and 1.22

(95% C.I. 1.15 -1.29), $P<0.001$, for each one hour increase in hypotension duration. Longer period can also be calculated based on the above. For example, a systolic blood pressure of 70 mm Hg on ICU day two increases in the relative risk of mortality by 3.52 (95% C.I. 2.44 –5.06). A hypotension in ICU day two for five hour adjusting for the increases the relative risk of mortality by 2.7 (95% C.I. 2.01 – 3.57).

Controlling for ISS and ED disposition (representing the subjection to surgery before ICU admission), we found that lowest second ICU day SBP, duration of hypotension on ICU day two, hypothermia on ICU day one, age, and the status of brain injury vs. multiple trauma were the strongest predictors for the adverse outcome of shock.

Trauma patients go through a critical course of illness and might have volatile presentations and progresses. Most of previous studies, which suggested further evaluation of critically ill ICU patients, were related to predicting systems such as APACHE and TRISS. These systems tend to stratify the risk for group of patients that assessing the individual's severity of the risk and complication (25, 26). These systems required collecting many elements, very difficult to calculate and in many cases the results are not available readily and come too late when they are most needed (27). Many studies suggested that these sophisticated scores are in general no better than the clinical judgment of an experience physician (14, 15). In many situation physicians need a quick and easy way to predict and monitor the outcome of ICU trauma patients to provide prognosis and to better manage their efforts and hospital resources. Using readily available hemodynemic data such as blood pressure for monitoring, though it is not suitable by itself to triage patients, it can provide a sense of direction early on and until more sophisticated multiple scoring system such as APACHE become ready for use.

Blood pressure is contemplated as one of the vital sign that needs to be measured frequently in ICU settings and as long as there is much concern about the patient's critical stability. Hypotension can be described in two ways, depth how much the level of drop in blood pressure measured in mm Hg and duration, how much elapsed time in minutes of blood pressure $\leq$ 90 mm Hg. Obtaining frequent-measurements of blood pressure to more accurately assess the severity and duration of hypotension during the ICU stay of trauma patients provides additional prognostic value that exceeds the lowest reading of hypotension in ICU day 1 alone. A daily update of shock adverse outcomes can be accomplished more accurately when we monitor systolic blood pressure accounting for the depth and duration of hypotension.

Although the founding of our study is straightforward, this study does have some limitations. We do not know how many trauma patients had episodes of SBP $\leq$ 90 outside ICU. In addition, we do not know what was the outcome of these patients. The blood pressure measurements regarding the lowest recorded readings and duration of hypotension have been obtained without a standardized protocol since we are using the available vital signs data recorded by nurses in the realm of routine patients' critical care. Nurses usually record blood pressure every 1-2 hours, unless there is a need for more frequent readings. Nurses usually do not follow standardized methods in BP measurements regarding use of noninvasive BP cuff or invasive arterial line. Many elements of our data were collected manually since many were not abstracted from permanent data records. For instance, duration of hypotension was determined by adding the period in minutes for all episodes in which systolic blood pressure was $\leq$ 90 mm Hg.

Trauma patients might die of many reasons such as MODF, head injury, MI, or infection. We did not control for the etiology of hypotension episodes and therefore we do not know how they are related to the exact reason of death. For example, a patient might be suffering from ongoing hemorrhage causing severe hypotension, but die of a new myocardial infarction or embolism. Many of trauma patients presented with multiple injuries and in different parts of the body. We did not carry out a separate analysis based on the presence/absence of head injury however, we found that head injury increased the risk for death in shock patients. The effect of hypotension duration and magnitude may be different with or without head trauma. Finally, we did not account for all medications that affect blood pressure. Certain trauma patients were receiving vasopresser medications during the first 48 hours of ICU care and such treatment might mask the clinical manifestation of shock and hypotension.

The increase in duration of hypotension during the second ICU day to a limit exceeding four hours doubles the risk of mortality due to hypotension. The risk of prolong in hypotension duration can be independent of the risk hypotension depth measured in mm Hg but with considerable interactions. This study illustrates the importance of continuous blood pressure monitoring during the first 48 hours of ICU stay and the necessity of taking quick actions in correcting hypotension promptly. This study emphasizes a notion that a more current measurement of SBP can be more instrumental in predicting trauma patients prognosis than previous measurements. Future studies will include other related shock characteristics similar to hypothermia, quantity of blood transfusion, and medications given to improve circulation are necessary to provide more solid understanding of shock outcome and outcome prediction. In addition, it might be important for future studies to take into consideration the level of organ involvement and its affect on hypotension and related outcome. The results of this study add more understanding to the physiology of shock and resuscitation and this data will participate in improving trauma care management.

The practicality of monitoring hypotension severity over a period of time provides the ability to identify patients who are likely to expire surrendering to their illness, this is important in specific occasions such as communicating with patient or family, allocating the efforts and assuring the provision of resources. Also, those who are going to survive their trauma according to whatever clinical hints and clues might be available, hypotension severity from day one and two might predict the speed of the recovery. Such predication privilege might add another beneficial tool for the critical care provider.

In conclusion, hypotension on ICU day 2 is associated with an overall high mortality in those severely injured patients. Hypotension severity on ICU day 2 predicts the risk of adverse outcomes for those survived ICU day one. That prediction is more accurate than depending on ICU day one hypotension records. Patients who are prone to have episodes of hypotension should be seriously monitored and consistently hemo-dynamically stabilized.

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4. THIRD PAPER: PREDICTION OF HYPOTHERMIA AND RELATED MORBIDITY AND MORTALITY IN SEVERELY INJURED PATIENTS

Manuscript in preparation

4.1. Abstract

Background and Significance:

Trauma represents the leading cause of death for young adults in their most productive years and incurs substantial short and long term disability. Death from trauma results in an annual loss of 492 years of productivity per 100,000 and costs $230 million a day. Most mortality and related medical expenses were incurred early during critical care units stay. Trauma patients frequently develop hypothermia up to 66%. Hypothermia is a valuable indicator for shock outcome, yet it has not been utilized efficiently as much as other shock indicators to predict the outcome of shock and successfully resuscitate severely injured trauma patients.

Methods:

Trauma patients admitted to Intensive Care Unit (ICU) from 1999–2000 were evaluated and 455 patients included in the analysis. The lowest temperature and the cumulative duration in minutes of all episodes of temperature $\leq$ 36 °C were recorded during the first ICU day. Hypotension severity, total ICU Length of Stay (ICU LOS) and the survival status were recorded. Head injury status and many other pre-hospital (PRH) and Emergency Department (ED) variables have also been used for function and relationships adjustment. Chi-square statistics, Fisher exact, regression, survival analysis, and Cox regression were used in the analysis.

Results:

There were 243 (53%) hypothermic and 212 (47%) non-hypothermic patients in the collected data. Hypothermia depth and duration correlated with hypotension, ISS, and many other parameters. Patients with hypothermia had an increased in mortality rate, $P<0.0001$. Survivors

with hypothermia in the first ICU day had on average longer ICU LOS, $p<0.003$. This was also seen Cox regression . The relative risk of hypotherma, was 3.85, (95% C.I. 1.89 – 7.82) for multiple trauma injury and 2.91 (95% C.I. 1.15 – 3.18) for head trauma injury. The relative risk per one °C decrease in body temperature and one hour increase in hypothermia duration were also provided. Hypothermia in the first ICU day was a strong factor affecting trauma outcome on Cox regression. Both depth and duration of hypothermia were predictable using PRH and ED variables with linear regression models. Hypothermia status was predicted where pre-ICU hypotension, hypothermia, ED blood transfusion, and other hypoxia related conditions were statistically significant for multiple trauma patients. For head injury patients, ED hypotension and ED GCS were the most statistically significant predictors.

Conclusion:

Hypothermia in the first ICU day is a very important predictor of mortality and morbidity in trauma. Hypothermia in the first ICU day can be predicted based on PRE and ED information. Such prediction can aid in shock management and improve the overall trauma outcome.

4.2. Introduction

Trauma represents the leading cause of death for young adults in their most productive years and incurs substantial short and long term disability. Death from trauma results in an annual loss of 492 years of productivity per 100,000 in population and costs $230 million a day (1). Most of these mortality and related medical expenses were incurred early during critical care units' stay. Trauma patients frequently develop hypothermia with up to 66% occurrence. Hypothermia in trauma patients is generally regarded as an alarming feature of shock, yet the precise temperature at which hypothermia affects prognosis has not been determined. Many survivors noted with low temperature have been previously thought to have irreversible detrimental effects (2). Many risk factors determine the severity of hypothermia in trauma, including extraction time, transport time, severity of hemorrhage, extent of head injury, and the presence of drugs and Alcohol in the trauma victim's blood (3).

Hypothermia is marked by an unusual and significant drop in core body-temperature. Although the exact threshold that indicates hypothermia as a low core body temperature is unclear, patients are generally treated for hypothermia when core body temperature drops to around 36.0° (versus a normal body temperature of 37.0 °C) (4-5). Hypothermia is a life-threatening condition that can trigger extensive physiological reactions. It is regarded as a significant co-morbid factor in trauma patients. Hypothermia is one of the major manifestations and frequent complications of hemorrhagic shock in trauma patients (6). Many of these complications are related to the stimulation of physiologic stress response in the body and trigger pathological reactions in most organs and systems (3,7). Among these adverse effects are acidosis, coagulopathy, organic failure, and death (8-10). Hypothermia is associated with decreased cerebral blood flow, decreased oxygen requirement, reduced cardiac output, and decreased arterial pressure, thus it can affects the morbidity and mortality of trauma and interfere with the course of treatment. (11).

One major concern in the etiology of hypothermia is whether it is the result of shock itself or due to shock resuscitation. Answering such intriguing questions is not only important for hypothermia management but also essential to quantify the risk of hypothermia. Animal experiments have shown that changes in systolic blood pressure are associated with changes in core temperature during hemorrhage and resuscitation. These studies indicate that both hypotension and hypothermia are related to the pathophysiology of shock rather than to resuscitation itself (12). A study of severely injured intubated trauma patients showed that injury severity and survival correlate with hypothermia severity measured by an esophageal probe (13). It is well-documented that the incidence of hypothermia in trauma patients is significantly high and independent of the month of admission (14). In spite of the high incidence of hypothermia in multiple trauma patients, body temperature is not checked frequently and hypothermia usually underestimated (15 16). A study of a large cohort of 642 reveals that patients with severe or even moderate injury are less likely to have their temperature measured (64%) than those with mild injury severity (79%) (15). The incidence of hypothermia among injured patients on admission was up to 66% according to different studies (2, 13). Despite the high incidence and importance of hypothermia, it has been given a lower priority in monitoring shock patients compared to other manifestations such as hypotension, blood transfusion, and base deficit (12). Many studies encouraged the utilization of readily available hemodynamic and other measurements in assessing the severity of shock. In this study, we will examine the predictive utility of hypothermia severity in relation to survival and speed of recovery in severely injured trauma patients. We will also attempt to identify the related pre-hospital and emergency department variables that help in predicting hypothermia early in the surgical and trauma ICU units.

4.3. Patients and Methods

All trauma patients defined as those patients managed by trauma services who had been admitted to the ICUs at the University of Pittsburgh Medical Center from 1999 to 2000 were prospectively reviewed (n=783). Patients who had minimal injuries and were transferred to a ward in less than 48 hours after admission (n=247) were excluded. Such exclusion is necessary to eliminate intoxicated patients who seemed initially severely ill, but improved quickly upon Alcohol clearness. The selection of 48 hours as a cut-off is based upon clinical experience of improvement in the non-severely injured patients and as has been used in previous studies (17). We also excluded 62 patients from the above population due to incomplete data necessary for the analysis of this study leaving us with 474 as potential patients for this study. The data of all remaining eligible patients was obtained from the ICUs medical records including demographics, vital signs, laboratory test results, and other hemodynamic measurements. Additional data for the study subjects related to demographic, admission, emergency department, procedures, complications, and outcomes was gathered from the center's trauma registry and the hospital's medical records. We also excluded patients who had primary hypothermia as a main mechanism of injury (n=2) and patients with brain injuries who received hypothermia protocol in their critical care management (n= 17). Since these types of hypothermia (as primary injury and therapeutically induced respectively) are not a direct result from shock or trauma complications (5,181). The remaining (n=455) patients entered the study analysis. The study population consists of 329 men (72%) and 129 women (28%), which also approximately reflects the general gender ratio in trauma patients.

Hypothermia was defined as a temperature of $\leq$36 °C. The lowest temperature and duration in minutes of all episodes were retrieved during the first 24 hours of ICU care. A temperature of $\leq$36 °C was selected as a cut off based on the convention and in reference to many papers published in the trauma field (19-21). Duration of hypothermia was defined as the elapsed time in minutes from initial temperature of $\leq$36 °C until the next recorded temperature >36 °C. Hypotension was defined as a systolic blood pressure (SBP) $\leq$ 90 mm/Hg. Pre-terminal episodes of hypotension were excluded from these criteria. Hypotension duration was defined as the elapsed time in minutes from initial SBP of $\leq$90 until the next recorded SBP >90 mm Hg. The lowest SBP and the cumulative duration in minutes of all episodes of SBP $\leq$ 90 mm Hg were recorded during ICU days one and two for all patients in this study. An ICU day for this study is defined as a complete 24 hours from the time of ICU admission. Hypothermia and hypotension duration records for patients in this study were obtained from the available critical care records. ICU nurses gathered vital signs information and recorded values generally every 1-2 hours or more frequently as needed.

The primary outcome of interest was the probability that the patient would die during the ICU stay stay and the secondary outcome was the intensive care unit length of stay (ICU LOS). Other vital signs and other resuscitations variables such as blood transfusion, lowest 24 hours base deficit, highest 24 hours lactate, the recipient of vasopressers were also collected. We collected prehospital (PRH) variables such as mechanisms of injury, class of injury, lowest systolic blood pressure, lowest recorded temperature, and number of intervention procedures implemented before arriving to emergency department. All related Emergency Department (ED) variables were also obtained such as number and injury categories, lowest SBP, lowest temperature, quantity of blood, blood products transfused, intubation, ventilation, number of procedures in ED, and the subjection to CPR since the injury. In addition, we retrieved information regarding ISS, AIS Score, Revised Trauma Score, base deficit, pH, hematocrit, ethanol in blood, ED elapsed time, and ED disposition. Other variables related to Operating Room (OR) were also obtained including: number of surgical procedures, quantity of crystalloid given in OR, and blood transfusion. We also retrieved the number of all preexisting illnesses and number of all complications regarding the related trauma hospitalization. T-test and Wilcoxon rank sum test were used to compare continuous variables. Chi-squared test was used to test significance in categorical variables. A p value of $\leq$ 0.05 was used to determine statistical significance. Linear regression, survival analysis, and Cox regression were also used in the analysis.

4.4. Results

In the remaining 455 patients entered in the analysis, 130 (28.6%) died during the course of hospitalization and 325 (71.4%) survived. The average age for all patients was 48$\pm$ 23 years. The average ICU and the total hospital Length of Stay (LOS) for the entire group was 9.3 $\pm$ 10 days and 14.9 $\pm$ 14.8 days, respectively. The average injury severity score (ISS) and Revised Trauma Score was 27.8 $\pm$ 12.4. and 4.5 $\pm$ 2.9 respectively. Examining the differences of the average age and average ISS, we found that those who died were older ($p<0.001$) and more severely injured ($p<0.01$) (age 55.6 $\pm$ 25.7 years; ISS, 30.2 $\pm$ 13.6) than those who were discharged from the ICU alive after 48 hours (age 44.9 $\pm$ 21.0 years; ISS, 26.9 $\pm$ 11.7).

Of the total 455 patients in this study, 243 (53.4%) patients had at least one episode of hypothermia and 212 patients (46.6%) patients had no episodes of hypothermia. Of those 243 patients with hypothermia 98 (40%) died and 145 (60%) survived compared to the 212 patients without hypothermia 32 (15%) died and 180 (85%) survived. The above data provided an odds ratio of 3.8 (95% C.I. 2.4 – 5.99 ($p < 0.0001$). This indicates that patients with hypothermia during the first ICU day have a worse outcome than patients without hypothermia.

Of the 212 patients who were non-hypothermic, 148 (70%) had multiple trauma in which 138 (93%) survived and 10 (7%) died; and 64 (30%) had head trauma (expressing brain injury) as the main trauma in which 42 (66%) survived and 22 (34%) died. Of the 243 patients who had hypothermia, 143 (59%) had multiple trauma in which 104 (73%) survived and 39 (27%) died; and 100 (41%) had head injury as the main trauma in which 41 (41%) survived and 59 (59%) died. (Figure 24). The odds ratio of death for hypothermic patients in the multiple trauma group was 5.18 (with 95% C.I. 2.39 - 12.11) ($p<0.001$ on Chi^2 test). The odds ratio of death for hypothermic patients in head trauma as the main injury group was 2.74 (with C.I. 1.36 – 5.57) ($p<0.01$ on Chi^2 test).

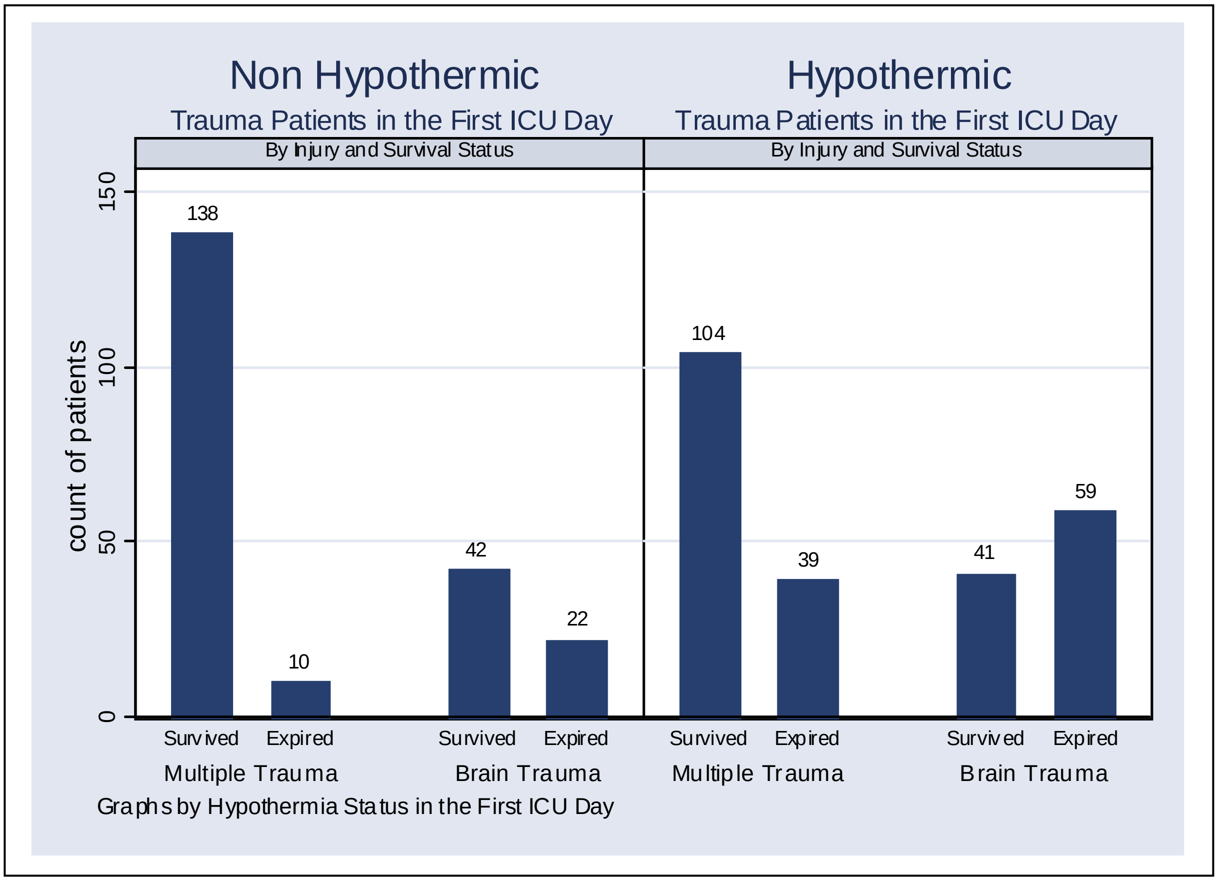

Figure 24. Illustrates the count of trauma patients according to hypothermia status on the first ICU day and survival by injury (multiple injury vs. brain injury mainly)

The average ICU LOS of hypothermic surviving patients was 12.66 ($\pm$ 11) and for the non-hypothermic survived patients was 10.23 ($\pm$ 9.8). A t-test indicate statistically significant differences with a $p < 0.0367$. Trauma patients with hypothermia had a longer ICU length of stay when survived compared with patients without hypothermia. When we plotted the duration of hypothermia against ICU LOS using linear regression the length of stay increased in the survivors as hypothermia duration increased ($P<0.0001$) (Figure 25). The length of stay in contras is negatively related to hypothermia duration in expired patients due to quicker death. (P <0.03).

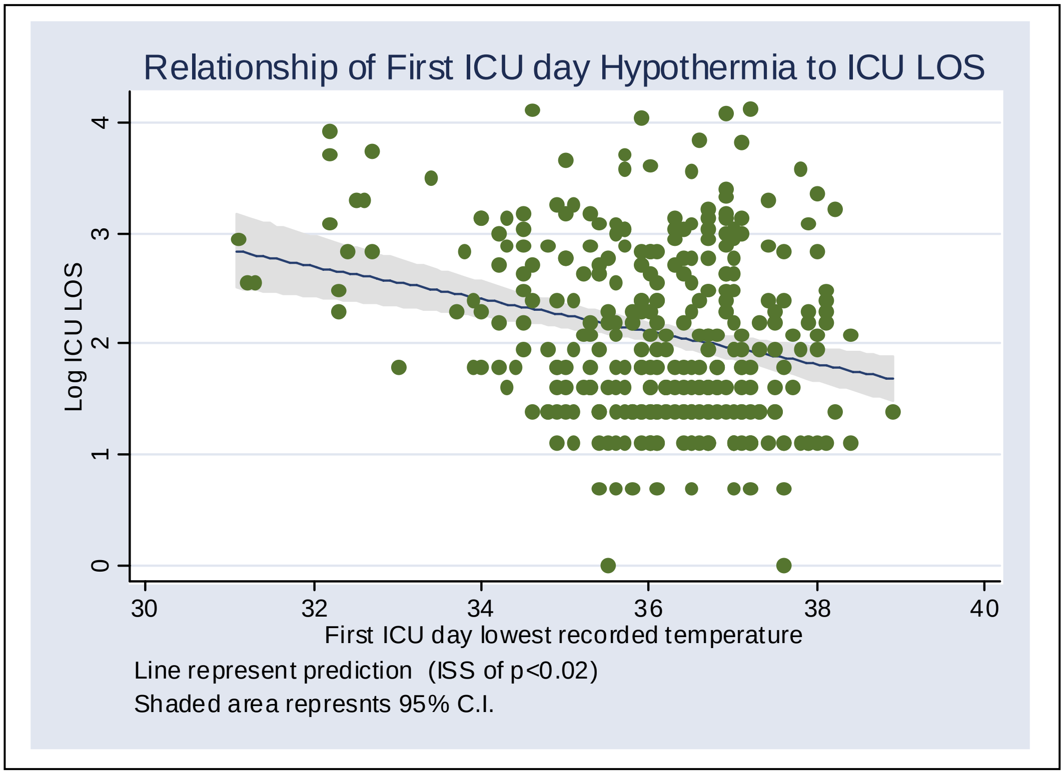

Figure 25. Shows the relationship between hypothermia on the first ICU day (°C) and ICU LOS

In the 240 hypothermic patients, a negative correlation has been observed between the lowest recorded temperature (representing the depth of hypothermia) and the sum duration of all hypothermic episodes in minutes (representing duration of hypothermia) by Spearman's Correlation Test with rho= -0.47 and p<0.001. Figure 26.

A positive association has been observed between hypothermia depth in °C of ICU day one and lowest recorded SBP in mm Hg of the ICU day one using Spearman's rank test for both survived and expired patients, rho = 0.22, P<0.0001 & rho = 0.34, P<0.001 respectively, (Figure 27). A linear regression was also significant for the above relation (P<0.001).

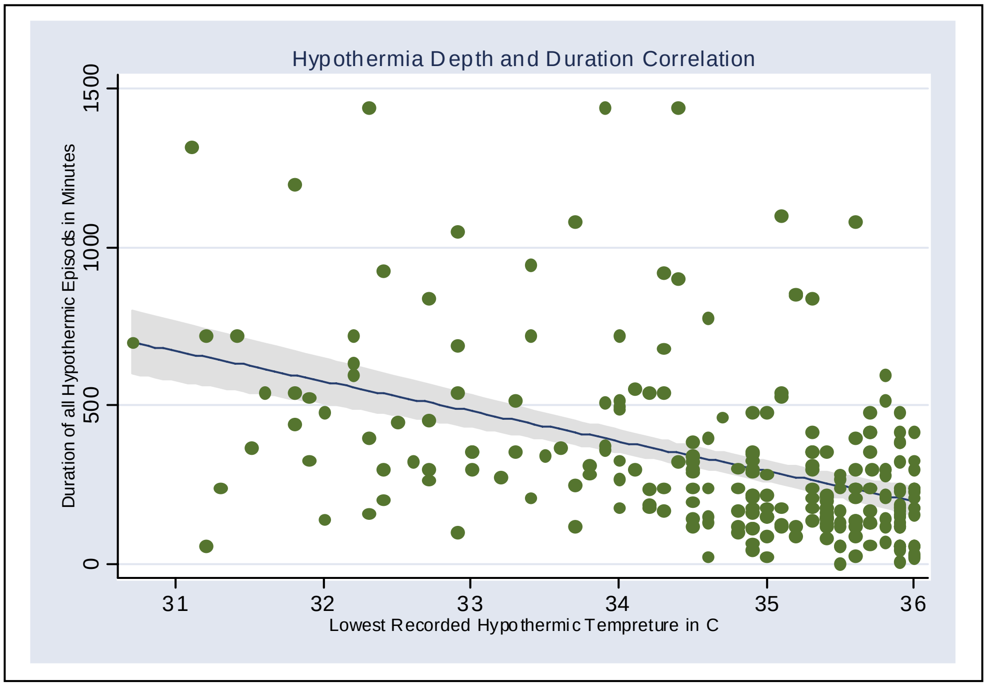

Figure 26. Hypothermia on the first ICU day depth and duration correlation

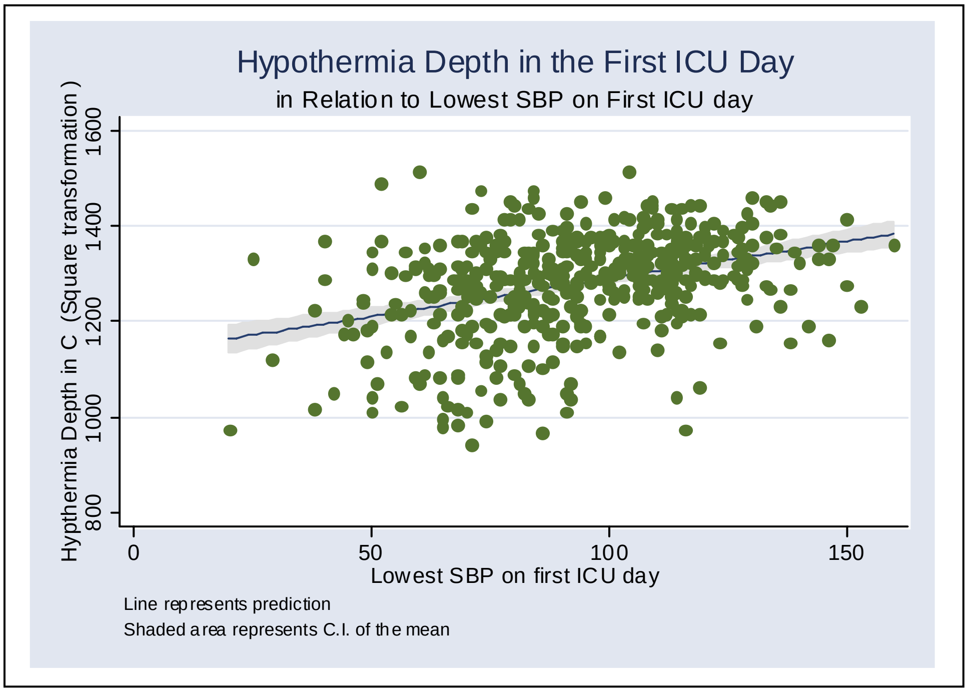

Figure 27. The association between ICU day one lowest systolic blood pressure to the depth of ICU day one hypothermia

A negative association has been observed between the lowest SBP in mm Hg of the first ICU day and hypothermia duration in minutes of ICU day one. A linear egression indicated a significant fit of p<0.01 which indicate the hypotension severity predicts hypothermia duration of ICU day one (figure 28)

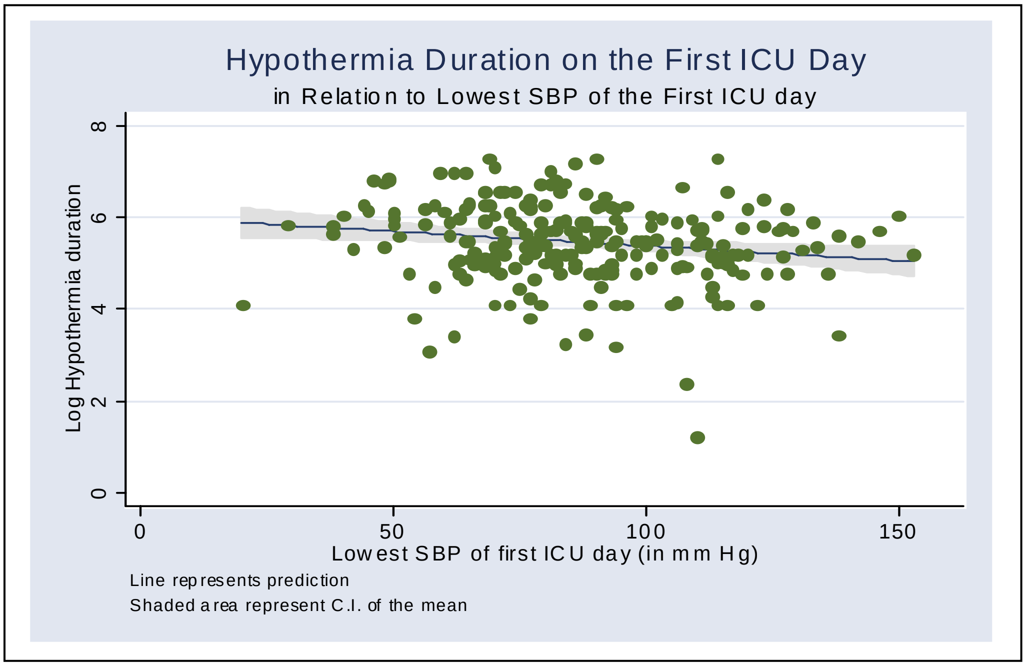

Figure 28. The association between ICU day one lowest systolic blood pressure and the duration of ICU day one hypothermia

Additionally, a positive association has been observed between hypothermia duration on ICU day one (in minutes) and hypotension duration on ICU day one (in minutes) using Spearman's rank test for both survived and expired patients, rho = 0.20, P<0.001 & rho = 0.23, P<0.01 respectively, (Figure 29).

A negative association has been observed between ISS and lowest recorded ICU day one temperature (in square root of °C). ISS has been shown to predict the severity of hypothermia using linear regression (p<0.001), (Figure 30).

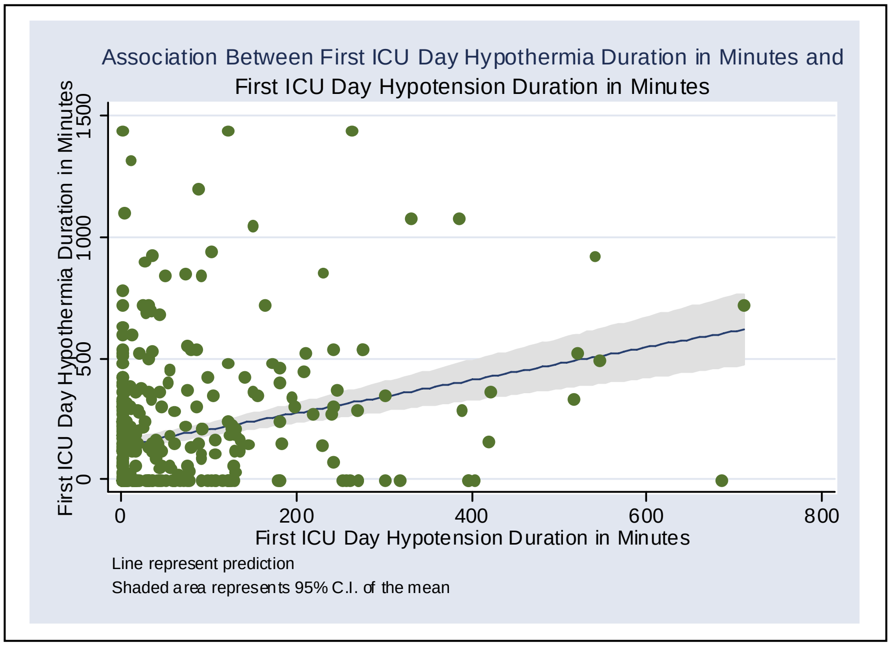

Figure 29. The association between the hypothermia duration on ICU day one and hypotension duration on ICU day one.

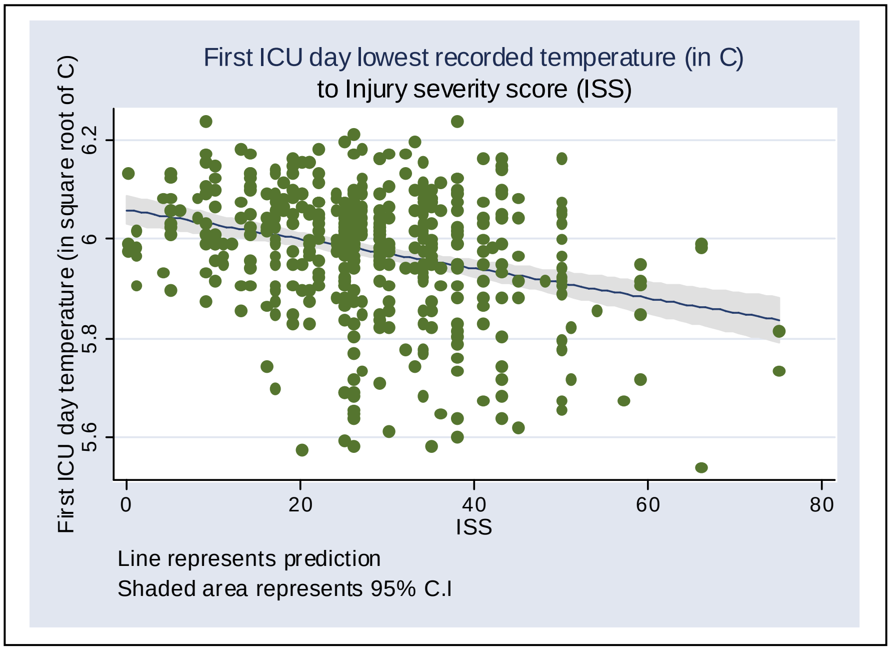

Figure 30. The association between ICU day one hypothermia depth and injury severity score.

A positive association has been observed between hypothermia duration of ICU day one in minutes and ISS using Spearman's Rank test for both survived and expired patients, rho = 0.20, P<0.001 & rho = 0.20, P=0.02 respectively. The above relations were also significant on linear regression, (Figure 31).

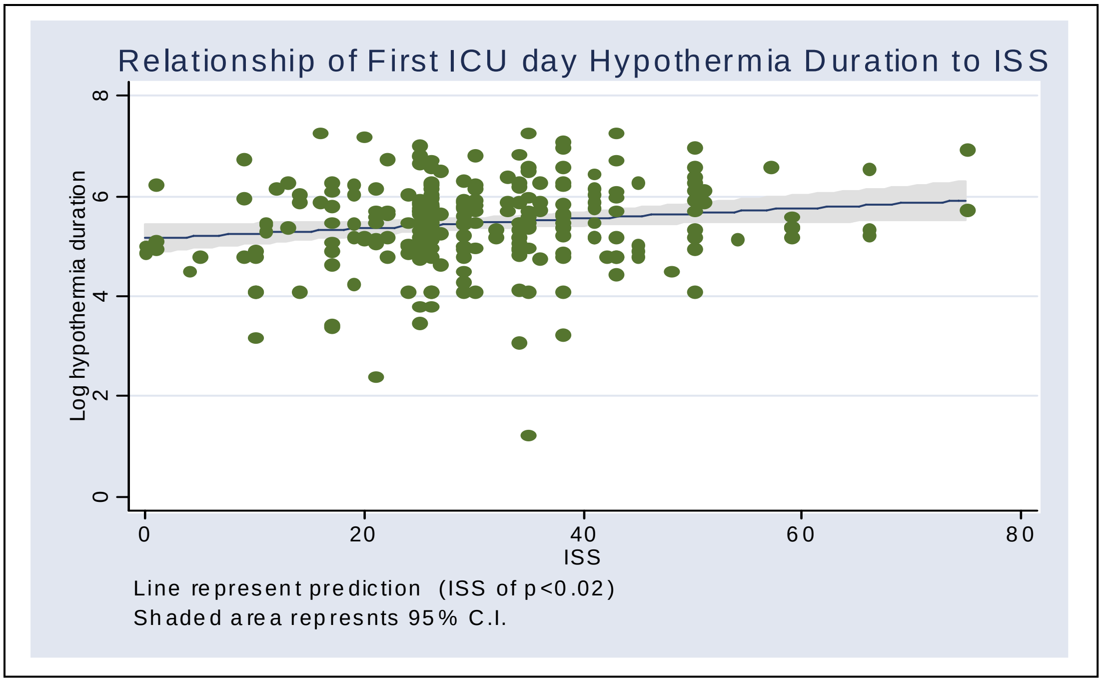

Figure 31. The association between ICU day one hypothermia and injury severity score

Univariately, our data revealed differences between ICU hypothermic and non hypothermic groups (expressed in depth and duration) according to many variables and in all stages of resuscitation including pre-hospital arrival, emergency department, operating room, and intensive care units. The difference was statistically significant in ISS, AIS score, Glasgow Coma Score (GCS) recorded in ED, lowest pre ICU temperature, hematocrit tested in ED, blood transfused in ED, Ethanol tested in ED, and ED time in minutes. We could not see any differences in age, ED base deficit, or pH tested in ED. The difference was also significant according to number of operations, OR procedures across hospitalization, and OR crystalloid, blood, fresh frozen plasma and platelet transfusion. The first ICU day differences between hypothermic and non-hypothermic groups were also statistically significant according to the lowest recorded ICU day one systolic blood pressures (SBP), ICU base deficits, highest recorded ICU lactate values, Pao2/Fio2 ratios, and ICU blood transfusions (Table 6).

Table 6. Continuous variables sorted by hypothermia status and tested for significance differences

	Non Hypothermic			**Hypothermic**			**significance**
Continuos variables	**Obs.**	**mean**	**SD**	**Obs.**	**mean**	**SD**	**P value**
Age	212	48.4	22.8	243	47.6	23.3	0.656 ++
ISS	212	24.92	10.8	243	30.34	13.03	**<0.0001*** +
AIS Score	212	18.72	11.5	243	21.50	13.35	**0.027*** ++
GCS in ED	206	9.27	5.58	242	7.35	5.39	**<0.001*** ++
Lowest pre-ICU Temp. °C	171	36.03	0.83	182	35.68	0.96	**<0.001*** +
Hematocrit in ED	190	37.75	7.05	212	35.23	7.3	**<0005*** +
Blood in ED	211	0.32	1.11	241	1.19	2.46	**<0.0001*** ++
PH tested in ED	131	7.2	0.12	174	7.29	0.139	0.199 +
Base deficit in ED	127	-4.65	5.7	167	-5.77	7.27	0.154 +
Alcohol tested in ED	134	49.77	85.7	143	75.03	104	0.075 ++
Ed time in minutes	211	120.8	88.7	241	90.63	68.53	**<0.001*** +
Number of operations	212	1.08	1.23	242	1.48	1.63	**<0.01*** ++
Blood in OR trasf..	211	2.3	7.23	243	4.42	9.22	**<0.001*** ++
Crystalloid in OR	212	3.03	4.61	243	3.89	5.07	0.06 ++
FFP in OR	212	0.84	3.65	243	2.26	5.72	**<0.001*** ++
Platelets in OR	212	0.929	4.91	243	2.44	6.99	**<0.002*** ++
Lowest ICU day 1 SBP	212	100.1	22.8	243	87.13	23.9	**<0.0001*** +
ICU day 1 base Deficit	137	-4.84	0.36	196	-7.47	0.38	**<0.0001*** +
ICU day 1 highest lact.	81	3.74	0.32	125	8.0	1.00	**<0.001*** ++
ICU blood trasf.	207	378	750	241	1340	268	**<0.0001*** ++
PaO2/FiO2	133	2.78	1.47	193	2.42	1.68	**<0.01*** ++

+ t-test,
++ Wilcoxon rank-sum test

We used Fisher's Exact test to illustrate any differences in the median of first ICU day hypothermia status according to all categorical variables in our data. We ran the test using both lowest recorded first ICU day temperature measured in °C, (depth) and the sum of all hypothermia episodes in minutes, (duration). (Table #7). Patients with prehospital hypotension and ED hypotension had a lower average ICU temperature and longer hypothermia duration than those with no hypotension at these points. Patients with pre-ICU hypothermia had lower average ICU temperature and longer hypothermia duration than patients with no pre-ICU hypothermia. Patients subjected to intubation in pre-hospital period, had pre-ICU ventilation, and received CPR pre-ICU had lower ICU temperature and longer hypothermia duration. The ED disposition of OR vs. ICU was also statistically different in trauma patients according to hypothermia status. Patients sent to surgery following ED disposition were at higher risk for developing hypothermia than patients sent directly to ICU following ED disposition. There were significant differences between patients who had brain injuries as a main insult compared to those with multiple injury groups. Our data showed no differences in sex, race, injury season, injury class (blunt vs. penetrating), and the subjection to surgery in the entire course of hospitalization. Figures 32 & 33 visually show the above variables against the median of lowest temperature and duration of ICU day one hypothermia.

Table 7. Categorical variables tested against median differences in hypothermia depth and duration for differences

Categorical variables *(All Yes vs. No unless specified)*	**Differences in median reporting 2-sided Fisher's Exact**[++] *(split equally the values equal to median)*	
	ICU day one hypothermia depth in °C	**ICU day one hypothermia duration in minutes**
Sex (male vs. female)	P=1.00	P=0.916
Race (white vs. others)	P=0.819	P=0.567
Pre hospital hypotension	**P<0.001***	**P<0.001***
Hypotension in ED	**P<0.001***	**P<0.001***
Hypotension In ICU day 1	**P<0.001***	**P<0.001***
Vasopressers given in 1st ICU day	**P<0.001***	**P<0.001***
Pre ICU hypothermia	**P=0.011***	**P=0.011***
Pre-hospital CPR	**P<0.001***	**P=0.001***
CPR in the ICU	P=0.413	P=0.188
Pre hospital intubation	**P=0.025***	**P=0.003***
Pre ICU ventilation	**P<0.001***	**P<0.001***
Post Ed disposition (OR vs. ICU)	**P<0.001***	**P=0.001***
Surgery in course of hospitalization	P=0.332	P=0.494
Injury class (blunt vs. penetrating)	P=0.106	P=0.078
Injury season (cold vs. warm)	P=0.694	P=0.767
Arrival (air vs. ambulance)	P=0.356	P=0.471
Brain injury as a main injury	**P=0.014***	**P=0.040***
Death	**P<0.001***	**P<0.001***

[++] *Split equally the values equal to median between the two groups*

We looked at the relation of pre-ICU hypothermia and ED hypotension in relation to lowest recorded ICU day one temperature. We found on linear regression that these pre ICU measures of lowest systolic blood pressure and lowest temperature predicts hypothermia on ICU day one with $p< 0.001$and $p>0.01$ respectively. (Figures 33 and 34)

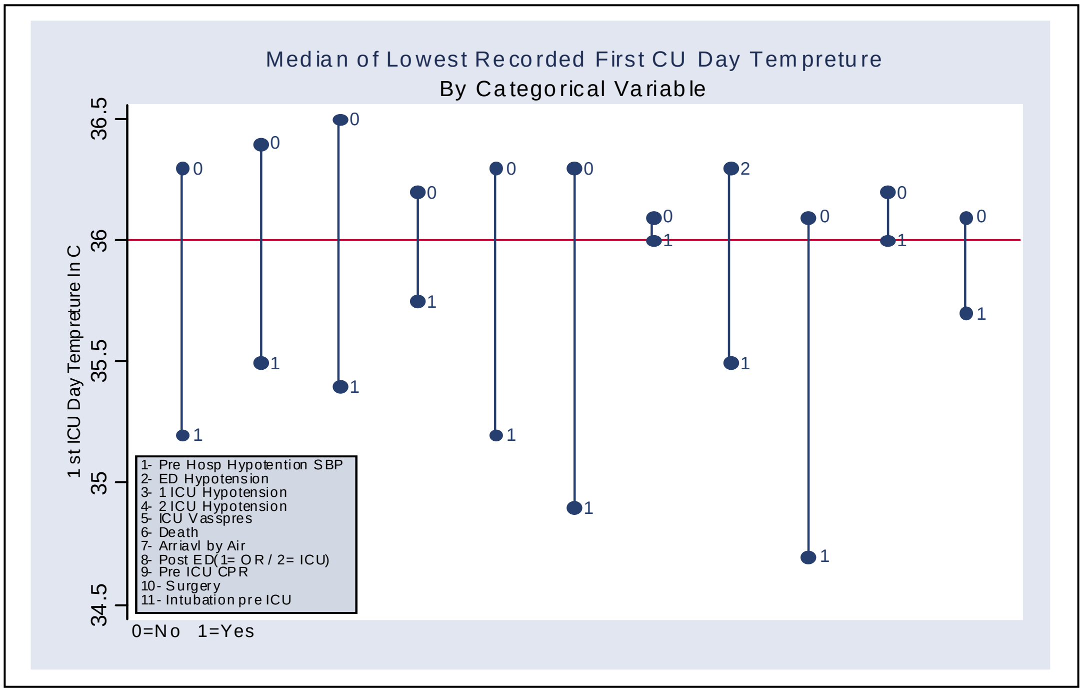

Figure 32. **Categorical variables against the median lowest ICU day one temperature.**

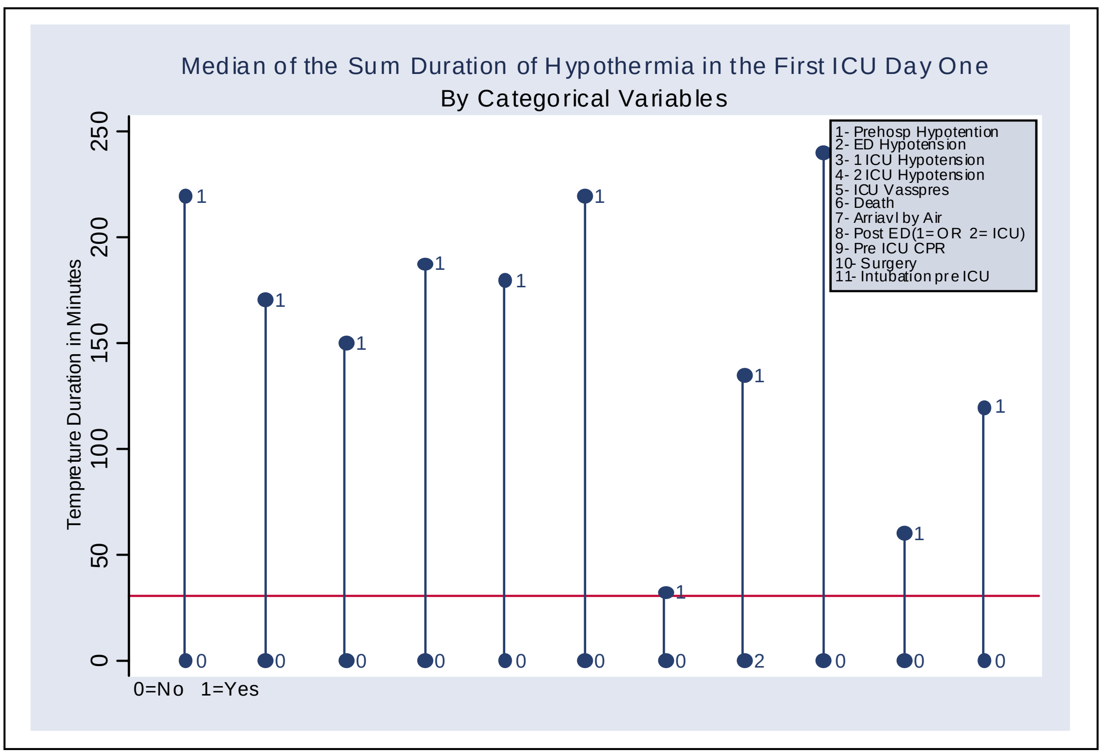

Figure 33. Categorical variables against the median of duration of ICU day one hypothermia

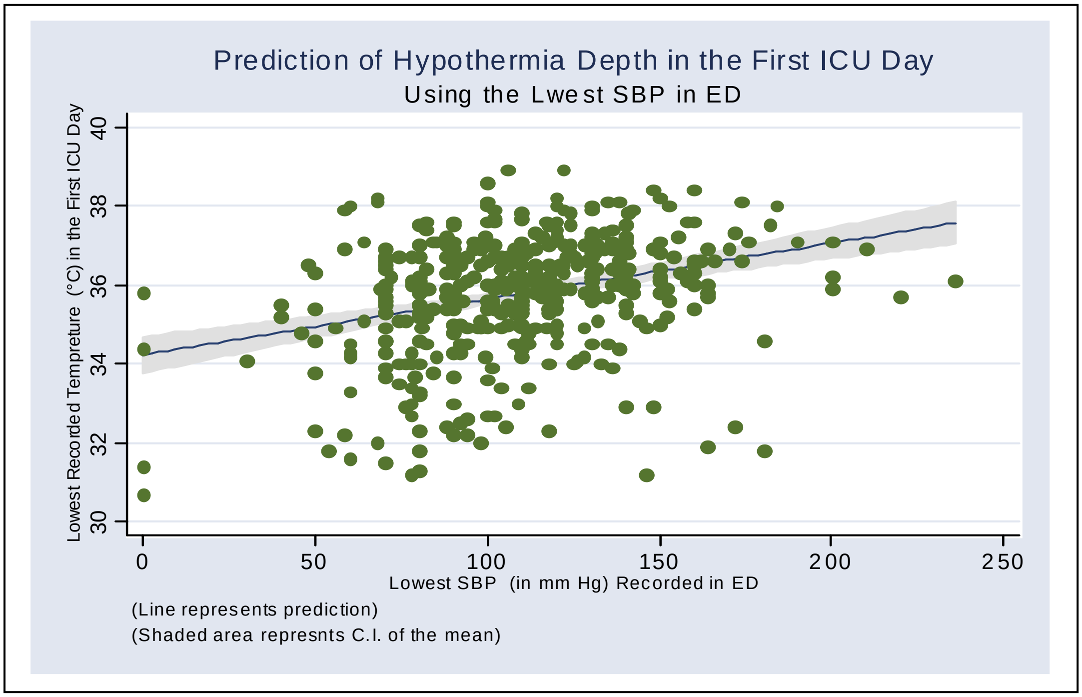

Figure 34. The prediction of hypothermia based on ED lowest systolic blood pressure

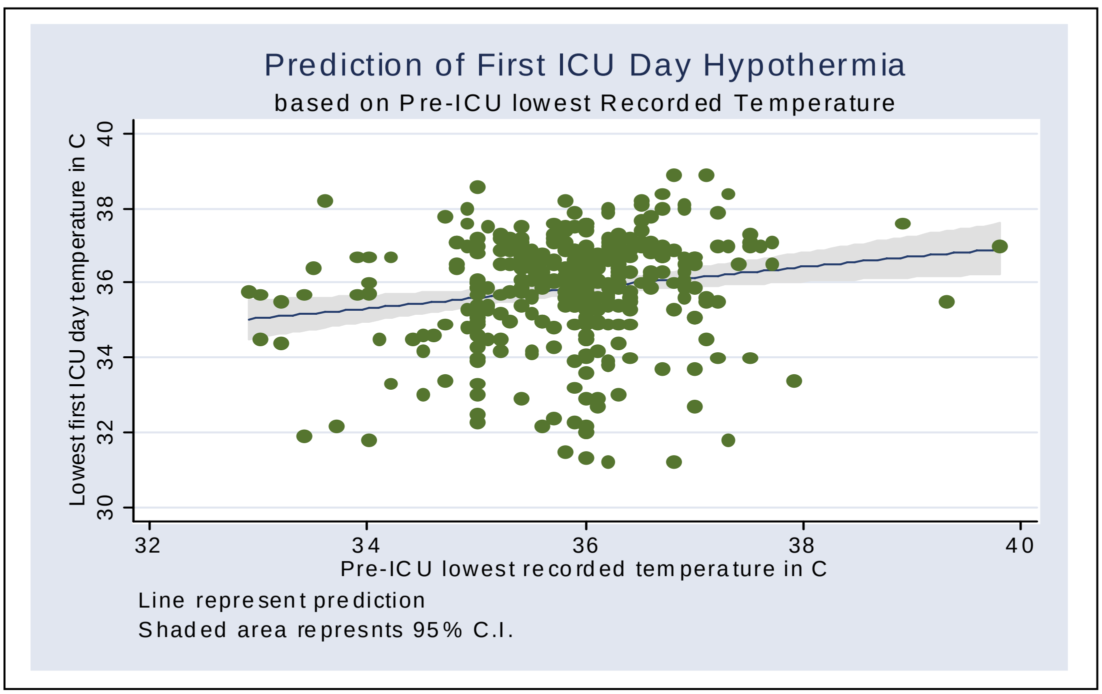

Figure 35. The prediction of hypothermia based on pre-ICU lowest recorded temperature in °C

We attempted to fit a linear regression model in order to indicate the most related variables that can be associated and predicting the duration and depth of hypothermia in the first ICU day. We managed to fit the lowest recorded first ICU day temperature without any transformation. A log transformation was necessary for the first ICU day hypothermia duration. We have realized that the status of brain injury strongly affects the quality of fit; therefore, we decided to perform the test separating the data by brain injury status.

First, we attempted to test predictors for the lowest recorded ICU day one temperature, which represents the depth of hypothermia. In the group with multiple trauma, the quantity of blood transfused in ED, the subjection to CPR pre-ICU, ventilation pre-ICU, the disposition to OR vs. ICU, older age, and higher ISS were statistically significant. The model were highly significant ($F<0.001$), with 289 observation and successfully represented 30 % of the data variability (table 8). Similarly, in the group with mainly brain trauma, only hypotension in ED, GCS, and ED disposition were highly statistically significant after controlling for injury class, age and ISS. In addition, the model was highly significant ($F<0.01$) with 157 observation and successfully representing 25 % the data variability (table 8).

Next, we attempted to test predictors for the sum log duration in minutes for all episodes of first ICU day one temperature of $\leq$36 °C, which represents the duration of hypothermia. In the group with multiple-trauma, the quantity of blood transfused in ED, subjected CPR pre- ICU, penetrating vs. blunt injury, older age, and higher ISS were statistically significant. The model was highly significant ($F<0.001$) with 141 patients and successfully represented 17 % of the data variability (table 9). Similarly, in the group with mainly brain trauma, only low GCS and quantity of blood transfused in the OR were highly statistically. The model again was significant (F<0.01) with 97 observation and successfully represented by 12% of the data variability (table 9).

Table 8. ICU day one hypothermia depth (°C) predictors based on multiple injury vs. brain injury

Linear regression , lowest recorded temperature in ICU as the outcome variable					
	Independent Variables	**Coef.**	**Std. Err.**	**P> |z |**	**95% C.I.**
Multiple Injury	Blood transfused in ED	-0.18	0.04	0.001	-0.25 -0.11
Observations 289	CPR pre-ICU	-1.02	0.29	0.001	-1.60 -0.44
F<0.0001,	Ventilation pre ICU	-0.41	0.15	0.009	-0.72 -0.11
R^2= 0.30	ED disposition	0.58	0.15	0.001	0.27 0.90
	Age	-0.01	0.004	0.005	-0.02 -0.003
	ISS	-0.02	0.006	0.003	-0.03 -0.007
Head Injury	Hypotension in ED	-1.1	0.27	0.0001	-1.63 -0.56
Observations = 157	Drop in GCS in ED	0.08	0.02	0.004	0.27 0.14
F<0.001	ED disposition	0.84	0.28	0.003	0.30 1.39
R2=0.25					

Table 9. ICU day one hypothermia duration (in minutes) predictors based on multiple injury vs. head injury

Linear regression , ICU day one hypothermia duration in minutes as the outcome variable					
	Independent Variables	**Coef.**	**Std. Err.**	**P> |z |**	**95% C.I.**
Multiple Injury	Blood transfused in ED	0.72	0.02	0.003	-0.24 -0.12
Observations = 141	CPR pre-ICU	0.34	0.2	0.089	-0.53 0.74
F<0.001,	Injury class	0.29	0.17	0.093	-0.05 - 0.64
R2= 0.17	Age	0.007	0.003	0.02	0.001 0.013
	ISS	0.12	0.004	0.014	0.0023 0.02
Head Injury	Blood transfused in OR	0.1	0.05	0.034	0.007 0.19
Observations = 97	Drop in GCS in ED	-0.09	0.03	0.001	-0.14 -0.37
F<0.001					
R2=0.12					

We also tried stepwise Logistic Regression, which examined a binary outcome of hypothermia (temperature $\leq$36 °C) on the first ICU day. For the entire data collected, pre-ICU hypotension and hypothermia were together the most statistically significant factors without the correction of other variables. This was also observed on linear regression (Figure 34 & 35). We sorted our date on the bases of head trauma vs. multiple-trauma. Pre-hospital hypotension, blood transfused in ED, the subjection to CPR pre ICU, age increase by decade, and ISS by ten points were the most significant predictors for multiple-trauma patients with hypothermia on ICU day one. For head trauma group only hypotension observed in ED and decrease in GCS measured in ED were the most predictors for ICU day one hypothermia. Table 10 illustrates the above and provide all related odds ratio and confidence intervals.

Table 10. Hypothermia predictors based on multiple injury vs. brain injury

Logistic regression, developing hypothermia in ICU as the outcome variable					
	Independent Variables	**Odds Ratio**	**Std. Err.**	**P> |z |**	**95% C.I.**
Without sorting Observations = 351 P<0.001, R2= 0.03	Hypotension in ED	2.13	0.54	0.01	1.31 – 3.49
	Hypothermia pre-ICU	1.64	0.37	0.03	1.05 – 2.55
Multiple injury Observations = 223 P<0.0001, R2= 0.12	Hypotension pre-Hosp.	2.1	0.76	0.04	1.02 - 4.27
	Blood transfused in ED	1.28	0.13	0.02	1.04 - 1.56
	CPR pre-ICU	3.88	2.7	0.05	0.98 – 15.4
	Age increase by decade	1.17	0.08	0.03	1.02 - 1.34
	ISS by 10 points	1.34	0.17	0.02	1.04 – 1.72
Brain injury Observations = 157 P<0.001, R2= 0.08	Hypotension in ED	4.73	2.47	0.003	1.71 – 13.1
	Drop in GCS in ED	0.92	0.04	0.037	0.85 – 0.99

To test and illustrate the relation of survival to hypothermia status on the first ICU day, we performed a survival analysis to show the differences in survival during ICU LOS for patients with and without hypothermia. We also sorted the data according to brain injury status, (Figure 36 &37). A comparison of survival curves using log rank test for equality of survivor function showed a significant statistical difference with a $p < 0.0001$ for the group of multiple injury and $P<0.0001$ for the group with brain injury as main trauma.

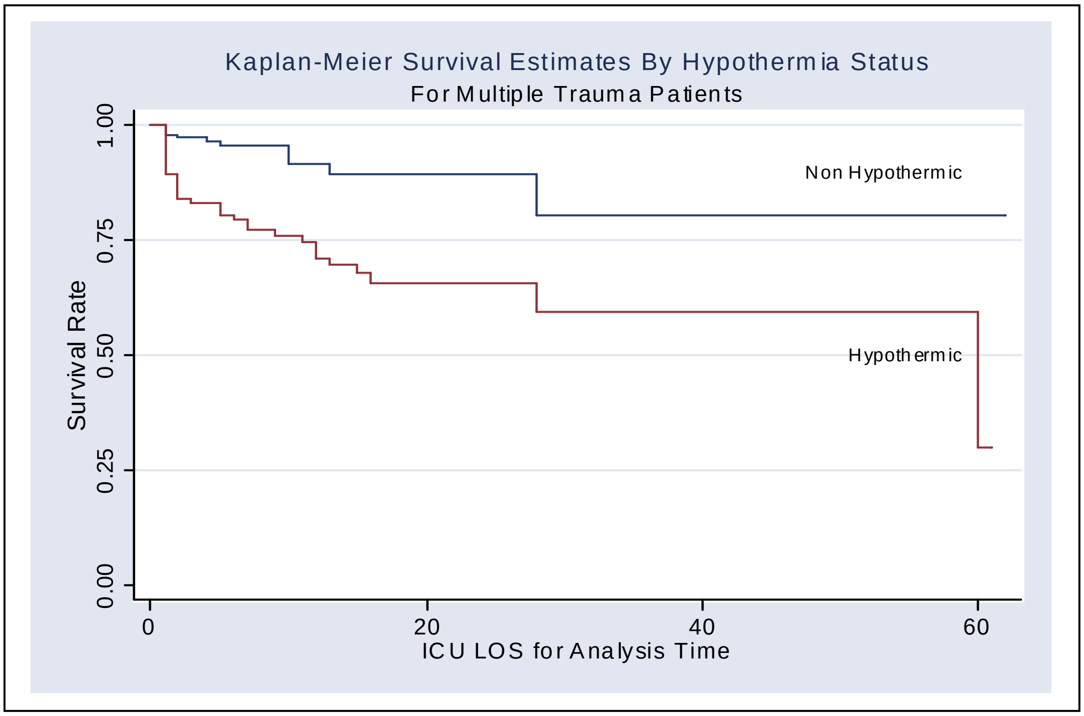

Figure 36. Kaplan-Meier by hypothermia status for multiple-trauma group

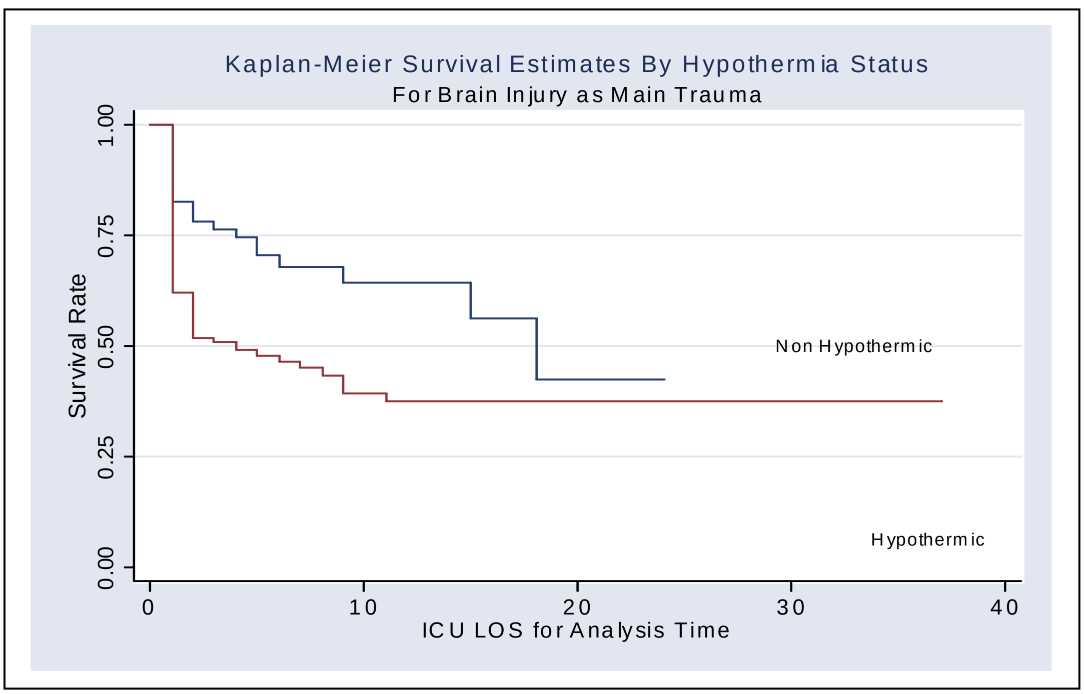

Figure 37. Kaplan-Meier by hypothermia status for brain trauma group

To quantify the risk of hypothermia, we used Cox regression. We compared the hypothermic group to the non-hypothermic group on ICU day 1 after controlling for age and ISS. For the multiple-trauma group, the risk ratio was 3.85 $\pm$ 1.39 (Standard Error) with statistical significance of $P<0.001$ (with 95% C.I. 1.89 – 7.82). For the brain injury group, the risk ratio was 1.91 $\pm$ 0.49 (Standard Error) and statistical significance of $P=0.012$ (with 95% C.I. 1.15 - 3.18).

We used Cox regression adjusting for age and ISS to quantify the risk of first ICU day hypothermia for each 1°C decrease in temperature of $\leq$ 36 degree. For the multiple trauma group, the relative risk was 1.51 per 1 **°C** decrease in temperature with statistically significant p-value of < 0.001 (with 95% C.I. = 1.28 to 1.79). For the brain injury group, the relative risk was 1.41 per one °C decrease in temperature with a statistically significant p-value of < 0.001 (with 95% C.I. = 1.23 to 1.62).

We also applied Cox regression adjusting for age and ISS to quantify the risk of first ICU day hypothermia for each one hour increase hypothermia duration (temperature $\leq$ 36 degree). For the multiple trauma groups, the relative risk was a 1.10 per one hour increase in hypothermia duration with statistically significant p value of < 0.001 (with 95% C.I.= 1.06 - 1.15). For the brain injury group the relative risk was a 1.08 per one hour increase in hypothermia duration with statistically significant p value of < 0.001 (with 95% C.I.= 1.03 - 1.12). We can calculate the increase in relative risk for any reduction in temperature and any increase in hypothermia duration based on the above. Table #11 summarized the above relative risk and related 95% C.I..

Table 11. Quantifying the risk of hypothermia in depth and duration by Cox regression

Cox regression	Groups	R.R.	Std. Err.	z	P	95% C.I.
Hypothermia vs. Non hypothermia	Multi-trauma injury	3.85	1.39	3.73	<0.0.01	1.89 – 7.82
	Mainly brain injury	1.91	0.49	2.51	0.012	1.15 - 3.18
Reduction in hypothermia depth in °C	Multi-trauma injury	1.51	0.06	4.98	<0.001	1.28 -1.79
	Mainly brain injury	1.41	0.05	4.82	<0.001	1.23 - 1.62
Increase in hypothermia duration by one hour	Multi-trauma injury	1.10	0.02	4.56	<0.001	1.06 - 1.15
	Mainly brain injury	1.08	0.02	3.49	<0.001	1.03 - 1.12

Finally, and based on the above survival analysis sorted by hypothermia status in the first ICU day, we adjusted for hypotension based on the phase of occurrence. We did the adjustment based on four phases starting with prehospital hypotension through Emergency Department hypotension ending in ICU days one and two hypotension, (Figure 38 & 39).

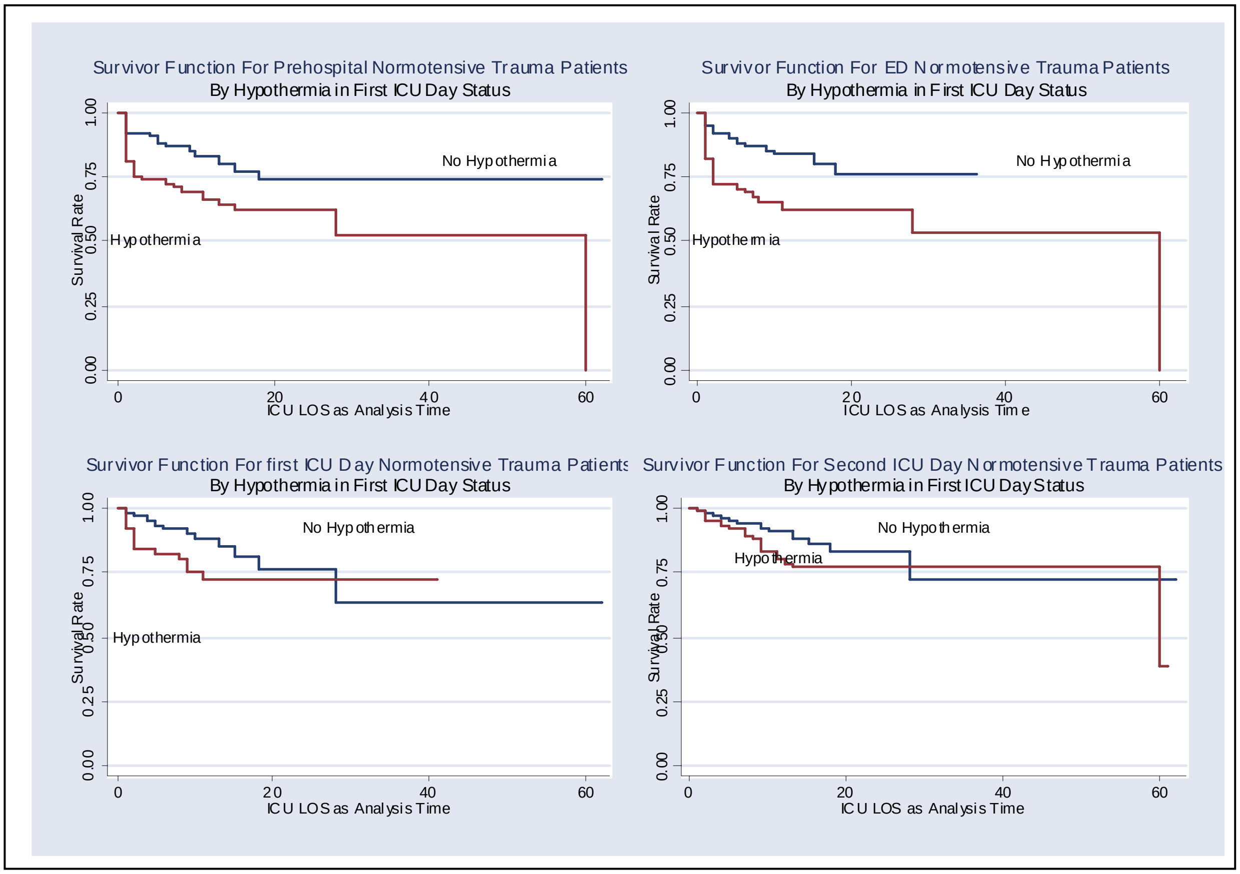

Figure 38. Kaplan-Meier by hypothermia adjusting for no hypotension on pre-hospital, Emergency Department, and Intensive Care Units.

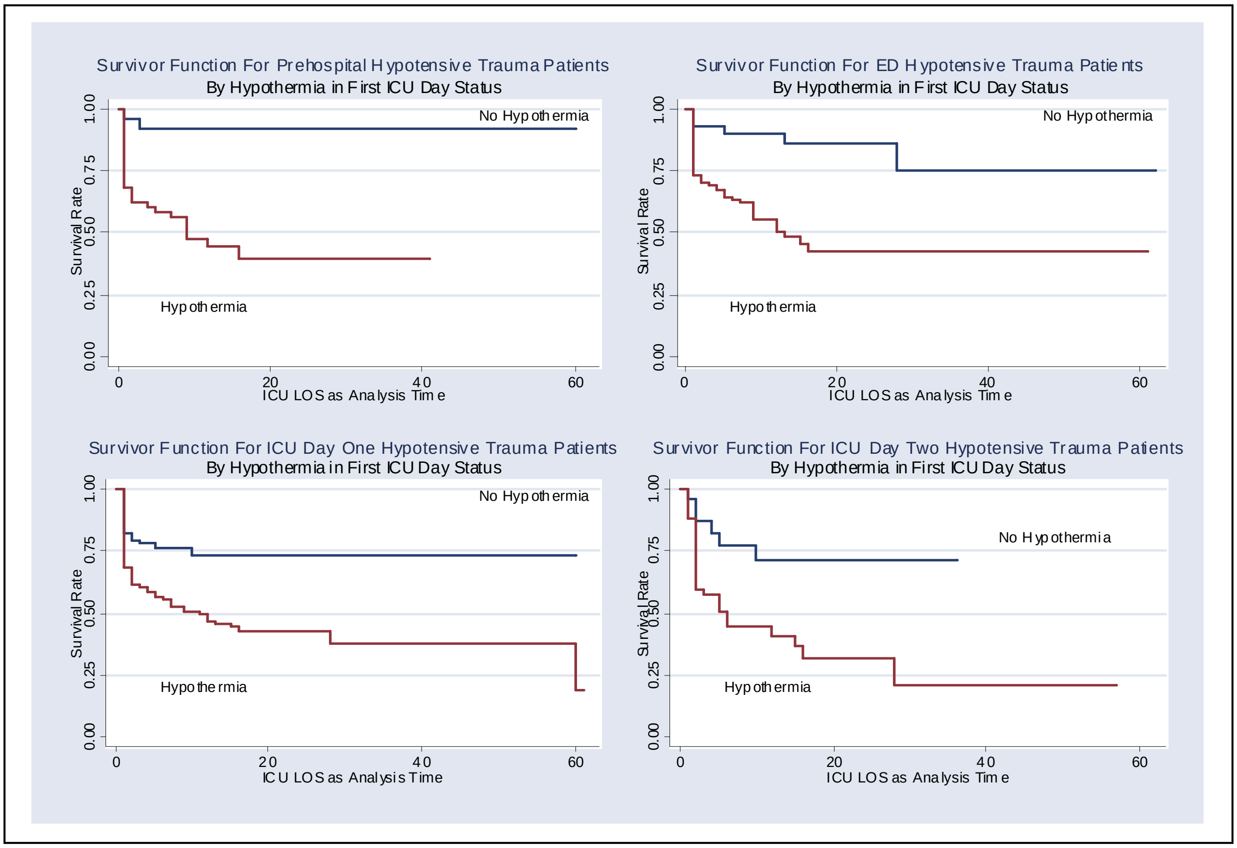

Figure 39. Kaplan-Meier by hypothermia status adjusting for hypotension on pre-hospital, Emergency Department, and Intensive Care Units.

We performed a Cox regression-based test for quality of survival curves. The test was significant for all the above conditions except in relation to no hypotension on the second ICU day by hypothermia status on the first ICU day. The relative hazard and related p value are summarized in table 12.

Table 12. Relative hazard of first ICU day hypothermia status based on hypotension status in prehospital, emergency department, ICU days one and two

Phase of hypotension status		Hypothermia status in ICU day one	Relative hazard	Pr>chi2
Pre-hospital	No	No	0.69	<0.002*
	No	Yes	1.52	
	Yes	No	0.25	<0.001*
	Yes	Yes	1.94	
Emergency department	No	No	0.66	<0.002*
	No	Yes	1.63	
	Yes	No	0.39	<0.001*
	Yes	Yes	1.71	
ICU day one	No	No	0.75	<0.03*
	No	Yes	1.55	
	Yes	No	0.57	<0.001*
	Yes	Yes	1.33	
ICU day two	No	No	0.78	0.126
	No	Yes	1.28	
	Yes	No	0.54	<0.01*
	Yes	Yes	1.60	

4.5. Discussion

Hypothermia on the first ICU day has not been given enough attention compared to other shock manifestations in critically ill trauma patients. We have showed in a previous analysis that just one episode of hypotension on ICU day one increases mortality and morbidity in critically ill trauma patients (19). In this study, we have attempted to illustrate the effect of hypothermia on trauma outcome. We also attempted to quantify the risk of hypothermia on ICU day 1. We used hypothermia duration as a novel element. Our study has analyzed the severity of hypothermia in two different ways. We have used both depth and duration of hypothermia in minutes. Linear regression and survival analyses were very appropriate in recognizing the importance of hypothermia depth and duration. We have managed to illustrate that quantifying the risk of hypothermia added further precision to the outcome prediction for patients with hypovolemic shock. We have also attempted to predict the occurrence of hypothermia on the first ICU day based on pre-hospital and ED data using linear regression. We sorted our analysis based on the occurrence of multiple-trauma vs. head injury as main trauma. Using survival analysis, we were able to quantify the risk of hypothermia depth and duration based on one **°C** reduction on temperature and one hour increase in hypothermia duration.

Our data showed that hypothermia on the first ICU day is associated with high mortality and longer ICU length of stay for the surviving patients. The analysis showed that hypothermia is associated with hypotension on both levels of depth and duration. The severity of hypothermia correlated with Injury Severity Score and other ED parameters. Hypothermia predicts ICU hypoxemia, the usage of vasopressers and days on ventilators.

We realized that many ED and ICU variables interact with the status of hypothermia and thus we have considered all related variables in our analysis. We have observed that the effect of duration and magnitude of hypotension and hypothermia were different with or without head trauma. In predicting hypothermia in the ICU, we realized that trauma patients with head trauma mostly developed hypothermia in the ICU when their SBP pressure dropped severely in the ED. Multiple trauma patients, develop severe hypothermia when they subjected to deeper level of hypoxemia. The ED disposition to OR, penetrating vs. blunt injury, severity of injury, and older age and higher ISS were also predicting hypothermia in patients with multiple trauma. Blood transfused in the OR for head trauma group can predict the duration of hypothermia.

Applying survival analysis in our data, we were able to show how hypothermia independently affects the length of stay. Hypothermia has been found to increase the length of stay in survivals for both the multi-trauma and head trauma groups. We were able to use Cox regression to quantify the relative risk of hypothermia. We found that hypothermic patients with multiple trauma had almost four times the risk of dying than non-hypothermic trauma patients. For the head trauma group, the hypothermic patients had almost two times the risk of dying than non-hypothermic. In addition, we were able to do the above quantification based on one unit °C reduction in temperature and one hour increase in hypothermia duration. One °C reduction from 36 °C**,** increases the risk of death by 1.51 times for multiple trauma and 1.41 times for head injury trauma. Similarly, one-hour increase in hypothermia duration (controlling for the depth of hypothermia) increases the relative risk of dying by 1.10 for the multiple trauma patients and 1.08 for head trauma patients.

We have realized that hypotension in all resuscitation stages (pre-hospital, Ed, and ICU) has a significant effect on hypothermia and related adverse outcome. However such dependency was not conclusive, hypothermia still by itself showed a significant effect on trauma outcome. This interaction disserves a dedicated future investigation.

Body temperature need to be frequently measured pre-ICU arrival since it showed a significant correlation with ICU temperature and can serve as a valuable predictor for future hypothermia during ICU phase. Assessing body temperature is an easy task and can be standardized and evaluated as much as needed. Hypothermia can be described in two ways, depth as how much the drop in body temperature and duration, as how much elapsed time in minutes. Obtaining frequent measures of body temperature provides additional prognostic value exceeding the lowest reading of body temperature on ICU day 1. Depending only on the lowest recorded temperature might underestimate or overestimate hypothermia based on many factors, such as transferring patients between wards, subjection to surgery, blood transfusion, and other related diagnostic tests. The increase in duration of hypothermia during the first ICU day is directly proportional to the mortality in shock patients. The ability to early predict hypothermia will provide the privilege to act quickly to prevent it or treat it upon its emergence.

This also illustrates the importance of continuous blood pressure and temperature monitoring during the ED and the first 24 hours of ICU stay. It also reveals the necessity of taking quick actions in treating shock promptly. It might be important for future studies to take into consideration the level of organ involvement and cause of death to contemplate how these factors might affect hypothermia and related outcomes.

Our findings are clear and significant. However, our study has some limitations that should be acknowledged. Temperature in pre-hospital and in the ED is not usually measured very frequently or even at all. The lowest recorded temperature measurements and duration of hypothermia have been obtained without standardized protocol since we used the available vital signs. The temperature of trauma patients might fluctuate frequently since these patients might be needed to be moved back and forth to OR and other hospital facilities for further diagnostic tests. Most trauma patients are frequently receiving blood transfusions and other intravenous solutions, which might also affect body temperature. We did not depend on automated data collection in certain variables since many were not available in the trauma registry. For instance, duration of hypothermia was determined by adding the period in minutes for all episodes in which body temperature was $\leq$ 36 **°C**. We do not know if the severity of hypothermia directly contributed to death or the death was happening due to other etiologies unadjusted for in our analysis. There are many causes and patterns of trauma injury, although we stratified our data based on head injury but we did not adjust for other body sites.

The result of this study might aid in evaluating shocked patients to determine the appropriate treatment and guide related clinical management in the seriously ill trauma patients. Hypothermia severity from day one may serve to predict the speed of the recovery. The use of hypothermia duration will add more prediction accuracy to the lowest recorded temperature in hypothermic patients. The ability to predict hypothermia early before ICU phase of treatment might add substantial benefit in clinical management. This will provide enough time to plan the most appropriate intervention to treat hypothermia promptly or prevent its severe occurrence.

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5. DISCUSSION

5.1. Encapsulate the background, rational, and methods of the preceding three papers

Trauma represents the leading cause of death for young adults in their most productive years and incurs substantial short and long term disability. Death from trauma results in an annual loss of 492 years of productivity per 100,000 and costing $230 million a day. Most of these mortality and related medical expenses were incurred early during critical care units' stay. Trauma patients have a high risk of shock during their early hours after injury. Shock may lead to high morbidity and mortality. Hypotension and hypothermia are among the important manifestations of hypovolemic shock, where both are associated with high mortality and morbidity. What is not clear in the literature is to what degree precisely hypotension and hypothermia predicts the severity of shock and related outcomes. What is not known as well, whether the above measures indicate the prognosis and how much that will differ depending on the time elapsed after injury? It has not yet been established when we should expect the occurrence of these events after a traumatic injury and how to quantify shock easily using these readily available measures.

The preceding three papers attempted to answer the above questions using injury data obtained from University of Pittsburgh Trauma Center. All injured patients (783) admitted to the intensive care unit of the University of Pittsburgh Medical Center from 1999 - 2000 were reviewed. Patients who were transferred to a ward within 48 hours of admission were excluded. Patients with final diagnoses not related to trauma and patients transferred early (before having enough data for analysis) from the hospital during their hospitalization due to insurance reasons were excluded from the study. Approximately 530 patients were eligible to the start-point analysis of this research. The outcome variables were the discharged life/death status and ICU length of stay. We collected data related to hypotension and hypothermia. The lowest recorded ICU measurements of hypotension and hypothermia duration were obtained. Additional data from prehospital, emergency department, operating room and intensive care units were also used when appropriate in the analysis.

5.2. Review of the studies results

Paper 1

- Patients with hypotension during the first ICU day had an increased mortality rate. A brief ($\leq$10 minutes) episode of hypotension was associated with the increase of mortality that also related to the prolonged hypotension duration (p=0.001). ICU length of stay also increased with duration of hypotension for the survived patients (p=0.0001)

Paper 2

- Patients who had a hypotensive episode on ICU day 2 had an increased mortality rate. Patients who survived their first day in the ICU, but experienced hypotension on ICU day 2, had approximately 2.5 more risk for mortality compared those who had on day 1. Similarly, the occurrence of hypotension on ICU day two that lasted for approximately four hours doubled the risk for mortality. Survived patients who had hypotension on ICU day two encountered with longer ICU stay. Both the lowest reading of SBP and hypotension duration of ICU day 2 were able to be successfully fitted in to a Cox regression with P<0.001.

Paper 3

- Patients with hypothermia had an increased mortality rate, P<0.0001. Survival patients with hypothermia in the first ICU day had on average longer ICU LOS p<0.003. The relative risk of hypothermic was 3.85, (95% C.I. 1.89 – 7.82) for patients with multiple trauma injury and 1.91 (95% C.I 1.15 – 3.18) head trauma as main injury. The relative risk per one °C decrease in temperature below 36 °C and one hour increase in hypothermia was also provided. Hypothermia in the first ICU day was a strong factor affecting trauma outcome on logistic regression. Applying linear regression, we were able predicted both depth and duration of hypothermia based upon prehospital and ED variables. Similarly, on logistic regression pre-ICU hypotension, pre ICU hypothermia, increase in blood transfusion, and other hypoxia related conditions predicted the first ICU day hypothermia in multiple trauma patients. For brain injury patients, ED hypotension and reduction in GCS measured in emergency department were the most statistically significant predictors.

5.3. How to interpret the results of the three papers

Brief episodes of hypotension on ICU day one are associated with increased risk of death in patients requiring admission to the ICU after injury and longer recovery of those who survived. Hypotension on ICU day 2 is associated with an overall high hospital mortality and morbidity. For those survived ICU day one, hypotension depth and duration on ICU day 2 predicts the risk of in-hospital adverse outcomes better than hypotension depth and duration of ICU day 1. Hypothermia in the first ICU day can be predicted based on prehospital and ED information. Hypothermia in the first ICU day is a very important predictor of mortality and morbidity in trauma and can aid in shock management improving the over all trauma outcome.

It might be intuitive to know that hypotension and hypothermia are risk factors for mortality and morbidity in trauma patients, but the issue here is to quantify that risk. In other words, is a certain drop in blood pressure of particular length and definite time of occurrence considered an important risk and when should we expect to see its effects on the case progress for a trauma patient? In the three papers of this dissertation, we examined hypotension and hypothermia data based on the lowest recorded ICU reading and based on the duration of all episodes expressing hypotension and hypothermia. Other methods might be also used such as repeated measures and mean measures. We found the method followed in our study more appropriate for our hypothesis and give wider conceptualization for the whole picture of hypovolemic shock. The severity of hypotension in ICU day one and two contributes to early death in ICU, however episodes of any period have considerable risk. Injury severity score appeared as an important factor participated in determining the severity of hypotension. Pre-ICU effects of hypotension and hypothermia predicted many shock manifestations in ICU period. This indicates that any early insult can develop hypoperfussion in which related consequences may delay to appear later during ICU stay.

We have shown that brain injury has distinguishable effects on shock, which is different from that of multiple trauma injury. In patients with head trauma, the severity of hypotension measured in mm Hg had a stronger effects on the outcome than the effect of duration of hypotension measured in minutes. This is also related the level of neurological deficit measured by GCS. In brain injury patients, the quantity or the need for blood transfusion in OR was considerable factor in predicting shock manifestations during ICU period. In the multiple injury patients, the level of hypoxia is strongly related to the outcome. Patients who had been subjected to CPR pre-ICU period and who required large quantity of blood transfusion in ED will develop shock more frequently than those with less hypoxia. In these patients, the duration of hypotension measured in minutes was a strong factor determining the outcome.

Through our analysis, we have noticed that hypotension and hypothermia are not completely independent. Hypotension has some effect on hypothermia and vise versa but both have in part distinguishable effects on the overall mortality and morbidity of trauma patients. That interaction was not completely understood particularly in relation to clinical management and prognosis. We would like further study to examine how such interaction effect the outcome and be able to understand precisely their independent influences.

5.4. What did these three papers added to our knowledge? What is the related clinical application?

Both hypotension and hypothermia can be used together in monitoring shock patients and both can be expressed with depth and duration. Hypotension and hypothermia duration which both have not been used frequently in quantifying the risk of shock are indeed good parameters for monitoring shock patients. The duration of hypotension and hypothermia in minutes can be used beside the unit measurement of lowest recorded SBP in mm Hg and the lowest temperature in **°C** respectively, for better quantification of the risk of hypovolemic shock. Accurate quantification of the risk of shock can aid in patient management and improving trauma outcome. Hypotension should be continuously monitored from the early moment of injury occurrence throughout the intensive care stay. Any episode of hypotension should be taking into consideration and aggressively treated. Hypotension in ICU day two provides a good indication for the outcome and should be used to correct whatever prediction obtained during ICU day one. Since hypothermia in ICU can be predicted based on prehospital and emergency department data, it can also be treated as soon as it occurs. It is also more appropriate to prevent any prolonged episodes of hypotension and hypothermia from the early moment of injury. As we have indicated, shock outcome is strongly related to the early tissue insult and hypoperfussion, therefore, prevention is more effective than treatment. All efforts have to be directed toward early response to trauma with quick transportation and accurate triage. Hypotension and hypothermia are very important prognostic criteria and therefore, both deserve serious trauma system activation and higher priority in triage.

5.5. How to put all together into one concept

Hypotension is not equal to shock, but it may be associated with the later stages of shock. The definition of shock is “A condition arising from diminished perfusion of tissues that is leading to oxygen delivery which is inadequate to maintain the function and structural integrity of cells”. This results in “cellular metabolic dysfunction”. Many investigators have expressed hypotension as shock, once the complete picture of shock was developed. Hypothermia is a life threatening condition that can trigger extensive physiological reactions and regarded as a significant co-morbid factor in trauma patients. It is defined as a low core body temperature. Both hypotension and hypothermia are not classified as diseases but both as important manifestation for shock.

The ‘Golden Hour’ concept in shock resuscitation was observed long ago, specifically during World War I by French doctors (1). These doctors observed that mortality markedly increased in proportion to the amount of time that elapsed between wounding and treatment for shock. The lapse of time between the wounding event and the administration of adequate treatment for shock was shown to be remarkably significant. When treatment was administered within one hour, the mortality rate was 10 percent; that rate increased progressively with delay of treatment, reaching 75 percent when treatment was delayed for eight hours. The same data was used recently by Adams supporting his “Golden Hour” concept. He first explored the concept of treating shocked patients very quickly, within the first 60 minutes after injury. John Warren, famously described shock as “a momentary pause in the act of death”. Shock continues to be associated with high mortality and morbidity, primarily because of delay in diagnosis and therapy.

Hypotension severity in animal models is associated with the degree of tissue injury, magnitude of inflammatory response, and survival rate (2). In addition to the above stated ‘Golden Hour’ concept, a new notion has been recently emerged calling for the detection and correction of occult hypoperfusion within the first 24 hours of trauma. This new concept has been expressed as the “Silver Day” (3,4). Both the “Golden Hour” and the “Silver Day” concepts go hand in hand with the pathophysiology of shock and with the related compensated-reversible and decompensated irreversible stages. Our study results support strongly the above foundations and in a clinically oriented perception. We have indicated that any period of hypotension is important and should not be only aggressively treated but also seriously prevented.

Although prolonged occult hypoperfusion has been associated with a worsened outcome (5), reperfusion after shock is also associated with the production of endogenous oxidants that cause cytotoxicity and activate the inflammatory response (6). This process might take hours and perhaps days after the initial traumatic injury and shock; during that period, a disseminated injury may occur due to the release of cytokines, proteases, and other additional oxidants. Death occurring more than 12 hours after injury relates primarily to occult hypoperfusion and multiple organ failure, which continue to pose a risk for days and weeks after the traumatic injury (7). Such factors suggested and as our data has indicated, there is a great necessity to update the severity shock indicators to accurately be able to predict the outcome. Many studies connected the temporal physiological changes of shock and circulatory dysfunction with the outcomes through invasive and non-invasive methods of monitoring during the early hours and days of trauma and shock (8-11). Our findings give a strong support for the above concept. We have also found in our analysis that for those patients who survived ICU day one, hypotension on second ICU day is a very good predictor for outcome

Mortality rate following admission to trauma and surgical critical care units reaches 23% in general and might reach a higher rate with brain injury patients according to one study (12). Usually statistical analysis overestimate survivability in patients who were less severely injured while trauma audit based on clinical peer review may overestimate preventable deaths in the critically ill patients (13). The reality indicated that there is much more that can be done to improve trauma care. Many errors in the processes of trauma care keep occur repeatedly. These include delay in diagnosis or management, delay in trauma team activation and error in judgment (14). Many of these errors were due to failure to use available patient measurements and insensitivity to field and hospital triage. Assertive intensive care intervention is essential to reduce complications and other additional offenses caused by multi-organic dysfunction syndrome that usually related to hypoperfussion. Our results indicate that all episodes of hypotension and hypothermia should be treated promptly or better yet prevented completely. Early signals of shock are very important and should be used for structured clinical management.

Trauma is responsible for 140,000 deaths annually in USA. This mortality results in approximately 4 million years loss of potential working-life. The above loss is double that of coronary heart disease or malignancy (15). Considering such large mortality and morbidity, closer attention should be paid to these severely injuries and as early as the occurrence of their injuries on the scene. Also it is not effective spending longer time at the scene resuscitating trauma patients, and delaying hospital arrival, however, faster transportation using aero-medical transport vs. ground transport improve the outcome by reducing hospital stay, and hospital charges (16). In comparison between American medical transport in which depends on paramedic, and German system, in which rely on trauma surgeons as flight personnel. When controlling for injury severity, the German system has been found favorably improving the outcome (16). We think that our trauma system needs further evaluation and improvement to reduce mortality and morbidity. Innovative methods in speedy arrival to the scene and faster transportation are very crucially needed to all trauma patients. More advanced methods in resuscitation are similarly on demand. Taking advantage, as early as possible, of whatever clinical clues available in trauma patients and implement the related appropriate clinical management as quickly as possible should also improve trauma outcome.

5.6. Future studies might be important based on the results of this dissertation

We have noticed that there is considerable interaction between hypotension and hypothermia and we would like to pinpoint the exact outcome of each individually and the join effects taking into account all related factors. We have found that certain earlier hypoxic events can cause hypothermia later in the ICU period. We might need to design a future study to investigate the effects of CPR and electroconversion of cardiac dysrhythmias on the later occurrence of hypotension and hypothermia. It is of great benefit to look at all related procedure and treatment that are affecting the outcome. A similar study might also be important including all reasons of death, and more precise injury descriptions. We would like also to see the effect of early re-warming shock patients based on the hypothermia prediction criteria of our study looking for the differences in the outcomes. We would like also to test the effects of continuous SBP and temperature monitoring from the early moments of injury and the effect of aggressive shock treatment on the basis of such devoted monitoring. We would like to address the mechanism of injury in future study since that might influence the outcome and related to many other related demographic factors. Mechanism of injury is also affecting ISS, level of hemorrhage, and resuscitation. When taking care of accounting for mechanism of injury we will be able to better understand the effect of shock and related manifestation on the outcome.

5.7. How is this study representing a clinical epidemiological research?

Clinical observation based on theoretical knowledge is very important in determining the clinical management but in many circumstances, such approach might lead to fallacy and inappropriate practices. Implementing clinical research in population-based studies may clear confusion and establish the good standards in clinical practice. Clinical research on intensive care data is very rewarding. Patients in ICUs are severely ill and in life threatening situations. The benefit of clinical research therefore is directly applicable to clinical practice. The data that can be gathered in intensive care settings are enormous and very beneficial for outcome studies. Clinical epidemiology can be employed effectively for the advancement in clinical care and management. The preceding three papers are examples of how implementing clinical epidemiology can yield very practical studies in which the results can be used efficiently in improving the fields of critical care and trauma.

5.8. What are the public health benefits of the preceding papers?

Despite the proliferation of trauma systems, only recently has population-based data describing the epidemiolgy of traumatic injury and related death become available. Injury is a very important public health problem in the United Sate and Globally. It is the leading cause of death in young adults up to age 44 years and cause more loss of potential years of life than all other diseases combined (17-21).

More attention has been recently directed toward acute care research. Just recently CDC announced a reformed agenda in which expanded the support for acute injury care research (22). Trauma care is saving lives and reducing the disabilities after severe injuries. It has been shown that improving acute care and trauma system through the advancement in clinical research is very cost effective and in the long-run can reduce both mortality and health care costs. Considering the years of potential life lost through trauma and the latent burden of injury in the society, the investment in improving the science of acute care is not only justified but also greatly rewarding.

Outcome research is very essential for evaluating clinical effectiveness and improving clinical management. Clinical epidemiology is used successfully in outcome research to quantify the association between risk factors in relation to outcome and to determine the usefulness of clinical interventions.

Following the above fundamentals in reference to injury and related epidemiological clinical research to improve critical care in severely injured patients, we can see how the preceding papers of this study were constructing on this attribute. The presented three papers discussed a very important topics related to shock. Shock as we have indicated repeatedly, is the main killer in the severely injured trauma patients. This study added more understanding to shock manifestations and contributed in improving critical care management for severely injured trauma patients. As we have elucidated earlier that most of deaths in relation to trauma happened in early period of injury and during the early stay at intensive care units. In addition most of the critical care cost were spent during the lengthy ICU stay in which trauma patient typically experienced. The above supports the general aims of this study in improving the critical care outcome decreasing the morbidity and reducing the length of ICU stay.

Specifically, hypotension and hypothermia in ICU have adverse effects. Any period of hypotension can be deadly. It should not only be treated quickly, but also seriously prevented. The results of this paper support the golden hour concept and call for more speed in rescuing injured patients by faster scene arrival and faster transportation to trauma centers. The results of this study support the concept of initiating the actual resuscitation as early as getting the victims from the scene. Hypotension and hypothermia should be closely watched in prehospital phase, emergency department, operating room, and the first and second ICU days. The ability to predict the occurrence of hypotension and hypothermia in the ICU, based on prehospital and ED data, is very important and offer an edge in critical care management providing enough time for planning and allocating resources.

Public health can be accomplished when we manage to save lives, reduce morbidity, and have the ability to get back injury victims to their regular life in relatively short time. The reduction of the cost of injury and critical care has a vast public health value. Such saving can be re-deployed in further advancement in health care, reduction in health disparity and further improvement in health care accessibility. Trauma does not only have its effect on the related victims but also expand to encompass their family members, and the whole society. Improving the outcome of trauma will have its effect on the entire population.

5.9. In conclusion

Hypotension and Hypothermia are very important manifestation of shock. Both can be predicted and quantified. It is not only important to treat both hypotension and hypothermia promptly as they appear but it is also very crucial to prevent their occurrences.

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