Troponin I in Patients without Chest Pain

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Background: Testing for troponin has important clinical value for patients who present with typical symptoms of acute coronary syndromes (ACS) such as chest pain (CP). Much less is known about the value of troponin testing for patients who present with other symptoms of ACS (anginal equivalent symptoms).

Methods: The utilization and prognostic value of cardiac troponin I (cTnI) were evaluated at a Veterans Affairs Acute Care Facility. Clinical charts of 1184 predominantly male patients, who submitted specimens for initial cTnI testing by AxSYM, were evaluated for demographic data, cardiovascular risk factors, major diseases, and complaints at the time of testing. The endpoint was defined as all-cause death during a 200-day period after initial testing.

Results: Sixty-one percent of cTnI tests were ordered for patients who did not present with CP. Patients presenting with symptoms other than CP did not have significantly lower plasma cTnI than patients with CP. However, patients with symptoms other than CP were rarely diagnosed with ACS unless cTnI was ≥2 μg/L. The mortality during the follow-up period was several fold higher among patients presenting with symptoms other than CP (CP, 6%; without CP, 22%; P < 0.0001, χ² test). cTnI ≥0.2 μg/L provided significant additional predictive information for patients who presented with anginal equivalent symptoms such as shortness of breath or general weakness.

Conclusion: Patients with anginal equivalent symptoms of ACS and low-positive cTnI are less often diagnosed with ACS and have a higher mortality than patients with CP.

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Cardiac troponin T (cTnT) and cTnI are currently used as sensitive and specific laboratory markers to assess the presence of myocardial damage (1, 2). Furthermore, numerous studies have revealed the value of cTnI and cTnT as predictive markers for adverse outcomes (3–5). However, most of this research has been directed toward the applicability of these laboratory tests for patients with typical symptoms of acute coronary syndromes (ACS), specifically those presenting with unstable angina (3–5). It has been recognized that older patients or females with ACS frequently present with symptoms other than chest pain (CP; anginal equivalent symptoms), such as shortness of breath (SOB), general weakness (WK), or pain at a site other than the chest (PAIN) (6, 7). For clinicians, it is often difficult to recognize the cardiac origin of anginal equivalent symptoms because patients with diseases other than ACS often present with the same complaints. In addition, other cardiac diseases, such as heart failure, may be associated with myocardial necrosis and increased cTnI similar to ACS, leading to further confusion. In contrast to ACS, the clinical value of a positive cTnI is currently not well established for other cardiac diseases, and we are not aware of consensus documents that state how to follow up these patients. A survey completed at our hospital indicated that low-positive cTnI values are frequently not used for diagnostic or prognostic purposes when patients’ complaints, clinical histories, and other diagnostic procedures do not support the diagnosis of ACS.

More recently, some research has focused on the prognostic value of cTnI and cTnT in patients with chronic renal failure (8, 9), hypovolemic shock, sepsis (10), or heart failure (11). Preliminary results of these studies have been limited, in part because of small study sizes, limited statistical analyses, or various underlying mechanisms not necessarily related to coronary artery disease.
For example, with regard to increased cTnT in asymptomatic patients with end-stage renal failure, it has been shown that the kidney is unlikely to be the source of circulating cTnT (12). However, it is currently not known whether the release of cTnT in patients with renal failure is related to cardiac ischemia or to another type of mechanism.

The purpose of this study was to evaluate the utilization and prognostic value of cTnI testing in a population of patients presenting with anginal equivalent symptoms of ACS. We first investigated the frequencies of completed cTnI tests for patients with and without CP. We then compared the value of cTnI for predicting adverse outcome among patients with CP, patients with anginal equivalent symptoms, and patients with a history of congestive heart failure (CHF).

Materials and Methods

Patients

This study was conducted at the metropolitan Veterans Affairs Medical Center. Approval for the study was obtained from the local Institutional Review Board. We included all veterans who submitted specimens to the clinical laboratory for initial cTnI testing during 5 consecutive months. Patients who underwent repeated testing for cTnI were included only once in the study, using the initial test result. Patients were excluded when no cTnI results were available (rejected or lost specimens). Patients were excluded from outcome analysis when there was no documentation of follow-up visits after initial cTnI testing, as described in the section on outcome/follow-up.

Environment and Assays

Testing for cTnI was performed at a central laboratory that serves an acute-care facility and several outpatient clinics. On receipt, the heparin-plasma specimens were immediately processed and analyzed for cTnI with the AxSYM immunoanalyzer (Abbott Laboratories). The limit of detection for the AxSYM cTnI assay was determined by testing aliquots of normal pooled plasma for cTnI on 22 consecutive days. The 95th percentile limit of detection (2SD) was 0.146 μg/L (mean rate readings at 0.0 and 2.3 μg/L cTnI, 11.27 and 42.77; SD, 1.02). The upper limits of the reference intervals for cTnI containing 99% of test results in middle-aged or older patients without evidence of cardiac disease have been determined previously and were 0.4 (13) or 0.6 μg/L (14), respectively. The CV were ~45%, 20%, and <10% at 0.2, 0.5, and 2.0 μg/L (13), respectively. Although values <0.5 μg/L were reported as negative to clinicians, for the purposes of this study we recorded all results independent of this clinical cutoff.

Data Collection

In addition to cTnI, this prospective cohort study evaluated patients’ clinical charts for complaints at the time of cTnI testing, demographic data (age, gender, and race), risk factors [body mass index (BMI), cholesterol, mean blood pressure, history of coronary artery disease, previous cerebrovascular accident, angioplasty, serum creatinine, and smoking], major diseases [e.g., diabetes, CHF, chronic obstructive pulmonary disease (COPD), and cancer] and severity of current conditions (outpatient vs inpatient). Furthermore, medical charts were evaluated for documentation of final diagnoses or explanations of the complaints that prompted cTnI testing. To avoid reviewer bias, investigators were blinded to the cTnI results during the collection of clinical data and adverse outcome data. The electronic medical charts were reviewed by four medically trained investigators for patients’ symptoms at the time of cTnI testing. A single reviewer examined each patient’s chart, and spot reviews were performed to assure consistency among the four reviewers. Charts containing discrepant or incomplete information underwent a repeated review by an independent investigator. Advice from a board-certified cardiologist was sought for settlement of discrepancies. The study group was then classified into six groups according to the following clinical presentations, based on the likelihood of a possible underlying cardiac disorder: (a) CP; (b) arrhythmia (ARRY); (c) SOB/WK; (d) PAIN; (e) mental status changes (MSC); and (f) patients with a history of surgery (SURG). Patients presenting with more than one of these symptoms were categorized according to the above ranking, starting with CP (e.g., a patient presenting with CP and MSC was placed in the CP group). The diagnoses of CHF as recorded in the medical charts were based mostly on clinical criteria (signs found at physical examination, echocardiogram, and chest x-ray findings).

Accuracy of Chart Review

One hundred charts underwent a second review by an independent reviewer to estimate the accuracy of chart review by the four reviewers. There was a 100% concordance between initial and repeat chart review (95% confidence interval, 96–100%) for dates of testing or death, demographics, laboratory test results, and type of outcome. The concordance rates for clinical symptoms and presence of major diseases were 98% (93–100%) and 96% (90–99%), respectively.

Outcome/Follow-up

The clinical endpoint was chosen to be all-cause death because the cardiac contribution to death is often difficult to evaluate in patients with multiple medical conditions. Patients were followed up for 200 days from the time of their initial enrollment in the study, through review of each patient’s electronic medical chart at the St. Louis Veterans Affairs Medical Center or through inquiry at the Regional Office of the Department of Veterans Affairs in St. Louis. A follow-up period of 200 days was chosen for comparability with other studies (15, 16). The electronic charts were updated during the patients’ scheduled visits, and information about a patient’s death was documented in the database. We were unable to determine the out-
come of patients who had no activities recorded at the Veterans Affairs Medical Center or at the Regional Office during a time period extending 200 days after the initial cTnI testing. These individuals were excluded from the outcome analysis of the study.

**DEFINITION OF TIERS**

For the estimation of odds ratios, patients were divided into four groups according to their cTnI (see Table 4). The first tier consisted of patients with cTnI below the limit of detection. The second tier included patients with cTnI higher than the limit of detection but not exceeding the 99th percentile cutoff for cTnI in healthy middle-aged individuals (13). The third tier was composed of patients with cTnI between the upper limit of the 99th percentile and the former cutoff for acute myocardial infarction (2.0 μg/L), which was used (17) before the introduction of new guidelines by the American College of Cardiology (18). The final tier comprised patients with cTnI at or above the former cutoff for myocardial infarction.

**STATISTICAL ANALYSIS**

Characteristics of study groups were evaluated for significant differences by ANOVA or χ² test. The association between mortality and each of the other continuous variables was analyzed by the Student t-test. The association between mortality and each of the dichotomous variables was analyzed by the Fisher exact test. Those variables that appeared to be significant by either the Student t-test or Fisher exact test were further examined by multivariate logistic regression analysis, using the Statistical Package for the Social Sciences, Ver. 11 (SPSS Inc.). A two-tailed P value <0.05 was considered significant. Multivariate logistic regression analysis with backward deletion was performed to identify independent predictors of adverse outcome, with all-cause mortality as the dependent variable and the independent variables in the following order: BMI, creatinine, mean blood pressure, age, cerebrovascular accident, cancer, and cTnI. Troponin was entered into the model either as a continuous value or as a categorical value as defined above. Separate logistic regression models were run for the following populations: group with CP, group with SOB/WK, group with ARRY/PAIN/MSC, group with SURG, group with CHF. Standard measures of logistic regression model fit, such as the model χ² and Nagelkerke's $R^2$, were calculated (19). The limit of detection was calculated with the EP Evaluator software, Ver. 5 (David Rhoads Associates).

**Results**

**CLINICAL PRESENTATION OF PATIENTS**

A total of 1184 individuals underwent testing for cTnI between July and November 2000. Patients were evaluated for their clinical symptoms at the time of presentation and were then classified according to complaints as shown in Table 1. There were 69 patients with CP who also had at least one of the other symptoms listed in Table 1. Similarly, 5 patients with ARRY, 16 patients with SOB/WK, 8 patients with PAIN, and no patients with SURG or MSC presented with more than one of the complaints as shown in Table 1. Very few patients reported irregular, slow, or fast heart beat in the absence of CP (ARRY). The second largest group consisted of patients who presented with shortness of breath, general weakness, low systemic blood pressure, or unexpected swelling of extremities (SOB/WK). Patients classified as having atypical pain (PAIN) presented with pain in the head, neck, upper or lower extremities, or abdomen, without pain in the thorax region. Symptoms of mental status changes (MSC) included loss of consciousness, nausea, confusion, numbness, dizziness, or sudden paresis. The surgery group consisted of patients who underwent surgery but otherwise did not have any of the symptoms listed in Table 1. Almost all of these surgeries involved repair of noncardiac tissue. According to chart review, cTnI testing was performed in three surgical patients for preoperative cardiac risk assessment and in five additional patients with postsurgical complications (e.g., infection or poor recovery) for exclusion of myocardial infarction. Possible reasons for cTnI testing of the remaining surgical patients may have been related to perioperative evaluation for myocardial infarction.

<table>
<thead>
<tr>
<th>Complaints</th>
<th>n</th>
<th>%</th>
<th>cTnI ≤0.1 μg/L</th>
<th>cTnI 0.2–0.4 μg/L</th>
<th>cTnI 0.5–1.9 μg/L</th>
<th>cTnI ≥2.0 μg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>462</td>
<td>39.0</td>
<td>9</td>
<td>13</td>
<td>21</td>
<td>81</td>
</tr>
<tr>
<td>ARRY</td>
<td>34</td>
<td>2.9</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>SOB/WK</td>
<td>409</td>
<td>34.5</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>PAIN</td>
<td>90</td>
<td>7.6</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>MSC</td>
<td>152</td>
<td>12.8</td>
<td>3</td>
<td>0</td>
<td>8</td>
<td>88</td>
</tr>
<tr>
<td>SURG</td>
<td>37</td>
<td>3.1</td>
<td>10</td>
<td>20</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

* Differences among the six patient groups with various complaints were assessed by χ² test for independence.
* NS, not significant.
The percentages of patients who were diagnosed with ACS or myocardial infarction after initial cTnI testing are listed in Table 1. For example, 9% of all patients with CP and initial cTnI ≤ 0.1 μg/L were subsequently diagnosed with ACS, whereas 91% of these patients received another diagnosis. The frequencies of the final diagnosis of ACS were not significantly different among patients with cTnI ≤ 0.1 μg/L whether they presented with CP or with other symptoms. In contrast, the patient groups with intermediate cTnI values (0.2–1.9 μg/L) differed significantly with respect to the recognition of ACS. Patients with CP, ARRY, or SURG and intermediate cTnI were most often diagnosed with ACS. Finally, a diagnosis of ACS was given to most or all patients with initial cTnI > 2 μg/L regardless of their complaints at the time of the initial presentation. Patients with cTnI > 2 μg/L and no diagnosis of ACS were judged by the treating physicians to have myocardial necrosis not related to coronary artery disease (cardiac procedures such as cardioversion, heart failure, and systemic hypoperfusion) as documented in the medical notes.

### Demographics and Other Characteristics

Demographics, cardiac risk factors, and information about major diseases were collected from the patients as shown in Table 2. ANOVA revealed that the six patient groups did not differ by median cTnI concentrations. However, the groups differed significantly with respect to cardiac risk factors (BMI and blood cholesterol) and a history of coronary artery disease, with patients in the CP group having the highest values for these characteristics. Likewise, the groups differed with respect to serum creatinine, age, and the frequency of patients with CHF, with the greatest values in the SOB/WK group. Other significant differences among the groups were for COPD, cancer, and proportion of inpatients with the highest values in the group undergoing surgery. Significant differences did not exist between the groups for the remaining characteristics: mean blood pressure, gender, smoking, and diabetes.

### DISCHARGE DIAGNOSIS OF ACS

The percentages of patients who were diagnosed with ACS or myocardial infarction after initial cTnI testing are listed in Table 1. For example, 9% of all patients with CP and initial cTnI ≤ 0.1 μg/L were subsequently diagnosed with ACS, whereas 91% of these patients received another diagnosis. The frequencies of the final diagnosis of ACS were not significantly different among patients with cTnI ≤ 0.1 μg/L whether they presented with CP or with other symptoms. In contrast, the patient groups with intermediate cTnI values (0.2–1.9 μg/L) differed significantly with respect to the recognition of ACS. Patients with CP, ARRY, or SURG and intermediate cTnI were most often diagnosed with ACS. Finally, a diagnosis of ACS was given to most or all patients with initial cTnI > 2 μg/L regardless of their complaints at the time of the initial presentation. Patients with cTnI > 2 μg/L and no diagnosis of ACS were judged by the treating physicians to have myocardial necrosis not related to coronary artery disease (cardiac procedures such as cardioversion, heart failure, and systemic hypoperfusion) as documented in the medical notes.

#### Table 2. cTnI, demographic characteristics, and disease frequencies for patients with CP or anginal equivalent symptoms.

<table>
<thead>
<tr>
<th>Presented with</th>
<th>CP</th>
<th>ARRY</th>
<th>SOB/WK</th>
<th>PAIN</th>
<th>MSC</th>
<th>SURG</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median cTnI, μg/L</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
<td>0.0</td>
<td>0.1</td>
<td>0.0</td>
<td>NS&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>0.5 ≤ cTnI &lt; 2.0 μg/L, %</td>
<td>16</td>
<td>18</td>
<td>22</td>
<td>14</td>
<td>17</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>cTnI ≥ 2.0 μg/L, %</td>
<td>6</td>
<td>6</td>
<td>7</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>29</td>
<td>27</td>
<td>27</td>
<td>27</td>
<td>26</td>
<td>24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/L</td>
<td>1870</td>
<td>1930</td>
<td>1740</td>
<td>1710</td>
<td>1810</td>
<td>1550</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine, mg/L</td>
<td>15</td>
<td>13</td>
<td>20</td>
<td>16</td>
<td>18</td>
<td>10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean blood pressure, mmHg</td>
<td>97</td>
<td>101</td>
<td>99</td>
<td>98</td>
<td>97</td>
<td>90</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>61</td>
<td>65</td>
<td>67</td>
<td>64</td>
<td>62</td>
<td>67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>African American, %</td>
<td>44</td>
<td>17</td>
<td>43</td>
<td>53</td>
<td>56</td>
<td>24</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Male, %</td>
<td>95</td>
<td>100</td>
<td>98</td>
<td>100</td>
<td>98</td>
<td>95</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>73</td>
<td>67</td>
<td>73</td>
<td>64</td>
<td>64</td>
<td>71</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>30</td>
<td>21</td>
<td>37</td>
<td>40</td>
<td>31</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td>CHF, %</td>
<td>15</td>
<td>13</td>
<td>40</td>
<td>9</td>
<td>16</td>
<td>10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>47</td>
<td>29</td>
<td>45</td>
<td>35</td>
<td>31</td>
<td>33</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Angioplasty, %</td>
<td>23</td>
<td>13</td>
<td>16</td>
<td>13</td>
<td>11</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Cerebrovascular accident, %</td>
<td>14</td>
<td>17</td>
<td>20</td>
<td>15</td>
<td>17</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>Cancer, %</td>
<td>13</td>
<td>29</td>
<td>17</td>
<td>18</td>
<td>12</td>
<td>52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD, %</td>
<td>17</td>
<td>17</td>
<td>28</td>
<td>18</td>
<td>17</td>
<td>33</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Outpatients, %</td>
<td>84</td>
<td>50</td>
<td>66</td>
<td>70</td>
<td>82</td>
<td>14</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup> Comparisons among presentations were conducted using ANOVA for continuous variables and χ² analysis for categorical values.

<sup>b</sup> NS, not significant.

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![Fig. 1. Survival for patients who presented with CP or with anginal equivalent symptoms of ACS.](image-url)
BMI, serum creatinine, blood pressure, age, and history of cancer were also identified as predictors of adverse outcome in the SOB/WK patient group (Table 3). cTnI results were not significantly associated with subsequent adverse outcome among patients with PAIN, ARRY, or MSC (Table 3). However, other variables, such as BMI and age, were predictors of death for patients with PAIN/ARRY/MSC. There was no significant association between mortality and the variables listed in Table 3 for patients who had undergone surgery (data not shown). The χ² and Nagelkerke’s R² for the analyses for patients with CP, SOB, and PAIN/ARRY/MSC were 11.73, 22.72, and 6.35 and 0.25, 0.28, and 0.31, respectively.

**ODDS OF ADVERSE OUTCOME FOR PATIENTS WITH DETECTABLE cTnI**

We investigated in more detail the relationship between cTnI and subsequent adverse outcome for patients with CP or SOB/WK. To calculate the odds of adverse outcome, we used four tiers of cTnI concentration ranges as defined in the Materials and Methods. Patients presenting with CP and a cTnI in the second or third tier did not have a significantly increased mortality compared with the tier one baseline. The odds of adverse outcome were signifi-

### Table 3. Multivariate predictors and P values for 200-day mortality among patients with various complaints at the time of laboratory testing.

<table>
<thead>
<tr>
<th>Complaints*</th>
<th>CP</th>
<th>SOB/WK</th>
<th>Other, excluding surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio</td>
<td>P</td>
<td>Odds ratio</td>
<td>P</td>
</tr>
<tr>
<td>BMI</td>
<td>0.93 (0.86–1.01)</td>
<td>NSb</td>
<td>0.93 (0.89–0.97)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.26 (1.12–1.43)</td>
<td>VR</td>
<td>0.98 (0.96–0.99)</td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td>1.02 (1.01–1.05)</td>
<td>0.05</td>
<td>1.09 (1.05–1.13)</td>
</tr>
<tr>
<td>Age</td>
<td>3.50 (1.44–8.48)</td>
<td>0.01</td>
<td>1.88 (1.02–3.47)</td>
</tr>
<tr>
<td>Cancer</td>
<td>4.70 (1.52–14.56)</td>
<td>0.01</td>
<td>See Table 4</td>
</tr>
<tr>
<td>cTnI &lt; 2 μg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cTnI ≥ 2 μg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 95% confidence intervals are shown in parentheses.

b NS, not significant; VR, variable removed from final step of equation; CVA, cerebrovascular accident.

### Table 4. Odds of death within 200 days for patients presenting with SOB/WK of any cause or for patients with any complaint and a previous history of CHF.

<table>
<thead>
<tr>
<th>cTnI, μg/L</th>
<th>Presentation</th>
<th>n</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0–0.1</td>
<td>SOB/WK</td>
<td>178</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>117</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2–0.4</td>
<td>SOB/WK</td>
<td>108</td>
<td>3.07</td>
<td>1.61–5.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>76</td>
<td>4.34</td>
<td>1.66–11.30</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>0.5–1.9</td>
<td>SOB/WK</td>
<td>89</td>
<td>2.81</td>
<td>1.44–5.50</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>62</td>
<td>5.68</td>
<td>2.09–15.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 2.0</td>
<td>SOB/WK</td>
<td>30</td>
<td>6.58</td>
<td>2.65–16.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>19</td>
<td>13.04</td>
<td>3.74–45.48</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
cantly higher among patients with CP when they had a cTnI within the fourth tier (Table 3). Patients presenting with SOB/WK and a cTnI in the second tier had an increased adverse outcome compared with patients with a cTnI in the tier one baseline. Patients with cTnI within the third and fourth tiers also showed a significantly higher mortality (Table 4). Thus, in contrast to the CP group, SOB/WK patients exhibited an increased mortality at cTnI values that exceeded the first tier.

**Odds of Adverse Outcome in Other Patient Subgroups**

We determined whether cTnI had prognostic value for patients according to diagnosis. Among the 1,175 patients, there were 274 patients who had previously been diagnosed with CHF. Of these patients, 218 survived and 56 patients died within the 200-day period after initial laboratory testing. The odds of adverse outcome were significantly higher for patients with cTnI in the second, third, or fourth tier compared with patients with cTnI in the first tier (Table 4). cTnI also provided significant prognostic information when patients were classified according to diseases other than CHF. cTnI predicted the adverse outcome for patients with histories of diabetes, coronary artery disease, cerebrovascular accident, or COPD (data not shown).

More than one-third of the 405 patients with SOB/WK had documentation of increased serum creatinine (>14 mg/L) before or at the time of clinical presentation, suggesting that they may have had impaired renal function. The prognostic value of cTnI was examined in the remaining 264 patients with SOB/WK who had serum creatinine concentrations within the reference interval. Patients with cTnI in the second (odds ratio, 3.12; 95% confidence interval, 1.33–7.32; n = 66; P <0.01) or fourth tier (odds ratio, 7.02; 95% confidence interval, 1.93–25.64; n = 14; P <0.01) continued to have an increased mortality during the 200-day follow-up period compared with patients with normal renal function and cTnI in the first tier (n = 139). The difference in outcome was not significant for patients with cTnI in the third tier (odds ratio, 2.56; 95% confidence interval, 0.97–6.78; n = 45).

**Discussion**

The diagnostic and prognostic utility of cTnI or cTnT testing has been firmly established among patients with ACS, e.g., patients who present with unstable angina or with evidence of non-ST-segment-elevation myocardial infarction (20). However, older patients with ACS frequently present with other symptoms, such as pain in areas other than the chest, SOB, weakness, or mental status changes (6, 7). Because our hospital serves a patient population with a mean age of ~65 years, we asked how often testing for cTnI is requested for patients who present with symptoms other than CP. We found that cTnI was ordered most often for patients who did not present with angina at our institution. We hypothesize that the high number of cTnI requests for patients with symptoms other than CP at our hospital is not unusual and may be similar at other hospitals that serve an older patient population (7). To our knowledge, there is currently little published information about the predictive value of cTnI for patients with anginal equivalent symptoms of ACS.

Patients are classified into three groups according to their likelihood of ACS (18). Algorithms have been developed for further evaluation and management of patients with possible or definite ACS. In contrast, there is currently no consensus as to whether to follow up patients with a low likelihood of ACS, such as patients without a recent history of CP, nondiagnostic echocardiographic findings, or cTnI below the 99th percentile of normal. We investigated how many of the patients with cTnI orders received a final diagnosis that was consistent with ACS. At our institution, only a few of the patients with symptoms other than CP or ARRAY and initial cTnI <2 μg/L were diagnosed with ACS at the time of their hospital visit. In contrast, most patients with anginal equivalent symptoms and higher cTnI concentrations were found to have ACS. This suggests that the laboratory test result was an important component of the diagnostic process.

We believe that the rare diagnosis of ACS among patients with anginal equivalent symptoms and low-positive cTnI is not unique to this institution because many of our physicians also practice at other hospitals, including two University Medical Centers. It has been recognized that the diagnosis of ACS among patients with anginal equivalent symptoms remains a challenge for the clinician.

We next investigated the outcome for the study patients. We categorized patients without CP according to major clinical manifestations. We identified five types of manifestation or clinical circumstances, as shown in Table 1, that may have been associated with a cardiac etiology. The endpoint all-cause death was chosen because cause-specific death is often difficult to determine for patients with multiple major diseases. Follow-up information was available for >99% of study patients. It is unlikely that the exclusion of the remaining patients without available outcome information had a major effect on our observations and conclusions.

All-cause mortality differed significantly among patients according to the type of manifestation. Patients with CP had a low mortality that was similar to the mortality of patients with cardiac ischemia, as described in previous studies (4, 5). The low mortality may have been attributable to the fact that these patients were most likely considered to have ACS, and therapeutic intervention has led to significant improvement of patient outcome in this patient population. On the other hand, patients with a history of recent surgery had the highest mortality rate during the follow-up period. These patients were mostly inpatients and frequently had diseases of poor prognosis, such as cancer. Patients with SOB/WK had a mortality rate that was severalfold higher than that of patients with
asthma, neuromuscular disease, or COPD). Testing for lying diseases other than cardiac decompensation (e.g., SOB/WK may have been symptomatic because of under-
without coronary artery disease. Similarly, patients with This group of patients may have included individuals 
whether the patients with CP had acute cardiac ischemia. The first limitation is that patients were classified accord-
to symptoms. For example, we did not examine 
The performance of commercial cTnI assays. Indeed, cTnI 
variable results, especially in the low-positive range. This may have been attributable to small study sizes, lack of control for confounding factors, or variability in the performance of commercial cTnI assays. Indeed, cTnI 
rate of cTnI in patients with heart failure is highly variable among different commercial assays. In the current study, a commercial cTnI assay was used that has previously been found to detect the low cTnI concentrations that circulate in pa-
tients with unstable heart failure (22). However, the prog-
nostic value of cTnI or cTnT for patients with unstable 
heart failure is currently unclear because previously pub-
blished studies have reported inconsistent results (23–27).

There are several limitations that apply to our study. The first limitation is that patients were classified accord-
ing to symptoms. For example, we did not examine whether the patients with CP had acute cardiac ischemia. This group of patients may have included individuals without coronary artery disease. Similarly, patients with SOB/WK may have been symptomatic because of under-
lying diseases other than cardiac decompensation (e.g., asthma, neuromuscular disease, or COPD). Testing for cTnI may have led to the identification of patients with heart failure because patients with SOB and other pulmo-
nary diseases usually test negative for cTnI. Therefore, 
cTnI may have diagnostic rather than prognostic utility for patients with SOB/WK. The second limitation is that study patients were predominantly male and presented with acute symptoms. The findings from this study cannot be applied to patients with stable or asymptomatic 
heart failure. The third limitation is that several other 
variables have been found to be strong predictors of out-
come in CHF, e.g., plasma norepinephrine, brain natri-
uretic peptide, left ventricular ejection fraction, peak O2 
consumption, or therapeutic medications (30). These fac-
tors were not assessed in our patients with SOB/WK or 
CHF. Therefore, it is unclear whether cTnI truly provides 
independent prognostic value. However, testing for cTnI is readily available in most emergency departments and 
may be used as a simple tool to identify patients with poor prognoses. The fourth limitation is that the current generation of commercial cTnI assays (including the first-
generation assay used in this study) is imprecise at low 
cTnI concentrations and does not meet clinical requirements (13, 18). Therefore, it is very likely that several study 
patients with cTnI in the first through third tiers were 
incorrectly classified because of the inherent test impreci-

cation. Random assay imprecision will lead to underestima-
tion of the prognostic value for cTnI. Nevertheless, the 
large size of our study population allowed us to clearly 
demonstrate the potential of cTnI testing for symptomatic 
patients despite the technical limitations of the current 
assay(s). However, test results indicating detectable but 
very low cTnI concentrations should not be used for 
treatment decisions unless assays are used with improved 
low-end analytical sensitivity and precision.

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