Issue 6: October 2018 to April 2019

USU | SC2i Surgical Critical Care Initiative

NEWSLETTER

In this issue

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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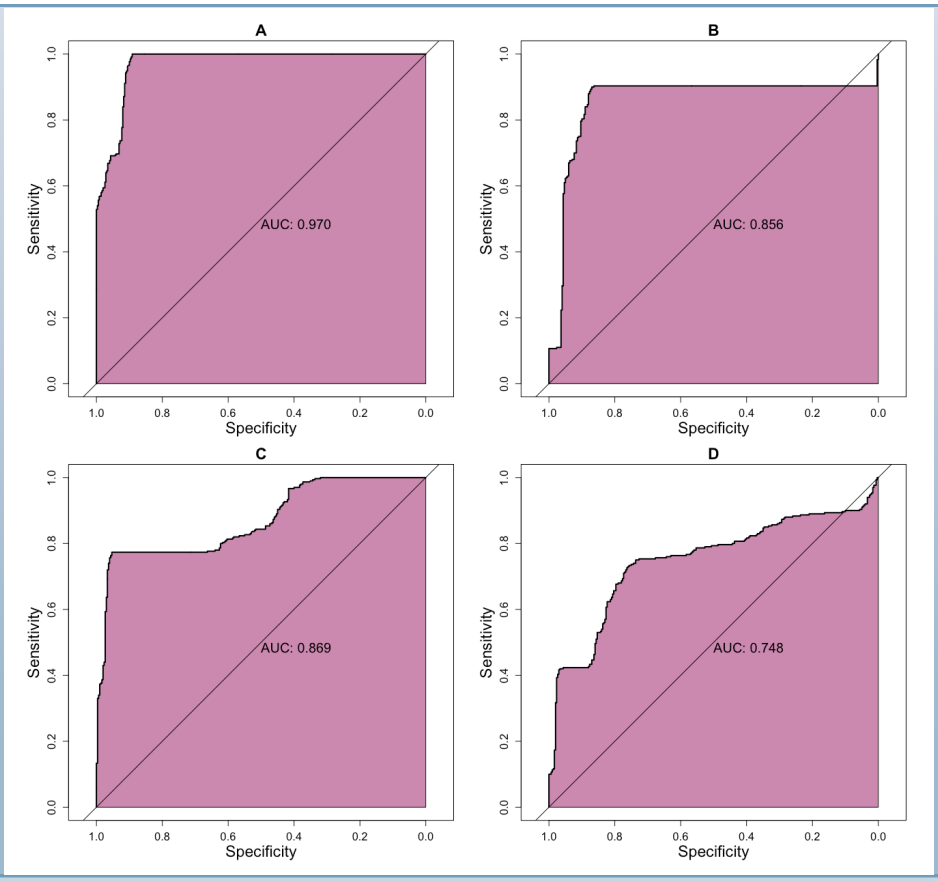
A RANDOM FORESTS MODEL TO PREDICT PNEUMONIA IN COMBAT TRAUMA PATIENTS

Pneumonia is a common nosocomial infection that is experienced by combat and civilian trauma patients. The ability to predict pneumonia development could allow for prophylactic treatments. Here, we have developed prediction models that may be applicable to combat trauma and civilian patients as well.

Our study consisted of 73 primarily blast-injured casualties with combat extremity wounds; the incidence of pneumonia was 12% (9/73). Binary classification models were developed with measurements of injury severity, transfusion blood products and serum protein levels. Predictive models were generated with leave-one-out-cross-validation (LOOCV) using the variable selection method of backwards elimination (BE) and the machine learning algorithms of Random Forests (RF) and Logistic Regression (LR). BE was attempted with 2 predictor sets: (1) all variables (2) serum proteins alone. The latter approach was taken due to the hypothesis that more generalizability may be demonstrated by a model with serum proteins alone. Using both variable sets, an RF was generated with AUCs of 0.95 and 0.87- both higher than LR algorithms.



ROC Curves. **(A)** RF with variables ISS, AIS chest, and cryoprecipitate. **(B)** LR with same variables as in A. **(C)** RF with variables FGF-basic, IL-2R, and IL-6. **(D)** LR with same variables as **C**

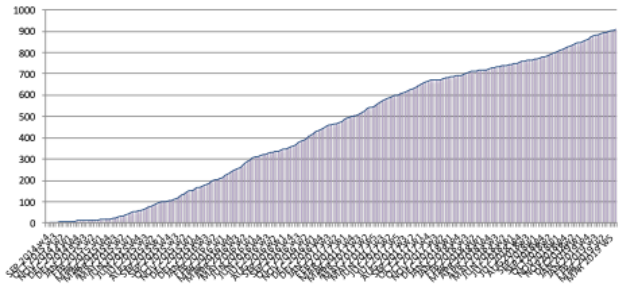
STUDY ENROLLMENTS

The center has enrolled ~1,800 patients to date, contributing to a growing biobank (67,000 specimens) and databank (40,000,000 elements) to power the development of 'precision' clinical decision support tools.

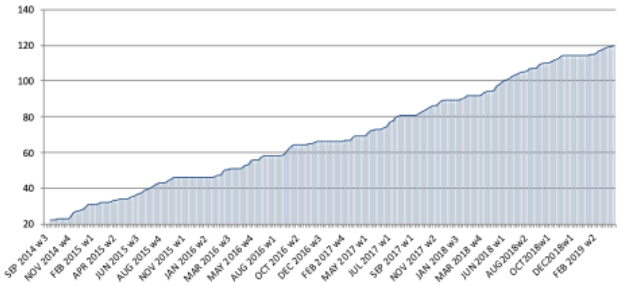
Enrollment by Study

Study	Focus	Cohort	Patients	Status	Location
WoundVac	Military Trauma (extremity injuries)	Military	75	Closed enrollment	WRNMMC
ProCT	Military Trauma (Procalcitonin / wound healing)	Military	220	Closed enrollment	WRNMMC
Viper	Civilian Trauma (snakebites / immune response)	Civilian	12	Closed enrollment	Duke
TDAP	Military and Civilian Critically Ill or Injured (omnibus bio / databank)	Mixed	911	Open enrollment	WRNMMC Emory-Grady Duke
WounDX	Civilian Trauma (extremity injuries)	Civilian	120	Open enrollment	Emory-Grady Duke
MTP	Civilian Trauma (requiring blood transfusion)	Civilian	363	Open enrollment	Emory-Grady
sTBI	Civilian Trauma (w/severe Traumatic Brain Injury)	Civilian	55	Open enrollment	Emory-Grady

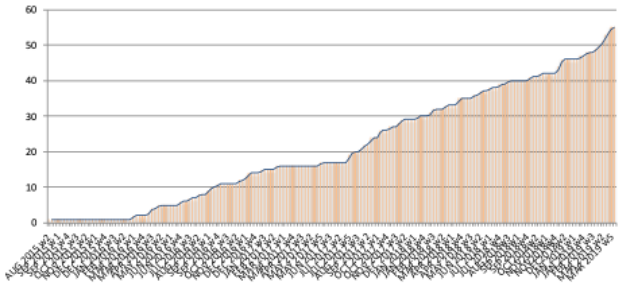
Tissue Data Acquisition Protocol (TDAP)



WoundDX (Extremity Injuries)



Severe Traumatic Brain Injury (sTBI)

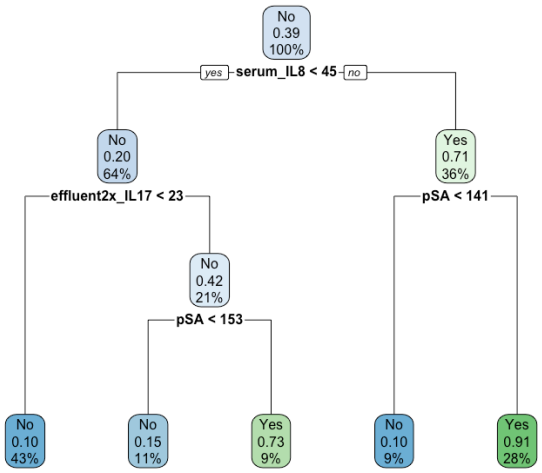


RESEARCH HIGHLIGHTS

EARLY PREDICTION OF HETEROTOPIC OSSIFICATION USING MACHINE LEARNING

Purpose: Heterotopic ossification (HO) represents a significant complication of traumatic war injuries often effecting both recovery and physical functionality of wounded service members. HO is the formation of mature bone from osteoblastic progenitor cells within soft skeletal tissues, most often in the extremity, frequently associated with acute local trauma, spine/nervous system trauma, and surgery. HO begins forming within 48 hours of injury, however, there is a window of opportunity for preventive measures as clinical symptoms often take 1-3 months to develop. Nonsteroidal anti-inflammatory drugs have been shown to inhibit HO formation, if provided with temporal proximity to the point of trauma. HO significantly affects recovery as it can impede physical therapy as well as prosthetic fitting and use in extremity amputations.

CART Model for the identification of HO



Methods & Results: Our study population consisted of 73 patients with 116 wounds, which were used for predicting the occurrence of HO (45/116 or 39%). Two modeling approaches were utilized: (1) variable selection with the Boruta algorithm followed by Random Forests (2) a subset of features associated with HO were used to construct a Classification and Regression Tree (CART). Approaches 1 and 2 resulted in an AUCs of 0.82 and 0.83, sensitivities of 0.88 and 0.8, and specificities of 0.61 and 0.9. Both approaches selected cytokines as well as wound surface area.

Future Steps: There are currently no available models to accurately predict the development of HO in military trauma patients. The models developed here suggests the interaction between the biomarkers and wound surface area is predictive of HO formation.

USING MACHINE LEARNING TO ESTIMATE TIMING OF DELAYED WOUND CLOSURE IN TRAUMATIC EXTREMITY WOUNDS

Purpose: The management of open, traumatic, contaminated wounds remains challenging and largely driven by experiential clinical judgment. The increased prevalence of extremity wounds in recent military conflicts has driven the development of the Surgical Critical Care Initiative (SC2i), currently a Uniformed Services University of Health Sciences Center designed to capture data from these patients and develop statistical models working as clinical decision support tools (CDSTs). In patients with traumatic extremity wounds, we designed CDSTs to target the inflammatory response associated with each wound during surgical debridements and estimate the time of successful definitive wound closure. In addition to aid in the treatment of injured service members, these CDSTs are also developed to be by applied by the civilian sector in the treatment of similar patients with the goal of decreasing times to wound closure and wound failure rates.

Methods & Results: These CDSTs were based in Random Forest models trained to estimate successful wound closure (binary models, figure 1A) and the necessary number of surgical debridements (multiclass model, figure 1B) to treat traumatic extremity wounds. Analysis of surgical treatment regimens showed a more similar cytokine response when civilian patients follow a military-like wound debridement schedule interval of, at most 72 hours. Binary model performance degraded approximately 35% if including civilians who had surgical debridemets in excess of 72 hours.

Future Steps: Considering model performance, the multiclass model would serve as a screening tool to estimate the number of debridements after patient admission and the binary model would work as a confirmatory tool to aid in the decision to close each wound in the next operation. Protocolized care allowed for the development of accurate biomarker based CDSTs to predict the number of debridements and timing of delayed wound closure. Therefore, these models can be developed using biologically compatible civilian and military populations and provide objectivity to difficult clinical situations, highlighting the benefit of protocolized operative plans.

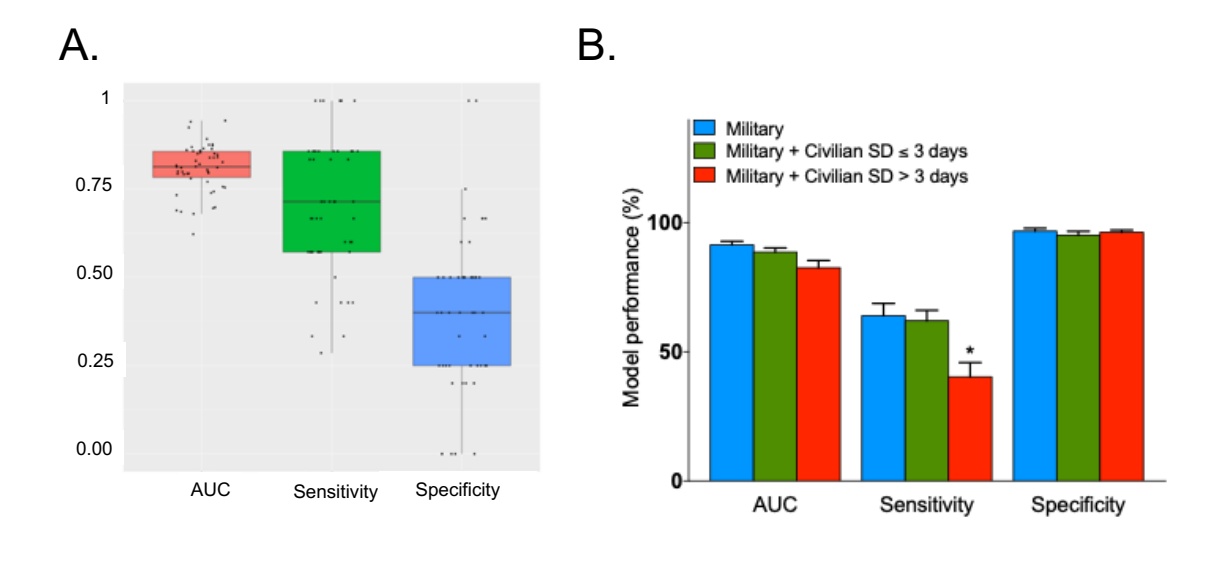


Figure 1: Performance of a Random Forests model. **A** – Multiclass model performance estimating the number of surgical debridements for independent treatment of each extremity wound. Area under the receiver operator characteristic curve (AUC), sensitivity and specificity are shown for estimations in military patients. **B** – Binary models trained to estimate when wounds should be closed based on the level of 14 cytokines. Area under the receiver operator characteristic curve (AUC), sensitivity and specificity are shown for models trained for military patients, civilians with a similar surgical schedule, and civilians with a variable surgical schedule. * Represent a statistically significant difference ($p<0.05$) as indicated.

RECENT PUBLICATIONS AND PRESENTATIONS

MANUSCRIPTS:

Random Forest Modeling Can Predict Infectious Complications Following Trauma Laparotomy Gelbard R, Hensman H, Schobel S, Khatri V, Tracy B, Dente C, Buchman T, Kirk A, Elster E. (Published- Journal of Trauma and Acute Care Surgery)

Advanced Modeling to Predict Pneumonia in Combat Trauma Patients Bradley M, Dente C, Khatri V, Schobel S, Lisboa F, Shi A, Hensman H, Kirk A, Elster E. (Published – Journal of Surgical Research)

Damaged- And Pathogen-Associated Molecular Patterns Play Differential Roles in Late Mortality After Critical Illness Eppensteiner J, Kwun J, Scheurmann U, Barbas A, Limkakeng A, Elster E, Kirk A, Lee J. (Published – Journal of Clinical Investigation Insight)

POSTERS/PRESENTATIONS:

ASC 2019: Circulating Caspase Activity in Trauma Patients as a Biomarker of Injury Severity and Short Term Outcomes (Bishawi-M)

ASA 2019: WounDX (Dente- C/Elster EA)

EAST 2019: Driving Biology: The Effect of Standardized Wound Management on Wound Biomarker Profiles (Nemati et al)

SAEM 2019: Understanding the Cost of Care for Emergent Operative Trauma Patients (Chang-F/ Elster EA)

AAST 2019: Random Forest Model Predicts Acute Kidney Injury After Trauma Laparotomy (Schobel)

AAST 2019 A Random Forest Model to Predict Bacteremia in Combat Trauma Patients (Bradley)

MHSRS 2019: Continuing Towards Early Prediction of Vasospasm and Mortality Following Severe Traumatic Brain Injury (sTBI) (Khatri)

Predicting Severe Sepsis in Surgical ICU Patients (Schobel)

Predicting Acute Respiratory Distress Syndrome in Surgical ICU Patients (Schobel)

Trauma Patients Wound Infection and The Relations with Injury and Clinical Progress (Song)

A Possible Role for Vascular Endothelial Growth Factor in Predicting Duration of Mechanical Ventilation After Cardiac Surgery (Lisboa)

Estimating the Development of Heterotopic Ossification in Combat-related Extremity Trauma (Lisboa)

Surgical Critical Care Initiative: Consensus-driven Harmonization and Standardization of Biorepository Terminology (Joshi)

Surgical Critical Care Initiative: Maintenance of Good Clinical Laboratory Practices Through Proficiency Testing of Peripheral Blood Mononuclear Cells (Osborne)

Woundx-sc2i Program for Tissue and Data Acquisition: Supporting Advances in Precision Medicine for Wound Closure in The Military and Civilian Sectors (Iwakoshi)

Characterization of Cellular MicroRNA In Polytrauma Patients (Vicente)

Clinical Risk Factors and Inflammatory Biomarkers of Post-traumatic Acute Kidney Injury in Combat Patients (Muñoz)

Composition, Function, And Relevance of The Microbial Microenvironment in Wounds from Combat Injuries (Be)

A Random Forest Model to Predict Pneumonia in Combat Trauma Patients (Bradley)

ON THE HORIZON

- 2019 Military Health System Research Symposium (MHSRS), 2019 August, TBD: Location and Dates
- 2019 American Association for the Surgery of Trauma (AAST), 2019 September, Dallas Texas
- 2020 Academic Surgical Congress (ASC) 2020 February, Orlando Florida