Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2019;44(2):486-493
DOI: 10.17826/cumj.431825

ARAŞTIRMA / RESEARCH

Assessment of a point-of-care assay for cardiac biomarkers of patients suspected of acute myocardial infarction

Akut miyokard enfarktüsü şüphesi olan hastalarda kardiyak biyobelirteç ölçümünde kullanılan hasta başı test cihazlarının değerlendirilmesi

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Cukurova Medical Journal 2019;44(2):486-493

Abstract

Purpose: Hospitals and outpatient clinics are now using point-of-care testing (POCT) devices that contract for the use of diagnostic analyses at the site of patient care delivery, so, facilitating earlier decision-making besides proper treatment. In our study, the aim was to assess the quantitative Nano-Ditech (Cranbury, NJ, USA), CK-MB, cTnIandmyoglobin POC assays and to compare them with the Getein 1100 (Nanjing, China) CK-MB, cTnI and myoglobin POC assays.

Materials and Methods: Lithium heparin plasma samples (Terumo Europe N.V. Leuven, Belgium,) for Getein 1100 and Nano-Ditech cardiac marker samples were randomly collected from among routine samples from 100 patients (53 male and 47 female) with chest pain complaint who admitted to BilecikGolpazarı Government Hospital between August-September 2017 and all analyses were performed using the Nano-Ditechanalyzer and comparative analyses were performedby the Getein 1100) assays.

Results: In our study, the correlation between the two devices was found to be r = 0.023 and p=0.017 for troponin, r = 0.130 and p=<0.001 for CK-MB and there is no correlation for myoglobin.

Conclusion: According to evaluation of both devices' analytical performances, it was found that the comparison of the all values of troponin, CK-MB and myoglobin, which are important for the diagnosis and exclusion of acute myocardial infarction(AMI), is discordant with the method comparison protocol proposed by the Clinical and Laboratory Standards Institute (CLSI) (EP-9).

Key words: Acute myocardial infarction; point-of-care testing, cardiac markers

Öz

Amaç: Hastaneler ve poliklinikler artık hasta bakımı sunumunda tanısal analizlerin kullanılmasına izin veren hasta başı test (POCT) cihazları kullanmaktadırlar. Çalışmamızda kantitatif Nano-Ditech (Cranbury, NJ, USA) CK-MB, cTnI ve miyoglobin POC testlerinin değerlendirilmesi ve Getein 1100 (Nanjing, Çin) CK-MB, cTnI ve miyoglobin POC testlerinin analitik performans karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Bilecik Gölpazarı İlçe Devlet Hastanesi'ne göğüs ağrısı şikayeti ile Ağustos-Eylül 2017 tarihleri arasında başvuran 100 hastadan (53 erkekve 47 kadın), Getein 1100 ve Nano-Ditech kardiyak cihazları için lityum heparinli plazma örnekleri (Terumo Europe NV Leuven, Belçika) rastgele olarak alındı.

Bulgular: Bizim çalışmamızda, iki cihaz arasındaki korelasyon, troponin için r = 0.023 ve p = 0.017, CK-MB için r = 0.130 ve p = 0.001 olarak bulunmuştur ve miyoglobin için iki cihaz arasında herhangi bir korelasyon bulunmamıştır.

Sonuç: İki cihazın analitik performansı değerlendirildiğinde, Akut Miyokard Enfarktüsü'nün teşhisi, tanı ve dışlanması için önemli olan troponin, CK-MB ve miyoglobinin mutlak değerlerinin karşılaştırılmasının Klinik ve Laboratuvar Standartları Enstitüsü (CLSI)'nin önerdiği yöntem karşılaştırma protokolü ile uyumsuz olduğunu bulduk (EP-9).

Anahtar kelimeler: Akut miyokard enfarktüsü, hasta başı test ,kardiyak belirteçler.

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Geliş tarihi/Received: 07.06.2018 Kabul tarihi/Accepted: 27.10.2018 Çevrimiçi yayın/Published online: 24.02.2019

INTRODUCTION

Clinical guidelines published by the laboratory[1], emergency medicine[2] and cardiology[3] have demonstratedthe importantrole of cardiac markers, especiallycardiac troponin, in the diagnosis and ruleout of acute myocardial infarction (AMI).By means ofconcluded in a consensuspaperof the European Society of Cardiology (ESC) and the American College of Cardiology (ACC), the standards for the diagnosis of acute myocardial infarction (AMI) have been lately redefined[4,5]. At least two of the three nextfeatures must be met to appropriately diagnose an AMI: (a) characteristic symptoms; (b) specific rise-and-fall form of a cardiac panel sign (myoglobin, creatine kinase-MB isoenzyme [CK-MB], cardiac troponin I [cTnI]); (c) a typical electrocardiogram pattern concerning the change of Q waves. If the characteristicsigns are observed, electrocardiographic testing is extremely specific for AMI. But, even in these cases, initial studies demonstrate only about 50% sensitivity for AMI[6]. These restrictionsregularly result in the common of patients acknowledged to the hospital undergoing biochemical testing for cardiacmarkers to check or rule out AMI. So, cardiacmarker testing has become very essential in the evaluation of patients for the diagnosis and screening of AMI and heart failure, for example, the prognosis of cardiovascular diseases (CVD)[7,8].

Cardiac markers are regularly used not only in central laboratories but also in emergency departments and outpatient clinics to provide fast diagnostic reports. Myoglobin is an early indicator in the diagnosis of AMI that can be detected 1–2 hours after indication onset and remains high for up to 24 hours. However, myoglobin has important limitations, including low specificity for AMI[9], and therefore it is frequently used in combination with CK-MBor cTnI. CK-MB is an 86 kDa cytosolic enzyme that is mainlysituated in the myocardium and is released into the circulation in the setting of AMI. Typically, CK-MB becomes raised up in the circulation 3–6 hours after symptom onset in AMI and remains elevated for 24–36 hours. The specificity of CK-MB for diagnosing AMI is restricted by the fact that it may be raised as a result of acute or chronic muscle damage or during the clearance of abnormalities in renal failure and hypothyroidism[10]. Even so, CK-MB is one of the cardiac biomarkers often used in the diagnosis of AMI. The N-terminal amino acid sequence of cTnI has specific residues that are not current in the two iso-types of cTnI in skeletalmuscle; so, antibodies against these specific residues are used for immunoassays in the assessment of AMI patients[11]. The concentration of cTnI in the blood becomes raised between 4 and 8 hours following an AMI, peaks between 12 and 16 hours, and leftoversraised for 5 and 9 days next damage to the myocardium[12]. The methodical specificity and the enlarged duration of the advancement make cTnI asignificantindicator in the diagnosis and assessment of patients suspected of having an AMI[13]. Combined measurements of myoglobin, CK-MB, and cTnI have been proposed to criticallysupportdoctors in the diagnosis and administration of AMI patients[14, 15].

Hospitals and outpatient clinics are now applying point-of-care testing (POCT) devices that let for the use of diagnostic analyses at the site of patient care delivery, so, facilitating quicker decision-making besidesfast treatment. The emergence of quantitative point-of-care (POC) assays offer an attractive alternative because of the potential for bedside analysis, obviating the need to deliver the sample to the lab, shorter assay times and the use of whole blood, thereby eliminating the time necessary for full clot retraction, and the centrifugation step[16,17]. The (POC) cardiac marker assays have a large dynamic range, which reduces the need for additional sample dilution. The manufacturer has not found any hook effect for cTnI, myoglobin, or CK-MB up to 2000 mg/ L, 20 000 mg/L and 4000 mg/L, respectively. Rapid testing for troponins has been demonstratedto be of notable prognostic value [18]. Many of the recent bedside tests pose limitations for cardiac marker determinations: qualitative rapid testing for cardiac markers remains subject to reading errors, with substantial inter-observer variability. Besides these advantages, we have to consider that the expense of these tests. In our study, the aim was to assess the quantitative Nano-Ditech cardiac marker assays and to compare them with the Getein 1100 cardiac marker assays. Nano-Ditech cardiac troponin I (cTnI), Nano-Ditech Myoglobin (Myo) and Nano-Ditech creatine kinase MB (CK-MB are in routine for patients admitted into our hospital with suspected acute myocardial infarction.

MATERIALS AND METHODS

Methods

All analyses were performed using the Nano-Ditech analyzer (Cranbury, NJ, USA), and comparative

analyses were undertaken with the Getein 1100(Nanjing, China) assays.

The Nano-Check AMI 3 IN Test is an immunochromatography assay for the quantitative determination of three biochemical markers (cTnI, CK-MB and Myoglobin) simultaneously in human whole blood, serum and plasma specimens at the cut off concentrations of 0.5ng/ml, 5.0ng/ml, and 80ng/ml respectively. The membrane strip encloses three test lines and one control line, printed with specific antibodies or receptor against each target molecules, monoclonal mouse antibody against CK-MB, monoclonal mouse antibody against Myoglobin, streptavidin for biotinylatedcTnI, and rabbit anti-goat antibody for control line. A dye pad is placed at the end of the membrane containing biotinylatedcTnI antibody and gold colloidal particles coupled with CK-MM, cTnI and Myoglobin antibodies. When a sample is applied, into the sample well, the cardiac makers present in the sample bind to the specific antibodies coupled with gold particles on the dried dye pad. cTnI in a sample binds to both cTnI specific dye coupled antibody and biotinylated antibody. These main immune complexes move along the nitrocellulose membrane through the test lines and bind to their corresponding capture antibodies or receptor molecules immobilized on the test line. Free immune complexes pass through the test line and are captured by goat anti-mouse antibody in the control line.

If the concentration of any of these three indicators in the sample is overhead the cut off level, red bands seem at the corresponding test lines and the control line. If the concentration of the markers in the sample is lower than the cut off level, only the colored control line can be seen in the test window. This colored control band need continuously appear at the control line position (Con) for valid test results. A test result is not valid if the colored control line does not seem in the test window.

The Getein1100 Immunofluorescence Quantitative Analyseris an ımmunofluorescence assay for the quantitative determination of three biochemical indicators (cTnI, CK-MB and Myoglobin) simultaneously in human whole blood, serum and plasma specimens in point-of-care and laboratory settings. The principle of test uses the fluorescent conjugated CK-MB /cTnI/Myo monoclonal antibodies to detect any CK-MB/cTnI/Myo appeared in blood samples. The fluorescence intensity of each test line increases proportionally to the amount of CK-MB/cTnI/Myo in a sample.

Then test card is inserted into Getein 1100.Getein1100. The concentration of CK-MB/cTnI/Myo in a sample will be determined and showed on the screen.

Collection of Biological Samples

Lithium heparin plasma samples (Terumo Europe N.V. Leuven, Belgium,) for Getein 1100 and Nano-Ditech cardiac marker determinations were randomly collectedfromamong routine samples from 100 patients (53 male and 47 female) with chest pain who Government Hospital between 22.08.2017and 03.09.2017 dates. The lithium heparin tubes were centrifuged at 2000 g for 10 min. The supernatant plasma analyzed immediately on both two devices and the results were recorded after the analysis. All participants were given an informed consent for this study after the approval of study by the local ethics committee.

Statistical analysis

The statistical analyses were performed with the SPSS 23.0 for Windows (SPSS Inc, USA) package program. Descriptive statistics; mean, standard deviation, minimum, maximum, median, categorical variables for numerical variables were given as numbers and percentages. CK-MB/cTnI/Myo values obtained from Getein 1100 and Nano-Ditech systems for statistical analysis were recorded as the mean ± standard deviation. Student t-test was used when the comparison of numerical variables was Gaussian distributioncondition in two independent groups, Mann Whitney U test was used when the Gaussiandistribution condition was not provided.Relationships between numerical variables were analyzed by Spearman Correlation Analysis.Differences in numerical variables in the dependent group (when comparing the results of two different devices of each patient) were analyzed by the Wilcoxon test since the Gaussian distributioncondition was not met. The statistical agreement between the results was obtained by the two-way random in-class correlation coefficient and the concordance correlation coefficient. The compatibility and bias status of the devices was examined by the Youden and Bland Altman graphs. The Statistical significance level of alpha was accepted as $p < 0.05$.

RESULTS

The results of the Nano-Check AMI 3 IN test are determined visually and interpreted commercially defined to the programmedcut off values of 0.5 ng/ml for cTnI, 5ng/ml for CK-MB and 80 ng/ml for Myoglobin. The cut off levels were determined by comparison to the immunofluorescence assay system of Getein 1100.There was no statistically significant difference in the mean values of troponin, CK-MB, Myoglobin in male and female gender ($p>0.05$) (Table 1).

Spearman's correlation coefficient, class correlation coefficient (two-way randomness), correlation coefficient and bias for Troponin, CK-MB and Myoglobin values measured with Nano-Ditech and Getein 1100 systems are presented in Table 2. Correlation, Bland-Altman and Youden plots are given in Figure 1.

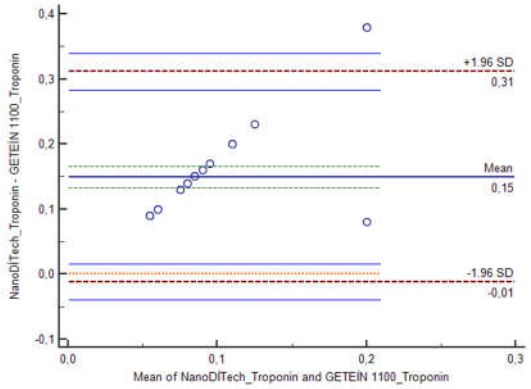
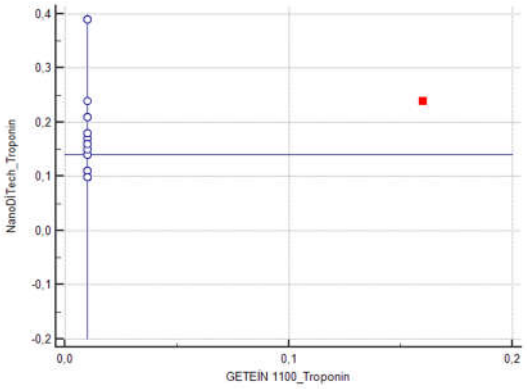
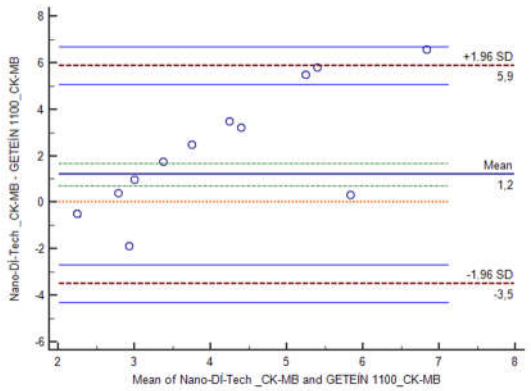


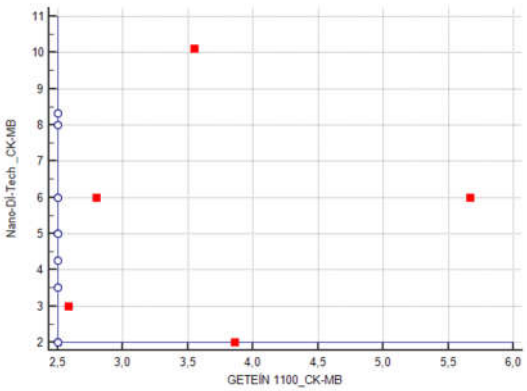
Figure 1.A) Bland-Altman Plot for Troponin



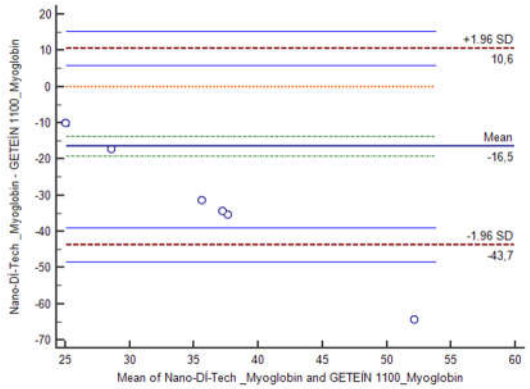
B)Youden Plot for Troponin



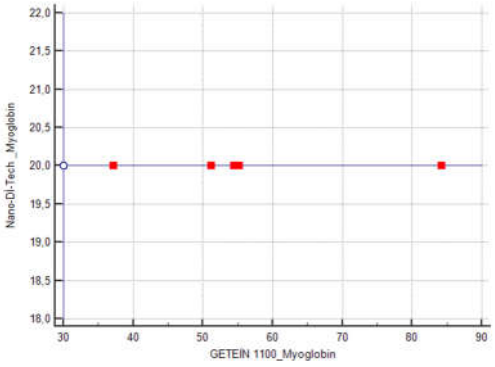
C) Bland-Altman Plot for CK-MB



D)Youden Plot for CK-MB



E)Bland-Altman Plot for Myoglobin



F)Youden Plot for Myoglobin

Table 1. Participiants by gender, troponin, myoglobin and CK-MB levels

	Total(n:100)		Male(n:53)		Female(n:47)		
	Mean±SD	Min-Max	Mean±SD	Median	Mean±SD	Median	p
Troponin(ng/ml)							
Nano-Dİ-Tech	0.16±0.08	0.10-0.39	0.15±0.05	0.15	0.18±0.11	0.14	0.490
GETEIN 1100	0.01±0.03	0.01-0.16	0,02±0.03	0.01	0.01±0.00	0.01	0.099
CK-MB(ng/ml)							
Nano-Dİ-Tech	3.99±2.50	2.00-10.11	4.08±2.81	2	3.90±2.12	3	0.650
GETEIN 1100	2.80±0.76	2.50-5.67	2.90±0.95	2,5	2,68±0,42	2.5	0.515
Myoglobin (ng/ml)							
Nano-Dİ-Tech	20.00±0.00	20.00-20.00	20,00±0.00	20	20.00±0.00	20	1,000
GETEİN 1100	36.53±13.86	30.00-84.20	39.79±17.41	30	32.86±6.70	30	0.094

(mean ± standard deviation (SD) and reference intervals are presented on the table.

Table 2. Comparison of Troponin, CK-MB and Myoglobin values in both devices.

	Troponin(ng/ml)	CK-MB(ng/ml)	Myoglobin(ng/ml)
	Nano-Ditech& GETEIN 1100	Nano-Ditech& GETEIN 1100	Nano-Ditech& GETEIN 1100
Wilcoxon Signed Ranks Test	z:-8.723p<0.001	z:-2.597p=0.009	z:-9.194 p<0.001
Spearman's	rho: 0.239p=0.017	rho:0.351p<0.001	-
Intraclass Correlation Coefficient	0.023 (%95 CI -0.037-0.101)	0.131 (%95 CI 0.040-0.302)	0.000 (%95 CI 0.073-0.092)
Concordance Correlation Coefficient	0.023 (%95 0.005 – 0.051)	0.130 (%95 CI 0.041-0.217)	-
Bias	0.145 (%95 CI 0.133-0.166	-0.197 (%95 CI 0.721-1.671)	-16.534 (%95 CI -19.284-13.784)
	Min:-0.012 Max:0.312	Min:-3.498 Max:5.891	Min:-43.701 Max:10.633

DISCUSSION

The testing of cardiac markers is important for the determination of AMIsince ECG testing only is not permanently available and has a low accuracy in determining AMI[19].A number of groups of acute coronary syndrome patients with variable clinical requests are goals for the implementation of point-of-care testing of markers of myocardial injury, including patients with acute MI (ST-segment

elevation and depression, Q-wave and non-Q-wave or non-ST-segment elevation) and patients with non-cardiac chest pain[20].

The National Academy of Clinical Biochemistry (NACB)[1] and the IFCC[21] issued commendations for the use of cardiac markers in coronary artery disease in 1999. According to these commendations, institutions that cannot constantly deliver cardiac marker target turnaround times on hour should implement point-of-care devices.Two cardiac markers shouldbeused for routine diagnosis of AMI: an initial marker (a reliable increase in blood within 6 h after the onset of symptoms, such as myoglobin) and an absolute indicator (an increase in blood after 6 – 9 h, with sensitivity and specificity for myocardial injury and long-term irregularity for numerous days after the onset of symptoms, such as cardiac troponin I or T and CK-MB mass). CK-MB mass can also be considered a re-infarction marker, which returns to the baseline concentration reasonably early.

The correlation between the two devices was found to be r = 0.023 and p=0.017for troponin, r = 0.130 and p<0.001 for CK-MB and there is no correlation for myoglobin. It is suggested that the correlation coefficient according to the CLSI's method compliance protocol (EP-9)[22] is not sufficient, alone, but should be higher than 0.97[23]. According to this study's results, the proposed correlation was not found. When these values are evaluated according to the confidence intervals, it was found that the two devices are incompatible for troponin, CK-MB and myoglobin measurements and there is animportantdifference among the two devices in terms of troponin, CK-MB and myoglobin values

When the compatibility between two devices is evaluated, the intra-class correlation coefficient (ICC) is taken as the basis. When evaluating, it was interpreted that in some publications, the coefficient of correlation intra-class was over 0.90 and the fit was very good[24] and that some of them are between 0.90-0.95 as moderate compliance[25].

In our study, the ICC values for troponin and CK-MB were found to be as 0.023 and 0.130, respectivelyand there is no correlation for myoglobin. In addition, it is clearly clarified that the troponin, CK-MB and myoglobin values are incompatible between the two devices.

Moreover, there were incompatible cTnI results in the comparative study between Nano-Ditech and Getein1100 such asin (Figures1A, 1C,1E). The differences in these consequences can be described by the use of different antibodies in the assays and probably by the fact that, depending on the situations (time after the onset of MI, size of the infarction zone and rate of perfusion) or by heterophilic antibodies. Commercial assays differ in their capacity to detect cTnI. The different distributions of cTnI forms in the early vs. late phase of myocardial infarction might explain the differences. Besides, occurring as free cTnI and binary complexes with TnI and TnT (IC or ICT), cTnI could occur in phosphorylated, oxidized andproteolyticallyruined forms[26]; similarly, comprehend a review in[27]. All these forms might have different recognition forms in different immunoassays.

In separate studies, P. Hedberg and his friends have found InnotracAio which is a Poct device, is particularly suitable for use in emergency rooms, coronary care units, satellite laboratories and central laboratories and have good correlation with automated immunoassay systems (The coefficients were ≥0.970 for all the cardiac markers) (17). Alan H.B. Wu et al. showed that the RAMP (Response Biomedical) CK-MB and cTnI POC assays and compared results against the Triage (Biosite) POC and the Dimension RxL (Dade Behring) meets most of the quality specifications established by the IFCC C-SMCD and good correlation with each other (correlation coefficient was >0.95)[28]. These studies showed a good correlation with automated immunoassay systems and POCT assays. We compared both two POCT assays and we couldn't find good correlation each device.

One more problem with the commercial assays is the lack of international standardization[29]. This reasonleads to wide variations in reported cTnI concentrations. False-positive AxSYM auto analyzer cTnI due to the presence of rheumatoidfactors has also been demonstrated [30]. In the Bland-Altman graphs, it is mentionedthat the values are farther away from the mean line for the troponin values after 0.1ng/ml, the CK-MB values after 4 ng/ml and myoglobin values after 40 ng/ml and the scatterings are<95% confidence interval (Figures 1A, 1C,1E).

As a limitation, it was determined whether there is an equimolar response for the antibodies used when tested against different forms (i.e., free, binary and ternary complexes) of cardiac troponin.v Another limitation was that this study was conducted due to the change of laboratory personnel from different shifts. The determined of the assay is to be used at

bedsideor satellite laboratory by caregivers. It is probable that the performance might be reduced when testing is done by the clinical staff, e.g., imprecision in the dilution step. And finally, lack of comparison with automated immunoassay systems was a limitation for this study.

As a conclusion we found that the comparison of absolute values of troponin, CK-MB and myoglobin an important for the diagnosis of AMI, between these two devices, was incompatible with CLS's method comparison protocol (EP-9). Thereforewe recommend that the method should be compared with other existing protocols and well-known devices without being bound to single protocols and devices.

Yazar Katkıları: Çalışma konsepti/Tasarımı: SÇ; Veri toplama: SÇ; Veri analizi ve yorumlama: SÇ; Yazı taslağı: SÇ; İçeriğin eleştirel incelenmesi: SÇ; Son onay ve sorumluluk: SÇ; Teknik ve malzeme desteği: SÇ; Süpervizyon: SÇ; Fon sağlama (mevcut ise): yok.
Bilgilendirilmiş Onam: Katılımcılardan yazılı onam alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

Author Contributions: Concept/Design : SÇ; Data acquisition: SÇ; Data analysis and interpretation: SÇ; Drafting manuscript: SÇ; Critical revision of manuscript: SÇ; Final approval and accountability: SÇ; Technical or material support: GÖ; Supervision: GÖ; Securing funding (if available): n/a.
Informed Consent: Written consent was obtained from the participants.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

REFERENCES

1. Wu AHB, Apple FS, Gibler WB, Jesse RL, Warshaw MM, Valdes J R. National Academy of Clinical Biochemistry Standards of Laboratory Practice: recommendations for use of cardiacmarkers in coronary artery diseases. ClinChem 1999;45:1104-21.
2. Fesmire FM, Decker WW, Howell JM, Kline JA. Clinical policy: critical issues in the evaluation and management of adult patients presenting with suspected acute myocardial infarction or unstable angina. Ann Emerg Med. 2000;35:521-44.
3. Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined—a consensus document of the joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. Eur Heart J. 2000;21:1502-13.
4. Epstein AE, Di Marco JP, Ellen bogen KA, Mark Esteset N.A, Roger A, Freedman al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: A report of the American College of Cardiology Foundation/American Heart Association Task Forceon Practice Guidelines and the Heart Rhythm Society. Circulation. 2013;127:e283–e352
5. European Heart Rhythm A, European Society of C, Heart Rhythm S, et al. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: Implant and follow-up recommendations and management. Heart Rhythm. 2012;9:1524-76.
6. Lefebvre CW, Hoekstra J. Approach to non-ST-segment elevation acute coronary syndrome in the emergency department: Risk stratification and treatment strategies. Hosp Pract. 2010;38:40-9.
7. Tiwari RP, Jain A, Khan Z, Kohli V, Bharmal R.N, Kartikeyan S et al. Cardiac troponins I and T: Molecular markers for early diagnosis, prognosis, and accurate triaging of patients with acute myocardial infarction. Mol Diagn Ther 2012;16:371-81.
8. Friess U, StarkM. Cardiac markers: A clear cause for point-of-care testing. Anal Bioanal Chem. 2009;393:1453–62.
9. de Winter RJ, Koster RW, Sturk A, Sanders GT. Value of myoglobin, troponin T, and CK-MBmass in ruling out an acute myocardial infarction in the emergency room. Circulation. 1995;92:3401-07.
10. Gruberg L, Sudarsky D, Kerner A, Hammerman H, KapeliovichM, Beyar R. Troponin-positive, CK-MB-negative acute myocardia linfarction: Clinical, electrocardiographic and angiographic characteristics. J Invasive Cardiol. 2008;20:125–8.
11. Yang Z, Yamazaki M, Shen QW, Swartz DR. Differences between cardiac and skeletal troponin interaction with the thin filament probed by troponin exchange in skeletal myofibrils. Biophys J. 2009;97:183–194.
12. Eggers KM, Venge P, Lindahl B, Lind L. Cardiac troponin I levels measured with a high-sensitive assay increase over time and are strong predictors of mortality in an elderly population. J Am Col Cardiol. 2013;61:1906–13.
13. Diercks DB, Peacock WF 4th, Hollander JE, Singer Adam J, Birkhahn R, Shapiro N et al. Diagnostic accuracy of a point-of-care troponin I assay for acute myocardial infarction within 3 hours after presentation in early presenters to theemergency department with chestpain. AmHeart J. 2012;163:74–80.
14. Chan D, Ng LL. Biomarkers in acute myocardial infarction. BMC Med. 2010;8:34.
15. Lackner KJ. Laboratory diagnostics of myocardial infarction-Troponins and beyond. Clin Chem. Lab Med. 2013;51:83–9.
16. Apple FS, Christenson RH, ValdesJr. R, Andriak AJ, Berg A, Duh SH et al. Simultaneous rapid measurement of whole blood myoglobin, creatine kinase MB, and cardiac troponin by the Triage Cardiac Panel for detection of myocardial infarction. ClinChem. 1999;45:199–205.

17. Apple FS, Anderson FP, Collinson P, Jesse RL, Kontos MC, Levitt MA et al. Clinicalevaluation of the First Medical whole blood point-of-caretesting device for detection of myocardial infarction. ClinChem. 2000;46:1604–9.
18. Hamm C, Goldmann B, Heeshen C, Kreymann G,Berger J, Meinertz T. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I.N Engl J Med. 1997;337:1648–53.
19. Bingisser R, Cairns C, Christ M, Hausfater P, Lindahl B, Mair J et al. Cardiac troponin: A critical review of the case for point-of-care testing in the ED. Am J Emerg Med. 2012;30:1639–49.
20. Hedberg P1, Valkama J, Puukka M. Analytical performance of time-resolvedfluorometry-based InnotracAio! cardiac marker immunoassays. Scand J Clin Lab Invest. 2003;63:55-64.
21. Panteghini M, Apple F, Christenson R, Dati F, Mair J, Wu A. Use of biochemical markers in acute coronary syndromes: IFCC Scientific Division, Committee on Standardization of Markers of Cardiac Damage. ClinChem Lab Med. 1999;37:687–93.
22. Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline. 2nd ed. Vol. 22 No. 19 CLSI document EP9-A2. Wayne, PA: Clinical and Laboratory Standards Institute. 2002.
23. Ellidağ H, Eren E, Aydın Ö, Arslan İnce F, Gök İ,Yılmaz N. Talasemi taramasında Agilent 1100 (Chromsystems) ve Tosoh HLC-723 G8 HPLC sistemlerinin karşılaşılaştırılması.Türk Biyokimya Dergisi. 2014;39:544-8.
24. Fleiss JL. The design and analysis of clinical experiments. New York, John Wiley and Sons. 1986.
25. Lawrence I, Lin K. A concordance correlation coefficient to evaluate reproducibility. Biometrics.1989;45:255-68.
26. Katrukha A, Bereznikova A, Filatov V, EsakovaT, Kolosova O, Pettersson K et al. Degradation of cardiac troponin I: implication for reliable immunodetection. Clin Chem. 1998;44:2433–40.
27. Hedberg P, Melkko T, Valkama J, Puukka M. Higher CK-MB mass value in heparin plasmathan in serum measured with the Abbott AxSYM system. Clin Chem Lab Med. 2001;39:872-4.
28. Wu AH, Smith A, Christenson RH, Murakami MM, Apple FS. Evaluation of a point-of-care assay for cardiac markers for patients suspected of acute myocardial infarction. Clin Chim Acta. 2004;346:211-9.
29. Wu A, Apple F, Gibler W, Jesse R, Warshaw M, Valdes R Jr. National Academy of Clinical Biochemistry Standards of Laboratory Practice: recommendations for use of cardiac markers in coronary artery diseases. ClinChem. 1999;45:1104 -21.
30. Dasgupta A, Banerjee SK, Datta P. False hyphen positive troponin. I in the MEIA due to the presence of rheumatoid factors in serum. Elimination of this interference by using a polyclonal antisera against rheumatoid factors. Am J Clin Pathol. 1999;112:753–6.