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; \( P \leq .001 \)). 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 TROPOININ (cTn) I and T are regulatory proteins that control the calcium-mediated interaction of actin and myosin, producing myocardial contraction. 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.

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METHODS

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.8 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 studies9,10 in the sepsis subgroup analysis and included results from the nonseptic patients (controls) in the nonsepsis 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-
maintaining 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, 17,23,25 2 studies were excluded because cTn measurements were not performed on all patients, 13,27 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. 9-12, 14-16, 18-22, 24-26, 28, 30, 31, 33-37. We therefore included 23 studies in this systematic review.

Interobserver agreement for study selection was excellent ($\kappa=0.91$; 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 (Table 1). Different ICU types
The types of patients included 1826 trauma patients (40.7%), 903 surgical patients (20.2%), patients (18.5%) with noncardiac conditions (defined as diagnoses other than acute coronary syn-

were represented and included the following: 8 medical, 10 medical-
surgical, and 5 surgical-trauma.

<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,33 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>113 121</td>
<td>... 3.12 (2.31 to 4.22)</td>
<td>... ...</td>
</tr>
<tr>
<td>Quenet et al,34 2005</td>
<td>cTn; Dimension Xpand (Dade Behring, Deerfield, III)</td>
<td>&gt;0.1 ng/mL</td>
<td>Admission</td>
<td>... 35 23</td>
<td>... 5.59 (2.93 to 10.70)</td>
<td>5.90 (4.14 to 7.66)</td>
<td>2.80 (~5.00 to 10.60)</td>
</tr>
<tr>
<td>Kim et al,35 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 20</td>
<td>2.59 (1.40 to 4.78)</td>
<td>... ...</td>
</tr>
<tr>
<td>King et al,36 2005</td>
<td>cTn; Access (Beckman, Indianapolis)</td>
<td>&gt;0.7 ng/mL</td>
<td>Admission (within 6 h)</td>
<td>... 15 9</td>
<td>7.00 (2.68 to 18.27)</td>
<td>4.20 (~2.87 to 11.27)</td>
<td>... ...</td>
</tr>
<tr>
<td>Landesberg et al,37 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: &gt;1.5 ng/mL</td>
<td>Once daily</td>
<td>38/101 (38)</td>
<td>21 14</td>
<td>9.50 (3.31 to 27.27)</td>
<td>4.32 (1.81 to 10.35)</td>
</tr>
</tbody>
</table>

| Wu et al,38 2004 | cTn; OPUS (Behring, Marburg, Germany) | >0.5 ng/mL | Admission | Prevalence: 49/108 (45) | 36 20 | 3.40 (1.48 to 7.81) | 5.40 (2.35 to 12.41) | 6.10 (~0.36 to 12.56) |
| Edouard et al,39 2004 | cTn; ACS180SE (Bayer) | 0.4 µg/L | Admission, then 6-12 h and every ICU day | Incidence: 96/728 (12) | 33 90 | 3.82 (2.34 to 6.22) | ... ... | ... ... |
| Mehta et al,40 2004 | cTn; AxSYM (Abbott) | 1.0 ng/mL | Enrollement, 24 and 48 h Admission, next morning, and 24 h after second sample | Incidence: 16/37 (43) | 10 5 | 5.33 (1.28 to 22.19) | 5.09 (1.77 to 14.12) | ... ... |
| Klein Gunnewiek van de Leur,41 2003 | cTn; Elecsys 2010 (Roche, Indianapolis) | >0.1 µg/L | Admission, next morning, and 24 h after second sample | Overall frequency: 11/34 (32); prevalence: 8/34 (24); incidence: 3/34 (9) | 4 4 | 1.54 (0.16 to 6.13) | 1.81 (0.21 to 16.19) | ... ... |
| Book er et al,42 2003 | cTn; AxSYM (Abbott, ACS (Bayer) | >2.0 µg/L | Enrollement, 24 and 48 h Admission, next morning, and 24 h after second sample | Prevalence: 12/76 (16) | ... ... | 7.00 (4.07 to 12.06) | ... ... | ... ... |
| Relos et al,43 2003 | cTn; NS | <0.4 µg/L; MI: <2 µg/L | NS | ... 64 18 | 5.25 (1.39 to 21.16) | ... ... | ... ... | ... ... |
| Ammann et al,44 2003 | cTnT and cTnI; Access (Beckman, Fullerton, Calif); Elecsys 2010 (Roche) | <0.1 µg/L; <2 measurements | Enrollement, 3, 12, 24, 48, 96, and 192 h | 32/58 (55) | 13 3 | 6.35 (1.73 to 23.34) | 7.68 (2.07 to 28.43) | ... ... |
| Baillard et al,45 2003 | cTn; Stratus II (Dade International, West Sacramento, Calif) | >0.5 ng/mL | Admission and 24 h | Prevalence: 13/71 (18) | 8 10 | 9.17 (0.96 to 87.78) | ... ... | ... ... |
| Ammann et al,46 2003 | cTn; Access (Beckman) | >0.1 µg/L | Within 24 h of symptom onset | Incidence: 17/20 (85) | 5 1 | 3.56 (1.05 to 12.05) | ... ... | ... ... |
| Ariti et al,47 2001 | cTn; OPUS (Dade Behring) | ≥0.5 ng/mL; 2.5 µg/mL | 12, 24, and 48 h after enrollment | Incidence: 23/31 (74); 11/19 (58) | 8 3 | 8.33 (1.25 to 55.36) | ... ... | ... ... |

(continued)
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 enrolment 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, and 3 case-control 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 cTn once during the patient’s ICU stay, and 15 studies measured cTn 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

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**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 Elevated cTn</th>
<th>Frequency of Elevated cTn, No./Total (%)</th>
<th>Hospital Mortality</th>
<th>ICU Length of Stay</th>
<th>No. of Hospital Deaths</th>
<th>Unadjusted OR (95% CI)</th>
<th>Unadjusted WMD (95% CI), d</th>
</tr>
</thead>
</table>
| Ver Elst et al, 2000 | cTnI and cTnT; Stratus II (Baxter, Dudingen, Switzerland) | >0.4 µg/L | Every 4 h for 24 h then daily for 7 d | 12/15 (80) in cases; (septic shock): 1.6 (17) in controls | ... | ... | 1.93 (0.88 to 4.26) | ... | ...
| Spies et al, 1998 | cTnI; ES300 (Boehringer Mannheim) | >=0.2 µg/L | Enrollment, 24 and 48 h | 23/46 (50) cTnI 16/45 (36) cTnT | ... | ... | 5.67 (0.26 to 125.55) | 8.05 (0.38 to 172.57) | ...
| Turner et al, 1999 | cTnI; Stratus II (Baxter, Deerfield) | >=0.4 ng/mL | Hospital mortality | 77/109 (71) in cases; 0% in controls | ... | ... | 1.93 (0.88 to 4.26) | ... | ...
| Noble et al, 1999 | cTnI; Access (Beckman) | >=0.1 µg/L | Daily for cases, on admission for controls | 6/10 (60) | ... | ... | ... | ... | ...
| Fernandes et al, 1999 | cTnI; Stratus (Baxter) | >0.6 ng/mL; MI: >=1.6 µg/L | Within 12 h of admission | 2/17 (12) | ... | ... | ... | ... | ...
| Kollof et al, 1997 | cTnI; ELISA (Baxter) | >1.5 ng/L | Daily | 41/260 (16) | ... | ... | 1.40 (0.27 to 2.53) | 3.50 (0.31 to 6.69) | ...
| Guest et al, 1995 | cTnI; Stratus (Baxter) | >3.6 µg/L | Daily | 32/209 (15) | ... | ... | 2.25 (0.40 to 4.10) | 3.02 (0.98 to 9.50) | 2.18 (-0.57 to 4.93; P = .12)

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.

*Six-month data used.

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137 patients (3.9%) with sepsis or septic shock, 24, 10, 12, 14, 19, 21, 34, 35

101 cardiac and high-cardiac risk patients (2.3%), 11 71 patients (1.6%) with chronic obstructive pulmonary disease exacerbation, 22 and 12 patients (0.3%) with hemorrhagic or hypovolemic shock. 24 and 578 patients (12.9%) were unselected critically ill patients with a variety of diagnoses.25,30,31 The proportion of patients requiring mechanical ventilation (reported in 9 studies) ranged from 34% to 100%. Intubates and/or vasopressors were used in 38% to 100% of patients (reported in 12 studies); however, their use exceeded 60% in the studies enrolling patients with sepsis or septic shock.
cTn until the patient was discharged from the ICU. 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%), and cTn level was elevated in all patients with hypovolemic shock in 1 study.

**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 data (Table 2). Another 2 studies reported length of stay, but we were unable to obtain a standard deviation required for the calculation. An elevated cTn level was associated with an increased mean length of ICU stay of 2.18 days (95% CI, 0.98 to 5.05 days; P = .004). Results were heterogeneous (I² = 73.3%; P < .001). Hospital length of stay was reported in 3 studies with 686 patients. A study did not include a standard deviation. 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, 3.28 to 4.60; 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. 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 statistical heterogeneity in either subgroup.
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.5 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 cTnI level, although studies using the first-generation cTnT may potentially overestimate patients with an elevated cTnI level. Second, detection of elevated cTnT levels depends on the timing and frequency of measurement, and studies that measured cTnT only once may be less likely to detect elevated cTnT levels. Finally, elevated cTnT 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 cTnT 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 cTnT 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 infarction in the ICU is challenging because cTn may be elevated for different reasons. Furthermore, patients can rarely communicate classic ischemic symptoms because of endotracheal intubation, sedation, or analgesia, underscoring how ischemic events are usually asymptomatic. Despite this, elevated cTn levels in the ICU are often ignored or attributed to other conditions.39 Accordingly, there is no consensus on the appropriate diagnostic approach and management of elevated cTn in the ICU. Many studies we included did not systematically assess for the presence of myocardial ischemia or indicate alternate diagnoses that might explain 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.15,16,30 Of these 3 studies, 1 study found an association between an elevated cTn level and mortality,40 but 2 studies did not.15,30 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 anti-thrombotic agents or percutaneous coronary interventions. Indeed, current management ranges from ig-

<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.20 2005</td>
<td>1081</td>
<td>2.26 (1.53-3.35)</td>
</tr>
<tr>
<td>Quenot et al.34 2005</td>
<td>217</td>
<td>2.09 (1.36-4.11)</td>
</tr>
<tr>
<td>King et al.30 2005</td>
<td>128</td>
<td>2.82 (0.87-9.20)</td>
</tr>
<tr>
<td>Landesberg et al.11 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>Ballard et al.22 2003</td>
<td>71</td>
<td>6.52 (2.13-24.47)</td>
</tr>
<tr>
<td>Pooled Random Effects Estimate, P=.001</td>
<td></td>
<td>2.53 (1.89-3.38)</td>
</tr>
</tbody>
</table>

Figure 2. Mortality associated with an elevated cardiac troponin (cTn) level (adjusted analysis). CI indicates confidence interval; OR, odds ratio.

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norning the problem to urgent catheterization even in the absence of persistent ST elevation.

The strengths of this systematic review are the rigorous review methods and the multivariable analyses used in the assessment of the relationship 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 measure of association between cTn and mortality, which is suitable for both cohort and case-control study designs. We used the conservative random effects model to pool results across studies.

Our systematic review suggests that critically ill patients commonly have elevated cTn levels, and that clinicians should not dismiss these elevated levels because they are associated with adverse clinical outcomes. Additional large studies in the ICU are needed to determine a more comprehensive profile of the various causes of elevated cTn in this population, and to clarify the association between elevated cTn and mortality and length of stay. Because the significance 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 clinical prognostication. Understanding elevated cTn in the ICU setting is a pressing clinical challenge; interdisciplinary collaboration among cardiology, critical care, and vascular medicine investigators is necessary to identify critically ill patients with elevated cTn levels who are potentially responsive to therapeutic anti-ischemic interventions and to evaluate them in rigorous randomized trials.

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