

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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AN INTERPRETABLE ALGORITHM FOR PREDICTING SEPSIS

Sepsis is among the leading causes of morbidity and mortality in critically ill patients and is the most expensive condition by healthcare spending. The major tenet of sepsis care is prompt recognition and initiation of treatment. However, no clinically validated system exists for accurate, real-time prediction of sepsis onset. Our multidisciplinary team at the Emory Department of Biomedical Informatics set out to design a high-performance prediction model for ICU-onset sepsis (sepsis-3) using a retrospective ICU database that included dynamical features from high-resolution vitals time series from bedside monitors, as well as electronic medical record (EMR) data. Additionally, we focused on an interpretable class of models, which make it possible to see which variables are most important in a particular risk calculation for a patient (i.e., local interpretability).

Consecutive admissions to the intensive care unit (ICU) at two large, academic medical centers for three years were identified. A total of 27,527 ICU patients from the Emory Hospital and an additional 42,411 patients from an external publicly available ICU database (MIMIC-III) were used for model development and validation. For 4-hour ahead sepsis prediction window, development (AUROC=0.85, specificity=0.67, sensitivity=0.85) and validation (AUROC=0.84, specificity=0.64, sensitivity=0.85) cohorts demonstrated accurate predictive ability. Moreover, as shown in Fig. 1 the algorithm provided locally interpretable explanations of the contributing factors to the sepsis risk score.

Using data available in the ICU in real-time, our algorithm was able to accurately predict the onset of sepsis in ICU patients hours prior to clinical recognition. Prediction of the onset of sepsis prior to clinical recognition will allow for earlier intervention (e.g., antibiotic). Earlier administration of antibiotics has the potential to decrease sepsis-related morbidity, mortality and healthcare costs. We are currently designing a prospective study to determine the clinical utility of our prediction model in decreasing mortality, LOS, and hospital costs.

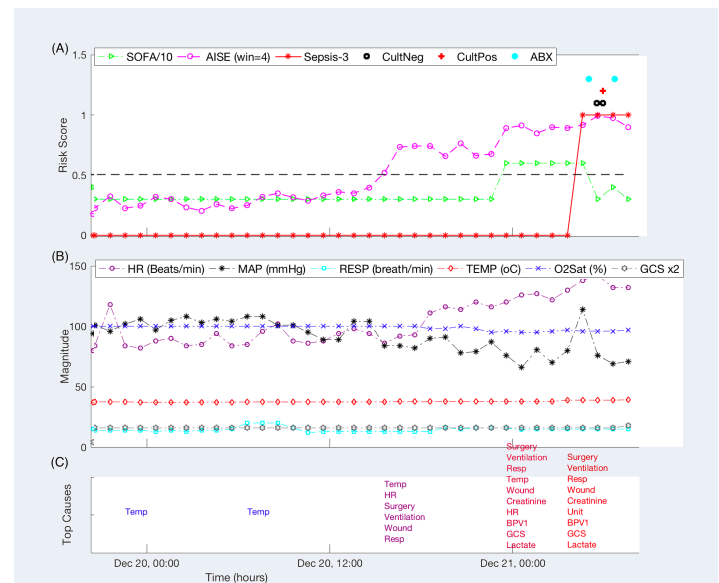
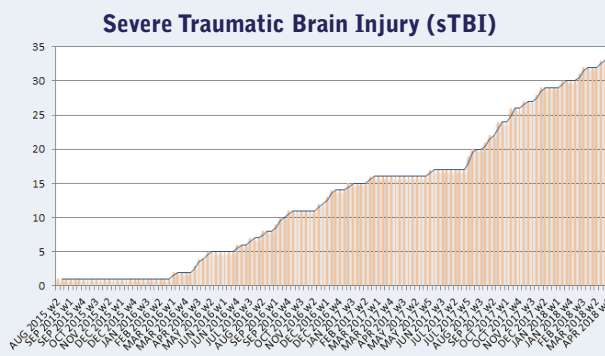
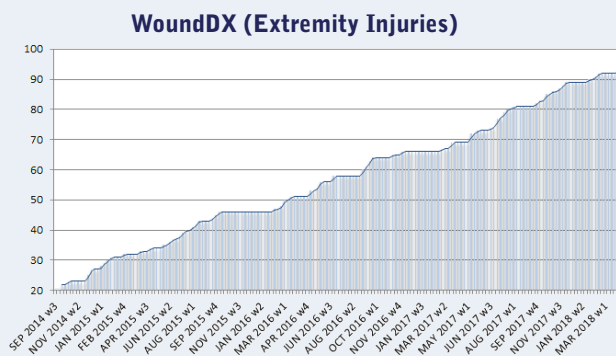
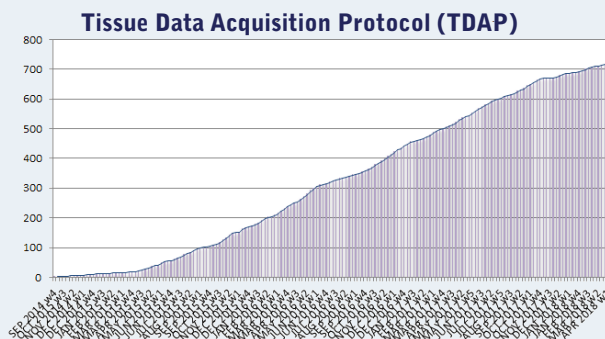
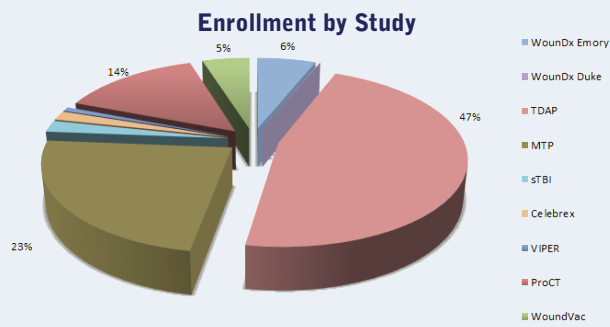


Figure 1. An illustrative example of the developed Artificial Intelligence Sepsis Expert (AISE) prediction performance. Hourly calculated Sequential Organ Failure Assessment (SOFA) Score, Sepsis-3 definition, and the AISE score are shown for one patient in Panel (A). Commonly recorded hourly vital signs are shown in Panel (B). Most significant features contributing to the AISE score (for clarity of presentation only selected time-points are shown). Notably, around 4pm on December 20th, roughly 8 hours prior to any change in the SOFA score, the sepsis score starts to increase. The top contributing factors were slight changes in HR, RESP, and TEMP, given that the patient had surgery in the past 12 hours with a contaminated wound, and was on a mechanical ventilator. Close to midnight on December 21st, other factors such as multiscale entropy of blood pressure time series (BPV1), GCS, and Lactate show abnormal changes. Five hours later, the patient met the sepsis-3 definition of sepsis.

STUDY ENROLLMENT

The Center has enrolled 1,522 patients to date, contributing to a growing biobank (53,000 specimens) and databank (21,000,000 elements) to power the development of 'precision' clinical decision support tools.



RESEARCH HIGHLIGHTS

STBI UPDATE

CEREBRAL VASOSPASM: EARLY DETECTION WITHOUT TRANSCRANIAL DOPPLER RADIOGRAPHY

Purpose: Severe traumatic brain injury (sTBI) accounts for approximately 1% of all head injuries in military service members worldwide since 2000, and contributes to significant morbidity and mortality. Initial treatment targets the prevention of secondary brain injury by optimizing cerebral oxygenation and perfusion. Cerebral vasospasm is a major post-injury secondary complication that can result in additional injuries such as delayed ischemia. Currently, Transcranial Doppler Radiography (TCD) is the primary method by which vasospasm is diagnosed. Here, we investigate whether the predictive ability of computed tomography (CT) can be improved with a panel of serum protein biomarkers.

Project Status: Together—the SC2i BiCS and Dr. Boulis’ team at Emory—are using Random Forests with features extracted via forward selection to predict the presence of cerebral vasospasm. Sensitivity and specificity are reported at the threshold where their product is maximized. The baseline model (the CT measure of Marshall Classification alone) results in an AUC of 0.81, sensitivity of .71, and specificity of 0.99. The inclusion of EGF and IL-8 increases the AUC to 0.93, sensitivity to 0.88, and specificity is essentially unchanged at 0.98.

Way Forward: The current findings point to a potential predictive approach for determining the risk of developing cerebral vasospasm. This may lead to a decision support tool capable of accurately predicting cerebral vasospasm prior to the subsequent usage of TCD.

ROC CURVE FOR PREDICTION OF CEREBRAL VASOSPASM WITH MARSHALL CLASSIFICATION, EGF, AND IL8

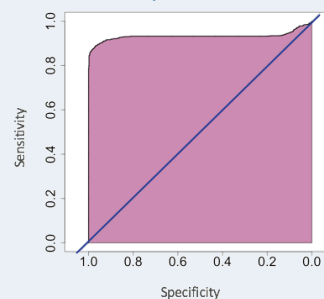


Figure X. Random Forest prediction accuracy: AUC of 0.93, sensitivity of 0.88, specificity of 0.98

BEYOND WOUND CLOSURE – ADDITIONAL CORRELATES OF INTEREST IN ABDOMINALLY INJURED PATIENTS

Purpose: Within the SC2i the Open Abdomen (OA) study has been an area of intense research. Past efforts included predictive modeling of wound healing outcomes in patients after damage control surgery. Our current focus of research is following two distinct tracts. First we are examining the association of bacterial contaminants on wound healing and complication outcomes in this patient cohort. Second we are examining the correlation between Procalcitonin and complications of injury in the OA cohort and our wider TDAP trauma cohort. The purpose of both efforts is to refine our understanding of disparate healing outcomes and complications in traumatically injured patients, utilizing novel host-pathogen interaction biomarkers and existing Procalcitonin data.

Project Status: Bacterial contaminants have been shown to be predictive in wound closure outcomes in OA patients. Through LASSO modeling we have shown that specific bacterial Genus can be associated with failed fascial closure, such as *Corynebacterium*, *Pasteurella*, *Pseudomonas*, and *Vibrio*. Procalcitonin has been observed at higher levels within the OA cohort and is also associated with higher rates of complications. The nature of this relationship is currently under examination.

Future Steps: Our next steps are to expand the modeling efforts for both projects by utilizing additional modeling methodologies and comparing results across techniques. Through these efforts we hope to better understand the role of bacterial contaminants and Procalcitonin on a variety of healing and complications outcomes in several SC2i cohorts.

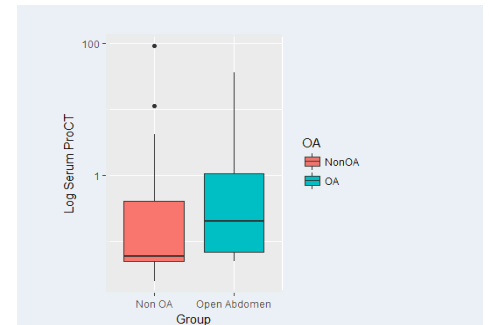


Figure 1. Plot of the distributions of median serum Procalcitonin levels between OA (0.205 ng/ml) and non-OA cohorts (0.06 ng/ml).

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)

An Interpretable Machine Learning Model for Accurate Prediction of Sepsis in the ICU. Holder A, Razmi F, Stanley M, Clifford G, Buchman T. (Published – Critical Care Medicine)

Battlefield to Bedside: Bringing Precision Medicine to Surgical Care. Belard M, Schobel S, Bradley M, Dente C, Kirk A, Potter B, Buchman T, Elster E. (Published – Journal of the American College of Surgeons)

Preclosure Spectroscopic Differences Between Healed and Dehiscd Traumatic Wounds. Radowsky J, Neely R, Forsberg J, Lisboa F, Dente C, Elster E, Crane N. (Submitted – Public Library of Science)

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. (Under Internal Review-Pending revisions – Journal Trauma Acute Care Surgery)

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 – PLOS)

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, Jhunjunwala R, Dougherty S, Buchman T, Elster E, Gelbard R, Kirk A. (Under Internal Review – Pending revisions)

POSTERS/PRESENTATIONS:

- ACS 2017:** Battlefield to Bedside: Bringing Precision Medicine to Surgical Care. (Elster – Oral)
- MHSRS 2018:** Surgical Critical Care Initiative Tissue and Data Acquisition Protocol: Clinical Data Standardization Across Multi-Site Consortia (Davis et al)
- Invasive Fungal Infection Clinical Decisions Support Tool Validation Data Suggests Clinical Utility Interrogation of combat wound infection through integrative metagenomic analyses of the wound microenvironment and corresponding clinical outcomes (Schobel et al)
- Establishing acceptance criteria for validation of the Pro-calcitonin quantitation assay using different immune-assay platforms (Upadhyay et al)
- An Improved Model to Predict Pneumonia in Combat Trauma Patients (Bradley et al)
- Increased Sensitivity for Prediction of Bacteremia in Combat Trauma Patients (Bradley et al)
- 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)
- 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)
- Estimating Timing of Delayed Closure in Wounds with Persistent Critical Colonization (Lisboa et al)
- Surgical Critical Care Initiative: Implementation of Good Clinical Laboratory Practices Across the Consortium (Osborne et al)
- Surgical Critical Care Initiative: Harmonization and Implementation of a Biobanking and Assay Standard Terminology Across the Consortium (Joshi et al)
- Circulating caspase activity in trauma patients as a biomarkers of injury severity and short term outcomes (Bishawi 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)
- 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)
- Towards Early Prediction of Vasospasm and Mortality Following Severe Traumatic Brain Injury (sTBI) Surgical Critical Care Initiative (SC2i) Severe Traumatic Brain Injury (sTBI) Protocol (Rindler et al)
- Complication rates after early cranioplasty for severe traumatic brain injury (James et al)
- Correlation of Bacterial Strains to Open Abdomen Closure Outcomes Establish Importance of Bacterial Contaminants to Complications of Healing (Gelbard et al)
- Tissue and Data Acquisition Protocol: A Two-Year Data Review (Schobel et al)
- Understanding the Likelihood of Acute Respiratory Distress Syndrome in Trauma Patients (Schobel et al)
- Differential Procalcitonin Levels in Patients with Abdominal Versus Non-Abdominal Injuries and its Use as a Prognostic Biomarker (Gelbard et al)
- An FHIR-Enabled Streaming Sepsis Prediction System for ICUs Operationalizing A Clinical Decision-Support Tool Within An Electronic Health Record (Nemati et al)
- AAST 2018:** Changing Milieu's: Implications for a military CDST caused by variability in a civilian trauma centers wound manage paradigms (Dente et al)
- SER 2018:** Impact of a Change in Sepsis Definition on Intensive Care Epidemiology and Cost: Comparison of Sepsis-2 and Sepsis-3 Definitions. (Chang et al)
- SAE 2018:** Immune Response Profiling in Patients with Traumatic Injuries Associated with Alcohol Ingestion. (Limkakeng et al)
- HEC 2018:** Expanding Critical-Care Capacity with Predictive Analytics. (Chang et al)
- EAST 2018:** Traumatic injury and stress: assessing the relationship of physical trauma, mortality, and the human inflammatory response. (Irons et al)

ON THE HORIZON

- 2018 Military Health System Research Symposium (MHSRS), 2018 August, TBD: Location & Dates
- 2018 American Association for the Surgery of Trauma (AAST), 26-29 September, San Diego, CA
- 2019 Eastern Association for the Surgery of Trauma (EAST), 15-19 January, Austin, TX