Elevated Cardiac Troponin Measurements in Critically Ill Patients

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Background: The clinical significance of elevated cardiac troponin (cTn) level in patients in the intensive care unit (ICU) is uncertain. We reviewed the frequency of cTn elevation and its association with mortality and length of ICU stay in these patients.

Methods: Studies were identified using MEDLINE, EMBASE, and reference list review. We included observational studies of critically ill patients that measured cTn at least once and reported the frequency of elevated cTn or outcome (mortality and length of ICU or hospital stay). We pooled the odds ratios (ORs) using the inverse variance method in studies that conducted multivariable analysis to examine the relationship between elevated cTn and mortality (adjusted analysis). We calculated the weighted mean difference in length of stay between patients with and without elevated cTn and pooled the results using the inverse variance method (unadjusted analysis).

Results: A total of 23 studies involving 4492 critically ill patients were included. In 20 studies, elevated cTn was found in a median of 43% (interquartile range, 21% to 59%) of 3278 patients. In adjusted analysis (6 studies comprising 1706 patients), elevated cTn was associated with an increased risk of death (OR, 2.5; 95% confidence interval [CI], 1.9 to 3.4; \(P<.001\)). In the unadjusted analysis (8 studies comprising 1019 patients), elevated cTn was associated with an increased length of ICU stay of 3.0 days (95% CI, 1.0 to 5.1 days; \(P=.004\)) and an increased length of hospital stay of 2.2 days (95% CI, −0.6 to 4.9; \(P=.12\)).

Conclusions: Elevated cTn measurements among critically ill patients are associated with increased mortality and ICU length of stay. Research is needed to clarify the underlying causes of elevated cTn in this population and to examine their clinical significance.

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CARDIAC TROPONIN (cTn) I and T are regulatory proteins that control the calcium-mediated interaction of actin and myosin, producing myocardial contraction. In injury to myocardial cells results in cTn release into blood, which can be detected using commercially available immunoassays. The specificity and sensitivity of cTn for detecting myocardial necrosis is substantially superior to other biomarkers, and myocardial infarction was redefined in 2000 by a joint European Society of Cardiology/American College of Cardiology (ESC/ACC) Committee, based on the detection of elevated cTn measurements in the appropriate clinical setting.

Elevated cTn levels are not only useful in the diagnosis of myocardial infarction but also have predictive value in identifying patients at risk for adverse outcomes. Patients with acute coronary syndromes (ST-elevation and non–ST-elevation myocardial infarction and unstable angina) and elevated cTn levels have an increased risk of death and recurrent ischemic events compared with patients with cTn levels below the detection limit; furthermore, increasing cTn levels are associated with proportionate increases in mortality.

However, among critically ill patients, there is uncertainty regarding the prognostic significance of an elevated cTn measurement. Elevated cTn levels are commonly observed in the intensive care unit (ICU), and because they may occur in conditions other than acute coronary syndromes, there is a tendency to disregard elevated cTn levels and to prioritize other aspects of patients’ critical illness. There is no consensus on the appropriate approach and management of an elevated cTn level in the general medical and surgical ICU setting. We undertook a systematic review of studies of critically ill patients to evaluate the frequency of cTn elevation and to examine the association between an elevated cTn measurement and mortality and length of stay in the ICU and hospital.
STUDY IDENTIFICATION

We searched for published studies that measured cTn in critically ill patients in an ICU setting using the MEDLINE (1966 to February, week 2, 2006) and EMBASE (1980 to week 7, 2006) electronic databases with no language restrictions.

We hand searched our personal files and the reference lists of all included articles to identify additional studies.

STUDY SELECTION

Volunteers translated non-English language studies to allow the assessment of study eligibility. Study selection was performed independently and in duplicate.

A third reviewer resolved disagreements.

Studies were included if they (1) enrolled critically ill adult patients in an ICU setting (excluding coronary care units); (2) measured cTn at least once in the ICU in all patients; or (3) reported at least 1 of the following: the frequency of an elevated cTn level (prevalence or incidence) or the association of elevated cTn with mortality or with length of stay.

We excluded studies that exclusively enrolled cardiac surgery patients, studies examining cTn in the context of pulmonary embolism, and studies that enrolled patients in both critical care and noncritical care settings from which we could not extract the ICU-specific data.

DATA ABSTRACTION

Two investigators (W.L. and either A.S.I., I.Q., or F.L.) independently abstracted data on study design, patient and cTn characteristics, specified outcomes (frequency of elevated cTn, mortality, and length of stay), and study quality. Disagreements between reviewers were resolved through discussion. If we could not abstract required data from the published report, we contacted the corresponding author to request additional data, with a second request if we received no response.

The primary outcome was overall mortality. We abstracted the proportion of nonsurvivors among patients with and without elevated cTn measurements for the unadjusted analysis of mortality. For those studies that used multivariable analysis to assess the association between elevated cTn and mortality, we abstracted the adjusted odds ratios (ORs) or hazard ratios. We also assessed ICU and hospital mortality. Intensive care unit mortality was defined as death occurring during ICU stay or mortality reported at 30 days or less.

Studies reporting mortality but not specifying the time frame were classified as reporting ICU mortality. Hospital mortality was defined as mortality occurring during hospitalization or mortality reported after 30 days. For studies that reported both ICU and hospital mortality, we used the mortality associated with the longest follow-up to define our primary outcome of overall mortality.

Study quality was abstracted as follows: (1) study design, prospective vs retrospective studies; (2) method of patient enrollment (applicable for prospective studies), consecutive vs nonconsecutive; (3) duration of follow-up, greater than 30 days vs less than 30 days; (4) number of cTn measurements, measured more than once vs measured once; and (5) analysis relating cTn level to outcome, multivariable vs univariable.

STATISTICAL ANALYSIS

To assess the agreement between reviewers for study selection, we used the kappa coefficient (κ), which measures chance-corrected agreement. The frequency of elevated cTn was evaluated using median and interquartile range (IQR).

In our unadjusted analyses, we calculated the weighted mean difference and 95% confidence interval (CI) for the length of stay in ICU and in hospital, and the OR and 95% CI for overall mortality (comparing patients with vs without an elevated cTn measurement) for each study.

In our adjusted analysis evaluating the independent association between an elevated cTn measurement and mortality, we pooled the adjusted ORs for overall mortality from the studies that used multivariable regression.

Data were pooled for both the adjusted and unadjusted analyses using the inverse variance method and a random effects model using Review Manager software (RevMan version 4.2.8 for Windows; The Cochrane Collaboration, Oxford, England; 2005) and a macro written in S-PLUS (version 6.2; Insightful Corp, Seattle, Wash).

We evaluated statistical heterogeneity using the I² statistic, which measures the extent of inconsistency among study results not attributable to chance and reports the proportion of total variance due to heterogeneity of results.

We performed 1 a priori subgroup analysis based on the results of the unadjusted mortality analysis, examining the effect of elevated cTn level on outcomes in the subgroup of patients with sepsis vs all other critically ill patients (without sepsis). We included results from septic patients (cases) reported in 2 case-control studies in the sepsis subgroup analysis and included results from the nonseptic subgroup analysis (and hence patients from these 2 studies appear in both groups). Because none of the 6 studies assessing elevated cTn and mortality using multivariable analysis specifically enrolled patients with sepsis, this analysis was unadjusted.

We performed 1 a priori sensitivity analysis to examine the relationship between an elevated cTn measurement and mortality, including studies that reported ICU mortality and subsequently those that reported hospital mortality.

RESULTS

Our search identified 538 published studies: 167 studies from MEDLINE and 417 from EMBASE; 46 studies were duplicated in the 2 databases (Figure 1). We excluded 513 studies after title and abstract screening and retrieved the re-
Table 1. Study and Patient Characteristics

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design; Patient Enrollment (ICU Type)</th>
<th>No. of Patients; Type</th>
<th>APACHE II*</th>
<th>Mechanical Ventilation Use</th>
<th>Inotrope Use</th>
<th>Septic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin et al,30 2005</td>
<td>Retrospective cohort; NA (TICU)</td>
<td>1081; Trauma</td>
<td>29</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Quenot et al,24 2005</td>
<td>Prospective cohort; consecutive (MICU)</td>
<td>217; Noncardiac</td>
<td>SAPS II, 47 ± 23</td>
<td>79 (36)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Kim et al,25 2005</td>
<td>Prospective cohort; NS (MICU)</td>
<td>215; Noncardiac</td>
<td>SAPS II, 39 ± 16</td>
<td>NS</td>
<td>NS (57)</td>
<td>122</td>
</tr>
<tr>
<td>King et al,26 2005</td>
<td>Prospective cohort; consecutive (MICU)</td>
<td>128; Noncardiac</td>
<td>15.3 ± 8.9</td>
<td>NS</td>
<td>48 (38)</td>
<td>46 (36)</td>
</tr>
<tr>
<td>Landesberg et al,11 2005</td>
<td>Prospective cohort; consecutive (MICU, TICU)</td>
<td>101; Cardiac and high-risk cardiac</td>
<td>23.0 ± 9.8</td>
<td>67 (66)</td>
<td>26 (26)†</td>
<td>57 (56)</td>
</tr>
<tr>
<td>Wu et al,14 2004</td>
<td>Prospective cohort; consecutive (MICU)</td>
<td>108; Noncardiac</td>
<td>21.6 ± 8.2</td>
<td>57 (53)</td>
<td>44 (41)†</td>
<td>77 (71)</td>
</tr>
<tr>
<td>Edouard et al,15 2004</td>
<td>Prospective cohort; consecutive (STICU)</td>
<td>728; Trauma</td>
<td>ISS, 28 ± 16; RTS, 8.3 ± 3.3; SAPS, 28 ± 17</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mehta et al,31 2004</td>
<td>Prospective cohort; consecutive (MICU)</td>
<td>37; Septic shock (noncardiac)</td>
<td>23.6 ± 6.3</td>
<td>21 (57)</td>
<td>26 (70)</td>
<td>37 (100)</td>
</tr>
<tr>
<td>Klein Gunnewiek and van de Leur,16 2003</td>
<td>Prospective cohort; consecutive (MICU)</td>
<td>34; Surgical</td>
<td>16.6</td>
<td>21 (62)</td>
<td>16 (47)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Booker et al,32 2003</td>
<td>Prospective cohort; consecutive (MICU)</td>
<td>76; Noncardiac</td>
<td>14.8</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Rellos et al,33 2003</td>
<td>Retrospective cohort; NA (SICU)</td>
<td>868; Surgical</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>41 (5)</td>
</tr>
<tr>
<td>Ammann et al,34 2003</td>
<td>Prospective cohort; consecutive (MICU)</td>
<td>58; Noncardiac</td>
<td>SAPS II, 42 ± 15</td>
<td>NS</td>
<td>24 (41)</td>
<td>51 (88)</td>
</tr>
<tr>
<td>Baillard et al,35 2003</td>
<td>Prospective cohort; consecutive (MICU)</td>
<td>71; COPD exacerbation</td>
<td>SAPS II, 38 (26-69)</td>
<td>24 (34)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Ammann et al,36 2001</td>
<td>Prospective case-control; consecutive (MICU)</td>
<td>40; Noncardiac cases (20 sepsis and controls (20 nonseptic)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>20 (50)</td>
</tr>
<tr>
<td>Arlati et al,37 2000</td>
<td>Prospective cohort; NS (MICU)</td>
<td>31; Sepsis and 12 hypovolemic shock</td>
<td>MODS, 7.91 ± 0.84</td>
<td>NS</td>
<td>25 (81)</td>
<td>19 (61)</td>
</tr>
<tr>
<td>ver Elst et al,38 2000</td>
<td>Prospective cohort; consecutive (MICU)</td>
<td>46; Septic shock (noncardiac)</td>
<td>24 (20-30)</td>
<td>NS</td>
<td>46 (100)</td>
<td>46 (100)</td>
</tr>
<tr>
<td>Spies et al,39 1998</td>
<td>Prospective cohort; NS (SICU)</td>
<td>26; Sepsis</td>
<td>APACHE III, 48 (24-68)</td>
<td>20.71 (3-39)</td>
<td>NS</td>
<td>16/26 (total) (62)</td>
</tr>
<tr>
<td>Turner et al,40 1999</td>
<td>Prospective case-control; consecutive (MICU)</td>
<td>21; Noncardiac cases (15 sepsis and controls (6 nonseptic))</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>16 (26)</td>
</tr>
<tr>
<td>Noble et al,41 1999</td>
<td>Prospective case-control; consecutive (MICU)</td>
<td>109; 109 Cases and 58 controls (healthy volunteers)</td>
<td>18.9</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Fernandes et al,42 1999</td>
<td>Prospective cohort; NS (MICU)</td>
<td>10; Sepsis (noncardiac)</td>
<td>24.9</td>
<td>6 (60)</td>
<td>6 (60)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Edouard et al,43 1998</td>
<td>Prospective cohort; NS (STICU)</td>
<td>17; Trauma (noncardiac)</td>
<td>SAPS II, 33 (14-47); ISS, 27 (17-45)</td>
<td>17 (100)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Kollef et al,44 1997</td>
<td>Prospective cohort; consecutive (MICU)</td>
<td>260; General medicine</td>
<td>16.8 ± 7.6</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Guest et al,45 1995</td>
<td>Prospective cohort; consecutive (MICU)</td>
<td>209; General medicine</td>
<td>NS</td>
<td>72 (34)</td>
<td>63 (30)</td>
<td>16 (7)</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; ISS, Injury Severity Score; MSICU, medical ICU; MODS, Multiple Organ Dysfunction Score; SICU, surgical ICU; SAPS, Simplified Acute Physiology Score; STICU, surgical-trauma ICU; TICU, trauma ICU; NA, not applicable; NS, not specified; RTS, Revised Trauma Score; SIRS, systemic inflammatory response syndrome.

*Data are given as mean, mean ± SD, or mean (range) score.
†Multiple inotropes reported; data for dopamine reported.

mainly 25 studies for further evaluation. Of the 25 retrieved studies, 6 were excluded (3 studies involved critically ill patients in the emergency department, burn center, or tertiary center specializing in postpartum hemorrhage). 2 studies were excluded because cTn measurements were not performed on all patients, and 1 study was excluded because it contained data from a study already included in our systematic review. Four additional studies identified through manual review of references met our inclusion criteria. We therefore included 23 studies in this systematic review. Interobserver agreement for study selection was excellent (κ=0.91; 95% CI, 0.82 to 0.99).

**STUDY CHARACTERISTICS**

A total of 4492 patients were included; individual study sizes ranged from 10 to 728 patients for prospective studies and 1081 patients in one retrospective cohort. Different ICU types...
Table 2. Cardiac Troponin (cTn) Characteristics and Unadjusted Analyses for Mortality and Length of Stay

<table>
<thead>
<tr>
<th>Source</th>
<th>cTn Type; Instrument (Manufacturer)</th>
<th>cTn Threshold</th>
<th>Frequency of cTn Measures</th>
<th>Frequency of Elevated cTn, No./Total (%)</th>
<th>No. of Hospital Deaths</th>
<th>Unadjusted OR (95% CI)</th>
<th>Unadjusted WMD (95% CI), d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin et al., 2005</td>
<td>cTn; NS</td>
<td>&gt;1.2 µg/L</td>
<td>Within 24 h of admission, daily until normalized</td>
<td>308/1081 (28)</td>
<td>113</td>
<td>121</td>
<td>...</td>
</tr>
<tr>
<td>Quenot et al., 2005</td>
<td>cTn; Dimension Xpand (Dade Behring, Deerfield, Ill)</td>
<td>&gt;0.1 ng/mL</td>
<td>Admission</td>
<td>...</td>
<td>35</td>
<td>23</td>
<td>...</td>
</tr>
<tr>
<td>Kim et al., 2005</td>
<td>cTn; ADVIA Centaur (Bayer, West Haven, Conn)</td>
<td>≤0.1 µg/L</td>
<td>Within 24 h of admission</td>
<td>120/215 (56)</td>
<td>49</td>
<td>20</td>
<td>2.59 (1.40 to 4.78)</td>
</tr>
<tr>
<td>King et al., 2005</td>
<td>cTn; AxSYM (Abbott, Abbott Park, Ill)</td>
<td>&gt;0.7 ng/mL</td>
<td>Admission</td>
<td>...</td>
<td>15</td>
<td>9</td>
<td>7.00 (2.68 to 18.27)</td>
</tr>
<tr>
<td>Landesberg et al., 2005†</td>
<td>cTnT and cTnI; Elecsys 2010 (Boehringer Mannheim, Indianapolis, Ind); Stratus II (Dade Behring)</td>
<td>cTnT: &gt;0.1 ng/mL; cTnI: ≥1.5 ng/mL</td>
<td>Once daily</td>
<td>38/101 (38)</td>
<td>21</td>
<td>14</td>
<td>9.50 (3.31 to 27.27)</td>
</tr>
<tr>
<td>Wu et al., 2004</td>
<td>cTn; OPUS (Behringer, Marburg, Germany)</td>
<td>&gt;0.5 ng/mL</td>
<td>Admission</td>
<td>Prevalence: 49/108 (45)</td>
<td>36</td>
<td>20</td>
<td>3.40 (1.48 to 7.81)</td>
</tr>
<tr>
<td>Edouard et al., 2004</td>
<td>cTn; ACS180SE (Bayer)</td>
<td>≤0.4 µg/L</td>
<td>Admission, then 6-12 h and as per ICU team</td>
<td>Incidence: 98/78 (12)</td>
<td>33</td>
<td>90</td>
<td>3.82 (2.34 to 6.22)</td>
</tr>
<tr>
<td>Mehta et al., 2004</td>
<td>cTn; AxSYM (Abbott)</td>
<td>≤1.0 ng/mL</td>
<td>Enrollment, 24 and 48 h</td>
<td>Incidence: 16/37 (43)</td>
<td>10</td>
<td>5</td>
<td>5.33 (1.28 to 22.19)</td>
</tr>
<tr>
<td>Klein Gunnewiek and van de Leur, 2003</td>
<td>cTnT; Elecsys 2010 (Roche, Indianapolis)</td>
<td>≤0.1 µg/L</td>
<td>Admission, next morning, and 24 h after second sample</td>
<td>Overall frequency: 11/34 (32); prevalence: 8/34 (24); incidence: 3/34 (9)</td>
<td>4</td>
<td>4</td>
<td>1.06 (0.16 to 6.87)</td>
</tr>
<tr>
<td>Booker et al., 2003</td>
<td>cTn; AxSYM (Abbott), ACS (Bayer)</td>
<td>≥2.0 µg/L (AxSYM); ≥1.5 µg/L (ACS)</td>
<td>Admission and 24 h 6-12 h after 24-48 h telemetry discontinued</td>
<td>Prevalence: 12/76 (16)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Rebs et al., 2003</td>
<td>cTn; NS</td>
<td>≤0.4 µg/L*, Ml: =2.0 µg/L</td>
<td>NS</td>
<td>...</td>
<td>64</td>
<td>18</td>
<td>5.25 (1.39 to 21.10)</td>
</tr>
<tr>
<td>Ammann et al., 2003</td>
<td>cTn and cTnT; Access (Beckman, Fullerton, Calif); Elecsys 2010 (Roche)</td>
<td>&gt;0.1 µg/L × 2 measurements</td>
<td>Enrollment, 3, 12, 24, 48, 96, and 192 h</td>
<td>32/58 (55)</td>
<td>13</td>
<td>3</td>
<td>3.65 (1.73 to 23.34)</td>
</tr>
<tr>
<td>Baillard et al., 2003</td>
<td>cTn; Stratus II (Dade International, West Sacramento, Calif)</td>
<td>&gt;0.5 ng/mL</td>
<td>Admission and 24 h</td>
<td>13/71 (18)</td>
<td>8</td>
<td>10</td>
<td>9.17 (0.96 to 87.78)</td>
</tr>
<tr>
<td>Ammann et al., 2001</td>
<td>cTn; Access (Beckman)</td>
<td>≥0.1 µg/L</td>
<td>Within 24 h of symptom onset</td>
<td>17/20 (85) in cases (sepsis, septic shock, SIRS); 0% in controls</td>
<td>5</td>
<td>1</td>
<td>3.56 (1.05 to 12.05)</td>
</tr>
<tr>
<td>Ariati et al., 2000</td>
<td>cTn; OPUS (Dade Behring)</td>
<td>≥0.5 ng/mL*, Ml: &gt;2.5 ng/mL</td>
<td>12, 24, and 48 h after enrollment</td>
<td>23/31 (74); 11/19 (58) septic shock; 12/12 (100) hypovolemic shock</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

(continued)

were represented and included the following: 8 medical, 10 medical-surgical, and 5 surgical-trauma. The types of patients included 1826 trauma patients (40.7%), 903 surgical patients (20.2%), 828 patients (18.5%) with noncardiac conditions (defined as diagnoses other than acute coronary syn-


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Eighteen studies used cTnI, 2 used cTnT, and 3 studies used both assays (Table 2). Troponin levels were drawn on ICU admission or at study enrollment in all but 1 study.

### STUDY QUALITY

Study quality characteristics are presented in Table 1 and Table 2. The included studies consisted of 18 prospective cohort,

† 2 retrospective cohort,

‡ 3 case-control,

§ 10, 23 studies. Consecutive patients were enrolled in 13 of the 18 prospective cohort studies (patient accrual was not specified in the other 5) and in all 3 case-control studies. Nine studies followed patients during their ICU stay, 4 studies followed patients until hospital discharge, and 6 studies did not report these data. Two studies had a longer follow-up: one recorded mortality at 1 month, 6 months (these data were used in the mortality analysis), and 2 years, and another study evaluated mortality at 6 months. Seven studies measured cTnI once during the patient's ICU stay, and 15 studies measured cTnI repeatedly using different screening schedules (testing frequency not specified in 1 study). Cardiac troponin was frequently measured at 24-hour intervals, with 4 studies measuring daily

Table 2. Cardiac Troponin (cTn) Characteristics and Unadjusted Analyses for Mortality and Length of Stay (cont)

<table>
<thead>
<tr>
<th>Source</th>
<th>cTn Type; Instrument (Manufacturer)</th>
<th>cTn Threshold</th>
<th>Frequency of cTn Measures</th>
<th>Frequency of Elevated cTn, No./Total (%&lt;i&gt;±&lt;/i&gt;)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Unadjusted WMD (95% CI), d</th>
<th>No. of Hospital Deaths</th>
<th>ICU Mortality</th>
<th>Hospital Length of Stay</th>
<th>ICU Mortality</th>
<th>Hospital Length of Stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>ver Elst et al, 2000</td>
<td>cTnI and cTnT; Stratus II (Dade Behring), Elecsys 2010 (Roche)</td>
<td>cTnI ≥ 0.4 µg/L cTnT ≥ 0.1 µg/L</td>
<td>Enrollment, 24 and 48 h</td>
<td>23/46 (50) cTnI 16/45 (36) cTnT</td>
<td>14 7 5.67 (0.26 to 125.55) 8.05 (0.38 to 172.57)</td>
<td>... ...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Spies et al, 1998</td>
<td>cTnI: ES300 (Boehringer Mannheim)</td>
<td>≥ 0.2 µg/L</td>
<td>Every 4 h for 24 h then daily for 7 d</td>
<td>18/26 (69)</td>
<td>15 3 3.00 (0.19 to 47.96)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Turner et al, 1999</td>
<td>cTnT; Stratus II (Baxter, Deerfield)</td>
<td>≥ 0.4 ng/mL Daily until no longer septic</td>
<td>12/15 (80) in cases; 1/6 (17) in controls</td>
<td>...</td>
<td>4 0 12.78 (0.51 to 321.75)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Noble et al, 1999</td>
<td>cTnI; Access (Beckman)</td>
<td>≥ 0.1 µg/L</td>
<td>Daily for cases, on admission for controls</td>
<td>77/109 (71) in cases; 0% in controls</td>
<td>...</td>
<td>...</td>
<td>1.93 (0.88 to 4.29)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Fernandes et al, 1999</td>
<td>cTnI; Stratus (Baxter)</td>
<td>≥ 0.6 mg/mL</td>
<td>Within 12 h of admission</td>
<td>6/10 (60)</td>
<td>3 1 3.97 (1.75 to 9.01)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Guest et al, 1995</td>
<td>cTnI; ELISA (Baxter)</td>
<td>≥ 1.6 µg/L</td>
<td>Admission, 12 h, then daily for 7 d</td>
<td>6/17 (35) for cTnI &gt; 1.6 µg/L</td>
<td>2 0 ...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Kollef et al, 1997</td>
<td>Summary</td>
<td>&gt; 1.5 ng/L Daily</td>
<td>41/260 (16)</td>
<td>11 35 ...</td>
<td>...</td>
<td>1.40 (0.27 to 2.53)</td>
<td>3.50 (0.31 to 6.69)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 3.6 µg/L Daily</td>
<td>32/209 (15)</td>
<td>13 26 ...</td>
<td>...</td>
<td>2.25 (0.40 to 4.10)</td>
<td>3.02 (0.98 to 10.50)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACS, automated chemiluminescence system; CI, confidence interval; cTnI, cardiac troponin I; cTnT, cardiac troponin T; ICU, intensive care unit; NA, not applicable; NS, not specified; OR, odds ratio; SIRS, systemic inflammatory response syndrome; WMD, weighted mean difference; +, positive for elevated cTn level; −, negative for elevated cTn level; ellipses, not assessed.

*Cardiac troponin value used in the unadjusted analysis.

†Six-month data used.

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cTn until the patient was discharged from the ICU.11,23,30,31 Nine studies used multivariable analyses to adjust for confounding variables when evaluating the relationship between cTn and mortality.

**STUDY FINDINGS**

**Frequency of Elevated cTn in Critically Ill Patients**

Among 3278 patients in 20 studies reporting the frequency of cTn elevation, elevated cTn was observed in 12% to 85%, with a median frequency of 43% (IQR, 21% to 59%) (Table 2). The frequency of an elevated cTn measurement among medical ICU patients was 53% (IQR, 16% to 63%), 43% (IQR, 29% to 64%) in medical-surgical ICU patients, and 32% (IQR, 16% to 61%) in surgical-trauma ICU patients. Among patients admitted with sepsis or septic shock, the frequency was 60% (IQR, 50% to 80%).9,10,16,24,26,29,30,31 and cTn level was elevated in all patients with hypovolemic shock in 1 study.24

**Association of cTn With Length of Stay and Mortality**

**Length of Stay.** In the unadjusted analysis, length of ICU stay was calculated as a weighted mean difference in 8 studies (1019 patients) reporting these data14,16,18,30,31,34,35,37 (Table 2). Another 2 studies reported length of stay, but we were unable to obtain a standard deviation required for the calculation.19,20 An elevated cTn level was associated with an increased mean length of ICU stay of 2.18 days (95% CI, 1.25 to 3.11; P=.001). Results were heterogeneous (I² = 73.3%; P<.001). Hospital length of stay was reported in 3 studies with 686 patients30,31,34; 1 study did not include a standard deviation.20 An elevated cTn level was associated with a trend toward an increase in the mean length of hospital stay of 2.18 days (95% CI, −0.57 to 4.93 days [P=.12]; I² = 8.7 [P=.33]).

**Mortality.** Overall mortality was calculated in 20 studies (4276 patients) in an unadjusted analysis (Table 2). Elevated cTn level in critically ill patients was associated with an increased risk of death (37.1% vs 13.6% [OR, 3.88; 95% CI, 2.38 to 6.0; P<.001]). There was no heterogeneity among study results (I² = 0%; P=.58).

Nine studies used multivariable analyses to adjust for other confounding factors assessing elevated cTn and mortality, although we were unable to obtain data from 3 authors who did not report their results.15,16,30 Consequently, a total of 6 studies involving 1706 patients used multivariable analyses (Table 3 and Figure 2). Meta-analysis of these studies adjusting for other confounders demonstrated that elevated cTn predicted an increased risk of death (OR, 2.53; 95% CI, 1.89 to 3.38; P<.001; results were not heterogeneous [I² = 0%; P = .62]).

**Subgroup and Sensitivity Analyses**

For the subgroup of patients admitted to the ICU with sepsis and an elevated cTn level in 6 studies, the unadjusted OR for mortality was 3.49 (95% CI, 1.73 to 7.04), which was similar to the 16 studies enrolling patients without the exclusive diagnosis of sepsis (unadjusted OR, 3.96; 95% CI, 3.24 to 4.83; P = .73 for the difference). There was no statistically significant association of cTn level with mortality.

### Table 3. Adjusted Analyses for Mortality in Critically Ill Patients With Elevated Cardiac Troponin (cTn) Levels

<table>
<thead>
<tr>
<th>Source</th>
<th>Factors Adjusted For</th>
<th>Adjusted OR for Mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ICU Mortality</td>
</tr>
<tr>
<td>Martin et al.23</td>
<td>cTn &gt;1.2 µg/L, age &gt;55 y, sex,</td>
<td>...</td>
</tr>
<tr>
<td>2005</td>
<td>base deficit &gt;5, APACHE score</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>25, ISS &gt;20, hypotension, GCS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>score ≥8, and mechanism (blunt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or penetrating)</td>
</tr>
<tr>
<td>Quenot et al.24</td>
<td>cTn &gt;0.1 ng/mL, SAPS II, and</td>
<td>...</td>
</tr>
<tr>
<td>2005</td>
<td>mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td>King et al. 25</td>
<td>cTn and APACHE II score</td>
<td>2.82 (0.87 to 9.20)</td>
</tr>
<tr>
<td>Landesberg et al.</td>
<td>cTn &gt;0.1 ng/mL or cTn &gt;1.5</td>
<td>...</td>
</tr>
<tr>
<td>11 2005</td>
<td>ng/mL, mechanical ventilation,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>intropes, hemodialysis</td>
</tr>
<tr>
<td>Wu et al.16</td>
<td>Elevated cTn level &gt;0.5 ng/mL, high</td>
<td>...</td>
</tr>
<tr>
<td>2004</td>
<td>APACHE II score, and underlying cancer</td>
<td></td>
</tr>
<tr>
<td>Eduard et al.15</td>
<td>cTnI release, age, revised trauma</td>
<td>Nonsignificant result*; data not</td>
</tr>
<tr>
<td>2004</td>
<td>score, ISS, SAPS, and shock</td>
<td>presented</td>
</tr>
<tr>
<td>Mehta et al. 36</td>
<td>Not specified</td>
<td>Significant result;</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td>data not presented</td>
</tr>
<tr>
<td>Ballard et al. 22</td>
<td>cTn &gt;0.5 ng/mL, mechanical</td>
<td>...</td>
</tr>
<tr>
<td>2003</td>
<td>ventilation, GCS score, and</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SAPS II</td>
</tr>
<tr>
<td>Kollef et al.30</td>
<td>cTn &gt;1.5 ng/mL; APACHE II;</td>
<td>Nonsignificant result*; data not</td>
</tr>
<tr>
<td>1997</td>
<td>multorgan dysfunction; cardiac</td>
<td>presented</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dysfunction; pneumonia; sepsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or septic shock; renal, pulmonary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bone marrow, hepatic, CNS, or GI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dysfunction; intraabdominal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>infection; bacteremia; race;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and vascular thrombosis</td>
</tr>
<tr>
<td>Pooled OR for</td>
<td></td>
<td>2.53 (1.89 to 3.38; P&lt;.001)</td>
</tr>
<tr>
<td>overall mortality</td>
<td></td>
<td>heterogeneity: I² = 0% (P = .62)</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; CNS, central nervous system; cTnI, cardiac troponin I; cTnT, cardiac troponin T; GCS, Glasgow Coma Scale; GI, gastrointestinal; ICU, intensive care unit; ISS, Injury Severity Score; NA, not applicable; OR, odds ratio; SAPS, Simplified Acute Physiology Score; ellipses, not assessed.

Studies performing multivariable analysis with backward stepwise elimination and found no statistically significant association of cTn level with mortality.
ranges. Consequently, cTnI assays require the appropriate reference laboratories are required to deter-
mine if the elevated cTn measurements. Consequently, we are unable to determine if the elevated cTn measurements are due to silent ischemic events that confer increased risk of mortality or whether there are other undiagnosed reasons for the elevated cTn level that are also associated with increased mortality. In one prospective study of 115 ICU patients, those meeting criteria for myocardial infarction (elevated cTn level and ischemic electrocardiographic changes) had higher mortality compared with patients with elevated cTn alone.40

There are limitations in our systematic review. First, although we included 6 studies in our adjusted analysis for mortality, 3 additional studies did not report the results of their multivariable analysis and were unable to be included in the analysis.13,16,30 Of these 3 studies, 1 study found an association between an elevated cTn level and mortality,40 but 2 studies did not.13,30 We were unable to obtain details of these analyses, which could potentially attenuate the increased risk of mortality we found in the meta-analysis. Second, none of the included studies systematically reported conditions known to increase cTn in the ICU setting. Because these studies did not formally evaluate the effect of therapies on patients with elevated cTn levels, we cannot make any recommendations regarding management such as anti-ischemic or antithrombotic agents or percutaneous coronary interventions. Indeed, current management ranges from ig-

For the sensitivity analysis assessing mortality in 2 different time frames, elevated cTn was associated with a similar risk of ICU mortality (OR, 3.95; 95% CI, 3.06 to 5.10) and hospital mortality (OR, 4.19; 95% CI, 3.13 to 5.59). There was no statistical heterogeneity in either analysis.

The results of this systematic review demonstrate that elevated cTn levels are common during critical illness, are associated with increased ICU length of stay, and appear to independently predict mortality.

Elevated cTn levels were observed in 12% to 85% of critically ill patients, with a median frequency of 43%. This variable frequency is likely attributable to multiple factors. Because there is currently no standard to calibrate cTnI assays,38 individual laboratories are required to determine the appropriate reference ranges. Consequently, cTnI assays are not equivalent, and different assays will result in differing values. Although cTnT is not affected by standardization issues, measurements from the first-generation cTnT assays were elevated in patients with renal failure; this limitation has been overcome in the current assays. The standardization issues with cTnI are unlikely to affect our classification of patients with an elevated cTn level, although studies using the first-generation cTnT may potentially overestimate patients with an elevated cTn level. Second, detection of elevated cTn levels depends on the timing and frequency of measurement, and studies that measured cTn only once may be less likely to detect elevated cTn levels. Finally, elevated cTn levels may occur in conditions frequently seen in the ICU, including sepsis, hypotension, arrhythmias, congestive heart failure, pulmonary embolism, increased intracranial pressure, and renal failure.5,7 Differences in the case mix of patients would produce widely varying frequencies, particularly if conditions associated with elevated cTn levels are overrepresented in that particular ICU.

Elevated cTn appears to confer prognostic importance similar to that found in patients with acute coronary syndromes. The presence of elevated cTn in critically ill patients was associated with an increased risk of death in unadjusted meta-analysis, and when examined in multivariable analyses to adjust for confounding factors and generate the strongest inferences, elevated cTn was an independent predictor of mortality. We also identified a 3-day increase in ICU length of stay in patients with elevated cTn levels compared with those without, suggesting that more health care resources are consumed by these critically ill patients.

Since elevated cTn indicates myocardial injury, it is possible that the increased mortality and length of stay is due to unrecognized myocardial infarction. Diagnosing myocardial

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin et al.50 2005</td>
<td>1081</td>
<td>2.26 (1.53-3.35)</td>
</tr>
<tr>
<td>Quemot et al.34 2005</td>
<td>217</td>
<td>2.09 (1.36-4.11)</td>
</tr>
<tr>
<td>King et al.39 2005</td>
<td>128</td>
<td>2.82 (0.87-9.20)</td>
</tr>
<tr>
<td>Landesberg et al.41 2005</td>
<td>101</td>
<td>2.71 (1.11-7.96)</td>
</tr>
<tr>
<td>Wu et al.14 2004</td>
<td>108</td>
<td>4.84 (2.05-15.09)</td>
</tr>
<tr>
<td>Baillard et al.22 2003</td>
<td>71</td>
<td>6.52 (2.13-34.47)</td>
</tr>
<tr>
<td>Pooled Random Effects Estimate, P=.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity Test: Q = 3.54, P = .62

L2 = 0

Figure 2. Mortality associated with an elevated cardiac troponin (cTn) level (adjusted analysis). CI indicates confidence interval; OR, odds ratio.
norning the problem to urgent cath-
erization even in the absence of persistent ST elevation.

The strengths of this systematic re-
view are the rigorous review meth-
ods and the multivariable analyses
used in the assessment of the rela-
tionship between elevated cTn and
mortality, which allowed the strength
of association between elevated cTn
and mortality to be examined after
adjustment for other confounding
variables. We used ORs as the mea-
sure of association between cTn and
mortality, which is suitable for both
cohort and case-control study de-
signs. We used the conservative ran-
donm effects model to pool results
across studies.

Our systematic review suggests
that critically ill patients commonly
have elevated cTn levels, and that cli-
nicians should not dismiss these el-
levated levels because they are asso-
ciated with adverse clinical outcomes.
Additional large studies in the ICU
are needed to determine a more com-
prehensive profile of the various
causes of elevated cTn in this popula-
tion, and to clarify the association
between elevated cTn and mortality
and length of stay. Because the sig-
nificance of elevated cTn level may
vary depending on the mechanism of
myocardial injury, identifying the
cause of the elevated cTn level may
allow for risk stratification and clin-
ical prognostication. Understanding
elevated cTn in the ICU setting is a
pressing clinical challenge; interdis-
ciplinary collaboration among car-
diology, critical care, and vascular
medicine investigators is necessary
to identify critically ill patients with
 Elevated cTn levels who are poten-
tially responsive to therapeutic anti-
 ischemic interventions and to evalu-
te them in rigorous randomized
trials.

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Lauzier, Ismaila, and Heels-

Ansdell. Analysis and interpretation
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Ansdell, and Cook. Drafting of the
manuscript: Lim, Devereaux, Heels-
Ansdell, and Cook. Critical revision
of the article for important intellec-
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