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PUBLICATIONS

Akinboro O, Larkins E, Pai-Scherf LH, Mathieu LN, Ren Y, Cheng J, Fiero MH, Fu W, Bi Y, Kalavar S, Jafri S, Mishra-Kalyani PS, Fourie Zirkelbach J, Li H, Zhao H, He K, Helms WS, Chuk MK, Wang M, **Bulatao I**, Herz J, Osborn BL, Xu Y, Liu J, Gong Y, Sickafuse S, Cohen R, Donoghue M, Pazdur R, Beaver JA, Singh H. FDA Approval Summary: Pembrolizumab, Atezolizumab, and Cemiplimab-rwlc as Single Agents for First-Line Treatment of Advanced/Metastatic PD-L1-High NSCLC. Clin Cancer Res. 2022 Jun 1;28(11):2221-2228. doi: 10.1158/1078-0432.CCR-21-3844. PubMed PMID: 35101885.

Croteau D, Pinnow E, Wu E, Muñoz M, **Bulatao I**, Dal Pan G. Sources of Evidence Triggering and Supporting Safety-Related Labeling Changes: A 10-Year Longitudinal Assessment of 22 New Molecular Entities Approved in 2008 by the US Food and Drug Administration. Drug Saf. 2022 Feb;45(2):169-180. doi: 10.1007/s40264-021-01142-3. Epub 2022 Feb 3. PubMed PMID: 35113347.

Cherkaoui S, Pinnow E, **Bulatao I**, Day B, Kalaria M, Brajovic S, Dal Pan G. The Impact of Variability in Patient Exposure During Premarket Clinical Development on Postmarket Safety Outcomes. Clin Pharmacol Ther. 2021 Dec;110(6):1512-1525. doi: 10.1002/cpt.2320. Epub 2021 Jul 8. PubMed PMID: 34057195; PubMed Central PMCID: PMC8595500.

Bulatao I, Pinnow E, Day B, Cherkaoui S, Kalaria M, Brajovic S, Dal Pan G. Postmarketing Safety-Related Regulatory Actions for New Therapeutic Biologics Approved in the United States 2002-2014: Similarities and Differences With New Molecular Entities. Clin Pharmacol Ther. 2020 Dec;108(6):1243-1253. doi: 10.1002/cpt.1948. Epub 2020 Sep 8. PubMed PMID: 32557564; PubMed Central PMCID: PMC8159207.

Wickwire EM, Tom SE, Scharf SM, Vadlamani A, **Bulatao IG**, Albrecht JS. Untreated insomnia increases all-cause health care utilization and costs among Medicare beneficiaries. Sleep. 2019 Apr 1;42(4). doi: 10.1093/sleep/zsz007. PubMed PMID: 30649500; PubMed Central PMCID: PMC6448286.

Harris DG, **Bulatao I**, Oates CP, Kalsi R, Drucker CB, Menon N, Flohr TR, Crawford RS. Functional status predicts major complications and death after endovascular repair of abdominal aortic aneurysms. J Vasc Surg. 2017 Sep;66(3):743-750. doi: 10.1016/j.jvs.2017.01.028. Epub 2017 Mar 1. PubMed PMID: 28259573; PubMed Central PMCID: PMC5572312.

Giesbrandt KJ, **Bulatao IG**, Keaveny AP, Nguyen JH, Paz-Fumagalli R, Taner CB. Radiologic Characterization of Ischemic Cholangiopathy in Donation-After-Cardiac-Death Liver Transplants and Correlation with Clinical Outcomes. AJR Am J Roentgenol. 2015 Nov;205(5):976-84. doi: 10.2214/AJR.14.13383. PubMed PMID: 26496544; PubMed Central PMCID: PMC4841999. (KJG and IGB contributed equally)

Bulatao IG, Heckman MG, Rawal B, Aniskevich S, Shine TS, Keaveny AP, Perry DK, Canabal J, Willingham DL, Taner CB. Avoiding stay in the intensive care unit after liver transplantation: a score to assign location of care. Am J Transplant. 2014 Sep;14(9):2088-96. doi: 10.1111/ajt.12796. Epub 2014 Aug 1. PubMed PMID: 25088768.

Wadei HM, **Bulatao IG**, Gonwa TA, Mai ML, Prendergast M, Keaveny AP, Rosser BG, Taner CB. Inferior long-term outcomes of liver-kidney transplantation using donation after cardiac death donors: single-center and organ procurement and transplantation network analyses. Liver Transpl. 2014 Jun;20(6):728-35. doi: 10.1002/lt.23871. PubMed PMID: 24648186.

Burcin Taner C, **Bulatao IG**, Perry DK, Sibulesky L, Wllingham DL, Kramer DJ, Nguyen JH. Agonal period in donation after cardiac death donors. Transpl Int. 2013 Mar;26(3):e17-8. doi: 10.1111/tri.12056. PubMed PMID: 23405915.

Taner CB, **Bulatao IG**, Arasi LC, Perry DK, Willingham DL, Sibulesky L, Rosser BG, Canabal JM, Nguyen JH, Kramer DJ. Liver transplantation in the critically ill: donation after cardiac death compared to donation after brain death grafts. Ann Hepatol. 2012 Sep-Oct;11(5):679-85. PubMed PMID: 22947529.

Taner CB, **Bulatao IG**, Perry DK, Sibulesky L, Willingham DL, Kramer DJ, Nguyen JH. Asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors. Transpl Int. 2012 Aug;25(8):838-46. doi: 10.1111/j.1432-2277.2012.01508.x. Epub 2012 Jun 15. PubMed PMID: 22703372.

Wadei HM, Zaky ZS, Keaveny AP, Rosser B, Jones M, Mai ML, **Bulatao I**, Gonwa TA. Proteinuria following sirolimus conversion is associated with deterioration of kidney function in liver transplant recipients. Transplantation. 2012 May 27;93(10):1006-12. doi: 10.1097/TP.0b013e31824bbd01. PubMed PMID: 22357174.

Taner CB, Willingham DL, **Bulatao IG**, Shine TS, Peiris P, Torp KD, Canabal J, Nguyen JH, Kramer DJ. Is a mandatory intensive care unit stay needed after liver transplantation? Feasibility of fast-tracking to the surgical ward after liver transplantation. Liver Transpl. 2012 Mar;18(3):361-9. doi: 10.1002/lt.22459. PubMed PMID: 22140001.

Taner CB, **Bulatao IG**, Willingham DL, Perry DK, Sibulesky L, Pungpapong S, Aranda-Michel J, Keaveny AP, Kramer DJ, Nguyen JH. Events in procurement as risk factors for ischemic cholangiopathy in liver transplantation using donation after cardiac death donors. Liver Transpl. 2012 Jan;18(1):100-11. doi: 10.1002/lt.22404. PubMed PMID: 21837741.

Perry DK, Willingham DL, Sibulesky L, **Bulatao IG**, Nguyen JH, Taner CB. Should donation after cardiac death liver grafts be used for retransplantation?. Ann Hepatol. 2011 Oct-Dec;10(4):482-5. PubMed PMID: 21911889.

Taner CB, **Bulatao IG**, Keaveny AP, Willingham DL, Pungpapong S, Perry DK, Rosser BG, Harnois DM, Aranda-Michel J, Nguyen JH. Use of liver grafts from donation after cardiac death donors for recipients with hepatitis C virus. Liver Transpl. 2011 Jun;17(6):641-9. doi: 10.1002/lt.22258. PubMed PMID: 21618684.

ABSTRACTS AND PRESENTATIONS

Bulatao IG, Pinnow E, Day B, Cherkaoui S, Kalaria M, Brajovic S, Dal Pan G
Postmarket safety outcomes for new therapeutic biologics approved by the Food and Drug Administration between 2002 and 2014
35th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Philadelphia, PA August 24-28, 2019;
FDA Science Forum, September 2019

Bulatao IG, Man B, Gibeily G, Loyo-Berrios N, Du D
Surgical stapler malfunctions: a systematic review of the literature
FDA Annual Summer Student Poster Day, August 2018;
35th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Philadelphia, PA August 24-28, 2019

Day B, Pinnow E, **Bulatao IG**, Cherkaoui S, Kalaria M, Brajovic S, Dal Pan G
Characterizing safety issues in post-marketing label changes for new molecular entity drugs and original therapeutic biologics approved by the U.S. Food and Drug Administration between 2002 and 2014
FDA Science Forum, September 2019

Cherkaoui S, Pinnow E, **Bulatao I**, Brendan D, Kalaria M, Brajovic S, Dal Pan G
Patient exposure during pre-market trials and relationship with post-market safety outcomes.
35th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Philadelphia, PA August 24-28, 2019;
FDA Science Forum, September 2019

Bulatao IG, Tom SE, Brandt N, Geiger-Brown J, Guralnik J, Hale LE, Li W, Womak Cr, Zaslavsky O, LaCroix AZ, Scharf SM
Longitudinal association between sleep medication use and physical performance measures in older women
Johns Hopkins Sleep and Circadian Research Day 2015, Baltimore, MD;
Graduate Research Conference 2016, University of Maryland Baltimore, Baltimore, MD

Harris D, Oaetes C, **Bulatao I**, Drucker C, Goldstein C, Toursavadkohi S, Sarkar R, Crawford R. Functional status predicts major complications and death after endovascular repair of abdominal aortic aneurysms
Vascular Annual Meeting 2016, Washington, DC

Kalsi R, Hao S, Harris D, Benalla O, Naseer Z**, Bulatao I**, Drucker C, Bhardwaj A, Fajardo A, Crawford R
Minority race is independently associated with need for late intervention in medically managed type B aortic dissection
Journal of Vascular Surgery 2016 May; 64 (3): 871

Taner CB, **Bulatao IG**, Heckman MG, Rawal B, Aniskevich S, Perry D, Keaveny AP.
Avoiding stay in the intensive care unit after liver transplantation: a score to assign location of care.
World Transplant Congress 2014, San Francisco, CA

Wadei H, **Bulatao I**, Gonwa A, Keaveny A, Mai M, Taner B.
Outcomes of simultaneous liver-kidney transplantation (SLK) from donation after cardiac death (DCD) donors and donation after brain death donors (DBD).
ATC 2013, Seattle, Washington
Giesbrandt K, **Bulatao I**, Paz-Fumagalli R, Taner CB.
Cholangiographic patterns of ischemic cholangiography correlated with clinical outcomes in donation after cardiac death liver transplants.
RSNA 2013, Chicago, IL

Giesbrandt K, **Bulatao I**, Paz-Fumagalli R, Taner CB.
Radiologic characterization and clinical correlation of ischemic cholangiopathy in liver transplants using donation after cardiac death donors.
ILTS 18th Annual International Congress, 2012, San Francisco, CA
Awarded - Rising Star Symposium
Liver Transplantation 2012 May; 18(S1): S84 Abstract #O-12

Wadei HM, **Bulatao I**, Gonwa T, Mai M, Taner B.
Outcomes of simultaneous liver-kidney transplantation (SLK) is similar in donation after cardiac death (DCD) compared to donation after brain death donors (DBD) donors.
ILTS 18th Annual International Congress, 2012, San Francisco, CA
Awarded - Poster of Distinction
Liver Transplantation 2012 May; 18(S1):S258 Abstract #P-359

Willingham DL, **Bulatao IG**, Shine TS, Torp, KD, Peiris P, Nguyen JH, Kramer DJ, Taner B. Should ICU admission after liver transplantation be mandatory? Fast-tracking to the surgical ward following liver transplantation.
ILTS 18th Annual International Congress, 2012, San Francisco, CA
Interactive Concurrent Session: Pre-Transplant Workup and Cardiac Topics Liver Transplantation 2012 May; 18(S1):S127 Abstract #O-136

Taner B, **Bulatao IG**, Perry DK, Sibulesky L, Willingham DL, Kramer DJ, Nguyen JH.
Asystole to cross clamp duration is predictor of ischemic type biliary strictures in liver transplantation using DCD grafts.
ILTS 18th Annual International Congress, 2012, San Francisco, CA Plenary Session I
Liver Transplantation 2012 May; 18(S1):S81 Abstract #O-2

Taner CB, Willingham DL, **Bulatao IG**, Shine TS, Canabal J, Nguyen JH, Kramer DJ.
Feasibility of early extubation and fast tracking after liver transplantation – The Mayo Clinic Florida experience.
62nd Annual Meeting of the AASLD, 2011, San Francisco, CA
Awarded - Presidential Poster of Distinction

Taner CB, **Bulatao IG**, Perry DK, Sibulesky L, Willingham DL, Kramer DJ, Nguyen JH.
Agonal period warm ischemia times and risk for biliary complications in donation after cardiac death liver grafts.
62nd Annual Meeting of the AASLD, 2011, San Francisco, CA

Taner CB, **Bulatao IG**, Willingham DL, Perry DK, Sibulesky L, Pungpapong S, Canabal JM, Keaveny AP, Aranda-Michel J, Kramer DJ, Nguyen JH.
Successful liver transplantation using donation after cardiac death donors.
11th American Transplant Congress, 2011, Philadelphia, PA
American Journal of Transplantation 2011; 11(s2): 201 Abstract #576

Taner CB, **Bulatao IG**, Canabal JM, Willingham DL, Arasi LC, Nguyen JH, Kramer DJ.
N-Acetylcysteine use and perioperative transfusion requirements in OLT.
ILTS 16th Annual International Congress, 2010, Hong Kong, China

RESEARCH IN PREPARATION

Bulatao I, Buchanan L, Mackenzie C, Terrin M, Chen H, Hu P, Smith G.
The predictive accuracy of Shock Index in trauma outcomes in older injured patients

Bulatao I, Buchanan L, Mackenzie C, Terrin M, Chen H, Hu P, Smith G.
The effect of alcohol and comorbidities on the accuracy of shock index in predicting death and massive transfusion in injured patients

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Gerontological Society of America
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ABSTRACT

Title of Dissertation: The predictive accuracy of Shock Index in trauma outcomes in older injured patients

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The elderly is an increasing proportion of all cases treated at trauma centers. Shock index (SI) calculated as heart rate (HR) divided by systolic blood pressure (SBP), has been shown to be a good predictor of mortality and transfusion in injured patients. One limitation of SI is that its accuracy in different age groups, especially the elderly has not been fully evaluated.

We studied the accuracy of admission SI in predicting early, 48-hour and in-hospital mortality, and major interventions (massive transfusion, ICU admission and surgery in 24 hours) in trauma patients admitted to a major trauma center. We examined whether age, injury severity, injury type, blood alcohol and comorbidities affected the predictive accuracy of SI. Of particular interest is the accuracy of SI in the elderly. We also compared the predictive accuracy of SI, HR and SBP. Optimal cut-points for SI were determined.

SI had acceptable accuracy in predicting mortality outcomes, and ICU admission overall. Accuracy was good in the prediction of massive transfusion, and poor in the prediction of surgery in 24 hours. SI was better than HR or SBP in predicting mortality outcomes (all ages, elderly, and younger patients). However, in older patients, accuracy

of SI in predicting major interventions was not different from that of SBP. Accuracy of SI in predicting 48-hour and all in-hospital mortality, and ICU admission was better in younger patients. Accuracy was also better among those with lower injury severity than in those who were more severely injured. Accuracy of SI in predicting massive transfusion was similar in older and younger trauma patients. Optimal cut-offs for predicting outcomes were lower for older patients (0.5-0.7 for mortality and major interventions) than in younger patients (0.6-0.9 for mortality and 0.6-0.8 for major interventions). Accuracy of SI in predicting all in-hospital death and massive transfusion was less among patients with elevated blood alcohol while comorbidities did not affect accuracy.

In conclusion, SI is less accurate in in predicting mortality among older patients and is less accurate in predicting mortality and massive transfusion among blood alcohol-positive patients, potentially affecting its utility in triage and clinical management.

The Predictive Accuracy of Shock Index in Trauma Outcomes in Older Injured Patients

by
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Dissertation submitted to the Faculty of the Graduate School of the
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Words cannot express my gratitude to my family, my father Peter, my mother Helen and my siblings, Peter Jr., and Aimee. Their love, prayers and encouragement have motivated me to push through and persevere throughout graduate school and especially while working on the dissertation during a difficult period in world history, the COVID-19 pandemic.

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LIST OF ABBREVIATIONS

AUC	Area Under the Curve
ED	Emergency Department
EMS	Emergency Medical Services
FPR	False Positive Rate
GCS	Glasgow Coma Scale
HR	Heart Rate
ICD	International Classification of Diseases
ICU	Intensive Care Unit
ISS	Injury Severity Score
NTDB	National Trauma Data Bank
NTTP	National Trauma Triage Protocol
RBC	Red Blood Cells
ROC	Receiver Operating Characteristic
RTS	Revised Trauma Score
SBP	Systolic Blood Pressure
SI	Shock Index
SIPA	Shock Index, Pediatric Age Adjusted
STC	Shock Trauma Center
TPR	True Positive Rate

CHAPTER 1: SPECIFIC AIMS

The elderly is an increasing proportion of all cases treated at trauma centers and other hospitals. Survival of seriously injured patients is dependent on triage to trauma centers, in-hospital trauma care, and post-discharge management. Increased heart rate and low blood pressure are utilized in rapid triage and management decision making both in the field and at initial hospital presentation. Shock index, calculated as heart rate divided by systolic blood pressure, has been shown to be a good predictor of mortality and transfusion in injured patients. There is no universal agreement on its importance in initial patient assessment in trauma triage protocols. One limitation to the use of shock index is that its accuracy in different age groups, especially the elderly, has not been fully evaluated. Altered physiology, cardiac conduction defects, presence of concomitant illness, and alcohol intake, may all cause blunted responses to shock, especially in older individuals, and therefore may affect the accuracy of the shock index. Elevated blood alcohol may also affect shock index because of both pressor and depressor effects. Because shock index is a continuous value, identification of the most appropriate cut-off points in predicting outcomes especially in older versus younger individuals is important. In addition, studies comparing the accuracy of shock index in predicting trauma outcomes to standard vital signs used in triage protocols rarely involve adjusting for variables which may confound accuracy. There is a need for studies looking specifically at both younger and older patients, and that adjust for confounders. To our knowledge, no studies looked at the effect of pre-existing conditions, and blood alcohol on the accuracy of shock index in predicting outcomes in injured patients, particularly in the elderly.

The objective of this research is to examine the accuracy of the shock index, in comparison with heart rate and systolic blood pressure, as an initial indicator of hospital mortality (early (2-hour), 48-hour, and in-hospital), receiving massive transfusion, and undergoing major interventions, in older compared to younger injured patients. We hypothesize that the accuracy of shock index is not as accurate in older injured patients compared to younger ones and is better than heart rate or systolic blood pressure alone in predicting outcomes in injured patients. We will identify optimal cut-off points for shock index in predicting outcomes in younger and older patients. We will also examine the effect of pre-existing conditions, and blood alcohol on the accuracy of shock index. Data from the R Adams Cowley Shock Trauma Center Registry data was used to accomplish our objective.

Aim 1: Examine the accuracy of heart rate, systolic blood pressure and shock index in predicting mortality in patients with blunt and penetrating trauma (early (2 hours), 48-hour and all in-hospital mortality) stratified by age groups.

Hypothesis: Accuracy of heart rate, systolic blood pressure and shock index in predicting early, 48-hour and all in-hospital mortality outcomes differ by age and is less accurate in the elderly.

Sub-aim 1a: Compare accuracy of shock index with that of heart rate and systolic blood pressure

Hypothesis: Accuracy of shock index is better than that of heart rate or systolic blood pressure alone.

Sub-aim 1b: Determine cut-off points for shock index in predicting outcomes in older and younger patients.

Aim 2: Examine the accuracy of heart rate, systolic blood pressure and shock index in predicting undergoing major interventions (surgery within the first 24 hours, ICU admission, or massive transfusion) by age group

Hypothesis: Accuracy of heart rate, systolic blood pressure and shock index in predicting undergoing major interventions differ by age and is less accurate in the elderly

Sub-aim 1a: Compare accuracy of shock index with that of heart rate and systolic blood pressure

Hypothesis: Accuracy of shock index is better than that of heart rate or systolic blood pressure alone

Sub-aim 1b: Determine cut-off points for shock index in predicting outcomes in older and younger patients.

Aim 3: Examine how adjusting for age, blood alcohol concentration (BAC) and comorbidities affects the accuracy of shock index in predicting in-hospital mortality, and massive blood transfusion.

Hypothesis: Blood alcohol and comorbidities in combination with age, modify the accuracy of shock index especially in outcomes in older injured patients

Sub-aim: Determine the incremental value of age, blood alcohol, and comorbidities to improving the classification of shock index in predicting outcomes

CHAPTER 2: BACKGROUND

Introduction

Survival and prevention of disabilities of seriously injured patients is dependent on triage to trauma centers, in-hospital trauma care, and post-discharge management (Choi, Carlos, Nassar, Knowlton, & Spain, 2021; Haas et al., 2010; E. J. MacKenzie et al., 2006; Staudenmayer, Weiser, Maggio, Spain, & Hsia, 2016). Patients with severe injuries had lower mortality rates if treated in level I trauma centers compared with those treated in lower-level centers (Candefjord, Asker, & Caragounis, 2022; Choi et al., 2021; Newgard et al., 2011). Increased heart rate and low blood pressure are utilized in rapid triage and management decision making both in the field, and at initial hospital presentation (Damme, Luo, & Buesing, 2016; Eastridge, Holcomb, & Shackelford, 2019; Sasser et al., 2012). Shock index, calculated as heart rate divided by systolic blood pressure (heart rate/systolic blood pressure), has been shown to be a good predictor of mortality and transfusion in injured patients (Koch, Lovett, Nghiem, Riggs, & Rech, 2019; Newgard et al., 2020; Vandromme et al., 2011). While the recently updated National Guideline for the Field Triage of Injured Patients (formerly the NTTP) included heart rate greater than systolic blood pressure (essentially equal to shock index > 1), it was noted that the evidence for this inclusion is low (Newgard et al., 2022). One limitation in the evaluation of shock index in comparison with other markers of trauma outcomes such as heart rate and blood pressure is that studies comparing receiver operating characteristic (ROC) curves have not involved adjustment for covariates such as age which may affect the ROC curve. Covariates may affect ROC curves, leading to over or underestimation of the accuracy of the marker or test (Inacio & Rodríguez-

Álvarez, 2022; Janes, Longton, & Pepe, 2009; Janes & Pepe, 2009; Pardo-Fernández, Rodríguez-Álvarez, & Keilegom, 2014). To our knowledge, none of the studies have used covariate-adjusted ROCs in evaluating markers in the prediction of outcomes in trauma; however, recent advances in statistical packages have made this approach more available.

Another limitation to the use of shock index is that its accuracy in different age groups in adults has not been fully evaluated (Koch et al., 2019). Altered physiology, cardiac conduction defects, presence of concomitant illness, medications such as beta-blockers and antihypertensive agents, and alcohol intake, especially in older individuals, may cause blunted responses to shock (Bonne & Schuerer, 2013; Heffernan et al., 2010; Lilitsis et al., 2018; Martin, Alkhoury, O'Connor, Kyriakides, & Bonadies, 2010; Victorino, Chong, & Pal, 2003) and therefore may affect the accuracy of shock index. One limitation to using shock index in triage, the effect of comorbidities needs to be considered.

Because shock index is a continuous value, if the accuracy of shock index differs by age groups, identification of cut-off points in predicting outcomes may be of considerable clinical importance. Different cut-offs for systolic blood pressure by age group was first included as a special consideration in the 2011 version of the National Trauma Triage Protocol (NTTP) (Sasser et al., 2012), and it was relocated as part of the Mental Status and Vital Signs section of the most recent version, revised in 2021, with its name revised to National Guideline for the Field Triage of Injured Patients, and published in late 2022 (Newgard et al., 2022). In addition, a pediatric specific shock index was developed, with different shock index cut-offs identified for children's age groups. This pediatric specific shock index was shown to be effective in predicting transfusion needs, mortality, and intensive care unit (ICU) admission in pediatric age groups (Acker et al., 2017; Acker, Ross, Partrick, Tong, & Bensard, 2015; Hietanen, 2020; Phillips et al., 2020; Phillips et al., 2021). One study in Japan examined shock index cut-offs in adults by 10-year age groups in predicting early death in Japanese injured patients (Shibahashi, Sugiyama, Okura, Hoda, & Hamabe, 2019), and suggested caution on the use of shock index in older age groups. Performance of shock index was worse with older age groups. However, this study did not adjust for covariates or comorbidities.

The objective of this research is to examine the accuracy of shock index, as an initial indicator of mortality (early (2-hour), 48-hour, and all in-hospital), receiving massive transfusion, and undergoing major interventions, in older and younger injured patients. Other than age, we also examined the effect of factors that affect the accuracy or discriminatory performance of shock index in the prediction of trauma outcomes. We compared the discriminatory performance of shock index in comparison with heart rate, systolic blood pressure and revised trauma score in the prediction of outcomes in injured patients, and by age groups. ROC regression techniques, available in STATA, now allow comparison of accuracy of shock index, heart rate and blood pressure using ROC curves adjusted for covariates and enables evaluation of covariate-specific adjusted ROC curves. We hypothesize that the accuracy of shock index in predicting outcomes in trauma is less accurate in the elderly compared to younger injured patients and is better than heart rate or systolic blood pressure alone, especially when adjusted for covariates. We will identify cut-off points for shock index in predicting outcomes in older and younger patients. We will also examine the effect of pre-existing conditions, and blood alcohol on the accuracy of shock index. Data from the R Adams Cowley Shock Trauma Center (STC) Registry data was used to accomplish our objective.

Burden of injuries

Injuries are among the leading causes of death in the USA. Unintentional injuries are the third leading cause of death in the country and were responsible for over 170,000 deaths in 2019 (CDC, 2021). Injuries are more common among younger individuals, with unintentional injuries being the top cause of death among individuals <45 years of age and the seventh leading cause of death among those >65 years of age in 2019 (CDC, 2021). Injuries are costly to public health. The total estimated lifetime medical and work loss costs associated with fatal and non-fatal injuries in the US was $671 billion in 2013. The costs associated with fatal injuries was $214 billion, that for nonfatal injuries, over $456 billion. More than 3 million people are hospitalized, 27 million people are treated in emergency departments and released each year (CDC, 2021).

As of 2018, 16% of the US population was more 65 years old (Federal Interagency Forum on Aging Related Statistics, 2021). The 2017 National Population Projections estimates that by 2034, older adults will outnumber children under the age of 18 years, and by 2030, 23.4% of the US population will be over 65 years (US Census, 2018). As more people grow older, this group of individuals represents a growing population at risk of suffering an injury. The occurrence of injury in older individuals has increased over the years. The increase in rate was most noticeable among the older compared to younger individuals (Murphy, Baker, Leo-Summers, & Tinetti, 2014). It is estimated that by year 2050, around 40% of trauma admissions will be in this age group (Banks & Lewis, 2013; Campbell, Degolia, Fallon, & Rader, 2009).

Unintentional injury is the seventh leading cause of death among adults ≥65 years of age. In 2019, of the approximately 26.9 million patients seen in emergency departments for injuries, 4.9 million were among patients 65 years and older (CDC, 2021). Although there is a higher prevalence of injuries among younger individuals, older injured patients usually have longer hospital stays than younger individuals, had higher total health care costs and they use more resources following discharge (J. M. Keller, Sciadini, Sinclair, & O'Toole, 2012; van der Vlegel et al., 2020). A systematic review pooled mortality rates from 17 studies to estimate mortality in severely injured (ISS 16 or higher) trauma patients aged 65 and over. It is estimated that of older patients seen at emergency departments (EDs) mortality is at around 15% (Hashmi et al., 2014) while another US study estimated that in all admitted older injured patients regardless of severity in-hospital mortality was at 1.6% (Newgard, Lin, Yanez, et al., 2019). We believe that current mortality rates are closer to what Newgard estimated as a study by Maxwell has noted that rates of mortality in older patients admitted for trauma has decreased over the last few decades (Maxwell, Miller, Dietrich, Mion, & Minnick, 2015). Labib, et al estimates that 27-30% of older individuals who are admitted for severe trauma die in-hospital (Labib et al., 2011).

Table M 1Triage

Around 18% of injured patients seen in emergency departments (ED) are transported by Emergency Medical Services (EMS) providers (Sasser et al., 2012). Triage by EMS personnel is a very important characteristic of trauma systems. Its goal is to identify potentially seriously injured individuals and to make transport decisions (Baxt & Moody, 1987; E. J. MacKenzie et al., 2006; van Rein et al., 2018). Appropriate decision-making about transport is critical because survival and improved clinical outcomes of seriously injured patients is greatly dependent on them being triaged appropriately to trauma centers and receiving both appropriate in-hospital trauma care and post-discharge management (Fuller et al., 2021; Haas et al., 2010; E. J. MacKenzie et al., 2006; van Rein et al., 2018). It is therefore crucial that EMS personnel have evaluation tools that are reliable, accurate and easy to use.

Heart rate (heart rate) and systolic blood pressure (systolic blood pressure) are the most commonly used markers in decision making following injury (Brekke, Puntervoll, Pedersen, Kellett, & Brabrand, 2019; Eastridge et al., 2019; D. Kim & Jin, 2022; H. Wang, Chen, Zheng, & Zheng, 2019). Hypovolemic shock is a life-threatening condition that occurs when a one loses more than about 20% of one's blood volume. It is a leading cause of preventable deaths after an injury (Gruen et al., 2012) and is associated with disability and decreased functional status (J. W. Cannon, 2018; Kauvar, Lefering, & Wade, 2006; Mitra, Gabbe, et al., 2014; Pratt et al., 2015). The Centers for Disease Control and Prevention, and the American College of Surgeons developed the National Trauma Triage Protocol (NTTP) as a guide for EMS personnel in identifying patients who would need higher levels of trauma care. In the 2011 version of the NTTP (2011 NTTP), a systolic blood pressure of <90 mm Hg is one of the key indicators in Step 1 for transport to a trauma center, indicating hypovolemic shock (Sasser et al., 2012). However, studies have shown that hypotension and tachycardia may not present early following injury, and therefore the need for a higher level of trauma care may be underrecognized (Bardes, Benjamin, Schellenberg, Inaba, & Demetriades, 2019; Guly et al., 2011; Newgard, Lin, Eckstrom, et al., 2019; Pacagnella et al., 2013; Parks, Elliott, Gentilello, & Shafi, 2006). The 2011 NTTP had incorporated as a special consideration, a higher systolic blood pressure threshold of <110 mmHg for patients >65 years of age. In the 2021 update of the NTTP, now renamed the National Guideline for the Field Triage of Injured Patients, this higher threshold criterion for older patients was moved to the Mental Status and Vital Signs section for clarity and consistency (Newgard et al., 2022).

Shock Index

The Shock Index (shock index), calculated as heart rate (heart rate) divided by systolic blood pressure (systolic blood pressure), was first presented in 1967 by Allgower and Burri as a means of evaluating hypovolemia in hemorrhagic and infectious shock (Allgöwer & Burri, 1967). The normal range of shock index in healthy adults is currently accepted to be 0.5-0.7 (Berger et al., 2013; Koch et al., 2019; Vandromme et al., 2011). It is a scoring system or marker which can be easily utilized in rapid triage and management decision making both in the field and at initial hospital presentation.

Shock index can be a better predictor of outcomes and need for trauma center management compared with heart rate or systolic blood pressure alone (Birkhahn, Gaeta, Terry, Bove, & Tloczkowski, 2005; C. M. Cannon et al., 2009; Rady, Smithline, Blake, Nowak, & Rivers, 1994; Zarzaur, Croce, Fischer, Magnotti, & Fabian, 2008). Rady, et al, and Birkhan, et al suggest that shock index can detect hypovolemia in the presence of normal heart rate and systolic blood pressure values (Birkhahn et al., 2005; Rady et al., 1994). Studies have shown that shock index is a good predictor for hypovolemic shock (Cancio, Wade, West, & Holcomb, 2008; DeMuro, Simmons, Jax, & Gianelli, 2013; Hagiwara et al., 2010; Mitra, Fitzgerald, & Chan, 2014; Mutschler et al., 2013; Vandromme et al., 2011). Higher values of shock index are associated with higher likelihood of blood transfused (DeMuro et al., 2013), massive blood transfusion (Cancio et al., 2008; DeMuro et al., 2013; Hagiwara et al., 2010; Mitra, Fitzgerald, et al., 2014; Mutschler et al., 2013; Vandromme et al., 2011) and undergoing hemostatic interventions (DeMuro et al., 2013). Most of the studies comparing shock index and heart rate or systolic blood pressure were conducted using descriptive or traditional studies of association. Head-to-head comparison of diagnostic or predictive accuracy of shock index and heart rate or systolic blood pressure is limited (Newgard et al., 2020).

In injured individuals, elevated shock index has been shown to be associated with increased likelihood of death (C. M. Cannon et al., 2009; Newgard et al., 2010; Odom et al., 2016) and greater injury severity, and organ failure (Grimme et al., 2005). In a retrospective study of 2445 injured patients admitted to a level 1 trauma hospital, mortality was 9.3% among those with an admission shock index of >0.9 while it was

5.8% among those with lower shock index values (C. M. Cannon et al., 2009). Haider, et al reported that a shock index of >1.0 was a better predictor of mortality compared to a systolic blood pressure of <90 mmHg (Haider et al., 2016). Higher shock index values have also been shown to be associated with longer hospital stays (McNab, Burns, Bhullar, Chesire, & Kerwin, 2013; Newgard et al., 2010), mechanical ventilation (McNab et al., 2013) and likelihood of admission to the ICU (A. S. Keller et al., 2010).

In 2021, The American College of Surgeons Committee on Trauma revised the NTTP. In the revision, heart rate > systolic blood pressure, which corresponds to a shock index of >1 for adults and older adults was included in the Mental Status and Vital Signs section (Newgard et al., 2022). The revision does not consider different thresholds for younger and older adults despite considering different thresholds for systolic blood pressure.

Vital Signs and Older Individuals

Older injured patients seem to be less likely to experience preventable adverse events, are more likely to be discharged home and are more likely to have a lower mortality if treated at trauma centers (Caterino et al., 2016; Nathens et al., 2006; Rogers et al., 2012; van Rein et al., 2018). Despite improved outcomes for older injured patients managed in trauma centers, studies have shown that older adults may not benefit as much because of undertriage (Alshibani, Alharbi, & Conroy, 2021; Alshibani, Banerjee, et al., 2021; Alshibani, Singler, & Conroy, 2021; Kodadek, Selvarajah, Velopulos, Haut, & Haider, 2015; Uribe-Leitz et al., 2020). One of the reasons given for undertriage of older injured patients is that of factors at a patient level such as comorbid conditions, polypharmacy, frailty, and perceived insignificant mechanisms of injury (Alshibani, Alharbi, et al., 2021; Uribe-Leitz et al., 2020).

Many issues make the older injury patient different from younger ones. They include physiological and functional factors, presence of co-morbidities, and intake of medications (Alshibani, Alharbi, et al., 2021; Alshibani, Banerjee, et al., 2021; Uribe-Leitz et al., 2020). These same factors may influence the interpretation of vital signs among older injured patients may influence the predictive utility of shock index in this population.

Older individuals may present with different vital signs in response to trauma in comparison with younger individuals (Boulton, Peel, Rahman, & Cole, 2021; Martin et al., 2010; Newgard et al., 2016; Newgard, Lin, Eckstrom, et al., 2019). The prevalence of hypertension is higher in older patients but at the same time there is altered compensation to stress leading to a greater risk for hypotension (Chester & Rudolph, 2011). While a younger individual might be of increased risk of mortality when they present with a heart rate of >130 beats/min or a systolic blood pressure of <95 mmHg, the cut-off points for older individuals may be as low as a heart rate of >90 beats/minute and a systolic blood pressure of <110 mg Hg (Bonne & Schuerer, 2013; Heffernan et al., 2010). Evaluation of vital signs is further complicated by presence of baseline hypertension (Bonne & Schuerer, 2013; Victorino, Battistella, & Wisner, 2003). Studies have shown that triage criteria utilizing heart rate and systolic blood pressure are insufficient when utilized in older injured patients, leading to under-triage and a higher risk of (Martin et al., 2010; Rogers et al., 2012). This is the reason why in the current National Guideline for the Field Triage of Injured Patients, (formerly called the NTTP guidelines) now consider a systolic blood pressure of <110 mm Hg to indicate hypovolemic shock in injured patients >65 years of age (Newgard et al., 2022; Sasser et al., 2012).

Many older individuals also receive anticoagulation therapy as management of pre-existing cardiovascular ailments. Anticoagulation therapy may cause bleeding that may be undetected (Dalton, 2015). Acute alcohol intake has also been shown to affect heart rate and blood pressure, therefore possibly causing confusion in the evaluation of hypovolemic shock (Reed, 1999; Rossinin, 1997; Kawano, 2010; Pietila, 2019; Tasnim, 2020).

Shock Index and the Older Patient

While studies have shown that shock index might be a better predictor of mortality, massive transfusion and need for trauma center management in injured adults compared with just heart rate or systolic blood pressure alone (Birkhahn et al., 2005; C. M. Cannon et al., 2009; Vandromme et al., 2011), these studies utilized statistical methods involving the odds ratio. It has been illustrated that the odds ratio and other traditional measures of association in traditional epidemiological studies may be inadequate in assessing the accuracy of a test (Feng, 2010; M. S. Pepe, Janes, Longton, Leisenring, & Newcomb, 2004; Ware, 2006). Extremely strong associations are needed to discriminate between persons with the outcome and those without the outcome using odds ratios. Odds ratios also do not characterize the discrimination between patients with and without the outcome that can be achieved by a marker because different pairs of sensitivity and false positive fractions may be consistent with a particular odds ratio value (M. S. Pepe et al., 2004; Ware, 2006). Analyses involving ROC curves are suggested as better tools in the evaluation of the accuracy of continuous markers.

In studies of markers or tests predicting outcomes, other factors may affect the accuracy of markers and tests. Confounding occurs in evaluating the accuracy of markers or tests when covariates are associated with both the marker/test or the outcome of interest. If marker values depend on covariates, failure to calibrate to account for covariates may result in attenuation or improvement of the accuracy of the marker. Comparison of markers without adjustment may result in incorrect interpretations (Inacio & Rodríguez-Álvarez, 2022; Janes et al., 2009; Janes & Pepe, 2008; M. Pepe, Longton, & Janes, 2009). Zarzauret.al. compared shock index with systolic blood pressure alone in predicting mortality in adults using comparison of ROC curves (Zarzaur et al., 2008). Shock index had better accuracy than systolic blood pressure. However, the comparison does not account for possible confounding for covariates. The studies which evaluated shock index using methods involving odds ratios (Birkhahn et al., 2005; C. M. Cannon et al., 2009; Rady et al., 1994; Vandromme et al., 2011) did not adjust for confounding in their models either.

The accuracy of shock index in predicting outcomes in injured adults may be different in older and in younger patients. As previously mentioned, the present NTTP guidelines indicate that in individuals >65 years old a systolic blood pressure of <110 might represent shock (Sasser et al., 2012). Because shock index is calculated using heart rate and systolic blood pressure and because evaluation of these parameters in older individuals might not be accurate, there is a need to evaluate shock index in older and younger individuals. Several studies have examined shock index in older injured patients (Pandit et al., 2014; Shibahashi et al., 2019; Zarzaur et al., 2008).

In a retrospective analysis of National Trauma Data Bank (NTDB) data from 2007-2010, Pandit, et al examined shock index as a predictor for morbidity and mortality in injured patients ≥65 years old (Pandit et al., 2014). Shock index of >1 was shown to be associated with higher odds of mortality (OR=3.1) compared with shock index ≤1. Shock index >1 was also found to be associated with increased odds of blood transfusion, undergoing an exploratory laparotomy and post-surgical complications. Shock index > 1 was also shown to be better than systolic blood pressure and heart rate in predicting mortality in the study population. The study did not compare the utility of shock index among older and younger individuals (Pandit et al., 2014).

Newgard, et al evaluated field physiological indices of injury among 44,890 adults aged ≥55 years transported by EMS to 122 hospitals in 7 regions in the USA during 2006-2008 (Newgard et al., 2014). The study demonstrated an increased probability of serious injury (ISS≥16) among patients with shock index>1, although there was little relationship between shock index and serious injury among the oldest patients. Younger patients were not included in the study.

Zarzaur et al., in a study of 16,077 adult patients admitted to a trauma center in 1996-2005 (Zarzaur et al., 2008), Age × shock index was proposed for predicting the need for transfusion of ≥4 units, and for mortality within 48 h. When used in all patients, Age × shock index performed worse than shock index alone, but when only applied to patients ≥55 years old, the ROC area under the curve (AUC) was increased from 0.79 to 0.81 for blood transfusion, and 0.79 to 0.83 for early mortality. Zarzaur re-examined Age × shock index in predicting 48-hour mortality in a study utilizing NTDB data of 189,574 injured adults from 2007 (Zarzaur, Croce, Magnotti, & Fabian, 2010). The study showed that for patients <55 years old, there was no difference between systolic blood pressure and shock index in predicting 48-hour mortality while for patients ≥55 years old, Age × shock index was a better predictor of mortality compared with heart rate, systolic blood pressure and shock index.

A study was conducted in Korean injured patients aged ≥65 years showed that age × shock index was more accurate that shock index in predicting mortality. No young patients were enrolled in the study (S. Y. Kim et al., 2016).

A study examined the accuracy of shock index at a cut-off of ≥0.9 in predicting early mortality in 146,802 adult injured patients in Japan (Shibahashi et al., 2019). Accuracy was lower in the older age groups. In order to "adjust for age", it also examined the accuracy of age × shock index in predicting early mortality by age groups. Accuracy of age × shock index was also lower by age group.

Cut-offs for shock index utilized in the studies to evaluate "need" for massive blood transfusion vary. Mitra et al reported a field shock index cut-off of 1 to have >90% sensitivity to predict massive transfusion (Mitra, Fitzgerald, et al., 2014). Vandromme, et al showed that a field shock index cut-off of 0.9-1.1 produced a risk ratio of 1.6, and a cut-off of 1.1-1.3 resulted in a risk ratio of 5.6 for receiving massive transfusion (Vandromme et al., 2011). They suggested a field shock index cut-off of >0.9 for determining hypotension in triage protocols. Mutschler, et al suggested shock index cut-offs of 0.6-1.0 to indicate mild shock, 1.0-1.4 to indicate moderate shock, and more than 1.4 to indicate severe shock (Mutschler et al., 2013).

Possible cut-offs for shock index in predicting trauma outcomes in adults by age is not well explored. A pediatric specific shock index, called shock index, pediatric age adjusted (SIPA) was developed, with shock index cut-offs identified for age groups in children. Cutoffs for shock index were: shock index>1.22 (age 4-6 years), >1.0 (7-12 years), and >0.9 (13-16 years) (Acker et al., 2017; Acker et al., 2015; Hietanen, 2020; Phillips et al., 2020). If the accuracy of shock index differs significantly by age, a similar age adjusted shock index for adults based on different cut-offs may be a good tool for possible use in triage. Other than the study by Shibahashi mentioned previously, shock index cut-offs by age in predicting outcomes in adult trauma has not been evaluated(Shibahashi et al., 2019). Cut-offs in this study were estimated by 10-year age groups, making the application in the setting of triage protocols difficult.

Aside from few studies considering confounding or effect modification by age in studies examining the accuracy of shock index in predicting trauma outcomes, a limitation which is often mentioned is the failure to account for the effect of comorbidities, medications or presence of alcohol in the system, all of which may affect the accuracy of shock index (Koch et al., 2019). A study was conducted in Denmark examining whether age, diabetes, hypertension and use of beta- or calcium channel blockers modified the association between shock index and 30-day mortality among patients admitted to the emergency department. Old age, hypertension and medications seemed to weaken the association on logistic regression models. The study population is not solely in injured patients(Kristensen, Holler, Hallas, Lassen, & Shapiro, 2016). Another paper examined shock index in predicting massive transfusion and mortality in injured patients, adjusting for age and whether the patient was receiving antihypertensives or not (Park et al., 2021). Association between shock index and massive transfusion and 30-day mortality was evaluated using multivariable logistic regression with age and antihypertensive treatment in the model. While results are not clear, it concludes that a shock index with a cut-off of >1 was optimal in predicting massive transfusion in older patients taking antihypertensives.

In summary, studies comparing the accuracy of shock index in predicting trauma outcomes to standard vital signs used in triage protocols rarely involve adjusting for variables which may confound accuracy. Because of reported under triage in older patients. there is a need for studies looking specifically at both younger and older patients, and that adjust for confounders. To our knowledge, no studies looked at the effect of pre-existing conditions, and blood alcohol on the accuracy of shock index in predicting outcomes in injured patients, particularly in the elderly.

The objective of this research is to examine the accuracy of the shock index, in comparison with heart rate and systolic blood pressure, as an initial indicator of hospital mortality (early (2-hour), 48-hour, and in-hospital), receiving massive transfusion, and undergoing major interventions, in older compared to younger injured patients. We hypothesize that the shock index is not as accurate in older injured patients compared to younger ones and is better than heart rate or systolic blood pressure alone in predicting outcomes in injured patients. We identified optimal cut-off points for shock index in predicting outcomes in younger and older patients. We examined the effect of injury type, injury severity, pre-existing conditions, and blood alcohol on the accuracy of shock index. We hypothesize that shock index is not as accurate among injured patients who were blood alcohol-positive and among patients with comorbidities.

Additional sensitivity analyses were also conducted to examine the impact of severe neurologic injury on Shock Index evaluation. These analyses were done excluding patients with severe head injury based (Glasgow Coma Scale (GCS) <9) from analyses.

CHAPTER 3: METHODS

Study Design

This is a diagnostic accuracy study (Mallet, 2012). While most observational studies examine strengths of associations, diagnostic accuracy studies focus on the ability of a diagnostic test, marker or a predictive model to make accurate predictions. This study examines how covariates such as age, co-existing conditions, and alcohol intake affect the accuracy of a marker or predictor, shock index, in the prediction of outcomes or future events. Analysis of retrospectively collected injury data was done.

Data Set

This study utilized R Adams Cowley Shock Trauma Center (STC) registry data. The STC is the busiest civilian trauma center in the USA. It is located in Baltimore, Maryland and it serves as the clinical hub of Maryland's statewide system of trauma care. It is categorized as a Level I trauma center by the American College of Surgeons' Committee on Trauma and serves as the regional adult center for seriously injured patients in Maryland (Shock Trauma, 2021). Data available include information on trauma patients such as admission vital signs; admission and discharge status; patient demographics; injury and diagnosis; procedure codes; injury severity scores; and patient disposition.

Study Population

Patients with blunt force or penetrating trauma who were ≥18 years old seen at the Shock Trauma Center during the period January 1, 2008-December 31, 2016 were included in the study. Patients transferred to the trauma center were excluded from analysis. Patients' type of injury (blunt or penetrating) was identified using International Classification of Diseases (ICD)-9 and ICD-10 external cause codes, and E-codes. Patients with both intentional and unintentional trauma were included.

Variables

Tables M1, M2 and M3 present the exposure variables/test, outcome variables and covariates which were included in the analyses for Aims 1, 2 and 3. respectively.

Table M1. Variables for Aim 1

EXPOSURE VARIABLE /MARKER	OUTCOME VARIABLE	MAIN COVARIATE	OTHER COVARIATES
Shock index, systolic blood pressure, heart rate	2-hour mortality, 48-hour mortality; all in-hospital mortality	Age	Injury severity; Injury type (blunt, penetrating)

Table M2. Variables for Aim 2

EXPOSURE VARIABLE/MARKER	OUTCOME VARIABLE	MAIN COVARIATE	OTHER COVARIATES
Shock Index, systolic blood pressure, heart rate	Massive transfusion; ICU admission; Surgery in the first 24 hours	Age	Injury severity; Injury type (blunt, penetrating)

Table M3. Variables for Aim 3

EXPOSURE VARIABLE/MARKER	OUTCOME VARIABLE	MAIN COVARIATE	OTHER COVARIATES
Shock Index	Massive transfusion; all in-hospital mortality	Age	Blood alcohol, comorbidities (cardiovascular disorders; thyroid disorders; diabetes mellitus; coumadin therapy)

Marker/test variables:

Shock Index – shock index is the main indicator of interest in our study. It is calculated as heart rate divided by systolic blood pressure. Heart rate and systolic blood pressure measured on arrival at the STC emergency department (ED) were utilized to calculate shock index

Heart rate – heart rate (beats per minute) was the heart rate recorded on arrival at the STC ED

Systolic blood pressure – systolic blood pressure was the systolic blood pressure in mmHg recorded on arrival at the STC ED

Outcome variables for Aims 1:

The outcomes for Aim 1 were mortality at different points after admission to the ED. The STC patient disposition for patients who died in-hospital is labelled as "Expired", and the discharge time and date for these patients are the date and time of death as recorded in death certificate. Length of time from admission to time of death was determined using interval between admission time to the ED, and ED/hospital discharge date and time (ie, death and time of death minus death and time of admission).

2-hour mortality – We recorded whether the patient died within 2 hours of the ED admission.

48-hour mortality – We recorded whether the patient died within 48 hours of the ED admission

All in-hospital mortality – We recorded whether the patient died any time while in hospital/case fatality

Outcome variables for Aim 2:

The outcomes for Aim 2 were need for major interventions: massive transfusion, surgery within the first 24 hours of admission and admission to the ICU. Massive transfusion is defined as transfusion of 4 units or more of packed red blood cells (RBC) in a one-hour period or 10 units or more of packed RBC in a 24-hour period. ICU admission information was based on ICD-10 or Current Procedural Terminology (CPT) codes. To identify patients who underwent surgery within the first 24 hours, time to surgery was calculated using admission time and time or start of surgery.

Outcomes variables for Aim 3:

The outcomes for Aim 3 were all in-hospital mortality and massive transfusion, as defined previously.

Covariates

We also looked at variables which may alter the predictive accuracy of shock index in assessing the outcomes of interest.

Covariates for Aims 1 and 2:

<u>Age group</u>

Age on admission was recorded and grouped into two age groups: 18-64 years and ≥65 years. The age cut-off of 65 years was utilized because it is the conventional age often referred to as “elderly” (Ataguba, Bloom, & Scott, 2021; Singh & Bajorek, 2014).

The age of 65 is also the cut-off utilized in the most current National Trauma Triage Protocol (NTTP) (Newgard et al., 2022; Sasser et al., 2012).

Injury severity

Because severity of disease can influence classification performance of markers or tests (Janes, STATA, 2009), we decided to look at whether injury severity may influence the performance of shock index in predicting trauma outcomes. We decided to utilize injury severity score (ISS), a scoring system which provides an overall score for injured patients as the main measure of injury severity. ISS is an anatomic-based system that takes values from 0 to 75 (unsurvivable injuries are automatically assigned a score of 75) (Baker, O'Neill, Haddon, & Long, 1974; Javali et al., 2019). Injured patients with ISS score >15 are considered as having 'severe' trauma (Bolorunduro et al., 2011; Javali et al., 2019).

Because ISS is an anatomic-based scoring system of injury severity that may not be determined in the field, sensitivity analysis was conducted where analyses was done using two physiologic scores which may be available in the field instead of ISS. The first one is Glasgow Coma Scale (GCS), which was developed to assess impaired consciousness in patients with head injuries (Teasdale & Jennett, 1974). We utilized the head injury classification: Mild (14–15), Moderate (9–13), or Severe (3–8) (Mena et al., 2011). The other physiologic injury severity scoring system we utilized in the sensitivity analysis is the Revised Trauma Score (RTS) which Glasgow Coma Scale, systolic blood pressure and respiratory rate ranges are given a coded value of 0-4. The RTS is then calculated by adding the coded values, for a range of 0-12 (Champion et al., 1989). A lower score indicates higher injury severity and need for trauma center care. In this study, we use a cut-off of ≤8 to indicate severe injury.

Injury type

Patients were classified as having blunt or penetrating injury.

Covariates for Aim 3:

Age group – as described previously.

Blood alcohol – Blood alcohol is routinely tested in trauma patients. Patients were grouped as being blood alcohol positive (any blood alcohol detected) or blood alcohol negative.

Comorbidities - Patients with comorbidities which may alter heart rate or blood pressure were identified. Comorbidites considered were cardiovascular disorder (any cardiovascular disorder, including hypertension and heart disorders); diabetes mellitus (type 1 or type 2 diabetes mellitus); thyroid disorder; and receiving coumadin therapy.

Analysis

Analysis for Aims 1, 2 and 3:

Demographics and descriptive statistics

The population’s baseline characteristics were described by the two age groups. We examined the means, and distribution of heart rate, systolic blood pressure and shock index by age group. t-test and Chi-square tests were used in comparing groups as appropriate.

Histograms of shock index, heart rate and systolic blood pressure were plotted by age group, and by outcomes. Frequencies of outcomes by shock index, heart rate and systolic blood pressure were also plotted.

ROC curves

Traditional methods used to assess associations in epidemiological studies (i.e., odds ratios) may not be adequate to examine the performance of tests or markers for classifying or predicting outcomes (Boyko & Alderman, 1990; Kattan, 2003; M. S. Pepe et al., 2004; Ware, 2006). Authors have shown that strong statistical associations between tests or markers and outcomes may not mean the test can discriminate between those who would likely have the outcome and those who do not (Campbell et al., 2009; M. S. Pepe et al., 2004; Ware, 2006).

Because shock index, heart rate and systolic blood pressure are continuous values, we utilized methods involving receiver operating characteristic (ROC) curves. ROC curves provide a means of examining the predictive accuracy of a continuous predictor in discriminating between two states (i.e., diseased vs not diseases; cases and controls; etc.). We refer to these states in our study as presence or absence of the outcome of interest.

The ROC curve is a graph of the true positive rate (TPR) (sensitivity) versus false positive rate (FPR) (1 minus specificity) of a continuous test or marker, in our case, heart rate, systolic blood pressure and shock index, at different classification thresholds or cut-offs. A marker with reasonable accuracy is expected to have an ROC curve in the upper left triangle above the y=x (TPR=FPR) line. The area under the ROC curve (AUC) is a global measure of the ability of a test or marker to discriminate whether a specific condition or event is present or not present. An AUC of 0.5-0.6 suggests poor discrimination (i.e., ability to identify patients with and without the disease or outcome based on the marker or test), 0.7- 0.8 is considered acceptable, 0.8-0.9 is considered excellent, and > 0.9 is considered outstanding (Hoo, Candlish, & Teare, 2017; Hosmer, Lemeshow, & Sturdivant, 2013; M. Pepe et al., 2009; M. S. Pepe, 2000).

ROC curves in this study were generated by running logistic models using PROC LOGISTIC in SAS 9.4 (SAS, 2019; Wicklin, 2018) and the roctab, rocreg and rocregplot packages in STATA 15 (STATA, 2019a, 2019b, 2019d, 2019e).

Accommodating covariates in ROC analysis

Motivation for the accommodation of covariates in ROC analysis

Independent host factors may affect prediction in patients without the trauma outcomes of interest (controls). Factors that increase marker scores among controls, might increase the false-positive test rate, while characteristics that decrease or increase scores in cases might reduce or increase sensitivity. Characteristics such as disease severity, might also influence the classification performance of the test or marker (Janes et al., 2009; Janes & Pepe, 2008; STATA, 2019b). Therefore, characteristics or covariates that shift marker or test distribution among cases and controls should be accounted for when evaluating accuracy or discriminatory performance tests (Janes et al., 2009; Janes & Pepe, 2008; Margaret Sullivan Pepe, 2004).

The performance of markers or tests, and their discriminatory capacities can be affected by the presence of covariates. The incorporation of covariates into the ROC curve might be done for different purposes. The first is when the performance of a marker is affected by covariates but the classification performance (differentiating cases from controls) is not affected, akin to confounding in traditional epidemiological disorders (Inacio & Rodríguez-Álvarez, 2022; Janes et al., 2009; Janes & Pepe, 2008; Pardo-Fernández et al., 2014). A second purpose is when classification performance of discriminating capacity of the marker is affected by the covariate. Classification performance differs in different levels of a covariate such as older or younger age. A third purpose is to examine the incremental value of covariates or the ability of the combination of the marker and covariates to discriminate between patients who had or did not have the event (Janes et al., 2009; Janes & Pepe, 2008). Characteristics or covariates that contribute to accurate classification might be combined with the marker/test to create a combination risk score with improved accuracy or predictive performance.

ROC regression

ROC regression is a method that models the ROC curve of a test as a function of covariates (Alonzo & Pepe, 2002; Janes et al., 2009; M. Pepe et al., 2009; STATA, 2019b). Implementation of ROC regression occurs in 2 steps, the first of which is modeling the distribution of the test of interest among controls (those that did not have the event) as a function of covariates. The case percentile values are calculated. The covariates used in this step for adjustment are those that affect the test distribution in controls (i.e., similar to confounding in traditional association studies). The second step involves modeling the CDF or the ROC curve as a function of covariates.

Covariates may affect the distribution of the test among cases. They can impact the discriminatory accuracy of the ROC curve itself (i.e., affecting the separation between case and Control test distributions). The second step in ROC regression described previously involves modeling the ROC curve as a function of covariates (covariate-specific curve or ROC curve by covariate group, akin to effect modification in traditional association studies). In this study, this generalized linear model-based regression methodology which models the ROC curves as a function of age and other covariates was performed using the rocreg package in STATA 15 (Janes et al., 2009; M. Pepe et al., 2009; STATA, 2019b, 2019c, 2019d).

Covariate-adjusted ROC curves

When covariates affect the distribution of a marker among controls or those that did not have the event, thresholds for the test being classified as abnormal may be chosen that vary with the covariate values. These conditional thresholds will be more accurate than the marginal thresholds that would normally be used, because they take into account the specific distribution of the marker under the given covariate values as opposed to the marginal distribution over all covariate values (Janes et al., 2009; Janes & Pepe, 2008, 2009; Margaret Sullivan Pepe, 2004). This is akin to confounding of the test by a covariate.

We then examined the control adjustment model and assess the effect of the covariates under the control population. We ran the rocreg package in STATA 15 for ROC analysis of markers while adjusting for the covariate effects. At $P<0.05$ level, we will reject that the contribution to the marker is zero (i.e., the covariate may confound the interpretation of the marker in the prediction of outcomes).

Covariate adjustment in ROC analysis done here is different from using covariates in a predictive model or in incremental value analysis as how it is done in traditional epidemiologic association studies with modeling usually done using logistic regression. In traditional association studies, covariates are added to a model and these added covariates contribute to the predicted probability of the outcome of interest. Here when we perform covariate adjustment in ROC analysis, the classification accuracy of the marker is characterized conditional on the covariate.

Covariate-specific ROC curves

We examined whether the accuracy or discriminatory capacity (differentiating cases from controls) of our markers changes according to the value of a covariate. We first examined the accuracy of the tests by covariate groups through methods involving ROC curves from logistic models generated using PROC LOGISTIC in SAS 9.4 fit to independent samples (i.e., age group) (SAS, 2019). Comparison of ROC areas under the curves (AUC) generated per group was done using a test described by Gonen (Gonen, 2007): Chi-Sq = $(AUC1 - AUC2)^2 / (s1^2 + s2^2)$, 1 df, where AUC1 and AUC2 were the AUCs per age group, and s1 and s2 were the respective standard errors.

Using rocreg package in STATA 15, we then examined the case adjustment model, and assess the effect of the covariates under the population that had the event (cases) (STATA, 2019b, 2019d). The variables were included in the "ROC model" (examining whether the covariate affected the ROC curve itself). At $P<0.05$ level, we reject that the contribution to the marker is zero (ie, the covariate affects the marker in the prediction of outcomes).

The covariate-adjusted ROC curves for shock index in predicting death outcomes at different age groups were plotted at fixed injury severity (ISS>15; severe injury) and fixed injury type (blunt trauma). These covariate-specific ROC curves (by age groups) are then compared at a fixed false positive rate (0.7) using a Wald test (STATA, 2019c). When covariates are found to affect the distribution of the test among cases, it would be best to model ROC curves by covariate groups separately.

Incremental value of covariates

Janes asserts that covariate adjustment is commonly confused with other uses for covariates in evaluating classification accuracy. In prediction, the predicted probability is the probability of the outcome as a function of marker and covariate information and is commonly estimated by using logistic regression, where the outcome is regressed on one or more markers and other covariate information (Janes et al., 2009; Janes & Pepe, 2008, 2009). Janes emphasize that the ROC curve for the predicted probability (ie, the combination score) is different from the covariate-adjusted ROC curve for the marker. The ROC curve for the combination score describes the ability of the combination of marker and covariates to discriminate between cases and controls. This method of "adjusting" for covariates is the method commonly utilized in studies examining prediction of outcomes in clinical studies and in trauma (i.e., traditional association studies). In incremental value analysis, we ask whether the addition of additional covariates improve prediction or classification performance of a marker or test.

To determine the incremental value of the covariates to SI, we compared the ROC curves for SI alone with the ROC curves for SI in combination with the covariates. We will first fit logistic regression models with SI alone, and then fit logistic regression models with SI in combination the covariates. The ROC curves' AUCs will be compared using the method described by DeLong (DeLong, DeLong, & Clarke-Pearson, 1988). Within this framework, the covariates are allowed to help in discriminating between cases and controls. Analyses was done using the ROCCONTRAST option under PROC LOGISTIC in SAS (Wicklin, 2018).

Comparison of Tests (shock index, heart rate and systolic blood pressure)

The accuracy of shock index, heart rate and systolic blood pressure were compared by comparing crude ROC AUC and covariate-adjusted ROC curve AUCs, generated through STATA's rocreg package (STATA, 2019b, 2019d). AUCs were compared using the method described by DeLong (DeLong et al., 1988).

Sensitivity analyses

The purpose of the study is to examine the effect of characteristics such as age and injury severity on the accuracy or discriminatory performance of shock index in the prediction of trauma outcomes. However, as previously mentioned, using an injury severity scoring system which may be available in the field as a covariate may contribute to potential building of a prediction model or scoring system for prediction in the field. Sensitivity analysis was done using two physiologic scores which may be available in the field instead of ISS. The first one is Glasgow Coma Scale (GCS) and the other was the Revised Trauma Score.

Because severe head injury may heavily influence hemodynamics and is highly associated with mortality, analysis was also conducted excluding patients with severe head injury from the cohort.

Because patients who died within the first 24 hours since admission might not be able to have an outcome of massive transfusion (i.e., death in the first 24 hours is a competing risk), Analysis was also done with a composite outcome: massive transfusion or death in the first 24 hours.

Cut-offs/optimal cut-points for shock index

Determining the cut-offs for shock index is important as these cut-offs can be valuable in triage decision making. ROC AUCs for each of the two age groups were determined, and cut-offs for the shock index calculated. Exploration of sensitivity and specificity values of different cut-point values for shock index was conducted using roctab package in STATA (STATA, 2019e).

Optimal cut-offs were determined using the following methods: Youden index; absolute difference between sensitivity and specificity; and the distance from the cut point to the point where sensitivity=0 and 1 minus specificity=1 (upper left corner of the ROC plot) (Habibzadeh, Habibzadeh, & Yadollahie, 2016). Cut-offs for shock index were determined using the Youden Index, which defines the maximum potential effectiveness of a test or marker (Youden, 1950) . Youden Index can be defined as maxc (Se (c) + Sp (c) – 1). The cut-point that achieves this maximum is referred to as the optimal cut-point (c*) because it is the cut-point that optimizes the marker or test's differentiating ability when equal weight is given to sensitivity and specificity. Its value ranges from 0 indicating test is useless to a maximum value of 1 indicating there are no false positives or false negatives.

Determination of optimal cut-point using the Sensitivity, Specificity equality method of cut-off determination, the cut point with the minimum absolute difference between sensitivity and specificity is determined. With the Distance to (0,1) method of determining optimal cut-point, the distance from the "perfect" point at the upper-left corner of the ROC plot where 1-Specificity=0 and Sensitivity=1 were determined using the formula [Distance to (0,1) = $\sqrt{(1\text{-Sensitivity})^2+(1\text{-Specificity})^2}$] (Perkins & Schisterman, 2006). The cut-points using the different methods were determined using the rocplot.sas program provided by SAS (SAS, 2019).

Sample Size and Power

Null hypotheses:

Aims 1 and 2: We will compare the ROC AUC of SI with those of SBP and HR (H0: $ROC_{SI} = ROC_{SBP}$; H0: $ROC_{SI} = ROC_{HR}$). We will also compare the ROC AUC of SI in older patients.

All the aims require comparison of ROC AUCs derived from the same set of subjects, and therefore would require the same sample sizes. Sample sizes were calculated as described and tabulated by Hajian-Tilaki (Table M4) (Hajian-Tilaki, 2014). The following illustrates the calculation of sample size for the comparison of ROC AUC of test results from the same subjects. For comparison of two AUCs, AUC_1 and AUC_2, the null and alternative hypothesis are:

$$H_0 :\ AUC_1 = AUC_2 \text{ versus } H_1 :\ AUC_1 \neq AUC_2$$

One wishes to determine how many patients with and without the event are needed to detect an effect size between the two AUCs as defined by $\delta = \mathrm{AUC}_1 - \mathrm{AUC}_2$ under H_1 with $(1 - \alpha)\%$ confidence level and $(1 - \beta)\%$ power. By constructing the confidence interval for the parameter of interest $\mathrm{AUC}_1 - \mathrm{AUC}_2$ using normal approximation under H0 and H1, then the required sample sizes for each group are:

$$n = \frac{\left[Z_{\frac{\alpha}{2}}\sqrt{V_{\mathrm{H0}}(\widehat{\mathrm{AUC}}_1 - \widehat{\mathrm{AUC}}_2)} + Z_{\beta}\sqrt{V_{\mathrm{H1}}(\widehat{\mathrm{AUC}}_1 - \widehat{\mathrm{AUC}}_2)}\right]^2}{[\mathrm{AUC}_1 - \mathrm{AUC}_2]^2}$$

where

$$V(\widehat{\mathrm{AUC}}_1 - \widehat{\mathrm{AUC}}_2) = n\mathrm{Var}(\widehat{\mathrm{AUC}}_1) + n\mathrm{Var}(\widehat{\mathrm{AUC}}_2) - 2n\mathrm{Cov}(\widehat{\mathrm{AUC}}_1, \widehat{\mathrm{AUC}}_2)$$

$\mathrm{Var}(\widehat{\mathrm{AUC}})$ is estimated parametrically based on binormal assumption. The two parameters of ROC curves based on the binormal assumption are defined as $a = \frac{\mu_2 - \mu_1}{\sigma_1}$ and $b = \frac{\sigma_1}{\sigma_2}$ where μ_1 and σ_1 represent the mean and standard deviation of distribution for non-events and μ_2 and σ_2 are for events, respectively. $\mathrm{AUC} = \varphi[\frac{a}{1+b^2}]$ where φ is the cumulative distribution function. Delta method is used to estimate variance and SE of AUC. With an approximation when the ratio of SD is close to one (i.e. $b = 1$) the binormal estimator of variance of $(\widehat{\mathrm{AUC}})$ is

$$\mathrm{Var}(\widehat{\mathrm{AUC}}) = (0.0099 \times e^{-a^2/2}) \times \left(\frac{5a^2 + 8}{n_2} + \frac{a^2 + 8}{n_1}\right)$$

where $a = \varphi^{-1}(\mathrm{AUC}) \times 1.414$ and n_1 and n_2 are the sample size for event and non-event.

The required sample size for each group (event vs. no event) for detecting an effect of 0.05 with 95% confidence and 80% power in comparison of two AUCs from the same population is equal to 804 for low accuracy/AUC and 172 for high accuracy/AUC. Assuming the accuracy of SI corresponding to an AUC=0.75, in order to detect an effect of 0.05 with 95% confidence and 80% power, we will need a sample with at least 667 each in the event, and non-event groups. Table M4 presents the estimated total sample sizes and the number of events in the data sets.

Table M4. The required sample sizes for each group of patients with and without the event for comparison of two ROCs.

Comparison is made on the same subjects for detection an effect of δ = AUC1 − AUC2 and for different AUCs and effects (δ) with 95% confidence level and 80% power. (Hajian-Tilaki, 2014)

AUC1	n δ = 0.03	n δ = 0.05	n δ = 0.07	n δ = 0.10	n δ = 0.12	n δ = 0.15
0.6	2243	804	408	198	136	86
0.65	2176	777	393	189	130	81
0.7	2065	733	369	176	120	74
0.73	1972	697	348	165	111	68
0.75	1896	667	332	156	105	67
0.78	1758	614	303	140	93	56
0.8	1648	571	280	128	84	50
0.83	1453	497	240	107	69	41
0.85	1301	439	209	91	59	35
0.88	1041	342	158	66	44	–
0.9	846	270	121	52	–	–
0.93	527	172	69	–	–	–
0.95	310	–	–	–	–	–

CHAPTER 4: RESULTS

Population

A total of 52,152 patients were seen at the STC ED during the period January 1, 2008-December 31, 2016. Transfers to the ED (n=14,301), patients with missing admission blood pressure or heart rate (n=57) information were excluded. We also had to exclude patients whose systolic pressure on arrival were zero as this would not allow us to calculate a shock index value (n=801; 633 arrived with no discernible vital signs and declared dead on admission). A total of 36,993 patients were included in the analysis.

Table 1.1 presents the characteristics of the study population. Most of the trauma patients were male (68.71%), white (57.58%) and had an injury severity score of <16 (82.56 %). The population was relatively young, with a mean age of 43.1 years (median, 40 years). The most frequent mechanisms of injury were motor vehicle crashes (n=14,706; 39.75%) and falls (n=8882; 24.01%), with 86.67% of the population sustaining blunt injuries and 69.65% of patients had negative blood alcohol test results.

A total of 5619 (15.19%) patients were ≥65 years of age. While patients who were <65 years old were more likely to be male, sex distribution among those ≥65 years old was similar between men and women (49.12% and 50.88%, respectively). A higher proportion of older patients were white (81.33%) compared to the proportion in younger patients (53.33%). Older patients were more likely to have falls as the mechanism of injury (59.03% vs. 17.74%) and less likely to be involved in a motor vehicle crash (22.12% vs. 39.75%) than younger patients. While blunt injuries were the most frequent type of injuries in both age groups, the proportion was higher among older patients than in younger patients (98.40% vs. 84.57%).

There were 1010 (2.73%) in-hospital deaths in the population, 433 of which were in patients who were ≥65 years of age; 503 trauma patients (1.36%) died within 48 hours of presenting to the ED while 71 died within 2 hours of admission (Table 1.1). A higher proportion of patients <65 years of age died within the first 2 hours of admission compared with the proportion of younger patients ≥65 years old (0.28% vs. 0.18% data not shown); the opposite was noted with death within 48 hours of admission and all-hospital deaths (3.70% vs. 0.94% and 7.74% vs. 1.84%, respectively). Younger trauma patients were more likely to have penetrating injuries compared with older patients (15.43 vs. 1.60%) (Table 1.1).

Systolic blood pressure was lower (mean 142.25 vs. 159.78) among younger trauma patients compared to older trauma patients (P<0.001). However, heart rate was higher among younger trauma patients (mean, 91.93 vs 85.13) and mean shock index values were higher among younger patients than those who were older (0.65 vs. 0.55; P<0.001).

Table 1.1. Demographic and clinical characteristics of the study population

Variables		**All patients (n=36,993)**		**Age<65 (n=31,374)**		**Age≥65 (n=5619)**		**P^a**
		n	**%**	**n**	**%**	**n**	**%**	
Sex	Female	11,568	31.27	8,709	27.76	2,859	50.88	<.0001
	Male	25,419	68.71	22,659	72.22	2,760	49.12	
	Unknown	6	0.02	6	0.02	0	0	
Race	White	21,302	57.58	16732	53.33	4,570	81.33	<.0001
	Black	12,853	34.74	12,021	38.32	832	14.81	
	Other	2,838	7.67	2,621	8.35	217	3.86	
Injury Severity Score	<16	30,542	82.56	26,116	83.24	4,426	78.77	<.0001
	≥16	6,451	17.44	5,258	16.76	1,193	21.23	
Mechanism of Injury	Beating/hit by object	2,233	6.04	2,180	6.95	53	0.94	<.0001
	Fall	8,882	24.01	5,565	17.74	3,317	59.03	
	Firearm	1957	5.29	1919	6.12	38	0.68	
	Motor vehicle crash	14,706	39.75	13,463	42.91	1,243	22.12	
	Pedestrian	2,238	6.05	2,027	6.46	211	3.76	
	Stab/sharp object	2,306	6.23	2,278	7.26	28	0.5	
	Other	4,671	12.63	3,942	12.56	729	12.97	
Injury Description	Blunt	32,063	86.67	26,534	84.57	5,529	98.4	<.0001
	Penetrating	4,930	13.33	4,840	15.43	90	1.6	
Blood alcohol	negative	25,767	69.65	20876	66.54	4891	87.04	<.0001
	positive	10,321	27.9	9743	31.05	578	10.29	
	Unknown	905	2.45	755	2.41	150	2.67	

Table 1.1 Continued

Variables		All patients (n=36,993)		Age<65 (n=31,374)		Age≥65 (n=5619)		P[a]
		n	%	n	%	n	%	
Comorbidities	Thyroid	1,057	2.86	525	1.67	532	9.47	<.0001
	Cardiovascular	6,982	18.87	4371	13.93	2,611	46.47	<.0001
	Diabetes	2,929	7.92	1744	5.56	1,185	21.09	<.0001
	Coumadin treatment	150	0.41	32	0.1	118	2.1	<.0001
	Any comorbidity	9,044	24.45	5592	17.82	3452	61.43	<.0001
Major procedure	ICU admission	4,145	11.2	3225	10.28	920	16.37	<.0001
	Surgery in the first 24 hours	2,358	6.37	2,033	6.48	325	5.78	0.049
	Massive transfusion	524	1.42	462	1.47	56	1	0.004
	ICU admission, surgery in the first 24 hours or massive transfusion	6,375	17.23	5,171	16.48	1,204	21.43	<.0001
Death	Early	71	0.19	55	0.18	16	0.28	<.0001
	48-hour	503	1.36	295	0.94	208	3.7	<.0001
	All in-hospital	1,010	2.73	577	1.84	433	7.71	<.0001

Table 1.1 Continued

Variables		**All patients (n=36,993)**	**Age<65 (n=31,374)**	**Age≥65 (n=5619)**	**P^a**
Systolic blood pressure	mean (SD), median	148.0 (28.05), 143	145.53 (26.1), 142	161.47 (34.0), 161	<.0001
Heart rate		90.9 (19.82), 89	91.93 (19.7), 90	85.13 (19.47), 83	<.0001
Shock index		0.64 (0.20), 0.61	0.65 (0.19), 0.62	0.55 (0.20), 0.517	<.0001

P^{a} - Chi-square for categorical variables, t-test for continuous variables; older vs. younger patients

Aim 1 Results

Distributions of shock index, heart rate and systolic blood pressure

We looked at the distributions of shock index, heart rate and systolic blood pressure among patients who died in-hospital and those who did not, by age groups (Figures 1.1, 1.2, 1.4, 1.5, 1.7 and 1.8). We also looked at the frequencies of all in-hospital deaths by shock index, heart rate and blood pressure (Figures 1.3, 1.6 and 1.9). Among younger patients, the majority of those who died in hospital had shock values of around >0.8-0.9. Among older patients, the majority of both patients who died had shock index values at around >0.6 (Figure 1.1 and 1.2).

Among younger patients, frequencies of death were low and flat over lower shock index values (starting at SI>0.3) with values starting to rise at around 0.9-1.0. Deaths were higher among older patients compared with younger patients, and deaths seeming to increase at around SI=0.7. Frequencies of death seem to be higher however at SI values of ≤0.3 compared with SI of 0.4-0.9. When we excluded patients with severe head injury from the analysis, this increased frequency of death among patients with SI values of ≤0.3 remained only in patients who were ≥65 years old.

Heart rates tended to be higher and systolic blood pressure tended to be lower among those who had the outcomes of interest compared to those who did not (Figures 1.4, 1.5, 1.7 and 1.8). However, the differences in distributions between vital signs of those who died and those who did not were not as pronounced among older patients as the differences in younger patients.

Frequency of deaths seemed to be higher a heart rates of <60 beats/min, flattened over heart rates of 60-120 beats/min and rose at >120 beats/min (Figure 1.6). Deaths were higher among patients over all heart rate values. Excluding patients with severe head injury from the analysis, there is no increased mortality among those with heart rates of <60 beats/min. Deaths in general was higher as blood pressures fell, with frequencies noticeably increasing after values below 110 mmHg. Mortality was higher among older patients over all ranges of blood pressure, with frequencies rising after reaching around 130 mmHg (Figure 1.9).

Figure 1.1. Distribution of shock index, by age group, comparing patients who died in hospital and those who did not

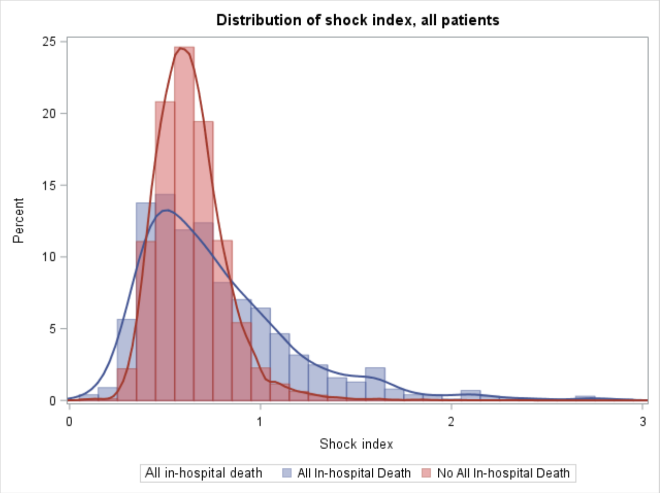
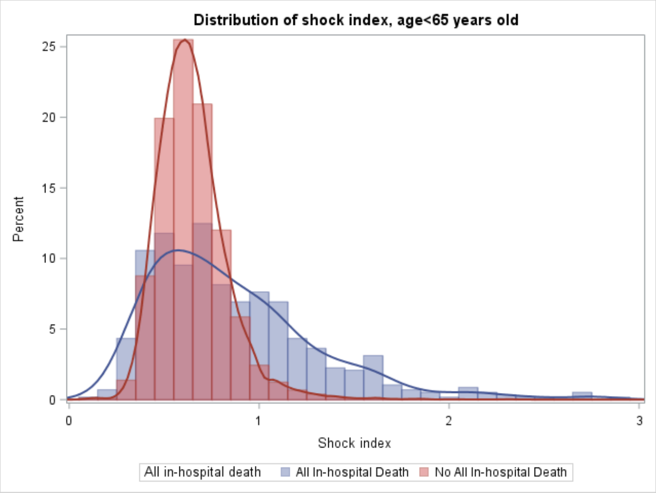
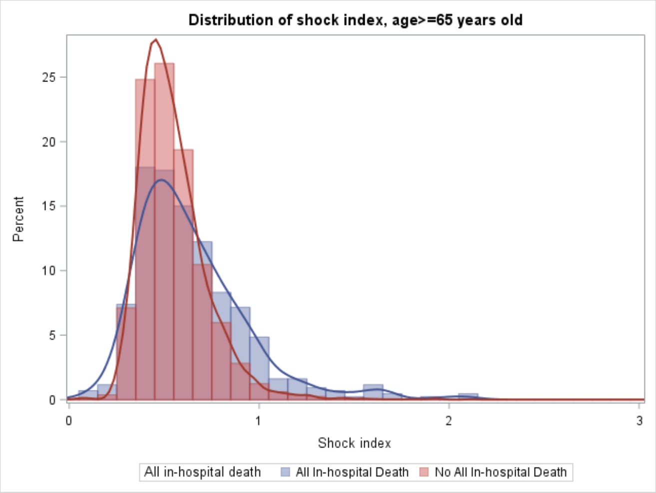
All Patients		🟦 All in-hospital death 🟥 No all in-hospital death
<65 years old		
≥65 years old		

Figure 1.2. Distribution of shock index, by in-hospital death status, comparing trauma patients <65 and ≥65 years old

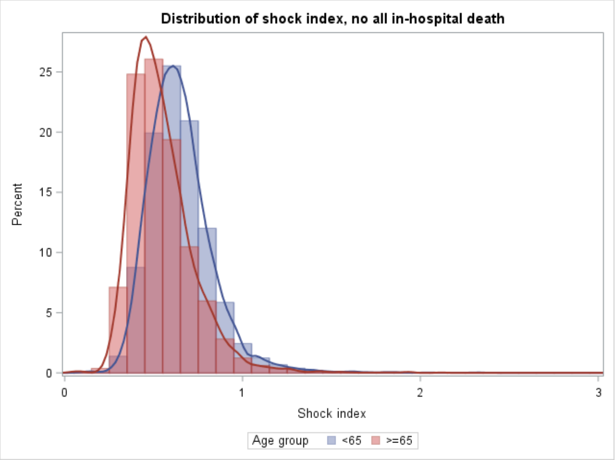
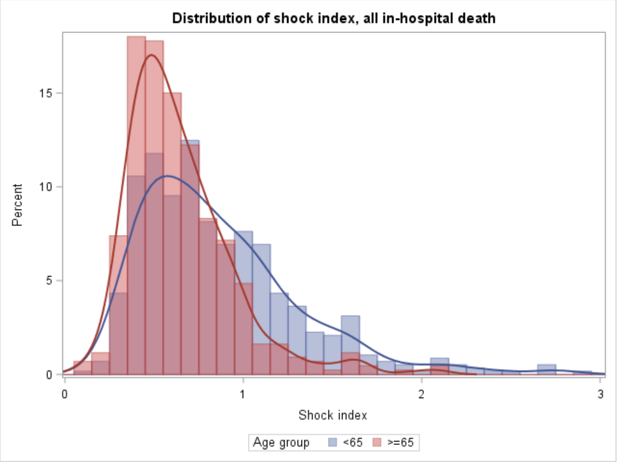
No in-hospital death		🟦 <65 years old 🟥 ≥65 years old
In-hospital death		

Figure 1.3. In-hospital deaths by shock index in all trauma patients and according to age.

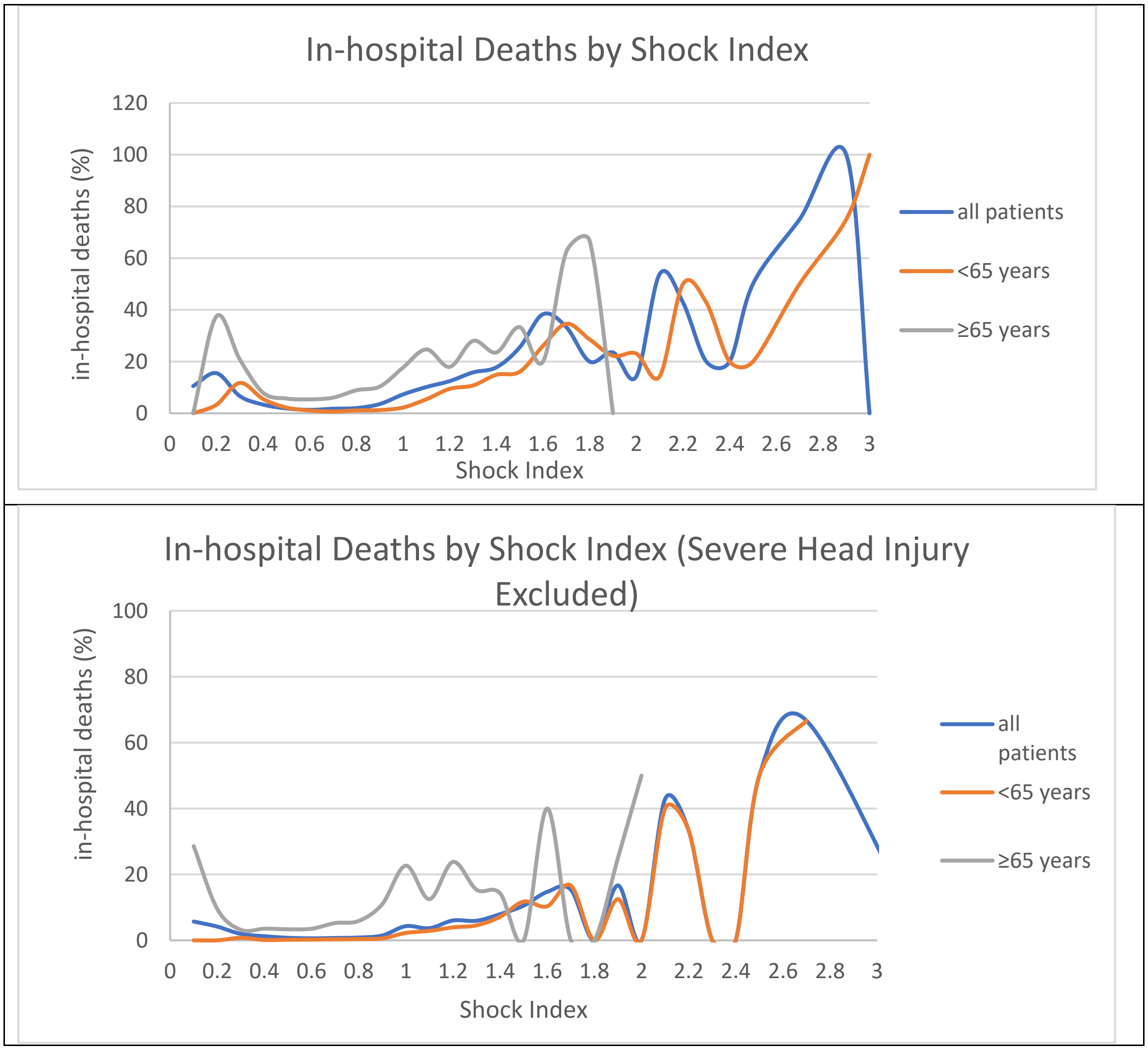


Figure 1.4. Distribution of heart rate, by age group, comparing patients who died in hospital and those who did not

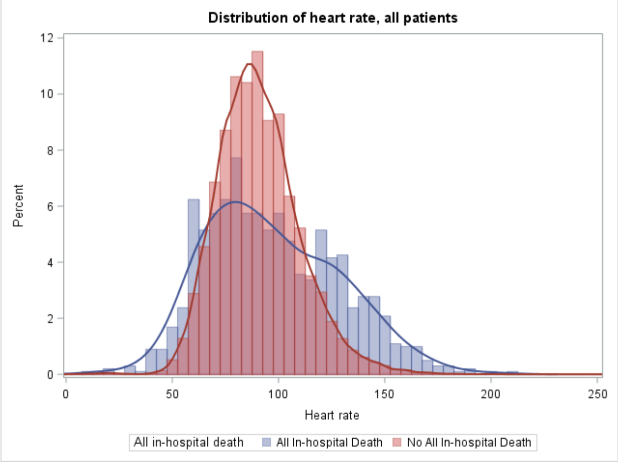
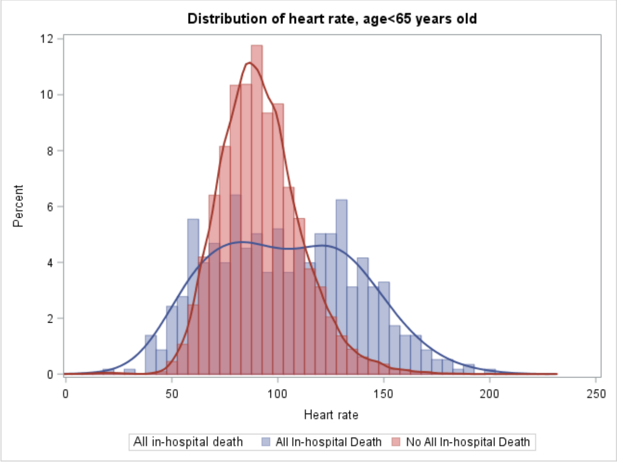
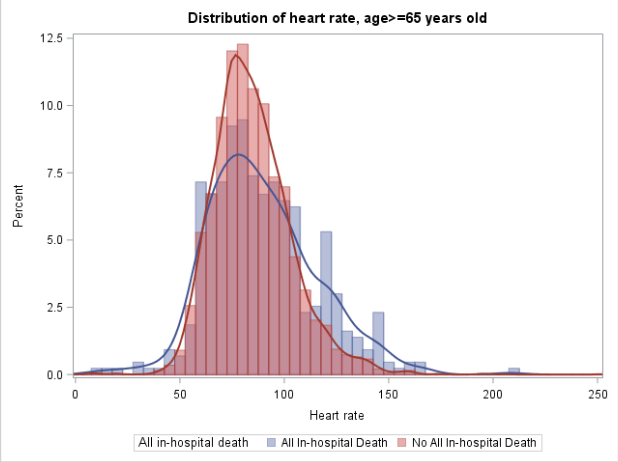
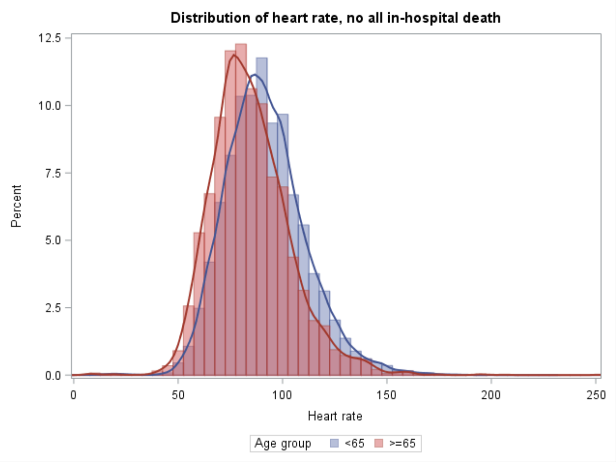
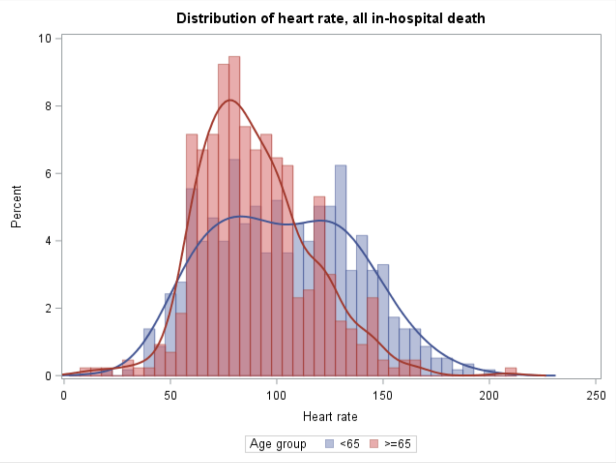
All Patients	 🟦 All in-hospital death 🟥 No all in-hospital death
<65 years old	
≥65 years old	

Figure 1.5. Distribution of heart rate, by in-hospital death status, comparing trauma patients <65 and ≥65 years old

<table>
<tr>
<td>No in-hospital death</td>
<td>


</td>
<td>🟦 <65 years old
🟥 ≥65 years old</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>


</td>
<td></td>
</tr>
</table>

Figure 1.6. In-hospital deaths by heart rate in all trauma patients and according to age.

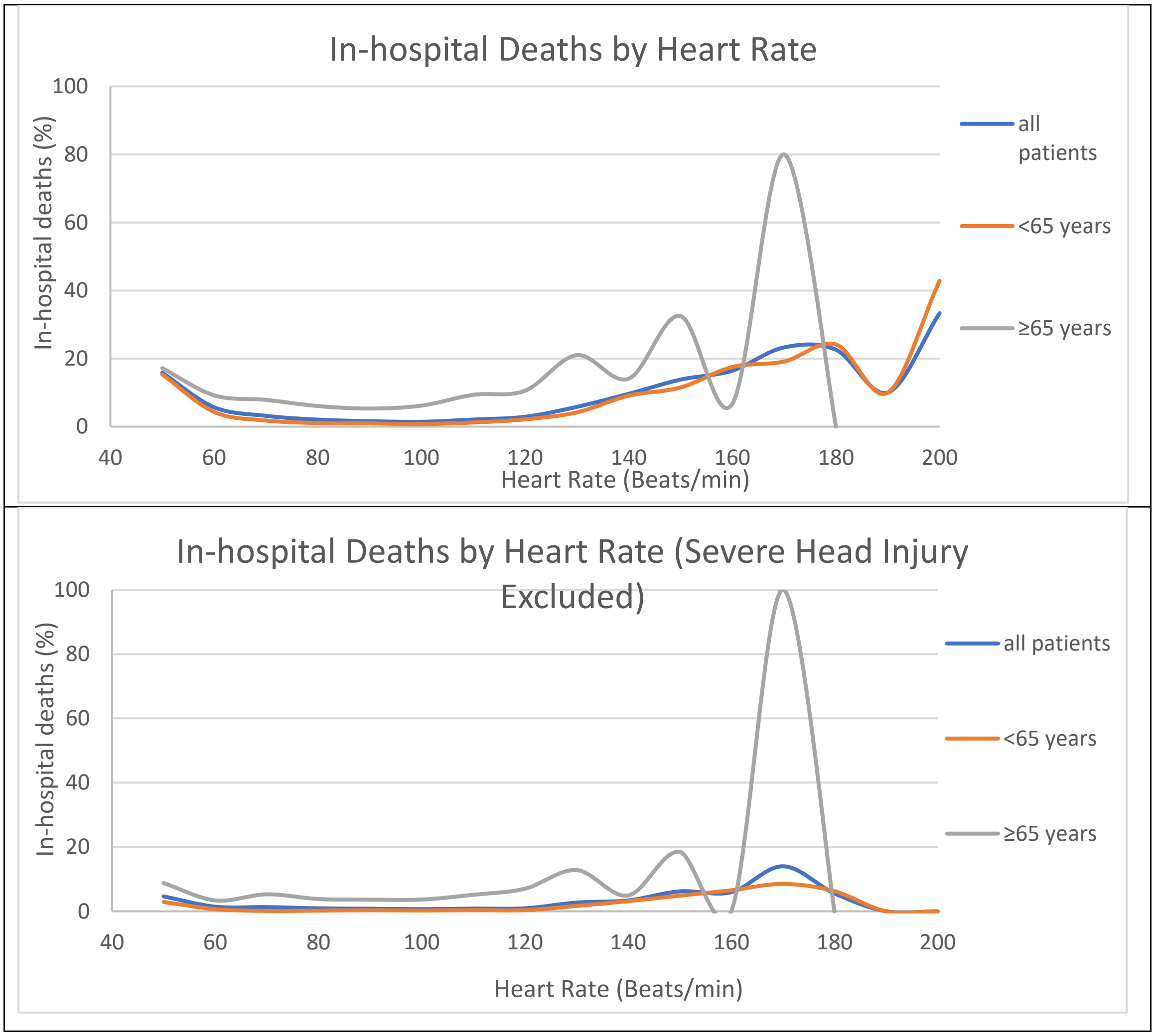


Figure 1.7. Distribution of systolic blood pressure, by age group, comparing patients who died in hospital and those who did not

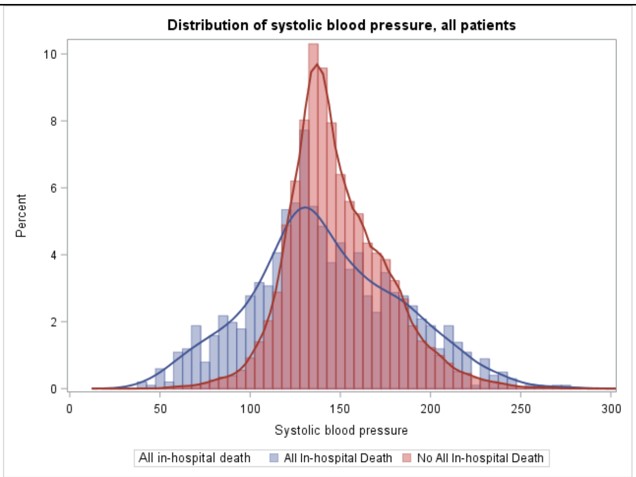
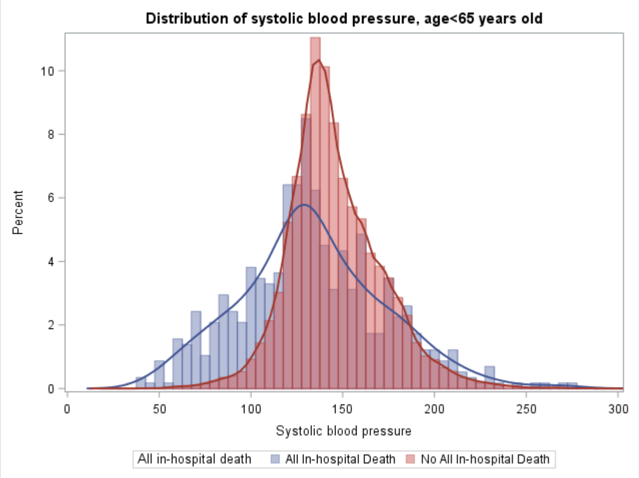
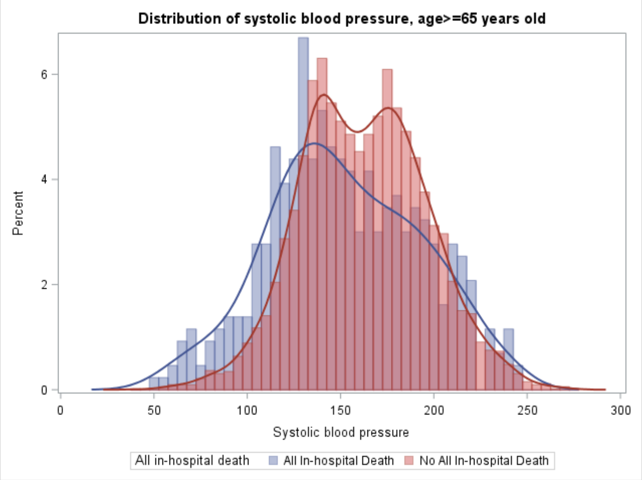
All Patients		🟦 All in-hospital death 🟥 No all in-hospital death
<65 years old		
≥65 years old		

Figure 1.8. Distribution of systolic blood pressure, by in-hospital death status, comparing trauma patients <65 and ≥65 years old

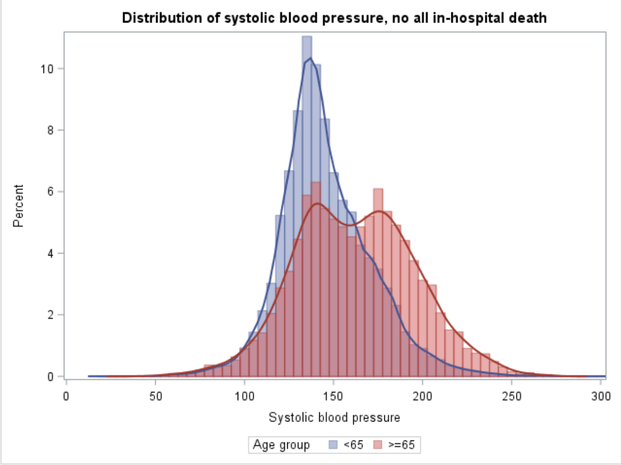
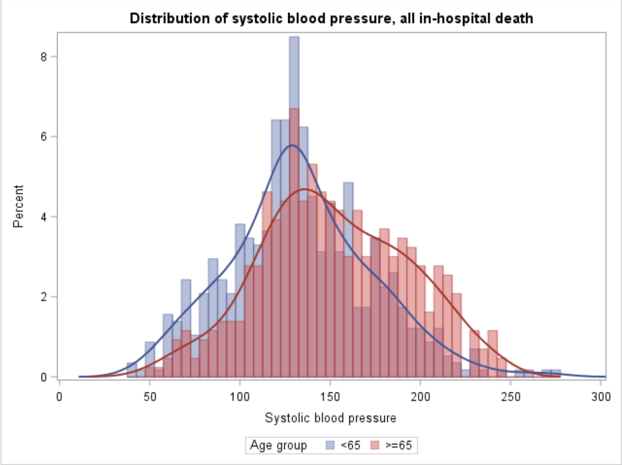
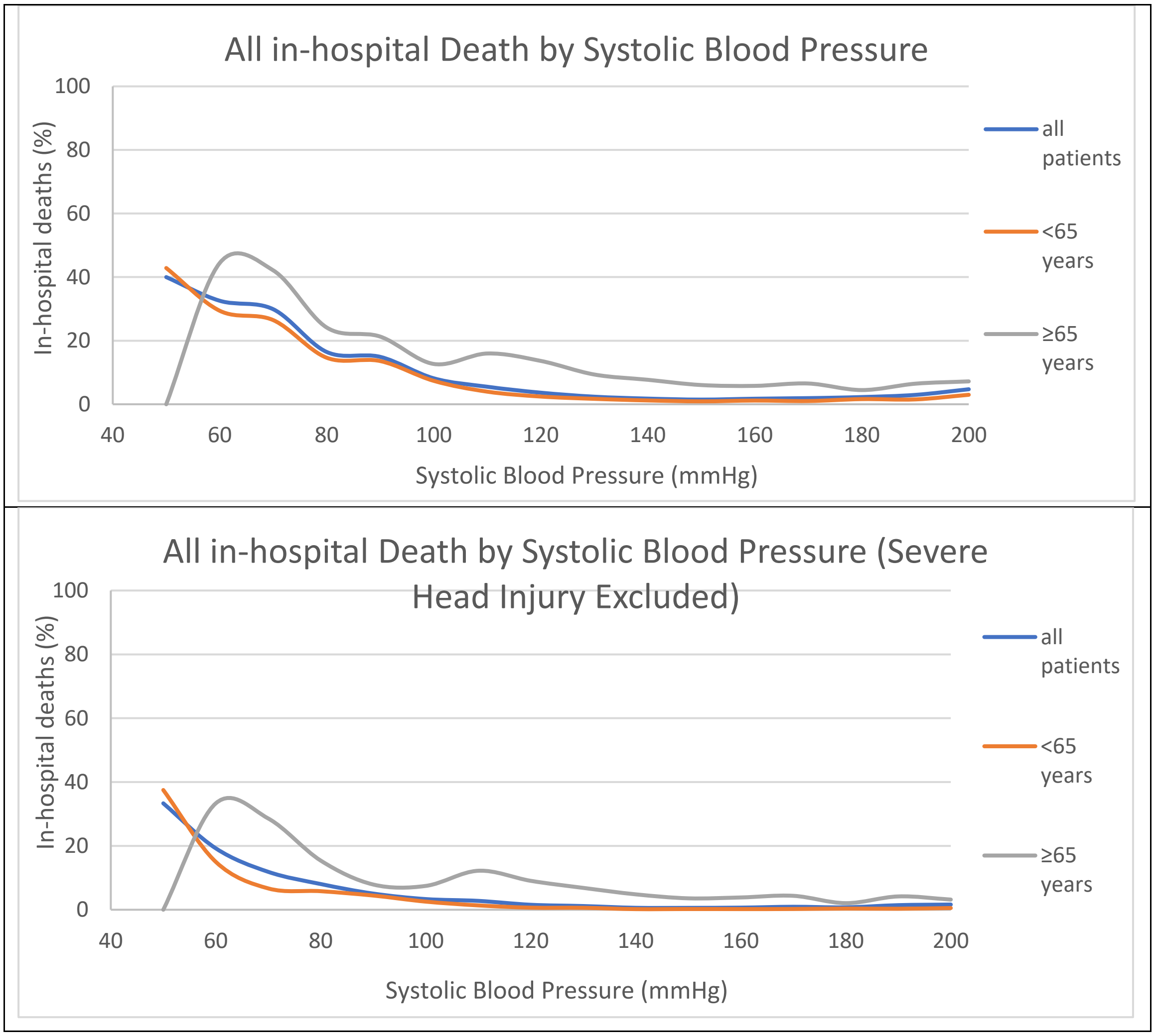
No in-hospital death	 Distribution of systolic blood pressure, no all in-hospital death	🟦 <65 years old 🟥 ≥65 years old
In-hospital death	 Distribution of systolic blood pressure, all in-hospital death	

Figure 1.9 In-hospital deaths by systolic blood pressure in all trauma patients and according to age.



Evaluation of effects of covariates on the ROC curve of shock index in predicting mortality

Table 1.2 presents the results of the first step of the ROC regression procedure, modeling the distribution of the test of interest (shock index) among controls as a function of covariates during the prediction of 2-hour, 48-hour and all in-hospital mortality. The distribution of shock index seems to significantly differ among different age group, injury type and injury severity (all P<0.001), indicating that these covariates may confound the interpretation of the ROC for shock index in predicting mortality outcomes in trauma patients. There may be a need to adjust for these covariates when examining the accuracy of shock index in evaluating mortality outcomes.

Figure 1.10 presents the unadjusted ROC graphs plotted using the ROCCONTRAST option in SAS PROC LOGISTIC. Shock index did not predict early (less than 2 hours from arrival) mortality and 48-hour mortality differently by age groups (<65 years old vs. ≥65 years old) through the comparison of independent ROC AUCs. The unadjusted ROC AUC for shock index when predicting all in-hospital mortality was higher in younger patients compared to the ROC AUC older patients indicating that shock index tended to have better accuracy in predicting all in-hospital mortality in younger trauma patients than older patients (AUC=0.633 vs 0.590; P=0.053).

The second step of ROC regression analyses models the distribution of the test of interest (ie, shock index) among cases. It examines whether covariates can impact the discriminatory accuracy of the ROC curve itself (i.e., affecting the separation between case and Control test distributions). Table 1.3 presents the results of this step. Adjusting for the presence of age, injury type and injury severity, the accuracy of shock index in predicting death in 48 hours and all in-hospital death were different by age group (P=0.04 and P<0.001, respectively), while the accuracy of shock index in predicting all-in hospital death was different by injury severity group (P=0.02). The results differ from that of the unadjusted analyses in Figure 1.10 which show that the accuracy of shock index does not seem to differ by age group.

Table 1.4 presents the ROC model adjusting for the presence of covariates. In the final model, age and injury severity seem to attenuate the accuracy of shock index in predicting all in-hospital death while only age seems to have a significant negative effect on the accuracy of ROC in the prediction of death in 48 hours. Comparison of covariate-adjusted ROC curves in predicting death outcomes at different age groups at fixed injury severity (ISS>15; severe injury) and fixed injury type (blunt trauma) compared at a fixed false positive rate (0.7) shows that SI is more accurate in younger patients than in older patients in predicting 48-hour and all in-hospital mortality (Figure 1.11).

We generated ROC areas under the curve (AUC) for shock index in predicting mortality outcomes, in all patients and by age (Table 1.5). The AUCs for the prediction of mortality outcomes ranged from poor to acceptable: from 0.618 to 0.726 for shock index, 0.554 to 0.665 for systolic blood pressure and 0.571 to 0.644 for heart rate. While ROC regression analysis showed that age, injury type and injury severity may affect prognostic performance of shock index in predicting mortality outcomes (Table 1.2), adjusting for these covariates did not result in significant differences in the unadjusted and adjusted AUCs (Table 1.5) except for in patients <65 years old where adjusting for injury severity and injury type resulted in a lower AUC (P=0.02). Comparing AUCs for shock index in predicting mortality outcomes, adjusted AUCs for younger patients were significantly better than those for older patients when the outcome of interest is all-hospital mortality.

Table 1.2. Modeling the distribution of shock index among controls as a function of covariates, prediction of death outcomes

SHOCK INDEX					
Death in 2 hours					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-0.09	0.003	<0.001	-0.10	-0.09
Injury type	0.06	0.003	<0.001	0.06	0.07
Injury severity	0.07	0.003	<0.001	0.07	0.08
Death in 48 hours					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-0.10	0.00	<0.001	-0.10	-0.09
Injury type	0.06	0.00	<0.001	0.05	0.06
Injury severity	0.07	0.00	<0.001	0.06	0.07
All In-hospital death					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-0.10	0.00	<0.001	-0.10	-0.09
Injury type	0.06	0.00	<0.001	0.05	0.06
Injury severity	0.07	0.00	<0.001	0.06	0.07

Figure 1.10. ROC curves. Accuracy of shock index in predicting mortality (early, 48-hour and all-in hospital) in trauma patients by age group

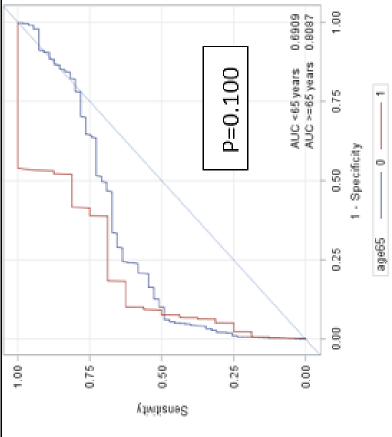
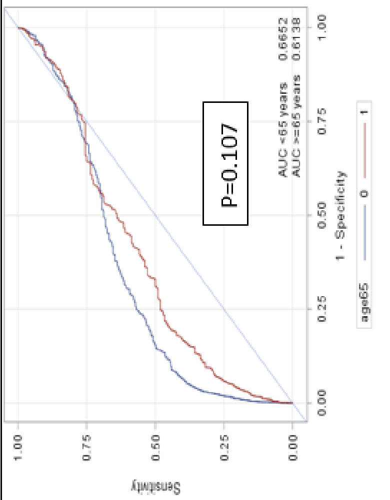
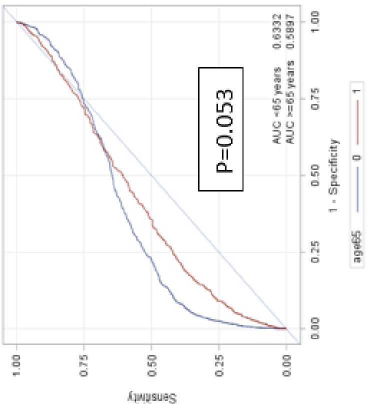
Mortality		
Early	48-hour	All in-hospital
		

Table 1.3. Modeling the distribution of shock index among cases as a function of covariates, prediction of death outcomes

SHOCK INDEX					
Death in 2 hours					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-0.05	0.15	0.72	-0.34	0.23
Injury type	-0.15	0.12	0.22	-0.39	0.09
Injury severity	0.03	0.11	0.77	-0.19	0.25
Death in 48 hours					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-0.09	0.04	0.04	-0.18	-0.01
Injury type	0.06	0.05	0.23	-0.04	0.15
Injury severity	-0.05	0.04	0.25	-0.13	0.03
All In-hospital death					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-0.10	0.03	<0.001	-0.15	-0.05
Injury type	0.04	0.03	0.19	-0.02	0.11
Injury severity	-0.07	0.03	0.02	-0.12	-0.01

Table 1.4. ROC regression model, shock index in the prediction of death outcomes, adjusting for the presence of covariates

SHOCK INDEX					
Death in 2 hours					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	1.02	0.47	0.03	0.10	1.95
Age group	-0.11	0.32	0.72	-0.74	0.51
Injury type	-0.33	0.27	0.22	-0.85	0.20
Injury severity	0.07	0.25	0.77	-0.41	0.56
slope constant	0.42	0.04	<0.001	0.35	0.49
Death in 48 hours					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.38	0.18	0.03	0.04	0.73
Age group	-0.21	0.10	0.04	-0.40	-0.01
Injury type	0.13	0.11	0.23	-0.08	0.34
Injury severity	-0.11	0.10	0.25	-0.30	0.08
slope constant	0.43	0.01	<0.001	0.40	0.45
All In-hospital death					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.40	0.13	<0.001	0.16	0.65
Age group	-0.25	0.07	<0.001	-0.39	-0.12
Injury type	0.11	0.08	0.19	-0.05	0.27
Injury severity	-0.16	0.07	0.02	-0.30	-0.03
slope constant	0.46	0.01	<0.001	0.44	0.48

Figure 1.11. Covariate-adjusted ROC curves for shock index by age group.

Covariate-adjusted ROC curves (adjusting for age group, injury severity and injury type) in predicting death outcomes at different age groups at fixed injury severity (ISS>15; severe injury) and fixed injury type (blunt trauma). ROCs compared at a fixed false positive rate (0.7) using a Wald test.

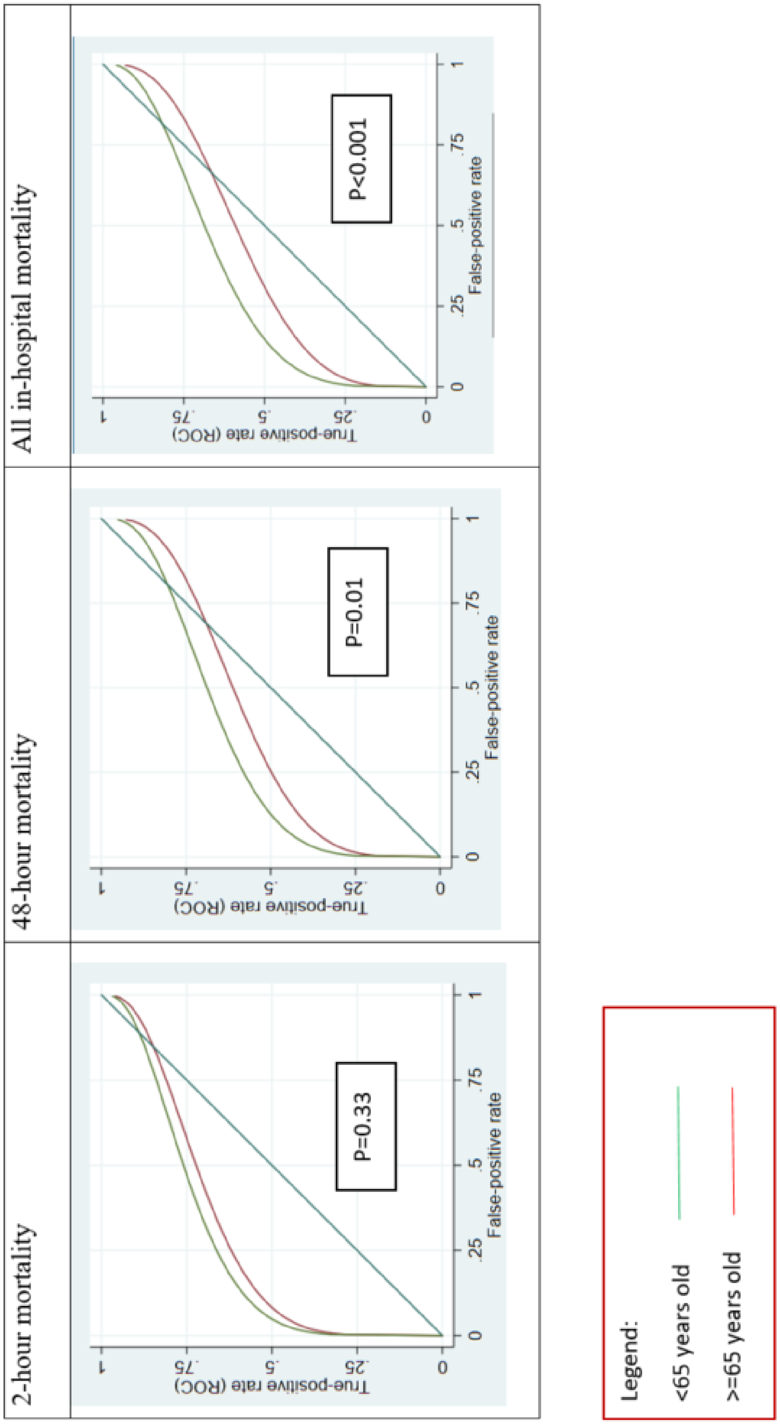


Table 1.5. Unadjusted and adjusted AUCs for shock index in predicting mortality outcomes, by age group.

Outcome	All Patients			<65 years old			≥65 years old				
	AUC Unadjusted	AUC Adjusted*	P^a	AUC Unadjusted	AUC Adjusted**	P^a	AUC Unadjusted	AUC Adjusted**	P^a	P^b	P^c
Death at 2 hours	0.726	0.694	0.47	0.721	0.68	0.43	0.782	0.756	0.71	0.47	0.25
Death at 48 hours	0.648	0.637	0.52	0.692	0.654	0.07	0.639	0.616	0.39	0.52	0.14
All In-hospital death	0.618	0.612	0.64	0.669	0.632	0.02	0.609	0.589	0.3	0.64	0.02

*Adjusted for age, injury severity and type of injury

**Adjusted for injury severity and type of injury

P^a comparing unadjusted and adjusted AUCs

P^b comparing unadjusted AUCs of younger and older age groups

P^c comparing adjusted AUCs of younger and older patients

Evaluation of effects of covariates on the ROC curve of heart rate in predicting mortality

We also examined the effect of the presence of confounders on the accuracy of heart rate in predicting mortality outcomes. We examined whether the distribution of heart rate differed by age group, injury type and injury severity among controls by ROC regression analyses (Table 1.6). The distribution of heart rate seems to differ by age group, injury type and injury severity among controls/did not have the outcome for death in 48 hours and all in-hospital death, indicating that these covariates may confound the accuracy of heart rate in predicting these outcomes (P<0.001). We would need to adjust for these confounders when examining the accuracy of heart rate in the prediction of death in 48 hours and all-in hospital death. These covariates do not seem to be confounders in the prediction of death in 2 hours.

Table 1.6. Modeling the distribution of heart rate among controls as a function of covariates, prediction of death outcomes

HEART RATE					
Death in 2 hours					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-4.15	11.25	0.71	-26.20	17.91
Injury type	-3.50	9.40	0.71	-21.93	14.92
Injury severity	12.49	8.72	0.15	-4.60	29.58
Death in 48 hours					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	4.47	0.30	<0.001	3.88	5.06
Injury type	-6.39	0.29	<0.001	-6.95	-5.83
Injury severity	3.00	0.27	<0.001	2.47	3.54
All In-hospital death					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-6.41	0.29	<0.001	-6.98	-5.84
Injury type	4.37	0.30	<0.001	3.78	4.96
Injury severity	2.88	0.27	<0.001	2.34	3.41

We examined whether covariates affected the discriminatory accuracy of the ROC curve itself (ie, affecting the separation between case and Control test distributions), with accuracy of heart rate being different by covariate groups. Table 1.7 presents the results of modeling of heart rate as a function of age, injury type and injury severity. The accuracy of heart rate in the prediction of death in 2 hours and all in seem to be different by age group (older compared with younger), injury type (blunt vs. penetrating) and injury severity (severe vs. non-severe).

Looking at the covariate-adjusted ROC regression model for heart rate in predicting mortality outcomes (Table 1.8), the negative significant coefficient for age group indicates that age group seem to attenuate the ROC. Accuracy of heart rate in predicting 48-hour mortality and all in-hospital mortality seem to be better in younger trauma patients than older patients.

Table 1.7. Modeling the distribution of heart rate among cases as a function of covariates, prediction of death outcomes

HEART RATE					
Death in 2 hours					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	4.69	0.30	<0.001	4.10	5.29
Injury type	-6.30	0.29	<0.001	-6.87	-5.74
Injury severity	3.24	0.27	<0.001	2.71	3.77
Death in 48 hours					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-6.48	3.23	0.05	-12.80	-0.16
Injury type	2.19	3.51	0.53	-4.70	9.07
Injury severity	-4.74	3.14	0.13	-10.89	1.42
All In-hospital death					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-5.09	2.08	0.01	-9.16	-1.01
Injury type	4.50	2.52	0.07	-0.43	9.44
Injury severity	-4.27	2.07	0.04	-8.33	-0.21

Table 1.8. ROC regression model, heart rate in the prediction of death outcomes, adjusting for the presence of covariates

HEART RATE					
Death in 2 hours					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.31	0.42	0.46	-0.51	1.13
Age group	-0.12	0.30	0.70	-0.71	0.48
Injury type	-0.10	0.27	0.71	-0.63	0.43
Injury severity	0.35	0.26	0.17	-0.15	0.86
slope constant	0.55	0.04	<0.001	0.47	0.64
Death in 48 hours					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.37	0.17	0.03	0.05	0.70
Age group	-0.20	0.09	0.03	-0.38	-0.02
Injury type	0.07	0.11	0.56	-0.16	0.29
Injury severity	-0.14	0.09	0.12	-0.33	0.04
slope constant	0.59	0.02	<0.001	0.56	0.62
All In-hospital death					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.21	0.13	0.11	-0.05	0.46
Age group	-0.17	0.06	0.01	-0.29	-0.04
Injury type	0.15	0.09	0.11	-0.03	0.33
Injury severity	-0.14	0.07	0.03	-0.27	-0.01
slope constant	0.63	0.01	<0.001	0.60	0.66

Evaluation of effects of covariates on the ROC curve of blood pressure in predicting mortality

As with shock index and heart rate, we examined the effect of confounders in the accuracy of systolic blood pressure in predicting mortality outcomes. The results of the ROC regression analysis where we modeled the distribution of systolic blood pressure among controls (ie, those who did not have the mortality outcome) as a function of covariates showed that age group, injury type and injury severity all seem to be potential confounders of the accuracy of systolic blood pressure in predicting mortality outcomes (all $P<0.001$) (Table 1.9). Modeling the distribution of systolic blood pressure among cases (those that had the mortality outcome) as a function of covariates, accuracy of systolic blood pressure in the prediction of mortality outcomes seems to not differ by age group (Table 1.10). The covariate-adjusted ROC regression model for heart rate in predicting mortality outcomes in trauma patients only showed attenuation of the ROC by injury severity in predicting all in-hospital death (Table 1.11).

Sensitivity Analyses

Because severe neurologic injury may have an effect on cardiogenic factors, and a “U-shaped” relationship observed with mortality in patients with head trauma admitted with hypotension and hypertension (Krishnamoorty, 2017), analyses was done where patients with severe head injury based (Glasgow Coma Score <9) were excluded from analyses. There were no significant differences with the results where patients were not excluded from analyses (tables in Appendix; Tables A1-A3)

While the purpose of the study is not to develop a model for use in the field, and instead investigate what characteristics may affect the predictive performance of shock index, there are concerns about the use of Injury Severity Score as the scoring system used to categorize patients into severely or non-severely injured because it is difficult to assess in the field. Injury Severity Score is also an anatomical based scoring system of injury severity, and some consider physiologic based scoring systems better in assessing injury severity. We conducted analyses where we used Revised Trauma Score and Glasgow Coma Scale, both physiologic scoring systems of trauma injury as the methods of categorizing patients as being severely or non-severely injured patients. The results of our analyses had similar results as those obtained when Injury Severity Score was used as the scoring system for injury severity (tables in Appendix, Tables A4-A9).

Table 1.9. Modeling the distribution of systolic blood pressure among controls as a function of covariates, prediction of death outcomes

SYSTOLIC BLOOD PRESSURE					
Death in 2 hours					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	5.04	0.42	<0.001	4.21	5.86
Injury type	-15.66	0.40	<0.001	-16.44	-14.88
Injury severity	7.46	0.37	<0.001	6.73	8.20
Death in 48 hours					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	4.77	0.42	<0.001	3.94	5.60
Injury type	-15.90	0.40	<0.001	-16.68	-15.11
Injury severity	7.19	0.38	<0.001	6.45	7.93
All In-hospital death					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-15.99	0.41	<0.001	-16.78	-15.19
Injury type	4.80	0.42	<0.001	3.97	5.63
Injury severity	7.22	0.38	<0.001	6.47	7.98

Table 1.10. Modeling the distribution of systolic blood pressure among cases as a function of covariates, prediction of death outcomes

SYSTOLIC BLOOD PRESSURE					
Death in 2 hours					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	19.81	13.42	0.14	-6.49	46.11
Injury type	-12.41	11.21	0.27	-34.38	9.57
Injury severity	-5.93	10.40	0.57	-26.32	14.46
Death in 48 hours					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	2.34	4.15	0.57	-5.79	10.47
Injury type	4.16	4.52	0.36	-4.70	13.01
Injury severity	-4.54	4.04	0.26	-12.45	3.38
All In-hospital death					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-0.95	2.74	0.73	-6.31	4.41
Injury type	1.70	3.31	0.61	-4.80	8.19
Injury severity	-8.17	2.73	<0.003	-13.52	-2.83

Table 1.11. ROC regression model, systolic blood pressure in the prediction of death outcomes, adjusting for the presence of covariates

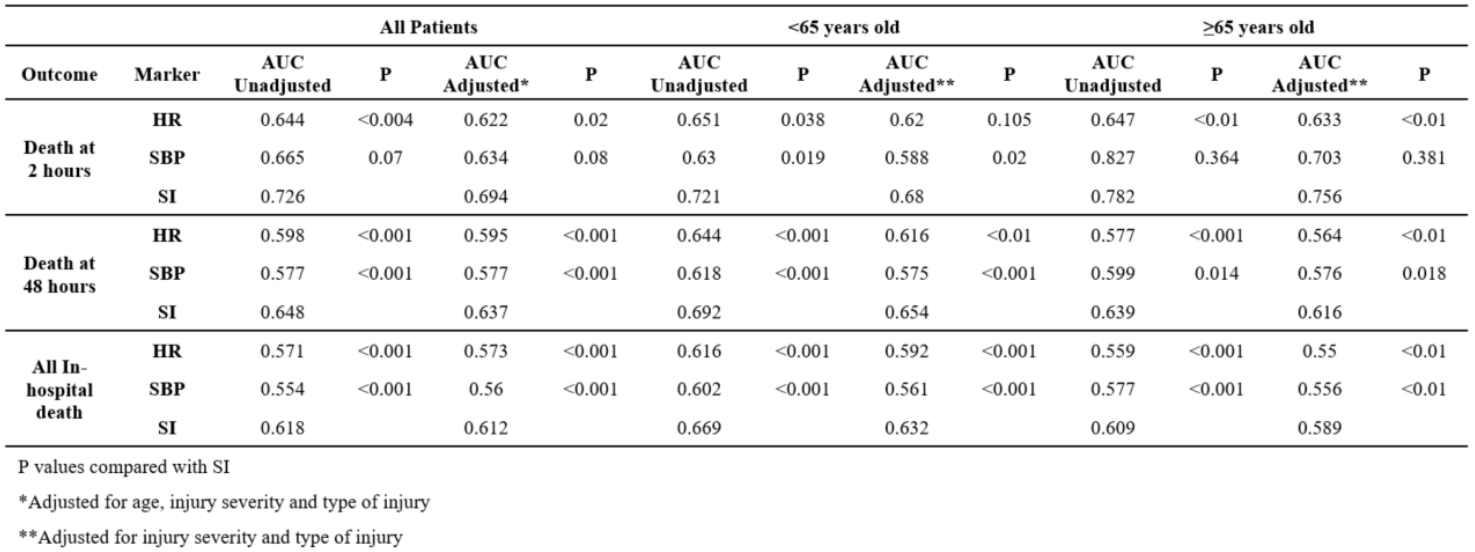
SYSTOLIC BLOOD PRESSURE					
Death in 2 hours					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.84	0.49	0.09	-0.13	1.81
Age group	0.47	0.24	0.05	0.00	0.95
Injury type	-0.30	0.27	0.27	-0.82	0.23
Injury severity	-0.14	0.26	0.58	-0.65	0.36
slope constant	0.65	0.05	<0.001	0.55	0.74
Death in 48 hours					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.15	0.17	0.37	-0.18	0.49
Age group	0.06	0.10	0.56	-0.13	0.25
Injury type	0.10	0.10	0.34	-0.10	0.30
Injury severity	-0.11	0.10	0.26	-0.30	0.08
slope constant	0.64	0.02	<0.001	0.61	0.68
All In-hospital death					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.28	0.13	0.03	0.03	0.52
Age group	-0.02	0.07	0.73	-0.16	0.11
Injury type	0.04	0.08	0.60	-0.12	0.20
Injury severity	-0.20	0.07	<0.002	-0.33	-0.07
slope constant	0.67	0.01	<0.001	0.64	0.70

Comparing the accuracy of shock index, heart rate and systolic blood pressure in the prediction of mortality outcomes in injured adult patients

Table 1.12 presents the comparison of ROC AUCs between shock index and heart rate, and between shock index and systolic blood pressure both unadjusted and adjusted for age, injury severity and type of injury. There were minimal changes from the unadjusted AUCs to the adjusted AUCs. It is noted however that adjustment resulted generally in lower accuracy (ie, lower AUCs) in comparison with before adjustment. Shock index had better accuracy than heart rate in predicting all death outcomes among all trauma patients.

Among younger patients, on unadjusted ROC analysis, shock index had better accuracy in predicting death at 2 hours compared with heart rate and systolic blood pressure. On adjusted analyses, shock index had similar accuracy. Among patients who were older, shock index had similar accuracy to systolic blood pressure in predicting death at 2 hours both on unadjusted and adjusted ROC analysis. It had better accuracy than heart rate in predicting death at 2 hours. Shock index had better accuracy than systolic blood pressure in predicting death at 48 hours and in-hospital death for all trauma patients, those less than 65 years old and those who were 65 years and older.

Table 1.12. ROC AUCs for heart rate, systolic blood pressure and shock index in predicting death outcomes in injured patients (all patients, <65 years old and ≥65 years old)



		All Patients				<65 years old				≥65 years old			
Outcome	**Marker**	**AUC Unadjusted**	**P**	**AUC Adjusted***	**P**	**AUC Unadjusted**	**P**	**AUC Adjusted****	**P**	**AUC Unadjusted**	**P**	**AUC Adjusted****	**P**
Death at 2 hours	**HR**	0.644	<0.004	0.622	0.02	0.651	0.038	0.62	0.105	0.647	<0.01	0.633	<0.01
	SBP	0.665	0.07	0.634	0.08	0.63	0.019	0.588	0.02	0.827	0.364	0.703	0.381
	SI	0.726		0.694		0.721		0.68		0.782		0.756	
Death at 48 hours	**HR**	0.598	<0.001	0.595	<0.001	0.644	<0.001	0.616	<0.01	0.577	<0.001	0.564	<0.01
	SBP	0.577	<0.001	0.577	<0.001	0.618	<0.001	0.575	<0.001	0.599	0.014	0.576	0.018
	SI	0.648		0.637		0.692		0.654		0.639		0.616	
All In-hospital death	**HR**	0.571	<0.001	0.573	<0.001	0.616	<0.001	0.592	<0.001	0.559	<0.001	0.55	<0.01
	SBP	0.554	<0.001	0.56	<0.001	0.602	<0.001	0.561	<0.001	0.577	<0.001	0.556	<0.01
	SI	0.618		0.612		0.669		0.632		0.609		0.589	

P values compared with SI

*Adjusted for age, injury severity and type of injury

**Adjusted for injury severity and type of injury

Optimal cut-offs for shock index in the prediction of mortality

Because it seems that the accuracy of shock index in the prediction of mortality outcomes differ by age group, we identified optimal cut-off points for the prediction of mortality (early, 48-hour and all-in hospital) (Table 1.13). Optimal shock index cut-offs for all trauma patients were from 0.6 to 0.9 for all patients and for those <65 years old, but was 0.5-0.7 for older patients.

At the most commonly used shock index cut-off for shock index, 0.9, sensitivity and specificity for predicting in-hospital death were 45.3% and 88.8%, respectively, for younger patients, and 19.4% and 94.7%, respectively, for the elderly. A lower shock index cut-off of 0.7 for those ≥65 years old improves sensitivity to 40.0% at the expense of lower specificity, 77.9% (Appendix Table A19).

We assigned age-specific shock index cut-offs were assigned as follows: ≥0.9 to those who were <65 years old and ≥0.7 for those who were ≥65 years old. Age-specific shock index cut-offs demonstrated improved prediction of death in 48-hours and all in-hospital deaths. AUCs were significantly better with the age-specific shock index cut-offs compared with shock index cut-off of ≥0.9 (Table 1.14).

Table 1.13. Shock index cut-offs, predicting mortality (early, 48-hour and all in-hospital) in injured patients, by age group.

	Optimal SI cut-off		
Criterion	**All ages**	**<65 years**	**≥65 years**
	Early death		
Distance to 0, 1	0.7	0.7	0.6
Sensitivity-Specificity	0.6	0.6	0.6
Youden	0.9	0.9	0.7
	Death in 48 hours		
Distance to 0, 1	0.6	0.7	0.5
Sensitivity-Specificity	0.6	0.6	0.5
Youden	0.8	0.8	0.6
	All in-hospital death		
Distance to 0, 1	0.6	0.7	0.5
Sensitivity-Specificity	0.6	0.6	0.5
Youden	0.8	0.8	0.6

Table 1.14. Accuracy of age-specific shock index cut-offs in comparison with shock index cut-off of 0.9 in the prediction of death outcomes in trauma patients

Cut-point	AUC	P*	Sensitivity	Specificity
	Death 2 hours			
SI≥0.9	0.684	0.14	47.9%	89.0%
<65 years old SI≥0.9 ≥65 years old SI≥0.7	0.707		54.9%	86.5%
	Death 48 hours			
SI≥0.9	0.630	<0.001	36.6%	89.3%
<65 years old SI≥0.9 ≥65 years old SI≥0.7	0.662		45.5%	86.9%
	All in-hospital death			
SI≥0.9	0.610	<0.001	32.5%	89.6%
<65 years old SI≥0.9 ≥65 years old SI≥0.7	0.642		41.3%	87.2%

P* comparison of AUCs

Aim 2 Results

Distributions of shock index, heart rate and systolic blood pressure

A total of 6375 (17.23%) patients underwent at least one of the major interventions examined: 4145 (11.3%) were admitted to the ICU, 2358 underwent surgery in the first 24 hours of arrival at the STC ED (6.37%), and 524 underwent massive transfusion (1.42%).

In Figure 2.1 we present the distribution of shock index by age group, comparing patients without massive transfusion. Patients who did not have massive transfusion tended to have lower shock index values, with the majority of patients having values of <0.9, and a narrower range of values compared with patients who received massive transfusion. The majority of patients who had massive transfusion had shock index values of >0.9.

Comparing shock index between older and younger age group among those that did not undergo massive transfusion, we do see that older patients seemed to have lower shock index values compared with older patients (Figure 2.2). However, among those who underwent massive transfusion, the distribution of shock index in older and younger patients were similar.

Frequency of massive transfusion was constant over SI of 0.3-0.8, with frequency at SI ≥0.9 (Figure 2.3). This pattern was similar for older and younger patients, and when excluding patients with severe head injury. Frequency of massive transfusion was higher at ≤0.3 compared with that of SI of 0.3-0.8.

Trauma patients who had massive transfusions had higher heart rates compared to those who did not (Figure 2.4). However, the difference does not seem to be as pronounced among older patients. Comparing the distribution of heart rates between older and younger patients, older patients tended to have slower heart rates (Figure 2.5). However, the difference between heart rates of older versus younger patients was more pronounced when looking at patients who had massive transfusion.

In Figures 2.4-2.9 we looked at massive transfusion frequencies and HR and systolic blood pressures. Frequency of massive transfusion was higher with higher HR values, and lower blood pressure values (Figures 2.6 and 2.9). Frequency of massive transfusion was lower however among older patients at similar blood pressure values.

Patients who had massive transfusion had lower systolic blood pressure values compared to those who did not have massive transfusion (Figure 2.7). The histogram for massive transfusion in patients ≥65 years old has a bimodal shape, with peaks occurring at around 130 mmHg and 180 mmHg, respectively. (Figure 2.7 and 2.8).

Figure 2.1. Distribution of shock index, by age group, comparing patients with and without massive transfusion

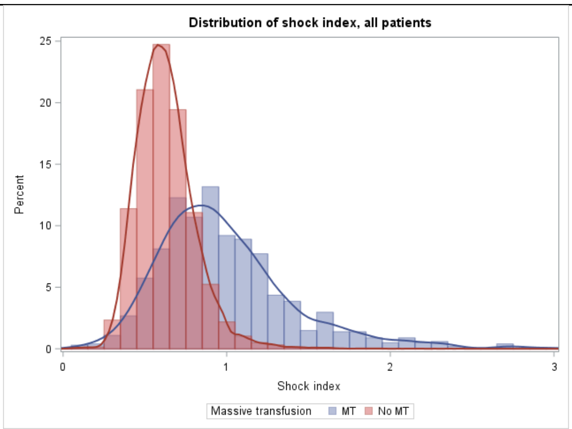
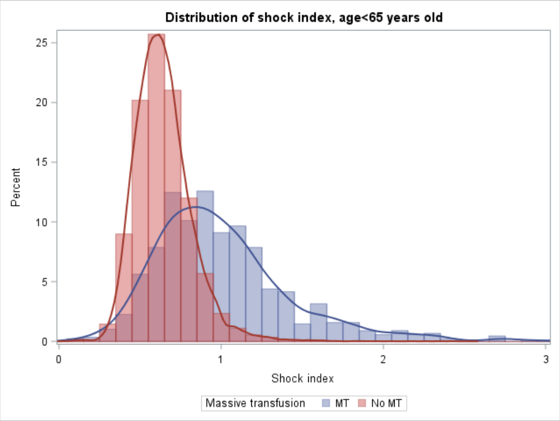
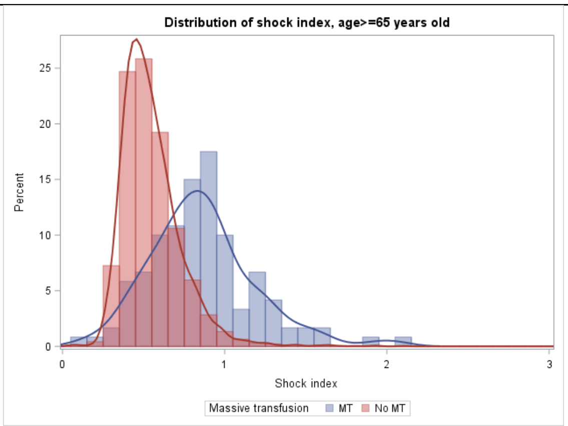
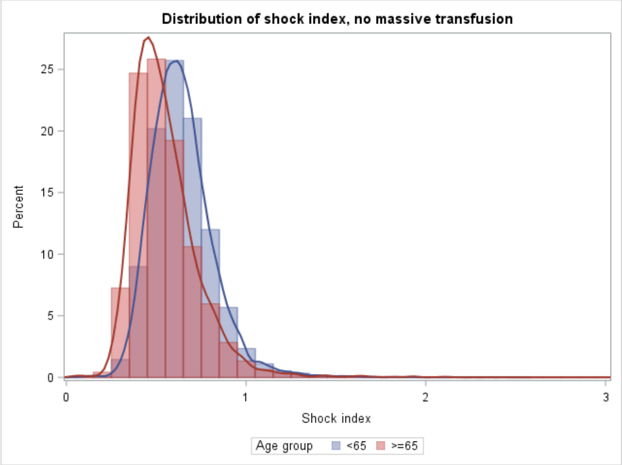
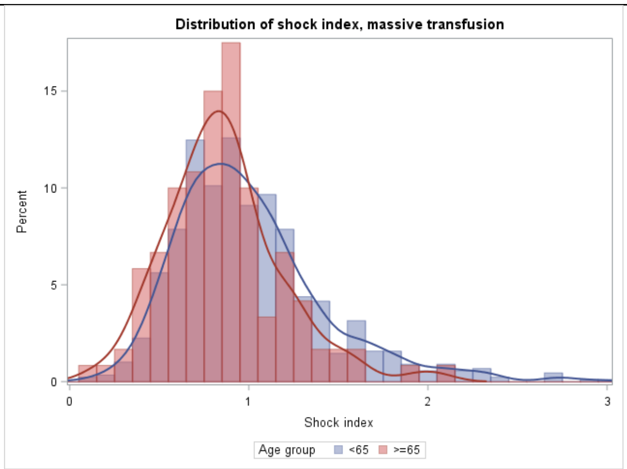
All Patients		🟦 Massive transfusion 🟥 No massive transfusion
<65 years old		
≥65 years old		

Figure 2.2. Distribution of shock index, by massive transfusion status, comparing trauma patients <65 and ≥65 years old

<table>
<tr>
<td>No massive transfusion</td>
<td>


Distribution of shock index, no massive transfusion

</td>
<td>
🟦 <65 years old

🟥 ≥65 years old
</td>
</tr>
<tr>
<td>Massive transfusion</td>
<td>


Distribution of shock index, massive transfusion

</td>
<td></td>
</tr>
</table>

Figure 2.3. Massive transfusion by shock index in all trauma patients and according to age.

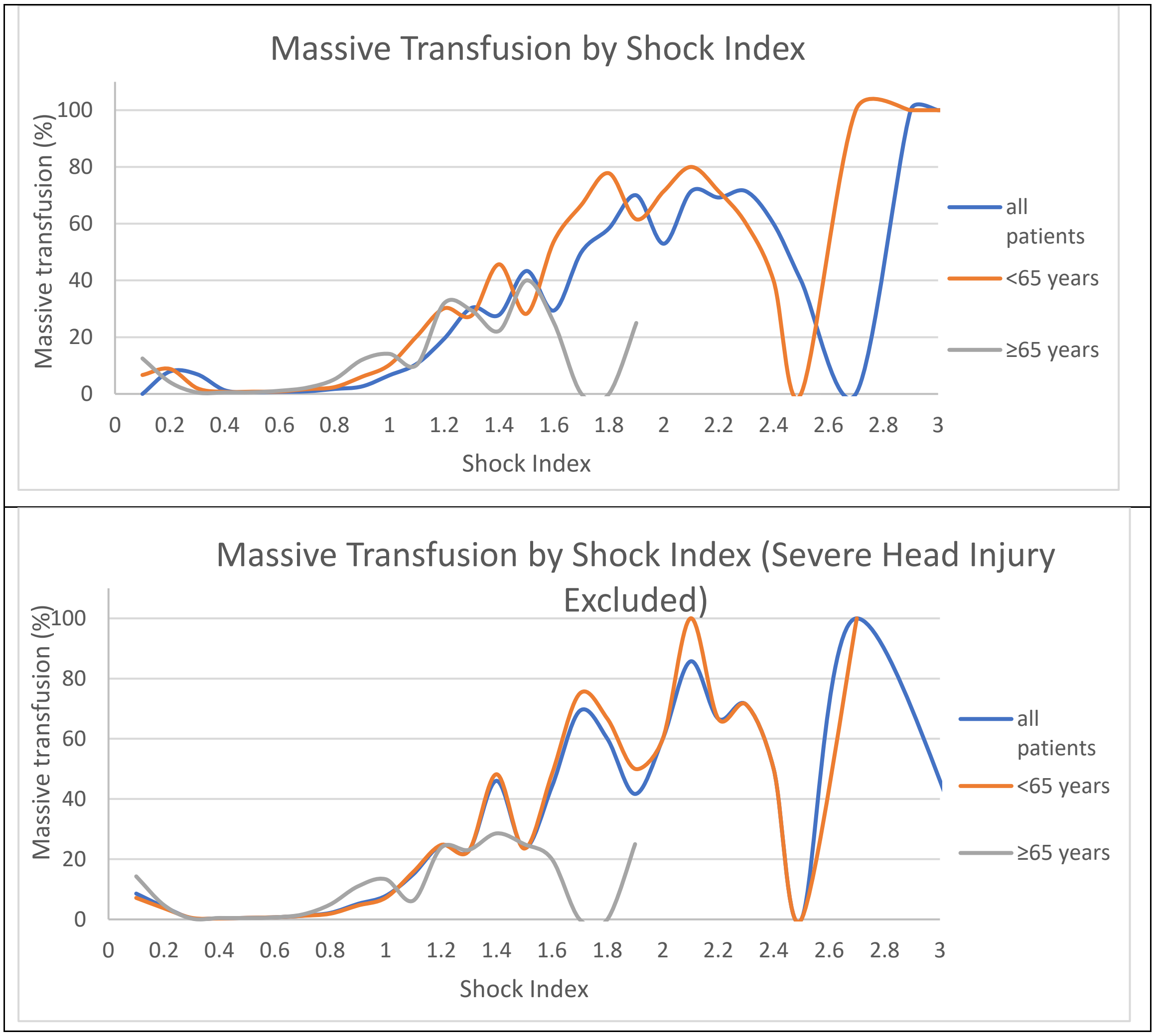
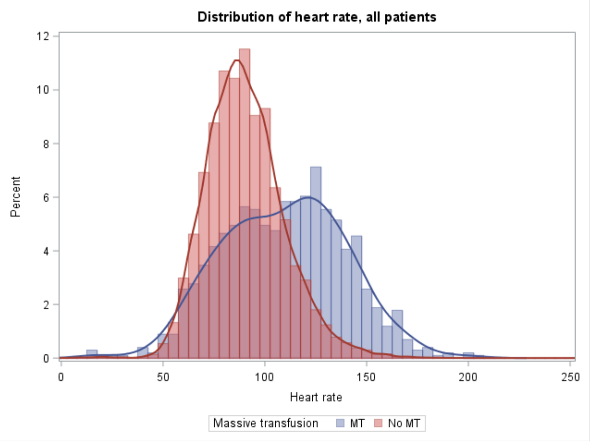
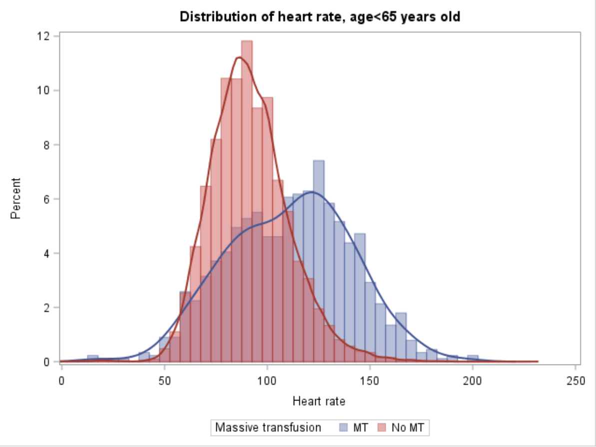
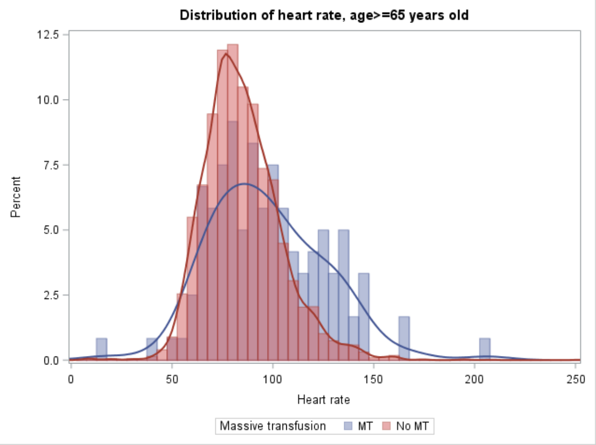


Figure 2.4. Distribution of heart rate, by age group, comparing patients with and without massive transfusion

<table>
<tr>
<td>All Patients</td>
<td>


</td>
<td>🟦 Massive transfusion
🟥 No massive transfusion</td>
</tr>
<tr>
<td><65 years old</td>
<td>


</td>
<td></td>
</tr>
<tr>
<td>≥65 years old</td>
<td>


</td>
<td></td>
</tr>
</table>

Figure 2.5. Distribution of heart rate, by massive transfusion status, comparing trauma patients <65 and ≥65 years old

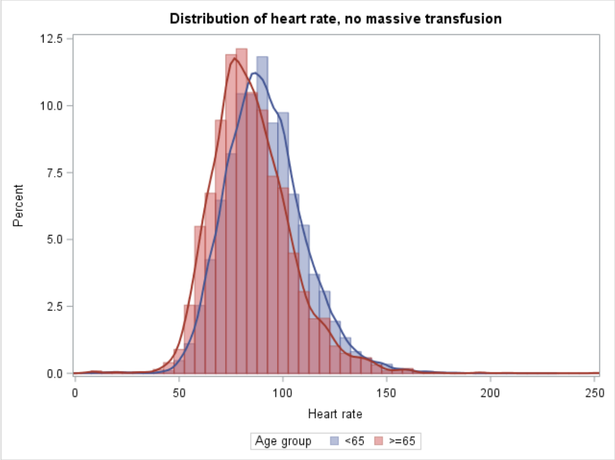
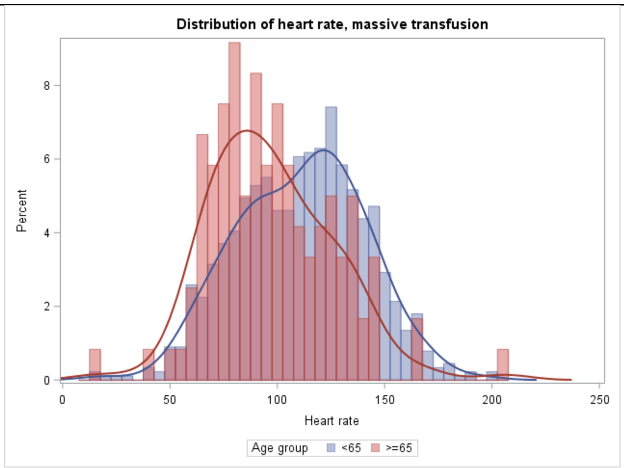
No massive transfusion		🟦 <65 years old 🟥 ≥65 years old
Massive transfusion		

Figure 2.6. Massive transfusion by heart rate in all trauma patients and according to age.

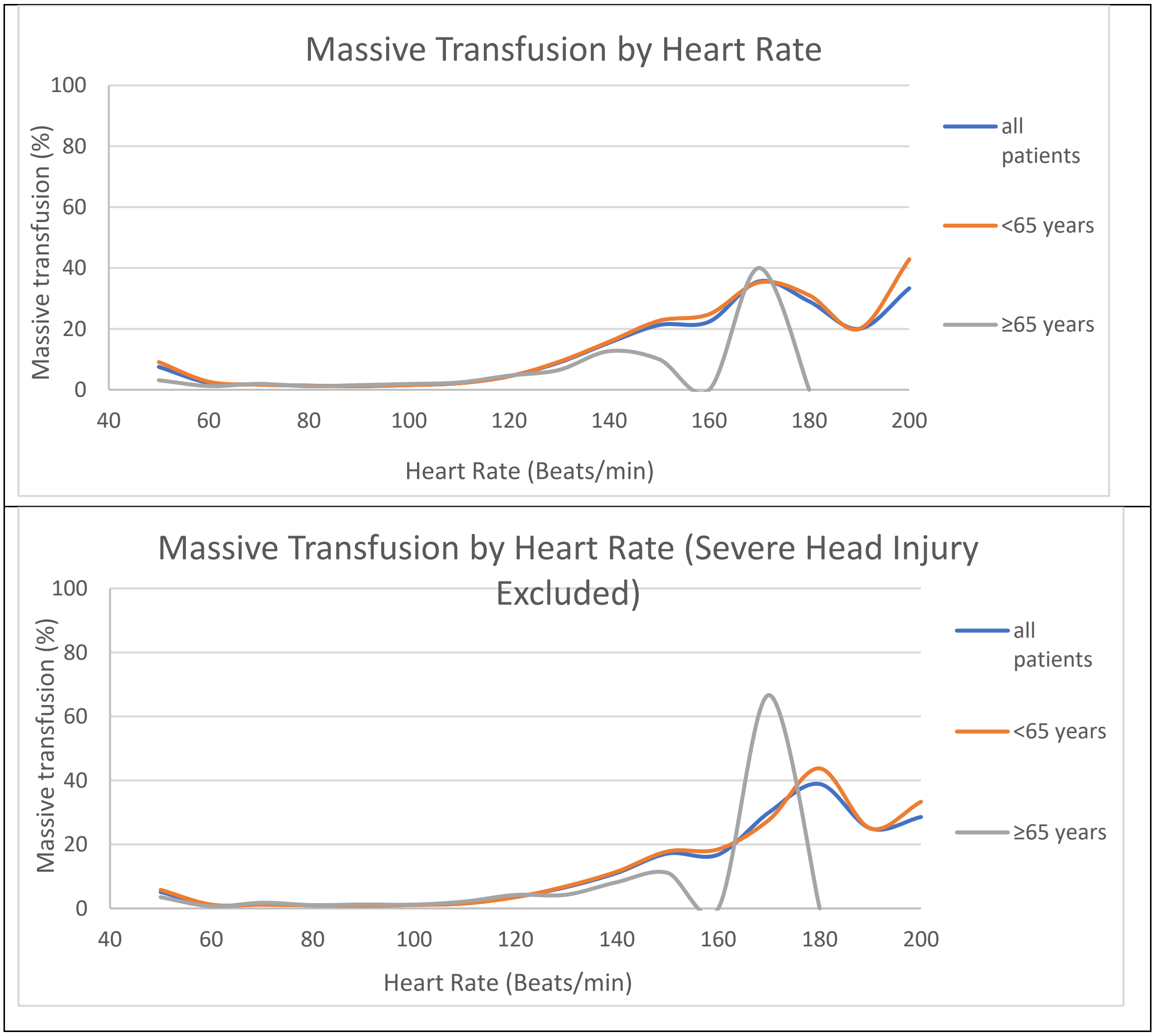


Figure 2.7. Distribution of systolic blood pressure, by age group, comparing patients with and without massive transfusion

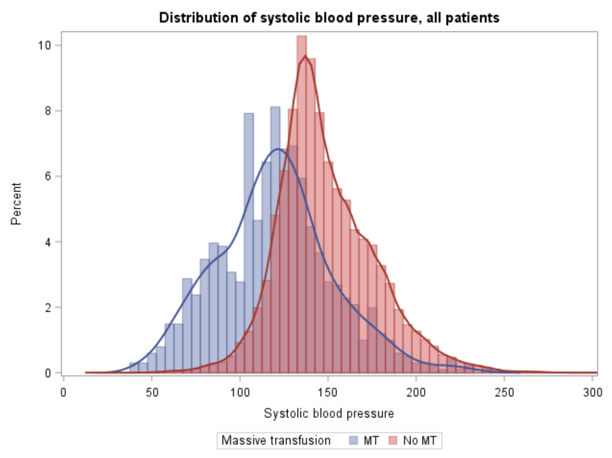
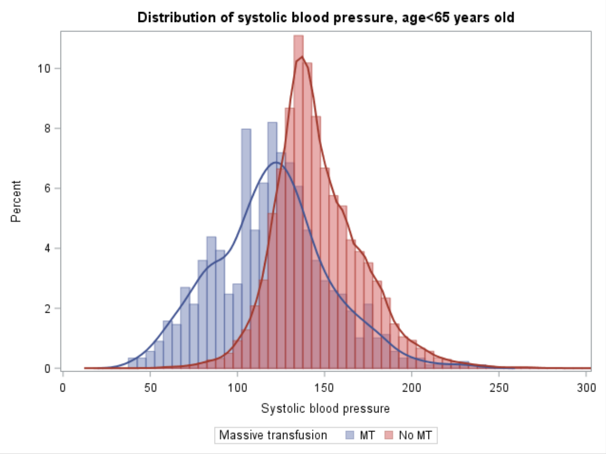
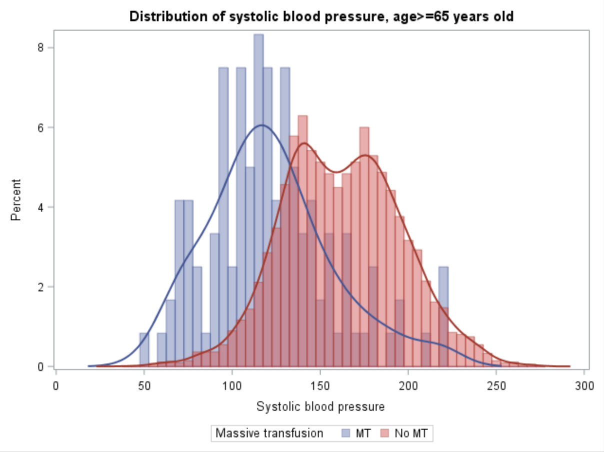
All Patients		🟦 Massive transfusion 🟥 No massive transfusion
<65 years old		
≥65 years old		

Figure 2.8. Distribution of systolic blood pressure, by massive transfusion status, comparing trauma patients <65 and ≥65 years old

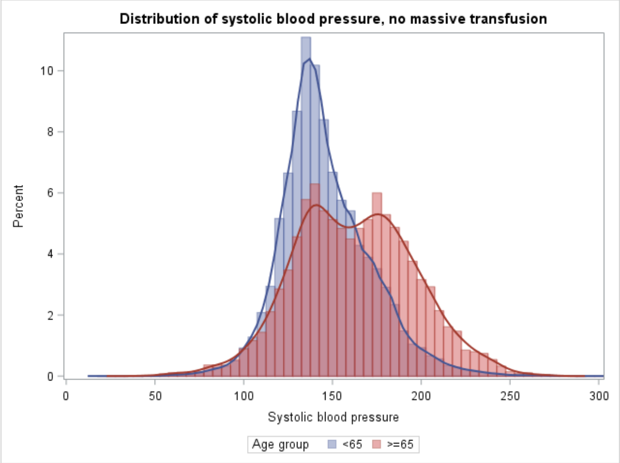
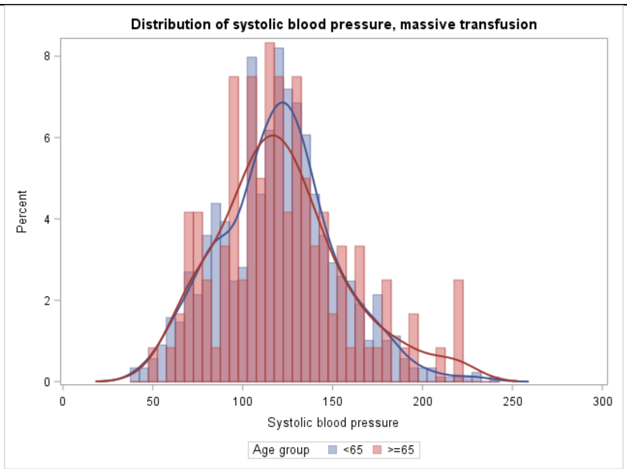
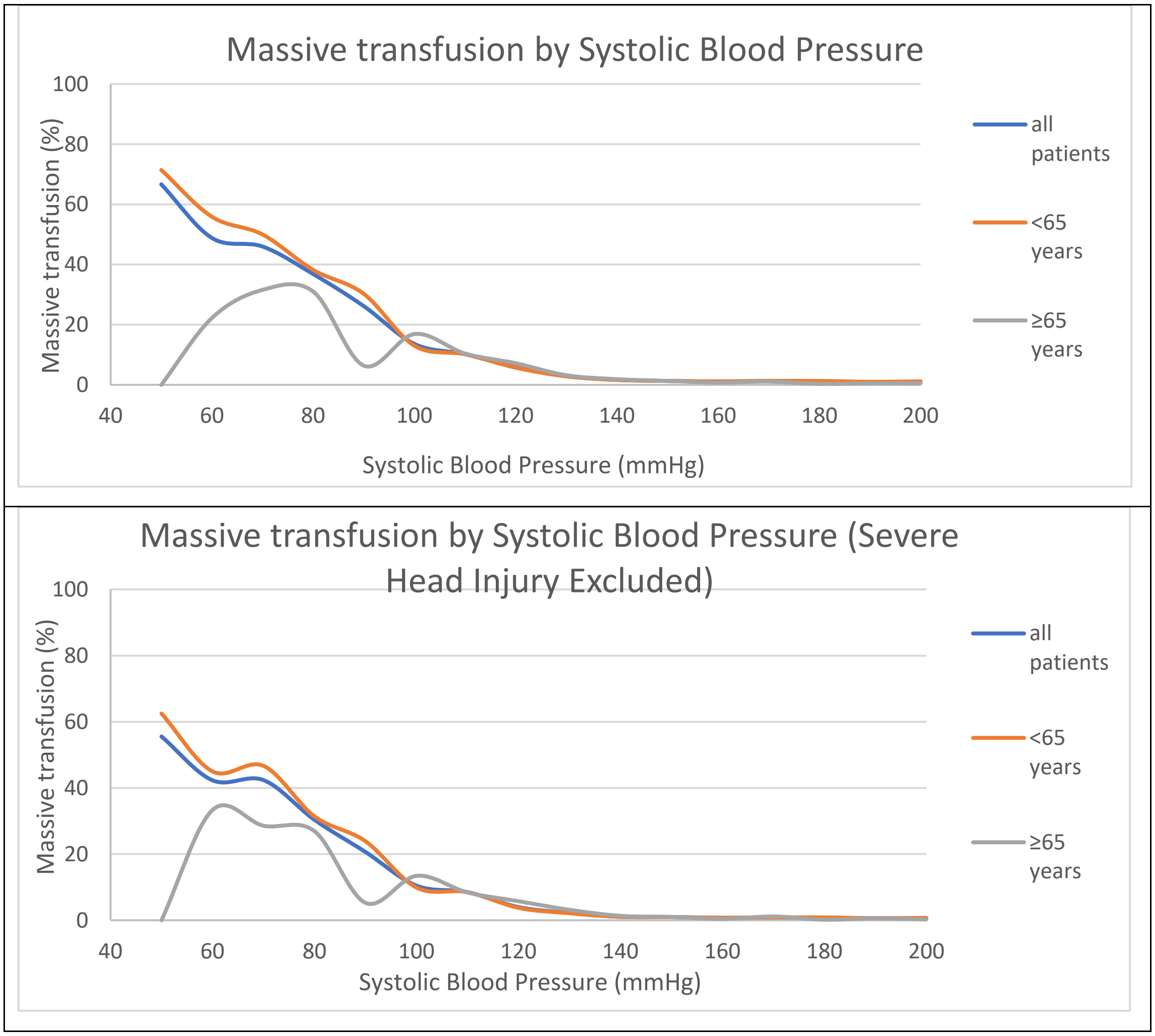
No massive transfusion		🟦 <65 years old 🟥 ≥65 years old
Massive transfusion		

Figure 2.9. Massive transfusion by systolic blood pressure in all trauma patients and according to age.



Evaluation of effects of covariates on the ROC curve of shock index in predicting major interventions in injured patients

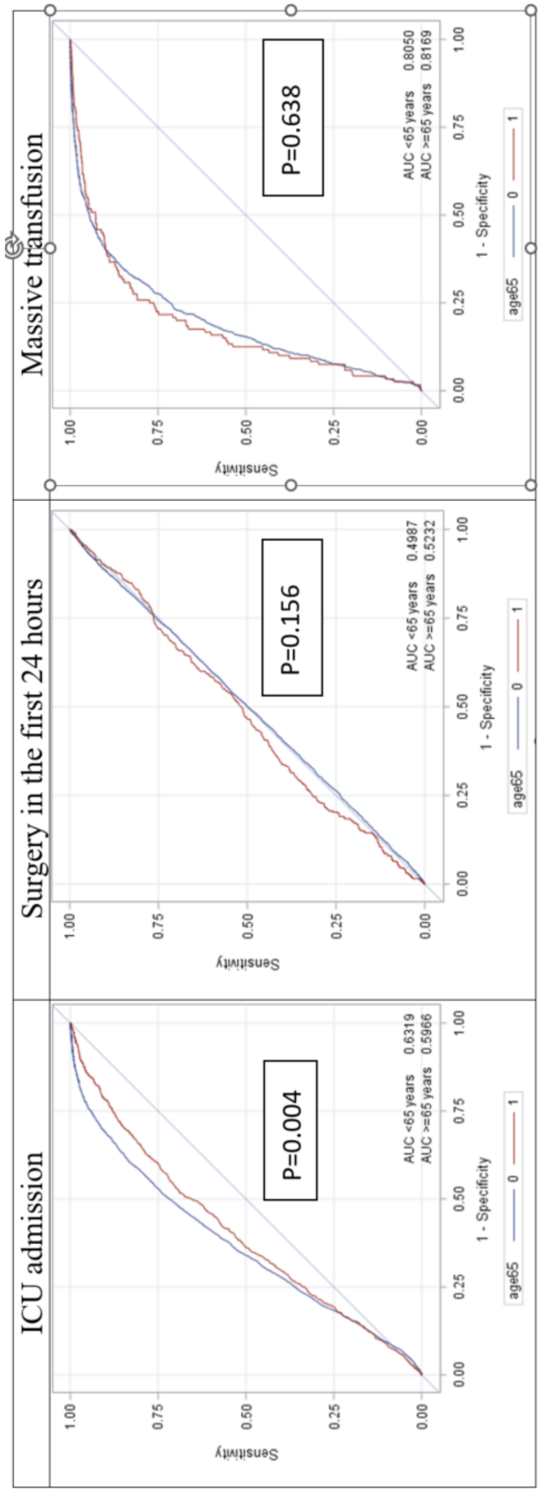
We examined the effect of covariates (age, injury severity and injury type) on the accuracy of shock index in predicting undergoing major interventions. Table 2.1 presents the results of the ROC regression analysis, modeling the distribution of shock index among controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and injury severity. Age, injury severity and injury type significantly affect the distribution of shock index among controls (those that did not undergo surgery in the first 24 hours, were not admitted to the ICU, or had massive transfusion (all P<0.001), and therefore needs to be adjusted for in ROC analyses of shock index.

Figure 2.10 presents the unadjusted ROC graphs examining the accuracy of shock index in predicting undergoing major interventions by younger (blue line) and older patients, accuracy is significantly better among younger patients when predicting admission to the ICU compared with older patients(P=0.004) . The differences were not significantly different in the accuracy of shock index in predicting surgery within the first 24 hours, massive transfusion or undergoing a major intervention between the two age groups.

Table 2.1. Modeling the distribution of shock index among controls as a function of covariates, prediction of major interventions

SHOCK INDEX					
ICU admission					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-0.089	0.003	<0.001	-0.095	-0.084
Injury type	0.059	0.003	<0.001	0.053	0.065
Injury severity	0.035	0.003	<0.001	0.029	0.041
Surgery in the first 24 hours					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-0.093	0.003	<0.001	-0.098	-0.087
Injury type	0.064	0.003	<0.001	0.058	0.070
Injury severity	0.079	0.003	<0.001	0.073	0.084
Massive transfusion					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-0.090	0.003	<0.001	-0.096	-0.085
Injury type	0.049	0.003	<0.001	0.044	0.055
Injury severity	0.048	0.027	<0.001	0.043	0.053

Figure 2.10. ROC curves. Accuracy of shock index in predicting major interventions (ICU admission, surgery in the first 24 hours, and massive transfusion) in trauma patients by age group



Examining the effects of covariates on the ROC curve itself through ROC regression, modeling the distribution of shock index among cases (those that had the outcome of interest) as a function of covariates (Table 2.2), age significantly affects the ROC curve of shock index in the prediction of ICU admission (P<0.001). Older age had a negative effect on the curve (coeff = -0.055), indicating that shock index is a better predictor in younger patients than in older patients when predicting ICU admission. The accuracy of shock index in predicting massive transfusion (P=0.717) and surgery in the first 24 hours (P=0.214) is the same in both age groups. Injury severity had a negative effect on the ROC curve of shock index in predicting surgery in the first 24 hours; shock index was a better predictor in less severely injured patients (coeff = -0.028; P=0.006).

Table 2.2. ROC regression analyses. Modeling the distribution of shock index among cases as a function of covariates, prediction of major interventions

SHOCK INDEX					
ICU admission					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-0.055	0.012	<0.001	-0.079	-0.032
Injury type	0.005	0.014	0.740	-0.022	0.031
Injury severity	-0.004	0.011	0.744	-0.025	0.018
Surgery in the first 24 hours					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-0.005	0.013	0.717	-0.030	0.020
Injury type	0.006	0.010	0.578	-0.015	0.026
Injury severity	-0.028	0.010	0.006	-0.048	-0.008
Massive transfusion					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-0.051	0.041	0.214	-0.133	0.030
Injury type	-0.045	0.028	0.111	-0.101	0.010
Injury severity	0.030	0.027	0.263	-0.023	0.084

In the ROC regression model (Table 2.3), after adjusting for age, injury type and injury severity, age seems to attenuate the accuracy of shock index in the prediction of ICU admission (coeff = -0.182; P<0.001) with accuracy being better in younger patients. Age does not seem to affect the accuracy of shock index in predicting surgery in the first 24 hours and massive transfusion (P=0.701 and P=0.133, respectively). These results are consistent with that of the unadjusted ROC curves (Figure 2.1).

Table 2.3. ROC regression model, shock index in the prediction of major interventions, adjusting for the presence of covariates

SHOCK INDEX					
ICU admission					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.364	0.064	<0.001	0.239	0.489
Age group	-0.182	0.033	<0.001	-0.248	-0.116
Injury type	0.015	0.048	0.756	-0.079	0.108
Injury severity	-0.012	0.034	0.731	-0.078	0.055
slope constant	0.573	0.013	<0.001	0.547	0.599
Surgery in the first 24 hours					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	-0.066	0.076	0.387	-0.215	0.084
Age group	-0.023	0.059	0.701	-0.139	0.093
Injury type	0.029	0.059	0.628	-0.087	0.144
Injury severity	-0.137	0.061	0.024	-0.256	-0.018
slope constant	0.952	0.032	<0.001	0.889	1.015
Massive transfusion					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.899	0.122	<0.001	0.661	1.137
Age group	-0.123	0.082	0.133	-0.283	0.037
Injury type	-0.108	0.070	0.125	-0.246	0.030
Injury severity	0.073	0.063	0.252	-0.052	0.197
slope constant	0.423	0.017	<0.001	0.390	0.456

We generated ROC areas under the curve (AUC) for shock index in predicting major interventions, in all patients and by age (Table 2.4). The AUC for shock index in the prediction of surgery in the first 24 hours of arrival at the emergency department was poor, at 0.503, generally no better than tossing a coin. That for ICU admission and massive transfusion were acceptable to good, 0.626 and 0.784, respectively (Table 2.4). While ROC regression analysis showed that age, injury type and injury severity may affect prognostic performance of major interventions, adjusting for these covariates did not result in significant differences in the unadjusted and adjusted AUCs.

Sensitivity analysis

Sensitivity analysis was conducted using the composite outcome of massive transfusion or death in 24 hours to account for cases that would not have had the opportunity to receive massive transfusion because they died. Age seemed to attenuate the accuracy of shock index in the prediction of this outcome (coeff= -10.87, P<0.001).

Table 2.4. Unadjusted and adjusted AUCs for shock index in predicting major interventions in trauma patients, by age group.

	All Patients			<65 years old			≥65 years old				
Outcome	AUC Unadjusted	AUC Adjusted*	P^a	AUC Unadjusted	AUC Adjusted**	P^a	AUC Unadjusted	AUC Adjusted**	P^a	P^b	P^c
Surgery in the first 24 hours	0.503	0.48	0.01	0.504	0.481	0.01	0.478	0.472	0.79	0.13	0.61
ICU admission	0.626	0.614	0.06	0.647	0.622	<0.01	0.598	0.582	0.28	<0.001	<0.01
Massive transfusion	0.784	0.764	0.06	0.783	0.761	0.05	0.797	0.782	0.62	0.53	0.37
Massive transfusion and Death in 24 hours	0.749	0.736	0.19	0.771	0.749	0.05	0.695	0.677	0.44	<0.001	<0.001

*Adjusted for age, injury severity and type of injury

**Adjusted for injury severity and type of injury

P^a comparing unadjusted and adjusted AUCs

P^b comparing unadjusted AUCs of younger and older age groups

P^c comparing adjusted AUCs of younger and older patients

Evaluation of effects of covariates on the ROC curve of heart rate in predicting major interventions in injured patients

We examined the effect of covariates on the ROC curve of heart rate in predicting undergoing different major interventions. Modeling the distribution of heart rate among controls (those that did not have the outcome of interest) as a function of covariates (Table 2.5), except for injury severity in the prediction of admission to the ICU (P=0.078), all three covariates significantly affected the distribution of heart rate among controls and should be adjusted for in ROC analyses (all P<0.001). Higher age seems to attenuate the accuracy of heart rate.

Modeling the distribution of heart rate among cases (those that had the outcome of interest) as a function of covariates (Table 2.6), age group significantly affected the ROC curve itself in the prediction of ICU admission and massive transfusion (coeff = -4.408, P<0.001 and coeff = 6.842, P=0.020). On the covariate-adjusted ROC regression model (Table 2.7), heart rate was a better predictor of ICU admission and massive transfusion among younger patients than older patients.

Table 2.5. Modeling the distribution of heart rate among controls as a function of covariates, prediction of major interventions

HEART RATE					
ICU admission					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-5.926	0.295	<0.001	-6.504	-5.349
Injury type	4.691	0.306	<0.001	4.091	5.292
Injury severity	0.577	0.328	0.078	-0.065	1.219
Surgery in the first 24 hours					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-6.297	0.295	<0.001	-6.876	-5.719
Injury type	4.857	0.320	<0.001	4.229	5.485
Injury severity	3.511	0.281	<0.001	2.962	4.061
Massive transfusion					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-6.068	0.282	<0.001	-6.619	-5.516
Injury type	3.963	0.304	<0.001	3.367	4.559
Injury severity	1.810	0.272	<0.001	1.278	2.343

Table 2.6. Modeling the distribution of heart rate among cases (as a function of covariates, prediction of major interventions

HEART RATE					
ICU admission					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-4.408	1.040	<0.001	-6.446	-2.370
Injury type	-1.579	1.177	0.180	-3.886	0.729
Injury severity	0.760	0.945	0.421	-1.092	2.612
Surgery in the first 24 hours					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	0.056	1.242	0.964	-2.378	2.489
Injury type	0.105	1.017	0.918	-1.889	2.099
Injury severity	-1.089	0.983	0.268	-3.017	0.838
Massive transfusion					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-6.842	2.948	0.020	-12.620	-1.063
Injury type	-2.048	2.023	0.311	-6.013	1.917
Injury severity	3.491	1.939	0.072	-0.309	7.292

Table 2.7. ROC regression model, heart rate in the prediction of major interventions, adjusting for the presence of covariates

HEART RATE

ICU admission

ROC model	Coeff	SE	P	95% CI	
intercept constant	0.331	0.066	<0.001	0.201	0.462
Age group	-0.170	0.037	<0.001	-0.243	-0.097
Injury type	-0.061	0.048	0.205	-0.041	0.099
Injury severity	0.029	0.036	0.411	-0.041	0.099
slope constant	0.712	0.009	<0.001	0.694	0.730

Surgery in the first 24 hours

ROC model	Coeff	SE	P	95% CI	
intercept constant	-0.081	0.073	0.265	-0.223	0.061
Age group	0.003	0.058	0.961	-0.110	0.116
Injury type	0.005	0.055	0.923	-0.102	0.113
Injury severity	-0.055	0.056	0.329	-0.166	0.055
slope constant	0.989	0.019	<0.001	0.952	1.027

Massive transfusion

ROC model	Coeff	SE	P	95% CI	
intercept constant	0.623	0.116	<0.001	0.396	0.851
Age group	-0.230	0.099	0.020	-0.424	-0.037
Injury type	-0.069	0.069	0.320	-0.205	0.067
Injury severity	0.118	0.065	0.070	-0.010	0.245
slope constant	0.640	0.014	<0.001	0.612	0.668

Evaluation of effects of covariates on the ROC curve of systolic blood pressure in predicting major interventions in injured patients

We also examined the effect of age, injury severity and injury type on the accuracy of blood pressure and heart rate in the prediction of undergoing major interventions. Table 2.8 presents the results of the ROC regression analysis, modeling the distribution of systolic blood pressure among controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and injury severity. As in the case of shock index, age group, injury type and injury severity affected the distribution of shock index among controls and need to be adjusted for in analyses involving the ROC curve (all $P<0.001$).

Examining the effects of the presence of the covariates age, injury severity and injury type on the ROC curve itself of systolic blood pressure in the prediction of undergoing major interventions (Table 2.9), injury severity significantly affects the ROC curve of blood pressure in the prediction of ICU admission, surgery in the first 24 hours and massive transfusion ($P=0.023$, $P=0.16$ and $P=0.27$, respectively). Blood pressure is a better predictor among those who are less severely injured than those who are not. Looking at blood pressure in the prediction of massive transfusion, age group, injury severity and injury type all affected the ROC curve itself ($P<0.001$, $P=0.030$ and $P=0.027$, respectively). Blood pressure seems to be a better predictor among older patients, those who are less severely injured, and among those who have blunt injuries. These results can also be seen the covariate-adjusted ROC regression model for systolic blood pressure in the prediction of major interventions, adjusting for the presence of covariates (age group, injury type and injury severity) (Table 2.10).

Table 2.8. Modeling the distribution of systolic blood pressure among as a function of covariates, prediction of major interventions

BLOOD PRESSURE					
ICU admission					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-16.181	0.417	<0.001	-16.998	-15.365
Injury type	4.387	0.434	<0.001	3.537	5.237
Injury severity	5.203	0.463	<0.001	4.295	6.111
Surgery in the first 24 hours					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-15.479	0.411	<0.001	-16.284	-14.674
Injury type	5.030	0.446	<0.001	4.156	5.904
Injury severity	7.831	0.390	<0.001	7.066	8.597
Massive transfusion					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-15.801	0.397	<0.001	-16.578	-15.024
Injury type	3.991	0.428	<0.001	3.152	4.830
Injury severity	5.766	0.383	<0.001	5.016	6.516

Table 2.9. Modeling the distribution of systolic blood pressure among cases as a function of covariates, prediction of major interventions

BLOOD PRESSURE					
ICU admission					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	1.308	1.374	0.341	-1.384	4.001
Injury type	2.609	1.554	0.093	-0.436	5.655
Injury severity	-3.004	1.252	0.016	-5.458	-0.549
Surgery in the first 24 hours					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	-1.874	1.757	0.286	-5.317	1.569
Injury type	0.247	1.438	0.864	-2.572	3.066
Injury severity	-3.162	1.391	0.023	-5.888	-0.436
Massive transfusion					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Age group	13.632	3.282	<0.001	7.199	20.065
Injury type	-4.915	2.261	0.030	-9.347	-0.483
Injury severity	-4.797	2.166	0.027	-9.042	-0.552

Table 2.10. ROC regression model, systolic blood pressure in the prediction of major interventions, adjusting for the presence of covariates

BLOOD PRESSURE					
ICU admission					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.176	0.062	0.005	0.054	0.298
Age group	0.038	0.044	0.386	-0.048	0.125
Injury type	0.076	0.043	0.076	-0.008	0.161
Injury severity	-0.088	0.037	0.016	-0.160	-0.016
slope constant	0.767	0.012	<0.001	0.743	0.791
Surgery in the first 24 hours					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.007	0.069	0.914	-0.128	0.142
Age group	-0.067	0.077	0.384	-0.218	0.084
Injury type	0.009	0.051	0.862	-0.091	0.108
Injury severity	-0.113	0.053	0.034	-0.217	-0.009
slope constant	0.973	0.018	0.000	0.938	1.007
Massive transfusion					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.999	0.115	<0.001	0.773	1.224
Age group	0.414	0.107	<0.001	0.205	0.623
Injury type	-0.149	0.069	0.030	-0.284	-0.014
Injury severity	-0.146	0.064	0.023	-0.271	-0.020
slope constant	0.812	0.020	<0.001	0.773	0.851

Comparing the accuracy of shock index, heart rate and systolic blood pressure in predicting major interventions in injured patients

We compared the accuracy of shock index, systolic blood pressure and heart rate in predicting undergoing major intervention. Table 2.11 presents the comparison of ROC AUCs between shock index and heart rate, and between shock index and systolic blood pressure. Unadjusted ROC AUCs for the prediction of undergoing major interventions were mostly higher than covariate-adjusted ROCs for shock index, heart rate and systolic blood pressure indicating that failure to adjust for covariates age, injury severity and type of injury could result in an overestimation of the accuracy of blood pressure, heart rate and shock index.

In the prediction of surgery among all trauma patients, in the first 24 hours, on comparison of unadjusted ROCs, there was no significant difference between shock index ROC AUC and that of systolic blood pressure (P=0.200). On adjusting for covariates, systolic blood pressure was a better predictor than shock index (P=0.009). In comparing the unadjusted ROC AUCs for shock index and heart rate, shock index was a better predictor than heart rate (P=0.003). On adjusted analysis, comparison of the AUCs showed no significant difference (P=0.279). Again, these results show the impact of not adjusting for potential covariates when conducting ROC analyses to compare the accuracy of tests. In predicting ICU admission and massive transplantation, shock index was significantly better than both systolic blood pressure and heart rate on both unadjusted and adjusted analysis (Table 2.11). Results for younger patients were consistent with those seen in the all-trauma patient group.

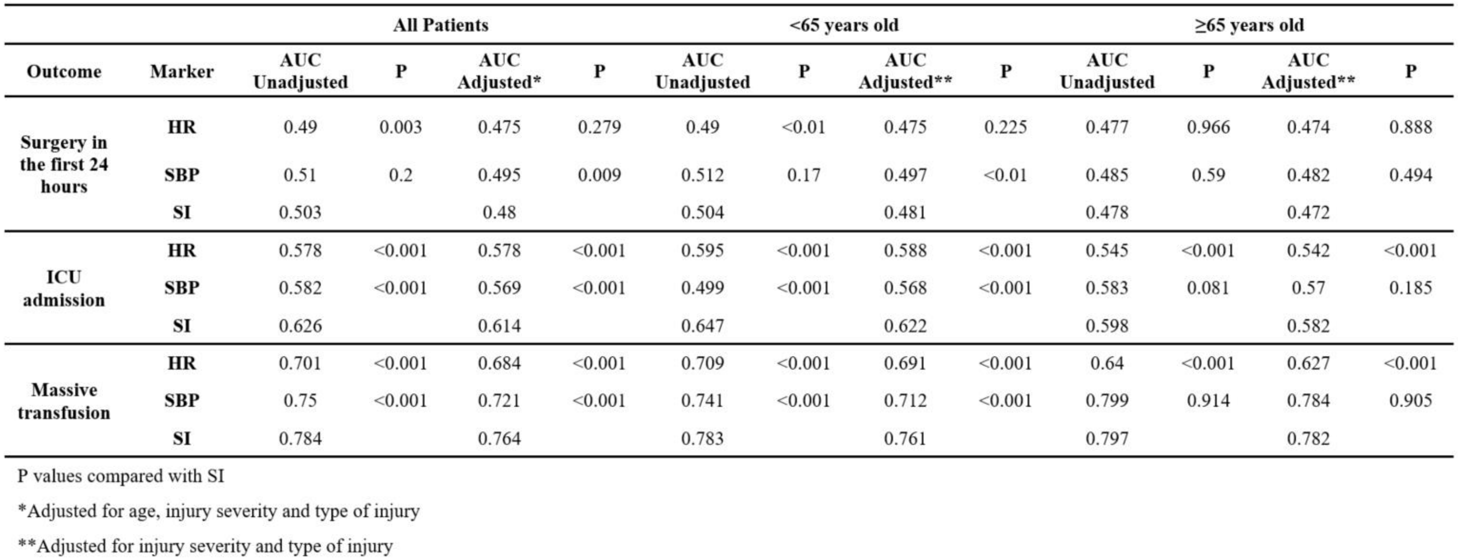
Among older patients, shock index seems to be better than heart rate in predicting ICU admission and massive transfusion both on unadjusted and adjusted ROC analyses. There was no significant difference between the accuracy of shock index with that of systolic blood pressure.

Sensitivity Analyses

Because severe neurologic injury may have an effect on cardiogenic factors, and because head injury may increase risk of death, analyses was done where patients with severe head injury based (GCS <9) were excluded from analyses. There were not significant differences with the results where patients were not excluded from analysis (tables in Appendix; Tables A10-A12).

While the purpose of the study is not to develop a model for use in the field, and instead investigate what characteristics may affect the predictive performance of shock index, there are concerns about the use of Injury Severity Score as the scoring system used to categorize patients into severely or non-severely injured because it is difficult to assess in the field. Injury Severity Score is also an anatomical based scoring system of injury severity, and some consider physiologic based scoring systems better in assessing injury severity. We conducted analyses where we used Revised Trauma Score and Glasgow Coma Scale, both physiologic scoring systems of trauma injury as the methods of categorizing patients as being severely or non-severely injured patients. The results of our analyses had similar results as those obtained when Injury Severity Score was used as the scoring system for injury severity (tables in Appendix, Tables A13-A18).

Table 2.11. ROC AUCs for heart rate, systolic blood pressure and shock index in predicting of major interventions in trauma patients (all patients, <65 years old and ≥65 years old)



		All Patients				<65 years old				≥65 years old			
Outcome	**Marker**	**AUC Unadjusted**	**P**	**AUC Adjusted***	**P**	**AUC Unadjusted**	**P**	**AUC Adjusted****	**P**	**AUC Unadjusted**	**P**	**AUC Adjusted****	**P**
Surgery in the first 24 hours	**HR**	0.49	0.003	0.475	0.279	0.49	<0.01	0.475	0.225	0.477	0.966	0.474	0.888
	SBP	0.51	0.2	0.495	0.009	0.512	0.17	0.497	<0.01	0.485	0.59	0.482	0.494
	SI	0.503		0.48		0.504		0.481		0.478		0.472	
ICU admission	**HR**	0.578	<0.001	0.578	<0.001	0.595	<0.001	0.588	<0.001	0.545	<0.001	0.542	<0.001
	SBP	0.582	<0.001	0.569	<0.001	0.499	<0.001	0.568	<0.001	0.583	0.081	0.57	0.185
	SI	0.626		0.614		0.647		0.622		0.598		0.582	
Massive transfusion	**HR**	0.701	<0.001	0.684	<0.001	0.709	<0.001	0.691	<0.001	0.64	<0.001	0.627	<0.001
	SBP	0.75	<0.001	0.721	<0.001	0.741	<0.001	0.712	<0.001	0.799	0.914	0.784	0.905
	SI	0.784		0.764		0.783		0.761		0.797		0.782	

P values compared with SI

*Adjusted for age, injury severity and type of injury

**Adjusted for injury severity and type of injury

Optimal cut-offs for shock index in the prediction of major interventions

Although it seems that the accuracy of shock index in the prediction of major intervention outcomes did not differ by age group, we identified optimal cut-off points for prediction of the interventions (ICU admission, surgery in the first 24 hours and massive transfusion) (Table 2.12). Optimal shock index cut-offs for all trauma patients were from 0.6 to 0.8 for all patients and for those <65 years old, but was 0.5-0.7 for older patients.

At the most commonly used shock index cut-off for shock index, 0.9, sensitivity and specificity in the prediction of massive transfusion were 60.1% and 89.6%, respectively, for younger patients, and 48.3% and 94.2%, respectively, for older patients. A lower shock index cut-off of 0.7 for those ≥65 years old improves sensitivity to 74.2% with specificity dropping to 77.7% (Appendix Table A19).

Assigning age-specific shock index cut-off (≥0.9 for <65 year old patients, ≥0.7 for ≥65-year-old patients) did not result in significant improvement in discrimination when predicting massive transfusion in comparison to a cut-off of ≥0.9; there was significant improvement when predicting ICU admission and surgery in 24 hours (Table 2.13). Different shock index cut-offs by age group did not result in significant improvement in accuracy over a cut-off of 0.9.

Table 2.12. Shock index cut-offs, predicting major interventions in injured patients, by age group.

	Optimal SI cut-off		
Criterion	**All ages**	**<65 years**	**≥65 years**
	ICU Admission		
Distance to 0, 1	0.7	0.7	0.6
Sensitivity-Specificity	0.6	0.6	0.5
Youden	0.8	0.8	0.6
	Surgery in the first 24 hours		
Distance to 0, 1	0.6	0.6	0.5
Sensitivity-Specificity	0.6	0.6	0.5
Youden	0.8	0.8	0.6
	Massive Transfusion		
Distance to 0, 1	0.7	0.7	0.7
Sensitivity-Specificity	0.7	0.7	0.6
Youden	0.8	0.8	0.7

Table 2.13. Accuracy of age-specific shock index cut-offs in comparison with shock index cut-off of 0.9 in the prediction of major interventions

Cut-point	**AUC**	**P***	**Sensitivity**	**Specificity**
		ICU admission		
SI≥0.9	0.591	<0.001	27.10%	91.00%
<65 years old SI≥0.9 ≥65 years old SI≥0.7	0.603		31.9%	88.7%
		Surgery within 24 hours		
SI≥0.9	0.505	0.049	11.9%	89.3%
<65 years old SI≥0.9 ≥65 years old SI≥0.7	0.502		13.9%	86.4%
		Massive transfusion		
SI≥0.9	0.745	0.328	58.7%	90.3%
<65 years old SI≥0.9 ≥65 years old SI≥0.7	0.748		61.8%	87.8%

P* comparing AUCs

Aim 3 Results

A total of 1057 patients (2.86%) of the patients had thyroid disorders, 6982 (18.87%) had cardiovascular disorders, 2929 (7.92%) had diabetes and 150 (0.41%) were receiving coumadin therapy; 9044 patients (24.45%) had at least one of the conditions (Table 1.1). Older patients were more likely to have at least one of the conditions we considered; 61.43% of older patients had any of the conditions while only 17.82% of younger patients had at least one condition. 25,767 (69.65%) trauma patients had negative blood alcohol results while 10,321 (27.90%) had positive results. Older patients tended to be negative for blood alcohol compared with younger patients (10.29% of older patients vs. 31.05% of younger patients).

Evaluation of the effects of blood alcohol on the ROC curve of shock index in predicting all in-hospital mortality and massive transfusion

The effect of the presence of various conditions on the accuracy of shock index in predicting all in-hospital death and massive transfusion was evaluated using ROC regression. Table 3.1 presents the results of the initial step of the procedure, modeling the distribution of shock index among patients who did not have the outcome of interest as a function of age and presence of blood alcohol. The distribution of shock index significantly differed between younger and older patients, and between those who were blood alcohol positive and those who were not (both P<0.001). There may be a need to adjust for blood alcohol when examining the accuracy of shock index in predicting in-hospital death and massive transfusion.

Table 3.1. Modeling distribution of shock index among controls as a function of presence of the covariates age and blood alcohol

SHOCK INDEX					
All In-hospital death					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Alcohol	0.071	0.002	<0.001	0.067	0.075
Age group	-0.087	0.003	<0.001	-0.092	-0.081
Massive transfusion					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Alcohol	0.071	0.002	<0.001	0.066	0.075
Age group	-0.079	0.003	<0.001	-0.085	-0.074

Figures 3.1 and 3.2 illustrate the unadjusted ROC plotted using ROCCONTRAST in SAS PROC LOGISTIC, for shock index in the prediction of all in-hospital death and

massive transfusion by age group, and blood alcohol status, respectively. Shock index has better accuracy in predicting all in-hospital mortality in younger patients than in older patients (P=0.053); this difference in accuracy in the age groups was not seen in the prediction of massive transfusion. Shock index has better accuracy in predicting massive transfusion in patients who are blood alcohol negative compared than in patients who were blood alcohol positive (P<0.001); this difference was not observed in the prediction of all in-hospital mortality.

The results of the ROC regression analyses, modeling the distribution of shock index among cases (patients with the outcome of interest) (Table3.2) support those observed in the graphs seen in Figures 3.1 and 3.2. Adjusting for age, alcohol seemed to impact the discriminatory accuracy of the ROC curve. The accuracy of shock index in predicting all in-hospital death and massive transfusion is different in blood alcohol positive and negative patients (both P<0.001).

Table 3.3 presents the ROC model of shock index predicting all in-hospital death and massive transfusion, adjusting for the presence of the covariates age and blood alcohol. In the final model, both being blood alcohol positive and of older age seemed to attenuate the accuracy of shock index in predicting all in-hospital death, while only blood alcohol had a significant effect in predicting massive transfusion.

Figure 3.1. ROC curves. Accuracy of shock index in predicting all in-hospital death and massive transfusion in trauma patients by age group.

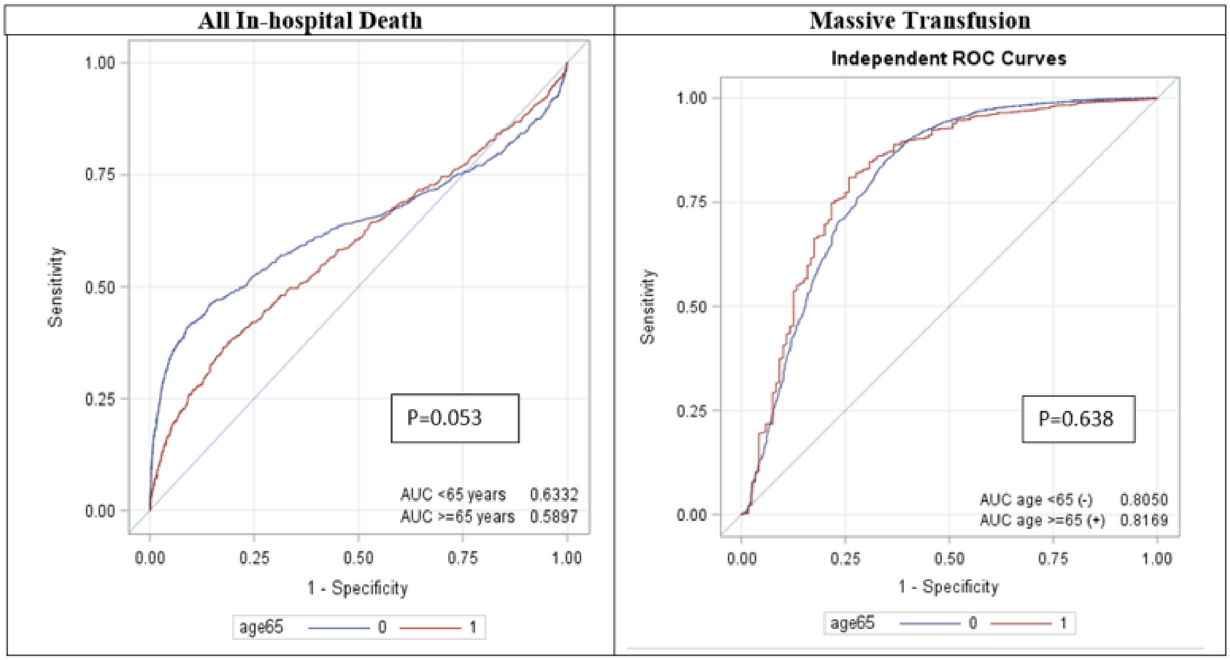


Figure 3.2. ROC curves. Accuracy of shock index in predicting all in-hospital death and massive transfusion in trauma patients by blood alcohol status.

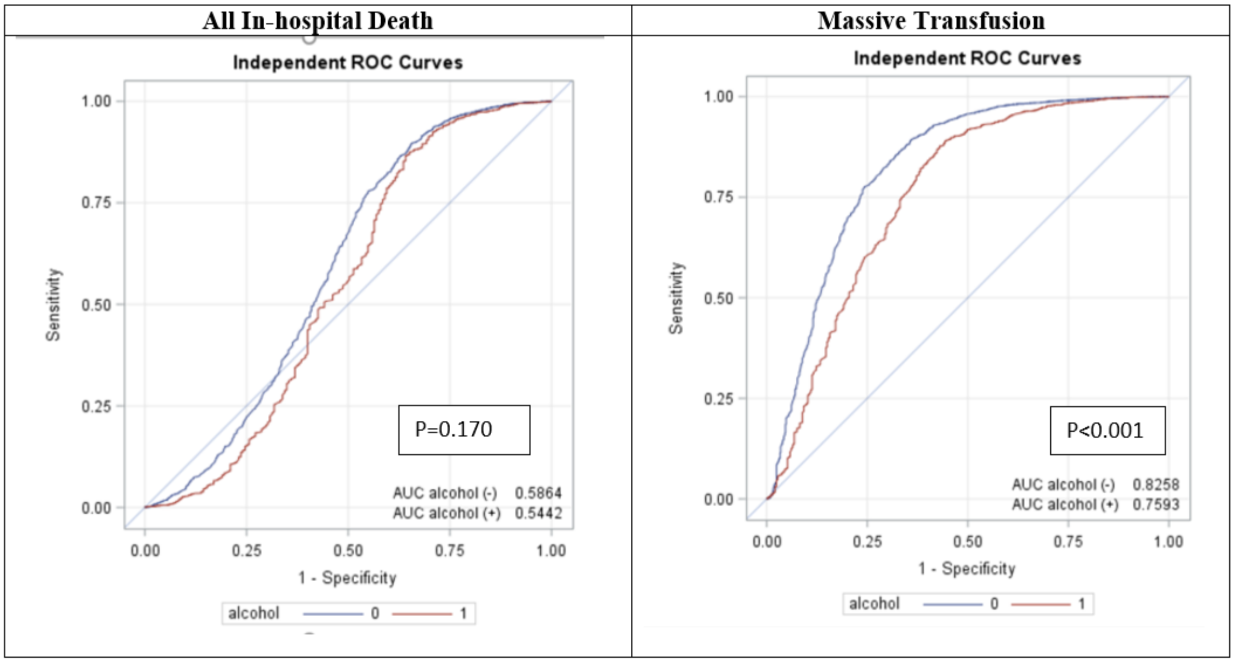


Table 3.2. Table 3.2 ROC regression analyses. Modeling the distribution of shock index among cases (those that had the outcome of interest) as a function of covariates, age and blood alcohol

SHOCK INDEX					
All In-hospital death					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Alcohol	-0.126	0.034	<0.001	-0.192	-0.060
Age group	-0.141	0.027	<0.001	-0.195	-0.088
Massive transfusion					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Alcohol	-0.115	0.030	<0.001	-0.173	-0.057
Age group	-0.074	0.042	0.077	-0.156	0.008

Table 3.3. ROC regression model, shock index in the prediction of all in-hospital death and massive transfusion, adjusting for the presence of covariates age and blood alcohol

SHOCK INDEX					
All In-hospital death					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.633	0.052	<0.001	0.532	0.735
Alcohol	-0.314	0.084	<0.001	-0.478	-0.149
Age group	-0.352	0.068	<0.001	-0.487	-0.218
slope constant	0.458	0.011	<0.001	0.437	0.478
Massive transfusion					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.958	0.047	<0.001	0.866	1.050
Alcohol	-0.274	0.071	<0.001	-0.413	-0.134
Age group	-0.176	0.100	0.078	-0.371	0.019
slope constant	0.417	0.010	<0.001	0.398	0.436

Evaluation of the effects of cardiovascular disorder status on the ROC curve of shock index in predicting all in-hospital mortality and massive transfusion

The ROC regression model, modelling the distribution of shock index among those who did not have the outcome of interest (Table 3.4) as a function of the presence the covariates age group and cardiovascular disorder status showed that in the prediction of all in-hospital mortality and massive transfusion, the distribution of shock index seemed to differ between those with and without cardiovascular disorders (both P<0.001). Cardiovascular disorder status may confound the interpretation of the accuracy of shock index, and therefore there may be a need to adjust for cardiovascular status in studies involving the examination of the accuracy of shock index in predicting all in-hospital mortality and massive transfusion.

Table 3.4. ROC regression analyses. Modeling distribution of shock index among controls (those that did not have the outcome of interest) as a function of presence of the covariates age and cardiovascular disorder status

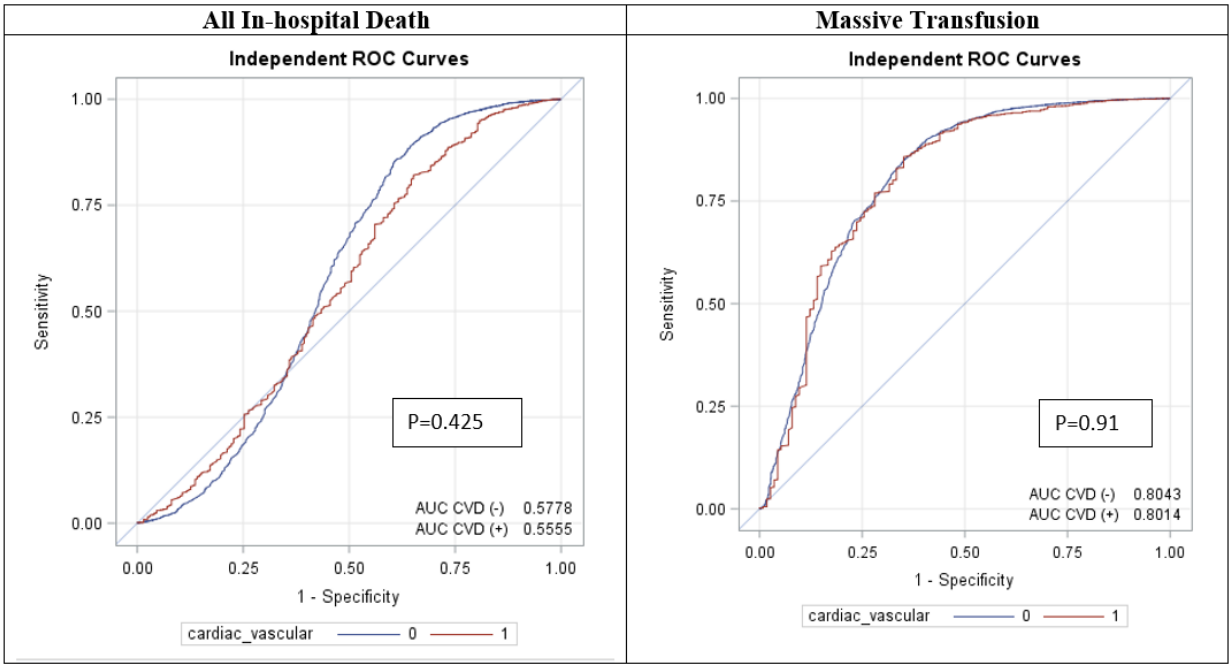
SHOCK INDEX					
All In-hospital death					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Cardiovascular disorders	-0.050	0.003	<0.001	-0.055	-0.045
Age group	-0.085	0.003	<0.001	-0.091	-0.079
Massive transfusion					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Cardiovascular disorders	-0.047358	0.002	<0.001	-0.052	-0.042
Age group	-0.079159	0.003	<0.001	-0.085	-0.074

Examining whether the accuracy of shock index in predicting all in-hospital mortality and massive transfusion differed by cardiovascular disorder status, unadjusted ROC curves were not significantly different between patients with cardiovascular disorder and those that did not (P=0.425 and P=0.910, respectively) (Figure 3.3). Results were similar to those obtained ROC regression analyses modeling the distribution of shock index among cases as a function of age and cardiovascular disorder status show that adjusting for age (Table 3.5), as well as looking at the ROC regression model (Table 3.6).

Evaluation of the effects of thyroid disorder status on the ROC curve of shock index in predicting all in-hospital mortality and massive transfusion

Examining the results of the ROC regression analyses modeling the distribution of shock index among trauma patients who did not have the outcome of interest (all in-hospital death and massive transfusion) as a function of age and thyroid disorder status, the distribution of shock index was significantly different between patients with and without thyroid disorders (both P<0.001) (Table 3.7). Thyroid disorders may have a confounding effect on the interpretation of the accuracy of shock index when prediction all in-hospital mortality and massive transfusion.

Figure 3.3. ROC curves. Accuracy of shock index in predicting all in-hospital death and massive transfusion in trauma patients by cardiovascular disorder status.



The unadjusted ROC curves by thyroid disorder status (Figure 3.4), as well as the ROC regression models modeling the distribution of shock index among cases a function of covariates, age and thyroid disorder status (Table 3.8), and the ROC regression model (Table 3.9) adjusting for age showed that the accuracy of shock index in predicting all in-hospital mortality and massive transfusion did not differ significantly by thyroid disorder status.

Table 3.5. ROC regression analyses. Modeling the distribution of shock index among cases (those that had the outcome of interest) as a function of covariates, age and cardiovascular disorder status

SHOCK INDEX					
All In-hospital death					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Cardiovascular disorders	0.018	0.034	0.604	-0.049	0.084
Age group	-0.130	0.027	<0.001	-0.183	-0.077
Massive transfusion					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Cardiovascular disorders	0.001	0.044	0.982	-0.085	0.087
Age group	-0.054	0.043	0.206	-0.138	0.030

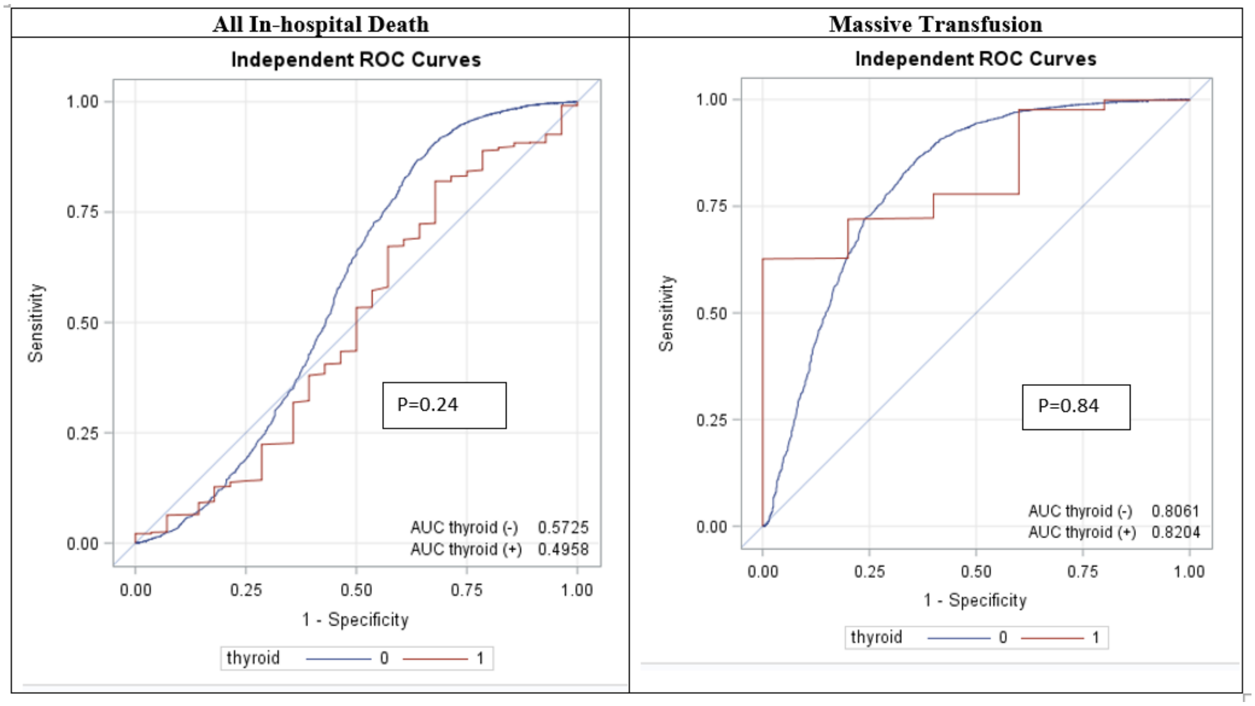
Table 3.6. ROC regression model, shock index in the prediction of all in-hospital death and massive transfusion, adjusting for the presence of covariates age and cardiovascular disorder status

SHOCK INDEX					
All In-hospital death					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.534	0.044	<0.001	0.448	0.620
Cardiovascular disorders	0.044	0.084	0.604	-0.121	0.209
Age group	-0.325	0.068	<0.001	-0.458	-0.191
slope constant	0.464	0.010	<0.001	0.444	0.485
Massive transfusion					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.861	0.040	<0.001	0.784	0.939
Cardiovascular disorders	0.002	0.105	0.982	-0.203	0.207
Age group	-0.129	0.102	0.206	-0.330	0.071
slope constant	0.423	0.010	<0.001	0.404	0.442

Table 3.7. ROC regression analyses. Modeling distribution of shock index among controls (those that did not have the outcome of interest) as a function of presence of the covariates age and thyroid disorder status

SHOCK INDEX					
All In-hospital death					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Thyroid disorders	-0.026	0.006	<0.001	-0.037	-0.014
Age group	-0.100	0.003	<0.001	-0.105	-0.094
Massive transfusion					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Thyroid disorders	-0.023	0.0057	<0.001	-0.034	-0.011
Age group	-0.093	0.003	<0.001	-0.098	-0.088

Figure 3.4. ROC curves. Accuracy of shock index in predicting all in-hospital death and massive transfusion in trauma patients by thyroid disorder status.



All In-hospital Death

Massive Transfusion

Table 3.8. ROC regression analyses. Modeling the distribution of shock index among cases (those that had the outcome of interest) as a function of covariates, age and thyroid disorder status

SHOCK INDEX					
All In-hospital death					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Thyroid disorders	-0.071	0.078	0.364	-0.224	0.082
Age group	-0.119	0.026	<0.001	-0.170	-0.068
Massive transfusion					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Thyroid disorders	-0.131	0.188	0.486	-0.500	0.238
Age group	-0.054	0.041	0.188	-0.134	0.026

Table 3.9. ROC regression model, shock index in the prediction of all in-hospital death and massive transfusion, adjusting for the presence of covariates age and thyroid disorder status

SHOCK INDEX					
All In-hospital death					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.545	0.043	<0.001	0.460	0.631
Thyroid disorders	-0.177	0.195	0.364	-0.558	0.205
Age group	-0.297	0.065	<0.001	-0.425	-0.169
slope constant	0.466	0.011	<0.001	0.446	0.487
Massive transfusion					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.869	0.039	<0.001	0.793	0.945
Thyroid disorders	-0.312	0.449	0.486	-1.192	0.567
Age group	-0.128	0.098	0.188	-0.319	0.063
slope constant	0.425	0.010	<0.001	0.406	0.444

Evaluation of the effects of diabetes mellitus status on the ROC curve of shock index in predicting all in-hospital mortality and massive transfusion

Table 3.10 show the results of the ROC regression analyses modeling the distribution of shock index among trauma patients who did not have the outcome of interest (all in-hospital death and massive transfusion) as a function of age and diabetes mellitus status. The distribution of shock index was significantly different between patients with and without diabetes mellitus (both P<0.001 for all in-hospital death and massive transfusion). There may be a need to control for diabetes mellitus status in order to adjust for the confounding effect of diabetes mellitus on the ROC curve.

Table 3.10. ROC regression analyses. Modeling distribution of shock index among controls (those that did not have the outcome of interest) as a function of presence of the covariates age and diabetes mellitus status

SHOCK INDEX					
All In-hospital death					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Diabetes mellitus	-0.035	0.004	<0.001	-0.042	-0.027
Age group	-0.096	0.003	<0.001	-0.102	-0.091
Massive transfusion					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Diabetes mellitus	-0.030	0.004	<0.001	-0.037	-0.023
Age group	-0.090	0.003	<0.001	-0.095	-0.085

The unadjusted ROC curves by diabetes mellitus status (Figure 3.5) showed that the accuracy of shock index in predicting all in-hospital mortality and massive transfusion did not differ significantly by diabetes mellitus status. Adjusting for the presence of age, ROC regression models modeling the distribution of shock index among cases as a function of age and diabetes mellitus status (Table 3.11), and the ROC regression model in Table 3.12 are similar to that with the unadjusted comparison.

Figure 3.5. ROC curves. Accuracy of shock index in predicting all in-hospital death and massive transfusion in trauma patients by diabetes status.

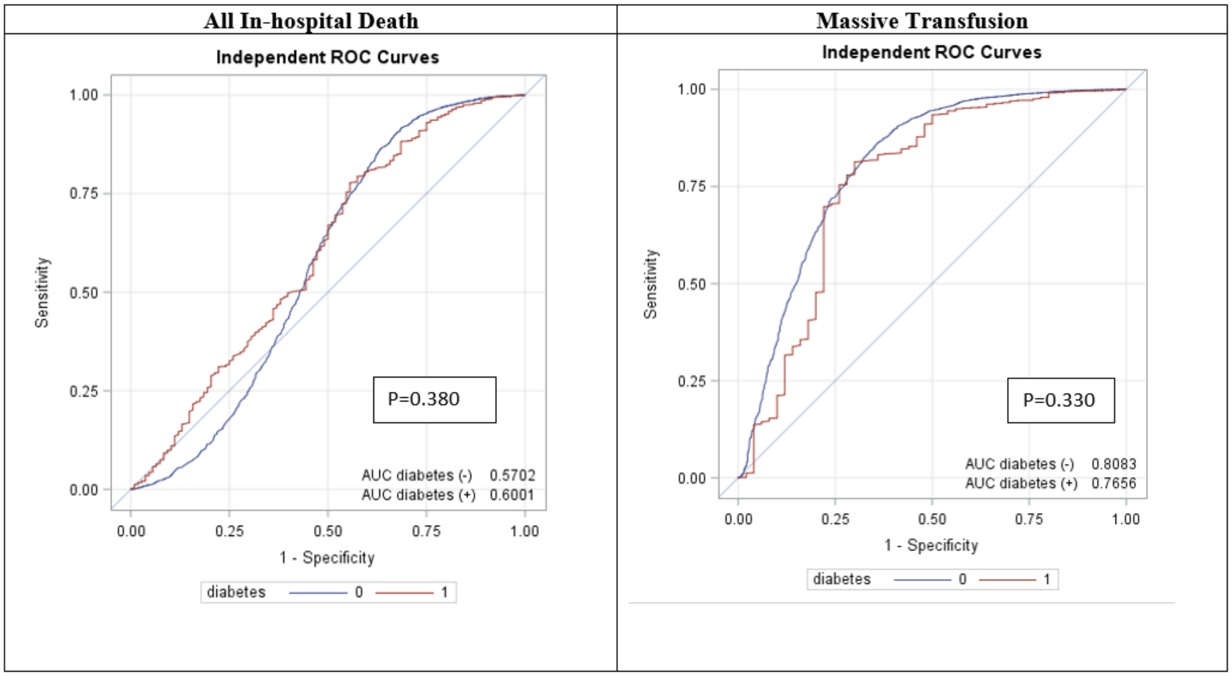


Table 3.11. ROC regression analyses. Modeling the distribution of shock index among cases (those that had the outcome of interest) as a function of covariates, age and diabetes mellitus status

SHOCK INDEX					
All In-hospital death					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Diabetes mellitus	0.034	0.042	0.419	-0.048	0.116
Age group	-0.127	0.026	<0.001	-0.179	-0.076
Massive transfusion					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Diabetes mellitus	-0.064	0.062	0.305	-0.186	0.058
Age group	-0.045	0.042	0.282	-0.127	0.037

Table 3.12. ROC regression model, shock index in the prediction of all in-hospital death and massive transfusion, adjusting for the presence of covariates age and diabetes mellitus status

SHOCK INDEX					
All In-hospital death					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.540	0.044	<0.001	0.454	0.626
Diabetes mellitus	0.085	0.105	0.419	-0.121	0.290
Age group	-0.318	0.066	<0.001	-0.447	-0.188
slope constant	0.466	0.011	<0.001	0.445	0.486
Massive transfusion					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.872	0.039	<0.001	0.796	0.949
Diabetes mellitus	-0.152	0.148	0.305	-0.443	0.138
Age group	-0.107	0.099	0.282	-0.302	0.088
slope constant	0.425	0.010	<0.001	0.406	0.444

Evaluation of the effects of coumadin therapy on the ROC curve of shock index in predicting all in-hospital mortality and massive transfusion

The results of the ROC regression model of the distribution of shock index among those who did not have the outcome of interest as a function of age and coumadin therapy status show that coumadin therapy does not seem to confound the accuracy of shock index in predicting the outcomes (Table 3.13).

Table 3.13. ROC regression analyses. Modeling distribution of shock index among controls (those that did not have the outcome of interest) as a function of presence of the covariates age and coumadin therapy status

SHOCK INDEX					
All In-hospital death					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Coumadin	0.011	0.016	0.516	-0.022	0.043
Age group	-0.102	0.003	<0.001	-0.107	-0.096
Massive transfusion					
Control covariate	**Coeff**	**SE**	**P**	**95% CI**	
Coumadin	0.009	0.015	0.554	-0.021	0.038
Age group	-0.095	0.003	<0.001	-0.021	-0.090

The unadjusted ROC curves by coumadin therapy status (Figure 3.6) showed that the accuracy of shock index in predicting all in-hospital mortality and massive transfusion did not differ significantly among patients who were on coumadin and those who were not. Adjusting for the presence of age, ROC regression models modeling the distribution of shock index among cases as a function of age and coumadin therapy status (Table 3.14), and the ROC regression model in Table 3.15 are similar to that with the unadjusted comparison.

Incremental addition of covariates

We examined the performance of shock index alone in comparison with a model with shock index in combination with covariates (age, blood alcohol, diabetes, thyroid disorders, cardiovascular disorders and coumadin therapy) in predicting all in-hospital mortality and massive transfusion (Figures 3.7 and 3.8). Comparing ROC AUCs, except for the covariate thyroid disorders, the combination of shock index and covariate were better in predicting all in-hospital mortality than shock index alone ($P<0.05$). The biggest improvements in the ROC seem to be with shock index, age combination and shock index, blood alcohol, in comparison with shock index alone (Figure 3.7).

In the prediction of massive transfusion, shock index alone and shock index with covariate combination seem to have similar accuracy in the prediction of massive transfusion (Figure 3.8). Looking at whether the addition of another covariate (blood alcohol, cardiovascular disorder, thyroid disorder, diabetes or coumadin therapy) to shock index, age combination would improve the accuracy in the prediction of all in-hospital mortality. A model with shock index, age, and diabetes combination was better in predicting all in-hospital death than shock index and age combination (Table 3.16).

Figure 3.6. ROC curves. Accuracy of shock index in predicting all in-hospital death and massive transfusion in trauma patients by coumadin treatment group.

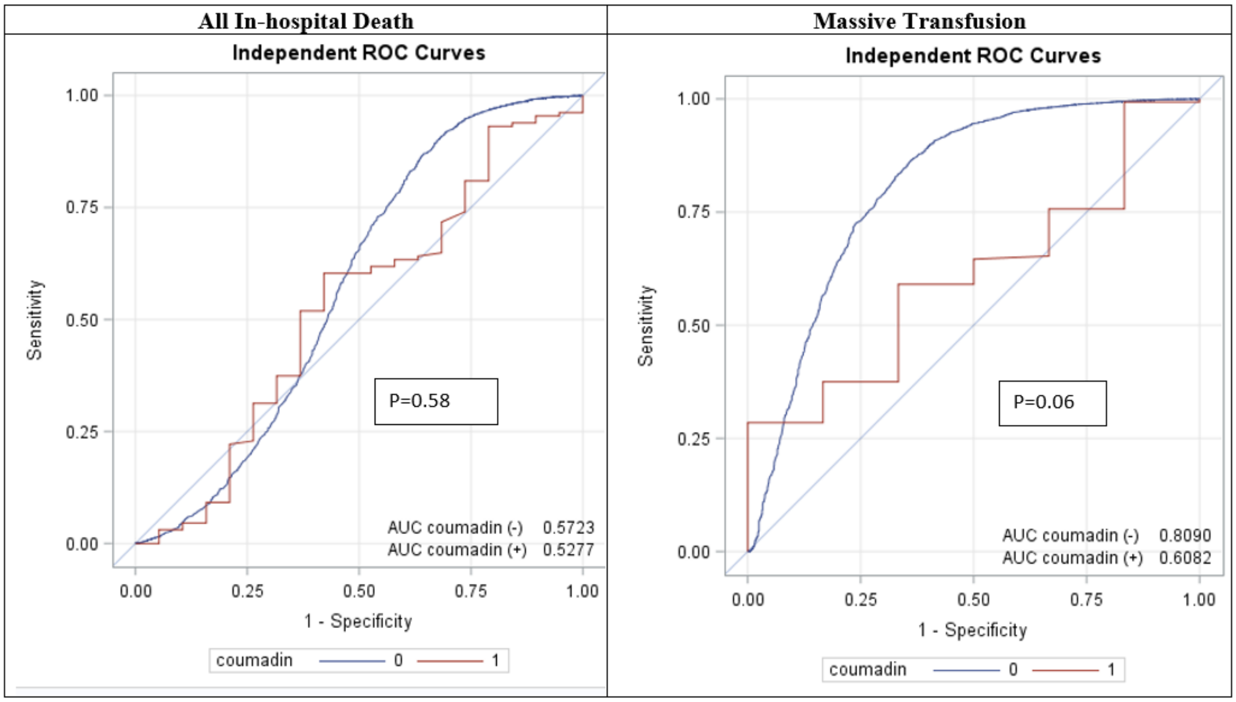


Table 3.14. ROC regression analyses. Modeling the distribution of shock index among cases (those that had the outcome of interest) as a function of covariates, age and coumadin therapy status

SHOCK INDEX					
All In-hospital death					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Coumadin	-0.070	0.095	0.465	-0.257	0.117
Age group	-0.119	0.026	<0.001	-0.170	-0.068
Massive transfusion					
Case covariate	**Coeff**	**SE**	**P**	**95% CI**	
Coumadin	-0.169	0.175	0.333	-0.513	0.174
Age group	-0.046	0.042	0.268	-0.127	0.035

Table 3.15. ROC regression model, shock index in the prediction of all in-hospital death and massive transfusion, adjusting for the presence of covariates age and coumadin therapy status

SHOCK INDEX					
All In-hospital death					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.545	0.043	<0.001	0.460	0.630
Coumadin	-0.174	0.238	0.465	-0.641	0.293
Age group	-0.297	0.065	<0.001	-0.425	-0.170
slope constant	0.466	0.011	<0.001	0.446	0.487
Massive transfusion					
ROC model	**Coeff**	**SE**	**P**	**95% CI**	
intercept constant	0.869	0.039	<0.001	0.793	0.945
Coumadin	-0.404	0.417	0.333	-1.221	0.414
Age group	-0.110	0.099	0.268	-0.303	0.084
slope constant	0.425	0.010	<0.001	0.406	0.444

Figure 3.7. ROC curves comparing shock index and shock index, covariate combination in predicting all in-hospital death.

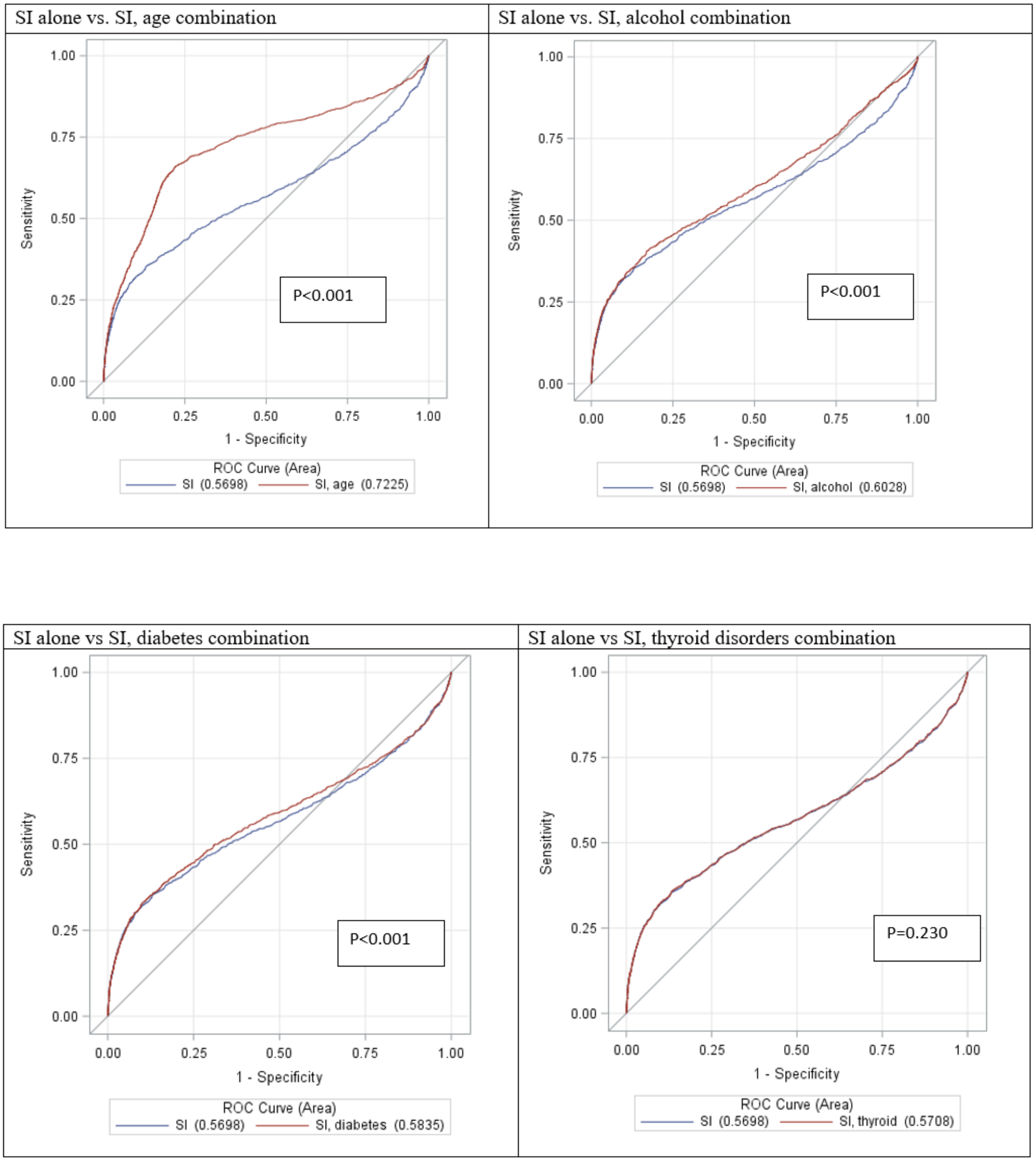
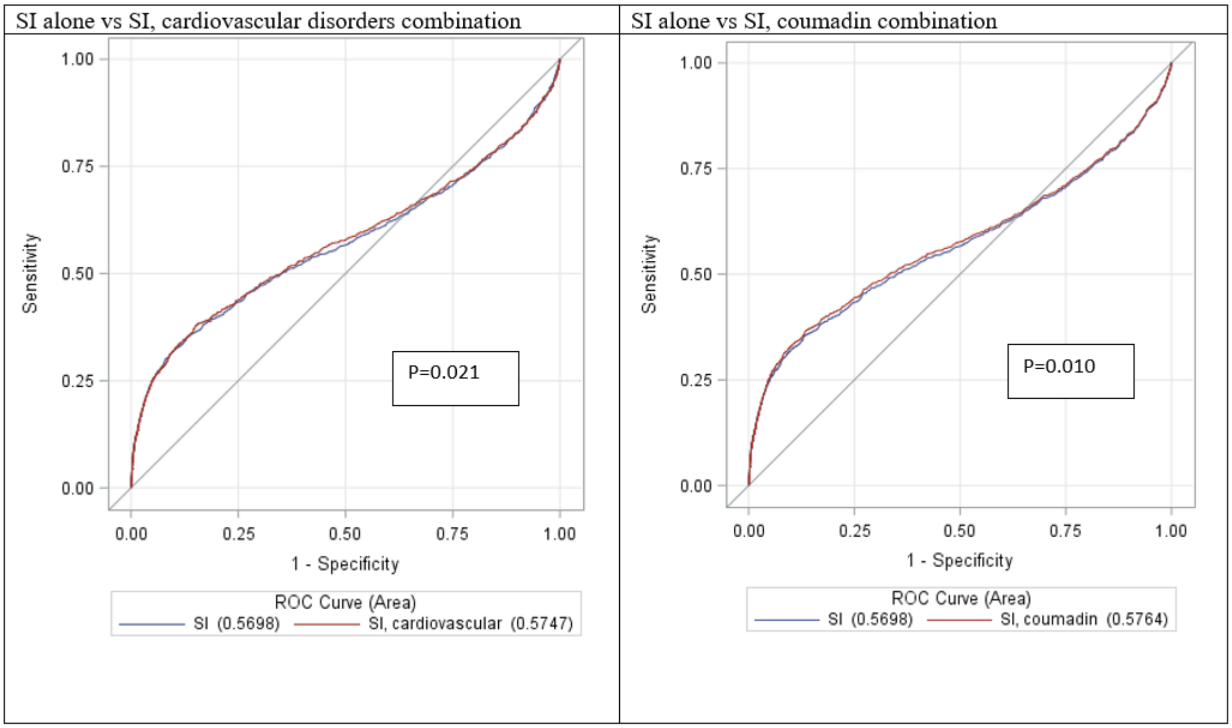
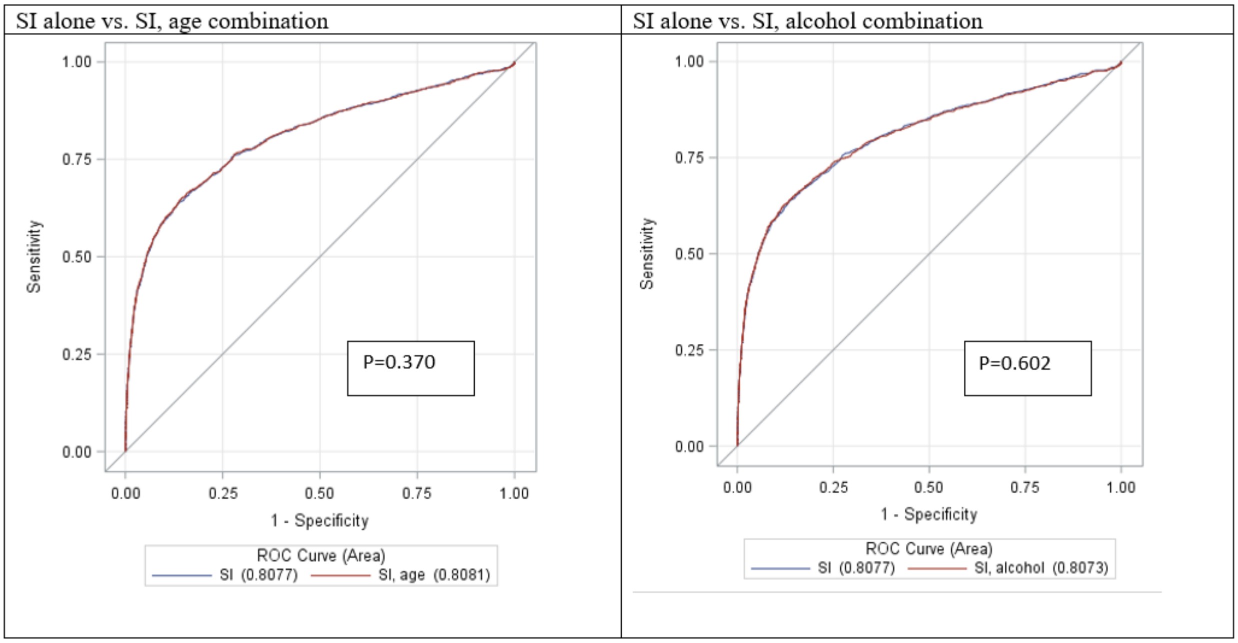


Figure 3.7 Continued

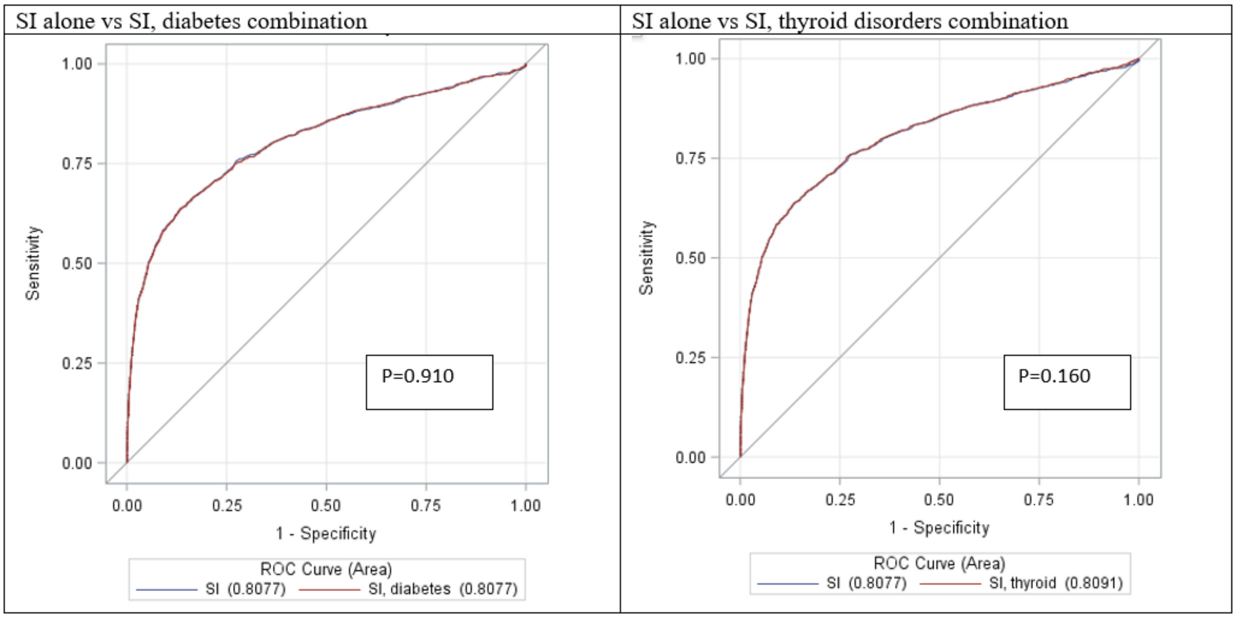

SI alone vs SI, cardiovascular disorders combination

SI alone vs SI, coumadin combination

Figure 3.8. ROC curves comparing shock index and shock index, covariate combination in predicting massive transfusion


SI alone vs. SI, age combination

SI alone vs. SI, alcohol combination


SI alone vs SI, diabetes combination

SI alone vs SI, thyroid disorders combination

Figure 3.8 Continued

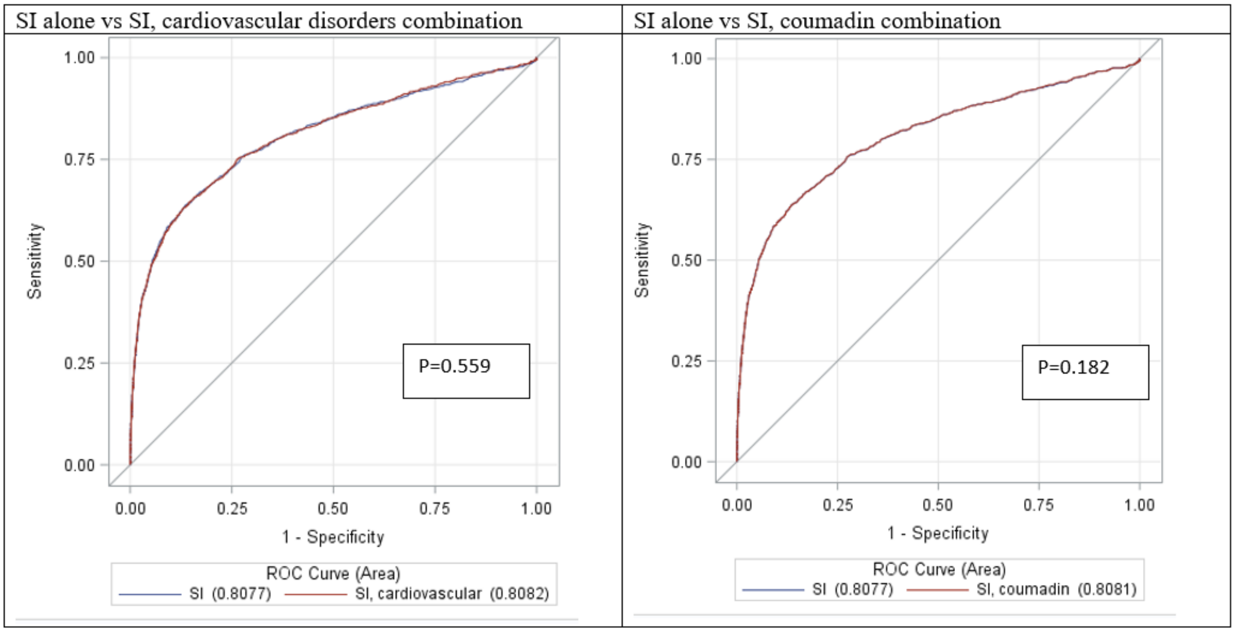


Table 3.16. AUC of ROC analyses comparing shock index and age combination, and shock index, age, and covariate combination in predicting all in-hospital death

		SI and age combination				SI, age and covariate combination				P
Outcome	**Covariate**	**AUC**	**SE**	**95% CI**		**AUC**	**SE**	**95% CI**		
All in-hospital death	Alcohol	0.723	0.010	0.702	0.743	0.723	0.010	0.703	0.743	0.764
	Cardiovascular disorder					0.722	0.010	0.702	0.743	0.767
	Thyroid disorder					0.724	0.010	0.704	0.744	0.060
	Diabetes mellitus					0.729	0.010	0.709	0.748	<0.001
	Coumadin					0.723	0.010	0.703	0.743	0.370

CHAPTER 5: DISCUSSION

Summary

In our study, we examined the accuracy of admission shock index in predicting early, 48-hour and in-hospital mortality, and resource utilization (massive transfusion, ICU admission and surgery in 24 hours) in trauma patients admitted to a major trauma center. We also examined whether characteristics such as age, injury severity, injury type, blood alcohol and comorbidities affected the predictive accuracy of shock index. Of particular interest is the accuracy of shock index in the older population. We confirmed our hypothesis that shock index is not as accurate in elderly injured patients compared to younger patients. We also compared the predictive accuracy of shock index, heart rate and systolic blood pressure in predicting mortality outcomes and resource utilization. Optimal cut-points for shock index for older and younger trauma patients in the prediction of mortality outcomes and resource utilization were determined.

In summary, shock index had acceptable predictive accuracy in predicting mortality outcomes, and ICU admission in injured patients. Accuracy was good in the prediction of massive transfusion, and poor in the prediction of surgery in 24 hours. Shock index was better than heart rate or systolic blood pressure alone in predicting mortality outcomes in injured patients (all ages, elderly, and younger patients). A similar result was seen in the prediction of major interventions for the overall injured population and among younger patients. However, the accuracy of shock index in predicting major interventions was not significantly different from that of systolic blood pressure alone among older patients.

Our results showed that the accuracy of shock index in predicting 48-hour and all in-hospital mortality, and ICU admission was better in younger injured patients than in the elderly. The accuracy was also better among those with lower injury severity than in those who were more severely injured. Accuracy of shock index in predicting massive transfusion was similar in older and younger trauma patients. Although injury type, injury severity and age significantly altered the distribution of shock index among patients that did not die or receive major interventions (and therefore have a possible confounding effect on prediction), adjustment for these covariates did not significantly alter the AUC for predictive performance. Optimal cut-offs for predicting trauma outcomes were lower for older patients (0.5-0.7 in predicting mortality and major interventions) than in younger patients (0.6-0.9 in predicting mortality and 0.6-0.8 for predicting major interventions).

ROC regression analysis among “controls” or patients that did not have the outcome of interest showed that a positive blood alcohol and presence of comorbidities may possibly confound prediction. However, when we adjusted for these covariates, there was no significant alteration of AUCs for predictive performance. ROC regression analysis among “cases” or patients that had the outcome of interest showed that accuracy of shock index in predicting outcomes was different by blood alcohol status; it was better among patients who were blood alcohol-negative. Assessing whether combining shock index with age, blood alcohol status, and comorbidities would improve accuracy in predicting trauma outcomes found that combining age or blood alcohol status improved the accuracy in predicting all in hospital mortality. However, combining covariates with shock index did not improve the accuracy of shock index in predicting massive transfusion.

The management of injured patients involves identifying those in need of specialized care in trauma centers from those who can receive care in non-trauma hospitals, and for those presenting to hospitals, identifying those in need of undergoing certain procedures. Procedures for identifying these patients have traditionally relied on vital signs in the field or at presentation to the hospital (Newgard et al., 2022; Sasser et al., 2012). In their systematic review, Newgard et al noted that there is a lack of research providing head-to-head comparisons of markers of circulatory compromise (Newgard et al., 2020). Our results provide head-to-head comparison of the predictive accuracy of shock index with that of systolic blood pressure and heart rate.   In our study, we show that the vital signs heart rate and systolic blood pressure are worse in comparison to shock index in predicting mortality outcomes (death at 2 hours, death at 48 hours and all in-hospital death) and undergoing major interventions (surgery in the first 24 hours of admission and admission to the ICU. Our results were similar to that obtained by Zarzaur et al whose study was conducted only in patients with blunt trauma with no significant neurological trauma and did not adjust for age or injury severity (Zarzaur et al., 2008). Brujins, et al also showed higher AUCs for shock index compared to heart rate or systolic blood pressure in the prediction of 48-hour mortality (Bruijns, Guly, Bouamra, Lecky, &

Wallis, 2014). However, we are not certain if this result was significant as direct comparison of AUC curves were not presented in their paper. Our study conducted comparisons using covariate-adjusted ROC analyses where the effects of age, injury severity and trauma type were considered. Most of the studies which had suggested that shock index would be better predictors of hypovolemia, mortality or emergent operation utilized traditional studies of association (Birkhahn et al., 2005; J. W. Cannon, 2018; Kheirbek et al., 2021; Vandromme et al., 2011), which may be inadequate in assessing predictive accuracy.

We remind the readers that covariate adjustment in ROC analysis in this thesis is different from using covariates in a predictive model or in incremental value analysis (which we did as part of Aim 3). When we perform covariate adjustment in ROC analysis, the classification accuracy of the marker is characterized conditional on the covariate. Traditional means of “adjusting for covariates” is usually done using logistic regression and is commonly seen in epidemiological studies.

Shock index in older patients (Aim 1 and 2)

While our results showed that the accuracy of shock index in predicting massive transfusion was not affected by increasing age, the accuracy of shock index in predicting mortality is attenuated by older age. Shock index is more accurate in younger patients than in older patients in predicting mortality outcomes. Plotting and comparing covariate-adjusted ROC curves in predicting 48-hour and in-hospital mortality at different age groups at fixed injury severity (ISS>15; severe injury) and fixed injury type (blunt trauma) using a Wald test showed that accuracy was better for younger patients (P=0.01 and P<0.001, respectively) (Figure 1.11). AUCs for adjusted ROC curves for shock index in predicting all in-hospital mortality were significantly higher in younger patients than in older patients (0.632 vs 0.589, respectively; P=0.02). A somewhat similar observation was noted in the study by Shibahashi where the AUCs of a shock index cut-off of ≥0.9 was estimated by different age groups. Shock index at a cut-off of ≥0.9 had decreasing accuracy in predicting early death in injured patients with increasing age (Shibahashi et al., 2019).

Factors or covariates, such as age, which typically affect the discriminatory performance of markers or tests are those which have different distributions of the markers by levels of the covariate among cases or those who had the outcome, in this case, among those who died. This different distribution of shock index among older and younger patients can be seen in Figure 1.2. We observed that while heart rates tended to be higher and systolic blood pressures tended to be lower among that died, (Figures 1.4, 1.5, 1.7 and 1.8), the differences in distributions between those who died and those who did not were not as pronounced in older patients. Older injured patients have increased risk of mortality following injury compared with younger patients (Caterino, Valasek, & Werman, 2010; Kuhne, Ruchholtz, Kaiser, & Nast-Kolb, 2005). This increased risk may arise from the decreased ability to adjust to increased physiologic burdens of injury from aging. Older patients also have multiple comorbidities, take medications, and have physiologic changes associated with aging. We observed in this study that older patients present with higher systolic blood pressures and lower heart rates, and higher postinjury mortality. This has been observed in previous studies (Brown et al., 2015; Zarzaur et al., 2010). We suspect however that heart rate and not so much blood pressure may be the driver of the lower accuracy of shock index in predicting mortality among older patients compared with that in younger patients. Accuracy of heart rate in predicting mortality was also lower in older patients than in younger patients.

While the differences in the distribution of shock index among different age groups, and the lower accuracy in older patients could be explained by the physiologic and pathologic processes which accompany aging, it can also be partially explained by the higher prevalence of traumatic head injury in older patients, and the hemodynamic changes that can occur during brain injury. These changes may explain why hypotension, hypertension, bradycardia and tachycardia in patients with traumatic brain injury are associated with a higher risk of death and shock. Severe trauma results in changes in systemic arterial pressure causing severe changes in cerebral blood flow leading to conditions such as hypoperfusion (brain ischemia) or hyper perfusion (e.g., hyperemia) (Czosnyka, 2009). Increased endogenous catecholamines causes vasoconstriction of peripheral vessels that elevates systemic arterial pressure (neurogenic hypertension) after traumatic brain injury leading to maintained arterial pressure even if hypovolemia exists (Kinoshita, 2004). To account for possible hemodynamic effects due to head injury, we conducted sensitivity analysis where patients with severe head injury were excluded from the cohort showed that the accuracy of shock index was still attenuated by older age and that accuracy was better in younger patients (Appendix Table A1).

While shock index was less accurate in predicting 48- and all in-hospital mortality in older trauma patients compared to younger trauma patients, accuracy of shock index in predicting massive transfusion was similar in older and younger trauma patients. These results are reflected by how among those who underwent massive transfusion, the distribution of shock index in older and younger patients were similar (Figure 2.2), while among those who died in hospital, if one compares the distribution of shock index among older and younger patients, the histograms are dissimilar (Figure 2.1). A search of the literature hasn't yielded any studies which looked at the effect of age on shock index in the prediction of massive transfusion. However, the dissertation of a member of this dissertation committee, Dr. Hu, utilized 3D-ROC method to determine threshold values for shock index in the prediction of massive transfusion in trauma patients of increasing age groups and he noted lower optimal thresholds with increasing age (P. F.-M. Hu, 2013). ROC AUCs did not seem to be different for the different age groups. We had similar results where optimal cut-offs were somewhat lower for older patients as well (0.6-0.7 vs. 0.7-0.8 for older and younger patients, respectively).

To address the under-triage that exists in elderly injured patients, the earlier 2011 revision of the NTTP guidelines recognized that a systolic blood pressure of <110 mmHg represented shock in older patients (Sasser et al., 2012). This was implemented as a special consideration in Step 4 of the guidelines. In predicting any of the outcomes Injury

Severity Score >15, ICU admission, urgent operation, or emergency department death, Brown, et al showed that systolic blood pressure of <110 mmHg had higher sensitivity but lower specificity in older and younger adult injured patients (Brown et al., 2015). In the recent 2021 update of the NTTP, systolic blood pressure of <110 mmHg cut-off for older patients was upgraded from being a special consideration to belonging to the main Mental Status and Vital Signs section (Newgard et al., 2022). The updated guidelines have also added shock index ≥1 in the form of heart rate > systolic blood pressure for adults as part of the Mental Status and Vital Signs section. Because we saw that the accuracy of shock index in predicting mortality is worse in older injured patients, we believe that there is utility in using different shock index cut-offs for older patients. In our study optimal cut-offs for shock index in predicting mortality outcomes and major interventions were lower in the elderly compared to younger adult injured patients. Shock index cut-off of ≤0.7 for older patients improves sensitivity at the expense of specificity in the prediction of all in-hospital death and massive transfusion. Shibahashi noted a similar trend of lower optimal cut-offs for shock index in predicting early death with increasing age (Shibahashi et al., 2019).

Acker, et al introduced the shock index, pediatric age adjusted for use in children (SIPA) (Acker et al., 2015). Elevated SIPA on presentation was defined as shock index greater than the maximum age adjusted shock index with cutoffs of: shock index > 1.22 (age 4–6 years), > 1.0 (age 7–12 years), and > 0.9 (age 13–16 years). This SIPA demonstrated improved prediction of severe injury, blood transfusion and in-hospital mortality in pediatric patients (Acker et al., 2017; Acker et al., 2015; Phillips et al., 2020;

Phillips et al., 2021). In our study, we used an age-specific shock index cut-off based on optimal cut-offs we obtained: ≥0.9 for <65-year-old patients and ≥0.7 for ≥65-year-old patients. When we used this age-specific shock index assignment there was an improvement in accuracy in the form of better AUCs over the use of a cut-off of ≥0.9 for all patients in predicting mortality, ICU admissions and surgery in 24 hours. There is also improvement in sensitivity with lower specificity. Utilizing different cut-offs for shock index for older and younger patients, similar to using a systolic blood pressure cut-off of <110 mmHg for older patients in NTTP guidelines may improve triage in older patients.

Comorbidities as covariates (Aim 3)

A major limitation of previous studies looking at shock index and other predictors of outcomes in trauma, in particular those impacting older patients, is that the effect of comorbidities on the accuracy of these predictors were not examined (Koch et al., 2019; Rau et al., 2016). Of particular interest are comorbidities which may have hemodynamic effects on patients. Both hyper- and hypothyroidism may present with hypertension. Hypothyroidism may present with bradycardia with hypertension (Berta et al., 2019). Thyroid disorders are also associated with higher risk of mortality (Brandt, Green, Hegedüs, & Brix, 2011).

We examined whether cardiovascular disorders, thyroid disorders, diabetes mellitus and coumadin medication affected the accuracy of shock index in predicting all in-hospital mortality and massive transfusion. ROC regression analysis in non-cases (those that did not have the outcomes) showed that diabetes mellitus seemed to have a significant effect on the adjusted ROC curve (P<0.05), indicating possible confounding of the interpretation of the ROC curve if not adjusting for diabetes in the analysis, coefficient of the ROC equation was very small, indicating a very small change. Cardiovascular disorders, thyroid disorders, and coumadin medication did not confound the accuracy of shock index in the prediction of mortality outcomes. ROC regression analysis in cases (those that had the outcomes) revealed that the accuracy of shock index did not differ between patients that had comorbidities and those that did not.

Kristensen, et al showed that old age, diabetes, and hypertension weakens the association between shock index and mortality (Kristensen et al., 2016). In traditional studies of association, one may need to show large differences in odds ratios in order to reflect differences in accuracy (M. S. Pepe et al., 2004; Ware, 2006). While the differences in odds ratios for shock index were large comparing older and younger patients, the differences in odds ratios between patients with and without diabetes, and between patients with and without hypertensions were small, indicating that there might be small differences in accuracy in predicting mortality. Kristensen's study was also conducted in a population of all emergency department admissions. In another paper looking at the association between shock index and massive transfusion and 30-day mortality, multivariable logistic regression with age and antihypertensive treatment in the model was conducted (Park et al., 2021). While results are not clear, it concluded that a shock index with a cut-off of >1 was optimal in predicting massive transfusion in older patients taking antihypertensives.

Alcohol as covariate (Aim 3)

To our knowledge, no study has examined the effect of alcohol on the predictive accuracy of shock index in the prediction of mortality in trauma patients. However, we found one study where ROC cut-offs were identified for shock index in the prediction of massive transfusion, stratifying on blood alcohol-positive or -negative status (Rau et al., 2016). Our results show that the accuracy of shock index in predicting massive transfusion and all in-hospital mortality is attenuated by the presence of blood alcohol; accuracy of shock index is better in patients who are negative for blood alcohol (ROC AUC for prediction of all in-hospital death in blood alcohol-negative and -positive patients, 0.586 and 0.569, respectively, and in predicting massive transfusion, 0.826 and 0.792, respectively). Rau, et al determined ROC cut-off value for shock index for blood alcohol-positive and -negative patients (1.05 and 0.95, respectively), and generated AUCs for these cut-offs (0.780 and 0.753, respectively) (Rau et al., 2016). Differing covariate-specific ROC curves can be explained by differing distributions of shock index by blood alcohol status among patients who died or who had massive transfusion. The differences in the distribution of shock index among patients who were positive and negative for blood alcohol may be explained by the physiologic changes that occur with acute alcohol intake.

A systematic review of randomized controlled trials comparing the acute effects of a single dose of alcohol and placebo on blood pressure and heart rate showed that while alcohol at low doses did not affect blood pressure, alcohol at medium or high doses caused decreases in blood pressure. Acute alcohol intake at any amount caused increases in heart rate (Tasnim, Tang, Musini, & Wright, 2020). Alcohol intake causes a dose-dependent effect in cardiac autonomic regulation, elevated heart rate, and delayed parasympathetic recovery (Ryan, 2002; Sagawa, 2011; Pietila, 2018) (Pietilä et al., 2018; Ryan & Howes, 2002; Sagawa et al., 2011). The effects in of alcohol on cardiac autonomic regulation occurs even with low doses of alcohol, and that being physically active and young appears to provide no protection from alcohol-induced suppression of parasympathetic regulation (Pietilä et al., 2018). Alcohol affects hemodynamic, metabolic, and inflammatory homeostasis following hemorrhage; blunts post-injury cathecolamine surge; impairs clot formation; and inhibits fibrinolysis (Hadjizacharia et al., 2011; Howard et al., 2018; Tien et al., 2006; I. J. Wang et al., 2021).

Alcohol is well known to increase the risk of injury occurrence. Gentilello conducted a systematic review and estimated that between 9% and 38% of patients admitted to emergency rooms being positive for alcohol (Gentilello, Ebel, Wickizer, Salkever, & Rivara, 2005). The rate of alcohol-positive trauma patients admitted in a study conducted in 6 Level I trauma hospitals in the USA in 2019-2020 were 32% and 39%, respectively (McGraw et al., 2021). Alcohol also increases the risk of death once a person is injured (DiMaggio, Avraham, Frangos, & Keyes, 2021). Knowing that the accuracy of shock index in predicting death and massive transfusion is affected by blood alcohol may be useful to improve clinical decision making and design of research studies looking at shock index, or vital signs as predictors of trauma outcomes. We did not look at different levels of blood alcohol in our study because we felt that any vs. no alcohol was a good starting point to explore the effect of blood alcohol on shock index. More work is needed to determine just how much how different levels of blood alcohol can affect SI accuracy.

Incremental value of covariates (Traditional “Adjusting for Covariates”) (Aim3)

Our study mainly used ROC regression analysis or covariate adjustment in ROC analysis, which is different from other studies using covariates in a predictive model as used in traditional studies of association. However, because to our knowledge the inclusion of comorbidities and alcohol in predictive models of mortality or massive transfusion have not been done, we also examined the incremental value of these covariates to the predictive ability of shock index. We examined whether age, alcohol and comorbidities “help” or contribute to the predicted probability of all in-hospital mortality and massive transfusion. We used logistic regression, the classic way of “adjusting for covariates” in ROC analysis. The combination of shock index and age, and the combination of shock index and alcohol had better accuracy in predicting all in-hospital mortality as reflected in the AUC curves over shock index alone. Combining shock index with age, alcohol or comorbidities did not improve prediction of massive transfusion in comparison to shock index alone.

It is expected that age improves the predictive performance of shock index in the prediction of mortality. Age on its own is a strong predictor of mortality in elderly patients in general. Several markers have previously been developed, incorporating age in the calculation, in attempts to improve the prediction of mortality and interventions in trauma patients, particularly in the elderly. Age-Shock Index combined age and shock index (albeit not in the form of a logistic regression model) by multiplying age and shock index (Lee, Jang, Kim, & Suh, 2020; Zarzaur et al., 2008; Zarzaur et al., 2010). For young patients, there was no difference between systolic blood pressure and shock index while for older patients, Age-Shock Index was a better predictor of 48-hour mortality compared with heart rate systolic blood pressure or shock index (Zarzaur et al., 2010). Another study explored blood pressure-age index was calculated by dividing systolic blood pressure by age (Bruijns et al., 2014). Both Age-Shock Index and Blood pressure-Age index had higher AUCs than heart rate or systolic blood pressure alone, and Age-Shock Index had higher AUCs than shock index alone (Bruijns et al., 2014).

Strengths and limitations

Our study has several strengths. The effect of covariates, particularly that of age, on the discriminatory performance of predictive markers is not commonly done in injury research. We explored whether confounding occurs in evaluating prediction accuracy of shock index in the presence of certain covariates. We also evaluated whether these covariates affect the ROC curve itself and are effect modifiers. Accuracy of shock index was lower in predicting all in-hospital mortality among those with severe injury than those with less severe injury. Several studies focusing on shock index have also excluded penetrating injuries from analyses because anatomic location of the penetrating injury carries more prognostic weight than hemodynamic stability when determining treatment (Zarzaur et al., 2008; Zarzaur et al., 2010). Cardiovascular response to injury may differ between blunt and penetrating trauma (El-Menyar et al., 2019). We found that accuracy of shock index in predicting mortality and major interventions in trauma patients was not affected by injury type.   Not evaluating the effect of comorbidities and alcohol on shock index is an often-mentioned limitation in research on shock index that our study takes into consideration. The recent systematic review of circulatory measures in trauma conducted by Newgard et al, also noted that few studies focus on older adults (Newgard et al., 2020).

Another strength of our study is that we conducted multiple sensitivity analyses. Injury Severity Score is an anatomic means of determining injury severity that is usually only available after investigation and not on presentation to ED. We also conducted ROC regression analyses using two physiologic measure of injury severity: Revised Trauma Score and Glasgow Coma Scale (Tables A4, A7). Adjusting for these measures of injury severity, accuracy of shock index in predicting mortality remained better among younger trauma patients than in older patients (Appendix Tables A4 and A7). Also, the accuracy of shock index in predicting mortality outcomes were better in patients with less severe injury severity as measured using Injury Severity Score, Revised Trauma Score or Glasgow Coma Scale. Because brain injury can also cause the hemodynamic physiological changes that may explain why accuracy is affected by age, we conducted ROC regression analysis excluding patients with severe head injury from the analysis (Appendix tables A1-A3, and A12-14). Accuracy of shock index was still better among younger injured patients when predicting mortality outcomes (Table A1).

At the suggestion of the dissertation committee, exploratory analyses were also done to examine the effect of age, alcohol and comorbidities on the predictive accuracy of Revised Trauma Score, in predicting in-hospital mortality and massive transfusion. Revised Trauma Score was kept on a continuous scale. Revised Trauma Score was a good predictor in predicting all in-hospital death (ROC AUC, 0.870), and had acceptable accuracy in predicting massive transfusion (ROC AUC 0.763). The accuracy of the Revised Trauma Score in predicting all in-hospital death and massive transfusion was affected by age. It was better in younger patients. Accuracy was not affected by blood alcohol status, thyroid disorders, and coumadin treatment. Accuracy in predicting all in-hospital death was better in patients who did not have diabetes, while accuracy in predicting massive transfusion was better in patients that did not have cardiovascular disorders, compared to those who did not have the disorders, respectively.

Our study was a single-institution one. An advantage/strength is that there is less variability in management, in data collection and in measurement of vital signs. However, the patients in the study did not include patients who were seen by EMS but were sent to non-trauma hospitals, other hospitals in the area or who were not transported to any medical institution, limiting generalizability of the results to those patients.

A possible limitation to the use of shock index in the clinical setting, as well as the interpretation of the value of shock index in predicting mortality is the possibility of increased mortality in extreme values of shock index. Several studies have shown that both hypotension and hypertension can predict mortality in injured patients (Ley et al., 2011; Odom et al., 2016), and, in patients with traumatic brain injury (Zafar et al., 2011). These motivated a study to examine how low and high shock index predicts mortality in injured patients (Odom et al., 2016) (Odom, 2016). Shock index had a U-shaped relationship with mortality in patients with isolated head injury, with increased mortality ≤0.4 and >0.8. A similar U-shaped relationship with mortality in patients with traumatic brain injury was seen with heart rate.

We also plotted the frequency of in hospital deaths (case-fatality) by shock index values (Figure 1.3). We noticed a similar bimodal relationship with deaths and shock index to that observed by Odom, et al. A higher frequency of deaths was observed among those that had shock index values ≤0.4 and >0.8 compared with those in the 0.4-0.8 shock index range. When we excluded patients with severe head injury from analyses, this bimodal relationship between shock index and frequency of deaths remained for those who were ≥65 years old. This relationship among older patients seem to be related to older patients having higher frequencies of moderate head injury, a population which was not excluded from analysis. The driver of the bimodal relationship between shock index and deaths seem to be the bimodal relationship between heart rate and frequency of death (Figure 1.6). Frequency of death seemed to rise at heart rates of below 50 beats/min, and above 100 beats/min. Excluding patients with severe head injury, the higher frequency of deaths remained only for those with higher heart rates.

In addition, we plotted frequency of massive transfusion with shock index (Figure 2.3). There seems to be a bimodal relationship, as seen with death and shock index. Frequency of deaths seemed to rise with shock index values ≤0.4 and >0.8 compared with those in the 0.4-0.8 shock index range. This relationship remained even when patients with severe head injury were excluded from analysis. This result is supported by the result of our sensitivity analyses where we saw that accuracy of shock index is attenuated by higher levels of head injury severity in predicting mortality. Shock index accuracy is better in patients with less severe head injury.

A possible approach to addressing this limitation is to look at extremes of shock index as cut-offs when examining prediction of mortality outcomes (ie, assigning ≤0.3 and ≥0.9 (or ≥0.7 for the elderly) as predictive values for shock index, and >0.3 and <0.9 as non-predictive values).

Another limitation to our study is the use of emergency department admission vital signs instead of those obtained out-of-hospital or at scene. For about 30% of admissions no scene vital signs data was available. Circulatory compensation can change over time especially after interventions such as intravenous fluid administration and vasopressors (Mutschler et al., 2013; Newgard et al., 2020). While Dihn, et al reported poor agreement between prehospital and ED recording of systolic blood pressure and heart rate in trauma patients (Dinh et al., 2013), Trust, et al reported that field systolic blood pressure and heart rate correlate well with first ED recordings (Trust et al., 2020). While it is unsure how field shock index values correlate with ED shock index, it has been reported that changing shock index values from the field to ED (delta shock index) of >0.1 is associated with increased in-hospital mortality and blood transfusion (D. K. Kim et al., 2021; Schellenberg et al., 2017).

Clinical utility and future research

We confirm other studies that shock index has better accuracy compared with heart rate or systolic blood pressure in predicting trauma outcomes. However as the recently released update to the NTTP triage guidelines note there have been few head-to-head comparisons (Newgard et al., 2022). Our study provides head-to-head comparison of shock index with systolic blood pressure and heart rate. The organized systematic review of circulatory measures to identify severe injury conducted in preparation for the updated NTTP triage guidelines reported comparisons with systolic blood pressure but not heart rate alone (Newgard et al., 2020). The updated guidelines also notes that "among five head-to-head studies comparing shock index to SBP, all favored shock index, although the quality of evidence was low" (Newgard et al., 2020; Newgard et al., 2022).

Calculating shock index may be considered difficult in the clinical setting. Shock index of >1 or > 0.9 are the most commonly accepted cut-off points for an increased risk of mortality and major interventions (Haider et al., 2016; Koch et al., 2019; Newgard et al., 2020; Newgard et al., 2010). The current update to the national guideline for the field triage of injured patients now included heart rate>systolic blood pressure, basically a shock index cut-off of >1 as new criteria because this was considered easy to calculate

(Newgard et al., 2022). If a cut-off of >0.9, or even cut-offs of >0.9 for younger adults and >0.7 for the elderly, which we suggest for improved sensitivity, are used, it can be more difficult to quickly calculate whether a patient meets this cut-off when the value of the quotient is extremely close to 0.9 or 0.7 (Kamikawa & Hayashi, 2020). The panel in charge of updating the national triage guidelines recently decided that use of the age-adjusted shock index (Shock Index Pediatric Age Adjusted (SIPAA); shock index cut-offs for certain pediatric age ranges are assigned) would be cumbersome and non-feasible for field use (Newgard et al., 2022). While this decision might also put in question the feasibility of the different cut-offs of shock index for older and younger patients, we argue that while the pediatric SIPAA has 3 shock index cut-offs, we only have 2 (below age 65 and 65+ years of age). We found using these two proposed age cutoffs led to better sensitivity in predicting all in-hospital mortality and massive transfusion. In addition, despite the utility of shock index, consensus on when and where to utilize in triage and in emergency departments has not been established (Kamikawa & Hayashi, 2020; Newgard, Lin, Eckstrom, et al., 2019).

Revised shock index measurements have been developed to improve its ability to predict mortality and resource utilization, including massive transfusion, in the general injured patient population and among the elderly. These include Age-Shock Index which we previously discussed (Lee et al., 2020; Zarzaur et al., 2008; Zarzaur et al., 2010); modified shock index which is the ratio of heart rate to mean arterial pressure (with mean arterial pressure = [(diastolic blood pressure x 2) + systolic blood pressure]/3) (Y. C. Liu et al., 2012); and reverse shock index, which is the ratio of systolic blood pressure to heart rate (Chuang et al., 2016; Kuo et al., 2016). These measurements, instead of making calculations simpler, can be more complicated and so therefore are avoided more by clinicians (Kamikawa & Hayashi, 2020).

The inherent limitations in traditional vital signs such as blood pressure and heart rate, and predictive markers derived from these such as shock index warrants the evaluation of new predictive markers for predicting mortality and interventions in trauma patients. These new predictive markers include machine learning algorithms and new vital signs such as heart rate variability, heart rate complexity (P. Hu et al., 2014; N. T. Liu, Holcomb, Wade, Batchinsky, et al., 2014; N. T. Liu, Holcomb, Wade, Darrah, & Salinas, 2014), automated analysis of pulse oximetry signals (C. F. Mackenzie et al., 2014; Shackelford et al., 2015), photopletysmograph wave forms (C. F. Mackenzie et al., 2015), and autonomous continuous noninvasive patient vital signs-based Bleeding Risk Index (Yang et al., 2021). It is noted however in the recent NTTP update that while these new markers hold promise for field triage, it is noted that more research is needed for field use (Newgard et al., 2022).

Conclusions

In conclusion, evidence from this study suggests that shock index is less accurate in the elderly in predicting mortality, and less accurate in predicting massive transfusion among patients with a positive blood alcohol potentially affecting its utility in triage and clinical management. We provide head-to-head comparison of shock index and heart rate and systolic blood pressure in the prediction of mortality and major interventions in injured patients, adjusting for covariates, in particular, age. We are the first to explore covariate adjustment using new ROC regression analyses in studying shock index in the prediction of mortality. We may be one of the very few to explore the effect of alcohol and comorbidities on the accuracy of shock index. This study highlights that the discriminatory performance of shock index and other predictive markers of trauma outcomes incorporating heart rate and blood pressure may be affected by covariates or characteristics such as age, alcohol, and injury severity.

APPENDIX

Supplemental Tables and Figures

Table A1. ROC regression analyses for effects of covariates on ROC curves for shock index in predicting mortality. Sensitivity analysis excluding severe head injury patients

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and injury severity (ISS). This analysis was conducted excluding patients with severe head injury from the cohort.

SHOCK INDEX			
Covariate	**Affects distribution in controls**	**Affects distribution in cases**	**Accuracy Better**
Death in 2 hours			
Age group	**<0.001**	0.2	
Injury type	**<0.001**	0.17	
Injury severity (ISS≤15)	**<0.001**	0.76	
Death in 48 hours			
Age group	**<0.001**	**0.03**	younger age
Injury type	**<0.001**	0.22	
Injury severity (ISS≤15)	**<0.001**	0.52	
All In-hospital death			
Age group	**<0.001**	**<0.001**	younger age
Injury type	**<0.001**	**0.03**	**blunt**
Injury severity (ISS≤15)	**<0.001**	0.14	

Table A2. ROC regression analyses for effects of covariates on ROC curves for heart rate in predicting mortality. Sensitivity analysis excluding severe head injury patients

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and injury severity (ISS). This analysis was conducted excluding patients with severe head injury from the cohort.

HEART RATE			
Covariate	**Affects distribution in controls**	**Affects distribution in cases**	**Accuracy Better**
Death in 2 hours			
Age group	**<0.001**	0.48	
Injury type	**<0.001**	0.44	
Injury severity (ISS≤15)	**<0.001**	0.82	
Death in 48 hours			
Age group	**<0.001**	**<0.01**	younger age
Injury type	**<0.001**	0.91	
Injury severity (ISS≤15)	**<0.001**	0.31	
All In-hospital death			
Age group	**<0.001**	**<0.01**	younger age
Injury type	**<0.001**	0.06	
Injury severity (ISS≤15)	<0.001	0.4	

Table A3. ROC regression analyses for effects of covariates on ROC curves for systolic blood pressure in predicting mortality. Sensitivity analysis excluding severe head injury patients

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and injury severity (ISS). This analysis was conducted excluding patients with severe head injury from the cohort.

SYSTOLIC BLOOD PRESSURE			
Covariate	**Affects distribution in controls**	**Affects distribution in cases**	**Accuracy Better**
Death in 2 hours			
Age group	**<0.001**	0.31	
Injury type	**<0.001**	0.74	
Injury severity (ISS≤15)	**<0.001**	0.48	
Death in 48 hours			
Age group	**<0.001**	0.48	
Injury type	**<0.001**	0.13	
Injury severity (ISS≤15)	**<0.001**	0.82	
All In-hospital death			
Age group	**<0.001**	0.32	
Injury type	**<0.001**	0.56	
Injury severity (ISS≤15)	**<0.001**	**<0.01**	lower severity

Table A4. ROC regression analyses for effects of covariates on ROC curves for shock index in predicting mortality. Sensitivity analysis with head injury severity as covariate

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and head injury severity

SHOCK INDEX			
Covariate	**Affects distribution in controls**	**Affects distribution in cases**	**Accuracy Better**
Death in 2 hours			
Age group	**<0.001**	0.62	
Injury type	**<0.001**	0.2	
Head injury severity	**<0.001**	**0.03**	Lower severity
Death in 48 hours			
Age group	**<0.001**	**0.003**	younger age
Injury type	**<0.001**	0.26	
Head injury severity	**<0.001**	**<0.001**	lower severity
All In-hospital death			
Age group	**<0.001**	**<0.001**	younger age
Injury type	**<0.001**	0.17	
Head injury severity	**<0.001**	**<0.001**	lower severity

Table A5. ROC regression analyses for effects of covariates on ROC curves for heart rate in predicting mortality. Sensitivity analysis with head injury severity as covariate

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and head injury severity

HEART RATE			
Covariate	**Affects distribution in controls**	**Affects distribution in cases**	**Accuracy Better**
Death in 2 hours			
Age group	**<0.001**	0.77	
Injury type	**<0.001**	0.77	
Head injury severity	**<0.001**	0.19	
Death in 48 hours			
Age group	**<0.001**	**0.01**	younger age
Injury type	**<0.001**	0.61	
Head injury severity	**<0.001**	**<0.001**	lower severity
All In-hospital death			
Age group	**<0.001**	**0.005**	younger age
Injury type	**<0.001**	0.08	
Head injury severity	**<0.001**	**<0.001**	lower severity

Table A6. ROC regression analyses for effects of covariates on ROC curves for systolic blood pressure in predicting mortality. Sensitivity analysis with head injury severity as covariate

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and head injury severity

SYSTOLIC BLOOD PRESSURE			
Covariate	**Affects distribution in controls**	**Affects distribution in cases**	**Accuracy Better**
Death in 2 hours			
Age group	**<0.001**	0.2	
Injury type	**<0.001**	0.24	
Head Injury severity	**<0.001**	0.14	
Death in 48 hours			
Age group	**<0.001**	**0.003**	younger age
Injury type	**<0.001**	0.26	
Head Injury severity	**<0.001**	**<0.001**	lower severity
All In-hospital death			
Age group	**<0.001**	0.13	
Injury type	**<0.001**	0.5	
Head Injury severity	**<0.001**	**<0.001**	lower severity

Table A7. ROC regression analyses for effects of covariates on ROC curves for shock index in predicting mortality. Sensitivity analysis with RTS as covariate

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and injury severity based on revised trauma score

SHOCK INDEX			
Covariate	**Affects distribution in controls**	**Affects distribution in cases**	**Accuracy Better**
Death in 2 hours			
Age group	**<0.001**	0.72	
Injury type	**<0.001**	0.23	
Severe injury (RTS≤8)	**<0.001**	0.06	
Death in 48 hours			
Age group	**<0.001**	**0.07**	younger age
Injury type	**<0.001**	0.22	
Severe injury (RTS≤8)	**<0.001**	**<0.01**	lower severity
All In-hospital death			
Age group	**<0.001**	**<0.001**	younger age
Injury type	**<0.001**	0.11	
Severe injury (RTS≤8)	**<0.001**	0.69	

Table A8. ROC regression analyses for effects of covariates on ROC curves for heart rate in predicting mortality. Sensitivity analysis with RTS as covariate

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and injury severity based on revised trauma score

HEART RATE

Covariate	Affects distribution in controls	Affects distribution in cases	Accuracy Better
Death in 2 hours			
Age group	**<0.001**	0.81	
Injury type	**<0.001**	0.81	
Severe injury (RTS≤8)	**<0.001**	0.32	
Death in 48 hours			
Age group	**<0.001**	**0.04**	younger age
Injury type	**<0.001**	0.52	
Severe injury (RTS≤8)	**0.04**	**<0.01**	lower severity
All In-hospital death			
Age group	**<0.001**	**<0.001**	younger age
Injury type	**<0.001**	0.07	
Severe injury (RTS≤8)	**<0.001**	0.68	

Table A9. ROC regression analyses for effects of covariates on ROC curves for systolic blood pressure in predicting mortality. Sensitivity analysis with RTS as covariate

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and injury severity based on revised trauma score

SYSTOLIC BLOOD PRESSURE			
Covariate	**Affects distribution in controls**	**Affects distribution in cases**	**Accuracy Better**
Death in 2 hours			
Age group	**<0.001**	0.16	
Injury type	**<0.001**	0.26	
Severe injury (RTS≤8)	0.09	0.14	
Death in 48 hours			
Age group	**<0.001**	0.36	
Injury type	**<0.001**	0.33	
Injury severity	**<0.001**	0.76	
All In-hospital death			
Age group	**<0.001**	0.13	
Injury type	**<0.001**	0.5	
Injury severity	**<0.001**	**0.02**	lower severity

Table A10. ROC regression analyses for effects of covariates on ROC curves for shock index in predicting major interventions. Sensitivity analysis excluding severe head injury patients

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and injury severity (ISS). This analysis conducted excluding patients with severe head injury from the cohort.

SHOCK INDEX

Covariate	**Affects distribution in controls**	**Affects distribution in cases**	**Accuracy Better**
ICU Admission			
Age group	**<0.001**	**<0.01**	younger age
Injury type	**<0.001**	0.33	
Injury severity (ISS≤15)	**<0.001**	0.76	
Surgery in the first 24 hours			
Age group	**<0.001**	0.69	
Injury type	**<0.001**	0.64	
Injury severity (ISS≤15)	**<0.001**	**0.02**	lower severity
Massive Transfusion			
Age group	**<0.001**	0.8	
Injury type	**<0.001**	0.4	
Injury severity (ISS≤15)	**<0.001**	0.02	lower severity

Table A11. ROC regression analyses for effects of covariates on ROC curves for heart rate in predicting major interventions. Sensitivity analysis excluding severe head injury patients

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and injury severity (ISS). This analysis conducted excluding patients with severe head injury from the cohort.

HEART RATE			
Covariate	**Affects distribution in controls**	**Affects distribution in cases**	**Accuracy Better**
ICU Admission			
Age group	**<0.001**	**<0.01**	younger age
Injury type	**<0.001**	0.18	
Injury severity (ISS≤15)	**<0.001**	**0.75**	**lower severity**
Surgery in the first 24 hours			
Age group	**<0.001**	0.91	
Injury type	**<0.001**	0.6	
Injury severity (ISS≤15)	**<0.001**	0.52	
Massive Transfusion			
Age group	**<0.001**	**0.02**	younger age
Injury type	**<0.001**	0.41	
Injury severity (ISS≤15)	**<0.001**	**<0.01**	lower severity
Massive Transfusion or Death in 24 hours			
Age group	**<0.001**	**<0.01**	younger age
Injury type	**<0.001**	0.48	
Injury severity (ISS≤15)	**<0.001**	**0.03**	lower severity

Table A12. ROC regression analyses for effects of covariates on ROC curves for systolic blood pressure in predicting major interventions. Sensitivity analysis excluding severe head injury patients

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and injury severity (ISS). This analysis conducted excluding patients with severe head injury from the cohort.

BLOOD PRESSURE			
Covariate	**Affects distribution in controls**	**Affects distribution in cases**	**Accuracy Better**
ICU Admission			
Age group	**<0.001**	0.07	
Injury type	**<0.001**	0.07	
Injury severity (ISS≤15)	**<0.001**	0.42	
Surgery in the first 24 hours			
Age group	**<0.001**	0.23	
Injury type	**<0.001**	0.98	
Injury severity (ISS≤15)	**<0.001**	**0.04**	lower severity
Massive Transfusion			
Age group	**<0.001**	**<0.001**	older
Injury type	**<0.001**	0.06	
Injury severity (ISS≤15)	**<0.001**	**<0.001**	lower severity
Massive Transfusion or Death in 24 hours			
Age group	**<0.001**	0.84	0.11
Injury type	**<0.001**	0.48	
Injury severity (ISS≤15)	**0.012**	**0.02**	lower severity

Table A13. ROC regression analyses for effects of covariates on ROC curves for shock index in predicting major interventions. Sensitivity analysis with head injury severity as covariate

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and head injury severity

SHOCK INDEX			
Covariate	**Affects distribution in controls**	**Affects distribution in cases**	**Accuracy Better**
ICU Admission			
Age group	**<0.001**	**<0.001**	younger age
Injury type	**<0.001**	0.95	
Head injury severity	**<0.001**	**<0.001**	lower severity
Surgery in the first 24 hours			
Age group	**<0.001**	0.51	
Injury type	**<0.001**	0.66	
Head injury severity	**<0.001**	0.72	
Massive Transfusion			
Age group	**<0.001**	0.227	
Injury type	**<0.001**	0.063	
Head injury severity	**<0.001**	0.644	
Massive Transfusion or Death in 24 hours			
Age group	**<0.001**	**<0.001**	younger age
Injury type	**<0.001**	**<0.05**	blunt trauma
Head injury severity	**<0.001**	**<0.001**	lower severity

Table A14. ROC regression analyses for effects of covariates on ROC curves for heart rate in predicting major interventions. Sensitivity analysis with head injury severity as covariate

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and head injury severity

HEART RATE			
Covariate	**Affects distribution in controls**	**Affects distribution in cases**	**Accuracy Better**
ICU Admission			
Age group	**<0.001**	**<0.001**	younger age
Injury type	**<0.001**	0.26	
Head injury severity	**<0.001**	**<0.001**	lower severity
Surgery in the first 24 hours			
Age group	**<0.001**	0.957	
Injury type	**<0.001**	0.907	
Head injury severity	**<0.001**	0.269	
Massive Transfusion			
Age group	**<0.001**	**0.02**	younger age
Injury type	**<0.001**	0.18	
Head injury severity	**<0.001**	0.01	lower severity
Massive Transfusion or Death in 24 hours			
Age group	**<0.001**	**<0.001**	younger age
Injury type	**<0.001**	0.15	
Head injury severity	**<0.001**	**<0.001**	lower severity

Table A15. ROC regression analyses for effects of covariates on ROC curves for systolic blood pressure in predicting major interventions. Sensitivity analysis with head injury severity as covariate

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and head injury severity

BLOOD PRESSURE

Covariate	Affects distribution in controls	Affects distribution in cases	Accuracy Better
ICU Admission			
Age group	**<0.001**	0.84	
Injury type	**<0.001**	0.34	
Head injury severity	**<0.001**	**<0.001**	lower severity
Surgery in the first 24 hours			
Age group	**<0.001**	0.19	
Injury type	**<0.001**	0.91	
Head injury severity	**<0.001**	0.18	
Massive Transfusion			
Age group	**<0.001**	**<0.001**	older
Injury type	**<0.001**	**0.03**	blunt trauma
Head injury severity	**0.012**	0.88	
Massive Transfusion or Death in 24 hours			
Age group	**<0.001**	**0.88**	
Injury type	**<0.001**	**0.08**	
Head injury severity	**0.012**	**<0.001**	lower severity

Table A16. ROC regression analyses for effects of covariates on ROC curves for shock index in predicting major interventions. Sensitivity analysis with RTS as covariate

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and injury severity based on revised trauma score

SHOCK INDEX			
Covariate	**Affects distribution in controls**	**Affects distribution in cases**	**Accuracy Better**
ICU Admission			
Age group	**<0.001**	**<0.001**	younger age
Injury type	**<0.001**	0.73	
Severe injury (RTS≤8)	**<0.001**	0.16	
Surgery in the first 24 hours			
Age group	**<0.001**	0.48	
Injury type	**<0.001**	0.63	
Severe injury (RTS≤8)	**<0.001**	0.74	
Massive Transfusion			
Age group	**<0.001**	0.32	
Injury type	**<0.001**	0.08	
Severe injury (RTS≤8)	0.07	0.09	
Massive Transfusion or Death in 24 hours			
Age group	**<0.001**	**<0.001**	younger age
Injury type	**<0.001**	0.06	
Severe injury (RTS≤8)	**<0.001**	0.53	

Table A17. ROC regression analyses for effects of covariates on ROC curves for heart rate in predicting major interventions. Sensitivity analysis with RTS as covariate

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and injury severity based on revised trauma score

HEART RATE			
Covariate	**Affects distribution in controls**	**Affects distribution in cases**	**Accuracy Better**
ICU Admission			
Age group	**<0.001**	**<0.01**	younger age
Injury type	**<0.001**	0.21	
Severe injury (RTS≤8)	0.22	0.13	
Surgery in the first 24 hours			
Age group	**<0.001**	0.90	
Injury type	**<0.001**	0.93	
Severe injury (RTS≤8)	**<0.001**	0.31	
Massive Transfusion			
Age group	**<0.001**	**0.02**	younger age
Injury type	**<0.001**	0.20	
Severe injury (RTS≤8)	0.25	0.12	
Massive Transfusion or Death in 24 hours			
Age group	**<0.001**	**<0.001**	younger age
Injury type	**<0.001**	0.19	
Severe injury (RTS≤8)	**<0.001**	**<0.01**	lower severity

Table A18. ROC regression analyses for effects of covariates on ROC curves for systolic blood pressure in predicting major interventions. Sensitivity analysis with RTS as covariate

Modeling the distribution of shock index among cases (those that had the outcome of interest) and controls (those that did not have the outcome of interest) as a function of covariates, age, injury type and injury severity based on revised trauma score

BLOOD PRESSURE			
Covariate	**Affects distribution in controls**	**Affects distribution in cases**	**Accuracy Better**
ICU Admission			
Age group	**<0.001**	0.15	
Injury type	**<0.001**	0.16	
Severe injury (RTS≤8)	**<0.001**	0.39	
Surgery in the first 24 hours			
Age group	**<0.001**	0.18	
Injury type	**<0.001**	0.99	
Severe injury (RTS≤8)	**<0.001**	0.97	
Massive Transfusion			
Age group	**<0.001**	**<0.001**	older
Injury type	**<0.001**	**0.04**	Blunt injury
Severe injury (RTS≤8)	0.09	0.11	
Massive Transfusion or Death in 24 hours			
Age group	**<0.001**	0.78	
Injury type	**<0.001**	0.09	
Severe injury (RTS≤8)	**0.012**	0.40	

Table A19. Sensitivity and specificity for cut-offs for shock index in predicting in-hospital death

Cutpoint	**All patients**		**<65 years**		**≥65 years**	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
≥0.5	79.3%	13.6%	84.2%	10.4%	72.8%	32.5%
≥0.6	64.9%	34.4%	72.4%	30.4%	55.0%	58.5%
≥0.7	53.1%	59.0%	62.9%	55.8%	40.0%	77.9%
≥0.8	40.7%	78.4%	50.4%	76.7%	27.7%	88.4%
≥0.9	32.5%	89.6%	42.3%	88.8%	19.4%	94.7%
≥1.0	25.4%	95.0%	35.2%	64.6%	12.2%	97.2%
≥1.1	19.0%	97.2%	27.7%	97.0%	7.4%	98.4%
≥1.2	14.4%	98.4%	20.8%	98.3%	5.8%	99.0%

Table A20. Sensitivity and specificity for cut-offs for shock index in predicting massive transfusion

Cutpoint	**All patients**		**<65 years**		**≥65 years**	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
≥0.5	95.5%	14.0%	96.2%	10.7%	90.8%	32.6%
≥0.6	89.8%	35.1%	90.6%	30.9%	84.2%	58.4%
≥0.7	81.7%	59.8%	82.7%	56.6%	74.2%	77.7%
≥0.8	69.4%	79.2%	70.2%	77.6%	63.3%	88.2%
≥0.9	58.7%	90.3%	60.1%	89.6%	48.3%	94.2%
≥1.0	45.6%	95.5%	47.6%	95.3%	30.8%	97.0%
≥1.1	36.4%	97.7%	38.5%	97.6%	20.8%	98.4%
≥1.2	27.5%	98.7%	28.9%	98.7%	17.5%	99.0%

REFERENCES

Acker, S. N., Bredbeck, B., Partrick, D. A., Kulungowski, A. M., Barnett, C. C., & Bensard, D. D. (2017). Shock index, pediatric age-adjusted (SIPA) is more accurate than age-adjusted hypotension for trauma team activation. *Surgery, 161*(3), 803-807. doi:10.1016/j.surg.2016.08.050

Acker, S. N., Ross, J. T., Partrick, D. A., Tong, S., & Bensard, D. D. (2015). Pediatric specific shock index accurately identifies severely injured children. *J Pediatr Surg, 50*(2), 331-334. doi:10.1016/j.jpedsurg.2014.08.009

Allgöwer, M., & Burri, C. (1967). Shock index. *Dtsch Med Wochenschr, 92*(43), 1947-1950. doi:10.1055/s-0028-1106070

Alonzo, T. A., & Pepe, M. S. (2002). Distribution-free ROC analysis using binary regression techniques. *Biostatistics, 3*(3), 421-432. doi:10.1093/biostatistics/3.3.421

Alshibani, A., Alharbi, M., & Conroy, S. (2021). Under-triage of older trauma patients in prehospital care: a systematic review. *Eur Geriatr Med, 12*(5), 903-919. doi:10.1007/s41999-021-00512-5

Alshibani, A., Banerjee, J., Lecky, F., Coats, T. J., Alharbi, M., & Conroy, S. (2021). New Horizons in Understanding Appropriate Prehospital Identification and Trauma Triage for Older Adults. *Open Access Emerg Med, 13*, 117-135. doi:10.2147/oaem.S297850

Alshibani, A., Singler, B., & Conroy, S. (2021). Towards improving prehospital triage for older trauma patients. *Z Gerontol Geriatr, 54*(2), 125-129. doi:10.1007/s00391-021-01844-4

Ataguba, J. E., Bloom, D. E., & Scott, A. J. (2021). A timely call to establish an international convention on the rights of older people. *Lancet Healthy Longev, 2*(9), e540-e542. doi:10.1016/s2666-7568(21)00178-1

Baker, S. P., O'Neill, B., Haddon, W., Jr., & Long, W. B. (1974). The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma, 14*(3), 187-196.

Banks, S. E., & Lewis, M. C. (2013). Trauma in the elderly: considerations for anesthetic management. *Anesthesiol Clin, 31*(1), 127-139. doi:10.1016/j.anclin.2012.11.004

Bardes, J. M., Benjamin, E., Schellenberg, M., Inaba, K., & Demetriades, D. (2019). Old Age With a Traumatic Mechanism of Injury Should Be a Trauma Team Activation Criterion. *J Emerg Med, 57*(2), 151-155. doi:10.1016/j.jemermed.2019.04.003

Baxt, W. G., & Moody, P. (1987). The impact of advanced prehospital emergency care on the mortality of severely brain-injured patients. *J Trauma, 27*(4), 365-369. doi:10.1097/00005373-198704000-00004

Berger, T., Green, J., Horeczko, T., Hagar, Y., Garg, N., Suarez, A., . . . Shapiro, N. (2013). Shock index and early recognition of sepsis in the emergency department: pilot study. *West J Emerg Med, 14*(2), 168-174. doi:10.5811/westjem.2012.8.11546

Berta, E., Lengyel, I., Halmi, S., Zrínyi, M., Erdei, A., Harangi, M., . . . Bodor, M. (2019). Hypertension in Thyroid Disorders. *Front Endocrinol (Lausanne), 10*, 482. doi:10.3389/fendo.2019.00482

Birkhahn, R. H., Gaeta, T. J., Terry, D., Bove, J. J., & Tloczkowski, J. (2005). Shock index in diagnosing early acute hypovolemia. *Am J Emerg Med, 23*(3), 323-326. doi:10.1016/j.ajem.2005.02.029

Bolorunduro, O. B., Villegas, C., Oyetunji, T. A., Haut, E. R., Stevens, K. A., Chang, D. C., . . . Haider, A. H. (2011). Validating the Injury Severity Score (ISS) in different populations: ISS predicts mortality better among Hispanics and females. *J Surg Res, 166*(1), 40-44. doi:10.1016/j.jss.2010.04.012

Bonne, S., & Schuerer, D. J. (2013). Trauma in the older adult: epidemiology and evolving geriatric trauma principles. *Clin Geriatr Med, 29*(1), 137-150. doi:10.1016/j.cger.2012.10.008

Boulton, A. J., Peel, D., Rahman, U., & Cole, E. (2021). Evaluation of elderly specific pre-hospital trauma triage criteria: a systematic review. *Scand J Trauma Resusc Emerg Med, 29*(1), 127. doi:10.1186/s13049-021-00940-z

Boyko, E. J., & Alderman, B. W. (1990). The use of risk factors in medical diagnosis: opportunities and cautions. *J Clin Epidemiol, 43*(9), 851-858. doi:10.1016/0895-4356(90)90068-z

Brandt, F., Green, A., Hegedüs, L., & Brix, T. H. (2011). A critical review and meta-analysis of the association between overt hyperthyroidism and mortality. *Eur J Endocrinol, 165*(4), 491-497. doi:10.1530/eje-11-0299

Brekke, I. J., Puntervoll, L. H., Pedersen, P. B., Kellett, J., & Brabrand, M. (2019). The value of vital sign trends in predicting and monitoring clinical deterioration: A systematic review. *PLoS One, 14*(1), e0210875. doi:10.1371/journal.pone.0210875

Brown, J. B., Gestring, M. L., Forsythe, R. M., Stassen, N. A., Billiar, T. R., Peitzman, A. B., & Sperry, J. L. (2015). Systolic blood pressure criteria in the National Trauma Triage Protocol for geriatric trauma: 110 is the new 90. *J Trauma Acute Care Surg, 78*(2), 352-359. doi:10.1097/ta.0000000000000523

Bruijns, S. R., Guly, H. R., Bouamra, O., Lecky, F., & Wallis, L. A. (2014). The value of the difference between ED and prehospital vital signs in predicting outcome in trauma. *Emerg Med J, 31*(7), 579-582. doi:10.1136/emermed-2012-202271

Campbell, J. W., Degolia, P. A., Fallon, W. F., & Rader, E. L. (2009). In harm's way: Moving the older trauma patient toward a better outcome. *Geriatrics, 64*(1), 8-13.

Cancio, L. C., Wade, C. E., West, S. A., & Holcomb, J. B. (2008). Prediction of mortality and of the need for massive transfusion in casualties arriving at combat support hospitals in Iraq. *J Trauma, 64*(2 Suppl), S51-55; discussion S55-56. doi:10.1097/TA.0b013e3181608c21

Candefjord, S., Asker, L., & Caragounis, E. C. (2022). Mortality of trauma patients treated at trauma centers compared to non-trauma centers in Sweden: a retrospective study. *Eur J Trauma Emerg Surg, 48*(1), 525-536. doi:10.1007/s00068-020-01446-6

Cannon, C. M., Braxton, C. C., Kling-Smith, M., Mahnken, J. D., Carlton, E., & Moncure, M. (2009). Utility of the shock index in predicting mortality in traumatically injured patients. *J Trauma*, *67*(6), 1426-1430. doi:10.1097/TA.0b013e3181bbf728

Cannon, J. W. (2018). Hemorrhagic Shock. *N Engl J Med, 378*(4), 370-379. doi:10.1056/NEJMra1705649

Caterino, J. M., Brown, N. V., Hamilton, M. W., Ichwan, B., Khaliqdina, S., Evans, D. C., . . . Shah, M. N. (2016). Effect of Geriatric-Specific Trauma Triage Criteria on Outcomes in Injured Older Adults: A Statewide Retrospective Cohort Study. *J Am Geriatr Soc*, *64*(10), 1944-1951. doi:10.1111/jgs.14376

Caterino, J. M., Valasek, T., & Werman, H. A. (2010). Identification of an age cutoff for increased mortality in patients with elderly trauma. *Am J Emerg Med, 28*(2), 151-158. doi:10.1016/j.ajem.2008.10.027

CDC. (2021). Web-based Injury Statistics Query and Reporting System (WISQARS). Retrieved from https://www.cdc.gov/injury/wisqars/index.html

Champion, H. R., Sacco, W. J., Copes, W. S., Gann, D. S., Gennarelli, T. A., & Flanagan, M. E. (1989). A revision of the Trauma Score. *J Trauma, 29*(5), 623-629. doi:10.1097/00005373-198905000-00017

Chester, J. G., & Rudolph, J. L. (2011). Vital signs in older patients: age-related changes. *J Am Med Dir Assoc, 12*(5), 337-343. doi:10.1016/j.jamda.2010.04.009

Choi, J., Carlos, G., Nassar, A. K., Knowlton, L. M., & Spain, D. A. (2021). The impact of trauma systems on patient outcomes. *Curr Probl Surg, 58*(1), 100849. doi:10.1016/j.cpsurg.2020.100849

Chuang, J. F., Rau, C. S., Wu, S. C., Liu, H. T., Hsu, S. Y., Hsieh, H. Y., . . . Hsieh, C. H. (2016). Use of the reverse shock index for identifying high-risk patients in a five-level triage system. *Scand J Trauma Resusc Emerg Med*, *24*, 12. doi:10.1186/s13049-016-0208-5

Damme, C. D., Luo, J., & Buesing, K. L. (2016). Isolated prehospital hypotension correlates with injury severity and outcomes in patients with trauma. *Trauma Surg Acute Care Open, 1*(1), e000013. doi:10.1136/tsaco-2016-000013

DeLong, E. R., DeLong, D. M., & Clarke-Pearson, D. L. (1988). Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics, 44*(3), 837-845. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/3203132

DeMuro, J. P., Simmons, S., Jax, J., & Gianelli, S. M. (2013). Application of the Shock Index to the prediction of need for hemostasis intervention. *Am J Emerg Med, 31*(8), 1260-1263. doi:10.1016/j.ajem.2013.05.027

DiMaggio, C. J., Avraham, J. B., Frangos, S. G., & Keyes, K. (2021). The role of alcohol and other drugs on emergency department traumatic injury mortality in the United States. *Drug Alcohol Depend*, *225*, 108763. doi:10.1016/j.drugalcdep.2021.108763

Dinh, M. M., Oliver, M., Bein, K., Muecke, S., Carroll, T., Veillard, A. S., . . . Ivers, R. (2013). Level of agreement between prehospital and emergency department vital signs in trauma patients. *Emerg Med Australas, 25*(5), 457-463. doi:10.1111/1742-6723.12126

Eastridge, B. J., Holcomb, J. B., & Shackelford, S. (2019). Outcomes of traumatic hemorrhagic shock and the epidemiology of preventable death from injury. *Transfusion, 59*(S2), 1423-1428. doi:10.1111/trf.15161

El-Menyar, A., Jabbour, G., Asim, M., Abdelrahman, H., Mahmood, I., & Al-Thani, H. (2019). Shock index in patients with traumatic solid organ injury as a predictor of massive blood transfusion protocol activation. *Inj Epidemiol, 6*, 41. doi:10.1186/s40621-019-0218-7

Federal Interagency Forum on Aging Related Statistics. (2021). Older Americans 2020. Retrieved from https://agingstats.gov/docs/LatestReport/OA20_508_10142020.pdf

Feng, Z. (2010). Classification versus association models: should the same methods apply? *Scand J Clin Lab Invest Suppl, 242*, 53-58. doi:10.3109/00365513.2010.493387

Fuller, G., Pandor, A., Essat, M., Sabir, L., Buckley-Woods, H., Chatha, H., . . . Turner, J. (2021). Diagnostic accuracy of prehospital triage tools for identifying major trauma in elderly injured patients: A systematic review. *J Trauma Acute Care Surg, 90*(2), 403-412. doi:10.1097/ta.0000000000003039

Gentilello, L. M., Ebel, B. E., Wickizer, T. M., Salkever, D. S., & Rivara, F. P. (2005). Alcohol interventions for trauma patients treated in emergency departments and hospitals: a cost benefit analysis. *Ann Surg, 241*(4), 541-550. doi:10.1097/01.sla.0000157133.80396.1c

Gonen, M. (2007). *Analyzing Receiver Operating Characteristic Curves with SAS*. Cary, NC, USA: SAS Institute Inc.

Grimme, K., Pape, H. C., Probst, C., Seelis, M., Sott, A., Harwood, P., . . . Allgöwer, M. (2005). Calculation of Different Triage Scores Based on the German Trauma

Registry. *European Journal of Trauma, 31*(5), 480-487. doi:10.1007/s00068-005-2026-8

Gruen, R. L., Brohi, K., Schreiber, M., Balogh, Z. J., Pitt, V., Narayan, M., & Maier, R. V. (2012). Haemorrhage control in severely injured patients. *Lancet, 380*(9847), 1099-1108. doi:10.1016/s0140-6736(12)61224-0

Guly, H. R., Bouamra, O., Spiers, M., Dark, P., Coats, T., & Lecky, F. E. (2011). Vital signs and estimated blood loss in patients with major trauma: testing the validity of the ATLS classification of hypovolaemic shock. *Resuscitation, 82*(5), 556-559. doi:10.1016/j.resuscitation.2011.01.013

Haas, B., Gomez, D., Zagorski, B., Stukel, T. A., Rubenfeld, G. D., & Nathens, A. B. (2010). Survival of the fittest: the hidden cost of undertriage of major trauma. *J Am Coll Surg, 211*(6), 804-811. doi:10.1016/j.jamcollsurg.2010.08.014

Habibzadeh, F., Habibzadeh, P., & Yadollahie, M. (2016). On determining the most appropriate test cut-off value: the case of tests with continuous results. *Biochem Med (Zagreb), 26*(3), 297-307. doi:10.11613/bm.2016.034

Hadjizacharia, P., O'Keeffe, T., Plurad, D. S., Green, D. J., Brown, C. V., Chan, L. S., . . . Rhee, P. (2011). Alcohol exposure and outcomes in trauma patients. *Eur J Trauma Emerg Surg, 37*(2), 169-175. doi:10.1007/s00068-010-0038-5

Hagiwara, A., Kimura, A., Kato, H., Mizushima, Y., Matsuoka, T., Takeda, M., . . . Sasaki, J. (2010). Hemodynamic reactions in patients with hemorrhagic shock from blunt trauma after initial fluid therapy. *J Trauma, 69*(5), 1161-1168. doi:10.1097/TA.0b013e3181d27c94

Haider, A. A., Azim, A., Rhee, P., Kulvatunyou, N., Ibraheem, K., Tang, A., . . . Joseph, B. (2016). Substituting systolic blood pressure with shock index in the National Trauma Triage Protocol. *J Trauma Acute Care Surg, 81*(6), 1136-1141. doi:10.1097/TA.0000000000001205

Hajian-Tilaki, K. (2014). Sample size estimation in diagnostic test studies of biomedical informatics. *J Biomed Inform, 48*, 193-204. doi:10.1016/j.jbi.2014.02.013

Hashmi, A., Ibrahim-Zada, I., Rhee, P., Aziz, H., Fain, M. J., Friese, R. S., & Joseph, B. (2014). Predictors of mortality in geriatric trauma patients: a systematic review and meta-analysis. *J Trauma Acute Care Surg, 76*(3), 894-901. doi:10.1097/TA.0b013e3182ab0763

Heffernan, D. S., Thakkar, R. K., Monaghan, S. F., Ravindran, R., Adams, C. A., Jr., Kozloff, M. S., . . . Cioffi, W. G. (2010). Normal presenting vital signs are unreliable in geriatric blunt trauma victims. *J Trauma, 69*(4), 813-820. doi:10.1097/TA.0b013e3181f41af8

Hietanen, C. (2020). Calculated decisions: Shock index, pediatric age-adjusted (SIPA). *Pediatr Emerg Med Pract, 17*(Suppl 1), Cd6-cd7.

Hoo, Z. H., Candlish, J., & Teare, D. (2017). What is an ROC curve? *Emerg Med J, 34*(6), 357-359. doi:10.1136/emermed-2017-206735

Hosmer, D. W., Lemeshow, S., & Sturdivant, R. X. (2013). *Applied Logistic Regression* (Third Edition ed.): John Wiley & Sons, Inc.

Howard, B. M., Kornblith, L. Z., Redick, B. J., Conroy, A. S., Nelson, M. F., Calfee, C. S., . . . Cohen, M. J. (2018). Exposing the bidirectional effects of alcohol on coagulation in trauma: Impaired clot formation and decreased fibrinolysis in rotational thromboelastometry. *J Trauma Acute Care Surg, 84*(1), 97-103. doi:10.1097/ta.0000000000001716

Hu, P., Galvagno, S. M., Jr., Sen, A., Dutton, R., Jordan, S., Floccare, D., . . . Mackenzie, C. (2014). Identification of dynamic prehospital changes with continuous vital signs acquisition. *Air Med J, 33*(1), 27-33. doi:10.1016/j.amj.2013.09.003

Hu, P. F.-M. (2013). Three Dimensional Receiver Operating Characteristic Analysis in Predicting Trauma Patient Outcomes Using Vital Signs Signals.

Inacio, V., & Rodríguez-Álvarez, M. X. (2022). The covariate-adjusted ROC Curve: The Concept and Its Importance, Review of Inferential Methods, and a New Bayesian Estimator. *Statist. Sci. , 34*(4), 541-561. Retrieved from https://www.imstat.org/publications/sts/sts_37_4/sts_37_4.pdf

Janes, H., Longton, G., & Pepe, M. (2009). Accommodating Covariates in ROC Analysis. *Stata J, 9*(1), 17-39.

Janes, H., & Pepe, M. S. (2008). Adjusting for covariates in studies of diagnostic, screening, or prognostic markers: an old concept in a new setting. *Am J Epidemiol, 168*(1), 89-97. doi:10.1093/aje/kwn099

Janes, H., & Pepe, M. S. (2009). Adjusting for covariate effects on classification accuracy using the covariate-adjusted receiver operating characteristic curve. *Biometrika, 96*(2), 371-382. doi:10.1093/biomet/asp002

Javali, R. H., Krishnamoorthy, Patil, A., Srinivasarangan, M., Suraj, & Sriharsha. (2019). Comparison of Injury Severity Score, New Injury Severity Score, Revised Trauma Score and Trauma and Injury Severity Score for Mortality Prediction in

Elderly Trauma Patients. *Indian J Crit Care Med, 23*(2), 73-77. doi:10.5005/jp-journals-10071-23120

Kamikawa, Y., & Hayashi, H. (2020). Equivalency between the shock index and subtracting the systolic blood pressure from the heart rate: an observational cohort study. *BMC Emerg Med, 20*(1), 87. doi:10.1186/s12873-020-00383-2

Kattan, M. W. (2003). Judging new markers by their ability to improve predictive accuracy. *J Natl Cancer Inst, 95*(9), 634-635. doi:10.1093/jnci/95.9.634

Kauvar, D. S., Lefering, R., & Wade, C. E. (2006). Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. *J Trauma, 60*(6 Suppl), S3-11. doi:10.1097/01.ta.0000199961.02677.19

Keller, A. S., Kirkland, L. L., Rajasekaran, S. Y., Cha, S., Rady, M. Y., & Huddleston, J. M. (2010). Unplanned transfers to the intensive care unit: the role of the shock index. *J Hosp Med, 5*(8), 460-465. doi:10.1002/jhm.779

Keller, J. M., Sciadini, M. F., Sinclair, E., & O'Toole, R. V. (2012). Geriatric trauma: demographics, injuries, and mortality. *J Orthop Trauma, 26*(9), e161-165. doi:10.1097/BOT.0b013e3182324460

Kheirbek, T., Martin, T. J., Cao, J., Hall, B. M., Lueckel, S., & Adams, C. A. (2021). Prehospital shock index outperforms hypotension alone in predicting significant injury in trauma patients. *Trauma Surg Acute Care Open, 6*(1), e000712. doi:10.1136/tsaco-2021-000712

Kim, D., & Jin, B. T. (2022). Development and Comparative Performance of Physiologic Monitoring Strategies in the Emergency Department. *JAMA Netw Open, 5*(9), e2233712. doi:10.1001/jamanetworkopen.2022.33712

Kim, D. K., Jeong, J., Shin, S. D., Song, K. J., Hong, K. J., Ro, Y. S., . . . Jamaluddin, S. F. (2021). Association between prehospital field to emergency department delta shock index and in-hospital mortality in patients with torso and extremity trauma: A multinational, observational study. *PLoS One, 16*(10), e0258811. doi:10.1371/journal.pone.0258811

Kim, S. Y., Hong, K. J., Shin, S. D., Ro, Y. S., Ahn, K. O., Kim, Y. J., & Lee, E. J. (2016). Validation of the Shock Index, Modified Shock Index, and Age Shock Index for Predicting Mortality of Geriatric Trauma Patients in Emergency Departments. *J Korean Med Sci, 31*(12), 2026-2032. doi:10.3346/jkms.2016.31.12.2026

Koch, E., Lovett, S., Nghiem, T., Riggs, R. A., & Rech, M. A. (2019). Shock index in the emergency department: utility and limitations. *Open Access Emerg Med, 11,* 179-199. doi:10.2147/oaem.S178358

Kodadek, L. M., Selvarajah, S., Velopulos, C. G., Haut, E. R., & Haider, A. H. (2015). Undertriage of older trauma patients: is this a national phenomenon? *J Surg Res, 199*(1), 220-229. doi:10.1016/j.jss.2015.05.017

Kristensen, A. K., Holler, J. G., Hallas, J., Lassen, A., & Shapiro, N. I. (2016). Is Shock Index a Valid Predictor of Mortality in Emergency Department Patients With Hypertension, Diabetes, High Age, or Receipt of β- or Calcium Channel

Blockers? *Ann Emerg Med, 67*(1), 106-113.e106. doi:10.1016/j.annemergmed.2015.05.020

Kuhne, C. A., Ruchholtz, S., Kaiser, G. M., & Nast-Kolb, D. (2005). Mortality in severely injured elderly trauma patients--when does age become a risk factor? *World J Surg, 29*(11), 1476-1482. doi:10.1007/s00268-005-7796-y

Kuo, S. C., Kuo, P. J., Hsu, S. Y., Rau, C. S., Chen, Y. C., Hsieh, H. Y., & Hsieh, C. H. (2016). The use of the reverse shock index to identify high-risk trauma patients in addition to the criteria for trauma team activation: a cross-sectional study based on a trauma registry system. *BMJ Open, 6*(6), e011072. doi:10.1136/bmjopen-2016-011072

Labib, N., Nouh, T., Winocour, S., Deckelbaum, D., Banici, L., Fata, P., . . . Khwaja, K. (2011). Severely Injured Geriatric Population: Morbidity, Mortality, and Risk Factors. *The Journal of trauma, 71*, 1908-1914. doi:10.1097/TA.0b013e31820989ed

Lee, K., Jang, J. S., Kim, J., & Suh, Y. J. (2020). Age shock index, shock index, and modified shock index for predicting postintubation hypotension in the emergency department. *Am J Emerg Med, 38*(5), 911-915. doi:10.1016/j.ajem.2019.07.011

Ley, E. J., Singer, M. B., Clond, M. A., Gangi, A., Mirocha, J., Bukur, M., . . . Salim, A. (2011). Elevated admission systolic blood pressure after blunt trauma predicts delayed pneumonia and mortality. *J Trauma, 71*(6), 1689-1693. doi:10.1097/TA.0b013e31823cc5df

Lilitsis, E., Xenaki, S., Athanasakis, E., Papadakis, E., Syrogianni, P., Chalkiadakis, G., & Chrysos, E. (2018). Guiding Management in Severe Trauma: Reviewing

Factors Predicting Outcome in Vastly Injured Patients. *J Emerg Trauma Shock, 11*(2), 80-87. doi:10.4103/jets.Jets_74_17

Liu, N. T., Holcomb, J. B., Wade, C. E., Batchinsky, A. I., Cancio, L. C., Darrah, M. I., & Salinas, J. (2014). Development and validation of a machine learning algorithm and hybrid system to predict the need for life-saving interventions in trauma patients. *Med Biol Eng Comput, 52*(2), 193-203. doi:10.1007/s11517-013-1130-x

Liu, N. T., Holcomb, J. B., Wade, C. E., Darrah, M. I., & Salinas, J. (2014). Utility of vital signs, heart rate variability and complexity, and machine learning for identifying the need for lifesaving interventions in trauma patients. *Shock, 42*(2), 108-114. doi:10.1097/shk.0000000000000186

Liu, Y. C., Liu, J. H., Fang, Z. A., Shan, G. L., Xu, J., Qi, Z. W., . . . Yu, X. Z. (2012). Modified shock index and mortality rate of emergency patients. *World J Emerg Med, 3*(2), 114-117. doi:10.5847/wjem.j.issn.1920-8642.2012.02.006

Mackenzie, C. F., Gao, C., Hu, P. F., Anazodo, A., Chen, H., Dinardo, T., . . . Shackelford, S. (2015). Comparison of Decision-Assist and Clinical Judgment of Experts for Prediction of Lifesaving Interventions. *Shock, 43*(3), 238-243. doi:10.1097/shk.0000000000000288

Mackenzie, C. F., Wang, Y., Hu, P. F., Chen, S. Y., Chen, H. H., Hagegeorge, G., . . . Shackelford, S. (2014). Automated prediction of early blood transfusion and mortality in trauma patients. *J Trauma Acute Care Surg, 76*(6), 1379-1385. doi:10.1097/ta.0000000000000235

MacKenzie, E. J., Rivara, F. P., Jurkovich, G. J., Nathens, A. B., Frey, K. P., Egleston, B. L., . . . Scharfstein, D. O. (2006). A national evaluation of the effect of trauma-center care on mortality. *N Engl J Med, 354*(4), 366-378. doi:10.1056/NEJMsa052049

Martin, J. T., Alkhoury, F., O'Connor, J. A., Kyriakides, T. C., & Bonadies, J. A. (2010). 'Normal' vital signs belie occult hypoperfusion in geriatric trauma patients. *Am Surg, 76*(1), 65-69.

Maxwell, C. A., Miller, R. S., Dietrich, M. S., Mion, L. C., & Minnick, A. (2015). The aging of America: a comprehensive look at over 25,000 geriatric trauma admissions to United States hospitals. *Am Surg, 81*(6), 630-636. doi:10.1177/000313481508100630

McGraw, C., Salottolo, K., Carrick, M., Lieser, M., Madayag, R., Berg, G., . . . Bar-Or, D. (2021). Patterns of alcohol and drug utilization in trauma patients during the COVID-19 pandemic at six trauma centers. *Inj Epidemiol, 8*(1), 24. doi:10.1186/s40621-021-00322-0

McNab, A., Burns, B., Bhullar, I., Chesire, D., & Kerwin, A. (2013). An analysis of shock index as a correlate for outcomes in trauma by age group. *Surgery, 154*(2), 384-387. doi:10.1016/j.surg.2013.05.007

Mena, J. H., Sanchez, A. I., Rubiano, A. M., Peitzman, A. B., Sperry, J. L., Gutierrez, M. I., & Puyana, J. C. (2011). Effect of the modified Glasgow Coma Scale score criteria for mild traumatic brain injury on mortality prediction: comparing classic and modified Glasgow Coma Scale score model scores of 13. *J Trauma, 71*(5), 1185-1192; discussion 1193. doi:10.1097/TA.0b013e31823321f8

Mitra, B., Fitzgerald, M., & Chan, J. (2014). The utility of a shock index ≥ 1 as an indication for pre-hospital oxygen carrier administration in major trauma. *Injury*, *45*(1), 61-65. doi:10.1016/j.injury.2013.01.010

Mitra, B., Gabbe, B. J., Kaukonen, K. M., Olaussen, A., Cooper, D. J., & Cameron, P. A. (2014). Long-term outcomes of patients receiving a massive transfusion after trauma. *Shock*, *42*(4), 307-312. doi:10.1097/shk.0000000000000219

Murphy, T. E., Baker, D. I., Leo-Summers, L. S., & Tinetti, M. E. (2014). Trends in Fall-Related Traumatic Brain Injury among Older Persons in Connecticut from 2000-2007. *J Gerontol Geriatr Res, 3*(4). doi:10.4172/2167-7182.1000168

Mutschler, M., Nienaber, U., Münzberg, M., Wölfl, C., Schoechl, H., Paffrath, T., . . . Maegele, M. (2013). The Shock Index revisited - a fast guide to transfusion requirement? A retrospective analysis on 21,853 patients derived from the TraumaRegister DGU. *Crit Care, 17*(4), R172. doi:10.1186/cc12851

Nathens, A. B., Rivara, F. P., MacKenzie, E. J., Maier, R. V., Wang, J., Egleston, B., . . . Jurkovich, G. J. (2006). The impact of an intensivist-model ICU on trauma-related mortality. *Ann Surg*, *244*(4), 545-554. doi:10.1097/01.sla.0000239005.26353.49

Newgard, C. D., Cheney, T. P., Chou, R., Fu, R., Daya, M. R., O'Neil, M. E., . . . Totten, A. M. (2020). Out-of-hospital Circulatory Measures to Identify Patients With Serious Injury: A Systematic Review. *Acad Emerg Med*, *27*(12), 1323-1339. doi:10.1111/acem.14056

Newgard, C. D., Fischer, P. E., Gestring, M., Michaels, H. N., Jurkovich, G. J., Lerner, E. B., . . . Bulger, E. M. (2022). National guideline for the field triage of injured patients: Recommendations of the National Expert Panel on Field Triage, 2021. *J Trauma Acute Care Surg, 93*(2), e49-e60. doi:10.1097/ta.0000000000003627

Newgard, C. D., Holmes, J. F., Haukoos, J. S., Bulger, E. M., Staudenmayer, K., Wittwer, L., . . . Hsia, R. Y. (2016). Improving early identification of the high-risk elderly trauma patient by emergency medical services. *Injury, 47*(1), 19-25. doi:10.1016/j.injury.2015.09.010

Newgard, C. D., Lin, A., Eckstrom, E., Caughey, A., Malveau, S., Griffiths, D., . . . Bulger, E. (2019). Comorbidities, anticoagulants, and geriatric-specific physiology for the field triage of injured older adults. *J Trauma Acute Care Surg, 86*(5), 829-837. doi:10.1097/ta.0000000000002195

Newgard, C. D., Lin, A., Yanez, N. D., Bulger, E., Malveau, S., Caughey, A., . . . Eckstrom, E. (2019). Long-term outcomes among injured older adults transported by emergency medical services. *Injury, 50*(6), 1175-1185. doi:10.1016/j.injury.2019.04.028

Newgard, C. D., Richardson, D., Holmes, J. F., Rea, T. D., Hsia, R. Y., Mann, N. C., . . . Western Emergency Services Translational Research Network, I. (2014). Physiologic field triage criteria for identifying seriously injured older adults. *Prehosp Emerg Care, 18*(4), 461-470. doi:10.3109/10903127.2014.912707

Newgard, C. D., Rudser, K., Hedges, J. R., Kerby, J. D., Stiell, I. G., Davis, D. P., . . . Emerson, S. (2010). A critical assessment of the out-of-hospital trauma triage guidelines for physiologic abnormality. *J Trauma, 68*(2), 452-462. doi:10.1097/TA.0b013e3181ae20c9

Newgard, C. D., Zive, D., Holmes, J. F., Bulger, E. M., Staudenmayer, K., Liao, M., . . . Hedges, J. R. (2011). A multisite assessment of the American College of Surgeons Committee on Trauma field triage decision scheme for identifying seriously injured children and adults. *J Am Coll Surg, 213*(6), 709-721. doi:10.1016/j.jamcollsurg.2011.09.012

Odom, S. R., Howell, M. D., Gupta, A., Silva, G., Cook, C. H., & Talmor, D. (2016). Extremes of shock index predicts death in trauma patients. *J Emerg Trauma Shock, 9*(3), 103-106. doi:10.4103/0974-2700.185272

Pacagnella, R. C., Souza, J. P., Durocher, J., Perel, P., Blum, J., Winikoff, B., & Gülmezoglu, A. M. (2013). A systematic review of the relationship between blood loss and clinical signs. *PLoS One, 8*(3), e57594. doi:10.1371/journal.pone.0057594

Pandit, V., Rhee, P., Hashmi, A., Kulvatunyou, N., Tang, A., Khalil, M., . . . Joseph, B. (2014). Shock index predicts mortality in geriatric trauma patients: an analysis of the National Trauma Data Bank. *J Trauma Acute Care Surg, 76*(4), 1111-1115. doi:10.1097/ta.0000000000000160

Pardo-Fernández, J. C., Rodríguez-Álvarez, M. X., & Keilegom, I. V. (2014). A review on ROC curves in the presence of covariates. *Revstat-statistical Journal, 12*, 21-41.

Park, S. J., Lee, M. J., Kim, C., Jung, H., Kim, S. H., Nho, W., . . . Son, S.-a. (2021). The impact of age and receipt antihypertensives to systolic blood pressure and shock index at injury scene and in the emergency department to predict massive transfusion in trauma patients. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine, 29*(1), 26. doi:10.1186/s13049-021-00840-2

Parks, J. K., Elliott, A. C., Gentilello, L. M., & Shafi, S. (2006). Systemic hypotension is a late marker of shock after trauma: a validation study of Advanced Trauma Life Support principles in a large national sample. *Am J Surg, 192*(6), 727-731. doi:10.1016/j.amjsurg.2006.08.034

Pepe, M., Longton, G., & Janes, H. (2009). Estimation and Comparison of Receiver Operating Characteristic Curves. *Stata J, 9*(1), 1.

Pepe, M. S. (2000). An interpretation for the ROC curve and inference using GLM procedures. *Biometrics, 56*(2), 352-359. doi:10.1111/j.0006-341x.2000.00352.x

Pepe, M. S. (2004). *The Statistical Evaluation of Medical Tests for Classification and Prediction*: Oxford University Press.

Pepe, M. S., Janes, H., Longton, G., Leisenring, W., & Newcomb, P. (2004). Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. *Am J Epidemiol, 159*(9), 882-890. doi:10.1093/aje/kwh101

Perkins, N. J., & Schisterman, E. F. (2006). The inconsistency of "optimal" cutpoints obtained using two criteria based on the receiver operating characteristic curve. *Am J Epidemiol, 163*(7), 670-675. doi:10.1093/aje/kwj063

Phillips, R., Acker, S., Shahi, N., Shirek, G., Meier, M., Goldsmith, A., . . . Bensard, D. (2020). The shock index, pediatric age-adjusted (SIPA) enhanced: Prehospital and emergency department SIPA values forecast transfusion needs for blunt solid organ injured children. *Surgery, 168*(4), 690-694. doi:10.1016/j.surg.2020.04.061

Phillips, R., Meier, M., Shahi, N., Acker, S., Reppucci, M., Shirek, G., . . . Bensard, D. (2021). Elevated pediatric age-adjusted shock-index (SIPA) in blunt solid organ injuries. *J Pediatr Surg, 56*(2), 401-404. doi:10.1016/j.jpedsurg.2020.10.022

Pietilä, J., Helander, E., Korhonen, I., Myllymäki, T., Kujala, U. M., & Lindholm, H. (2018). Acute Effect of Alcohol Intake on Cardiovascular Autonomic Regulation During the First Hours of Sleep in a Large Real-World Sample of Finnish Employees: Observational Study. *JMIR Ment Health*, *5*(1), e23. doi:10.2196/mental.9519

Pratt, C. M., Hirshberg, E. L., Jones, J. P., Kuttler, K. G., Lanspa, M. J., Wilson, E. L., . . . Brown, S. M. (2015). Long-term outcomes after severe shock. *Shock, 43*(2), 128-132. doi:10.1097/shk.0000000000000283

Rady, M. Y., Smithline, H. A., Blake, H., Nowak, R., & Rivers, E. (1994). A comparison of the shock index and conventional vital signs to identify acute, critical illness in the emergency department. *Ann Emerg Med, 24*(4), 685-690. doi:10.1016/s0196-0644(94)70279-9

Rau, C. S., Wu, S. C., Kuo, S. C., Pao-Jen, K., Shiun-Yuan, H., Chen, Y. C., . . . Liu, H. T. (2016). Prediction of Massive Transfusion in Trauma Patients with Shock Index, Modified Shock Index, and Age Shock Index. *Int J Environ Res Public Health, 13*(7). doi:10.3390/ijerph13070683

Rogers, A., Rogers, F., Bradburn, E., Krasne, M., Lee, J., Wu, D., . . . Horst, M. (2012). Old and undertriaged: a lethal combination. *Am Surg, 78*(6), 711-715. doi:10.1177/000313481207800628

Ryan, J. M., & Howes, L. G. (2002). Relations between alcohol consumption, heart rate, and heart rate variability in men. *Heart, 88*(6), 641-642. doi:10.1136/heart.88.6.641

Sagawa, Y., Kondo, H., Matsubuchi, N., Takemura, T., Kanayama, H., Kaneko, Y., . . . Shimizu, T. (2011). Alcohol has a dose-related effect on parasympathetic nerve activity during sleep. *Alcohol Clin Exp Res, 35*(11), 2093-2100. doi:10.1111/j.1530-0277.2011.01558.x

SAS. (2019). Plot and compare ROC curves from logistic models fit to independent samples. Retrieved from https://support.sas.com/kb/45/339.html

Sasser, S. M., Hunt, R. C., Faul, M., Sugerman, D., Pearson, W. S., Dulski, T., . . . Lerner, E. B. (2012). Guidelines for field triage of injured patients: recommendations of the National Expert Panel on Field Triage, 2011. *MMWR Recomm Rep, 61*(Rr-1), 1-20.

Schellenberg, M., Strumwasser, A., Grabo, D., Clark, D., Matsushima, K., Inaba, K., & Demetriades, D. (2017). Delta Shock Index in the Emergency Department Predicts Mortality and Need for Blood Transfusion in Trauma Patients. *Am Surg, 83*(10), 1059-1062. doi:10.1177/000313481708301009

Shackelford, S., Yang, S., Hu, P., Miller, C., Anazodo, A., Galvagno, S., . . . Mackenzie, C. (2015). Predicting blood transfusion using automated analysis of pulse oximetry signals and laboratory values. *J Trauma Acute Care Surg, 79*(4 Suppl 2), S175-180. doi:10.1097/ta.0000000000000738

Shibahashi, K., Sugiyama, K., Okura, Y., Hoda, H., & Hamabe, Y. (2019). Can the shock index be a reliable predictor of early mortality after trauma in older patients? A retrospective cohort study. *Acute Med Surg*, *6*(4), 385-391. doi:10.1002/ams2.427

Singh, S., & Bajorek, B. (2014). Defining 'elderly' in clinical practice guidelines for pharmacotherapy. *Pharm Pract (Granada), 12*(4), 489. doi:10.4321/s1886-36552014000400007

STATA. (2019a). roc - Receiver operating characteristic (ROC) analysis. Retrieved from https://www.stata.com/features/overview/receiver-operating-characteristic/

STATA. (2019b). rocreg - Receiver operating characteristic (ROC) regression. Retrieved from https://www.stata.com/manuals/rrocreg.pdf#rrocreg

STATA. (2019c). rocreg postestimation — Postestimation tools for rocreg. Retrieved from https://www.stata.com/manuals/rrocregpostestimation.pdf#rrocregpostestimation

STATA. (2019d). rocregplot - Plot marginal and covariate-specific ROC curves after rocreg. Retrieved from https://www.stata.com/manuals/rrocregplot.pdf#rrocregplot

STATA. (2019e). roctab — Nonparametric ROC analysis. Retrieved from https://www.stata.com/manuals/rroctab.pdf#rroctab

Staudenmayer, K., Weiser, T. G., Maggio, P. M., Spain, D. A., & Hsia, R. Y. (2016). Trauma center care is associated with reduced readmissions after injury. *J Trauma Acute Care Surg*, *80*(3), 412-416; discussion 416-418. doi:10.1097/ta.0000000000000956

Tasnim, S., Tang, C., Musini, V. M., & Wright, J. M. (2020). Effect of alcohol on blood pressure. *Cochrane Database Syst Rev, 7*(7), Cd012787. doi:10.1002/14651858.CD012787.pub2

Teasdale, G., & Jennett, B. (1974). Assessment of coma and impaired consciousness. A practical scale. *Lancet, 2*(7872), 81-84. doi:10.1016/s0140-6736(74)91639-0

Tien, H. C., Tremblay, L. N., Rizoli, S. B., Gelberg, J., Chughtai, T., Tikuisis, P., . . . Brenneman, F. D. (2006). Association between alcohol and mortality in patients with severe traumatic head injury. *Arch Surg, 141*(12), 1185-1191; discussion 1192. doi:10.1001/archsurg.141.12.1185

Trust, M. D., Schellenberg, M., Biswas, S., Inaba, K., Cheng, V., Warriner, Z., . . . Demetriades, D. (2020). Prehospital Vital Signs Accurately Predict Initial Emergency Department Vital Signs. *Prehosp Disaster Med, 35*(3), 254-259. doi:10.1017/s1049023x2000028x

Uribe-Leitz, T., Jarman, M. P., Sturgeon, D. J., Harlow, A. F., Lipsitz, S. R., Cooper, Z., . . . Haider, A. H. (2020). National Study of Triage and Access to Trauma Centers for Older Adults. *Ann Emerg Med, 75*(2), 125-135. doi:10.1016/j.annemergmed.2019.06.018

US Census. (2018). An Aging Nation: Projected number of children and older adults. Retrieved from https://www.census.gov/library/visualizations/2018/comm/historic-first.html

van der Vlegel, M., Haagsma, J. A., Geraerds, A., de Munter, L., de Jongh, M. A. C., & Polinder, S. (2020). Health care costs of injury in the older population: a prospective multicentre cohort study in the Netherlands. *BMC Geriatr, 20*(1), 417. doi:10.1186/s12877-020-01825-z

van Rein, E. A. J., van der Sluijs, R., Houwert, R. M., Gunning, A. C., Lichtveld, R. A., Leenen, L. P. H., & van Heijl, M. (2018). Effectiveness of prehospital trauma triage systems in selecting severely injured patients: Is comparative analysis possible? *Am J Emerg Med, 36*(6), 1060-1069. doi:10.1016/j.ajem.2018.01.055

Vandromme, M. J., Griffin, R. L., Kerby, J. D., McGwin, G., Jr., Rue, L. W., 3rd, & Weinberg, J. A. (2011). Identifying risk for massive transfusion in the relatively normotensive patient: utility of the prehospital shock index. *J Trauma, 70*(2), 384-388; discussion 388-390. doi:10.1097/TA.0b013e3182095a0a

Victorino, G. P., Battistella, F. D., & Wisner, D. H. (2003). Does tachycardia correlate with hypotension after trauma? *J Am Coll Surg, 196*(5), 679-684. doi:10.1016/s1072-7515(03)00128-5

Victorino, G. P., Chong, T. J., & Pal, J. D. (2003). Trauma in the elderly patient. *Arch Surg, 138*(10), 1093-1098. doi:10.1001/archsurg.138.10.1093

Wang, H., Chen, M. B., Zheng, X. W., & Zheng, Q. H. (2019). Effectiveness and safety of hypotensive resuscitation in traumatic hemorrhagic shock: A protocol for meta-analysis. *Medicine (Baltimore), 98*(48), e18145. doi:10.1097/md.0000000000018145

Wang, I. J., Bae, B. K., Cho, Y. M., Cho, S. J., Yeom, S. R., Lee, S. B., . . . Moon, S. Y. (2021). Effect of acute alcohol intoxication on mortality, coagulation, and fibrinolysis in trauma patients. *PLoS One, 16*(3), e0248810. doi:10.1371/journal.pone.0248810

Ware, J. H. (2006). The limitations of risk factors as prognostic tools. *N Engl J Med, 355*(25), 2615-2617. doi:10.1056/NEJMp068249

Wicklin, R. (2018). Create and compare ROC curves for any predictive model. Retrieved from https://blogs.sas.com/content/iml/2018/11/14/compare-roc-curves-sas.html

Yang, S., Mackenzie, C. F., Rock, P., Lin, C., Floccare, D., Scalea, T., . . . Hu, P. F. (2021). Comparison of massive and emergency transfusion prediction scoring systems after trauma with a new Bleeding Risk Index score applied in-flight. *J Trauma Acute Care Surg, 90*(2), 268-273. doi:10.1097/ta.0000000000003031

Youden, W. J. (1950). Index for rating diagnostic tests. *Cancer, 3*(1), 32-35. doi:10.1002/1097-0142(1950)3:1<32::aid-cncr2820030106>3.0.co;2-3

Zafar, S. N., Millham, F. H., Chang, Y., Fikry, K., Alam, H. B., King, D. R., . . . de Moya, M. A. (2011). Presenting blood pressure in traumatic brain injury: a bimodal distribution of death. *J Trauma, 71*(5), 1179-1184. doi:10.1097/TA.0b013e3182140d38

Zarzaur, B. L., Croce, M. A., Fischer, P. E., Magnotti, L. J., & Fabian, T. C. (2008). New vitals after injury: shock index for the young and age x shock index for the old. *J Surg Res, 147*(2), 229-236. doi:10.1016/j.jss.2008.03.025

Zarzaur, B. L., Croce, M. A., Magnotti, L. J., & Fabian, T. C. (2010). Identifying life-threatening shock in the older injured patient: an analysis of the National Trauma Data Bank. *J Trauma, 68*(5), 1134-1138. doi:10.1097/TA.0b013e3181d87488