Role of Admission Troponin-T and Serial Troponin-T Testing in Predicting Outcomes in Severe Sepsis and Septic Shock

Saraschandra Vallabhajosyula, MBBS; Ankit Sahuja, MBBS, FACP, FASN; Jeffrey B. Geske, MD, FACC; Mukesh Kumar, MBBS; Joseph T. Poterucha, DO; Rahul Kashyap, MBBS; Kianoush Kashani, MD, MSc, FASN, FCCP; Allan S. Jaffe, MD, FACC, FAHA; Jacob C. Jentzer, MD, FACC

Background—Troponin-T elevation is seen commonly in sepsis and septic shock patients admitted to the intensive care unit. We sought to evaluate the role of admission and serial troponin-T testing in the prognostication of these patients.

Methods and Results—This was a retrospective cohort study from 2007 to 2014 on patients admitted to the intensive care units at the Mayo Clinic with severe sepsis and septic shock. Elevated admission troponin-T and significant delta troponin-T were defined as ≥0.01 ng/mL and ≥0.03 ng/mL in 3 hours, respectively. The primary outcome was in-hospital mortality. Secondary outcomes included 1-year mortality and lengths of stay. During this 8-year period, 944 patients met the inclusion criteria with 845 (90%) having an admission troponin-T ≥0.01 ng/mL. Serial troponin-T values were available in 732 (78%) patients. Elevated admission troponin-T was associated with older age, higher baseline comorbidity, and severity of illness, whereas significant delta troponin-T was associated with higher severity of illness. Admission log10 troponin-T was associated with unadjusted in-hospital (odds ratio 1.6; P=0.003) and 1-year mortality (odds ratio 1.3; P=0.04), but did not correlate with length of stay. Elevated delta troponin-T and log10 delta troponin-T were not significantly associated with any of the primary or secondary outcomes. Admission log10 troponin-T remained an independent predictor of in-hospital mortality (odds ratio 1.4; P=0.04) and 1-year survival (hazard ratio 1.3; P=0.008).

Conclusions—In patients with sepsis and septic shock, elevated admission troponin-T was associated with higher short- and long-term mortality. Routine serial troponin-T testing did not add incremental prognostic value in these patients. (J Am Heart Assoc. 2017;6:e005930. DOI: 10.1161/JAHA.117.005930.)

Key Words: cardiac biomarkers • critical care • sepsis • shock • troponin

Sepsis is a leading cause of death and disability in the United States, resulting in a similar number of fatalities as acute myocardial infarction (AMI) each year.1,2 Cardiovascular dysfunction occurs in nearly 70% of septic patients and can manifest as hemodynamic instability, cardiac biomarker elevation, myocardial dysfunction on echocardiography, and end-organ hypoperfusion.3 Cardiovascular dysfunction in sepsis is associated with worse hospital and long-term outcomes, necessitating early diagnosis and management.1

Cardiac troponin-T (TnT) and troponin-I (TnI) are sensitive and specific markers of myocardial injury and have prognostic implications in many primary noncardiac illnesses including pulmonary embolism, subarachnoid hemorrhage, and stroke.4,5 Increased sensitivity of the contemporary TnT assay has resulted in more frequent clinical detection of myocardial injury from noncoronary causes, including critical illness.5,6 Elevations in TnT levels are present in up to 60% of all intensive care unit (ICU) patients and identify patients with increased risk of short-term and long-term mortality.6,7

Up to 85% of patients with sepsis and septic shock have detectable cardiac TnT levels using standard troponin assays, and troponin levels have demonstrated a variable association with mortality.1,8 Cardiac TnT levels correlate with the presence of left ventricular systolic and diastolic dysfunction and right ventricular dysfunction on echocardiography.8–10 TnT levels in patients with sepsis correlate with duration of hypotension and extent of vasopressor support.11–13 Prior
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Clinical Perspective
What Is New?
• Admission troponin-T was an independent predictor of in-hospital mortality and 1-year survival in patients with severe sepsis and septic shock; however, significant delta troponin-T did not influence these clinical outcomes.

What Are the Clinical Implications?
• Serial troponin-T testing in sepsis and septic shock does not confer any incremental prognostic ability over admission troponin-T.

studies evaluating the role of troponins in sepsis and septic shock were limited by the use of different troponin assays, small sample sizes, variations in definitions of elevated troponin levels, and loss of patients to follow-up. These studies display marked heterogeneity because of lack of uniform adaptation of the 99th percentile of the upper reference limit as the standardized cutoffs. Thus, the epidemiology and prognostic value of troponin levels in patients with sepsis depend not only on the assay used but also on the cutoff values used.

This study sought to evaluate the prognostic value of TnT in patients with sepsis and septic shock. We hypothesized that in patients with severe sepsis and septic shock, elevated admission TnT would correlate with short- and long-term mortality and length of stay. Furthermore, we hypothesized that an increase in TnT on serial measurement would be of incremental value in risk stratification of these patients.

Materials and Methods
This study was approved by the Institutional Review Board at the Mayo Clinic Rochester and was conducted in accordance with the amended Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective nature of the study. The study population included a historical cohort of all consecutive adult ICU admissions for severe sepsis and septic shock from January 1, 2007 through December 31, 2014. This study was designed and conducted before the publication of recently updated sepsis definitions, so the 2001 American College of Chest Physicians/Society of Critical Care Medicine consensus criteria were used to define sepsis. Severe sepsis was defined as consequent organ dysfunction, hypoperfusion, or hypotension, and septic shock was defined as hypotension refractory to fluid resuscitation of 30 mL/kg body weight. Hypoperfusion was defined as blood lactate level ≥2.3 mmol/L, organ dysfunction as Sequential Organ Failure Assessment score ≥2, and hypotension as systolic blood pressure ≤90 mm Hg or a reduction of ≤40 mm Hg from baseline. Patients with denial of research authorization, readmissions for severe sepsis, known pregnancy, and lack of available TnT levels were excluded from this study.

Cardiac TnT was measured with the fourth-generation TnT electrochemiluminescence immunoassay (Elecsys; Roche Diagnostics, Indianapolis, IN) using the Roche Cobas e411 analyzer. The 99th percentile of upper reference limit value for this assay is <0.01 ng/mL and the 10% coefficient of variability value is 0.035 ng/mL. Admission TnT values were defined as the first measured TnT level within 6 hours of ICU admission. An elevated admission TnT level was defined as TnT ≥0.01 ng/mL consistent with the assay used and prior data from our center. A significant delta TnT level was defined as a rise in 3- and 6-hour TnT ≥0.03 ng/mL compared with the admission TnT value. A delta TnT of >0.03 ng/mL exceeds the coefficient of variability for this assay, defining a change that cannot occur because of the imprecision of assay alone.

The Mayo Clinic Multidisciplinary Epidemiology and Translational Research in Intensive Care Laboratory ICU DataMart has comprehensive ICU data and uses previously validated electronic search algorithms for detection of sepsis and septic shock. Data were electronically abstracted from the electronic health record using validated search algorithms as previously described. Laboratory, imaging, and physiological parameters closest to ICU admission were abstracted. The severity of illness was measured using Acute Physiology and Chronic Health Evaluation III and Sequential Organ Failure Assessment scores. Mortality data were abstracted from the Mayo Clinic databases, the state of Minnesota electronic death certificates, and the Rochester Epidemiology Project death data system. Two independent reviewers (SV, MK) performed manual chart reviews to ensure accuracy and fidelity of data when needed.

The primary outcome was in-hospital mortality, and secondary outcomes included 1-year mortality, ICU length of stay, and hospital length of stay. In all patients, these outcomes were compared in patients with and without significant TnT elevation and between admission TnT quartiles. In patients with serial TnT measurements, these outcomes were compared across groups based on presence or absence of elevated admission and delta TnT levels.

Statistical Analysis
Continuous data are presented as median (interquartile range), and categorical data are presented as totals (percentages). Values of TnT with exponential distribution were log-transformed for the purpose of linear analyses. Mann–Whitney U test and χ² tests were used to evaluate continuous and categorical outcomes, respectively. Odds ratio (OR) with their corresponding 95% confidence interval (CI) was used to report categorical variables in the univariate and multivariate
analysis. Comparison between multiple groups was made using 1-way ANOVA or Kruskal–Wallis test.

For the multivariate analysis, outcomes of in-hospital and 1-year mortality were analyzed using models designed from predictors with P<0.10 in the univariate analysis and judgment of clinically relevant variables. Variables included in standardized scoring models (Acute Physiology and Chronic Health Evaluation III, Sequential Organ Failure Assessment, and Charlson comorbidity indices) were not included in the multivariable analysis to prevent duplication. The variables were assessed for collinearity before inclusion in the model, and only independent variables were included. OR (95% CI) were used to report predictors in the multivariate logistic regression analysis for in-hospital mortality and hazard ratio (95% CI) were used to report predictors using the Cox proportional hazards for 1-year survival. Two-tailed P<0.05 was considered statistically significant. All statistical analyses were performed with JMP version 10.0.1 (SAS Institute, Cary, NC).

Results

During this 8-year period, 1757 patients with severe sepsis and septic shock were admitted to the ICUs at Mayo Clinic Rochester. Sixty-nine (3.9%) patients did not have research authorization, and 744 (42.4%) did not have a measured TnT, leaving a final study population of 944 (53.7%) patients. Baseline characteristics and unadjusted outcomes of patients with and without measured TnT are presented in Table 1. Patients in whom TnT was measured had greater baseline cardiovascular comorbidity and higher severity of illness at ICU admission. Of the 944 patients with a measured admission TnT, 845 (89.5%) had elevated admission TnT, with a median TnT of 0.06 (interquartile range 0.03–0.14) ng/mL. Baseline characteristics of the cohorts with and without TnT elevation are detailed in Table 2. Patients with elevated admission TnT were older and had higher rates of coronary artery disease, pulmonary hypertension, atrial fibrillation, chronic kidney disease, and baseline comorbidity. Patients with elevated TnT had higher severity of illness (Acute Physiology and Chronic Health Evaluation III score) and received less fluid resuscitation during their ICU stay; there were no differences in the vasopressor or ventilatory requirements between the 2 cohorts.

Serial TnT testing at 3 hours and 6 hours was performed in 732 (77.5%) patients with a measured admission TnT level. An elevated delta TnT ≥0.03 ng/mL was present in 196 (26.8%) patients: 185 (27.4%) patients with an elevated admission TnT and 11 (19.6%) without an elevated admission TnT (P=0.27). Detailed baseline characteristics of patients with and without significant delta TnT are listed in Table 2. Elevated delta TnT was associated with higher severity of illness as evidenced by higher rates of septic shock, peak lactate levels, and Acute Physiology and Chronic Health Evaluation III and day 1 Sequential Organ Failure Assessment scores. N-terminal-pro B-type natriuretic peptide levels were recorded in 191 (25.7%) patients. There were no differences in N-terminal-pro B-type natriuretic peptide levels in patients with and without elevated TnT (4283 [1633–11542] versus 3356 [963–6205] pg/mL; P=0.25) and significant delta TnT (4435 [1561–9523] versus 4128 [1657–12053] pg/mL; P=0.79).

Clinical Outcomes

In-hospital and 1-year mortality rates in the overall cohort were 25.9% and 56.3%, respectively. Median follow-up was

| Parameter | Troponin-T Measured (N=944) | No Troponin-T Measured (N=744) | P Value |
|-----------|-----------------------------|-------------------------------|---------|
| Age, y    | 72.6 (62.2–82)              | 62.5 (52.1–74.4)              | <0.001  |
| Male sex  | 539 (57.1)                  | 381 (51.2)                   | 0.02    |
| Coronary artery disease | 353 (37.4) | 105 (14.1) | <0.001  |
| Prior myocardial infarction | 213 (22.6) | 68 (9.1) | <0.001  |
| Atrial fibrillation | 275 (29.1) | 122 (16.4) | <0.001  |
| Chronic kidney disease | 338 (35.8) | 148 (19.9) | <0.001  |
| Charlson comorbidity index | 7 (5–10) | 6 (3–8) | <0.001  |
| Aspirin | 355 (37.6) | 184 (24.7) | <0.001  |
| Statins | 424 (28.6) | 154 (20.1) | <0.001  |
| APACHE-III score | 87 (72–107) | 74 (58–92) | <0.001  |
| Acute kidney injury | 601 (63.7) | 358 (48.1) | <0.001  |
| Hemoglobin, g/dL | 10.3 (8.9–11.8) | 10.2 (8.8–11.7) | 0.26 |
| Leukocytes, ×10⁹/L | 13.5 (8.7–19.0) | 12.6 (7.2–18.8) | 0.004 |
| Platelets, ×10⁹/L | 182 (121.3–262.5) | 174 (107–264) | 0.11 |
| Creatinine, mg/dL | 1.8 (1.2–2.8) | 1.3 (0.9–2) | <0.001 |
| In-hospital mortality | 244 (25.9) | 119 (16) | <0.001 |
| 1-y mortality | 501 (56.3) | 310 (46) | <0.001 |
| Intensive care unit length of stay | 2.6 (1.5–5.1) | 2.0 (1.2–3.8) | <0.001 |
| Hospital length of stay | 8.1 (5–14.9) | 7.4 (4.6–14.2) | 0.10 |

Values represented as total (percentage) or median (interquartile range); APACHE-III indicates Acute Physiology and Chronic Health Evaluation III.
135 (interquartile range 11–903) days, with 53 (5.6%) patients lost to follow-up. Unadjusted 1-year survival using Kaplan–Meier survival analysis was lower in patients with elevated admission TnT \((P=0.03\) by log-rank test; Figure 1A). There was a stepwise increase in in-hospital mortality \((P=0.007)\) with increasing quartiles of admission TnT (Figure 2), but this was not seen for 1-year mortality \((P=0.20)\). Patients with an elevated admission TnT did not have a higher rate of in-hospital mortality than patients without elevated admission TnT \((26.3\% \text{ versus } 22.2\% ; P=0.47)\). Among hospital survivors, admission and delta TnT were not independent predictors of 1-year survival (Figure 3A and 3B).

### Table 2. Baseline Characteristics of Patients With Elevated Admission Troponin-T and Elevated Delta Troponin-T

| Parameter                                      | Admission Troponin-T (N=944) | Delta Troponin-T (N=732) | \(P\) Value | Significant (N=196) | Not Significant (N=536) | \(P\) Value |
|------------------------------------------------|-------------------------------|-------------------------|-------------|----------------------|-------------------------|-------------|
| Demographics                                   |                               |                         |             |                      |                          |             |
| Age, y                                         | 73 (63–82)                    | 70 (59–79)              | 0.03        | 74 (64–82)           | 73 (62–82)              | 0.27        |
| Male sex                                       | 491 (58.1)                    | 48 (48.5)               | 0.07        | 121 (61.7)           | 305 (56.9)              | 0.24        |
| Comorbidities and medications                  |                               |                         |             |                      |                          |             |
| Hypertension                                   | 506 (59.9)                    | 58 (58.6)               | 0.83        | 128 (65.3)           | 329 (61.3)              | 0.33        |
| Diabetes mellitus, type II                     | 354 (41.9)                    | 37 (37.4)               | 0.45        | 82 (41.8)            | 222 (41.4)              | 0.92        |
| Hyperlipidemia                                 | 390 (46.2)                    | 36 (36.4)               | 0.07        | 92 (46.9)            | 248 (46.3)              | 0.87        |
| Coronary artery disease                        | 325 (38.5)                    | 28 (28.3)               | 0.04        | 89 (45.4)            | 204 (38.1)              | 0.07        |
| Prior myocardial infarction                    | 192 (22.7)                    | 21 (21.2)               | 0.80        | 58 (29.6)            | 116 (21.6)              | 0.03        |
| Prior coronary intervention                    | 114 (13.5)                    | 10 (10.1)               | 0.43        | 37 (18.9)            | 76 (14.2)               | 0.12        |
| Prior coronary artery bypass graft surgery     | 124 (14.7)                    | 9 (9.1)                 | 0.17        | 36 (18.4)            | 76 (14.2)               | 0.16        |
| Peripheral vascular disease                    | 102 (12.1)                    | 10 (10.1)               | 0.74        | 25 (12.8)            | 67 (12.5)               | 0.93        |
| Prior atrial fibrillation                      | 259 (30.7)                    | 16 (16.2)               | 0.002       | 66 (33.7)            | 160 (29.9)              | 0.32        |
| Pulmonary hypertension                         | 77 (9.1)                      | 3 (3)                   | 0.04        | 16 (8.2)             | 54 (10.1)               | 0.44        |
| Obstructive sleep apnea                        | 172 (20.4)                    | 19 (19.2)               | 0.89        | 44 (22.5)            | 119 (22.2)              | 0.94        |
| Chronic obstructive pulmonary disease          | 222 (26.3)                    | 19 (19.2)               | 0.14        | 49 (25.0)            | 142 (26.5)              | 0.68        |
| Chronic kidney disease                         | 318 (37.6)                    | 20 (20.2)               | <0.001      | 75 (38.3)            | 197 (36.8)              | 0.71        |
| End-stage renal disease                        | 105 (12.4)                    | 5 (5)                   | 0.03        | 27 (13.8)            | 62 (11.6)               | 0.42        |
| Charlson comorbidity index                     | 8 (5–11)                      | 6 (4–9)                 | 0.001       | 7 (5–10)             | 8 (5–10.8)              | 0.83        |
| Prior aspirin use                              | 321 (38)                      | 34 (34.3)               | 0.51        | 89 (45.4)            | 200 (37.3)              | 0.05        |
| Prior statins use                              | 245 (29)                      | 25 (25.3)               | 0.48        | 59 (30.1)            | 162 (30.2)              | 0.98        |
| Prior ACE-i/ARB use                            | 220 (26)                      | 27 (27.3)               | 0.81        | 51 (26.0)            | 145 (27.1)              | 0.78        |
| Prior β-blockers use                           | 319 (37.8)                    | 31 (31.3)               | 0.23        | 77 (39.3)            | 203 (37.9)              | 0.73        |
| ICU characteristics                             |                               |                         |             |                      |                          |             |
| APACHE-III score                               | 88 (72–107)                   | 81 (66–103)             | 0.04        | 96 (80–120)          | 85 (70–104)             | <0.001      |
| Septic shock                                   | 560 (66.3)                    | 64 (64.7)               | 0.74        | 143 (73.0)           | 342 (63.8)              | 0.02        |
| Acute kidney injury                            | 543 (64.3)                    | 58 (58.6)               | 0.27        | 137 (69.9)           | 337 (62.9)              | 0.08        |
| Creatinine, mg/dL                              | 1.8 (1.2–2.9)                 | 1.4 (0.9–2.1)           | <0.001      | 1.7 (1.2–2.7)        | 1.8 (1.2–2.8)           | 0.59        |
| Highest lactate, mmol/L                        | 2.9 (1.7–5)                   | 3.2 (1.7–4.5)           | 0.69        | 4 (2.3–6.4)          | 2.8 (1.7–4.5)           | <0.001      |
| Crystalloid in ICU stay, L                     | 5.2 (2.8–8.9)                 | 5.9 (3.6–10.6)          | 0.03        | 4.6 (2.3–8.3)        | 5.1 (2.9–8.6)           | 0.42        |
| Total norepinephrine, mg                       | 10.2 (2.8–35.4)               | 10.4 (1.6–36.7)         | 0.97        | 12.4 (3.1–41.8)      | 9.9 (2.8–28.8)          | 0.15        |
| Noninvasive ventilation use                    | 242 (28.6)                    | 33 (33.3)               | 0.35        | 60 (30.6)            | 167 (31.2)              | 0.93        |
| Invasive mechanical ventilation use            | 387 (45.8)                    | 53 (53.5)               | 0.17        | 112 (57.1)           | 241 (45)                | 0.004       |

Values represented as total (percentage) or median (interquartile range). ACE-i indicates angiotensin-converting enzyme inhibitors; APACHE-III, Acute Physiology and Chronic Health Evaluation III; ARB, angiotensin II receptor blockers; ICU, intensive care unit.
Because of the skewed nature of admission TnT values, these values were converted to log10TnT for continuous analyses (Figure 4). Unadjusted admission log10TnT was associated with higher in-hospital (OR 1.6 [95% CI, 1.2–2.1]; P = 0.003) and 1-year mortality (OR 1.3 [95% CI, 1.1–1.7]; P = 0.04). Admission log10TnT did not demonstrate a significant correlation with ICU (estimate 0.18, SE 0.30; P = 0.55) or hospital length of stay (estimate 1.12, SE 0.94; P = 0.23). In a multivariate model using logistic regression, admission log10TnT remained an independent predictor of in-hospital mortality (unit OR 1.4 [95% CI, 1.1–2.1]; P = 0.04, Table 3). Using Cox proportional hazards model, admission log10TnT was an independent predictor of 1-year survival (hazard ratio 1.3 [95% CI, 1.1–1.6]; P = 0.008, Table 3).

In comparison to patients without significant delta TnT, patients with elevated delta TnT (≥0.03 ng/mL) had higher unadjusted in-hospital mortality (30.6% versus 23%; OR 1.48 [95% CI, 1.03–2.13]; P = 0.04), but no differences in 1-year survival (P = 0.23 by log-rank test; Figure 1B). Unadjusted log10delta TnT was not associated with higher in-hospital mortality (OR 1.3 [95% CI, 0.9–1.9]; P = 0.21), 1-year mortality (OR 1.2 [95% CI, 0.9–1.7]; P = 0.39) or longer ICU (estimate 0.35, SE 0.48; P = 0.46) and hospital length of stay (estimate −1.38, SE 1.35; P = 0.31). There were no differences in in-hospital (P = 0.06) and 1-year (P = 0.77) mortality across delta TnT quartiles (Figure 5). Log10delta TnT was not an independent predictor of short- or long-term mortality on multivariate analysis (Table 3).

**Discussion**

In the largest single-center cohort of patients admitted with severe sepsis and septic shock who had TnT levels measured, this investigation demonstrated that (1) elevated...
admission TnT was associated with higher baseline comorbidity, higher severity of illness, and multiorgan dysfunction; (2) elevated admission TnT was associated with higher unadjusted 1-year mortality, but not higher in-hospital mortality; (3) admission log 10TnT was independently associated with in-hospital and 1-year mortality on multivariate analysis; and (4) elevated delta TnT was associated with unadjusted in-hospital mortality but was no longer significant on multivariate analysis.

Prior studies on sepsis and septic shock have presented conflicting data on the association of clinical outcomes with troponin elevation. The timing of troponin measurement, troponin assay used (ie, TnT versus TnI), and hemodynamic stability at the time of troponin measurement differ substantially in prior studies.2,7,8 The majority of prior studies have examined short-term mortality, while this study included assessment of 1-year death rate. The importance of longer follow-up is underscored by the finding that TnT levels predicted both in-hospital and 1-year mortality. The skewed distribution of TnT values significantly affects the results when not using log-transformed TnT values.

We have previously demonstrated TnT to be a marker of short-term mortality using a similar cutoff of 0.01 ng/mL on septic patients admitted from 2001 through 2006.16 In contrast to the current findings, other authors have associated elevated troponins with longer lengths of ICU and hospital stays in septic patients.23,24 Landesberg et al demonstrated high-sensitivity TnT (hs-TnT) values to correlate with left ventricular diastolic dysfunction and right ventricular dysfunction at higher cutoff values, alluding to a likely cause of troponin release in these patients.9 Even though 14 pg/mL has been demonstrated as the 99th percentile of normal distribution for hs-TnT, serial increase in TnT has been shown to correlate with increase in mortality.9 Since observed rates of abnormal TnT values and delta TnT in our population would likely have been different with hsTnT, it is possible that the prognostic impact could be different as well. Further mechanistic studies are required to understand the echocardiographic correlates and appropriate cutoff values in this population. The lack of uniform catheterization and echocardiographic data in the current cohort limits determination of the cause of TnT elevation. Masson et al showed a correlation of serial delta in hs-TnT from day 1 to day 2 of ICU admission with mortality only in patients with shock at presentation, whereas serial testing in patients with sepsis did not show any correlation with outcomes.25 John et al found elevated TnT to be associated with higher severity of illness and worse 28-day mortality.24,26 A prior meta-analysis of observational studies demonstrated increased all-cause mortality in patients with elevated troponin (relative risk 1.9, 95% CI, 1.6–2.2). However, only 3 studies used TnT values.2 By contrast, other investigators have failed to validate troponin as an

![Figure 3. Unadjusted 1-y mortality in hospital survivors with and without elevated admission and delta troponin-T. A, Unadjusted 1-y mortality for hospital survivors with and without elevated admission TnT—log rank test: P=0.06. B, Unadjusted 1-y mortality for hospital survivors with and without elevated delta TnT—log rank test: P=0.75. TnT indicates troponin-T.](image-url)
independent predictor of mortality in addition to severity of illness scores.\textsuperscript{9,27–29} 

No prior studies have evaluated the role of serial TnT or TnI testing in septic patients. The current investigation demonstrated that elevated admission TnT predicted higher short- and long-term mortality without an incremental prognostic benefit of serial TnT testing in these patients. The presence or absence of cardiac injury, as defined by elevated admission TnT level, appears to be more relevant than the magnitude of cardiac injury, as defined by delta TnT levels. Nonetheless, log\textsubscript{10}TnT values had an independent linear association with short- and long-term mortality.

Despite its increasingly frequent recognition, the etiopathogenesis of TnT elevation in sepsis remains unclear.\textsuperscript{5} Flow-limiting coronary artery disease is infrequently documented in these patients, alluding to alternate mechanisms of TnT elevation other than AMI.\textsuperscript{8} Electrocardiography and echocardiography in these patients rarely demonstrate ischemic changes, and few patients have inducible ischemia on stress testing or occlusive coronary thrombus on autopsy.\textsuperscript{8,26,30} Postulated causes for troponin elevations in septic patients include ischemic mechanisms (eg, supply–demand imbalance or microvascular spasm or thrombosis) and nonischemic mechanisms (eg, reversible myocardial membrane leakage of cytosolic TnT pool or direct cellular toxicity from inflammatory mediators, microbial toxins, or excessive catecholamine levels).\textsuperscript{7,31,32} While relative hypovolemia, inadequate resuscitation, and prolonged hypotension may contribute to myocardial injury in patients with septic shock, fluid resuscitation does not appear to influence the subsequent values of hs-TnT on serial testing.\textsuperscript{12}

A characteristic rise and fall of TnT in the presence of ischemic symptoms or other evidence of myocardial ischemia defines AMI. Ischemia is often difficult to identify in critically ill patients, adding to uncertainty regarding the need for serial measurement of TnT.\textsuperscript{33} This study identified a significant delta TnT in one fifth of patients with elevated admission TnT, yet this carried no incremental prognostic value. The slow downslope of the time–concentration curve for TnT complicates interpretation of single TnT values or delta TnT values when the sampling time is not consistent with respect to sepsis onset time. A changing pattern of results is documented early after events when the concentration–time curve is rising, but subsequently even AMI does not always manifest a recognizable changing pattern of values.\textsuperscript{34} Thus, it is unclear how strong this consideration is for clinical care in the population with sepsis and septic shock, which could confound our assessment of this cardiac biomarker in the critically ill population.

A significant association between TnT levels and various markers of renal insufficiency was present, but the prognostic

\begin{figure}
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\includegraphics[width=\textwidth]{figure4.png}
\caption{Distribution of admission TnT and log\textsubscript{10}TnT in the total cohort. A, Admission troponin-T values with a significant skew towards the higher values. B, Log\textsubscript{10} troponin-T values with a more normalized distribution. TnT indicates troponin-T.}
\end{figure}
Table 3. Unadjusted and Adjusted Predictors of Short- and Long-Term Mortality

| Predictor                             | Unadjusted Hospital Mortality | Adjusted Hospital Mortality | Unadjusted 1-Y Mortality | Adjusted 1-Y Survival |
|---------------------------------------|-------------------------------|-----------------------------|--------------------------|-----------------------|
|                                       | OR (95% CI)*                   | P Value                     | OR (95% CI)*             | P Value               | HR (95% CI)*          | P Value               |
| Admission log₁₀TnT, ng/mL             | 3.3 (1.2–2.1)                 | 0.003                       | 1.4 (1.1–2.1)            | 0.04                  | 1.3 (1.1–1.7)         | 0.03                  | 1.3 (1.1–1.6)         | 0.008                 |
| Delta log₁₀TnT, ng/mL                 | 1.3 (0.9–1.9)                 | 0.21                        | 1.2 (0.7–1.9)            | 0.59                  | 1.2 (0.8–1.7)         | 0.39                  | 0.9 (0.7–1.2)         | 0.65                  |
| Age, y                                | 1.0 (0.9–1.1)                 | 0.34                        | 1.0 (0.9–1.1)            | 0.08                  | 1.1 (1.1–1.1)         | <0.001                | 1.0 (1.0–1.1)         | 0.01                  |
| Male sex                              | 0.7 (0.5–0.9)                 | 0.004                       | 0.6 (0.4–0.8)            | 0.003                 | 1.1 (0.8–1.4)         | 0.59                  | 0.9 (0.8–1.1)         | 0.40                  |
| Body mass index, kg/m²                | 1.0 (1.0–1.0)                 | 0.14                        | 0.9 (0.9–1.0)            | 0.06                  | 0.9 (0.9–0.9)         | 0.07                  | 1.0 (0.9–1.0)         | 0.78                  |
| Hyperlipidemia                        | 0.8 (0.6–1.1)                 | 0.23                        | 1.0 (0.7–1.6)            | 0.87                  | 0.8 (0.6–1.1)         | 0.20                  | 0.9 (0.7–1.1)         | 0.34                  |
| Coronary artery disease               | 0.7 (0.5–0.9)                 | 0.03                        | 0.9 (0.6–1.4)            | 0.62                  | 0.9 (0.7–1.2)         | 0.68                  | 1.0 (0.8–1.2)         | 0.72                  |
| Atrial fibrillation                   | 1.0 (0.7–1.4)                 | 1.00                        | 1.1 (0.7–1.7)            | 0.78                  | 1.6 (1.2–2.1)         | 0.002                 | 1.2 (0.9–1.4)         | 0.21                  |
| Pulmonary hypertension                | 0.9 (0.5–1.4)                 | 0.59                        | 1.2 (0.6–2.4)            | 0.57                  | 1.1 (0.7–1.7)         | 0.91                  | 1.2 (0.9–1.6)         | 0.26                  |
| Venous thromboembolism                | 1.0 (0.8–1.4)                 | 0.87                        | 1.4 (0.9–2.1)            | 0.14                  | 1.2 (0.9–1.6)         | 0.21                  | 1.1 (0.9–1.4)         | 0.25                  |
| Chronic kidney disease                | 0.7 (0.5–1.0)                 | 0.06                        | 0.7 (0.4–1.2)            | 0.21                  | 1.1 (0.8–1.4)         | 0.83                  | 0.9 (0.7–1.1)         | 0.27                  |
| End-stage renal disease               | 0.8 (0.5–1.3)                 | 0.49                        | 0.9 (0.5–1.9)            | 0.89                  | 1.1 (0.7–1.7)         | 0.61                  | 0.9 (0.7–1.3)         | 0.71                  |
| Charlson comorbidity index            | 1.0 (0.9–1.1)                 | 0.16                        | 0.9 (0.9–1.1)            | 0.74                  | 1.1 (1.1–1.1)         | <0.001                | 1.1 (1.1–1.1)         | 0.002                 |
| Prior aspirin use                     | 0.7 (0.5–0.9)                 | 0.007                       | 0.9 (0.6–1.3)            | 0.53                  | 1.0 (0.7–1.3)         | 0.78                  | 1.1 (0.9–1.4)         | 0.37                  |
| APACHE-III score                     | 1.1 (1.1–1.1)                 | <0.001                      | 1.0 (1.0–1.0)            | <0.001                | 1.1 (1.1–1.1)         | <0.001                | 1.1 (1.1–1.1)         | <0.001                |
| Septic shock                          | 2.0 (1.5–2.8)                 | <0.001                      | 1.1 (0.6–1.8)            | 0.75                  | 1.5 (1.2–2.0)         | 0.003                 | 1.1 (0.9–1.4)         | 0.78                  |
| Respiratory failure                   | 1.7 (1.2–2.3)                 | 0.001                       | 1.2 (0.8–1.7)            | 0.43                  | 1.4 (1.0–1.9)         | 0.04                  | 1.1 (0.8–1.3)         | 0.55                  |
| Acute kidney injury                   | 1.4 (1.0–2.0)                 | 0.03                        | 1.1 (0.7–1.7)            | 0.65                  | 1.1 (0.8–1.4)         | 0.73                  | 0.8 (0.7–1.1)         | 0.25                  |
| Total norepinephrine, mg              | 1.1 (1.1–1.1)                 | <0.001                      | 1.1 (1.1–1.1)            | <0.001                | 1.1 (1.1–1.1)         | <0.001                | 1.1 (1.1–1.1)         | 0.02                  |
| Crystalloid in ICU stay, L            | 1.1 (1.1–1.1)                 | <0.001                      | 1.0 (0.9–1.0)            | 0.43                  | 1.0 (1.0–1.0)         | 0.10                  | 0.9 (0.9–1.0)         | 0.24                  |

APACHE-III indicates Acute Physiology and Chronic Health Evaluation III; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; OR, odds ratio; TnT, troponin-T.

*Adjusted for age, sex, body mass index, Charlson comorbidity index, APACHE-III score, acute kidney injury, and respiratory failure.

significance of TnT for in-hospital mortality was independent of renal function, and excluding patients with acute and chronic kidney dysfunction did not change the nature of our results (results not demonstrated). Cardiac TnT and TnI have been previously evaluated in patients with renal disease including end-stage renal disease, but further dedicated studies are needed to guide the interpretation of the individual troponin subtypes in patients with sepsis and kidney dysfunction.35,36

This study has several important limitations. Use of a retrospective database carries inherent selection and informational bias in addition to the utilization of an older definition of sepsis that has since been revised. TnT levels were measured in approximately half of the septic population, with evidence of bias toward measuring TnT levels in sicker patients. Therefore, the true epidemiology of TnT elevation among unselected patients with sepsis and septic shock cannot be inferred, nor can determination of whether TnT values influenced clinical care be made. Likewise, one quarter of patients had only a single TnT level measured, limiting the ability to estimate the prevalence of elevated delta TnT. Few patients had downstream cardiac testing such as echocardiography or coronary angiography to help define the incidence of AMI among patients with elevated TnT levels. Our institution uses the TnT assay universally, so conclusions about the incidence and prognostic value of TnI elevations cannot be determined in this cohort. Additionally, since the hs-TnT assay was approved for use in the United States in 2017, we could not use these assays in our patients. Though the hs-TnT assay has demonstrated greater sensitivity and negative predictive value in AMI, there are limited data comparing these 2 assays in the septic population.37 The development of the sepsis-3 criteria could influence the interpretation of the results of this study.38 However, this cohort of severe sepsis and septic shock are less likely to be missed with either definition because they comprise the extreme spectrum of illness.39 The study duration also correlated with the evolution of critical care ultrasonography and changes in healthcare delivery at the Mayo Clinic, both of which conceivably could have influenced our study results.40,41 Finally, the single-region, single-institution, and referral center nature of the Mayo Clinic could impact the generalizability of findings to other populations.
Future directions for research include evaluating the utility of troponin testing in development of novel management strategies in sepsis. 26 Echocardiographic myocardial dysfunction is more common in patients with troponin elevation, suggesting that future research directed at the development of specific fluid and vasopressor strategies for this population may be of incremental value. 9,10 The use of advanced noninvasive imaging modalities, such as myocardial contrast echocardiography, may facilitate recognition of myocardial ischemia in patients with septic cardiomyopathy.42

Conclusions

In patients with sepsis and septic shock, elevations in TnT are common and are associated with increased prevalence of coronary artery disease and higher severity of illness. After correcting for these factors, elevations in TnT were independently associated with increased risk of short- and long-term mortality. Among patients with elevated TnT, one fifth displayed a significant delta TnT on serial testing. Patients with an elevated delta TnT were not at increased risk of adverse outcomes, calling into question the value of serial TnT testing in this population. Further research is warranted to better understand the cause, pathogenesis, clinical implications, and need for serial testing of TnT levels in patients with sepsis and septic shock.

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Figure 5. Unadjusted in-hospital and 1-y mortality across delta troponin-T quartiles. One-way analysis of variance test for trend—In-hospital mortality P=0.06, 1-y mortality P=0.77.

Author Contributions

Study design, literature review, data analysis, statistical analysis: Vallabhajosyula, Sakhuja, Geske, Jaffe, Jentzer; Data management, data analysis, drafting manuscript: Vallabhajosyula, Sakhuja, Kumar, Poterucha, Jentzer; Access to data: Vallabhajosyula, Sakhuja, Geske, Kumar, Poterucha, Kashyap, Kashani, Jaffe, Jentzer; Manuscript revision, intellectual revisions, mentorship: Geske, Kashani, Jaffe, Jentzer; Final approval: Vallabhajosyula, Sakhuja, Geske, Kumar, Poterucha, Kashyap, Kashani, Jaffe, Jentzer.

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Disclosures

None.

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