

Acute Coronary Syndrome vs Nonspecific Troponin Elevation

Clinical Predictors and Survival Analysis

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Background: Although troponin is considered a specific marker for the diagnosis of acute coronary syndrome (ACS), recent studies have shown troponin elevation in a variety of nonischemic conditions. Our aim was to determine the predictors for the diagnosis of ACS in the presence of an abnormal troponin level.

Methods: All patients with abnormal troponin T levels were analyzed. Demographic and clinical data were collected and death was recorded. The study group was divided into 2 subgroups: ACS vs nonthrombotic troponin elevation. A multivariate logistic regression analysis was performed to define variables that predict the diagnosis of ACS. The positive predictive value (PPV) for ACS diagnosis was calculated, and a survival analysis was performed.

Results: During the study period, 615 patients had elevated troponin T levels. Only 326 patients (53%) received a main diagnosis of ACS, while 254 (41%) had nonthrombotic troponin elevation; for 35 patients (6%), the diagnosis was not conclusive. Positive predictors for the

diagnosis of ACS were age between 40 and 70 years, history of hypertension or ischemic heart disease, normal renal function, and a troponin T level higher than 1.0 ng/mL. The overall PPV of troponin T for ACS diagnosis was only 56% (95% CI, 52%-60%). The PPV of troponin T level higher than 1.0 ng/mL in the presence of normal renal function was 90% but was as low as 27% for values of 0.1 to 1.0 ng/mL for elderly patients with renal failure. In-hospital and long-term survival rates were significantly better ($P < .001$) for patients with ACS.

Conclusions: Nonspecific troponin elevation is a common finding among hospitalized patients and correlates with worse prognosis. The diagnosis of myocardial infarction should still mostly be based on the clinical presentation. The predictors and algorithm suggested in this study might increase the diagnostic accuracy of ACS and direct the appropriate treatment.

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THE JOINT EUROPEAN SOCIETY of Cardiology/American College of Cardiology (ESC/ACC) Committee proposed a new definition of myocardial infarction (MI) based predominantly on the detection of the cardio-specific biomarkers troponin T and troponin I.¹ While this rapid and sensitive blood test is certainly valuable in the appropriate clinical setting, its widespread use in a variety of clinical scenarios may lead to the detection of troponin elevation in the absence of thrombotic acute coronary syndromes (ACSs).²

Other medical conditions, such as sepsis, hypovolemia, atrial fibrillation, congestive heart failure, pulmonary embolism, severe pulmonary infections, myocarditis, myocardial contusion, and renal failure, can be associated with an increase in troponin levels.³⁻⁹ These eleva-

tions may arise from various causes other than thrombotic coronary artery occlusion. Possible mechanisms include the following: mismatch between myocardial oxygen demand and supply in the absence of flow-limiting epicardial stenosis^{3,10}; imbalance of the autonomic nervous system with resulting excess of sympathetic activity and an increased catecholamine effect on the myocardial cells¹¹; direct myocardial cell injury by traumatic or inflammatory processes; volume and pressure overload resulting in an excessive increase in wall tension with secondary myofibrillary damage¹²; and impaired renal troponin excretion.¹³

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines indicate that the myocardial necrosis signified by troponin elevation may not necessarily be due to atherosclerotic coronary artery disease and that MI should

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therefore be diagnosed in conjunction with other supportive evidence.¹⁴ Nevertheless, the implementation of these new guidelines in clinical practice has led to a substantial increase in the frequency of MI diagnosis compared with diagnoses based on creatine phosphokinase (CPK)–MB criteria.¹⁵

Given the lack of any supportive data at present, patients with nonthrombotic troponin elevation (NTTE) should not be treated with antithrombotic and antiplatelet agents and should not undergo invasive cardiac assessment and treatment. Rather, the underlying cause of the troponin elevation should be targeted. However, the assessment of whether a troponin elevation is thrombotic or nonthrombotic in origin can be challenging.

The aims of this study were to better characterize the differences between patients presenting with ACS and NTTE in terms of clinical predictors and outcome and to define the predictive value of a positive troponin result in various settings. These predictors can help the clinician to better estimate the posttest probability of ACS in patients with a positive troponin result and guide the appropriate treatment for these patients.

METHODS

PATIENTS

The study group comprised all consecutive patients admitted to 2 hospitals of Hadassah-Hebrew University Medical Center in Jerusalem, Israel, between January 1, 2003, and October 1, 2003, who had troponin T elevation according to the laboratory-computerized database. The cutoff value for a positive result was 0.1 ng/mL. Children younger than 16 years and patients with out-of-hospital cardiac arrest who died within the first 48 hours of admission were excluded from this analysis. We collected demographic and clinical data including age, sex, cardiovascular risk factors, history of ischemic heart disease, left ventricular function (LVF) determined by echocardiogram prior to admission or on the first day of hospitalization, hospital department where troponin level was checked, and serum CPK and creatinine levels. For analysis, we used the highest level of troponin T and CPK during hospitalization and the creatinine levels on the same day the maximal troponin T level was measured.

DETERMINATION OF DIAGNOSIS

Based on previously published data reviewed by Jeremias and Gibson,² we divided the study group into 2 subgroups according to the principal diagnosis of hospitalization: thrombotic ACS and NTTE. Two expert physicians (R.A. and D.P.) in cardiology and internal medicine independently determined the principal diagnosis after revision of the patient records.

Diagnostic criteria for thrombotic ACS were in accordance with the ESC/ACC guidelines and included a typical rise and fall of cardiac-specific enzyme levels and one of the following: typical ischemic symptoms (chest pain or dyspnea); electrocardiographic changes indicative of ischemia (ST segment elevation or depression or development of new pathologic Q waves); and evidence of significant coronary lesion on coronary angiography.

A diagnosis of NTTE was made in the presence of another definitive diagnosis that is known to be associated with an increase in troponin levels (eg, sepsis, pulmonary embolism, and intracranial bleeding) and with the lack of sufficient criteria for the diagnosis of ACS. A diagnosis of NTTE was also made if normal coronary arteries were demonstrated on coronary an-

giography or when troponin T levels were constantly elevated at the same level.

In cases of disagreement concerning the diagnosis, an opinion of 1 physician favoring the diagnosis of thrombotic ACS was sufficient to make this diagnosis. Cases with insufficient information, in which neither of the investigators could determine the diagnosis, were excluded from the final analysis.

FOLLOW-UP

Patients were followed up for mortality for up to 2.5 years. We recorded death during hospitalization and during the follow-up period according to the national mortality registry. The date of last follow-up was July 1, 2005. The cause of death was determined for patients who died in hospital during the follow-up period, according to patient files and the report-of-death forms. The death causes were divided into 3 subgroups: infectious (in most cases sepsis or respiratory infection), cardiac (including ACS-related causes such as arrhythmia, congestive heart failure, or cardiac mechanical complication) and "other," which included all other causes (eg, malignancy, trauma, hemorrhage, neurological, and pulmonary embolism).

STATISTICAL ANALYSIS

Kappa (κ) was calculated for agreement between investigators about the principal diagnosis (ACS vs NTTE). Differences between ACS and NTTE groups were determined using χ^2 or Fisher exact tests for categorical variables, as appropriate, *t* test (unpaired, 2-tailed) for continuous variables normally distributed, and the Mann-Whitney test for variables without normal distribution.

Unconditional multiple logistic regression analysis was used to assess the independent odds ratios and their 95% confidence intervals (CIs) of predictor variables for the diagnosis of ACS. Variable were age in decades, sex, admission department, LVF (3 categories: ejection fraction <40%, >40%, and unknown), troponin levels (3 categories: 0.1-0.5, >0.5-1.0, and >1.0 ng/mL), creatinine level (3 categories: <1.13, 1.14-2.26, and >2.26 mg/dL [<100 , 101-200, and ≥ 201 $\mu\text{mol/L}$]), and the presence of diabetes mellitus and hypertension.

We validated the performance of troponin T for the diagnosis of ACS by calculating the positive predictive value (PPV) with corresponding 95% CIs in different subgroups according to age and creatinine troponin T levels.

In-hospital mortality rates were calculated in both ACS and NTTE groups. Cox proportional hazards models were used to assess the long-term risk for death among patients with ACS vs those with NTTE independent of the differences in demographic and clinical characteristics (age, sex, diabetes, LVF, and creatinine level).

Statistical analyses were performed with SPSS 12.0 software (SPSS Inc, Chicago, Ill). Data are presented as mean \pm SD unless stated otherwise. Tests were considered statistically significant at $P < .05$ (2-sided).

RESULTS

Throughout the 9 months of the study period, 12 553 troponin tests were performed. The results of 1591 tests (12.7%) were positive (cutoff, >0.1 ng/mL) in 635 different patients. According to the study protocol, 20 patients (3.3%) (children or patients who were admitted after out-of-hospital cardiac arrest) were excluded. The mean age of the study group was 68 ± 14.6 years (range, 20-100 years), 65% were male, 56% had hypertension,

Table 1. Patient Characteristics According to Principal Diagnosis During Hospitalization*

Characteristic	Diagnosis				P Value
	All Patients	ACS	NTTE	Unknown	
All patients	615	326	254	35	
Male sex	398 (65)	226 (69)	154 (61)	18 (51)	.02
Age, mean ± SD, y	68 ± 14.6	65 ± 13.4	71.4 ± 15.3	72.2 ± 13.9	<.001
HTN	346 (56)	190 (58)	139 (55)	17 (49)	.84
DM	231 (38)	119 (36)	98 (39)	14 (40)	.44
History of IHD	313 (51)	180 (55)	119 (47)	14 (40)	.06
Impaired LVF, EF <40%	157 (42)	95 (44)	53 (38)	9 (41)	.55
Creatinine, median, mg/dL	1.09	0.96	1.52	1.35	<.001
CPK, median, U/L	179	207	146.5	232	.01
Troponin T, mean ± SD, ng/mL	1.1 ± 0.08	1.5 ± 2.4	0.6 ± 0.9	0.98 ± 1.3	<.001

Abbreviations: ACS, acute coronary syndrome; CPK, creatine phosphokinase; DM, diabetes mellitus; EF, ejection fraction; HTN, hypertension; IHD, ischemic heart disease; LVF, left ventricular function; NTTE, nonthrombotic troponin elevation.

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

*Data are given as number (percentage) of patients unless otherwise specified. All comparisons are between the ACS and NTTE groups.

38% had diabetes, and 51% had a history of ischemic heart disease. Data on LVF were available for 377 patients (61%), 42% of patients had significantly impaired LVF, with an ejection fraction of lower than 40%. The mean troponin T level was 1.1 ± 0.08 ng/mL, the median CPK level was 179 U/L (interquartile range, 75-471 U/L), and the median creatinine level was 1.09 mg/dL (96 μmol/L) (interquartile range, 0.85-1.93 mg/dL [75-171 μmol/L]).

Surprisingly, the diagnosis of ACS was made for 326 patients, only 53% of the study cohort, while as many as 254 (41%) had NTTE. In 35 patients (6%), the diagnosis was undetermined despite careful examination of the patient files. These patients were excluded from the final analysis. The measurement for agreement between the physicians for determination of diagnosis was high ($\kappa=93\%$).

Among patients without ACS, the diagnoses were cardiac nonischemic (arrhythmias and myocarditis) in 11%, sepsis in 8%, pulmonary disease in 7%, neurological disease (mainly intracranial bleeding and stroke) in 5%, surgical disorder (trauma, massive gastrointestinal bleeding, and bowel obstruction) in 5%, renal failure in 2%, post-resuscitation in 2%, and other in 2%, and the cause was unknown in 6%. Patient characteristics according to principal diagnosis are summarized in **Table 1**. In the ACS patient group, there were significantly more men, mean age and median creatinine level were lower, and mean troponin and CPK levels were higher. There were no differences between the groups in ischemic risk factors, prevalence of left ventricular failure, or history of ischemic heart disease.

In multivariate analysis, the predictors for the diagnosis of thrombotic ACS were history of hypertension or ischemic heart disease, higher troponin levels, and normal creatinine levels. Extreme age groups (<40 years or >80 years) were negative predictors for ACS. Admission to a surgical (general or orthopedic) department was also a strong negative predictor for ACS diagnosis. Sex and history of diabetes mellitus and LVF were not predictors for ACS diagnosis. The results of the regression analysis are summarized in **Table 2**.

The PPV of a positive troponin T result for the diagnosis of thrombotic ACS among all hospitalized patients was only 56% (95% CI, 52%-60%). The PPV of troponin T levels between 0.1 and 1.0 ng/mL was 48% (95% CI, 43%-53%). For the older patients group (age >70 years) with impaired renal function (creatinine level, ≥ 1.13 mg/dL [≥ 100 μmol/L]), the PPV of troponin T levels of 1.0 ng/mL or lower was as low as 27% (95% CI, 20%-37%) (**Table 3**). In contrast, patients in the same age group who had troponin T levels higher than 1.0 ng/mL in the presence of normal renal function (serum creatinine level <1.13 mg/dL [<100 μmol/L]), the PPV for ACS was as high as 90% (Table 3).

The median follow-up for mortality in the study group was 22 months. The in-hospital mortality in the entire study group was 8%. The in-hospital mortality rate of patients with ACS was 3%, while the mortality rate of patients with NTTE was almost 8 times higher and reached 21% ($P<.001$). Long-term survival was also significantly better ($P<.001$) among the patients with ACS, even after adjustment for age, sex, diabetes, creatinine level, and LVF (**Figure 1**).

Causes of in-hospital death differ significantly between the study groups (**Table 4**). The main cause of in-hospital death for the study population during the follow-up period was infection (sepsis in most cases), and it was significantly higher in the NTTE group (33% vs 15%; $P=.01$). Cardiac-related in-hospital death rates were relatively low: 8 (8%) of 105 cases in the whole group, 5 (22%) of 23 in the ACS group, and only 3 (4%) of 82 cases in the NTTE group. Interestingly, the proportion of patients who died out of hospital was significantly higher in the ACS group (65% vs 41%; $P=.001$).

COMMENT

Troponin is considered both a sensitive and specific marker for the diagnosis of MI, and the use of this test turned out to be widespread in recent years. This led to a substantial increase in the incidence of MI diagno-

Table 2. Multivariate Regression Analysis for the Diagnosis of Thrombotic Acute Coronary Syndrome

Variable	Hazard Ratio (95% Confidence Interval)	P Value
Sex		
Male*	1.00	
Female	0.98 (0.62-1.56)	.94
Age, y		
<40*	1.00	
41-50	16.66 (4.02-69.04)	<.001
51-60	8.96 (2.61-30-72)	<.001
61-70	5.82 (1.73-19.6)	.004
71-80	3.84 (1.16-12.66)	.03
>80	1.96 (0.57-6.74)	.29
HTN		
No*	1.00	
Yes	1.70 (1.07-2.70)	.03
DM		
No*	1.00	
Yes	0.82 (0.52-1.31)	.42
History of IHD		
No*	1.00	
Yes	1.58 (1-2.51)	.05
LVF		
EF >40%*	1.00	
EF <40%	1.41 (0.78-2.56)	.26
Unknown	0.79 (0.48-1.28)	.34
Creatinine, mg/dL		
<1.13*	1.00	
1.13-2.26	0.41 (0.25-0.69)	.001
>2.26	0.17 (0.09-0.3)	<.001
Troponin T, ng/mL		
0.1-0.5*	1.00	
0.51-1	1.96 (1.09-3.52)	.02
>1	4.34 (2.46-7.64)	<.001
Department		
Cardiology*	1.00	
Internal medicine	0.25 (0.14-0.44)	<.001
Surgical	0.05 (0.02-0.17)	<.001
Emergency department	0.46 (0.24-0.87)	.02
Cardiac surgery	0.24 (0.11-0.53)	<.001

Abbreviations: DM, diabetes mellitus; EF, ejection fraction; HTN, hypertension; IHD, ischemic heart disease; LVF, left ventricular function.

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

*Reference value.

sis.¹⁵⁻¹⁷ Some centers report a 100% increase in the incidence of MI since troponin measurement became the standard of care for the diagnosis of ACS.¹⁶ This significant rise is, in part, a result of the high sensitivity of the troponin test to detect even minor myocardial damage, which shifts the diagnosis in some of the patients with unstable angina to non-ST elevation MI. A second reason for the increased incidence in the diagnosis of MI, possibly a more important one, is a misdiagnosis of other clinical conditions. These conditions are known to be associated with an elevated troponin level probably caused by secondary myocardial damage. The significance given to the troponin test in the practice guidelines made a lot of clinicians consider an elevated troponin level as a synonym to acute MI and made the clinical manifestation less important.

Table 3. Positive Predictive Value for the Diagnosis of Acute Coronary Syndrome in Different Patient Profiles*

Patient Profile	Troponin T Level		
	Any Positive Result	0.1-1.0 ng/mL	>1.0 ng/mL
All patients	56 (52-60)	48 (43-53)	76 (69-82)
Age <70 y and creatinine <1.13 mg/dL	78 (72-84)	73 (65-80)	89 (79-95)
Age <70 y and creatinine ≥1.13 mg/dL	44 (35-55)	40 (29-52)	59 (36-79)
Age >70 y and creatinine <1.13 mg/dL	52 (42-63)	42 (31-54)	90 (68-99)
Age >70 y and creatinine ≥1.13 mg/dL	37 (29-45)	27 (20-37)	59 (43-73)

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

*Data are given as positive predictive value in percentage (95% confidence interval).

The assessment of whether a troponin elevation is a result of a coronary event or is nonthrombotic in origin has become a major challenge and has a great implication to both in-hospital and long-term management. The situation is further complicated in critically ill patients, for whom the history is usually limited and the diagnosis is based on “objective” laboratory and imaging test results, namely, electrocardiographic changes and troponin elevation. In some cases, a misdiagnosis of acute MI, which is only based on the elevated troponin level, might lead to inappropriate and sometimes harmful management such as considering antithrombotic therapy in the presence of bleeding or coronary angiogram in the presence of renal failure.

Our findings support the evidence that a slight elevation in troponin level is common in hospitalized patients within a large spectrum of clinical settings, especially in the critically ill patients. According to our assessment, over 40% of the patients in whom we found an elevated troponin T level did not have ACS. The PPV of an elevated troponin T level for the diagnosis of ACS was only 56%, and in patients with a level of 1.0 ng/mL or lower, it was as low as 48%, which is undoubtedly not enough to rule in the diagnosis of MI. A positive troponin test result must be interpreted in the context of the presenting symptoms and other clinical predictors to improve the accuracy of the diagnosis. In this study, the most powerful predictors for NTTE were the extreme age groups (<40 years and >80 years), admission to a surgical or to a noncardiac department (a possible marker for alternative diagnosis), and impaired renal function.

We calculated the PPV of troponin T levels in various subgroups with the following conclusions: in patients with troponin T levels higher than 1.0 ng/mL, the likelihood of having ACS is very high (90%) at any age among those with normal renal function and moderate (60%) among those with renal failure (serum creatinine level ≥1.13 mg/dL [≥100 μmol/L]). On the other hand, in patients with troponin T levels of 1.0 ng/mL or lower, the likelihood of having ACS is generally low (<50%), and it is reasonable (73%) only among patients younger

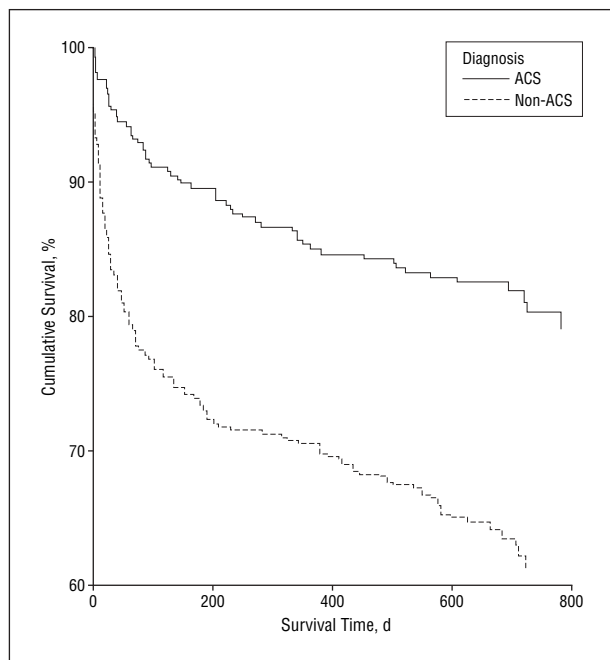


Figure 1. Survival curves according to principal diagnosis during hospitalization after adjustment for age, sex, diabetes, plasma creatinine levels, and left ventricular function. ACS indicates acute coronary syndrome.

Table 4. Cause of Death According Principal Diagnosis During Hospitalization*

Cause of Death	Diagnosis	
	ACS	NTTE
Infection	10 (15)	45 (33)
Cardiac	5 (8)	3 (2)
Other	8 (12)	34 (25)
Out of hospital	42 (65)	56 (41)
Total	65 (100)	138 (100)

Abbreviations: ACS, acute coronary syndrome; NTTE, nonthrombotic troponin elevation.

*Data are given as number (percentage) of patients. Percentages may not sum to 100% because of rounding. $P = .001$ for the comparison of the cause of death distribution between the ACS and the NTTE groups.

than 70 years with normal renal function. Based on these data, we proposed an algorithm for the more accurate diagnosis of ACS (**Figure 2**) that takes into consideration the clinical presentation, electrocardiographic changes, age, renal function, and troponin T level.

Our results strengthen the fact that even in a diagnostic test with a known excellent sensitivity and specificity, to ignore the pretest probability, namely the clinical evaluation, results in a high rate of misdiagnosis. When an elderly patient with renal failure is admitted with an alternative diagnosis or nonspecific symptoms, even when the troponin test result is “positive” (and especially when the result is only weakly positive), the posttest probability of MI is still low.

Based on previous definitions,² we defined the patients without ACS as having NTTE. While the characteristics and outcome of the ACS group were similar to

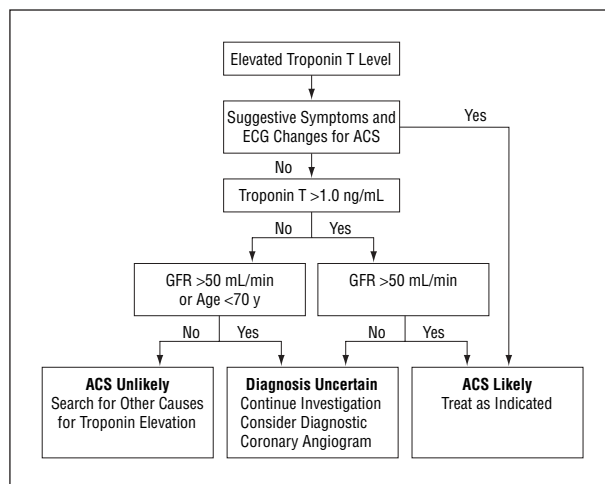


Figure 2. Proposed algorithm for the treatment of patients with indistinct clinical presentation and an elevated troponin T level. ACS indicates acute coronary syndrome; ECG, electrocardiographic; and GFR, glomerular filtration rate.

previously published data,¹⁸ the patients with NTTE were older, had more comorbid conditions, and had significantly lower short- and long-term survival rates. The high in-hospital mortality rate among the patients with NTTE, mainly from noncardiac-related causes, indicates that troponin level probably should serve as an indicator of a critical state of a noncardiac condition. In many cases, the troponin test was performed as a “screening” test for a patient with deteriorating health, and as such it is only a marker of multiorgan failure and poor prognosis. We think this attitude should be discouraged because it may lead to inappropriate treatment and interventions.

The survival analysis further strengthens our conclusion that the NTTE group is truly a distinct subset of patients separate from patients with ACS, since patients with NTTE had a worse prognosis despite the lower levels of troponin T. This is contradictory to the results of the ACS studies and registries, which show a linear correlation between troponin T level and risk of death.^{19,20} As expected, most of the patients with ACS died out of hospital during follow-up, presumably from sudden cardiac death.

The major limitation of this study is the fact that the determination of the diagnosis (ACS vs NTTE) was done retrospectively and is subject to misclassification bias. To minimize this bias, we performed the analysis in a relatively large number of patients, with careful inspection of the files by 2 independent physicians. The diagnostic determination was supported as much as possible by objective data such as laboratory and imaging results (especially coronary angiogram) and with maximal adherence to the guidelines definitions. The high level of agreement on the diagnosis between the physicians reflects this adherence. Our suggested algorithm for the diagnosis of ACS in the presence of a positive troponin test result obviously needs to be validated prospectively.

In conclusion, an elevated troponin level is a relatively common finding in hospitalized patients, even in the absence of clinical evidence of a coronary event. Although troponin elevation is an essential requirement for

the diagnosis of MI, it is not a sufficient one. Our results can help rule out or rule in the diagnosis of ACS in the presence of an elevated troponin level after considering the suggested predictors, mainly age, renal function, and maximal troponin value. These predictors can increase diagnostic accuracy and guide the appropriate treatment.

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