Syndecan-1: A Quantitative Marker for the Endotheliopathy of Trauma

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BACKGROUND: Endothelial glycocalyx breakdown elicits syndecan-1 shedding and endotheliopathy of trauma (EoT). We hypothesized that a cutoff syndecan-1 level can identify patients with endothelial dysfunction who would have poorer outcomes.

STUDY DESIGN: We conducted a prospective observational study. Trauma patients with the highest level of activation admitted from July 2011 through September 2013 were eligible. We recorded demographics, injury type/severity (Injury Severity Score), physiology and outcomes data, and quantified syndecan-1 and soluble thrombomodulin from plasma with ELISAs. With receiver operating characteristic curve analysis, we defined EoT+ as the syndecan-1 cutoff level that maximized the sum of sensitivity and specificity (Youden index) in predicting 24-hour in-hospital mortality. We stratified by this cutoff and compared both groups. Factors associated with 30-day in-hospital mortality were assessed with multivariable logistic regression (adjusted odds ratios and 95% CIs reported).

RESULTS: From receiver operating characteristic curve analysis (area under the curve = 0.71; 95% CI 0.58 to 0.84), we defined EoT+ as syndecan-1 level ≥40 ng/mL (sensitivity = 0.62, specificity = 0.73). Of the 410 patients evaluated, 34% (n = 138) were EoT+ patients, who presented with higher Injury Severity Scores ($p < 0.001$) and blunt trauma frequency ($p = 0.016$) than EoT− patients. Although EoT+ patients had lower systolic blood pressure (median 119 vs 128 mmHg; $p < 0.001$), base excess and hemoglobin were similar between groups. The proportion of transfused (EoT+ 71.7% vs EoT− 36.4%; $p < 0.001$) and deceased EoT+ patients (EoT+ 24.6% vs EoT− 12.1%; $p < 0.001$) was higher. EoT+ was significantly associated with 30-day in-hospital mortality (adjusted odds ratio = 2.23; 95% CI 1.22 to 4.04).

CONCLUSIONS: A syndecan-1 level ≥40 ng/mL identified patients with significantly worse outcomes, despite admission physiology similar to those without the condition. (J Am Coll Surg 2017;225: 419−427. © 2017 The Authors. Published by Elsevier Inc. on behalf of the American College of Surgeons. This is an open access article under the CC BY-NC-ND license [http://creativecommons.org/licenses/by-nc-nd/4.0/].)

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Hemorrhage is the leading cause of early and potentially preventable mortality in trauma patients, with 58% of these deaths occurring in the first 3 hours after hospital admission.[1] Hemorrhagic shock is the underlying mechanism responsible for this high mortality rate because it leads to exsanguination, inflammation, coagulopathy, endothelial dysfunction, and an increase in vascular permeability.[2,3] The endothelial glycocalyx (EGL) is a negatively charged complex layer of proteoglycans and glycoproteins on top of endothelial cells of which syndecans and hyaluronic acid are major components. This structure is responsible, in part, for the maintenance of vascular permeability.[4] Loss of the integrity of the EGL increases vascular permeability, leading to capillary leak,

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Abbreviations and Acronyms

ED = emergency department
EGL = endothelial glycocalyx
EoT = endotheliopathy of trauma
IQR = interquartile range
ISS = Injury Severity Score
ROC = receiver operating characteristic
sTM = soluble thrombomodulin

and results in exposure of endothelial cells to circulating platelets and leukocytes, which initiates an inflammatory response and alters coagulation.[3,5] Damage and thinning of the EGL have been linked to the deleterious effects of reperfusion damage (ie after post-cardiac arrest syndrome) and to other inflammatory states, such as hyperglycemia in diabetes mellitus.[6-8] Endothelial glycocalyx breakdown also disturbs blood flow-induced forces, such as shear stress and wall tension, due to the essential role that EGL plays as a mechanosensor.[9] Therefore, EGL breakdown can be the pivotal point where the downstream effects of trauma interact and lead to endothelial dysfunction, coagulopathy, edema, and organ dysfunction, which ultimately results in poor outcomes.[2,10] The systemic effects of these responses comprise the syndrome called the "endotheliopathy of trauma" (EoT).[11] Clinically, there is not yet a readily available method to quantify endothelial damage, but previous studies have shown a strong association between the shedding of EGL components—mainly syndecan-1—and coagulopathy, edema, and mortality.[2,5,10] Syndecan-1 (a heparan-sulfate proteoglycan expressed in both endothelial and epithelial cells) has been widely studied in relation to traumatic injury and is currently considered a main marker of EGL breakdown.[2,10,12,13] Thrombomodulin is an anticoagulant protein expressed on the endothelial surface and plays a role in the activation of the protein C anticoagulant pathway.[4,14-16] After trauma, the increase of the inflammatory cytokines tumor necrosis factor α and interleukin 6 results in downregulation of thrombomodulin and activation of neutrophils that can cleave thrombomodulin, releasing it into the circulation as soluble thrombomodulin (sTM), a less active form and a well-known marker of endothelial cell injury.[14-17]

Hemorrhagic shock induces shedding of syndecan-1, facilitating the exposure of the injured endothelium to pro-inflammatory mediators and altering its integrity, which results in increased permeability.[10,18] Recently, Johansson and colleagues demonstrated an association between sympathoadrenal activation, inflammation, coagulopathy, and shedding of syndecan-1.[2,3,19,20] Other studies have also shown the association between high circulating levels of syndecan-1 and increased endothelial permeability, which correlated with higher transfusion volumes and worse outcomes.[10] In addition, the protective effects of therapies that target EoT and EGL, such as plasma-based resuscitation, seem to be mediated in part by the modulation of syndecan-1, as demonstrated by in vitro studies.[5,21,22] Similarly, in a rodent model, Haywood-Watson and colleagues[5] showed that fresh frozen plasma repairs the EGL, restores endothelial syndecan-1, and modulates inflammation.

Syndecan-1 seems to be involved in several of the downstream effects after traumatic injury that lead to the EoT.[3,10,19,23] The aim of this study was to determine a quantitative index of EoT using circulating levels of syndecan-1, a biomarker of EGL breakdown. We hypothesized that there is a cutoff level of shed syndecan-1 that allows the identification of trauma patients with endothelial dysfunction, at risk of progressing into EoT, and who would have an increased need for blood transfusions and poorer outcomes.

METHODS

Study design and analysis sample

This prospective observational study was conducted at the Texas Trauma Institute Memorial at Hermann Hospital Texas Medical Center, a Level I trauma center, and The University of Texas Health Science Center at Houston. Earlier approval was obtained from The University of Texas Health Science Center at Houston IRB (HSC-GEN-12-0059). The current article reports additional analysis of data from 410 patients (14 patients were excluded because of missing essential laboratory and clinical data) of the 424 patients previously reported by Johansson and colleagues.[20] As we limited our patient data to having no missing values, there are minor differences between the articles. We included adult trauma patients admitted between July 2011 and September 2013 who met criteria for the highest level of trauma team activation. Consent was obtained from the patient or a legally authorized representative within 72 hours of admission. We obtained a waiver of consent for those patients discharged or who died within 24 hours of admission. We excluded cases where patients were younger than 18 years, pregnant, prisoners, and enrolled in other studies; patients who declined to give consent (their blood samples destroyed); and those from whom we could not obtain an initial blood draw. On emergency department (ED) arrival, 20 mL of blood was obtained, then transferred into Vacutainer tubes containing 3.2% citrate, and inverted to ensure proper anticoagulation.