

The value of ultra-sensitive troponin I in determining the prognosis of patients with the suspected acute coronary syndrome in the emergency department

 Osman Gursoy Unal¹,  Mustafa Korkut¹,  Aslihan Yuruktumen Unal²,  Cihan Bedel¹,  Manolya Yildiz Unal¹

¹Department of Emergency Medicine, Health Science University Antalya Training And Research Hospital, Antalya, Turkey

²Department of Emergency Medicine, Faculty of Medicine, Akdeniz University, Antalya, Turkey

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Abstract

Aim: Acute coronary syndromes (ACS) have significant mortality and morbidity in our country and the world. With the development of technology, early diagnosis and treatment may be possible. Ultra-sensitive troponin I (us-TnI) test developed a few years ago has provided accurate detection of even lower troponin concentrations using a microparticle immunoassay. There are very few studies in the literature about us-TnI showing prognosis. In this study, we aimed to find the value of the newly introduced us-TnI in determining mortality in one-month and three-month follow-ups.

Materials and Methods: The study included all patients who were admitted to our tertiary emergency department (ED) between November 2015 and June 2016 and whose us-TnI levels was studied considering ACS. Whether the follow-up of the patients included in the study resulted in death was determined. The patients were classified according to the date of death based on their mortality status at the end of the first month and third month.

Results: It was found that of the patients, 4.0% (n=264) died within 1 month after the first troponin measurement, while 6.8% (n=444) died within 3 months after the first troponin measurement. The AUC of the baseline us-TnI value in determining cardiac death at the end of the first month was 0.803 (95% CI: 0.793-0.813) and the AUC of the baseline us-TnI value in determining cardiac death at the end of the third month was 0.763 (95% CI: 0.752-0.773).

Conclusion: Us-TnI studied at the time of admission to ED is an early indicator of mortality in patients with the diagnosis of ACS.

Keywords: Acute coronary syndrome; emergency department; mortality; troponin; ultra-sensitive cardiac troponin

INTRODUCTION

Coronary Artery Disease (CAD) is the most common cardiovascular disease and is associated with high mortality and morbidity. CAD clinically presents with silent ischemia, stable angina pectoris, acute coronary syndrome (ACS), heart failure, and sudden death (1). In Europe, a significant portion of emergency hospitalizations for medical reasons consist of patients presenting with the complaint of chest pain, and approximately one-third of these presentations are ACS (2,3). Patients with ACS are of importance for emergency department (ED) physicians because of the high risk of mortality and morbidity when not correctly diagnosed (4). ACS results from the disruption of the integrity of the atherosclerotic plaque structure in the coronary vessels (5). In clinic, unstable angina pectoris, non-ST segment elevation acute myocardial infarction

or ST-segment elevation acute myocardial infarction presentation may arise (6).

About 20 years ago, there has been a revolution with the use of troponin test in ACS (7). In the following years, more specific troponin assays were developed to assist in the diagnosis of ACS (8). Numerous epidemiologic studies have demonstrated the utility of serum troponin not only for the diagnosis of ACS but also for predicting heart failure, cardiovascular events, and mortality, as well as in cases of post-traumatic cardiac injury (9-11). Ultra-sensitive troponin I (us-TnI) test developed a few years ago has provided accurate detection of even lower troponin concentrations using a microparticle immunoassay (12). Troponin concentrations have been reported to be effective in predicting CAD in patients with chest pain and also determining the prognosis of these patients (13,14). Therefore, in this study, we aimed to determine the efficacy

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Corresponding Author: Cihan Bedel, Department of Emergency Medicine, Health Science University Antalya Training And Research Hospital, Antalya, Turkey E-mail: cihanbedel@hotmail.com

of us-TnI in determining the prognosis of patients with potential ACS in ED.

MATERIALS and METHODS

Study Design and Setting

This retrospective cohort study included all patients who were admitted to our tertiary ED between November 2015 and June 2016 and whose us-TnI were studied considering ACS. The diagnosis of ACS was made by senior assistant doctor or specialist doctor. Patients who were admitted after the first admission (the second admission of the same patient), patients without identification numbers (foreign patients, patients with incorrect identification number), and patients with missing or incorrect us-TnI data in the electronic database of our hospital were excluded from the study (Figure 1). us-TnI value of the patients was obtained from the hospital electronic database. The patients who died and the dates of death were determined from the Death Notification System.

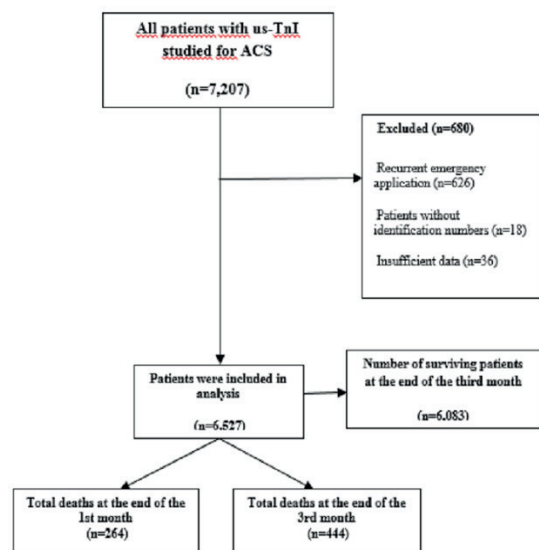


Figure 1: Patient flow chart

Data Gathering

us-TnI (Siemens, Advia Centaur) kit was used. When studied with this assay, serum levels within the range of 6 ng/L and 50,000 ng/L can be measured. The reference value is 0.06 ng/ml. Whether the follow-up of the patients included in the study resulted in death was determined. The effects of pathologies (sepsis, pulmonary embolism and kidney failure) that may affect troponin values on mortality were compared. The patients were then classified according to the date of death based on their mortality status at the end of the first month and third month.

Statistical Analyses

The data collected for the study were analyzed using the MedCalc. Numerical data were expressed as mean±standard deviation and median, while frequency data were expressed as a percentage. The value of us-TnI in determining cardiac death was found by Receiver Operating Characteristic (ROC) analysis. Sensitivity and specificity, positive and negative likelihood ratio (LR)

was used to determine the value of us-TnI in determining cardiac death and the cut-off value. Also, the diagnostic parameters were given with 95% confidence intervals (95% CI).

RESULTS

The study included 7,207 patients whose us-TnI levels were studied considering ACS. Of these patients, 626 were excluded from the study due to repetitive admission, 18 due to being foreign patients and 36 were excluded from the study due to incomplete data. The mean age of the 6527 patients included in the study was 58±18.04 years and 55.7% of the patients were male. Coronary angiography was performed in 554 patients with the diagnosis of ACS. There were 216 patients who underwent coronary angiography from patients with mortality. It was found that of the patients, 4.0% (n=264) died within 1 month after the first troponin measurement, while 6.8% (n=444) died within 3 months after the first troponin measurement. (Figure 1). The mean duration of follow-up troponin study in the emergency department was found to be 172 (152-185) min. It was observed that of the patients whose follow-up troponin was not studied, 2.3% (n=156) were exitus at the end of the first month, while the exitus rate at the end of the third month was 4% (n=265). Patients with mortality had significantly higher us-TnI levels in those with pathologies that could affect the troponin value (sepsis, pulmonary embolism and kidney failure) compared to those without additional pathology (3.30±1.22 vs. 0.36±0.08, P<0.001).

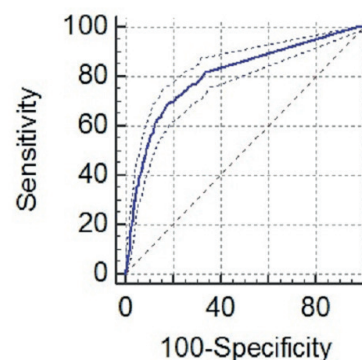


Figure 2. ROC curve of baseline ultra-sensitive troponin in determining one-month mortality

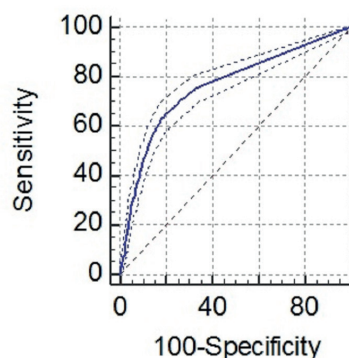


Figure 3. ROC curve of baseline ultra-sensitive troponin in determining three-month mortality

As a result of the ROC analysis, it was found that the AUC of the baseline us-TnI value in determining cardiac death at the end of the first month was 0.803 (95% CI: 0.793-0.813) and the AUC of the baseline us-TnI value in determining cardiac death at the end of the third month was 0.763 (95% CI: 0.752-0.773) (Figure 2-3). The efficacy of us-TnI in predicting mortality both at month 1 and month 3 was statistically significant ($P < 0.001$). For 0.04 ng/ml, the sensitivity, specificity, (+) LR and (-) LR of us-TnI in determining mortality at the end of the first month were 65.5% (95% CI: 59.5%-71.2%), 84.4% (95% CI: 83.5%-85.3%), 4.20 and 0.41, respectively, while the sensitivity, specificity, (+) LR and (-) LR of us-TnI in determining cardiac-related mortality at the end of the third month were 57.4% (95% CI: 52.7%-62.1%), 85.3% (95% CI: 84.4%-86.2%), 3.90 and 0.50, respectively. For a value of 0.06 ng/ml, which was designated as the upper limit, the sensitivity, specificity, (+) LR and (-) LR of us-TnI in determining mortality at the end of the first month were 56.6% (95% CI: 49.8%-62.1%), 89.3% (95% CI: 88.5%-90.0%), 5.22 and 0.49, respectively, while the sensitivity, specificity, (+) LR and (-) LR of us-TnI in determining mortality at the end of the third month were 46.2% (95% CI: 41.5%-50.9%), 89.8% (95% CI: 89.1%-90.6%), 4.56 and 0.60, respectively (Table 1-2).

Table 1. Validity of baseline Us-TnI values in determining mortality in the 1st month

Us-TnI values (ng/ml)	Sensitivity (%)	Specificity (%)	(+) LR	(-) LR
0.006	100.0%	2.09%	1.02	0.00
0.02	76.9%	71.8%	2.73	0.32
0.04	65.5%	84.4%	4.20	0.41
0.06	56.6%	89.3%	5.22	0.49
0.1	43.2%	92.9%	6.09	0.61

LR: Likelihood Ratio

Table 2. Validity of baseline Us-TnI values in determining mortality in the 3rd month

Us-TnI values (ng/ml)	Sensitivity (%)	Specificity (%)	(+) LR	(-) LR
0.006	99.6%	2.12%	1.02	0.21
0.02	71.2%	72.8%	2.62	0.40
0.04	57.4%	85.3%	3.90	0.50
0.06	46.2%	89.8%	4.56	0.60
0.1	33.33%	93.26%	4.95	0.71

LR: Likelihood Ratio

The efficacy of a baseline us-TnI of less than 0.06 ng/ml and a reduction of 29% after the baseline troponin in excluding mortality both at months 1 and 3 was statistically significant ($P < 0.001$). The sensitivity in excluding mortality in the first month was 100% (95% CI: 76.7-100.0), and the sensitivity in excluding mortality in the third month was 84.62% (95% CI: 69.5-94.1). (Figure 4-5). The efficacy of a 4.7-fold increase in excluding mortality in patients with

a baseline us-TnI value of less than 0.06 ng/ml both at months 1 and 3 was statistically significant ($P < 0.001$). The specificity for mortality in the first month was 85.27% (95% CI: 82.8-87.5) and the specificity for mortality in the third month was 85.09% (95% CI: 82.6-87.3).

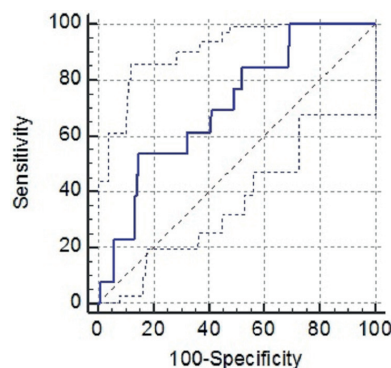


Figure 4. ROC curve of those with a baseline ultra-sensitive troponin value of less than 0.06 ng/ml and an absolute change in follow-up troponin in determining one-month mortality

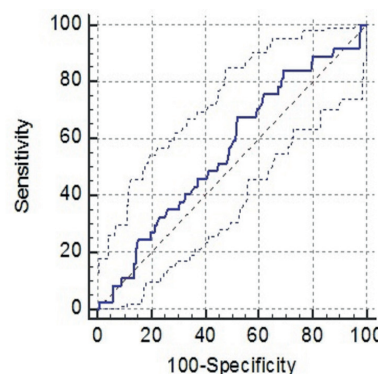


Figure 5. ROC curve of those with a baseline ultra-sensitive troponin value of less than 0.06 ng/ml and an absolute change in follow-up troponin in determining three-month mortality

DISCUSSION

One of the most difficult points in the management of patients presenting to ED with chest pain or similar symptoms and suspected of ACS is a diagnostic difficulty. The most important point affecting morbidity and mortality to determine the appropriate treatment method by making a diagnosis as soon as possible (4,5). To clarify the diagnosis of ACS, the patient should be followed up at intervals with cardiac markers. Cardiac troponins (cTn) have long been used as the gold standard to determine myocardial damage. Us-TnI test developed a few years ago is able to detect 10-100 times lower levels of cTn (15,16). For this purpose, many studies comparing the superiorities of cardiac markers over each other have been conducted and diagnostic and prognostic algorithms have been developed concerning the issue. In our study, we also demonstrated the efficacy of us-TnI in determining one-month and three-month mortality.

In our study, for an admission value of 0.04 ng/ml, which is the cut-off value for 99% of the normal population, we found the sensitivity, specificity, (+) LR and (-) LR in determining mortality at the end of the first month as

65.5% (95% CI: 59.5%-71.2%), 84.4% (95% CI: 83.5%-85.3%), 4.20 and 0.41, respectively. In a 2015 study by Ince et al. on 200 patients who presented to ED with chest pain and underwent coronary angiography, it was found that the sensitivity and specificity were 74% and 68%, respectively, the false-positive rate was 32% and the false-negative rate was 26% for a cut-off us-TnI value of 0.04 ng/ml (17). In a study of 371 patients by Apple et al., it was found that us-TnI determined 2-month mortality with a sensitivity of 96% and a specificity of 33% when the cut-off value was 0.006 ng/ml and with a sensitivity of 74% and a specificity of 84% when the cut-off value was 0.04 ng/ml (18). In our study, we found the sensitivity, specificity, (+) LR and (-) LR in determining one-month mortality as 100% (95% CI: 98.6%-100.0%), 2.06% (95% CI: 1.8%-2.5%), 1.02 and 0.00, respectively, for a limit of detection (LoD) of 0.006 ng/ml. In another study by Reichlin et al. investigating the accuracy of cardiac troponins in the diagnosis of myocardial infarction, it was reported that the 1-hour diagnostic sensitivity and specificity were 52% and 86%, respectively, (positive predictive value 83%, negative predictive value 53%) for a value of 0.04 ng/ml. (19).

In a study by Scharnhorst et al., us-TnI, myoglobin and CK-MB were measured at the time of admission and at 2 hours, and in this study in which a change above 30% in us-TnI was considered significant, the positive predictive value, negative predictive value, sensitivity and specificity in predicting myocardial infarction when the cut-off value was 0.06 ng/ml were found to be 70%, 100%, 100%, and 87%, respectively (20). In the study by Body et al., 1-hour and 12-hour us-TnI value was measured in patients with chest pain. The sensitivity and specificity of 1-hour us-TnI value in predicting myocardial infarction were found to be 75.6% and 94.3%, respectively, while the sensitivity and specificity of 12-hour us-TnI value were found to be 87.1% and 97.1, respectively. In the same study, the sensitivity and specificity in determining mortality within one month were found to be 69.8-97.6% and 60.4-87.2%, respectively (21). It is seen that the results of the study are substantially correlated with our results.

New generation troponins are known to be more successful in predicting prognosis compared to conventional troponins (22,23). In the study by Rubini et al., the diagnostic performance, as well as the prognostic value of high-sensitivity cardiac troponin I were investigated and the AUC value for mortality was found to be 0.75 (95% CI; 0.73-0.79) (24). In another study in which the patients were followed for 2 years, the AUC value for hs-cTnI was found to be 0.70 (95% CI: 0.64-0.76) (25). In our study, the AUC value was found to be 0.803 (95% CI: 0.793-0.813) considering the mortality in the first month and 0.763 (95% CI: 0.752-0.773) at the end of the third month. These results of ours also imply similar results with other studies.

Although there are many studies in the literature on traditional cardiac biomarkers, there are very few studies on us-TnI. For this reason, our study showed that us-TnI,

which has been in use recently, will be more beneficial for both the diagnostic value and the more comprehensive, detailed patient information, in which sensitivity and specificity increase, false positivity and negativity decrease, as well as conducting research on prognostic value.

LIMITATIONS

Our study has some limitations. The first of these is the retrospective design of our study; however, the sample size of our study increases the reliability of our study. Another limitation is that we could not determine the physical examination findings and the time of pain onset of the patients included in our study and that the time from complaint to sample collection was not recorded. Furthermore, the most important limitation of our study is that the factors that may affect mortality, such as comorbidities and drug use of the patients were not included in the study. Also, the fact that the causes of death were unknown since the deaths of the patients were determined from the Death Notification System is another limitation of our study.

CONCLUSION

Us-TnI studied at the time of admission to ED is an early indicator of mortality in patients with the diagnosis of ACS.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: This study was approved by the Ethics Committee Akdeniz University under no.2017/145.

REFERENCES

1. Gok G, Zoghi M, Sinan UY, et al. Demographics of patients with heart failure who were over 80 years old and were admitted to the cardiology clinics in Turkey. *Anatol J Cardiol* 2019;21:196-205.
2. Windecker S, Neumann FJ, Jüni P, et al. Considerations for the choice between coronary artery bypass grafting and percutaneous coronary intervention as revascularization strategies in major categories of patients with stable multivessel coronary artery disease: an accompanying article of the task force of the 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;40:204-12.
3. Bekler A, Altun B, Gazi E, et al. Comparison of the GRACE risk score and the TIMI risk index in predicting the extent and severity of coronary artery disease in patients with acute coronary syndrome. *Anatol J Cardiol* 2015;15:801.
4. Body R, Mueller C, Giannitsis E, et al. The use of very low concentrations of high-sensitivity troponin T to rule out acute myocardial infarction using a single blood test. *Acad Emerg Med* 2016;23:1004-13.
5. Crea F, Libby P. Acute coronary syndromes: the way forward from mechanisms to precision treatment. *Circulation* 2017;136:1155-66.

6. Noll S, Alvey H, Jayaprakash N, et al. The utility of the triage electrocardiogram for the detection of ST-segment elevation myocardial infarction. *Am J Emerg Med* 2018;36:1771-74.
7. Hamm CW, Giannitsis E, Katus HA. Cardiac troponin elevations in patients without acute coronary syndrome. *Circulation* 2002;106:2871-2.
8. Weber M, Bazzino O, Estrada JLN, et al. Improved diagnostic and prognostic performance of a new high-sensitive troponin T assay in patients with acute coronary syndrome. *Am Heart J* 2011;162:81-8.
9. Meigher S, Thode HC, Peacock WF, et al. Causes of elevated cardiac troponins in the emergency department and their associated mortality. *Acad Emerg Med* 2016;23:1267-73.
10. Apple FS, Sandoval Y, Jaffe AS, et al. Cardiac troponin assays: guide to understanding analytical characteristics and their impact on clinical care. *Clin Chem* 2017;63:73-81.
11. Mair J, Lindahl B, Hammarsten O, et al. How is cardiac troponin released from injured myocardium? *Eur Heart J Acute Cardiovasc Care* 2018;7:553-60.
12. Todd J, Freese B, Lu A, et al. Ultrasensitive flow-based immunoassays using single-molecule counting. *Clin Chem* 2007;53:1990-5.
13. Neumann JT, Havulinna AS, Zeller T, et al. Comparison of three troponins as predictors of future cardiovascular events—prospective results from the FINRISK and BiomaCaRE studies. *PloS one* 2014;9:e90063.
14. Aycicek GS, Unsal P, Esme M, et al. Could cardiac troponin I levels predict mortality in the elderly? *Aging Clin Exp Res* 2019;31:435.
15. Twerenbold R, Gimenez MR, Boeddinghaus J, et al. Comparing the prognostic value of ultra-sensitive cardiac troponin I versus high-sensitivity cardiac troponin T and I among patients with suspected myocardial infarction. *Eur Heart J Cardiovasc Pharmacother* 2018;39:566.
16. Tveit SH, Myhre PL, Røsjø H, et al. Relative Prognostic Merit of High-sensitivity Cardiac Troponin T and Ultra-Sensitivity Cardiac Troponin I in Patients with Suspected Acute Coronary Syndrome. *Circulation* 2018;138:16196.
17. Ince FD, Dogan N, Kahya Eren N, et al. The Diagnostic Value of Ultra-Troponin I in Patients Admitted to Emergency Department with Chest Pain and Performed Coronary Angiography. *Tepecik Eđit. ve Arařt. Hast. Dergisi* 2015; 25:33-7.
18. Apple FS, Smith SW, Pearce LA, et al. Use of the Centaur TnI-Ultra assay for detection of myocardial infarction and adverse events in patients presenting with symptoms suggestive of acute coronary syndrome. *Clin Chem* 2008;54:723-8.
19. Reichlin T, Irfan A, Twerenbold R, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. *Circulation* 2011;124:136-45.
20. Scharnhorst V, Krasznai K, van't Veer M, et al. Rapid detection of myocardial infarction with a sensitive troponin test. *Am J Clin Pathol* 2011;135:424-8.
21. Body R, Burrows G, Carley S, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a sensitive troponin I assay. *Ann Clin Biochem* 2015;52:543-9.
22. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37:267-315.
23. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;64:139-228.
24. Rubini Gimenez M, Twerenbold R, Reichlin T, et al. Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction. *Eur Heart J* 2014;35:2303-11.
25. Haaf P, Reichlin T, Twerenbold R, et al. Risk stratification in patients with acute chest pain using three high-sensitivity cardiac troponin assays. *Eur Heart J* 2014;35:365-75.