

PLATELET EXTRACELLULAR VESICLES AS A THERAPEUTIC AGENT IN HEMORRHAGIC SHOCK

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Invited Discussant: Matthew Neal, MD

Introduction: Hemorrhage accounts for the majority of preventable deaths after trauma. Resuscitation is guided by several studies that demonstrate improved outcomes in patients receiving whole blood or a balanced administration of blood products. Platelets present a logistical challenge due to a short shelf life and need for refrigeration. One alternative is platelet derived extracellular vesicles (PEVs). PEVs are particles secreted from platelets that express several important surface receptors, have hemostatic effects and mitigate inflammation and vascular injury similar to platelets. PEVs are lightweight, safe, easily transportable, stable over a wide temperature range and have a long shelf-life. This study aimed to elucidate the therapeutic effects of PEVs in a rat model of uncontrolled hemorrhage.

Methods: Male rats were anesthetized and femoral vessels cannulated. Vital signs (MAP, HR, and RR) were monitored. Electrolytes, lactate and ABG were obtained at baseline, 1-hour and 3-hours post injury. Laparotomy was performed, 50% of the middle hepatic lobe excised and the abdomen packed with gauze. Rats received 2 mL PEVs or lactated ringers (LR) over 6 min at the time of injury. Peritoneal blood loss was quantified using pre-weighed gauze at 5, 15, 30, 45 and 60 minutes. Laparotomy was closed 1-hour post-injury. Animals were monitored 3-hours post-injury then euthanized. Generalized Linear Mixed Effects models and ANOVA were done to assess effects of treatment and time on lactate and MAP.

Results: 21 rats were included (11 LR 10 PEV). Overall blood loss was between 6-10 ml and not significantly different between groups. There was a 19% mortality rate in the LR group and 0% mortality in the PEV group ($p=0.03$). The LR group had significantly higher lactates at 1 hour ($p = 0.025$) and 3 hours ($p = 0.016$). At baseline, 5 and 30 minutes, there was no difference in MAP. At 15, 45, 60, and 180 minutes the MAP of the PEV group was significantly higher than the LR group.

Conclusion: Early studies are encouraging regarding the potential use of PEVs in uncontrolled hemorrhagic shock based on improved survival, hemodynamics and end organ function.

THE INJURED MONOCYTE: THE LINK TO CHRONIC CRITICAL ILLNESS AND MORTALITY FOLLOWING INJURY

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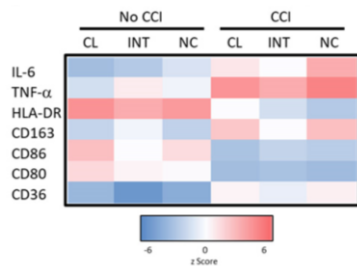
Invited Discussant: Scott Brakenridge, MD, MSCS

Introduction: Severely injured patients may go on to develop chronic critical illness (CCI). An altered innate phenotype is thought to play a role but remains poorly elucidated. The primary aim of this study was to characterize the innate immune populations following severe injury, and their relationship to the development of CCI and long-term outcomes.

Methods: In a 3-year study, patients that suffered severe trauma were followed up to 1 year following injury. Patient demographics and outcomes were collected. An ICU length of stay of ≥ 14 days with persistent organ failure defined CCI. Blood obtained at days 1 and 5 underwent flow cytometry for monocyte phenotypic expression (classical, CL; intermediate, INT; non-classical, NC), HLA-DR expression, and activation. Measures and outcomes were analyzed by Pearson's correlation and two-sided paired t-tests.

Results: Of the 80 patients enrolled, 26 (32.5%) developed CCI. Patients with CCI were more severely injured (32.4 ± 5.2 vs. 29.6 ± 4.1 , $p=0.01$) and received more pRBCs (8.9 ± 4.1 vs. 4.7 ± 3.8 , $p<0.01$) compared to patients without CCI. CL and INT monocytes were not different, but NC monocytes were significantly reduced by more than 2-fold in patients with CCI. Overall, significant changes in cytokine expression and cell receptors were noted within each monocyte subpopulation. These changes were consistent with an increased pro-inflammatory phenotype, but decreased phagocytic capacity and antigen presentation in patients with CCI (Figure). HLA-DR expression was significantly decreased in patients with CCI at both days 1 and 5. Development of CCI and presence of this unique monocyte phenotype was associated with a significant increased risk for infection, discharge to long-term care facility, and poor functional status and mortality at 1 year.

Conclusion: This altered NC phenotype with decreased phagocytic capacity and antigen presentation found in CCI likely contributes to poor long-term recovery. Early identification of this unique phenotype could help predict and treat patients at risk for CCI to improve outcome.



RISK-STRATIFIED THROMBOPROPHYLAXIS EFFECTS OF ASPIRIN VERSUS LOW-MOLECULAR-WEIGHT HEPARIN IN ORTHOPAEDIC TRAUMA PATIENTS

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Invited Discussant: Charles Wade, PhD

Introduction: A recent randomized trial concluded that thromboprophylaxis with aspirin was noninferior to low-molecular-weight heparin (LMWH) in preventing death in orthopaedic trauma patients. This planned secondary analysis sought to determine if these results apply to high-risk patients. We aimed to determine if the effect of aspirin versus LMWH differed based on patients' baseline risk of venous thromboembolism (VTE).

Methods: A pragmatic randomized controlled trial was conducted at 21 trauma centers in North America. 12,211 adult patients were enrolled who indicated for thromboprophylaxis due to an operatively treated extremity fracture or pelvis or acetabulum fracture. The Caprini Score was used to calculate patients' baseline risk of VTE, stratifying the sample into risk quartiles ranging from low (< 1%) to high risk (>10%). The primary outcome was a composite of thromboembolic outcomes within 90 days. We assessed treatment effects using the win ratio method. We compared the outcomes hierarchically; death, pulmonary embolism, deep vein thrombosis, and bleeding. The secondary outcome added an ordinal measure of patient-reported thromboprophylaxis satisfaction as the fifth component in the composite outcome.

Results: In the high-risk quartile (n=3052), 46% of patients had a femur fracture, 42% had a pelvis or acetabulum fracture, 48% had a thoracic injury, 39% had a spinal injury, and 35% had a head injury. In the high-risk quartile, there was no statistical difference in the effect of aspirin compared to LMWH on the composite outcome (win ratio, 0.95; 95% CI, 0.83 – 1.09, p=0.48). When patient-reported thromboprophylaxis satisfaction was considered, favorable outcomes were 68% more frequent when assigned to aspirin as compared to LMWH (win ratio, 1.68; 95% CI, 1.60 – 1.77; p< 0.001).

Conclusions: Thromboembolic outcomes are similar when either aspirin or LMWH is used for prophylaxis in trauma patients with orthopaedic injuries. This result held true even when considering patients at highest risk of VTE.

MULTICENTER EVALUATION OF FINANCIAL TOXICITY AND LONG-TERM PHYSICAL & MENTAL HEALTH AFTER INJURY

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Invited Discussant: Kristan Staudenmayer, MD, MS

Introduction: Financial toxicity (FT) encompasses the subjective and objective financial strain due to illness, treatment, and recovery. Although our understanding of long-term health-related quality of life (hrQoL) after injury is improving, little is known about long-term financial wellbeing after injury, risk-factors for FT, or the association between FT and hrQoL.

Methods: Patients from six trauma centers were contacted 1-18 months after discharge and evaluated for the five elements of FT: out-of-pocket (OOP) spending, medical debt, job or income loss, non-medical bills, and unaffordable care. Five measures of hr-QoL (Table) were also evaluated using the EuroQol-5D-5L. Multivariable regression models including 18 patient, injury, treatment, and system traits (Table) were used to evaluate for risk-factors of FT as well as associations between FT and hrQoL outcomes.

Results: Among the 256 respondents, 48% were female, median age was 63y, median ISS was 10, and median follow-up was 5.4 months (IQR: 2.6m-7.1m). Across the five FT elements, 37% had OOP spending >\$1000, 26% had medical debt, 31% had job or income loss, 29% had difficulty with non-medical bills, and 18% reported delayed/forgone care due to costs. On multivariable analyses evaluating patient, injury, and system traits, FT was not associated with inpatient treatment intensity (e.g ICU care, length of stay, operation); however, FT was associated with younger age, higher ISS, SVI, and insurance status. On risk-adjusted analyses, FT was independently associated with worse hrQoL in all five EuroQol-5D-5L domains (Table).

Conclusion: Two-thirds of trauma survivors from six hospitals experience some element of financial toxicity months after discharge. The independent

association between FT and hrQoL suggests that interventions to mitigate FT may optimize long-term recovery.

Table. Health-related quality of life outcomes, by increasing levels of Financial Toxicity

Moderate, Severe, or Extreme Difficulty with:	No FinTox	1-2 FinTox Elements	3-5 FinTox Elements	Risk-Adj P Value*
	(n= 86)	(n= 120)	(n= 50)	
Walking about	29%	38%	50%	<0.001
Washing and dressing self	11%	25%	28%	<0.001
Doing usual activities	31%	45%	52%	0.001
Pain or discomfort	28%	36%	58%	<0.001
Anxiety or depression	12%	23%	25%	<0.001

FinTox = Financial Toxicity, scale 0-5. *Risk-adjusted P-value across the three categories of Financial Toxicity; **Adjusted for:** age, sex, race/ethnicity, health insurance type, social vulnerability index (SVI), baseline comorbidities, prior mental health diagnosis, injury severity score (ISS), maximum head abbreviated injury scale (AIS), injury mechanism, operative intervention, intensive care unit (ICU) stay, non-home discharge, transfer status, trauma center, survey year, and months since discharge. Standard errors clustered at trauma centers.

**DAMAGE CONTROL VS. EARLY DEFINITIVE FIXATION OF
DIAPHYSEAL LOWER EXTREMITY FRACTURES IN TBI
PATIENTS: THE EAST BRAIN VS. BONE MULTI-
INSTITUTIONAL TRIAL**

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Invited Discussant: John Scott, MD, MPH

Introduction: The association between damage control orthopedics (DCO) vs. early definitive fixation (EDF) of lower extremity (LE) fractures & neurologic outcomes remains unclear. This study aimed to determine whether DCO vs. EDF & timing (≤ 24 hours vs. > 24 hours) of LE fracture fixation impact neurologic outcomes in patients with TBI.

Methods: A prospective observational study was conducted across 30 level-1 trauma centers between (03/2019-03/2022). Inclusion criteria were age ≥ 18 , head AIS score > 2 , & a femur or tibia diaphyseal fracture. Comparisons were made between the external fixation (Ex-Fix) with conversion to intramedullary nailing (IMN) group vs. the IMN only group, & the Ex-Fix with conversion to open reduction & internal fixation (ORIF) vs. the ORIF only group. Neurologic outcomes were measured by discharge Revised Rancho Los Amigos Scale score (R-RLAS). Multivariable regression models were used to identify independent predictors of a lower R-RLAS score at discharge.

Results: Of the 520 patients enrolled in the study, 42 (8.1%) underwent Ex-Fix to IMN, 171 (33%) underwent IMN, 51 (9.8%) underwent Ex-Fix to ORIF, & 142 (27%) underwent ORIF. After adjusting for confounders, neither method nor timing of LE fixation influenced the discharge R-RLAS score. However, head AIS (OR 6.92, 95% CI 3.2-15) was associated with a lower R-RLAS score at discharge in the IMN group. In the ORIF group, age (OR 1.03, 95% CI 1.01-1.05), & head AIS (OR 2.5, 95% CI 1.22-5.13) were associated with a lower R-RLAS score at discharge & higher post-resuscitation motor scores of 4-5 (OR 0.45, 95% CI 0.2-0.99) & motor score of 6 (OR 0.35, 95% CI 0.13-0.95) were associated with a higher R-RLAS score at discharge.

Conclusion: Neurologic outcomes in TBI patients with concomitant LE fractures are impacted by severity of the head injury itself & not the fracture fixation technique or timing. Therefore, the LE fracture fixation strategy may not need to be delayed or modified due to concern for worsening neurologic outcomes in this patient population.

THE SILENT KILLER IN TRAUMA: THE IMPLICATIONS OF MALNUTRITION ON OUTCOMES OF OLDER ADULTS

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Invited Discussant: Sharon Henry, MD

Introduction: The impact of malnutrition on both short-term & post-discharge outcomes in geriatric trauma patients remains unclear. We aimed to evaluate the impact of malnutrition on a multi-institutional cohort of patients.

Methods: This is a secondary analysis of the AAST Frailty Multi-institutional Trial. All patients (≥ 65 yrs) presenting to one of seventeen Level I/II trauma centers (2019-2021) were included and stratified by the simplified Geriatric Nutritional Risk Index (sGNRI=albumin (measured within 24 hrs in g/dL) + BMI (kg/m²)/10): severe (sGNRI <5), moderate ($5.5 > \text{sGNRI} \geq 5.5$), & mild malnutrition ($6 > \text{sGNRI} \geq 5.5$), & good nutritional status (sGNRI ≥ 6). Outcomes included index admission mortality, complications, discharge to skilled nursing facility/rehab (SNF/rehab), length of stay (LOS), & 3-month post-discharge readmissions, falls, complications, & mortality. Multivariable regression analyses were performed.

Results: 1,321 patients were identified. 22% suffered from malnutrition (Severe Malnutrition: 3%; Moderate Malnutrition: 7%; Mild Malnutrition: 13%). Mean age was 77 \pm 8 yrs; median ISS was 9 [5-13] & 69% had falls. Severe malnutrition had higher rates of sepsis, pneumonia, discharge to SNF/rehab, index-admission mortality, longer LOS & 3-month mortality (**Table**). On multivariable analyses, severe malnutrition was associated with sepsis (aOR 8.7, 95% CI [2.6-29.1], $p < 0.001$), pneumonia (aOR 4.4, 95% CI [1.2-16], $p = 0.025$), index-admission mortality (aOR 4.1, 95% CI [1.4-11.6], $p = 0.008$) & 3-month mortality (aOR 16.9, 95% CI [4.5-63.7], $p < 0.001$) compared to good nutrition. Moderate malnutrition was associated with index admission mortality (aOR 5.5, 95% CI [1.6-19.1], $p = 0.008$). On linear regression, improved nutritional status (increasing sGNRI) was associated with shorter hospital LOS ($\beta = -0.45$, 95% CI [-0.85, -0.058] $p = 0.025$).

Conclusion: In this large multi-center cohort of geriatric trauma patients, nearly 25% of patients suffered from malnutrition. Malnutrition was an independent predictor of worse index-admission and 3-month post discharge outcomes. These findings underscore the need for nutritional screening & interventions at admission to improve outcomes of geriatric trauma patients.

Malnutrition Status	Good (N=1,036)	Mild (N=166)	Moderate (N=86)	Severe (N=33)	p
Index Admission					
Mortality, n (%)	43 (4.2)	8 (4.8)	7 (8.1)	5 (15.2)	0.013
Sepsis, n (%)	19 (1.8)	3 (1.8)	3 (3.5)	4 (12.1)	<0.001
Pneumonia, n (%)	22 (2.1)	8 (4.8)	4 (4.7)	3 (9.1)	0.018
Discharge to SNF/rehab., n (%)	414 (40)	77 (46.4)	46 (53.5)	17 (52)	0.030
LOS, d, median [IQR]*	4 [2-6]	5 [3-8]	5 [3-8]	5 [3-8]	<0.001
3-month Post-Discharge**					
Mortality, n (%)	11 (1.3)	3 (2.1)	4 (6.3)	4 (14.3)	<0.001

DO HOSPITAL EMERGENCY MEDICAID PROGRAMS FOR THE UNINSURED BENEFIT TRAUMA CENTERS? A MIXED-METHODS STUDY

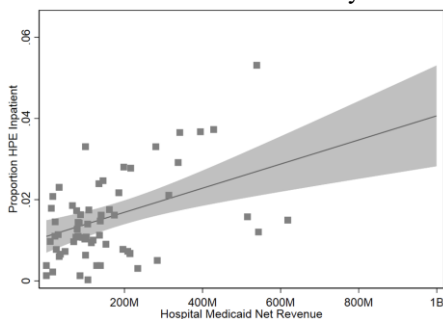
Lisa Knowlton, MD, MPH, FACS, FRCSC; Katherine Arnow, MSc;
Linda Tran, PhD; Amber Trickey, PhD; David Spain, MD, FACS;
Todd Wagner, PhD; Arden Morris, MD, MPH, FACS
Stanford School of Medicine
Invited Discussant: Joseph Minei, MD, MBA

Introduction: Hospital Presumptive Eligibility (HPE) is a temporary Medicaid insurance available to vulnerable uninsured patients at hospitalization. HPE insurance is intended to offset care costs for patients and hospitals and increase access by providing a pathway to sustaining long-term Medicaid. More than 70% of HPE approved trauma patients sustain Medicaid within the year, but less is known about the implications that HPE programs have on trauma centers. We aimed to characterize incentives for HPE participation across trauma centers statewide, as well as describe the association with HPE and hospital Medicaid reimbursement. We hypothesized that there would be financial and operational incentives for enrolling uninsured trauma patients in HPE.

Methods: We performed an explanatory sequential mixed-methods study analyzing a customized California Department of Health Care Services (DHCS) claims dataset for HPE-approved patients merged with Office of Statewide Planning and Development (OSHPD) annual hospital financial reports for state verified adult trauma centers (2016-22). Our primary outcome was Medicaid net revenue. We also conducted thematic analysis of semi-structured interviews with stakeholders (social workers, financial counselors) across select sites to understand incentives for HPE participation (n=10).

Results: Among 79 Level I-IV trauma centers, 67 (85%) treated adult HPE patients and were matched to state financial records. 24% were considered safety-net hospitals with a mission to provide care to the indigent, and 21% were Level I trauma centers. Median net Medicaid revenue was \$115,112,760 (IQR \$75,751,392-\$214,446,224) and increased over time with higher proportions of HPE patients. There was a significant positive association between % HPE patients and net Medicaid revenue (Figure 1). Stakeholder interviewees explanatory incentives for HPE participation included: improved patient satisfaction and equitable access to post-discharge care (e.g. rehabilitation), thus shortening hospital stay, and reduced need for hospital financial assistance alternatives.

Conclusion: HPE programs are a promising pathway not only for long-term insurance coverage for trauma patients, but also play a role in trauma center and safety-net viability, as well as equitable access to care. Future opportunities include patient interviews and longitudinal follow-up to better understand HPE implications on long-term health services utilization and financial health.



THE INTERACTION BETWEEN GERIATRIC & NEIGHBORHOOD VULNERABILITY: DELINEATING PRE-HOSPITAL RISK AMONG OLDER ADULT EGS PATIENTS

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 Yale School of Medicine

Invited Discussant: Vanessa Ho, MD, MPH

Introduction: When presenting for EGS care, older adults frequently experience increased risk of adverse outcomes owing to factors related to age ('geriatric vulnerability') and the social determinants of health unique to the places in which they live ('neighborhood vulnerability'). Little is known about how such factors collectively influence adverse outcomes. We sought to explore how the interaction between geriatric and neighborhood vulnerability influences EGS outcomes among older adults.

Methods: Older adults, ≥65 years, hospitalized with an AAST-defined EGS condition were identified in the 2016-2021 Florida State Inpatient Database. Latent variable models combined the influence of patient age, extent of multimorbidity, and Hospital Frailty Risk Score into a single metric of 'geriatric vulnerability.' Variations in geriatric vulnerability were then compared across differences in 'neighborhood vulnerability' as measured by variations in Area Deprivation Index, Social Vulnerability Index, Minority Health Social Vulnerability Index, and their corresponding subthemes (e.g. access to transportation).

Results: A total of 374,220 older adults were included. Risk-adjusted differences in 30- and 365-day mortality are presented in **Table 1**. For patients living in the least vulnerable neighborhoods, increasing geriatric vulnerability resulted in up to six-times greater risk of death (30-day HR[95%CI]: 6.32[4.49-8.89]). The effect was more than doubled among patients living in the most vulnerable neighborhoods, where increasing geriatric vulnerability resulted in up to fifteen-times greater risk of death (30-day HR[95%CI]: 15.12[12.57-18.19]). When restricted to racial/ethnic minority patients, the multiplicative effect was four-times as high, resulting in corresponding 30-day hazard ratios for mortality of 11.53(4.51-29.44) versus 40.67(22.73-72.78). Similar patterns were seen for differences in 30- and 365-day readmission and major morbidity.

Conclusions: Both geriatric and neighborhood vulnerability have been shown to affect pre-hospital risk among older patients. The results of this study build on that work, presenting the first in-depth look at the powerful multiplicative interaction between these two factors. The results show that where a patient resides can fundamentally alter expected outcomes for EGS care such that otherwise less vulnerable patients become functionally equivalent to those who are, at baseline, more aged, more frail, and more sick.

	Highest Neighborhood Vulnerability (Area Deprivation Index results)										
	All Older Adults				Racial/Ethnic Minority Patients						
	30-day Mortality		365-day Mortality		30-day Mortality		365-day Mortality				
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI			
Geriatric Vulnerability											
Q1-2 (lowest)	1.00	–	1.00	–	1.00	–	1.00	–			
Q3	3.52	2.83	4.37	3.27	2.70	3.96	8.72	4.62 16.44	7.29	4.29	12.37
Q4	5.26	4.29	6.46	4.62	3.85	5.54	12.20	6.58 22.62	10.42	6.24	17.37
Q5 (highest)	15.12	12.57	18.19	12.24	10.39	14.42	40.67	22.73 72.78	30.13	18.64	48.69
	Lowest Neighborhood Vulnerability (Area Deprivation Index results)										
	All Older Adults				Racial/Ethnic Minority Patients						
	30-day Mortality		365-day Mortality		30-day Mortality		365-day Mortality				
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI			
Geriatric Vulnerability											
Q1-2 (lowest)	1.00	–	1.00	–	1.00	–	1.00	–			
Q3	0.88	0.51	1.51	0.78	0.46	1.33	2.41	0.77 7.53	2.41	0.78	7.54
Q4	1.58	1.00	2.49	1.68	1.10	2.58	7.23	2.68 19.51	7.24	2.68	19.51
Q5 (highest)	6.32	4.49	8.89	5.61	4.04	7.79	11.53	4.52 29.44	11.53	4.51	29.44

Table 1. Risk-adjusted differences in 30- and 365- day mortality

DIMETHYL MALONATE PROTECTS THE LUNG IN A MURINE MODEL OF ARDS

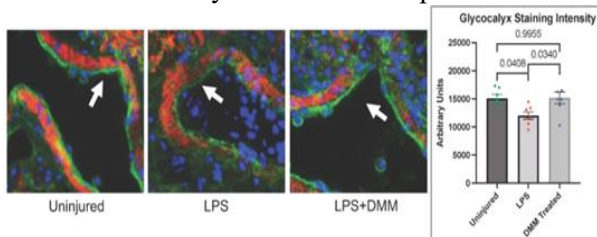
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Farhana Shaheen, BS; Derek Pociask, PhD;
Jay Kolls, MD; Olan Jackson-Weaver, PhD
Tulane School of Medicine
Invited Discussant: Rondi Gelbard, MD

Introduction: Succinate (SI) is a pro-inflammatory citric acid cycle metabolite that accumulates in tissues during certain pathophysiological states. Dimethyl malonate (DMM) is a competitive inhibitor of succinate dehydrogenase, which has been shown to reduce SI accumulation. We hypothesized that DMM would protect against inflammation in a murine model of ARDS.

Methods: C57BL/6 mice were given ARDS via 67.7 ug of intra-tracheally administered lipopolysaccharide (LPS). DMM (50 mg/kg) was administered via tail vein injection 30 minutes after injury, then daily for 3 days. The animals were sacrificed on day 4 after bronchoalveolar lavage (BAL). BAL cell counts were performed to examine cellular influx. Supernatant protein was quantified via Bradford protein assay. Animals receiving DMM (n=8) were compared to those receiving sham injection (n=8). Cells were fixed and stained with FITC-labelled wheat germ agglutinin to quantify the endothelial glycocalyx (EGX).

Results: Total cell counts in BAL was less for animals receiving DMM (6.93×10^6 vs. 2.46×10^6 , $p=0.04$). The DMM group had less BAL macrophages (168.6 vs. 85.1, $p=0.04$) and lymphocytes (527.7 vs. 248.3; $p=0.04$). DMM animals had less protein leak in BAL (1.48 vs. 1.15 ug/ul, $p=0.03$). Treatment with DMM resulted in greater staining intensity of the EGX in the lung (Figure). Untreated animals had a greater degree of weight loss than treated animals (14.3% vs. 4.8%, $p=0.04$). DMM prevented the upregulation of MCP-1 (1.66 vs. 0.92 RE, $p=0.02$) and ICAM-1 (1.40 vs. 1.01 RE, $p=0.05$).

Conclusions: DMM reduces lung inflammation and capillary leak in ARDS. This may be mediated by protection of the EGX and inhibition of MCP-1 and ICAM-1. DMM may be a novel therapeutic for ARDS.



DO VIRTUAL SURGICAL INTENSIVISTS ENHANCE ICU LIBERATION IN SURGICAL PATIENTS?

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Invited Discussant: Babak Sarani, MD

Introduction: Most critical care of surgical patients is managed by medical providers. Surgical Intensivists (SI) have a perioperative pattern recognition which facilitates rapid resuscitation and ICU liberation. We hypothesized that introduction of a Virtual Surgical Critical Care (VSCC) service, utilizing our Tele-Critical Care platform, may help reduce ventilator, ICU and hospital and days for surgical patients.

Methods: SI virtually evaluated surgical patients in 9 system-wide ICUs, provided consultation, and communicated with bedside medical and surgical teams. The SI recorded assessment of care prior to VSCC consultation as Optimal Practice (Opt), Generally Accepted Practice Standards (GAPS) met with Opportunity for Improvement (OFI), or GAPS not met (GAPSNM); reason for non-optimal care; and frequency of recommendation acceptance in a REDCap database. Reasons for non-optimal care were converted to measurements of opportunity days (Vent, ICU or hospital days) based on an assessment definition of 2 days for GAPSNM and 1 day for OFI. Multiple opportunities were only counted once per patient in order of highest to lowest priority (vent days, ICU days, hospital days).

Results: In initial 4 months of VSCC, 186 patients, the 3 most frequent opportunities were prolonged ventilation (7 GAPSNM, 34 OFI) for 48 excess ventilator days; delayed resuscitation (21 GAPSNM, 30 OFI) for 72 excess ICU days; delayed nutrition (9 GAPSNM, 33 OFI) for 51 excess hospital days. Excessive sedation contributed to 22% of the opportunities. As 55% of recommendations were accepted by bedside teams, annualized opportunities were 57.6, 86.4, 61.2 ventilator, ICU and hospital days respectively.

Conclusions: VSCC consultation identified opportunities to decrease ventilator, ICU and hospital days for surgical patients in a large healthcare system through optimal sedation practices, timely resuscitation and nutrition management. Incorporation of the VSCC recommendations could result in improved ICU outcomes with decrease in lengths of stay.

Session IIIA: Papers 9-19

Paper 11: 2:45 PM - 3:05 PM

SIRT1 DELETION EXACERBATES PNEUMONIA

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Invited Discussant: Matthew Lissauer, MD

Introduction: Despite antibiotic use and aggressive pulmonary toilet, pneumonia remains a common and highly lethal complication of traumatic injury. SIRT1, an NAD dependent deacetylase, has anti-inflammatory properties and has been shown to reduce the severity of ARDS in polymicrobial sepsis. The impact of SIRT1 in acute pneumonia, however, remains unknown. We hypothesize that SIRT1 deletion in pneumonia increases illness severity and recruitment of pro-inflammatory leukocytes.

Methods: 10–14-week-old male and female C57BL/6J (WT) mice and cre-inducible SIRT1 knockout (S1KO) mice were inoculated with 2.5×10^5 CFU *Pseudomonas aeruginosa*. Bronchoalveolar lavage fluid (BALF) and serum were plated on *Pseudomonas*-selective ceftrimide agar. Lung protein expression was evaluated by western blot and lung leukocyte populations quantified by flow cytometry. Data were analyzed by one-way ANOVA using Prism software.

Results: In WT mice, lung SIRT1 protein levels initially increased in the first 2hr following infectious insult ($p < 0.0001$) and then precipitously declined to below baseline from 4-12hr ($p < 0.01$). SIRT1 levels appeared to begin to recover between 24-48hr but were still significantly lower than baseline ($p = 0.04$). SIRT1 expression over time was inversely proportional to the severity of hypothermia and bacterial burden in the lung. By 12hr post-infection, SIRT1 levels in WT mice were comparable to levels in S1KO mice, and there was no difference in temperature or bacterial growth between these two groups. S1KO mice had a significantly higher percentage of immature neutrophils ($p = 0.029$) and a lower percentage of mature neutrophils compared to WT mice ($p = 0.038$).

Conclusion: Pneumonia creates a functional SIRT1 knockdown in mice, and this decrease correlates with clinical severity. SIRT1 deletion causes a left shift in neutrophil response within the first 12hrs, potentially indicating SIRT1 deletion leads to a more severe acute inflammatory response. Targeting SIRT1 may prevent excessive inflammation and subsequent lung injury seen in early pneumonia.

**USING MICROFLUIDIC SHEAR TO ASSESS TRANSFUSION
REQUIREMENTS IN TRAUMA PATIENTS**

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Kimi M. Tanaka, BS; Randi J. Mays, MSW, PMP;
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Invited Discussant: Christopher Dente, MD

Introduction: Viscoelastic assays have widely been used for evaluating coagulopathies but lack the addition of shear stress important to in vivo clot formation. Stasys technology subjects whole blood to shear forces over factor-coated surfaces. Microclot formation is analyzed to determine clot area (CA) and platelet contractile forces (PCF). We hypothesize this novel assay will provide utility about trauma-induced coagulopathy and transfusion requirements.

Methods: Blood samples were collected on adult trauma patients from a single-institution prospective cohort study of high-level activations. Patient and injury characteristics, transfusion data, and outcomes were collected. Thromboelastography (TEG), coagulation studies, and Stasys were run on paired samples collected at admission. Stasys clot area (CA) and platelet contractile forces (PCF) were quantified as area under the curve calculations and maximum values according to manufacturer normal ranges. Data was compared using Pearson's correlation.

Results: From March 2021-January 2023, 108 samples were obtained. Median age was 37 (IQR 28-52), patients were 78% male. 72% suffered blunt trauma, 26% had an injury severity score (ISS) ≥ 25 . A decrease in Stasys clot area (CA) correlated with transfusion of red blood cells (RBCs) at 12-24 hours ($p=0.04$), fresh frozen plasma (FFP) at 12-24 hours ($p=0.09$), and platelets (PLTs) at 6-12 hours ($p=0.08$). Elevated platelet contractile forces (PCF) positively correlated with prothrombin time (PT; $p=0.06$), while decreased PCF correlated with higher ISS ($p=0.047$). A decreased maximum PCF showed negative correlation with overall transfusion in 24 hours ($p=0.04$) as well as transfusion of RBCs, FFP, and PLT in the first six hours ($p=0.02$, $p=0.02$, $p=0.03$, respectively).

Conclusion: Assessing coagulopathy in real-time remains challenging in trauma patients. In this pilot study, we demonstrated that microfluidic approaches incorporating shear stress could predict transfusion requirements at time of admission as well as requirements in the first 24 hours.

**ENDOTHELIOPATHY OF TRAUMA IN CHILDREN:
ADMISSION SYNDECAN LEVEL IS ASSOCIATED WITH INJURY
AND OUTCOME**

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University of Pittsburgh Medical Center
Invited Discussant: Bindi Naik Mathuria, MD, MPH

Introduction: The contribution of the endothelium to trauma-induced coagulopathy has not been thoroughly investigated in injured children.

Methods: This is a prospective observational study of injured children (age <18) presenting to an academic pediatric trauma center as a highest-level trauma activation. Syndecan-1 level was collected at 0 and 24 hours following hospital arrival. Children were categorized by injured vs uninjured based on results of trauma evaluation. Demographics, injury characteristics, vital signs, and clinical labs were recorded. A composite clinical outcome was defined as death or receipt of any blood product transfusion within 24 hours of hospital arrival. Statistical tests were performed to 1) characterize Syndecan levels in a pediatric cohort; 2) assess impact of injury characteristics and therapeutics on Syndecan levels; and 3) assess for any association between Syndecan level and outcomes.

Results: There were 121 subjects included in the analysis: 96 (79%) injured and 25 (21%) uninjured. There were no differences between groups in age [median (IQR) 11 years (4-14)], sex (68% male), or race. The injured cohort had median (IQR) injury severity score (ISS) of 16 (9-21), 75% blunt mechanism, 26% received blood product transfusion, 3% 24-hour mortality, 6% in-hospital mortality rate. Median (IQR) Syndecan level on admission was significantly higher in injured vs uninjured cohort [44 (21-75) vs 25 (17-42); $p=0.04$]. Admission base deficit was significantly correlated with Syndecan level ($r=0.8$, $p<0.001$); no association with traumatic brain injury or injury mechanism was seen. Regarding outcomes, children with elevated Syndecan on admission had significantly increased odds of poor outcome; every 10 ng/mL increase in Syndecan was associated with 10% increase in the odds of death or transfusion ($p<0.001$). Transfusion with any blood product was associated with significant decrease in syndecan from 0 hours to 24 hours [Δ syndecan = -17 (-64- -5) vs -8 (-19-2); $p<0.001$].

Conclusion: Elevated admission Syndecan level, suggestive of endotheliopathy, was associated with shock and poor outcomes after injury in children. Larger cohort studies are required to fully describe the complexities of TIC and investigate the benefit of therapies targeting endotheliopathy in pediatric trauma.

NETOSIS OCCURS EARLY AFTER TRAUMA: DEVELOPMENT OF A MURINE POLYTRAUMA MODEL

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Dong Chen, MD; Jing-Fei Dong, MD; Rosemary A. Kozar, MD;
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Mayo Clinic

Invited Discussant: Joseph Rappold, MD

Introduction: Neutrophil Extracellular Traps (NETs) contribute to trauma-induced coagulopathy. We aimed to develop a murine polytrauma model that induces thromboinflammatory response i.e., NETosis and accelerated thrombin generation.

Methods: Male mice (8 – 12 weeks) were either subjected to polytrauma (n = 10) – gastrocnemius crush, femur fracture, and laparotomy – or placed in an uninjured control group (n = 9). The mice were sacrificed via cardiac puncture performed 3 hours after injury. Whole blood samples were processed to platelet poor plasma for thrombin kinetics (Calibrated Automated Thrombogram), myeloperoxidase (MPO), and von Willebrand Factor (vWF) measurements. Lung tissue was collected, and immunohistochemistry was performed to assess for Citrated H3 (Cit H3) and MPO. A cluster of NETosis was defined as three or more distinct neutrophils staining for Cit H3 at 400 X magnification. Data presented either as mean (SD) or median (IQR) with p value of < 0.05 being significant.

Results: Animals subjected to polytrauma had accelerated thrombin generation compared to controls, characterized by greater median peak height (nM) (61.3 [41.2, 73.2] vs. 28.4 [19.5, 37.5], p = 0.035), and shorter time to peak (min) (3.37 [2.81, 3.81] vs. 4.5 [4.08, 4.75], p = 0.046). Markers of neutrophil activation were greater following polytrauma than in controls (median MPO (ng/ml) 961.1 [858.1, 1116.8] vs. 481.3 [438.0, 648.9], p = 0.004). Paradoxically, plasma vWF, a marker of endotheliopathy, decreased following polytrauma compared to controls (median (ng/ml) 108.1 [99.5, 111.4] vs. 186.7 [166.4, 198.1], p < 0.001). NETosis, as evidenced by number of clusters of Cit H3 in the lung, was greater in polytrauma than in controls (mean 3 [2.9] vs. 0.2 [0.7], p = 0.009).

Conclusions: This murine polytrauma model demonstrates increased sequestration of NETs in lungs and accelerated thrombin generation, as early as three hours following injury.

**ENDOTHELIAL DYSFUNCTION IS DAMPENED BY EARLY
ADMINISTRATION OF FRESH FROZEN PLASMA IN A RODENT
BURN SHOCK MODEL**

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Invited Discussant: Samuel Mandell, MD, MPH

Introduction: Endothelial dysfunction has been implicated in the pathogenesis of burn shock affecting patients with large thermal injury. In response to injury, glycoalyx components like Syndecan-1 (SDC-1) are shed into circulation and have been used as a marker of endothelial damage. Previous work in our lab has shown crystalloid only resuscitation does little to mitigate the loss of endothelial function and resulting vascular leakage. However, we have also shown that plasma inclusive resuscitation (PIR) with fresh frozen plasma (FFP) ameliorates endothelial damage as demonstrated functionally with Evan's Blue Dye (EBD) assay. There remains a paucity of information regarding optimal timing and dosing of PIR and conflicting literature on the utility of SDC-1 as a marker. Therefore, we aimed to further examine the impact of PIR on endothelial dysfunction and glycoalyx shedding using clinically translatable timing and dosing.

Methods: Sprague-Dawley rats were used to create large thermal burns and uninjured controls. Rats were subjected to 40% total body surface area scald burn after which they were resuscitated with LR only or with LR plus early 1ml boluses of FFP (equivalent to a 250cc bolus in a 70kg human) at hours 0,2,4, and 8 hours post-injury. Blood was taken pre-injury and at hours 0,2,4,8,12 and 24 hours. Plasma SDC-1 levels were quantified by ELISA. Data are expressed as fold change from baseline.

Results: LR+early FFP administration reduced EBD extravasation when compared to LR only groups. LR only SDC-1 peaked at hour 8 (5.23, $p<0.05$). LR+early FFP SDC-1 peaked at hour 4 (2.60, $p<0.01$). When comparing LR only vs LR+FFP group, SDC-1 levels were reduced in the LR+FFP group at hour 8, 12 and 24 (5.23 vs. 2.07, $p<0.01$, 4.49 vs. 2.05, $p<0.01$, 3.82 vs 2.08, $p=0.01$, respectively).

Conclusions: Early administration of LR+FFP reduces the magnitude of SDC-1 shedding when compared to LR only resuscitation, consistent with our previous functional EBD assay results in this model. The present data add alignment of the two assays and provide further evidence of FFP's ability to mitigate endothelial dysfunction after thermal injury. The data also support the use of circulating SDC-1 as a surrogate marker of endothelial integrity.

DELAYED TXA AFTER TBI IMPEDES LEARNING, MEMORY: EARLY TXA IS FAVORABLE BUT NOT IN SHAM ANIMALS

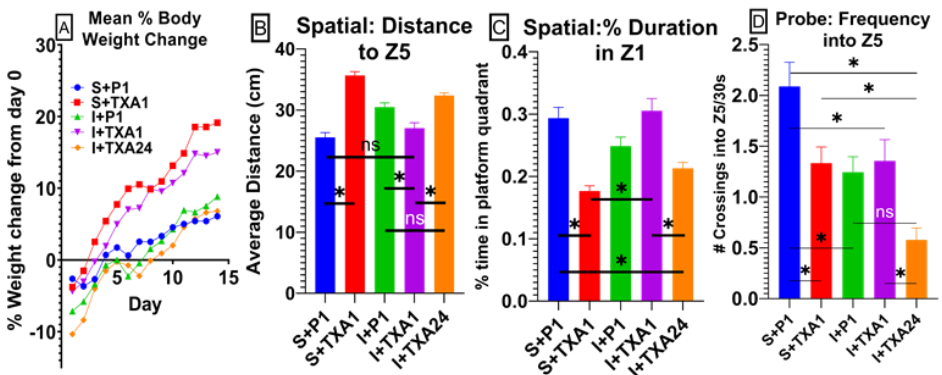
Michael Coons, BA; Matthew Culkin, BS; Advait Thaploo;
Priyanka Bele, MD; Kevin Browne; Christina Jacovides, MD;
Patricia Santos Carlin, MD; Lewis J. Kaplan, MD;
Douglas Smith, MD; Jose L. Pascual, MD, PhD
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Invited Discussant: Mayur Patel, MD, MPH

Introduction: Early but not late tranexamic acid (TXA) preserves blood-brain-barrier integrity, but it is unclear if dose timing affects cognitive recovery beyond hours post-injury. We hypothesized that early (1h post-TBI) TXA but not late (24h post-TBI) administration improves animal cognitive recovery for 14 days.

Methods: CD1 male mice (n=25) were randomized to severe TBI (Injury, I, controlled cortical impact) or sham craniotomy (S) followed by IV saline at 1h (placebo, P1) or 30mg/kg TXA at 1h or 24h (TXA1, TXA24). Daily body weights, Garcia Neurological Test (GNT) scores and Morris water maze exercises quantifying swimming traffic in the platform quadrant (Z1) & platform area (Z5) were recorded for up to 14 days.

Results: Of injured groups, I+TXA1 allowed fastest weight gain for 14 days (FigA) and only I+TXA1 showed rapid (day 1) normalization of GNT ($p=0.01$ vs. I+P1, I+TXA24). In summative spatial trials, compared to I+TXA1, I+TXA24 worsened learning (FigB: distance to Z5, FigC: % time in Z1, $*p<0.05$). Compared to I+TXA1, I+TXA24 worsened memory with less Z5 time (0.51 vs 0.16s, $p<0.01$) and crossing frequency into Z5 (FigD). Unexpectedly, TXA in uninjured animals (S+TXA1) demonstrated faster weight gain (FigA), but worse learning and memory (FigB-D).

Conclusion: TXA administration 24h post-TBI consistently worsens cognitive recovery compared to TXA administered 1h post injury. TXA in sham animals may lead to detrimental effects on cognition.



**A BENZODIAZEPINE-SPARING APPROACH TO PREVENTING
AND TREATING ALCOHOL WITHDRAWAL SYNDROME**

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Jason Hoth, MD, PhD, Andrew Nunn, MD
Wake Forest School of Medicine
Invited Discussant: Kaitlin Ritter, MD

Introduction: Alcohol withdrawal syndrome (AWS) represents significant cost to the hospitalized trauma population from a clinical and financial perspective. Historically, AWS has been managed with benzodiazepines. Despite their efficacy, benzodiazepines carry a heavy side effect profile. Recently, benzodiazepine sparing protocols for the prophylaxis and treatment of AWS have been used in medical patient populations. No such protocol has been developed and examined for safety and efficacy specifically within a trauma patient population.

Methods: In December of 2019, we implemented a benzodiazepine-sparing protocol for trauma patients identified as at risk for alcohol withdrawal on admission. Trauma patients admitted to an academic Level 1 trauma center before (CONV) and after (BS) the protocol implementation were compared. Outcomes examined include morphine milligram equivalent (MME) dosing rates, lorazepam equivalent dosing rates as well as CIWA scores, hospital length of stay (LOS), ICU LOS, and ventilator days.

Results: 387 conventional (CONV) and 135 benzodiazepine sparing (BS) patients were compared. ISS (13 vs 16, $p=0.08$) and admission alcohol levels (99 vs 147, $p=0.08$) were similar. Patients in the BS pathway had a lower maximum daily CIWA-Ar (3.98 vs 3.00, $p=0.03$). While MME/day was not different between groups (31.5 vs 33.4, $p=0.52$), mean lorazepam equivalents per day was significantly lower in the BS group (1.14 vs 0.23mg, $p<0.01$). LOS and vent days were not different between the groups.

Conclusion: Implementation of a benzodiazepine sparing pathway to both prevent and treat alcohol withdrawal syndrome in trauma patients is safe, reduces the daily maximum CIWA-Ar, and significantly decreases the need for benzodiazepines. Futures studies will focus on additional outcomes that are affected by avoiding AWS and benzodiazepines in the trauma population.

EXERCISE DOWN-REGULATES THE INFLAMMATORY RESPONSE AND DAMAGE ASSOCIATED MOLECULAR PATTERNS IN MURINE MODEL OF SEPSIS

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Krista Haines, DO, MA; Joseph Fernandez-Moure, MD, MS;
Sean Montgomery, MD, Suresh Agarwal, MD
Duke University

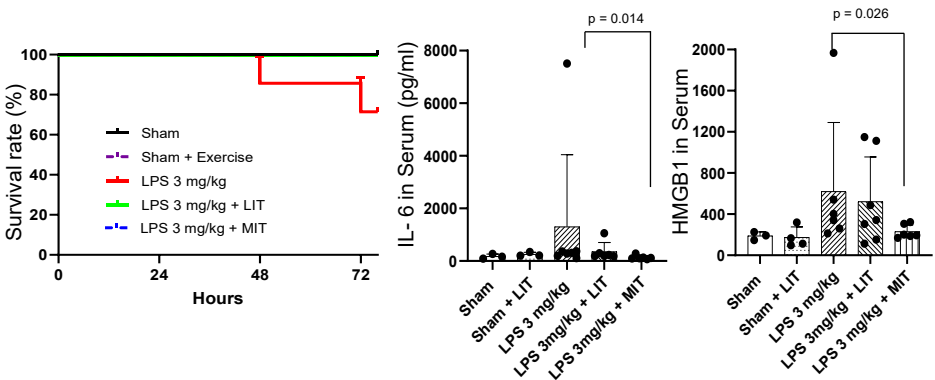
Invited Discussant: Kaushik Mukherjee, MD, MS

Introduction: Despite the adoption of the "Sick Role," exercise has been demonstrated to improve outcomes in ICU patients; however, the rationale for why it is beneficial remains elusive.

Methods: 22 week old, male wild-type mice were divided into 5 groups: Sham, Sham+Exercise, Lipopolysaccharide injection of 3mg/kg (LPS), LPS+Low Intensity Exercise (LIT), and LPS+Moderate Intensity Exercise (MIT). Exercise was performed 22 hrs after LPS injection and daily, with LIT being ambulation at 2 m/min and MIT being 4 m/min. In addition to mortality, Interleukin (IL)-1B, IL-6, IL-10, tumor necrosis factor (TNF), and High Mobility Group Box-type 1 (HMGB1) were assessed daily for 72 hrs.

Results: Non-exercised mice exposed to LPS survived of 71.43% at 72 hours whereas those exposed to LPS + exercise had a survival of 100%. TNF levels dropped within 24 hours in exercised mice; however these equalized over 72 h. At 72 hrs, IL-6 levels were significantly lower in MIT compared to LPS, where IL-1B and IL-10 levels were similar. HMGB1 levels were significantly lower in the MIT group compared to LPS alone.

Conclusions: Marked decreases in inflammatory response and damage associated molecular patterns are seen within 72 hours in septic mice exposed to exercise. More work is needed to elucidate the mechanistic underpinning of this phenomenon.



POST-TRAUMATIC PNEUMONIA EXACERBATES BONE MARROW DYSFUNCTION

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Philip Efron, MD; Alicia Mohr, MD

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Invited Discussant: Nicole Werner, MD, MS

Introduction: Pneumonia is a common complication after severe trauma, and these patients have worse outcomes with increased mortality. Critically ill trauma patients also have significant alterations in hematopoiesis that manifest as myeloid dysfunction and persistent anemia. Using a preclinical model of polytrauma and pneumonia, we sought to determine the impact on bone marrow function.

Methods: Male and proestrus female Sprague-Dawley rats (n=16/group) aged 9-11 weeks were subjected to either polytrauma (PT) (lung contusion, hemorrhagic shock, cecectomy, and bifemoral pseudofracture), or PT with postinjury day 1 *Pseudomonas pneumonia* (PT+PNA) and compared to naïve. Weight, urine norepinephrine (NE), % splenic erythroid progenitor cells (%CD45/71/117+), and bone marrow erythroid progenitors (CFU-GEMM, CFU-E, and BFU-E) were measured on day 7. Comparisons between naïve, PT and PT+PNA groups were performed with GraphPad. Significance was defined as *p<0.05 vs. naïve; **p<0.05 vs. PT counterpart.

Results: On day 7, PT+PNA rats lost significant weight compared to PT and naïve rats (-3.3g^{***} vs. +3.3g and +16.2g). Urine NE was significantly higher in PT+PNA rats compared to both PT and naïve (70^{***} vs. 27 and 31 ng/mL). Hemoglobin was significantly lower in PT+PNA compared to naïve (10.8^{*} g/dL vs. 12.1 g/dL). PT+PNA had more splenic erythroid progenitors and compared to PT and naïve (4.1^{***} vs. 1.1% and 0.8%). Growth of bone marrow CFU-GEMM, CFU-E, and BFU-E was all significantly inhibited following PT+PNA when compared with PT alone on day seven.

Conclusion: Pneumonia exacerbates persistent anemia and bone marrow dysfunction following polytrauma which impacts morbidity. In order to improve outcomes following trauma and critical illness, we need to better understand the pathophysiology during this chronic phase of illness.

ASSOCIATION BETWEEN GEOSPATIAL ACCESS TO TRAUMA CENTER CARE AND MOTOR VEHICLE CRASH MORTALITY IN THE UNITED STATES

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Madhu Subramanian, MD; Alistair Kent, MD, MPH; Mariuxi Manukyan, MD; Joseph Sakran, MD, MPA, MPH; Kent Stevens MD, MPH;
Elliott Haut, MD, PhD; Avery B. Nathens MD, PhD;
Carlos Brown, MD; James P. Byrne, MD, PhD
Johns Hopkins University
Invited Discussant: Cherisse Berry, MD

Introduction: Timely access to trauma care is highly variable across the United States (US). Motor vehicle crashes (MVC) remain a leading cause of trauma death. The objective of this study was to measure the association between geospatial access to trauma center care and MVC mortality in US counties.

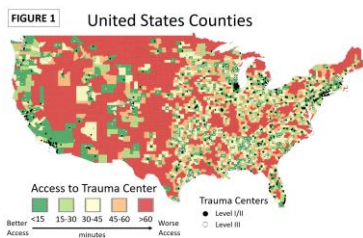
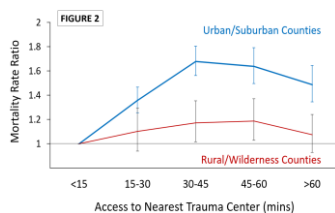
Methods: We performed a population-based analysis of MVC fatalities in 3,141 US counties representing the entire US population (2017-2020). ACS or state-verified level I-III trauma centers (n=1,054) were mapped using ArcMap. Geospatial network analysis estimated the ground transport time to the nearest trauma center from the population-weighted centroid of each county. In this way, the exposure was the average access time (AT) to trauma care for each county population. The outcome was county MVC mortality rate, derived using NHTSA's FARS database. Mixed-effects negative binomial regression was used to measure the association between AT and county MVC mortality, adjusting for population demographics (age, sex, race), social vulnerability index, rurality, population density, nearest trauma center level of designation, helicopter EMS access, and state traffic safety laws. Effect modification was explored between AT and rurality.

Results: During the study period 92,398 people died in fatal crashes in the US.

Approximately 60% of the US population resided in 536 (17%) counties with AT<15mins, while 6% of the population resided in 1,092 (35%) counties with AT>60mins (**Figure 1**). Longer AT was associated with higher risk-adjusted MVC mortality (AT, <15 vs >60mins; 5 vs. 15 deaths/100,000 person-years; Mortality Rate Ratio, 1.48; 95% CI, 1.42–1.55). This relationship differed significantly between

urban/suburban and rural/wilderness counties (P for interaction, <0.001). AT and MVC mortality were significantly lower in urban/suburban vs. rural/wilderness counties (median AT, 28 vs. 64 mins; MVC mortality, 6 vs. 17 deaths/100,000 person-years). However, the risk-adjusted association between longer AT and MVC mortality was significantly greater in urban/suburban counties (**Figure 2**), indicating that other crash or trauma system-related factors likely predominate in rural environments.

Conclusions: Access to trauma center care is significantly associated with MVC mortality across the spectrum of rurality. However, variations in access are associated with mortality to a lesser degree in rural/wilderness counties. These data highlight the need to elucidate the disparate roles of trauma system factors between rural and urban environments.



RCT TO STUDY EFFECT OF IMMEDIATE POST OPERATIVE PROSTHESIS VS CONVENTIONAL PROSTHESIS ON BALANCE & QOL IN BK AMPUTEES FOLLOWING TRAUMA

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A. S. Moorthy, PhD; Rajesh Sagar, MD; Pranabh Kushwaha, MS;
Subodh Kumar, MD; Amit Gupta; Biplab Mishra; Pratyusha Priyadarshini;
Abhinav Kumar, DNB, FNB, FACS; Narendra Choudhary; Dinesh Bagaria
All India Institute of Medical Sciences New Delhi India
Invited Discussant: Navpreet Dhillon, MD

Introduction: Lower-extremity amputations have a significant impact on an individual's mental and physical well-being. Amputee rehabilitation presents a number of challenges in providing holistic care to such patients. Immediate post-operative prosthesis (IPOP) application has multiple benefits which include quicker wound healing and early maturation of the stump, reduction in post-operative pain, edema, and phantom pain.

Methods: A total of 60 patients (30 in each group) were randomized. Intervention group patients received IPOP within 24 hours of amputation and control group patients were treated as per standard institute protocol and received conventional prosthesis post maturation of the stump.

Results: Both the groups were comparable in terms of age and gender distribution. 84.2% of patients in group A and 86.4% in group B had ISS and NISS scores less than 15. Majority of the patients in both the groups had MESS ≤ 7 . At 12 weeks, the mean scores of QOL for physical domain (29.0 ± 0.9 vs. 23.1 ± 1.3), psychological domain (23.0 ± 1.1 vs 19.6 ± 1.2), social domain (12.9 ± 1.2 vs. 8.2 ± 1.5) and environmental domain (30.2 ± 0.8 vs. 21.9 ± 1.9) were found to be statistically insignificant in IPOP group over conventional group. Statistically significant difference in AMP score was observed at 12 weeks (29.1 ± 3.5 vs 17.3 ± 2.9). Depression and anxiety decreased significantly in IPOP group. The mean scores of TAPES were found to be significant in group A over group B in psychosocial domain (47.6 ± 2.6 vs 33.6 ± 2.9), in activity restriction domain (21.3 ± 3.7 vs 13.5 ± 2.0) and in prosthetic satisfaction domain (20.3 ± 1.8 vs 15.3 ± 3.2) at 12 weeks. The mean scores of PST were significant in group A over group B for overall directional control (52.7 ± 9.3 vs 41.2 ± 6.7) and overall stability index (0.46 ± 0.22 vs 0.69 ± 0.20)

Conclusion: IPOP in below knee amputees following trauma improves overall quality of life, decreases depression and anxiety, increases mobility of the patient and improves balance as compared to the patients receiving standard treatment and conventional prosthesis.

IMPLEMENTATION OF THE 300CC-RULE SAFELY DECREASES CHEST TUBE PLACEMENT IN TRAUMATIC HEMOTHORAX

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Medical College of Wisconsin/Froedtert
Invited Discussant: Alexandra Briggs, MD

Introduction: Traumatic hemothorax (HTX) is effectively managed with a tube thoracostomy (TT); however, TT may carry a high complication rate. In 2017, a guideline was implemented at a Level I trauma center to observe any traumatic HTX ≤ 300 cc in hemodynamically normal patients. We hypothesized that this guideline would decrease TT placement with no increase in failure rates.

Methods: This is a single-center retrospective review of all adult patients admitted with a HTX on computed tomography (CT) before (2015-2016) and after (2018-2019) the guideline implementation. Exclusion criteria were TT placement prior to CT scan, absence of CT scan, death within 5 days of admission, and a concurrent pneumothorax >20 mm. HTX volume was calculated using Mergo's formula: $V=d^2 \times L$ (V: volume; d: depth; L: length). The primary outcomes included observation rates, TT placement, and observation failure, defined as the need for TT, video-assisted thoracoscopic surgery, or thoracotomy ≥ 24 hours after admission.

Results: A total of 391 patients met the inclusion criteria, of which 59% (n=230) were admitted after guideline implementation. There were no significant differences in demographics, comorbidities, or injury characteristics across both cohorts. After guideline implementation, there was a significant increase in observation rate (71% vs 52%; p-value <0.001) and a decrease in TT placement (42% vs 61%; p-value <0.001). A higher percentage of patients with a HTX ≤ 300 cc (80% vs 60%; p-value <0.001) were observed. On multivariate analysis, the post-implementation cohort were more than twice as likely to be observed (AOR: 2.39; 95%CI: 1.56-3.62; p-value <0.001). There were no significant differences in observation failure (18% vs 24%; p-value=0.34), pulmonary complications (20% vs 25%; p-value=0.34), 30-day readmission (7% vs 6%; p-value=0.22), or 30-day mortality (3% vs 5%; p-value=0.22) rates. The post-implementation group had a shorter hospital (10 vs 13 days; p-value=0.04) and intensive care unit (4 vs 6 days; p-value=0.04) length of stay (LOS).

Conclusion: The implementation of the 300cc guideline led to a decrease in TT placement correlated with a decreased LOS with no increase in failure or complication rates.

WHEN IS IT SAFE TO START VTE PROPHYLAXIS AFTER BLUNT SOLID ORGAN INJURY? A PROSPECTIVE AAST MULTI-INSTITUTIONAL TRIAL

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Tanya Egodage, MD; Patrick B. Murphy, MD; Chad G. Ball, MD;

Audrey L. Spencer, MD; Kelly Vogt, MD, PhD, FRCSC;

Jessica A. Keeley, MD; Stephanie Doris, DO; Marissa Beiling, DO;

Megan Donnelly, MD; Kenji Inaba, MD; The AAST VTE Prophylaxis Study Group

Los Angeles General Medical Center

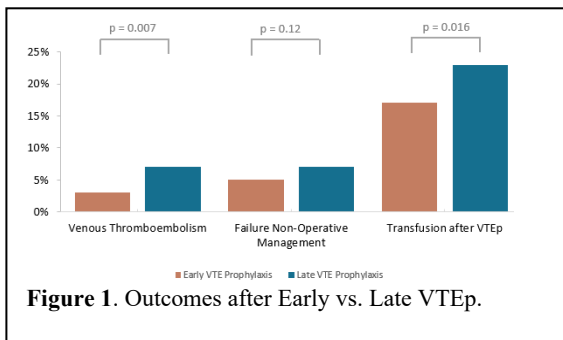
Invited Discussant: Douglas Schuerer, MD

Introduction: The optimal time to initiate venous thromboembolism (VTE) chemoprophylaxis (VTEp) after blunt solid organ injury remains controversial as VTE mitigation must be balanced against bleeding promulgation. Evidence from primarily small, retrospective, single-center work suggests VTEp ≤ 48 h is safe and effective. This study was undertaken to validate this clinical practice.

Methods: Blunt trauma patients presenting to 19 participating trauma centers in North America were screened over one year (08/2021-07/2022). Inclusions were age >15 years; ≥ 1 liver, spleen, or kidney injury; and initial nonoperative management (NOM). Exclusions were transfers, ED death, pregnancy, and concomitant bleeding disorder/anticoagulation/antiplatelet medication. *A priori* power calculation stipulated the need for 1158 patients. Time of VTEp initiation defined study groups: Early (≤ 48 h of admission) vs. Late (>48 h). Bivariate and multivariate analyses compared outcomes.

Results: In total, 1173 patients satisfied study criteria with 589 (50%) liver, 569 (49%) spleen, and 289 (25%) kidney injuries. Median patient age was 34 [25-49] years and 67% (n=780) were male. Median ISS was 22 [14-29] with AIS Abdomen 3 [2-3] and median AAST grade of solid organ injury 2 [2-3]. Early VTEp patients (n=864, 74%) had significantly lower rates of VTE (n=28, 3% vs. n=21, 7%, p=0.007); comparable rates of NOM failure (n=39, 5% vs. n=21, 7%, p=0.12); and lower rates of post-VTEp blood transfusion (n=145, 17% vs. n=71, 23%, p=0.016) when compared to Late VTEp patients (n=309, 26%) (Fig. 1). Late VTEp was independently associated with VTE (OR 2.23, p=0.049).

Conclusion: Early initiation of VTE chemoprophylaxis was associated with significantly reduced rates of VTE with no increase in bleeding complications. VTEp initiation ≤ 48 hours is therefore safe and effective and should be the standard of care for patients with blunt solid organ injury.



ASSOCIATION OF FOUR GEOGRAPHIC VULNERABILITY INDICES WITH FIREARM VIOLENCE IN A MAJOR US CITY

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William Ian McKinley, MD; Tanya Zakrisson, MD, MPH;
Selwyn Rogers, MD, MPH; Mark Slidell, MD, MPH;
Andrew Benjamin, MD, MS,
University of Chicago Medicine
Invited Discussant: Leah Tatebe, MD

Introduction: The recently developed Firearm Violence Vulnerability Index (FVVI) is a machine learning algorithm that uses population characteristics to predict shooting incidents at the census-tract level. FVVI was trained using firearm violence data from 7 major U.S. cities and showed precision when tested in Chicago, but it has not yet been compared to other pre-existing vulnerability indices. This study compares FVVI's accuracy to the Social Vulnerability Index (SVI), Area Deprivation Index (ADI), and Childhood Opportunity Index (COI).

Methods: Open-access 2015-2021 shooting incident data from the Chicago Data Portal was merged at the census tract level with risk scores from the FVVI, SVI, COI, and ADI.

Spatial autoregressive models were created for each index to

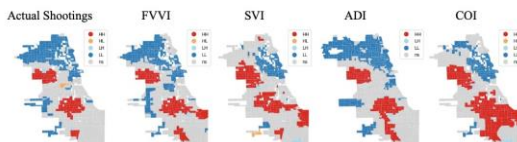
estimate the association between vulnerability and shooting incidents. Risk scores were re-scaled so that the regression coefficient represents the increase in shooting incidents within a census tract associated with each decile increase in vulnerability. Global and local Moran statistics were used to estimate geospatial associations, as shown on choropleth maps (Figure).

Results: All four vulnerability indices had a statistically significant positive association with shooting incidents (Table 1), though FVVI demonstrated the strongest association ($R^2 = 0.69$). For each decile increase in the FVVI, shooting incidents increased by 5.35 per 1000 population.

Conclusion: Each studied vulnerability index was predictive of shooting incidents at the census tract level, but FVVI outperformed the other pre-existing indices. Therefore, the FVVI might be the best measure for firearm violence risk stratification when developing public health prevention strategies, in policymaking and allocating resources, and for conducting firearm injury research.

Table 1. Comparison of Vulnerability Indices

Vulnerability Index	Regression Coefficient	R ²	p-value
FVVI	5.35	0.69	<0.001
SVI	1.94	0.28	<0.001
ADI	1.91	0.39	<0.001
COI	2.60	0.38	<0.001



WOULD YOU RATHER: QUANTIFYING PERCEPTIONS OF FUNCTIONAL STATUS AFTER TRAUMATIC BRAIN INJURY

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Mina Nordness, MD, MPH; Yue Gao, MS; Shayan Rakhit, MD;
Erika Rivera, MD; Frank Harrell, PhD; Mayur Patel, MD, MPH
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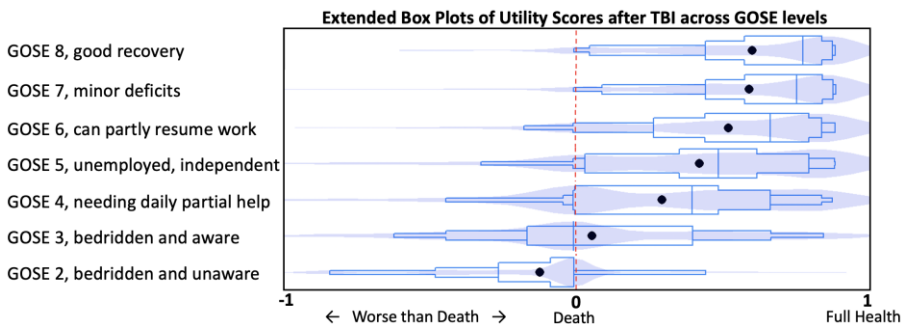
Invited Discussant: Weidun Alan Guo, MD, PhD

Introduction: Recovery after Traumatic Brain Injury (TBI) is variable and measured using the validated TBI clinical trial endpoint, Glasgow Outcome Scale-Extended (GOSE). A recent public survey quantified some GOSE states as worse than death. However, no health utilities exist for disability after an actual TBI. We hypothesized that intervals between GOSE health states are non-linear and unequal, with some states viewed worse than death.

Methods: This national computer-adaptive survey following EQUATOR/CHERRIES guidelines recruited adult surrogates of TBI dependents (injury >1 year prior). Using a standard gamble approach in randomized order, surrogates gave preferences for their loved ones' post-TBI categorical health states from GOSE 2-8. We calculated median [interquartile range, IQR] health utilities for each GOSE state, from -1 (worse than death) to 1 (full health), with 0 as reference (death, GOSE 1).

Results: Of 515 eligible, 298 surrogates (58%) consented and completed the scenarios on TBI patients' behalf. Their TBI dependents had a current median GOSE 5 [3-7], with 53% having undergone craniectomy or craniotomy, 35% feeding tube, and 24% tracheostomy. GOSE 2, GOSE 3, and GOSE 4 were rated worse than death by 89%, 64%, and 38%, respectively. The relationship was nonlinear, and intervals were unequal between states, with a bimodal distribution for GOSE 4 (see Figure).

Conclusion: In this index study of surrogate perceptions of patients' actual post-TBI disability, poor neurologic outcomes, GOSE 2-4, were perceived as worse than death by at least one in three. Acknowledging limitations of selection and response bias, these long-term perceptions may inform earlier post-TBI shared decision making.



GOALS OF CARE ARE RARELY DISCUSSED PRIOR TO FUTILE TRAUMA TRANSFER: IT'S OKAY TO SAY "NO"

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Invited Discussant: Anastasia Kunac, MD

Introduction: In 2020 the Critical Care Committee of the AAST ranked addressing goals of care in the acute care setting as the number one research priority. It is unknown how often the physician-to-physician transfer conversation includes discussion of patient goals of care. We hypothesized that physicians would rarely discuss goals of care (GOC) on transfer calls, even when faced with patients with catastrophic injuries.

Methods: We completed a retrospective cohort study of trauma patients between 2018 and 2022 who were transferred to a level 1 trauma center and died or were discharged to hospice without surgical intervention within 48 hours. Transfer call recordings were analyzed for GOC conversations.

Results: A total of 5,562 patients were accepted as transfers and 82 (1.5%) met criteria as potentially inappropriate. Eighty of the 82 patients had recorded transfer center calls and were analyzed. The most common transfer reason was traumatic brain injury (TBI) and need for neurosurgical capabilities (51%) followed by complex multisystem trauma (23%). There was explicit discussion of code status prior to transfer in 16/80 patients (20%) and a GOC conversation for 8/80 patients (10%). Appropriateness of transfer was discussed for 17/80 patients (21%) and at least one physician expressed explicit concerns of futility for 11/80 patients (14%), all of whom were subsequently transferred. Code status was changed immediately upon arrival for 12/80 patients (15%) and 8/41 patients (20%) transferred specifically for neurosurgical intervention were deemed to have non-survivable injuries based on the imaging and exam from the referring hospital.

Conclusions: Among a group of profoundly injured trauma patients, all of whom died or discharged to hospice within 48 hours of transfer, an explicit discussion of GOC and appropriateness of transfer occurred in less than 20%. This suggests that even when the catastrophic nature of patient injury is understood, transfers still occur, and patients and their families are subjected to an expensive, disruptive, and displacing experience with little to no anticipated benefit. A discussion of GOC and therapeutic objectives should be considered in all severely injured trauma patients prior to transfer.

DOES FRAILTY IMPACT FAILURE-TO-RESCUE IN GERIATRIC TRAUMA PATIENTS?

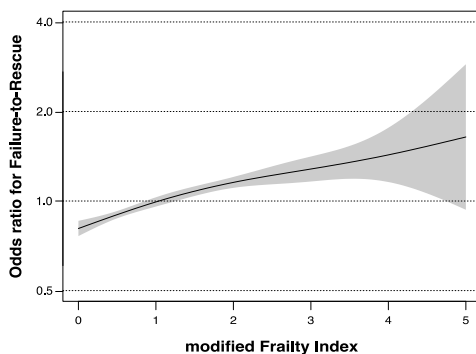
Mitsuaki Kojima, MD; Koji Morishita, MD; Tomohisa Shoko, MD;
Bishoy Zakhary, MPH; Todd Costantini, MD;
Laura Haines, MD; Raul Coimbra, MD, PhD
Tokyo Women's Medical University, Adachi Medical Center
Invited Discussant: Lisa Kodadek, MD

Introduction: Failure-to-rescue (FTR), defined as death after a major complication, has been studied as a metric of trauma quality. However, it is unclear whether FTR is affected by patient frailty, especially in the geriatric trauma population. We hypothesized that frailty increased risk of FTR in geriatric trauma patients

Methods: A retrospective cohort study was conducted using the TQIP database between 2015 and 2019. The cohort consisted of geriatric trauma patients (age ≥ 65 years) with an Injury Severity Score (ISS) of > 15 , who survived ≥ 48 hours after admission. Frailty was assessed using the modified 5-item frailty index (mFI). Patients were divided into two groups: frail (mFI ≥ 2) and non-frail (mFI < 2). Logistic regression analysis and a generalized additive model (GAM) were used to examine the association between FTR and patient frailty after controlling for age, sex, type of injury, level of trauma center, ISS, and vital signs on admission.

Results: A total of 65,384 geriatric trauma patients were included in the analysis, of whom 34.1% were frail (mean mFI; frail: 2.3 vs. non-frail: 0.9, $p < 0.001$). Compared with those in the non-frail group, frail patients were more likely to be older (age 77.0 vs. 75.0 years, $p < 0.001$), have a lower ISS (19 vs. 21, $p < 0.001$), and have a higher incidence of FTR (7.8% vs. 6.0%, $p = 0.002$). Logistic regression analysis revealed that frailty was an independent predictor of FTR (odds ratio [CI]: 1.32 [1.23–1.42], $p < 0.001$). The GAM plots also showed that the incidence of FTR increased linearly with the increase in mFI after adjusting for confounders (Figure).

Conclusion: Our study shows that frailty independently contributed to an increased risk of FTR in geriatric trauma patients. The impact of patient frailty must be considered if FTR is used as a measure of the quality of trauma care.



WHOLE BLOOD ON THE SCENE OF INJURY IMPROVES CLINICAL OUTCOME OF THE BLEEDING TRAUMA PATIENTS

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Invited Discussant: Juan Duchesne, MD

Introduction: Application of the whole blood to the trauma patients on the scene of injury is still not standard clinical approach. Nevertheless, initial data regarding the efficacy are positive.

Methods: We conducted single center, prospective, observational cohort study with application of one unit of packed red blood cells and one unit of fresh frozen plasma (during 2018 to 2020 years) or two units of low titer group 0 whole blood (during 2020 to 2022 years) to the bleeding trauma patients on the scene of injury by Helicopter emergency medical service. As an inclusion criteria, we used vital signs or severe anatomical injuries (hypotension below 100 mmHg, penetrating thoracic/abdominal injuries, unstable chest wall, unstable pelvis, open pelvic fracture and/or crush of lower limb). Primary outcomes were: feasibility, 24-hour and 30-day mortality, 24-hour transfusion requirements, 24-hour cumulative fluid balance and initial INR. As a control cohort there were included patients from prospective collected trauma database with the same inclusion criteria from the years 2016 to 2018.

Results: During the study periods there were enrolled 55, 43 and 47 patients respectively. The 24-hour mortality was the same, however, 30-day mortality was better in both intervention groups (16,3 % vs. 13,9 % vs. 14,8 %, $p=0,42$). We found significant decrease requirement of 24-hour transfusion volume (4986 ml vs. 4355 ml vs. 4121 ml, $p<0,05$), significant decrease of 24-hour cumulative fluid balance (10 207 ml vs. 8 038 ml vs. 7 869 ml, $p<0,05$) and significant decrease of the initial INR (1,17 vs. 1,13 vs. 1,10, $p<0,05$). There was no transfusion related reaction in any patients.

Conclusion: Application of the whole blood on the scene of injury to the trauma patients by HEMS is a safe procedure. There are positive effects on 30-day mortality, coagulation profile and decrease of the transfusion requirements. Likewise, multicenter prospective study is needed for confirmation of the positive effect of this treatment to mortality.

AN ANALYSIS ON THE USE OF COLD STORED PLATELETS IN COMBAT TRAUMA

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US Army

Invited Discussant: Jason Sperry, MD, MPH

Introduction: Damage control resuscitation has evolved over the past 20 years. The use of whole blood and/or components in 1:1:1 ratio of red blood cells, plasma, platelets, and cryoprecipitate are now the standard. However, there are limitations of room temperature stored platelets, mainly the short shelf-life of 5-7 days. Cold stored platelets while not lasting as long in circulation once transfused, can be stored for 10-14 days.

Methods: We used the Department of Defense Trauma Registry (DoDTR) and Armed Forces Medical Examiner System (AMFES) to identify casualties who received room temperature stored (RTSP) and/or cold stored platelets (CSP) between January 1, 2016 and February 29, 2020. Analysis was performed using Chi-square test, Fisher's exact, and Wilcoxon signed rank sum test. A logistic multivariable model was used to compare CSP to RTSP with outcome of death.

Results: A total of 302 patient were identified, with 158 (52.3%) in the RTSPs cohort and 144 (47.7%) in the CSPs cohort. In both groups, most were male and similar in age. The mean injury severity score (ISS) was higher in the CSPs cohort (24, standard deviation [SD] 13.6) vs RTSP cohort (21.6, SD 12.5, $p = 0.0236$). Twenty-four percent of the RTSPs cohort underwent surgery, whereas 13.2% of the CSPs cohort underwent surgery, $p = 0.016$. There was no difference in survival RTSP 88% and CSP 86.8%, $p = 0.7596$. Blood product and fluid administration was significantly higher in the CSP cohort. Massive transfusion was performed in 33.5% of the RTSP cohort and 53.5% of the CSP cohort, $p = 0.0005$.

Conclusion: This is the first analysis of recipients of CSPs compared to RTSPs from a combat setting, representing the initial US military experience with CSP transfusion. In our findings, the use of CSPs were not inferior to RTSPs. Given the improved logistics of a cold-stored product that facilitate availability in forward deployed locations, the desirable characteristics of CSP shown by in vitro studies, and the results of the initial US military experience, we recommend continued use of CSP in military environments.

GETTING OUT OF THE BAY FASTER: ASSESSING TRAUMA TEAM PERFORMANCE USING TRAUMA VIDEO REVIEW

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Daniel Holena, MD; Ryan Dumas, MD; TVRC Investigators
Vanderbilt University Medical Center
Invited Discussant: William Chiu, MD

Introduction: Minutes matter for trauma patients in hemorrhagic shock. While trauma team performance has been shown to impact patient outcomes, how team function impacts the time to the next phase of care has not been rigorously evaluated. We sought to measure trauma team performance. We hypothesized that better performance scores would be associated with decreased time to the next phase of trauma care.

Methods: This prospective multicenter observational study included hypotensive (SBP <90mmHg) trauma patients at 19 centers. Using Trauma Video Review, we analyzed team performance with the validated T-NOTECHS scale (nontechnical skills scale for trauma) in 5 domains: leadership, cooperation and resource management, communication, assessment/decision making, and situational awareness. The primary outcome was minutes from patient arrival in the trauma bay to next phase of care (e.g., operating room, interventional radiology); deaths in the bay were excluded. Secondary outcomes included time to initiation and completion of the first unit of blood. Associations between team dynamics and outcomes were assessed with a linear mixed effects model adjusting for injury severity score (ISS), injury mechanism, initial blood pressure and heart rate, number of team members, and the training level and gender of the trauma team lead.

Results: 442 patients met inclusion criteria. The median ISS was 22 [IQR 10-34] and the majority (61%) sustained blunt trauma. Median time to next phase of care was 24[17-35] minutes. Better leadership, communication, assessment/decision making, and situational awareness scores were all independently associated with faster times to next phase of care (all $p < 0.05$). Each 1-point worsening in the T-NOTECHS score (scale, 5-15) translated to 1.6 minutes more in the bay. The median number of resuscitation team members was 12[10-15], and larger teams were slower ($p < 0.05$). A better situational awareness score was associated with faster completion of the first unit of blood by 4-5 minutes on multivariate modeling ($p < 0.05$).

Conclusions: Better team performance is associated with faster transitions to the next phase of care in hypotensive trauma patients, and larger teams are not always faster. Trauma team training should focus on optimizing team performance towards hemorrhage control.

PROSPECTIVE VALIDATION OF A HOSPITAL TRIAGE PREDICTIVE MODEL TO DECREASE UNDERTRIAGE: AN EAST MULTICENTER STUDY

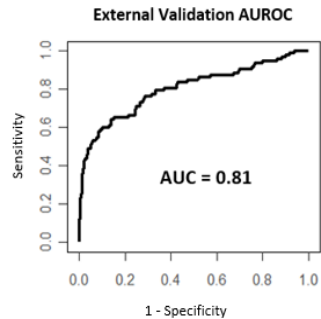
Elise A. Biesboer, MD; Courtney Pokrzywa, MD; Basil Karam, MD;
Benjamin Chen; Aniko Szabo, PHD; Bi Qing Teng, MS;
Sharfuddin Chowdhury, MBBS; Mark R. Hemmila, MD;
Michal Radomski, MD; Matthew Bernard; Brian K. Yorkgitis, DO;
Benjamin Weston, MD; Christopher J. Tignanelli, MD;
Marc A. de Moya, MD; Rachel S. Morris, MD
Medical College of Wisconsin
Invited Discussant: James Byrne, MD, PhD

Introduction: Tiered trauma team activation (TTA) allows systems to optimally allocate resources to an injured patient. Target under and overtriage rates of <5% and <45% are difficult for centers to meet, and high variability exists. Our objective was to externally validate a machine learning model deployed in the pre-hospital setting to predict Need for Emergent Intervention in Six hours (NEI-6), an indicator of need for TTA.

Methods: The model was previously developed, validated, and published using data from 31 US trauma centers. As part of an EAST multicenter trial, data was collected prospectively at 4 sites using a previously developed Trauma Intervention Prediction (TIP) mobile application. A weighted multiple logistic regression model was used to revise the previously developed model using the original dataset and 1 of the prospective sites. Three prospective sites (2 US, 1 International) were held out for external validation. Missing data was handled by median imputation and including indicator variables for missingness. An area under the receiver operating curve (AUROC) curve and area under the precision recall curve (AUPRC) was assessed in the validation cohort.

Results: A total of 14,421 patients were used in the training dataset. There were 579 patients in the external validation dataset across 3 sites. The model had an undertriage rate of 8.5% and an overtriage rate of 50.8% with AUROC of 0.81 and AUPRC of 0.63 in the validation set. Variables with the greatest association to NEI-6 included stab wound, assault intentionality, and central gunshot wound.

Conclusion: The revised TIP mobile platform hosting the NEI-6 predictive model approaches recommended under and overtriage rates, while significantly reducing variability of TTA across centers. A multi-institutional prospective randomized controlled trial is necessary to further compare TIP vs the standard of care.



**THIN AIR, THICK BLOOD: HIGH ALTITUDE TRAUMA CENTERS
HAVE INCREASED DEEP VEIN THROMBOSIS RATES**

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Michael W. Cripps, MD; Warren Dorlac, MD; Whitney Jenson, MD; Lauren
Steward, MD; Clay Cothren Burlew, MD;
Jen Baker, MD; Robert McIntyre, MD
University of Colorado
Invited Discussant: Eric Ley, MD

Introduction: Relative hypobaric and hypoxic conditions in high altitude environments produce physiologic consequences. Patients undergoing elective orthopedic procedures performed at altitudes > 4000 ft have higher deep vein thrombosis (DVT) and pulmonary embolism (PE) rates compared to those performed at ≤ 1000 ft. Similar findings are seen in patients with pelvic fractures and following bariatric surgery. We hypothesize that venous thromboembolism (VTE) rates will be elevated at high altitude centers.

Methods: This is a retrospective review of the American College of Surgeons Trauma Quality Improvement Program (TQIP) database from 2014-2019. Adults (age ≥ 18) are divided into LOW (< 1001 ft) or HIGH (> 4000 ft) altitude treatment by zip code analysis. VTE rates are compared by multivariable regression analysis as well as using a 1:2 propensity matched model.

Results: 79.1% of patient encounters occurred at low altitude (678 centers) and 4.8% were at high altitude (61 centers). DVT rates for all 4,052,240 patient encounters over 6 years were 0.32% at low altitude centers and 0.44% at high altitude centers; risk-adjusted odds ratio (OR) for DVT at high altitude was 1.51 [95% CI 1.41-1.62]. In patients with an Injury Severity Score (ISS) ≥ 16, the DVT rate was 1.08% (LOW) vs 1.56% (HIGH); risk-adjusted OR for DVT at high altitude with ISS ≥ 16 was 1.66 [1.52-1.82]. PE rates were 0.15% (LOW) vs 0.16% (HIGH) for all patients (risk-adjusted OR 1.13 [1.01-1.26]); in the ISS ≥ 16 sub-group the PE rates were 0.45% (LOW) vs 0.38% (HIGH) (risk-adjusted OR 0.96 [0.80-1.14]). Under the propensity matched model, DVT rates at higher altitude had an OR of 1.67 [1.52-1.81] for all patients.

Conclusion: Following traumatic injury, DVT rates are increased by 51-67% in higher altitude treatment facilities compared to their low elevation peers without a large effect on the PE rate. High altitude treatment is a risk factor for post-traumatic DVT and should be incorporated into risk models for post-traumatic complications.

LONG WAVELENGTH LIGHT EXPOSURE REDUCES SYSTEMIC INFLAMMATION AND ACUTE ORGAN INJURY FOLLOWING POLYTRAUMA IN MICE

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Patricia A. Loughran, PHD; Matthew R. Rosengart, MD;

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UPMC Presbyterian Hospital

Invited Discussant: Todd Costantini, MD

Introduction: Evidence suggests that variation in light exposure strongly influences the dynamic of inflammation, coagulation, and the immune system. Polytrauma induces systemic inflammation that can lead to end-organ injury. Here, we hypothesize that long-wavelength red light exposure reduces post-trauma inflammation and end-organ injury by comparison with short-wavelength blue light and ambient light.

Methods: C57Bl6 mice underwent a validated polytrauma model (cardiac puncture/hemorrhage, pseudo-femoral fracture, and liver crush injury) performed following 72 hours of exposure to red (617nm, 1,700lux), blue (321nm, 1,700lux), and fluorescent white light (300lux) (n = 6-8/group). The animals were sacrificed at 6- and 48-hours post-trauma. Plasma samples were evaluated and compared for pro-inflammatory cytokines expression level and markers of liver and renal injury. One-way ANOVA statistical tests were applied to compare study groups.

Results: Strikingly, long wavelength red light markedly reduced inflammatory response at 6 hours post-polytrauma compared to blue and ambient light, as evidenced by decreased levels of Il-6 (88.43 ± 32.95 vs 231.33 ± 122.49 and 211.60 ± 89.25 pg/ml, respectively; $p < 0.05$) and MCP-1 (214.06 ± 44.61 vs 408.97 ± 78.35 and 350.03 ± 27.92 pg/ml; $p < 0.001$ and 0.0001 , respectively). In addition, ALT concentrations in red-light-exposed animals were found to be lower at 6 hours post-polytrauma compared to ambient light (3100 ± 1089.26 vs 4710 ± 1008.41 IU/ml; $p < 0.05$), suggesting attenuation of acute liver injury. Concentration of cystatin C were also reduced following red-light exposure (2763.12 ± 228.58 and 3473.60 ± 328.26 pg/ml, ($p < 0.01$)), indicated reduced AKI.

Conclusion: Prophylactic exposure to long wavelength red light is associated with reduced systemic inflammation and minimized acute organ injury following polytrauma. Adjustments in light exposure may provide a novel strategy to reducing trauma related morbidity.

A HETEROGENOUS POPULATION OF EXTRACELLULAR VESICLES MOBILIZE TO LUNG POST-INJURY

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Jenny Kezios, BS; Jessica L. Weaver, MD, PhD;

Raul Coimbra, MD, PhD, FACS; Brian P. Eliceiri, PhD

University of California San Diego

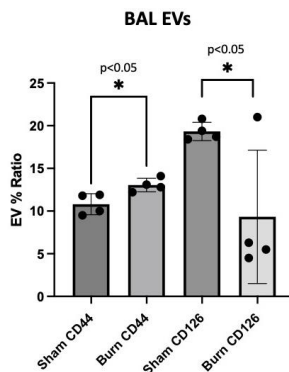
Invited Discussant: Timothy Pritts, MD

Introduction: Acute lung injury (ALI) and subsequent resolution following severe injury are coordinated by a complex lung microenvironment that includes extracellular vesicles (EVs). Here we focus on addressing the heterogeneity of EVs in the bronchioalveolar lavage (BAL) by applying recent advances in single vesicle flow cytometry (vFC). We hypothesized that specific immune-relevant mediators expressed on BAL EVs are candidate biomarkers of injury and injury resolution and are potential therapeutic targets in post-trauma ALI.

Methods: Mice were subjected to 30% TBSA cutaneous burn injury and underwent collection of BAL fluid 4 hours post-injury and compared to sham. EVs were purified from BAL by size exclusion chromatography (SEC) then subjected to size and concentration analysis. vFC was performed using fluorescent antibodies to quantify the expression of specific cell surface markers on individual EVs. Next, we evaluated human BAL specimens from injured patients to establish translational relevance of the mouse vFC analysis. Human BAL was collected from intubated patients following trauma or burn injury (n=4), EVs were purified by SEC and subjected to vFC analysis to evaluate for EV heterogeneity.

Results: A diverse population of EVs was mobilized to the alveoli after burn injury in mice. Quantitative BAL vFC identified significant increases in macrophage-derived CD44+ EVs (pre-10.8% vs. post-injury 13%, $p < 0.05$) and decreases in IL-6 receptor alpha (CD126) EVs (pre-19.3% vs. post-injury 9.3%, $p < 0.05$) (see Figure). BAL from injured patients also contained a heterogeneous population of EVs derived from myeloid cells, endothelium, and epithelium sources, with CD44+ EVs being highly detected.

Conclusion: Injury causes mobilization of a heterogeneous population of EVs in both animal models and injured patients. Defining EV release after injury will be critical in identifying diagnostic and therapeutic targets to limit post-injury ALI.



**THE EFFECT OF CIRCLE OF WILLIS ANATOMY ON OUTCOMES
FOR BLUNT CEREBROVASCULAR INJURIES**

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Maxwell Busch, MD; David Acuna, MD;
Samantha Greenseid, MD; Daniel Ojala, DO
Medical City of Plano
Invited Discussant: Ryan Dumas, MD

Introduction: Few small studies have evaluated the effect of the Circle of Willis (COW) anatomy among blunt cerebrovascular injuries (BCVI) on outcomes.

Methods: This retrospective cohort study included adult trauma patients with BCVI (7/17-8/21) admitted to 5 Level I and 13 Level II-IV trauma centers. Patients with abnormal COW anatomy were compared to those with normal COW anatomy. Those with anterior abnormalities (anterior cerebral artery, anterior communicating artery, and internal carotid artery) were further compared to those with posterior abnormalities (posterior cerebral artery). Outcomes included stroke, length of stay (LOS) intensive care unit LOS (ICULOS), intracranial hemorrhage (ICH), and mortality, $p < 0.05$.

Results: Of the 561 BCVIs, 17% (93) had an abnormal COW. There was a higher proportion of strokes (10% vs 4%, $p = 0.04$) among those with an abnormal COW than for those with a normal COW. Patients with an abnormal COW suffered ICHs more often than those with a normal COW (37% vs 20%, $p = 0.002$). There were no differences in the ICULOS (4 days vs 3, $p = 0.16$), LOS (7 days vs 7, $p = 0.66$), or the mortality rate (9% vs 7%, $p = 0.66$) for patients with an abnormal vs normal COW, respectively. Of those with an abnormal COW, 84% (78) had an anterior abnormality, 13% (12) had a posterior abnormality, 3% (3) patients had an abnormal posterior communicating artery. There was no difference in the stroke rate for anterior vs posterior abnormalities ($p = 0.41$). Patients with anterior abnormalities were more likely to have an ICH than those with posterior abnormalities (41% vs 0%, $p = 0.04$). ICULOS was significantly longer for patients with an anterior abnormality than for those with posterior abnormalities (5 days vs 2, $p = 0.01$). LOS was also significantly longer for those with anterior abnormalities than those with posterior (8 days vs 4, $p = 0.03$). Mortality rates were similar by anterior vs posterior abnormalities ($p > 0.29$).

Conclusions: Patients with an abnormal COW were significantly more likely to have a stroke and an ICH than those with a normal COW. Among patients with an abnormal COW, there was no difference in the stroke rate when comparing anterior to posterior abnormalities, but patients with anterior abnormalities were more likely to have an ICH, had a significantly longer LOS and ICU than patients with posterior abnormalities.

LOW-VOLUME PEDIATRIC TRAUMA CENTERS ACHIEVE BETTER OUTCOMES THAN HIGH-VOLUME ADULT TRAUMA CENTERS IN TREATING INJURED CHILDREN

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 Qaidar Alizai, MD; Audrey L. Spencer, MD;
 Hamidreza Hosseinpour, MD; Adam Nelson, MD;
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 The University of Arizona
 Invited Discussant: Eileen Bulger, MD

Introduction: Despite growing evidence of volume-outcome relationship in trauma, there is a paucity of data on the performance of high-volume adult trauma centers in managing pediatric trauma patients. We aimed to compare the outcomes of pediatric trauma patients managed at high pediatric volume adult Level I/II trauma centers (ATC) which are not pediatric verified to those managed at lowest volume pediatric level I/II trauma centers (LI/II PTC).

Methods: In this analysis of 2017 ACS-TQIP database, all pediatric trauma patients (<18 yrs) were included. Patients with missing information on facility identifiers were excluded. Patients were stratified based on the designation of the treating trauma center (TC) (level I/II ATC and level I/II PTC). TCs were classified into tertiles based on volume of patients (low [LV], middle [MV], and high volume [HV]). Outcomes were in-hospital complications and mortality. Multivariable logistic regression analyses were performed. Sub analysis was performed on patients with severe injuries (ISS >15).

Results: 83,419 patients managed at 393 centers (282 ATC; 111 LI/II PTC) were identified, of which 32% were treated at ATCs, 49% at LI PTCs, and 19% at LII PTCs. The mean age was 10 yrs, and 65% were male. The median ISS was 2 [1–6]. The overall rate of mortality and major complications were 1.5% and 1%, respectively. The median [IQR] number of pediatric trauma patients managed at HV ATC, LV LI PTC, and LV LII PTC were 276 [224 – 382], 318 [241 – 503], and 185 [141 – 211], respectively. On multivariable regression analyses, LV LI & LII PTCs were independently associated with lower odds of mortality and complications compared to HV ATC. The results of sub analysis on severely injured patients remained the same (**Table**).

Conclusions: LV PTCs outperform HV ATCs in the management of pediatric trauma patients. LV LII PTCs treat a smaller number of pediatric trauma patients compared to HV ATC, but still have better outcomes. These findings call for improved access to pediatric trauma centers.

Table: Independent Effect of ATC & PTC on Complications and Mortality (Overall)							
Complications	aOR	95% CI	p	Mortality	aOR	95% CI	p
HV ATC	Ref	Ref	Ref	HV ATC	Ref	Ref	Ref
LV LII PTC	0.63	0.44-0.91	0.02	LV LII PTC	0.64	0.44-0.92	0.02
LV LI PTC	0.72	0.54-0.95	0.01	LV LI PTC	0.52	0.38-0.70	<0.01
Independent Predictors of Complications and Mortality (ISS > 15)							
Complications	aOR	95% CI	p	Mortality	aOR	95% CI	p
HV ATC	Ref	Ref	Ref	HV ATC	Ref	Ref	Ref
LV LII PTC	0.49	0.31-0.79	0.04	LV LII PTC	0.60	0.39-0.92	0.02
LV LI PTC	0.58	0.40-0.82	0.03	LV LI PTC	0.44	0.31-0.63	<0.01

**PRIMARY CARE FOLLOW-UP IMPROVES OUTCOMES IN
OLDER ADULTS FOLLOWING EMERGENCY GENERAL
SURGERY ADMISSION**

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Invited Discussant: Marta McCrum, MD, MPH

Introduction: While pre-operative optimization improves outcomes for older adults undergoing major elective surgery, no such optimization is possible in the emergent setting. Surgeons must identify post-operative interventions to improve outcomes among older EGS (emergency general surgery) patients. Our objective was to examine the association between early follow-up with a primary care physician (PCP) and the risk of nursing home acceptance or death in the year following EGS admission among older adults.

Methods: Using population-based administrative health data in Ontario, Canada (2006-2016), we followed all older adults (≥ 65 years) for one year after hospital admission for EGS conditions. A multivariable Cox model was used to identify the association between early post-discharge follow-up with a patient's PCP and the time to nursing home acceptance or death while adjusting for confounders.

Results: Among 76,568 older EGS patients, 32,087 (41.9%) were seen by their usual PCP within 14 days of discharge and 9,571 (12.5%) were accepted to a nursing home or died within one year. PCP follow-up was associated with a lower risk of nursing home acceptance or death compared to no follow-up (HR 0.87, 95% CI 0.84–0.91). This effect was consistent across age and frailty strata, patients managed operatively and non-operatively, and patients who had both high and low baseline continuity of care with their PCP.

Conclusions: Timely follow-up with a familiar PCP was associated with a reduced risk of nursing home acceptance or death among older adults following EGS admission. Creating structures and processes of care to ensure that such follow-up is routinely arranged during discharge planning represents a potential key intervention as part of ongoing efforts to provide senior-friendly EGS care.

“DOOR-TO-PROPHYLAXIS TIME” AS A NOVEL QUALITY IMPROVEMENT METRIC IN PREVENTION OF VENOUS THROMBOEMBOLISM FOLLOWING TRAUMATIC INJURY

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Invited Discussant: Martin Schreiber, MD

Introduction: Numerous strategies have shown promise in decreasing venous thromboembolism (VTE) including early initiation of chemoprophylaxis, reducing missed doses, weight-based dosing, and dose adjustment using anti-Xa levels. However, many centers struggle with prolonged chemoprophylaxis initiation times. We hypothesized that door-to-prophylaxis initiation time would be the strongest modifiable risk for VTE, even after adjusting for competing risk factors.

Methods: A prospectively maintained trauma registry was queried for all patients admitted 07/17-10/21 who (1) were 18 years and older, (2) arrived as level-1 trauma activation, and (3) received emergency release blood products. Patients with deep vein thrombosis or pulmonary embolism were assigned to the VTE group, while those without were assigned to the No VTE cohort. Door-to-prophylaxis was defined as time from hospital arrival to first dose of VTE chemoprophylaxis (measured in hours). Univariate and multivariate analyses were then performed between the two groups.

Results: 2,047 patients met inclusion (106 VTE, 1,941 No VTE). There were no differences in baseline or demographic data. VTE patients had higher ISS (29 vs. 24), more evidence of shock by arrival lactate (4.6 vs. 3.9) and received more post-ED transfusions (8 vs 2 units); all $p < 0.05$. While there was no difference in need for enoxaparin dose adjustment or missed doses, door-to-prophylaxis time was longer in the VTE group (35 vs 25 hours; $p = 0.009$). Controlling for age, sex, ISS, lactate, and post-ED transfusions, every hour delay from time of arrival increased likelihood of VTE by 1.5% (OR 1.015, 95% CI 1.004-1.023, $p = 0.004$).

Conclusion: Increased door-to-prophylaxis time was significantly associated with an increased likelihood for VTE. Chemoprophylaxis initiation is one of the few modifiable risk factors trauma surgeons have to combat VTE, therefore, early initiation is paramount. Additionally, similar to door-to-balloon time in treating myocardial infarction and door-to-tPA time in stroke, “door-to-prophylaxis time” should be considered as a hospital metric for prevention of VTE in trauma.

FASTER REFILL IN AN URBAN EMS SYSTEM SAVES LIVES: A PROSPECTIVE PRELIMINARY EVALUATION OF A PREHOSPITAL ADVANCED RESUSCITATIVE CARE BUNDLE

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 Tulane University School of Medicine
 Invited Discussant: David Hampton, MD

Introduction: Military experience has shown a benefit to advanced resuscitative care (ARC) in severe hemorrhage. The benefits of ARC for trauma in civilian EMS systems with short transport intervals are still unknown. We hypothesized that ARC implementation in an urban EMS system would reduce hospital mortality.

Methods: This was a prospective analysis of ARC bundle administration between 2021 and 2022 in an EMS system with 70,000 annual responses. The ARC bundle consisted of calcium, tranexamic acid (TXA), and packed RBCs via a rapid infuser. ARC patients were compared to trauma registry controls from 2016 to 2019. Included were patients with penetrating injury and SBP \leq 90mmHg. Excluded were isolated head trauma or prehospital cardiac arrest. In-hospital mortality was the primary variable of interest.

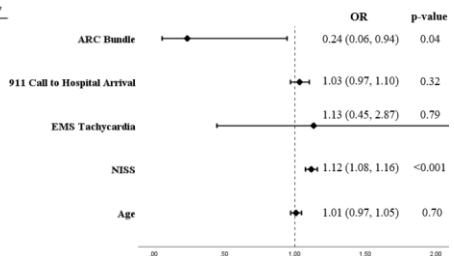
Results: Included were 195 patients (ARC=51, controls=144): median age of 32 years, with no difference in demographics, EMS vitals, or new injury severity score (NISS) between groups (A). At hospital arrival, ARC patients had lower median heart rate and shock index than controls (p=0.01). 24-hour mortality and in-hospital mortality were lower in the ARC group (p \leq 0.04). Multivariate regression revealed an independent reduction in hospital mortality with ARC (OR 0.24, 95%CI 0.06-0.94) (B).

Conclusion: Early ARC in a fast-paced urban EMS system is achievable and may improve physiologic derangements while decreasing patient mortality. ARC closer to the point of injury warrants consideration.

A. Univariate comparison of ARC vs controls.

Variable	Controls (n=144) median (IQR)	ARC Bundle (n=51) median (IQR)	p-value*
EMS Characteristics			
SBP, mmHg	80 (62-88)	71 (60-83)	0.22
HR, bpm	101 (72-126)	103 (72-136)	0.35
Shock Index	1.20 (0.87-1.60)	1.22 (0.77-1.77)	0.92
Endotracheal Intubation	11 (8%)	0 (0%)	0.04
911 Call to Hospital Arrival	20 (15-24)	24 (20-31)	<0.01
Hospital Characteristics			
ED SBP, mmHg	107 (80-124)	114 (88-140)	0.42
ED HR, bpm	97 (75-121)	79 (62-101)	0.01
ED Shock Index	0.88 (0.70-1.26)	0.79 (0.50-1.03)	0.01
NISS	17 (4-27)	18 (12-34)	0.07
24 Hour Mortality	27 (19%)	3 (6%)	0.03
In-hospital Mortality	33 (23%)	5 (10%)	0.04

B. Adjusted odds ratios for hospital mortality.



*Mann Whitney U for medians; Chi-square for frequencies
 Systolic Blood Pressure (SBP), Heart Rate (HR), Emergency Department (ED)

Odds ratio (OR), 95% confidence intervals (CI) derived from multivariable logistic regression

TO PLATE OR NOT TO PLATE: A PROPENSITY MATCHED ANALYSIS OF OUTCOMES IN PATIENTS UNDERGOING RIB FIXATION: AN MTQIP STUDY

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Invited Discussant: Raminder Nirula, MD, MPH

Introduction: Rib fractures account for nearly 15% of all trauma admissions in the United States, and have numerous downstream consequences post-injury, including chronic pain, decreased functional capacity, and inability to return to work. Historically, multi-modal pain control has been the accepted management strategy. Open reduction and internal fixation (ORIF) of rib fractures is now regularly performed but remains controversial due to lack of consensus on surgical indications. The aim of our study is to determine the impact of ORIF on patient outcomes.

Methods: Michigan Trauma Quality Improvement Program (MTQIP) data from January 1st, 2013, through June 30th, 2022, was used to identify patients who underwent ORIF for 3 or more traumatic rib fractures. 510 ORIF patients were propensity matched across 25 independent variables to 510 non-operatively managed (No-ORIF) patients. Primary outcomes included were death or hospice; secondary outcomes included were pulmonary complications (Acute Respiratory Distress Syndrome (ARDS), pneumonia, Ventilator Associated Pneumonia (VAP), pulmonary embolism (PE), and Intensive Care Unit (ICU) and hospital length of stay (HLOS).

Results: Forty seven out of 510 No-ORIF patients died or were transitioned to hospice, compared to 8 of the 510 ORIF patients ($p < 0.001$). For complications, VAP was higher in the ORIF cohort ($p = .05$). The ORIF group had a longer median ICU (6 versus 4 days $p < 0.001$) and median HLOS (10 days versus 6 days, $p < 0.001$). A sub-analysis of patients > 65 years of age identified 16 deaths or hospice in the No-ORIF group and 5 deaths in the ORIF group ($p = 0.038$), a mortality proportion that is almost three times higher in No-ORIF patients.

Conclusion: This study demonstrates a survival advantage for patients with 3 or more rib fractures who undergo rib fixation, even after accounting for other traumatic injuries and comorbid conditions through a robust propensity analysis. ORIF carries risks, it impacts VAP and increases both ICU and HLOS, however, the mortality benefit justifies these outcomes. The findings suggest that ORIF should be strongly considered in the rib fracture treatment algorithm, particularly for geriatric patients. This study provides additional support for performance of fixation in the elderly trauma patient with robust, validated data in well matched patient populations.

UNDERSTANDING FINANCIAL TOXICITY BURDEN AFTER INJURY: HIGHER TOXICITY ASSOCIATED WITH WORSE MENTAL HEALTH

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Kavitha Ranganathan, MD; Juan Herrera-Escobar, MD, MPH;
Ali Salim, MD; Geoff Anderson, MD, MPH
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Invited Discussant: Gregory Jurkovich, MD

Introduction: Financial toxicity (FT) is one of many challenges trauma survivors face. There is a lack of consensus on how to define and approach FT across all healthcare fields. We aimed to better understand post-trauma financial burden and how it affects long-term outcomes for patients.

Methods: Adult trauma patients with ISS ≥ 9 treated at one of three level-1 trauma centers were followed 6–12 months after discharge and interviewed.

Results: Of 567 total patients, 44% (250/567) suffered some form of FT after injury. FT was independently associated with younger age (OR 0.97 [95% CI: 0.95–0.98]), longer hospital stay (OR 1.05 [1.01-1.08]), lower education levels (OR 1.87 [1.26-2.75]), having two or more comorbidities (OR 2.20 [1.13-4.28]), and injury mechanisms including road accidents (OR 2.95 [1.59-5.48]) and intentional injuries (OR 4.23[1.33-13.44]). A strong social support network was protective against FT (OR 0.42[0.24-0.74]). No significant relationship was found with ISS, sex, race, ICU days, Medicaid status, or household size. After adjustment for confounding, patients with FT had worse mental health scores based on the Patient Reported Outcome Measure Index System (PROMIS). There was a significant negative linear relationship between the level of FT and worse mental health outcomes.

Conclusion: Nearly half of the surveyed patients experienced some form of FT after injury, demonstrating a substantial burden. Our findings suggest that patients who are younger, have less formal education, have multiple comorbidities, or have longer hospital stays may have a greater risk of FT and worse mental health outcomes. We must work to better understand the complex relationship between FT and patient, medical, and social factors to mitigate this undue burden of FT on our trauma patients.

Financial Toxicity component	Percent	Mental health scores and FT levels		
		FT Grade	Coefficient	P-value
1.Less income	23.09%	Grade 1	-2.15(-3.34 - -0.98)	0.000*
2.New governmental aid	18.74%	Grade 2	-4.58 (-6.03 - -3.14)	0.000*
3.Problem paying bills	22.46%	Grade 3	-5.47 (-7.30 - -3.62)	0.000*
4.Lost their job	8.99%	Grade 4	-5.56 (-8.18 - -2.92)	0.000*
5.No care because of the cost	6.41%			

**EXPLORING A NEW DEFINITION OF TRAUMA-INDUCED
COAGULOPATHY: TEG AND ROTEM ABNORMALITIES ARE
ASSOCIATED WITH MORTALITY**

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Madhu Subramanian, MD; Alison Smith, MD, PhD;
Mark J. Seamon, MD; Jeremy Cannon, MD
University of Pennsylvania
Invited Discussant: Matthew Kutcher, MD, MS

Introduction: Trauma-induced coagulopathy (TIC) carries significant risk, including increased mortality. Traditional TIC definitions rely on labs that result slowly and do not highlight therapeutic targets. We hypothesized that a TIC Score, based on TEG and ROTEM, is associated with packed red blood cell (pRBC) transfusion and in-hospital mortality.

Methods: This retrospective cohort study used a database of adult patients undergoing massive transfusion at seven level 1 trauma centers (2012-2018). A "TIC Score" was developed, with 1 point assigned for abnormal R-time (>8.9 min) for TEG or coagulation time (>79 sec) for ROTEM, α -angle (<65 degrees), or maximum amplitude (MA, <55 mm). TIC+ patients (TIC Score 1-3) were compared to TIC- patients (TIC Score 0). TIC Score composition and abnormal cutoff values were adjusted to investigate optimal thresholds. Multiple logistic and negative binomial regression were used to control confounders related to injury mechanism, presenting physiology, and hospital facility, while evaluating the association between abnormal TIC values, in-hospital mortality, and 24-hour pRBC transfusion.

Results: Of 1,499 total patients, 591 (39.4%) were TIC+ as defined by the baseline abnormal cutoff values. On adjusted analysis, patients with an abnormal maximum amplitude had increased pRBC transfusion volumes ($p<0.001$). Each unit increase in TIC Score was associated with a 24.8% increase in pRBC transfusion volume ($p<0.001$). Abnormal TIC Score components including α -angle ($p=0.015$) and maximum amplitude ($p=0.034$) also predicted mortality. Each increase in TIC Score was associated with a 53.1% increase in mortality risk ($p<0.001$). AUROC for TIC Score was 0.658; among patients with any TIC abnormalities, sensitivity and specificity were 59.5% and 67.8%, respectively. Unequal weighting of TIC Score components and adjustments to normal/abnormal cutoff thresholds maintained, but did not improve, the model's predictive power.

Conclusions: TIC Scores are independently associated with pRBC transfusion volume and mortality. This association persists with adjustment of abnormal cutoff thresholds and unequal weighting of TIC components.

KETAMINE FOR ACUTE PAIN AFTER TRAUMA (KAPT): A PRAGMATIC, RANDOMIZED CLINICAL TRIAL

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McGovern Medical School
Invited Discussant: Thomas Carver, MD

Introduction: Non-narcotic intravenous medications may be a beneficial adjunct to oral multimodal pain regimens (MMPRs) which reduce but do not eliminate opioid exposure and prescribing after trauma. We hypothesized that the addition of a sub-dissociative ketamine infusion (KI) to oral MMPR reduces inpatient opioid exposure.

Methods: Eligible adult trauma patients admitted to the intermediate or intensive care unit were randomized upon admission to our institutional MMPR per usual care (UC) or UC plus sub-dissociative KI for 24 to 72 hours after arrival. The primary outcome was morphine milligram equivalents per day (MME/d) and secondary outcomes included total MME, discharge with an opioid prescription (OP%), and rates of ketamine side effects. Bayesian posterior probabilities (pp) were calculated using neutral priors.

Results: A total of 300 patients were enrolled, 144 to KI and 156 to UC. Baseline characteristics were similar between groups. The injury severity scores for KI were 19 [14, 29] versus UC 22 [14, 29]. The KI group had a lower rate of long-bone fracture (37% versus 49%) and laparotomy (16% versus 24%). KI had an absolute reduction of 7 MME/day, 96 total MME, and 5% in OP%. Additionally, KI had a relative risk (RR) reduction of 19% in MME/day (RR 0.81 [0.69 – 0.95], pp = 99%), 20% in total MME (RR 0.80 [0.64, 0.99], pp = 98%), and 8% in OP% (RR 0.92 [0.76, 1.11], pp = 81%). The KI group had a higher rate of delirium (11% versus 6%, RR 1.37 [0.79, 2.21], pp = 86%); however, rate of other side effects such as arrhythmias and unplanned intubations were similar between groups.

Conclusion: Addition of a sub-dissociative ketamine infusion to an oral MMPR resulted in a decrease in opioid exposure in severely injured patients. Sub-dissociative ketamine infusions can be used as a safe adjunct to decrease opioid exposure in monitored settings.

WOULD YOU BE SURPRISED? PROSPECTIVE MULTICENTER STUDY OF THE SURPRISE QUESTION AS A SCREENING TOOL TO PREDICT MORTALITY IN TRAUMA PATIENTS

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Yan Shen, PhD; Dorraine Watts, PhD;

Ransom Wyse, MPH; Samir Fakhry, MD

Mission Hospital

Invited Discussant: Kathleen O'Connell, MD, MPH

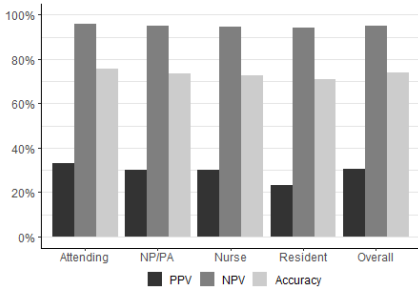
Introduction: The Surprise Question (SQ) (“Would I be surprised if the patient died within the next year?”) is a validated tool used to identify patients with limited life expectancy. As it may have potential to expedite palliative care interventions per ACS TQIP Palliative Care Best Practices Guidelines, we sought to determine if trauma team members could utilize the SQ to accurately predict 1-year mortality in trauma patients.

Methods: A multicenter, prospective, cohort study collected data (8/20-2/21) on trauma team members’ responses to the SQ at 24 hours from admission. One-year mortality was obtained via social security death index records. Positive/negative predictive values (PPV/NPV) and accuracy were calculated overall, by care team role, and by patient age.

Results: Ten Level I/II centers enrolled 1172 patients (87.9% blunt). Median age was 57 (IQR 36-74), median ISS 10 (IQR 5-14). Overall 1-year mortality was 13.3%. Positive predictive value (PPV), was low (30.1%) regardless of role (Fig 1). Mortality prediction minimally improved as age increased (PPV highest between 65-74 years old, 34.5%), but consistently trended to over-prediction of death, even in younger patients (Fig 2).

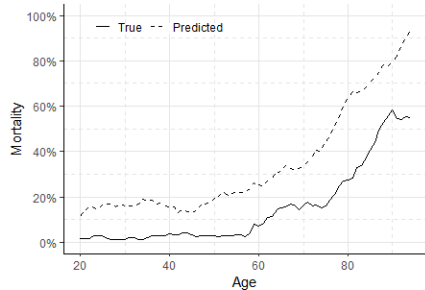
Conclusions: Trauma team members’ ability to forecast 1-year mortality using the SQ at 24 hours appears limited perhaps due to overestimation of injury effects, pre-injury conditions and/or team bias. This has implications for the TQIP Guidelines and suggests that more research is needed to determine the optimal time to screen trauma patients with the SQ.

Fig 1. Surprise Question Mortality Prediction by Provider Type



PPV: Correctly predicted death; NPV: Correctly predicted survival; Accuracy: Overall % correct

Fig 2. True and predicted mortality by age



Lines represent 10-year moving average mortality.

THE MORTALITY BURDEN FROM VARIATION IN PROVISION OF SURGICAL CARE IN EMERGENCY GENERAL SURGERY

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Wyatt P. Bensken, PhD; Elizabeth Pfoh, PhD; Jarrod Dalton, PhD;
Alfred Connors, MD; Jeffrey A. Claridge, MD; Adam Perzynski, PhD
MetroHealth Medical Center

Invited Discussant: Angela Ingraham, MD, MS

Introduction: For older adults with an emergency general surgery (EGS) condition (EGSc: appendicitis, diverticulitis, cholecystitis, hernia, peptic ulcer, bowel obstruction, ischemic bowel), guidance for operative decision-making guidance is limited. We hypothesized that patients who received treatment (either operative or nonoperative) which was discordant with a propensity model-driven likelihood of having an operation would have poorer outcomes than patients who received model-concordant care.

Methods: Adults aged 65+ with EGSc from the 2016-2017 National Inpatient Sample were identified. Each patient was assigned a propensity score (PS) for the likelihood of undergoing an operation, modeled from factors such as diagnosis, age, gender, race, shock, frailty, and hospital EGS volumes. A PS cutoff of 0.5 was used to define low probability (LP) and high probability (HP) for operation. Four groups were defined, of which two were model-concordant (LP-No Surgery, HP-Surgery) and two were model-discordant (HP-No Surgery, LP-Surgery). Adjusted logistic regression estimated the odds of in-hospital mortality for the four groups.

Results: Of 375,546 admissions (median age 77, 56% female), 21.2% underwent surgery. 14.5% had model-discordant care: 5.9% HP-No Surgery and 8.7% LP-Surgery. Model-discordant care was associated with significantly increased mortality (Table).

Conclusions: Nearly one in seven EGS patients received model-discordant care, which was associated with an increased odds of in-hospital mortality. Decreasing variation in use of operative management for EGS conditions may represent a substantial opportunity to improve care.

Factor	N (%)	Odds Ratio
Model Concordant: LP-No Surgery	274,025 (73.3%)	1 (ref)
Model Concordant: HP-Surgery	45,428 (12.2%)	0.83 (0.74-0.92)
Model Discordant: HP-No Surgery	21,879 (5.9%)	2.06 (1.86-2.27)
Model Discordant: LP- Surgery	32,655 (8.7%)	1.57 (1.49-1.65)

IMPROVING OUTCOMES IN EGS: CONSTRUCT OF A COLLABORATIVE QUALITY INITIATIVE

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Beckie Hoppe, RN, MSN; Laura Gerhardinger, MA; Kim Kramer, PA-C, MS;

Jill Jakubus, PA-C, MHSA, MS; Judy Mikhail, RN, PhD; Amanda Yang, MD;

Hugh Lindsey, MD; Roy Golden, MD; Eric Mitchell, MD;

John W. Scott, MD, MPH; Lena Napolitano, MD

University of Michigan

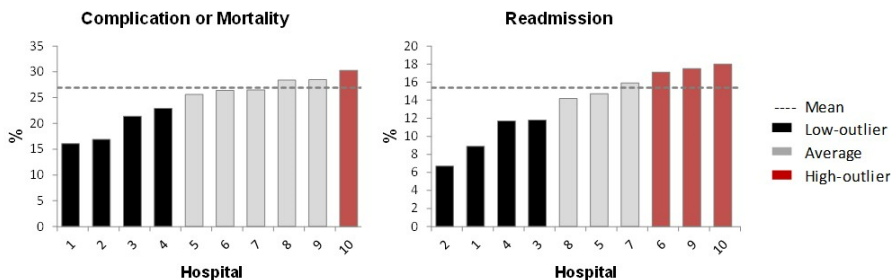
Invited Discussant: Garth Utter, MD

Introduction: Emergency general surgery (EGS) conditions are common, costly, and highly morbid. The proportion of excess morbidity due to variation in health systems and processes of care is poorly understood. We describe the construct of a collaborative quality initiative (CQI) for EGS.

Methods: Data were collected at 10 hospitals from 7/2019-12/2022. Five cohorts were defined: acute appendicitis, acute gallbladder disease, SBO, emergency laparotomy, and overall aggregate. Processes and outcomes investigated involved operative vs. non-operative mgmt, morbidity, mortality, and readmissions. Multivariable risk adjustment accounted for variations in demographic, comorbid, anatomic, and disease traits.

Results: There were 16,696 index cases and 2,847 patients with one or more readmission events. Overall aggregate mortality was 3.3%, morbidity 28%, and readmissions 17% (Table). Significant variation in outcomes between hospitals was observed after risk adjustment in the overall cohort (Figure).

EGS Disease Cohort	Index Cases	Non-op Cases	Mortality	Non-op Mortality	Complication or Mortality	Readmit
Acute Appendicitis	4,391	14%	0.3%	0.7%	21%	12%
Acute Gall Bladder Dx.	7,140	16%	1%	6%	23%	13%
Small Bowel Obstruction	3,283	66%	4%	4%	38%	27%
Emergency Laparotomy	1,882	0%	16%	--	64%	27%
Overall Aggregate	16,696	24%	3%	5%	30%	17%



Conclusions: A multihospital EGS collaborative reveals high morbidity with substantial variability in processes and outcomes among hospitals. Targeted collaborative quality improvement efforts can identify outliers in EGS care and are needed to optimize outcomes.

IS NON-OPERATIVE MANAGEMENT OF APPENDICITIS INFERIOR IN THE COVID-19 ERA?

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Ricardo Pietrobon, MD, PhD; Jose Diaz, MD; Paul C. Kuo, MD, MS, MBA;
Meagan Read, MD; on behalf of the N3C Consortium
University of South Florida Morsani College of Medicine
Invited Discussant: Shahin Mohseni, MD, PhD

Introduction: Previous studies on non-operative management (NOM) of acute appendicitis indicated comparable outcomes to surgery, but the effect of the COVID-19 pandemic on appendicitis outcomes remains unknown. The National COVID Cohort Collaborative (N3C) is a national database we use to study the effect of COVID-19 infection and pandemic-induced changes in healthcare delivery on patient outcomes. We compared outcomes of patients with acute appendicitis who underwent operative and NOM during the COVID-19 pandemic.

Methods: N3C was queried for adult patients with acute appendicitis who underwent NOM or appendectomy. We captured COVID-19 status: CA had positive test <2 weeks before treatment; CN tested negative on admission; and CR (recovered) had positive test >2 weeks before treatment. COVID vaccination status was noted, when available. Intention-to-treat was utilized for NOM. Propensity matching was performed.

Results: 50,383 patients: 18,738 underwent NOM (treatment failure rate 1.95%) and 31,645 appendectomy. NOM had higher mortality than operative (overall 2.1 vs. 0.4%, 30-day 0.4 vs. 0.1%, $p<0.01$). Amongst NOM, compared with CN, CA had longer LOS (1.78 vs. 1.42 days, $p<0.01$), higher 90-day mortality (1.2 vs. 0.7%, $p=0.04$), lower 90-day readmission (11.5 vs. 7.2%, $p<0.01$), but no difference in rate of failure of NOM (2.6 vs. 2.0%). Amongst operative, compared with CN, CA had no difference in LOS (1.31 vs. 1.29 days), 90-day readmission (5.6 vs. 5.8%), or 90-day mortality (0.1 vs. 0.1%). After propensity matching, CN-NOM (vs. CN-operative) had higher 90-day readmission (OR 2.09, $p<0.01$), 30-day complication (OR 1.28 $p<0.01$), and 90-day mortality (OR 5.11, $p<0.01$). COVID vaccination status did not significantly change outcomes when treatment and COVID status were held constant.

Conclusion: This study demonstrates a higher mortality rate amongst NOM of appendicitis than previously reported. After propensity matching, NOM of appendicitis remained inferior, indicating the altered healthcare delivery during the COVID-pandemic negatively affected patient outcomes.

**SURGICAL STABILIZATION OF RIB FRACTURES FOLLOWING
FLAIL CHEST: AN ANALYSIS OF CENTER-BASED
VARIABILITY IN PRACTICE AND OUTCOMES**

Mathieu Hylands, MD, MSc; David Gomez, MD, PhD;

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Avery B. Nathens, MD, PhD

Sunnybrook Health Sciences Center

Invited Discussant: Mark Seamon, MD

Introduction: There is wide variability in practice with regards to patient selection for surgical stabilization of rib fractures (SSRF). It is however not known whether this variation influences patient outcomes. Our objective is to determine if patients with a flail chest treated at trauma centers with a more liberal approach to SSRF have improved patient-important outcomes.

Methods: Using the Trauma Quality Improvement Project registry, we performed a retrospective cohort study of adults (16-80) admitted to a level I or II trauma center after sustaining a flail chest (2016-2020). We excluded patients treated at centers with 5 or fewer admission for flail chest per year. We used logistic regression to calculate the observed to expected rate of SSRF across centers, adjusted for case-mix. Hierarchical models were used to assess the association between the case-mix adjusted SSRF rate of the hospital at which a patient was treated and mortality. Secondary outcomes included days of mechanical ventilation, independent status at discharge, and tracheostomy. We performed a secondary analysis of associations between SSRF and outcomes, using an instrumental variable (IV) to adjust for measured and unmeasured characteristics that confound the decision to proceed with SSRF.

Results: We identified 26,575 patients with a flail chest across 354 trauma centers, of which 5,702 (21%) underwent SSRF. The median rate of SSRF across centers was 18% (IQR 7-33%), while case-mix adjusted rates ranged from 0 to 24%. Higher center-level quintiles of risk-adjusted rates of SSRF were not associated with mortality ($p=0.30$) or days of mechanical ventilation ($p=0.08$) but were associated with higher rates of tracheostomy ($p=0.04$) and lower rates of independent discharge ($p=0.04$). In the IV analysis, patient-level SSRF was associated with decreased hospital mortality (OR=0.75, 95% CI 0.72-0.77). As one would expect if patients survived in the SSRF cohort that would otherwise have died, SSRF was also associated with longer duration of mechanical ventilation (+1.58 days, 95% CI 1.52-1.65).

Conclusion: Patients treated at centers with a more liberal approach to SSRF do not appear to have lower hospital mortality, when compared to patients treated at centers with a more restrictive approach. There is a patient-level association between SSRF and improved mortality, but residual confounding by unmeasured institutional factors unrelated to SSRF cannot be ruled out.

ECONOMIC RISK FACTORS OF RURAL FIREARM VIOLENCE IN THE UNITED STATES

Sarabeth Spitzer, MD; Ali Salim, MD; Molly Jarman, PhD

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Invited Discussant: Ronald Stewart, MD

Introduction: The incidence of firearm injury in the US has increased steadily over the past thirty years. Urban and rural firearm violence are known to have very different epidemiology, especially considering intent of injury. While the relationship between socioeconomic factors and urban firearm injury is well established, less is known about socioeconomic risk factors for firearm injury in rural settings. We sought to identify community characteristics associated with firearm injury in rural communities.

Methods: We performed a nationwide, retrospective cohort study of rural census tracts using firearm injury incidence data from the Gun Violence Archive (2014-2019), linked with community-level socioeconomic data from the Agency for Healthcare. We used zero inflated negative binomial regression models to assess the relationship between per capita firearm injuries and median household income, median home price, median rental price, the Gini index (income inequality).

Results: Each year, 7,180 rural census tracts were included in our analysis. Over our study period, there were 4,617 individuals killed and 4,593 nonfatally injured in rural areas by firearms. Of the rural census tracts examined, all firearm injuries occurred in only 13.3% of tracts. When evaluating economic variables, median income, median rent, and Gini coefficient were statistically significant to $p < 0.0001$. For every \$1,000 increase in median income, there was an associated 4% decrease in firearm injuries per capita. For every \$100 increase in rent, there is an associated 10% increase in firearm injury per capita. Complete income inequality (Gini = 1.0) was associated with a 2.6x increase in incidence of firearm injury per capita, compared to complete equality (Gini = 0.0). Home value was not associated with incidence of firearm injury.

Conclusion: In rural settings, lower incomes, higher rent, and greater income inequality are associated with an increased incidence of firearm injury. This suggests economic distress may contribute to firearm injury in rural communities. Efforts to prevent firearm injury in rural settings should address socioeconomic factors as social determinants of health.

Session XIII: Papers 45-55

Paper 50: 2:55 PM - 3:15 PM

**STRUCTURAL RACISM, RESIDENTIAL SEGREGATION,
AND EXPOSURE TO TRAUMA: THE PERSISTENT
IMPACT OF REDLINING**

James M. Bradford, MD; Simin Golestani, MD; Maya Eldin;
Tatiana Cardenas, MD; Marc Trust, MD; Marissa Mery, MD;
Jayson Aydelotte, MD; Pedro GR Teixeira, MD; Joseph J. DuBose, MD;
Lawrence H. Brown, PHD; Michelle S. Bach, BS; Michelle Robert, MBA;
Sadia Ali, MPH; Deborah Salvo, PHD; Carlos VR Brown, MD
Dell Medical School

Invited Discussant: Randi Smith, MD, MPH

Introduction: As part of New Deal era federal housing policy, the Home Owners Loan Corporation (HOLC) developed maps grading US neighborhoods by perceived financial security. Neighborhoods with high concentrations of racial and ethnic minorities were deemed financially unstable and denied federal investment, a practice colloquially known as redlining. The aim of this study was to assess the association of historical redlining within a southern US city to spatial patterns of penetrating traumatic injury.

Methods: Retrospectively collected data from violent penetrating trauma admissions between January 1, 2014 – December 31, 2021, at the single Level 1 trauma center in a southern US city were utilized for analysis. Using ArcGIS, addresses where the injury took place were geocoded and spatial joining was used to match them to their corresponding census tract, for which 1935 HOLC financial designations are classified as: “Hazardous”, “Definitely Declining”, “Still Desirable” or “Best”. Tracts with financial designations of “Hazardous” and “Definitely Declining” were categorized as redlined. The incidence rate ratio comparing rates of penetrating trauma among historically redlined vs. non-redlined census tracts was calculated.

Results: 1,404 violent penetrating trauma admissions were identified for the study period, of which 226 occurred within the geographic boundary of the 1935 HOLC map and had valid location data for geospatial analysis. Among these, 58% occurred in historically redlined census tracts. The incident rate per 100,000 person years in redlined areas was 31.7 compared with 10.9 in non-redlined census tracts (IRR=2.9, 2.2-3.8, $p<0.001$).

Conclusions: Neighborhoods subjected to discriminatory redlining practices in 1935 continue to experience an almost 3-times higher incidence rate of violent penetrating trauma today. These results underscore the persistent impacts of structural racism and of historical residential segregation policies on exposure to trauma, and the need to address the social determinants of health to eliminate health disparities.

**IMPLEMENTATION EVALUATION OF TELE-TRIAGE
PATHWAYS FOR BURN CENTER
CONSULTATIONS AND TRANSFERS**

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Saman Arbabi, MD, MPH; Monica Vavilala, MD;

Fred Rivara, MD, MPH; Tam Pham, MD

University of Washington

Invited Discussant: Sharmila Dissanaiké, MD

Background: Consultation, outpatient referrals and transfers can be more efficient when injured patients are accurately triaged by urgency and complexity. In 2017, our regional burn center implemented a novel system in which transfer nurses (RNs) triage patients to defined pathways after review of securely transmitted images: green pathway for direct outpatient referral, blue pathway for discussion with the on-call burn provider, red pathway for consideration of transfer through the burn provider for non-severe burns, or black pathway for rapid transfer of severe burns. We analyzed trends in system adoption, resource optimization, and triage fidelity after pathway implementation.

Methods: The RE-AIM (reach, effectiveness, adoption, implementation, maintenance) framework was used to evaluate the implementation of this system. We analyzed transfer records for all acute burn referrals from 1/2017-12/2019 (reach). Primary outcomes were pathway assignment (adoption), change in provider call volume (adoption and effectiveness), and concordance of pathway assignment with disposition (implementation).

Results: 5,257 burn referrals were triaged between 2017-2019. In 9/2017, RN-directed training efforts increased pathway adoption from 22% to >90% by 2018. From 2018-2019, green pathway calls triaged by RNs reduced calls to burn providers by a mean of 40 ± 11 calls/month (27% of all calls). Over 84% of low acuity (green/blue) pathway patients were triaged to outpatient follow up ($p < 0.001$). There was substantial agreement between triage RN's and burn providers in determining triage to low- (green/blue) vs. high- (red/black) acuity pathways and transfer disposition ($\kappa = 0.74$). From 2018-2019, triage to red pathway decreased 10% and transfer from red pathway decreased by 9% ($p < 0.001$). This system remains in use.

Conclusion: We demonstrate successful implementation of well-adopted and high-fidelity tele-triage pathways. This model maintains the role of specialized centers while improving resource allocation by task-shifting triage of lower acuity patients, which may have positive implications for other transfer systems.

**TRAUMA SURGEONS EXPERIENCE COMPASSION FATIGUE – A
MAJOR METROPOLITAN AREA STUDY**

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Samuel Kingsley, MD; Grace Chang, MD Matthew Kaminsky, MD;
James Doherty, MD; David Hampton, MD
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Invited Discussant: Jennifer Hartwell, MD

Introduction: Compassion Fatigue (CF), the physical, emotional, and psychological impact of helping others, is composed of three domains, Compassion Satisfaction (CS), Secondary Traumatic Stress (STS), and Burnout (BO). Trauma surgeons (TS) experience work-related stress resulting in high rates of CF which can manifest as irritability, insomnia, or gastrointestinal disorders. We hypothesized that TS experience CF and there are potentially modifiable systemic factors to mitigate its symptoms.

Methods: All TS in a major metropolitan area were eligible. Personal and professional demographic information was obtained. Each participant completed five validated surveys: 1) Professional Quality of Life Scale (Pro-QOL), 2) Perceived Stress Scale (PSS), Multidimensional Scale of Perceived Social Support (MSPSS), 3) Adverse Childhood Events (ACE) Questionnaire, 4) Brief Coping Inventory (BCI), and 5) Toronto Empathy Questionnaire (TEQ). CF subscale scores (low risk:27-30, moderate:31-35, high:36-40, extremely high:>40) were recorded. Linear regression analysis assessed the demographic and environmental factors association with BO, STS, and CS. Variables significant on univariate analysis were included in multivariate models of BO, STS, and CF. Significance was $p \leq 0.05$.

Results: There were 57 TS (response rate:75.4% (n=43); Caucasian: 65% (n=28), male:67% (n=29)). TS experienced CF (BO:26 (IQR:21-32), STS:23 (IQR:19-32), CS:39 (IQR:34-45)). The PSS score was significantly associated with increased BO (Coef: 0.52, 95% CI:0.28-0.77) and STS (Coef: 0.44, 95% CI:0.15-0.73), and decreased CS (Coef: -0.51, 95% CI: -0.80- -0.23) ($p < 0.01$). Night shifts were associated with higher BO (Coef 1.55, CI 0.07-3.03, $p = 0.05$), conversely day shifts were associated with higher STS (Coef 1.94, CI 0.32-3.56, $p = 0.03$). Higher TEQ scores were associated with greater CS (Coef 0.33, CI 0.12-0.55, $p < 0.01$).

Conclusion: TS perform daily activities while experiencing moderate BO and STS. Identification of work- and system-related stressors may help inform CF reduction efforts.

VALIDATION OF THE TRAUMA CENTER FINANCIAL VULNERABILITY METRIC

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Invited Discussant: Robert Martin, MD

Introduction: Trauma centers serve some of the most vulnerable populations. Financial pressures may impact the lasting presence of these centers in communities. We evaluated the validity of the Financial Vulnerability Score (FVS) on changes to trauma center status and longevity.

Methods: Data was obtained from the RAND Corporation Hospital Cost Reports containing detailed financial characteristics and metrics. Hospital data were evaluated for calendar years 1996–2021. Adult trauma center levels (I, II, or III) were identified using the ACS Verified Trauma Center lists from 2003–present. Centers were matched to financial data using a probabilistic matching algorithm on name, address, city, and state. The FVS was calculated using six variables of financial liquidity and risk based on a national analysis and categorized as high, medium, or low risk. Exact logistic regression was performed to investigate multivariable probability for closure and loss of trauma verification.

Results: There were 558 adult trauma centers identified; 468 had full data to calculate the FVS: 160 (34%) were Level I, 184 (39%) were Level II, 102 (22%) were Level III, and 22 (5%) lost ACS verified status by the end of the study period. Among Level I hospitals, 28% were high risk compared to 30% of Level II and 49% of Level III ($p < 0.001$). There were 8 total closures detected, all in Level 2 or 3 centers. Closures among the high risk category were 3.7% vs. 0% in the moderate risk, and 1.2% in the low risk ($p = 0.041$). In the high-risk category, centers that lost their trauma verification were 14 times more likely to close compared to Level I centers ($p = 0.011$), and in the low risk category were 16.3 times more likely to close ($p = 0.058$).

Conclusion: The rate of closures over the study period was low but was significantly associated with higher financial vulnerability. Level 2 and 3 centers have significantly higher financial vulnerability and risk for closure or loss of verification. Association of ACS verification status and closure rate deserves further analysis.

DEEP LEARNING ALGORITHM FOR TRAUMATIC SPLENIC INJURIES DETECTION AND SEQUENTIAL LOCALIZATION

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Invited Discussant: Caroline Park, MD, MPH

Introduction: Splenic injury is the most common solid visceral injury in blunt abdominal trauma, and high-resolution abdominal computed tomography (CT) can adequately detect the injury. However, these lethal injuries sometime have been overlooked in current practice. Deep learning algorithms have proven their capabilities in detecting abnormal findings in medical images. The aim of this study is to develop a three-dimensional, unsupervised deep learning algorithm for detecting splenic injury on abdominal CT using a sequential localization and classification approach.

Methods: The data set was collected in a tertiary trauma center on 600 patients who underwent abdominal CT between 2008 and 2018, half of whom had splenic injuries. The images were split into development and test datasets at a 4:1 ratio. A 2-step deep learning algorithm, including localization and classification models, was constructed to identify the splenic injury. Model performance was evaluated using the area under the receiver operating characteristic curve (AUROC), accuracy, sensitivity, specificity, PPV, and NPV. Grad-CAM heatmaps from the test set were visually assessed.

Results: A total of 480 patients, 50% of whom had spleen injuries, were included in the development dataset, and the rest were included in the test dataset. All patients underwent contrast-enhanced abdominal CT in the emergency room. The automatic 2-step Efficient Net model detected splenic injury with an AUROC of 0.901 (95% CI:0.836-0.953). At the maximum Youden index, the accuracy, sensitivity, specificity, PPV, and NPV were 0.88, 0.81, 0.92, 0.91, and 0.83, respectively. The heatmap identified 96.3% of splenic injury sites in true positive cases.

Conclusions: The deep learning model can identify splenic injury on CT and further application in trauma scenarios is possible.

A COMPARATIVE ANALYSIS OF TRANEXAMIC ACID DOSING STRATEGIES IN TRAUMATIC MAJOR HEMORRHAGE

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Invited Discussant: Susan Rowell, MD, MBA

Introduction: Tranexamic acid (TXA) is a life-saving treatment for traumatic hemorrhage, but the optimal dose and timing of administration remain unknown. Different doses have been proposed for bleeding and traumatic brain injury, and alternative treatment strategies including single bolus, repeated bolus or a bolus plus infusion. The aim of this study was to determine the effect of different TXA dosing strategies on clinical outcomes in bleeding trauma patients.

Methods: This was a secondary analysis of a perpetual cohort study from a single Level 1 trauma center in the United Kingdom. Adult patients who activated the local major hemorrhage protocol (MHP) and received TXA were included. Primary outcome was 28-day mortality. Secondary outcomes were 24-hour mortality, multiple organ dysfunction syndrome (MODS), venous thromboembolism (VTE) and fibrinolysis measured by ROTEM.

Results: Over an 11-year period, 520 patients were included. Three dosing groups were identified: 1g bolus only (n=317), 1g bolus + 1g infusion over 12 hours (n=80), and 2g bolus (n=123). Demographics and admission physiology were similar, but there were moderate differences in injury severity (median ISS: 25, 29 & 25); and admission systolic blood pressure (median SBP: 99, 108, 99 mmHg) across the 1g, 1g+1g and 2g groups. 28-day mortality was 21% in each of the treatment groups. The incidence of MODS was significantly higher in the bolus+infusion group (84%) vs 1g bolus (64%) and 2g bolus (62%) group, $p=0.002$, but this relationship did not remain significant on multivariate analysis. VTE rates were similar in the 1g bolus (5%), 2g bolus (8%) and bolus+infusion groups (8%). There was no difference in ROTEM Maximum Lysis at 24 hours: 5% in both the 1g and 2g bolus groups vs 4% in bolus + infusion group.

Conclusion: In this study clinical outcomes and 24-hour fibrinolysis state were equivalent across the three different dosing strategies of TXA. Single bolus administration is likely preferable to a bolus+infusion regimen. A 1g bolus may be sufficient but further work is required in specific sub-populations, in particular patients with traumatic brain injury.

SEX-SPECIFIC DIFFERENTIAL EXPRESSION OF EXOSOMAL MIRNA FOLLOWING SEVERE TRAUMA

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Kolenkode Kannan, PhD; Valerie Polcz, MD; Jeremy Balch, MD;

Evan Barrios, MD; Shannon Wallet, PhD; Robert Maile, PhD;

Letitia Bible, MD; Philip Efron, MD; Alicia Mohr, MD

University of Florida College of Medicine

Invited Discussant: Niels Martin, MD

Introduction: Severe trauma disrupts bone marrow function and is associated with persistent anemia and altered hematopoiesis. Previously, plasma-derived exosomes isolated after trauma have been shown to suppress *in vitro* bone marrow function. However, the cargo contained in these vesicles has not been studied. We hypothesized that trauma plasma-derived exosomes exhibit microRNA (miR) changes that impact bone marrow function after severe injury.

Methods: Plasma was collected from a prospective, cohort study of trauma patients (n = 15; 7 males, 8 females) with hip and/or femur fractures and an injury severity score (ISS) ≥ 15 ; elective total hip arthroplasty (THA) patients (n = 8; 4 males, 4 females) served as operative controls. Exosomes were isolated from plasma with the Invitrogen Total Exosome Isolation Kit and RNA was isolated using a miRNeasy Mini Kit. Direct quantification of miRNA was performed by NanoString Technologies on a human miRNA gene panel and analyzed with nSolver with significance defined as $p < 0.05$.

Results: There were no differences in age or sex distribution between trauma and THA groups; the average ISS was 23. Trauma plasma-derived exosomes had 60 miR identities that were significantly downregulated and 3 miR upregulated when compared to THA ($p < 0.05$). Thirteen miR have a direct role in hematopoiesis regulation, including miR-223 and miR-451a. Further, male trauma plasma-derived exosomes demonstrated downregulation of 150 miR compared to male THA ($p < 0.05$). Female trauma plasma-derived exosomes demonstrated downregulation of only four miR and upregulation of two miR compared to female THA ($p < 0.05$).

Conclusion: We observed sexual dimorphism in miR expression from plasma-derived exosomes following severe trauma. Understanding sexually dimorphic miR expression provides new insight into sex-based changes in postinjury systemic inflammation, immune system dysregulation, and bone marrow dysfunction and will aid us in more precise future potential therapeutic strategies.

ALTERED PLATELET MITOCHONDRIAL FUNCTION ASSOCIATED WITH HYPERCOAGULABILITY IN A RODENT FRACTURE MODEL

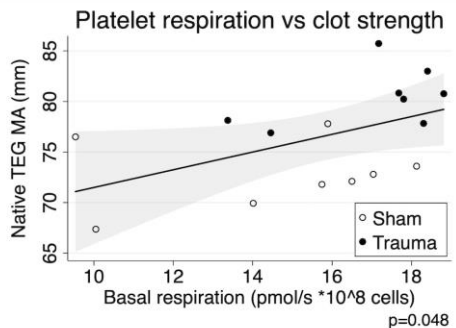
James B. Littlejohn, MD; Emily E. Grenn, MD; Kristen T. Carter, MD, MS;
Ana C. Palei, PharmD, PhD; Frank T. Spradley, PhD;
Jonathan P. Hosler, PhD; Ngoc H. Hoang, PhD;
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Invited Discussant: Julie Goswami, MD

Introduction: Post-injury hypercoagulability occurs in >25% of injured patients, increasing risk of thromboembolic complications. Understanding the specific role of platelets is challenging due to a lack of clinically relevant measures of platelet function. Platelet mitochondrial respirometry may serve as a marker of global platelet function, but has not yet been correlated with functional coagulation studies.

Methods: Wistar rats underwent isoflurane anesthesia, bilateral hindlimb fibula fracture, soft tissue and muscular crush injury, and bone homogenate injection (n=8), versus sham anesthesia (n=8). Animals were sacrificed at 24h. Basal respiration, mitochondrial leak rate, maximal oxidative phosphorylation, and Complex IV activity were measured in intact platelets using high-resolution oximetry (Oroboros Oxygraph O2k). Results were normalized to platelet cell number. Citrated native thromboelastography (TEG) was performed in triplicate.

Results: Citrated native TEG maximal amplitude (MA) was significantly higher (80.4 ± 2.9 vs. 72.7 ± 3.5 mm, $p < 0.001$) in trauma compared to sham rats 24h after injury. Injury was not significantly associated with differences in intact platelet mitochondrial leak rate ($p = 0.467$) or maximal oxidative phosphorylation ($p = 1.00$), but showed a trend towards increased basal respiratory rate in trauma vs. sham animals (17.0 ± 2.0 vs. 14.6 ± 3.2 pmol/s per 10^8 cells). Overall, platelet basal respiration significantly correlated with native TEG-MA (Pearson's $r = 0.501$, $p = 0.048$).

Conclusion: Platelet mitochondrial basal respiration correlates with the degree of post-injury hypercoagulability in this rodent hindlimb fracture model. Several mitochondrial-targeted therapeutics exist in common use that are under-explored but hold promise as potential antithrombotic adjuncts.



**SILENCING HEPATIC MCJ IN AGED MICE ATTENUATES ER
STRESS AND DECREASES LIVER INJURY
AFTER MAJOR TRAUMA**

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University of Colorado

Invited Discussant: Anupamaa Seshadri, MD

Introduction: Burns are a devastating form of trauma. Elderly burn patients exhibit a lower survival rate compared with their younger counterparts. The liver of elderly burn victims shows significant injury, contributing to poor outcomes. Burns induce mitochondrial dysfunction leading to endoplasmic reticulum (ER) stress and, ultimately, hepatocyte death. Aging alone is an important predisposing factor for mitochondrial and organelles dysfunction. Methylation-controlled J protein (MCJ) is a negative regulator of mitochondrial metabolism. The reduction or absence of MCJ promotes mitochondrial respiration without increasing reactive oxygen species promoting cellular homeostasis. Thus, we hypothesize that MCJ reduction can ameliorate burn-induced liver injury in aged animals.

Methods: Aged (20-months) female C57BL/6 mice were randomly assigned to 3 experimental groups, Sham, Burn Vehicle (BV), and Burn + Treatment (BT). The burn vehicle and burn treatment groups were subjected to boiling water using a template to generate full-thickness 20% total body surface area scald burn. While the burn vehicle received PBS, the treatment group received MCJ siRNA tagged to N-acetyl galactosamine (GalNac) subcutaneously 1 hour after the burn. Mice were euthanized 48 hours after the burn. Liver histology and western blots were compared.

Results: BV demonstrated a 60% increase of MCJ in liver tissue compared to the sham, and BT showed a 70% decrease in MCJ compared to the sham. While histology in BV showed edema, massive microvesicular steatosis, and enlarged stellate cells, the liver of BT exhibited minimal histological changes with a 40% reduction in the damage score compared to BV. Western blot analysis of ER stress markers in liver tissue showed a significant elevation (40% PDI, 50% eIF2 α , and 60% CHOP) in BV compared to the sham. The burn + GalNac MCJ siRNA-treated animals show a significant reduction of PDI, eIF2 α , and CHOP by 50%, 60%, and 65%, respectively, compared to the BV.

Conclusion: Silencing hepatic MCJ in aged mice after burn injury mitigates endoplasmic reticulum stress and decreases hepatic damage. Further mitochondrial and ER functional studies will complement these findings to elucidate MCJ's role in this pathology.

WHERE YOU GET HURT MATTERS: IMPACT OF GEOGRAPHY AND EMS SYSTEM RESOURCE AVAILABILITY ON AIR MEDICAL TRANSPORT AFTER TRAUMA

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Invited Discussant: Mark Gestring, MD

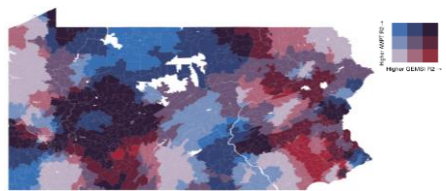
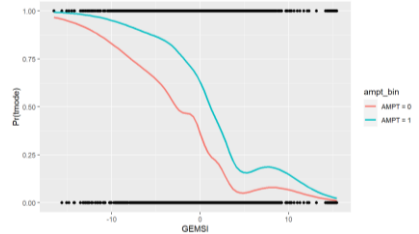
Introduction: Air medical transport (AMT) improves outcomes for severely injured patients. The decision to fly patients is complex and must consider both patient and system factors. Our objective was to evaluate the interaction between geography, patient factors, and EMS system resource availability on transport mode after trauma.

Methods: Patients transported by EMS in PTOS from 2000-2017 were included. We used our previously developed Air Medical Prehospital Triage (AMPT, ≥ 2 points triage to AMT) score and the Geographic EMS Index (GEMSI, higher indicates more/closer EMS/trauma system resources) as measures for patient factors and EMS system resource availability. Geographic weighted regression determined the association of AMT rate with AMPT score and GEMSI. R^2 values of each were mapped by zip code. A multilevel logistic regression model determined the association of AMT with variables selected by Gaussian process tree-boosting to compute feature importance.

Results: 275,053 patients were included. There was significant variation in the importance of both patient (AMPT score) and EMS system resources (GEMSI) on AMT rate (*Map*). A positive AMPT score had

less impact on AMT at both low and high GEMSI values (*Graph*). When stratified by GEMSI quartile, patient factors were more important in the 2nd and 3rd quartiles, while less important in the 1st and 4th quartiles.

Conclusion: There is significant geographic variation of the importance of patient and system factors associated with AMT. Patient factors become less important in low system resource settings with high AMT as well as high resource settings with low AMT. These findings can help tailor EMS transport mode triage strategies and warrants further study of the interplay between patient and system factors in prehospital care.



DIRECTED WORK-UP OF SELECT PENETRATING NECK INJURIES IS SAFE: HARD SIGNS CONTINUE TO SOFTEN

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James Babowice, DO; Emily K. Lenart, DO;
Andrew J. Kerwin, MD; Saskya Byerly, MD
University of Tennessee Memphis
Invited Discussant: Walter Biffel, MD

Introduction: Management of penetrating neck injuries (PNI) has evolved over time, more frequently relying on increased utilization of diagnostic imaging studies. Directed work-up following initial computed tomography imaging has resulted in increased use of angiography and decreased operative interventions. We sought to evaluate management strategies after directed work-up, hypothesizing increased use of non-operative therapeutic interventions and lower mortality.

Methods: Patients with PNI over a five-year period were identified from a single center trauma registry. Demographics, injuries, physical exam findings, diagnostic studies and interventions were collected. Patients were stratified by management strategy [directed work-up (DW) and immediate operative intervention (OR)] and compared. Outcomes included therapeutic non-operative intervention [endovascular stent, embolization, dual antiplatelet therapy (DAPT), or anticoagulation (AC)], non-therapeutic neck exploration, length of stay (LOS), and mortality.

Results: Of 436 patients with PNI, 143 (33%) patients had vascular and/or aerodigestive injuries. Of these, 115 (80%) patients underwent DW and 28 (20%) patients underwent OR. There were no differences in demographics or injury severity score between groups. Patients in the DW group were more likely to undergo therapeutic non-operative intervention compared to the OR group (25% vs 7%, $p=0.046$). There were no differences in post-intervention stroke, leak, or LOS. The DW group had fewer non-therapeutic neck explorations (0% vs 15%, $p < 0.0001$) and lower mortality (9% vs 26%, $p=0.020$) compared to the OR group. Of the 71 patients who presented on admission with hard signs (hemorrhage, expanding hematoma, massive subcutaneous air, hematemesis, focal neurological deficit), there was no difference in mortality between DW and OR groups (17% vs 21%, $p=0.546$). 60% of patients with vascular hard signs and 78% of patients with aerodigestive hard signs underwent DW.

Conclusion: Directed work-up for patients with PNI is associated with fewer non-therapeutic neck explorations and lower mortality. Selective use of endovascular management, AC and DAPT is safe.

CUES TO CARE: CHRONIC DISEASE DIAGNOSIS IN YOUNG ADULT TRAUMA PATIENTS

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Invited Discussant: Joshua Brown, MD, MS

Introduction: A trauma admission may be a young adult's sole contact point with the healthcare system and is a key opportunity for screening and early diagnosis of chronic disease. The burden of undiagnosed disease (UD) in the young adult trauma population is unknown. This study estimates the prevalence of undiagnosed diabetes (DM), hypertension (HTN), obesity, and alcohol and substance use specifically in a young adult trauma population, determines risk factors for UD, and compares outcomes between patients with and without UD.

Methods: This is a multicenter, retrospective cohort study of young adult trauma patients 18-40 years old admitted between 2018-2020. State trauma registry data and individual chart review were examined for evidence of undiagnosed DM, HTN, obesity, or substance and alcohol use. Patient demographics and outcomes were compared between cohorts with evidence of UD or no-UD. A multivariable regression model was built to assess risk factors predictive of UD.

Results: The analysis included 6,307 admitted patients. Of these, 4,843 (76.8%) had evidence of at least one UD, most commonly HTN or obesity. In multivariable models, the strongest predictors of UD were age (aOR: 0.98, 95% CI 0.98-0.99), male sex (aOR 1.43, 95% CI 1.26-1.64) and being uninsured (aOR 1.60, 95% CI 1.40-1.83). Only 24.5% patients had evidence of a primary care physician (PCP), and this did not decrease the odds of UD. Patients with UD were more often referred to a PCP on discharge (13.7% vs 7.5%, $p < 0.001$), and had lower readmission rates (4.0 vs 5.9%, $p = 0.002$). Inpatient complications and hospital length of stay did not differ between UD and no-UD groups.

Conclusion: Undiagnosed disease burden is high in young adult trauma patients, especially those with traditional sociodemographic risk factors and even in patients with access to primary care. Pre-trauma presence of a PCP does not improve rates of chronic disease diagnosis, but post-trauma referral to a PCP does decrease readmission rates. Shorter hospital stays in young adults may obscure the full impact of UD during a trauma admission. Early diagnosis of chronic disease requires rigorous, standard screening measures that are initiated by trauma centers.

ANALYSIS OF LIPID METABOLITES DERIVED FROM GUT MICROBIOTA IN ISCHEMIA-REPERFUSION MODEL

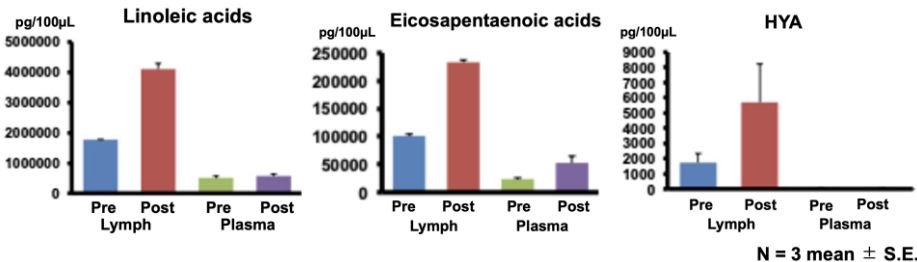
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Introduction: Disruption of intestinal barrier caused by intestinal ischemia due to hemorrhagic shock, is one of the major contributors of multiple organ damage (MOD) after severe trauma. Mesenteric lymph plays an important role as a route for transporting inflammatory mediators including lipids. Post-biotics such as 10-hydroxy-cis-12-octadecenoic acid (HYA), have received much attention and been applied as treatment for several diseases, however, the relation between post-biotics and MOD has not been clarified enough. The aim of the present study is to analyze lipid metabolites derived from gut microbiota in intestinal ischemia-reperfusion rat model.

Methods: Male Sprague-Dawley rats underwent laparotomy, and their mesenteric lymph duct and superior mesenteric artery (SMA) were exposure. The SMA was clamped in 60 minutes followed by 120 minutes-reperfusion. The mesenteric lymph and the plasma were collected before and after intestinal ischemia. The lipids in the samples were extracted and liquid chromatography/electrospray ionization mass spectrometry was performed.

Results: Linoleic acids increased after intestinal ischemia in both samples with predominance of lymph. Eicosapentaenoic acids and docosahexaenoic acid metabolized from linoleic acids, showed similar dynamics. In contrast, HYA which is formed when linoleic acids are metabolized by enterobacteria, was observed only in the lymph samples and highly increased after intestinal ischemia (before ischemia: 1730 ± 605 pg/ μ L vs. after: 5700 ± 2530 pg/ μ L).

Conclusion: HYA, one of the lipid metabolites derived from gut microbiota, increased in the mesenteric lymph after intestinal ischemia. Further studies are required to evaluate effect of HYA for MOD.



THROMBOPROPHYLAXIS AFTER SPLENIC ANGIOEMBOLIZATION: WHEN IS IT SAFE TO START?

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Invited Discussant: William Brigode, MD

Introduction: Thromboprophylaxis (TPX) in trauma is complicated by the risk of bleeding versus that of venous thromboembolism (VTE). Among blunt splenic injuries managed by angioembolization, we hypothesized that early initiation of TPX would be associated with increased risk of bleeding without decreasing the rate of VTE.

Methods: The ACS TQP database from 2017-19 was queried to identify all blunt trauma patients who underwent splenic angioembolization within 24 hours of arrival. Cases with missing data, <24-hour hospital length of stay, other serious injuries, and surgery prior to angioembolization were excluded. Bleeding complications were defined by splenectomy, additional embolization, or blood transfusion after the initiation of TPX. Thromboembolic complications were defined by DVT or PE. Data were compared with chi-squared and multi-variate logistic regression at the 95% confidence interval.

Results: Of 1,102 included patients, 84% had high grade (III-V) splenic injuries and 73% received TPX. Splenectomy after initial angioembolization was more common for those with TPX initiation within the first 24 hours (5.7% vs 1.7%, $p=0.004$), whereas delayed initiation of TPX (after 72 hours) were more likely to have PE (2.3% vs 0.2%, $p=0.001$). Overall, thromboembolic complications increased daily after day 3 and there were no bleeding complications with TPX initiated after day 5.

Grade of injury, ISS, age, race, BMI, gender, and type of TPX (heparin versus LMWH) were not independent risk factors for either bleeding or thromboembolic complications. However, time to TPX initiation was an independent risk factor for bleeding 0.983 (95% CI 0.97-0.996) and for thromboembolic complications 1.02 (95% CI 1.01-1.03).

Conclusion: This is the first study to address optimal timing of TPX after splenic angioembolization in trauma patients. Initiation of TPX between 24 and 72 hours achieves the safest balance in minimizing bleeding risk while reducing the risk of thromboembolic complications.

**DEATH BY THE MILE: INEQUITIES IN TRAUMA CARE FOR
BOSTON'S VICTIMS OF FIREARM VIOLENCE**

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Invited Discussant: Glen Tinkoff, MD

Introduction: Limited research has shown that access to an urban trauma center (TC) is uneven and trauma deserts, often described as a distance of 5 miles or more from a TC, are associated with increased mortality. We sought to evaluate the relationship of TC proximity with firearm injury mortality in Boston and describe racial inequities in access that may exist. We hypothesized that firearm injury mortality would increase with distance from a TC and that distance to care would be disproportionately larger for Black residents.

Methods: Firearm mortality data were obtained from the Gun Violence Archive between 9/2019-1/2023. Race and ethnicity for shooting victims was obtained from the Boston Police Department. Racial/ethnic composition as well as geographic data at the census tract level were obtained from the 2020 United States Decennial Census. TC locations were obtained from the American College of Surgeons. TC and shooting locations were geocoded with concentric buffers in increments of one mile for all TCs. Mortality and racial composition by distance to a TC was tabulated using Chi Square tests.

Results: During the study period, there were 825 shootings with complete addresses and 123 resultant deaths (14.9%). All city TCs (N=5) are level one. Black residents made up 23.5% of the Boston population, 84.4% of shooting victims and 89.4% of shooting deaths. Mortality significantly increased with each mile from a trauma center ($p=0.004$, Figure 1) and nearly doubled after two miles (11.6% to 21.0%, $p<0.001$, Figure 1). The proportion of Black residents per census tract was higher the further away the census tract was from a TC ($p<0.001$); the majority of Boston's Black population (60%) lives more than two miles from a TC.

Conclusions: Boston trauma deserts appear to begin even closer to TCs than in other cities. Increased distance from TC care is associated with increased mortality after a gunshot wound and access to life saving trauma care is not equal. Black residents bear the majority of firearm injuries and deaths but live disproportionately further from trauma care. Improving geographic access to a trauma center or otherwise reducing time to care could offset such inequities.

**GIFTS: GERIATRIC INTENSIVE FUNCTIONAL THERAPY
SESSIONS - FOR THE OLDER TRAUMA PATIENT**

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Invited Discussant: David Livingston, MD

Introduction: Focusing on cost and resource allocation for comprehensive geriatric (GERI) care models, we have observed older admitted patients (pts) have improved outcomes when ancillary therapeutics (AT) of physical (PT), occupational (OT), speech (SLP), respiratory (RT) and sleep wake hygiene (SWH) are prioritized against the medical treatment plan. Many GERI pts have met medical inflection, where AT is more contributory to positive outcomes than is medical care. This pilot describes outcomes of trauma pts in a hospital-wide program focused on GERI-specific AT.

Methods: GERI trauma pts, independent prior to admission, were screened for enrollment at one Level II trauma center from Aug 2021-Dec 2022. Enrolled pts (EP) were admitted to trauma or general medicine floors and received repetitive PT, OT, SLP, RT with attention to SWH throughout hospitalization and compared to non-enrolled pts (NEP) with similar DRGs. FRAIL pts (score of 5) or those from skilled care were excluded in both EP and NEP groups. Retrospective review of records for pt demographics, AT metrics and outcomes was completed, and data statistically evaluated.

Results: 224 EP (28 trauma-tr) were compared to 574 NEP (148 tr). EP had shorter length of stay (LOS) (3.8 vs 6.1, $p<0.0001$); ambulated earlier (13 hrs from admission vs 39 hrs, $p=0.0005$); and were more likely to discharge home (56% vs 27%, $p<0.0001$). Tr EP v NEP showed tr-EP had decreased LOS by one day; time to ambulation compared to medical EP (23 hrs v 11 hrs) but still sooner than all NEP (39h); There were no delirium events among tr-EP, but delirium accounted for 3% of all EP cohort versus 27% in NEP ($p<0.0001$).

Discussion: Although the tr-EP cohort was small in this pilot, results support feasibility to include GERI tr pts in hospital-wide programs with GERI specific AT. It is evident that GERI AT are beneficial and should emphasize the importance of mobility and cognitive strategies to yield shorter LOS and provide pts the best opportunity to avoid delirium and discharge home.

HYPOXIA DYSREGULATES THE TRANSCRIPTION OF MYOENDOTHELIAL JUNCTION PROTEINS INVOLVED WITH THE PRODUCTION OF NITRIC OXIDE

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Invited Discussant: Nikolay Bugaev, MD

Introduction: Myoendothelial junctions (MEJs) are distinct structures that form through the elastic lamina's fenestrae and allow endothelial cells to connect directly with vascular smooth muscle cells. As a result, these junctions promote heterocellular communication as well as the rapid transmission of chemical signals that control vascular tone. MEJs contain hemoglobin alpha (HBA) and endothelial nitric oxide synthase (NOS3) protein complexes. Evidence suggests that these proteins, along with the activity of cytochrome b5 reductase (CYTB5R3), appear to control the production, scavenging, and diffusion of nitric oxide (NO) in the vascular wall. This study aimed to examine how hypoxia affected the regulation of proteins involved in the production of nitric oxide (NO) in MEJs.

Methods: A cell culture model was used to conduct a longitudinal transcriptional study on primary human brain microvascular endothelial cells (HBMEC) exposed to cobalt chloride (CoCl₂), a hypoxia mimetic. In brief, HBMEC were cultured to a confluent monolayer and then exposed to CoCl₂ dose responses for up to 48 hours. After that, total RNA was isolated, and quantitative reverse transcription PCR was carried out with primers for NOS3, CYB5R3, and HBA2. Finally, $\Delta\Delta C_t$ gene expression was used to calculate the relative gene expression of these targets after normalization to the housekeeping gene GAPDH.

Results: When HBMEC were exposed to CoCl₂, the amount of detectable NOS3 and CYB5R3 mRNA in these cultures decreased in both a time- and dose-dependent manner (up to -100-fold and -23-fold respectively). CoCl₂ treatment, conversely, resulted in detectable levels of HBA2 mRNA being observed in these cells after 24 hours, with the elevation lasting for 48 hours.

Conclusions: These findings suggest that hypoxia may cause dysregulation of proteins and enzymes found in MEJs that control NO production. Furthermore, a loss of NO due to suppressed production and/or increased scavenging may contribute to the pathology of conditions characterized by loss of vascular control, such as cerebral vasospasm after subarachnoid hemorrhage or pulmonary hypertension. Further research into the expression of these factors in the presence of hypoxia and the production of NO in coculture models of brain endothelial cells and vascular smooth muscle cells with intact MEJ-like structures is warranted.