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Research Paper

Lessons of War: Turning Data Into Decisions☆,☆☆

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ABSTRACT

Background: Recent conflicts in Afghanistan and Iraq produced a substantial number of critically wounded service-members. We collected biomarker and clinical information from 73 patients who sustained 116 life-threatening combat wounds, and sought to determine if the data could be used to predict the likelihood of wound failure.

Methods: From each patient, we collected clinical information, serum, wound effluent, and tissue prior to and at each surgical débridement. Inflammatory cytokines were quantified in both the serum and effluent, as were gene expression targets. The primary outcome was successful wound healing. Computer intensive methods were used to derive prognostic models that were internally validated using target shuffling and cross-validation methods. A second cohort of eighteen critically injured civilian patients was evaluated to determine if similar inflammatory responses were observed.

Findings: The best-performing models enhanced clinical observation with biomarker data from the serum and wound effluent, an indicator that systemic inflammatory conditions contribute to local wound failure. A Random Forest model containing ten variables demonstrated the highest accuracy (AUC 0.79). Decision Curve Analysis indicated that the use of this model would improve clinical outcomes and reduce unnecessary surgical procedures. Civilian trauma patients demonstrated similar inflammatory responses and an equivalent wound failure rate, indicating that the model may be generalizable to civilian settings.

Interpretation: Using advanced analytics, we successfully codified clinical and biomarker data from combat patients into a potentially generalizable decision support tool. Analysis of inflammatory data from critically ill patients with acute injury may inform decision-making to improve clinical outcomes and reduce healthcare costs.

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1. Introduction

During the last decade of conflict in Afghanistan and Iraq, our military health system (MHS) treated a large number of critically-wounded servicemen and women (Casualty Report). Many of them sustained systemic polytrauma, mangled extremities and traumatic amputations from blasts. These devastating injuries pushed the physiologic reserves of these generally young, previously healthy patients to the extreme. Thanks to the combined effects of body armor, tourniquets, tactical combat casualty care, aggressive resuscitation techniques, and a robust trauma system, many service members who would have died in previous conflicts survived to reach tertiary care facilities (Elster et al., 2013; Sheridan et al., 2014). Because these survivors posed substantial reconstruction and rehabilitation challenges, we organized a coordinated effort to characterize the physiologic response of military patients to these devastating injuries, and determine if particular biomarkers predict perioperative complications.

Early in the conflicts, we noted that severely-injured patients demonstrate systemic inflammatory dysregulation and relative immunosuppression (Hawksworth et al., 2009). This suggests that the native inflammatory system, geared toward mitigating less severe injuries, is ill-equipped to regulate the massive physiologic insults produced by blast injuries (Hawksworth et al., 2009). Complications such as delayed wound healing and dehiscence (Forsberg et al., 2008), venous thromboembolism (Gillern et al., 2011), and ventilator-associated pneumonia (Landrum and Murray, 2008) occurred more frequently than expected; and unanticipated outcomes such as heterotopic ossification (Potter et al., 2007; Forsberg et al., 2009) and angioinvasive fungal infections (Warkentien et al., 2012) were frequently observed. In fact, even highly experienced military surgeons had difficulty risk-stratifying their patients' wounds (Forsberg et al., 2014) because the conventional manner of visually assessing wounds (Bartlett, 2003; Stromeyer, 1862; Moorhead, 1942a; Selcer, 2008) was inadequate.

The timing of wound closure is important. If a combat wound is closed prematurely, it is more likely to dehisce. When this happens, the injured service member requires additional surgical procedures that can jeopardize life, limb or residual limb length. However, if a wound is closed unnecessarily late, the delay and additional procedures prolong the patient's hospital stay, delay rehabilitation, and increase the risk that the patient will develop a hospital-acquired infection or other complication. In the hopes of optimizing care, we sought to characterize each patient's physiologic response to injury, with the goal of developing a decision support tool to guide the timing of wound closure.

2. Materials and Methods

2.1. Selection of Patients

Study participants were screened and treated at Walter Reed National Military Medical Center (WRNMMC), Bethesda, MD, between January 2007 and January 2012. Each candidate participant had been evacuated from Iraq or Afghanistan after sustaining a combat-related injury to one or more extremities. All had at least one extremity wound >75 cm^2 treated en route with negative pressure wound therapy.

To get a preliminary sense of the validity and generalizability of our findings, we also enrolled a civilian comparison group of patients who were treated in the Marcus Trauma Center of Grady Memorial Hospital, a civilian Level I trauma center in Atlanta, GA. Both groups, military and civilians, were enrolled using a common IRB approved study protocol.

2.2. Human Subject Considerations

Inclusion criteria for this study as at least one extremity wound >75 cm^2 treated with negative pressure wound therapy without immune or connective tissue disorders. Details of the consenting process are outlined below.

2.3. Walter Reed National Military Medical Center (Study Number 352334)

This study was reviewed and approved by the Walter Reed National Military Medical Center Institutional Review Board. We consider combat casualties to be a vulnerable patient population. Because of this, every effort was made to eliminate the appearance of military rank, authority, or the perception of coercion during the enrollment process. Patients were identified by the manifest of incoming combat casualties from overseas. Each prospective study participant received a standardized briefing by one of three research associates specifically trained in the informed consent process. Informed consent was obtained for each study participant. For those who were unconscious, or otherwise unable to communicate, we obtained informed consent from the patient's legally authorized representative in accordance with local and federal regulations. Patients enrolled by this method were re-consented after their cognitive status improved, after first being given the opportunity to withdraw from the study. Each study participant was given the opportunity to withdraw from the study at regular intervals, coinciding with the timing of sample collection.

2.4. Grady Memorial Hospital (Study Number 00058229)

This study was reviewed and approved by the Emory University Institutional Review Board and the Grady Hospital Research Oversight Committee. Patients were identified by one of the co-investigators during attendance at general surgery morning reports, attendance of trauma bay resuscitations, review of surgical operative logs and referrals from other admitting surgeons. Other admitting surgeons were contacted to ensure they are in agreement with patient enrollment prior to approach of the patient. Patients were informed that they could withdraw from the study at any time and for any reason without penalty or adjustments in their routine care. All patients with wounds that met inclusion criteria were approached by study personnel and the patient and/or the patient's family were engaged in a detailed discussion about the aims of the study and the potential risks and benefits of study participation. Potential subjects were also informed that wounds seen in the civilian setting would be analyzed and compared to similar findings in military patients with war wounds. For patient's unable to give personal consent for this study, the next-of-kin or legally authorized representative were approached and consent sought after appropriate discussion as described.

Any candidate study participant found to have a confounding comorbid condition, such as an immune or connective tissue disorder, was excluded. To guide the timing of closure, surgeons at both used the conventional “4C's”: color, consistency, contractility when stimulated, and the capacity to bleed when incised (Bartlett, 2003; Bowyer, 2006).

2.5. Demographics

We collected a comprehensive set of demographic and clinical information, including gender, age, body mass index (BMI), tobacco use, mechanism of injury, Injury Severity Score (ISS), time from injury, units of transfused blood products, and associated neurovascular or traumatic brain injuries. At the time of each surgical débridement, we also recorded the patient's APACHE II score, wound size, and time from injury. Each wound was followed for a minimum of six weeks following surgical closure. Successful closure was defined as greater than 90% split thickness skin graft acceptance, the absence of infection (Sherertz et al., 1992), and the absence of dehiscence following delayed primary closure. Dehiscence was defined as a reopened wound that required additional surgical treatment within 30 days of closure or coverage.