



USU

SC2i

Surgical Critical Care Initiative

NEWSLETTER

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SC2i Mission:

The Surgical Critical Care Initiative (SC2i) is a Uniformed Services University of the Health Sciences Center, funded by the Department of Defense, Defense Health Program.

SC2i was established in 2013 to develop biomarker-driven clinical decision support tools (CDSTs) for the critically ill, with the goal of improving clinical outcomes while reducing costs.

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CASPASE CYSTEINE PROTEASES

The caspase family of cysteine proteases play an essential role in the signaling pathways associated with apoptosis and inflammation. Circulating caspase activity levels may be an early indicator of overall cell death and inflammatory system activation in injured military personnel. We hypothesized that circulating caspase activity levels may correlate with injury severity in trauma patients, and early changes in these levels may predict short term patient outcomes.

To test our primary hypothesis, we performed an exploratory pilot sub study from the SC2i initiative. Longitudinal plasma samples derived from 11 trauma patients were used. The patients were divided into two groups based on their short term outcomes. Group A had an overall benign hospital stay, and group B were patients having a prolonged hospital stay with significant post injury morbidity and mortality. Caspase activities in all available plasma samples were measured using a commercially available bioluminescent assay kit (Promega Corporation Maddison WI). Group A patients (n=5) trended to be younger, had a trend of a higher presenting GCS score, and had a lower expanded ISS score (25.2 ± 11 vs. 43.5 ± 14 $p=0.03$) as compared to Group B patients (n=6). Caspase activity levels were similar between the groups early after injury, but significantly increased in group B patients over time while remaining unchanged for group A patients. (Figure)

In this pilot study, circulating caspase activity levels significantly increased in severely injured patients that experienced substantial midterm morbidity and mortality. A larger study including more patients to further explore the utility of caspase activity measurements in risk stratification for injured personnel is currently ongoing. If confirmed, caspase activity measurements may become an important biomarker that will help in post injury patient care and resource utilization to further improve outcomes.

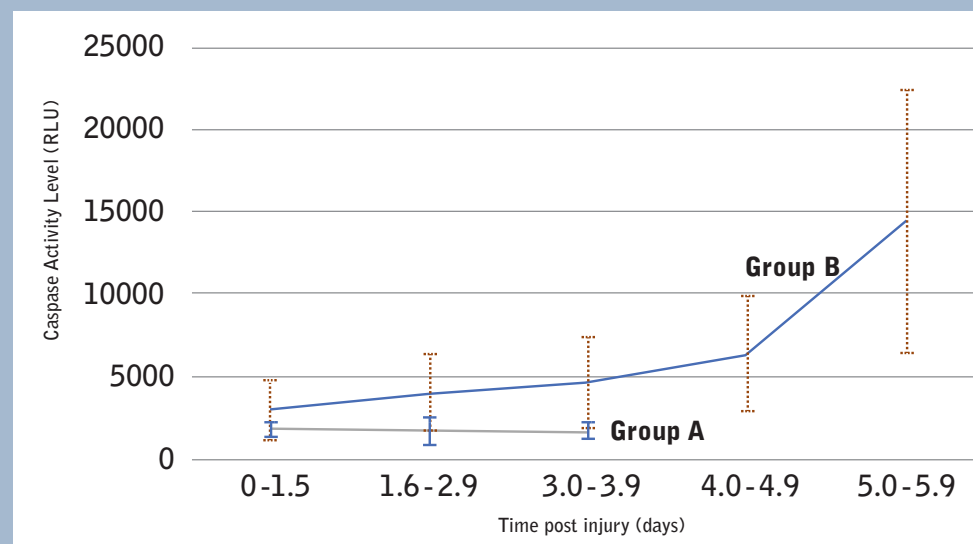
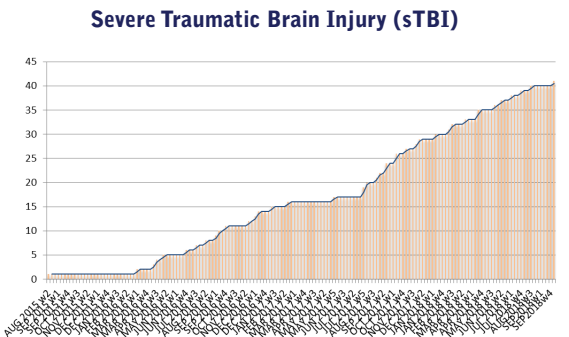
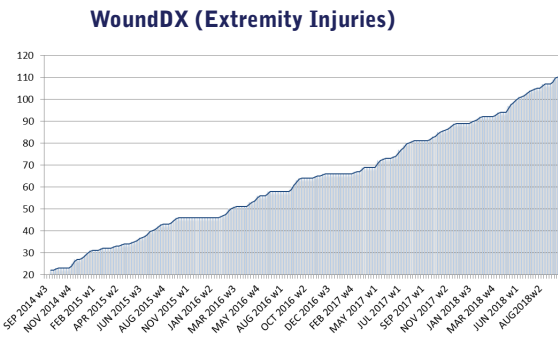
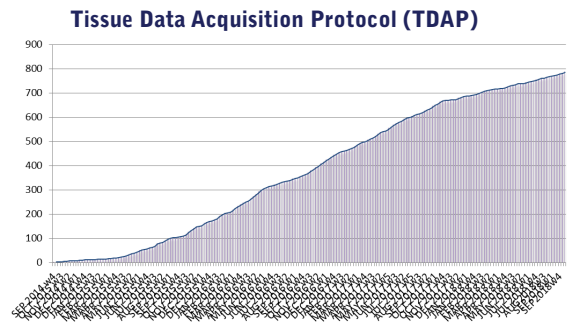
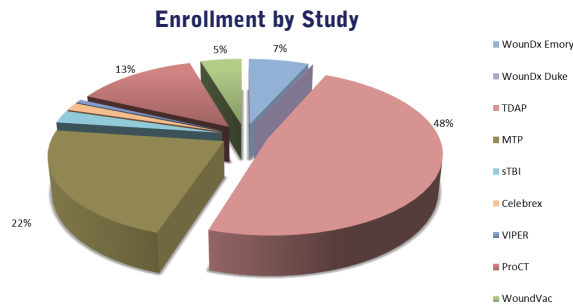


Figure 1. Caspase activity levels over time> Group A patients had a lower ISS, and an overall benign hospital stay. Group B patients had high morbidity and mortality following their injury during their early hospital period.

STUDY ENROLLMENTS

The center has enrolled ~1,600 patients to date, contributing to a growing biobank (57,800 specimens) and databank (30,000,000 elements) to power the development of 'precision' clinical decision support tools.



RESEARCH HIGHLIGHTS

PREDICTING THE NEED FOR THERAPEUTIC SURGERY AFTER SMALL BOWEL OBSTRUCTIONS

It is challenging to identify candidates who will require therapeutic surgery (TS) for non-emergent small bowel obstruction (SBO). The objective of this study was to use machine learning to identify patients who require TS for the management of SBO.

After excluding patients with the presence of peritonitis, closed loop obstruction on imaging, and virgin abdomens, 566 patients were available for model training and evaluation. Of the 566 patients, 156 (27.6%) patients underwent TS. Random Forest (RF) and logistic regression (LR) models were generated separately for both gastrografin challenge (GC) and non-GC patients (see results in Table below)

Accurate models for predicting the need for SBO TS were developed using a combination of clinical and radiographic data. Furthermore, incorporation of the GC significantly improves model performance and is an important clinical test during the workup of non-emergent SBO. The generalizability of these findings requires evaluation with an external validation dataset.

Cohort	Model	AUC	Sensitivity	Specificity
non-GC	RF	0.68	0.64	0.7
non-GC	LR	0.62	0.59	0.65
GC	RF	0.89	0.86	0.89
GC	LR	0.89	0.87	0.87
GC	GC Test	N/A	0.7	0.93

VTE UPDATE

Predicting Venous Thromboembolism (VTE)

Venous thromboembolism (VTE), a condition where a blood clot forms in a vein, is the third leading vascular diagnosis, affecting 300,000 to 600,000 Americans annually. Although preventive measures exist, clinicians lack the appropriate tools to identify patients' risk of developing VTE. We aim to develop a model to predict VTE by analyzing a cohort of 73 military trauma patients through exploring modeling techniques such as Random Forests, LASSO, and Bayesian networks.

We developed Random Forest models using backwards elimination for feature selection and LASSO regression models using recursive feature elimination. Our Random Forest model has an AUC of 0.936, sensitivity of 0.987, specificity of 0.798, and final features of IL15, MIG, VEGF, and units of blood products received after injury. Our LASSO model has an AUC of 0.968, sensitivity of 0.994, specificity of 0.864, and final features of IL1B, IL5, MCP1, MIG, VEGF, age, units of fresh frozen plasma received after injury, and presence of wounds in the lower body. The models listed in Table 1 are those with the highest AUC values. Sensitivities and specificities are reported at the threshold where their product is maximized. 95% confidence intervals for the AUCs are included.

Future Steps: Our next step will be to generate a three-fold cross-validated Bayesian network model and compare those results to our Random Forest and LASSO models. We will then externally validate the models and perform Decision Curve Analysis (DCA) with calibrated risk probabilities to evaluate potential clinical benefits. Our goal is the development of a decision support tool for predicting VTE, allowing preventive measures to be adopted early in patients at high risk of VTE.

Table 1. Performance of VTE predictive models

Modeling Method	AUC	95% Low	95% High	Sensitivity	Specificity	Threshold
Random Forest	0.936	0.925	0.947	0.987	0.798s	0.177
LASSO	0.968	0.960	0.975	0.994	0.864	0.116

RECENT PUBLICATIONS AND PRESENTATIONS

MANUSCRIPTS:

The Uniformed Services University's Surgical Critical Care Initiative (SC2i): Bringing Precision Medicine to the Critically Ill. Belard A, Buchman T, Dente C, Potter B, Kirk A, Elster E. (Published- Journal of military medicine)

Preclosure Spectroscopic Differences Between Healed and Dehisced Traumatic Wounds. Radowsky J, Neely R, Forsberg J, Lisboa F, Dente C, Elster E, Crane N. (Published – PLOS)

Combat-Related Invasive Fungal Infections: Development of a Clinically Applicable Clinical Decision Support System to Facilitate Early Risk Stratification. Potter B, Forsberg J, Silvius E, Wagner M, Schobel S, Belard A, Weintrob A, Tribble D, Elster E. (Published – Journal of Military Medicine)

Clinical Risk Factors and Inflammatory Biomarkers of Post-Traumatic Acute Kidney Injury in Combat Patients. Munoz B, Lisboa F, Schobel S, Gaucher B, Buchman T, Dente C, Kirk A, Elster E. (Under Internal Review – pending revisions)

Timing of Delayed Wound Closure May Be Estimated by Clinical Variables and the Cytokine Response of Patients with Combat-Related Extremity Wounds. Lisboa F, Bradley M, Forsberg J, Schobel S, Styrnisdottir E, Potter B, Hueman M, Munoz B, Dente C, Buchman T, Kirk A, Elster E. (Under Internal Review – pending revisions)

The Trauma Embolic Scoring System in military trauma: a sensitive predictor of venous thromboembolism. Walker P, Schobel S, Gaucher B, Caruso J, Rodriguez C, Bradley M, Elster E, Oh J. (Under Internal Review – pending revisions)

Machine Learning Algorithm Predicts Successful Fascial Closure After Trauma Laparotomy. Gelbard R, Schobel S, Dente C, Morse B, Subramanian A, Rhee P, Kirk A, Buchman T, Styrnisdottir E, Gaucher B, Elster E. (Under Internal Review – pending revisions)

Predicting the Need for Massive Transfusion Protocol Activation: Prospective Validation of a Smartphone-Based Clinical Decision Making application. Morse B, Mina M, Dente C, Jhunjhunwala R, Dougherty S, Buchman T, Elster E, Gelbard R, Kirk A. (Under Internal Review – pending revisions)

POSTERS/PRESENTATIONS:

- MHSRS 2018:** Link Between Extracellular Mitochondrial DNA and Soluble CD40 Ligand in Post-Traumatic Sterile Inflammation. (Lubkin et al)
- Immune Response Profiling with Alcohol Intake In The Setting of Trauma. (Limkakeng et al)
- An FHIR-Enabled Streaming Sepsis Prediction System for ICUs. (Nemati et al)
- Interrogation of combat wound infection through integrative metagenomic analyses of the wound microenvironment and corresponding clinical outcomes. (Be et al)
- An Improved Model to Predict Pneumonia in Combat Trauma Patients. (Bradley et al)
- Understanding the Likelihood of Acute Respiratory Distress Syndrome in Trauma Patients. (Schobel et al)
- Circulating caspase activity in trauma patients as a biomarkers of injury severity and short term outcomes. (Bishawi et al)
- Surgical Critical Care Initiative: Harmonization and Implementation of a Biobanking and Assay Standard Terminology Across the Consortium. (Joshi et al)
- Complication rates after early cranioplasty for severe traumatic brain injury. (Malcolm et al)
- Surgical Critical Care Initiative: Implementation of Good Clinical Laboratory Practices Across the Consortium. (Osborne et al)
- Establishing acceptance criteria for validation of the Pro-calcitonin quantitation assay using different immune-assay platforms. (Upadhyay et al)
- Surgical Critical Care Initiative (SC2i) Severe Traumatic Brain Injury (sTBI) Protocol. (Khatri et al)
- Surgical Critical Care Initiative Data Management: Systems and processes enabling research and Clinical Decision Support Tool development to improve precision medicine in acute care. (MacKelfresh et al)
- Estimating Timing of Delayed Closure in Wounds with Persistent Critical Colonization (Lisboa et al)
- Attributable Economic Benefit and Medical Innovation: A Case Study of a Clinical Decision Support Tool that Predicts the Onset of Venous Thromboembolism (Chang et al)
- Increased Sensitivity for Prediction of Bacteremia in Combat Trauma Patients (Bradley et al)
- Clinical Implementation of Research Data-Driven Protocol Between Military and Civilian Trauma Sites: The Model of the Surgical Critical Care Initiative Tissue and Data Acquisition Protocol Patients (Almond et al)
- Towards Early Prediction of Vasospasm and Mortality Following Severe Traumatic Brain Injury (sTBI) (Rindler et al)
- Correlation of Bacterial Strains to Open Abdomen Closure Outcomes Establish Importance of Bacterial Contaminants to Complications of Healing (Gelbard et al)
- Differential Procalcitonin Levels in Patients with Abdominal Versus Non- Abdominal Injuries and its Use as a Prognostic Biomarker (Gelbard et al)
- Tissue and Data Acquisition Protocol: A Two- Year Data Review (Schobel et al)
- Invasive Fungal Infection Clinical Decisions Support Tool Validation Data suggests Clinical Utility (Schobel et al)
- AAST 2018:** Economic Burden of Enteric Fistula After Damage-Control Laparatomies. (Chang et al)
- ASN 2018:** Variable Economic Impacts of Clinical Decision Support Algorithms that Predict Acute Kidney Injury among Postoperative Patients: A Nationwide Analysis. (Chang et al)
- SOMOS 2018:** Early prediction of heterotopic ossification using machine learning (Mueller et al)
- NEUROTRAUMA 2018:** Early Prediction of Vasospasm Following Severe Traumatic Brain Injury (sTBI) (Rindler et al)
- AAST 2019:** Circulating caspase activity in trauma patients as a biomarkers of injury severity and short term outcomes. (Bishawi et al)
- Predicting the Need for Operative Management of Small Bowel Obstruction with Machine Learning. (Bozzay et al)
- Role of Plasma Soluble CD154 in Post-Traumatic Systemic Inflammatory Response Syndrome. (Lubkin et al)
- SCCM 2018:** Estimating the Costs of Operating room Time for Critical Care Patients. (Chang et al)

ON THE HORIZON

- 2018 American Association for the Surgery of Trauma (AAST), 26-29 September, San Diego CA
- 2019 Academic Surgical Congress (ASC), 5-7 February, Houston TX
- 2019 Eastern Association for the Surgery of Trauma (EAST) 15 - 19 January, Austin TX