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Özgün Araştırma

The Value Of Ultra-Sensitive Troponin-I In Determining Mortality In Patients With Suspected Acute Coronary Syndrome

Akut Koroner Sendrom Şüpheli Hastalarda Mortalitenin Belirlenmesinde Ultra-Duyarlı Troponin-I'in Değeri

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ABSTRACT

Objective:
This study investigated the role of the reference value of ultra-sensitive troponin kits used in daily practice in determining mortality.

Material and Methods:
This study was conducted in the emergency department (ED) of Akdeniz University Hospital between January 1 2018 and June 30 2019. All patients admitted to the emergency department within a period of eighteen months and who had the result of the ultra-sensitive troponin level in the range of 0.06-0.1 ng/mL were included in the study. The recurrent admissions of the patients to the ED were included, and only the first troponin values of the patients were taken as s reference for the study.

Results:
It was determined that 1029 troponin values of 591 patients with initial troponin I value in the range 0.06-0.1 ng/mL were measured. It was found that 332 of these patients were discharged from the emergency department, and the others were hospitalized. It was found that 168 (28.43%) of the patients died. Considering the gender distribution of the patients who died, it was observed that 101 (60.11%) patients were male, and 67 (39.89%) patients were female. A statistically significant difference was found between the ages of the patients who died (mean 71.38±12.25) and the age of patients alive (mean 61.78 ± 15.89) ($p < 0.019$). In univariate analysis, in addition to the positive troponin value, DM ($p<0.022$) and hyperlipidemia ($p<0.018$) were found to be statistically significant.

Conclusion:
For high-sensitive troponin worked in the ED, the upper value of 0.06 ng/mL effectively determines mortality.

Key Words:
Ultra-Sensitive Troponin-I, Mortality, Acute coronary syndrome

ÖZ

Amaç:
Bu çalışmada, günlük pratikte kullanılan ultra-duyarlı troponin kitlerinin referans değerinin mortaliteyi belirlemedeki rolü araştırıldı.

Gereç ve Yöntemler:
Bu çalışma 1 Ocak 2018-30 Haziran 2019 tarihleri arasında Akdeniz Üniversitesi Hastanesi acil servisinde (AS) yapılmıştır. On sekiz ay içinde acil servise başvuran ve ultrasensitif troponin sonucu 0,06-0,1 ng/mL aralığında olan tüm hastalar çalışmaya dahil edildi. Hastaların acil servise tekrarlayan başvuruları dahil edildi ve hastaların sadece ilk troponin değerleri çalışma için referans olarak alındı.

Bulgular:
Başlangıç troponin I değeri 0,06-0,1 ng/mL aralığında olan 591 hastanın 1029 troponin değerinin ölçüldüğü belirlendi. Bu hastalardan 332'sinin acil servisten taburcu edildiği, diğerlerinin ise hastaneye kaldırıldığı öğrenildi. Hastaların 168'inin (%28,43) öldüğü belirlendi. Ölen hastaların cinsiyet dağılımına bakıldığında 101 (%60,11) hastanın erkek, 67 (%39,89) hastanın kadın olduğu görüldü. Ölen hastaların yaşları (ortalama 71,38±12,25) ile yaşayan hastaların yaşları (ortalama 61,78±15,89) arasında istatistiksel olarak anlamlı fark bulundu (p<0,019). Tek değişkenli analizde pozitif troponin değerine ek olarak DM (p<0,022) ve hiperlipidemi (p<0,018) istatistiksel olarak anlamlı bulundu.

Sonuç:
Acil serviste çalışılan yüksek duyarlı troponin için 0,06 ng/mL'lik üst değer etkin bir şekilde mortaliteyi belirler.

Anahtar Sözcükler:
Ultra-Sensitive Troponin-I, Mortalite, Akut koroner sendrom

INTRODUCTION
Despite the recent increase in published research on the diagnosis and treatment of acute chest pain in the emergency department (ED), evaluation of these patients in the ED is compeller. Chest pain is the main complaint in 3-6% of all patients admitted to the ED. The patients with the acute coronary syndrome (ACS), including acute myocardial infarction (AMI) and other high-risk conditions, should be timely and effectively recognized by the emergency physician to initiate specific clinical actions (1,2). In the ED, the risk level of the individual patient is determined by demographic characteristics, history, physical examination, ECG, and the laboratory markers for myocardial necrosis. However, despite all these efforts, 2-8% of the patients are discharged from the ED without a different definitive diagnosis for their chest pain (3).

Globally preferred biomarkers for myocardial damage are cTNs (I or T) with almost absolute myocardial tissue specificity as well as high sensitivity. This means that the microscopic areas of myocardial necrosis can be detected by new assays (4). These measurement kits can measure the troponin levels as low as 1/10 of the old troponin kits. However, while high sensitivity kits have increased sensitivity, their specificity is low, and these assays cause more ACS diagnoses, thus causing more invasive procedures with longer hospitalization periods without any effect on 6-month survival (5,6).

Studies conducted in EDs on high sensitivity troponin tests are generally conducted with cTnT, with fewer studies on cTnI. Lower and upper limits set as normal limits in troponin kits, which have been used as golden standard tests to determine myocardial damage in the world for a long time, are determined against the 99% reference range studied in the normal population. With the introduction of the newer generation hsTn-I kits into daily practice, in the management of patients presenting to the ED with symptoms suggestive of the ACS, there is serious confusion due to the difference between the reference ranges of the hsTn-I kits and the standard kits used in the past. The accepted normal range for older generation standard measuring kits falls in the high troponin level range for hsTn-I kits, and this causes patients discharged from the emergency department to be accepted as acute myocardial infarction (AMI) in the past, assuming that there was no myocardial necrosis. Many patients in this range bring the risk of keeping emergency department and cardiology services busy, patient care beyond the capacity, extra intervention on patients, unnecessary medical expenses, and a large loss of workforce with it. However, high diagnostic sensitivity prevents mortality in more patients.

In this study, the role of the reference value of ultra-sensitive troponin kits used in daily practice in determining mortality was investigated. On the other hand, by examining additional risk factors in patients with troponin values above the reference value and died, properties that may increase specificity in determining mortality with troponin were investigated.

MATERIAL and METHODS
Study Design
This retrospective study was conducted in the ED of Akdeniz University Hospital between January 1 2018 and June 30 2019. The study was approved, and the requirement for informed consent was waived by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (Decision number:773 Date:28th August 2019). The present study was conducted in line with the Declaration of Helsinki.

Sample Selection
All patients admitted to the emergency department within a period of eighteen months and who had the result of the ultra-sensitive troponin level in the range of 0.06-0.1 ng/mL were included in the study. The recurrent admissions of the patients to the ED were included, and only the first troponin values of the patients were taken as a reference for the study. The role of ultra-sensitive troponin kits used in daily practice in the range of 0.06-0.1 ng/mL in determining mortality was investigated.

Data Collection
The records of comorbidities, smoking status (diabetes mellitus, hypertension, hyperlipidemia, history of coronary artery disease) and ultra-sensitive were collected. Troponin I values was obtained from the Hospital Information Management System (MiaMed®) records. Patients who died and their dates of death were identified in the Ministry of Health, Turkey Public Health Institution, Death Reporting System.

High-Sensitive Troponin Kit

High-sensitive cTnI (Siemens, ADVIA Centaur® TnI-Ultra® Assay) kit was used, and the values between 6 ng/L and 50.000 ng/L can be measured in blood. The reference value was 0.06 ng/mL.

Dependent Variable

According to the cardiac risk scoring system, a decision was made for discharge and hospitalization. Mortality within a month was determined through the hospital information management system and the national death reporting system. How the hospital admissions of dying and not dying patients result in terms of discharge and hospitalization were determined.

The patients were classified in terms of their comorbid factors (diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, smoking, presence of the tumor, elevated serum creatinine).

Statistical Analysis

The data collected for the study were recorded in SPSS® (IBM Statistical Package for the Social Sciences) and MedCalc® programs. For statistical analysis, Chi-Square and Mann-Whitney U tests were used. Logistic regression analysis was performed for the association between comorbidities and deaths.

RESULTS

A total of 154.589 patients were presented to the ED during the study period, and it was found that troponin analysis was conducted in 16.927 of these patients with suspicion of ACS. It was determined that 1029 troponin values of 591 patients with initial troponin I value in the range of 0.06-0.1 ng/mL were measured.

Three hundred sixty eight of the 591 patients were male (62.26%). The average age was determined as 64.51±15.55. It was found that 332 of these patients were discharged from the emergency department, and the others were hospitalized. It was found that 168 (28.43%) of the patients died. Considering the gender distribution of the patients who died, it was observed that 101 (60.11%) patients were male, and 67 (39.89%) patients were female. It was understood that 51 (30.35%) of the patients who died were discharged from the ED (Table I).

Table I: Demographic and hospitalization data of patients.

Number of Patients Died	101 (60.11%)	67 (39.89%)	51 (30.35%)	117 (69.65%)	168
Number of Patients Alive	267 (63.12%)	156 (36.88%)	281 (66.40%)	142 (33.60%)	423
Total Number of Patients	368	223	332	259	591

Two hundred twenty-eight of the patients had DM, 379 had HT, 101 had HPL (according to the raised LDL level), and 340 had a history of late CAD. Smoking and family history parameters of all patients were not included in the analysis because they could not be reached (Table II).

Table II: Presence of CAD risk factors in patients.

Number of Patients Died	77 (33.77%)	108 (28.49%)	19 (18.81%)	99 (29.12%)
Number of Patients Alive	151 (66.23%)	271 (71.51%)	82 (81.19%)	241 (70.88%)
Total	**228**	**379**	**101**	**340**

Abbreviations: **DM**: Diabetes Mellitus; **HT**: Hypertension; **HPL**: Hyperlipidemia; **CAD**: Coronary Artery Disease

A statistically significant difference was found between the ages of the patients who died (mean 71.38±12.25) and the ages of patients alive (mean 61.78 ± 15.89) (p <0.019).

In univariate analysis, in addition to the positive troponin value, DM (p<0.022) and hyperlipidemia (p<0.018) were found to be statistically significant.

According to the multivariate (regression) analysis, the history of DM, HT, and HPL was found to be statistically significant in terms of determining death (Table III).

Table III: Logistic regression analysis.

DM	,016
HT	,026
HPL	,030
Late CAD	,643
Gender	,479
Age	,000
Constant	,000

Abbreviations: **DM**: Diabetes Mellitus; **HT**: Hypertension; **HPL**: Hyperlipidemia; **CAD**: Coronary Artery Disease

DISCUSSION

According to the results of our study, it was found that mortality was high (28.43%) in patients with high-sensitive troponin I levels (in the range of 0.06-0.1 ng/mL) compared to the current values. On the other hand, even if the troponin is slightly increased, it was determined that patients exceeding the reference value are at high risk for major cardiac events.

Several studies on the value of high-sensitivity troponin levels were conducted in previous years. Kavasoğlu et al., in their study, tested the effectiveness of the 14 pg/ml threshold value of high-sensitive troponin T in determining mortality. They found the sensitivity of the present value of troponin T to be 87% and the selectivity to be 69%. Their study found that the sensitivity of high-sensitivity troponin increased at low values and its selectivity increased at high values (7). Our study determined that the next generation high-sensitive troponin level is highly effective in predicting mortality at values above the reference value. It was determined that 168 of the total 591 troponin-positive patients died. Still, similarly, as the reference value increases, the selectivity of the test increases. From this point forth, it can be said that the high-sensitive troponin reference value is effective in determining mortality. On the other hand, our patient group in the study started from the lowest reference value of 0.06 ng/mL. In this case, it may be difficult to interpret in terms of determining the death of patients at values below the current reference value. In other saying, a study to determine a new lower threshold value may be helpful in terms of the value of the current threshold in determining the measurement. Indeed, in their article, Lippi, and Sanchez-Comar investigated the high-sensitivity troponins and stated that new threshold value studies would be useful in this regard (8).

The value of high-sensitivity cardiac troponin measurement in determining myocardial infarction has been recently investigated (9). Accordingly, it is stated that the diagnostic algorithms used safely in Europe can safely diagnose AMI, and these diagnostic algorithms can be applied in the USA. One of the algorithms used in this study is the Siemens ADVIA Centaur® TnI-Ultra® kit that we used in our study. According to the results of our study, it can be interpreted that the aforementioned high-sensitivity kit can be used safely in the diagnosis of AMI.

The value of cardiac troponins in predicting major adverse events, including death, is known (10). The relationship between high troponin levels and death has also been confirmed in our study. The use of risk scoring in terms of ACS evaluation in the ED is a class 1 recommendation (11). Accordingly, a positive cardiac troponin level is used in HEART and TIMI scores used for these patients (12). In the HEART scoring system, 1 point is given for an increase of 1-3 times the normal level of troponin, and 2 points are given for an increase of 3 times and above. According to our study, it was found that mortality increases significantly even with troponin levels increasing up to 70% of normal. Although the Heart score study determined risk factors with a very high number of patients and related regression analyses, it should be noted that troponin levels can currently be considered as an independent risk factor. High troponin value is an exclusively effective parameter in determining mortality. It may be useful to be more weighted when using risk scores. Besides, if a lower threshold value is determined, more patients can be identified in the ED. New studies to be conducted on this subject can be enlightening.

One of the most important factors in our study is the association between DM and cardiac adverse events. Hyperglycemia and insulin resistance seen in diabetes and prediabetes causes an increase in oxygen radicals that trigger intracellular molecular signaling. The increase in the resulting prothrombotic process and inflammatory mediators also accelerates atherosclerotic changes and the development of macrovascular complications. It has been shown that prediabetic states characterized by impaired fasting glycemia (IFG) or impaired glucose tolerance (IGT) are directly related to cardiac morbidity and mortality (13). In our study, DM was determined as an exclusively important risk factor in the occurrence of cardiac adverse events. DM is not the only parameter among the parameters used for ACS risk scoring in EDs (14). However, according to the results of our study, DM was identified as a parameter that can be used to determine death. Although risk evaluation of diabetes in patients with normal troponin levels has not been performed, it can be said that mortality will be high in patients with low troponin positivity who are considered to have diabetes and ACS. New risk assessment studies to be conducted can be a guide in this regard.

According to the results of our study, HPL is also seen as an independent risk factor. Although the retrospective nature of our research allows these patients to have their HPL evaluated, this information is not always available in the ED. Even so, HPL, if present, can be taken into account when performing risk evaluation. The absence of previously requested lipid panels in patients with suspected ACS may be requested from the ED.

Limitations

Due to the retrospective nature of the study, there may be question marks regarding data reliability. On the other hand, the fact that the hospitalization and discharge procedures of the patients in our hospital are conducted according to the current guidelines (AHA and ESC), also, the major parameter of the study, the measurement of which is done through the Death Reporting System (DRS) minimizes the importance of this problem. The cause of death was determined from the Ministry of Health, Turkey Public Health Institution, Death Reporting System (DRS). In this system, the exact cause of death of the patients may not be understood. On the other hand, although there is a possibility that patients might die from another cause, the death rate of 28.43% is a very high rate. While determining the number of patients who died, a certain time limitation for death was not taken into account. The duration of death in these patients is unclear. This situation does not meet the criteria for serious cardiac events and death generally accepted in the literature. On the other hand, there is a high mortality rate even when time is not taken into account. It should also be noted that the troponin value for these patients is sent with the prediagnosis of ACS. This study only provides information about the first high-sensitive troponin value studied at the time of admission. Consequently, it does not provide enough information about other troponin values that were studied repeatedly. Besides, since the troponin values of the patients at the time of applica-

tion were included in the study, it does not provide any information about the time of symptom onset. Troponin values in the range of 0.06 - 0.10 ng/mL were included in the study, and it would be possible to reach different results in a study to be conducted on all positive values. Studies to be conducted on this subject are needed. Besides, it is also thought that different practices varying from physician to physician and different preferences in sending troponin may affect the results.

CONCLUSION

For high-sensitive troponin measured in the ED, the upper value of 0.06 ng/mL is effective in determining mortality. However, studies to be conducted to lower the upper threshold value may be suitable for the reduction of false-negative patients. On the other hand, DM was determined as a parameter that can be used alone in determining mortality, and this may be a guide in the risk evaluation of patients.

Ethics Committee Approval:
The study was approved, and the requirement for informed consent was waived by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (Decision number:773 Date:28th August 2019). The present study was conducted in line with the Declaration of Helsinki.

Informed Consent:
Informed consent was not obtained as it was a retrospective clinical study.

Author Contributions:
Concept – C.E.A., M.K.; Design - CEA., M.K.; Supervision - C.E.A., M.K., M.D., E.G.; Resources - C.E.A., M.K., M.D., E.G; Materials C.E.A., M.K., M.D., E.G; Data Collection and/or Processing C.E.A., M.K., M.D., E.G; Analysis and/ or Interpretation - C.E.A., M.K., M.D., E.G; Literature Search - C.E.A., M.K., M.D., E.G; Writing Manuscript - C.E.A., M.K., M.D., E.G; Critical Review - C.E.A., M.K., M.D., E.G.

Conflict of Interest:
The authors have no conflict of interest to declare.

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