Serum transthyretin is a predictor of clinical outcomes in critically ill trauma patients

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Background. *In surgery patients, low preoperative serum transthyretin (TTR) level is associated with greater rates of infection and mortality. However, the predictive value of TTR on surgical outcomes after major trauma has not yet been studied.*
Methods. *Critically ill trauma patients who underwent surgery for trauma and had TTR preoperatively measured after admission to the surgical intensive care unit (ICU) at the LAC+USC Medical Center (01/2008–05/2014) were identified retrospectively. Univariable and multivariable regression analyses determined the significance of TTR on outcomes.*
Results. *We identified 348 patients. Univariable analysis indicated that patients with lower TTR had more infections (*$P < .001$*), higher mortality (*$P = .007$*), longer hospital stay (*$P < .001$*), longer ICU stay (*$P < .001$*), and increased ventilator days (*$P < .001$*). Even after adjusting for differences in patient characteristics, lower TTR level was associated with greater infectious complication rates (*$P = .001$*), greater mortality (*$P = .005$*), longer hospital stay (*$P = .013$*), longer ICU stay (*$P = .030$*), and increased ventilator days (*$P = .044$*).*
Conclusion. *In critically ill trauma patients, low serum TTR level is associated with poorer clinical outcomes, and its prognostic utility warrants further study. (Surgery 2015;158:438-44.)*

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Serum transthyretin (TTR) as a nutritional biomarker was initially thought to reflect nutritional intake directly. Low TTR levels were associated with inadequate protein calorie consumption or malnutrition. This inference stemmed from studies that observed not only low TTR levels in patients exhibiting other signs of malnutrition, but also rebounding TTR levels in the same patients after receiving dietary protein replacement.[1] Such initial studies served as the basis for subsequent studies assessing the significance of TTR as a prognostic biomarker as well as an index for tracking the adequacy of nutritional supplementation.[2-12]

TTR has also been identified as a significant predictor of clinical outcomes after surgical intervention. Elective surgery patients with low preoperative TTR have significantly longer hospital duration of stay, longer intensive care unit (ICU) duration of stay,[2] and higher rates of infectious complications,[3-5] mortality,[6,13] and other surgical complications.[7-9] The predictive value of serum TTR level after major trauma has not yet been studied.

Critically ill trauma patients represent a unique patient population, distinct from patients undergoing elective surgery. After major trauma, there is a substantial increase in inflammatory markers and an upregulation of acute phase proteins such as C-reactive protein (CRP).[14-18] Several studies have reported that TTR as a nutritional biomarker may not accurately reflect nutritional status in patients with this hyperinflammatory response and high serum CRP levels.[18-20] Likewise, this inflammatory milieu may alter the association between TTR and outcomes in the injured patient,

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unlike the elective surgery patient whose preoperative TTR level was measured without an inflammatory context. The practical utility of TTR as a predictor of clinical outcomes in trauma patients is therefore unclear. The purpose of this study was to assess the ability of serum TTR to predict clinical outcomes in critically ill trauma patients. Furthermore, the study also examined the impact of CRP level as a marker of the inflammatory state on the TTR association with clinical outcomes.

METHODS

Patient selection. The Institutional Review Board of the University of Southern California Health Sciences Campus approved this project. This is single-center, retrospective observational study included critically ill trauma patients admitted to the LAC+USC Medical Center surgical ICU between January 1, 2008, and May 31, 2014. To limit heterogeneity, this study included only trauma patients undergoing surgery, a group that is uniformly food-restricted during and immediately after surgery and thus more susceptible to malnutrition than nonsurgical patients.

All critically ill trauma patients admitted to the surgical ICU who underwent an acute operative procedure for trauma and had ≥1 serum TTR level measured within 24 hours after admission were included. For patients with multiple serum TTR measurements within this timeframe, the first measurement after ICU admission was used for statistical analysis. Serum CRP measurements were also extracted. Patient characteristics including age, sex, admission systolic blood pressure (SBP), admission Glasgow Coma Score (GCS), Injury Severity Score (ISS), Abbreviated Injury Scale by body part, and mechanism of injury were also collected. Mechanism of injury was categorized as penetrating, blunt, other (eg, burn), or a combination of the three. Clinical outcome variables included hospital duration of stay, ICU duration of stay, number of ventilator days (VD), infectious complications, and mortality.

Statistical analysis. The significance of TTR on outcome variables was determined using both univariable and multivariable regression analyses. In univariable analysis, patients were stratified into 2 groups according to the hospital's laboratory reference value: low TTR (<19 mg/dL) and normal TTR (≥19 mg/dL). The Mann–Whitney *U* test and Fisher's exact test were used to examine associations between TTR group and continuous outcome variables (hospital duration of stay, ICU duration of stay, and VD) and dichotomous outcome variables (infectious complication and mortality), respectively.

For multivariable analysis, TTR level was maintained as a continuous variable. Logistic regression analysis was used to assess the significance of TTR as a predictor of dichotomous outcome variables. Before multivariable linear regression analysis, satisfaction of all statistical assumptions necessary for linear regression was confirmed. This entailed transforming hospital duration of stay and ICU duration of stay via base 10 logarithmic ($\log_{10}$) transformations. VD was transformed via reciprocal transformation after adding a constant value of 1 to account for VD values of 0. Linear regression used the enter method and included clinically relevant independent variables: TTR, age, sex, admission SBP, admission GCS, ISS, and mechanism of injury.

Data were managed and analyzed using SPSS version 17.0 (IBM Corporation, Armonk, NY). All statistical tests were 2 sided.

Subgroup analysis. CRP subgroup analyses were conducted on patients with available CRP data. The univariable and multivariable analyses were repeated on a subset of patients with high CRP values. An abnormal high CRP value was initially defined as ≥10 mg/dL. Additional sensitivity analyses tested higher thresholds including ≥50 and ≥100 mg/dL.

RESULTS

During the study timeframe, 348 patients satisfied inclusion criteria (Figure). Patient age ranged from 5 to 95 years (mean, 41.3; standard error [SE], 1.1). Of all patients, 277 (80%) were male. The mean ISS and GCS at admission were 19.2 (SE 0.7) and 12.4 (SE 0.2), respectively. Overall, 246 (71%) and 83 (24%) patients were admitted for penetrating and blunt injuries respectively; 34 patients (10%) sustained other types of injuries (eg, burn, electrical shock; Table I). The most common mechanisms of injury were motor vehicle collision (84 patients, 24%), pedestrian or bicyclist thrown or run over (77 patients, 22%), gunshot (47 patients, 14%), and fall (46 patients, 13%; Table II). The most common surgeries were soft tissue (122 patients, 35%), orthopedic (103 patients, 30%), gastrointestinal tract (62 patients, 18%), central nervous system (54 patients, 16%), and cardiovascular (51 patients, 15%).

Of all patients, 159 (46%) had serum TTR levels of <19 mg/dL and were allocated to the low TTR group. Conversely, 189 patients (54%) had serum TTR levels of ≥19 mg/dL and were allocated to