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Research Article

STUDY ON CONVENTIONAL AND NOVEL CARDIAC BIOMARKERS IN ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Objective: Employment of the serum cardiac markers rather than noninvasive or invasive procedures in the right time for accurate diagnosis of acute myocardial infarction (AMI) is a more important to restore the patient, but using all of them is inappropriate and expensive. Therefore, this study is designed to determine promising marker for the diagnosis of AMI.

Methods: A total of 33 healthy volunteers and 42 AMI patients were enrolled, and the serial blood samples were obtained from the AMI patients at admission, 6th, 12th, 24th, and 48th hr from the time of onset. The diagnostic efficiency was determined for creatine kinase (CK), CK MB (CK-MB), N-terminal fragment of B-type natriuretic peptide (NTproBNP), high sensitive cardiac troponin I (hscTnI), ischemia modified albumin (IMA), heart-type fatty acid binding protein (H-FABP), and myoglobin using receiving operating characteristic (ROC) curves and compared for time periods.

Results: Lipid profile, fasting blood sugar (FBS), creatinine, alanine transaminase (ALT), and aspartate transaminase (AST) were significantly higher in AMI when compared to control. In the early stages of AMI, the ROC of H-FABP (0.89; 95% confidence interval [CI], 0.72-0.82), IMA (0.83; 95% CI, 0.74-0.90), hscTnI (0.81; 95% CI, 0.75-0.92), NTproBNP (0.82; 95% CI, 0.72-0.89) and myoglobin (0.86; 95% CI, 0.76-0.93), and displayed good diagnostic efficacy ($p<0.0001$).

Conclusion: Within 2-6 hrs from onset of the symptoms, H-FABP, IMA and Myoglobin showed good diagnostic ability and in the entire episode, hscTnI holds its superiority in the diagnosis of AMI.

Keywords: Acute myocardial infarction, Serum cardiac markers, Serial sampling, Diagnostic ability.

INTRODUCTION

In the health arena, the incidence of coronary artery diseases (CAD) is rampantly increasing and it is the leading cause of morbidity and mortality which has become global burden to the mankind as on today. Myocardial infarction (MI) is one of the five main manifestations of coronary heart disease, namely stable angina pectoris, unstable angina pectoris, MI, heart failure, and sudden death [1]. ECG is widely used in the clinical care setting of primary diagnosis of acute MI (AMI), which is highly specific and effective in localizing the region of ischemia. However, it is less accurate at predicting the coronary artery involved and detects only around 50% of life-threatening AMIs in patients admitted with chest pain. Misdiagnosis has been reported to be the main cause of treatment delays and, on the other hand, undetected infarctions remain a serious public health issue. The biochemical cardiac markers are more helpful in the diagnosis rather than these and other high end and expensive techniques [2]. Early diagnosis of cardiac malfunctioning is a very important to reverse the heart failure problem or to prevent the condition to clinically worsen further [3]. Existing studies shown that, the best diagnostic result will be obtained by analyzing serum sample, when it is obtained 6-9 hrs after the onset of chest pain and if the onset is unknown, the sampling at admission, at 6-9 hrs and at 12-24 hrs is recommended for the prompt diagnosis [4]. Currently, several serum cardiac markers are available for the diagnosis of AMI. However, diversified reports were expressed by authors regarding the diagnostic efficacy of these conventional and emerging markers in the field of CAD. Thus, in the current study, it is to measure the role of these biomarkers alone and in combination for the right approach to the diagnosis based on time frame of MI and identifying the ideal marker.

METHODS

Study population

The current study was approved by Institutional Ethical Committee of Maharajah's Institute of Medical Sciences (MIMS) and informed consent was obtained from the attendants of all subjects. Along with 33 control subjects, 54 AMI subjects were enrolled and finally 42 cases with an age group ranging from 31 to 70 years were included in the study from persons of either sex after meeting the diagnostic criteria of MI. The first sample was collected immediately soon after the admission to ICU of MIMS (preferably within 2-3 hrs from the onset of symptoms), and the subsequent samples were collected serially at 6th, 12th, 24th and 48th hr from the time of onset of chest pain.

Exclusion criteria

The patients with renal failure, renal transplantation, pregnancy, arrhythmias, aortic dissection, acute heart failure, cardiac contusion, chemotherapy, myocarditis, diabetes mellitus, sepsis, severe neurological disorders, pericarditis, extreme exertion, old AMI cases, nonatherosclerotic MI, left ventricular hypertrophy, muscular dystrophy and infectious diseases such as HIV, Hepatitis were excluded from our study as these conditions lead to changes in levels of some of the cardiac biomarkers in the serum. After preliminary screening for HIV and HbsAg, all the samples of controls, and infarction groups were centrifuged and preserved with necessary precautions at −70°C until assayed. Estimation of basic parameters like fasting blood sugar (FBS) FBS, urea, creatinine, lipid profile, liver function tests (LFT) and cardiac parameters such as IMA, CK-MB, CK, hscTnI, N-terminal fragment of B-type natriuretic peptide (NTproBNP), myoglobin, and heart-type

fatty acid binding protein (H-FABP) were carried out in the blood samples of the AMI subjects.

Assay for cardiac markers

The parameters analyzed were FBS by glucose oxidase-peroxidase method, normal range: 70-110 mg/dL) [5], blood urea (urease method, normal range: 15-45 mg/dL) [6], serum creatinine (Jaffe's method, normal range: 0.8-1.4 mg/dL) [7], LFT (total bilirubin - diazo method, normal range: 0.4-1.2 mg/dL [8], serum glutamate oxaloacetate transaminase - International Federation of Clinical Chemistry (IFCC) kinetic method, normal range: Up to 46 IU/L [9], serum glutamate pyruvate transaminase - IFCC kinetic method, normal range; up to 49 IU/L [10], alkaline phosphatase - IFCC method, normal range: 42-141 U/L [11], were assayed routinely in consideration of exclusion and inclusion criteria. Serum lipid profile (total cholesterol - CHOD-PAP method, normal range: 140-230 mg/dL [12], TAG - GPO-trinder method, normal range: 25-160 mg/dL [13], HDL - phosphotungstic acid method, normal range: 30-65 mg/dL (the values of low density lipoprotein [LDL] 60-160 mg/dL and very LDL [VLDL] =TAG/5 were calculated as per Friedewald formula) [14]. Standard controls and samples were assayed on Transasia Erba fully automated analyzer. Total CK activity was quantified by use of automated analyzer assay based on N-acetyl cysteine active with a normal limit of 24-170 IU/L [15]. The CK-MB was measured by immune inhibition kinetic method of Erba kit with a reference range <25 IU/L [16]. Serum myoglobin was determined by the accubind enzyme immunoassay method with normal limit ≤96 ng/mL and serum hscTnI with an upper limit of ≤1.3 ng/ml were assayed using Acculite CLIA microwells supplied by Monobind Inc (Lake Forest, CA, USA) [17]. Serum H-FABP was measured by double antibody sandwich ELISA using the kit of SunRed H-FABP ELISA kit (Shanghai) with minimum detection limit was 0.05ng/ml, serum NTproBNP was measured by double antibody sandwich ELISA using the kit of SunRed NTproBNP assay (Shanghai) with an assay range of 2-360 pg/ml. IMA was analyzed by a colorimetric method based on albumin cobalt binding assay and standardization was carried out [18].

Statistical analysis

SPSS version 17.0 (SPSS Inc., Chicago, Illinois, USA) software was used; independent sample t-test was employed for the comparison of markers between normal and infarction groups. A value of p≤0.001 was considered as significant. To evaluate the ability of marker levels in infarction patients, receiver operator characteristic curves (ROC) for each marker was obtained. Exact 95% confidence intervals (CI) for binomial proportions were calculated to determine the diagnostic ability of the markers.

RESULTS

A total of 54 cases of AMI were enrolled and finally 42 cases were considered for the study as 12 cases were excluded because of unspecified index diagnosis, improper documentation and expiration of few cases. In AMI cases, FBS (92.97±6.61, 97.95±9.91mg/dL, p=0.0153), creatinine (1.11±0.16, 1.033±0.15 mg/dL, p=0.037), and lipid profile showed the significant statistical difference when compared to control yet they were all within normal range. The serum total cholesterol (178.76±32.01, 256.57±35.61 mg/dL, p<0.0001), TAG (147.88±44.61, 180.33±39.06 mg/dL, p=0.01), HDL (42.48±4.39, 39.48±4.93 mg/dL, p=0.011), LDL (115.24±35.34, 141.57±31.46 mg/dL, p=0.001), and VLDL (29.76±8.37, 35.57±8.02 mg/dL, p=0.003) demonstrated significant difference as compared to control group. We also found that in AMI patients, serum aspartate transaminase (AST) and alanine transaminase (ALT) (p<0.0001) were elevated steeply, and there is no much raise of ALP (p=0.027) and TB (p=0.157). In comparison with control, the cardiac markers in AMI cases registered the significant difference in the early stages from the onset of the symptoms (Table 1). IMA (64.06 ±11.66, 95.67±16.14 U/ml), NTproBNP (56.11±35.51, 186.27±35.26 pg/ml), CK (121.21±29.90, 140.21 ±35.59 U/L) CK-MB (18.36±4.32, 42.73±18.42 U/L) hscTnI (0.49±0.27, 3.35±1.50 ng/ml), myoglobin (81.64± 13.53, 113.55±28.68 ng/ml), (p<0.001). In progression with time, i.e. at 6th hr, in comparison with control, the markers in AMI cases demonstrated the more significant difference (Table 2). IMA (64.06±11.66, 98.93±17.30), NTproBNP (56.11±35.51, 263.32±58.60), CK (121.21±29.90, 204.21±61.50) CK-MB (18.36±4.32, 54.57±21.92) hscTnI (0.49±0.27, 3.44±2.46), myoglobin (81.64±13.53, 168.01±43.36), (p<0.001). The median time period of drawing the first sample from the onset of symptom was 2.5 hrs.

AUC was calculated using ROC analysis to establish the diagnostic efficacy. A serial sampling of patients was made from admission period to 48th hrs but in the current article, the sampling data at admission period and 6th hr duration were given to emphasize the initial stages of AMI is very crucial to rescue the patient. The area under the curves (AUC) is shown in Figs. 1 and 2.

During admission period (within 2-3 hrs from the onset of symptoms), H-FABP shown AUC (0.89; 95% CI, 0.72-0.82), IMA (0.83; 95% CI, 0.74-0.90), hscTnI (0.81; 95% CI, 0.75-0.92) NTproBNP (0.82; 95% CI, 0.72-0.89), myoglobin (0.86; 95% CI, 0.76-0.93). NTproBNP, myoglobin, hscTnI, H-FABP and IMA were significantly higher in the early stages and the trend continued up to 6 hrs (p<0.0001). During 6th hr, NTproBNP (0.93; 95% CI, 0.90-0.96), CK-MB (0.92; 95% CI, 0.89-0.96) and hscTnI (0.94; 95% CI, 0.92-0.96) showed significant AUC and continue to increase for a prolonged period with high window period (p<0.0001).

DISCUSSION

Our study registered the significant increase of FBS, creatinine, lipid profile (except HDL) and LFT (except bilirubin) in AMI cases when compared to those of control group. FBS rise significantly yet they were present within the reference range indicates that stress hyperglycemia is a common feature and may be a marker for severe MI. This is due to

Table 1: Comparison of serum cardiac markers of AMI cases at admission (within 2-3 hrs of onset of symptoms) with normal group

Marker	Mean±SD		p value
	Control (n=33)	Cases (n=42)	
IMA	64.06±11.66	95.67±16.14	0.001
NTproBNP	56.11±35.51	186.27±35.26	0.016
CK	121.21 ±29.90	140.21±35.59	0.001
CK-MB	18.36±4.32	42.73±18.42	0.001
hscTnI	0.49±0.27	3.35±1.50	0.001
Myoglobin	81.64±13.53	113.55±28.68	0.001
H-FABP	2.73±1.06	10.85±5.31	0.001

p<0.001 is significant, IMA: Ischemia modified albumin, CK: Creatine kinase, CK-MB: Creatine kinase MB, NTproBNP: N terminal pro brain natriuretic peptide, hscTnI: High sensitive cardiac troponin I, SD: standard deviation, n: Number of cases, AMI: Acute myocardial infarction

Table 2: Comparison of serum cardiac markers of AMI cases at 6th hr from the onset of symptoms with normal group

Marker	Mean±SD		p value
	Control (n=33)	Cases (n=42)	
IMA	64.06±11.66	98.93±17.30	0.001
NTproBNP	56.11±35.51	263.32±58.60	0.001
CK	121.21±29.90	204.21±61.50	0.001
CK-MB	18.36±4.32	54.57±21.92	0.001
hscTnI	0.49±0.27	3.44±2.46	0.001
Myoglobin	81.64±13.53	168.01±43.36	0.001
H-FABP	2.73±1.06	23.53±11.40	0.001

p<0.001 is significant, IMA: Ischemia modified albumin, CK: Creatine Kinase, CK-MB: Creatine kinase MB, NTproBNP: N terminal pro brain natriuretic peptide, hscTnI: high sensitive cardiac troponin I. SD: Standard deviation, n: Number of cases

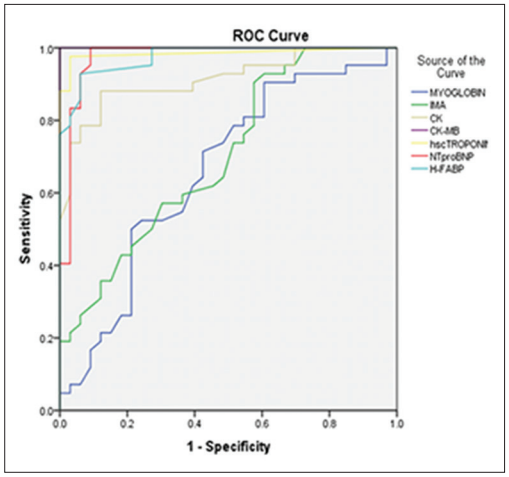

Fig. 1: Receiver operating characteristic curves (ROC) of markers at admission period in acute myocardial infarction cases, shown are ROC at 95% CI, for parameters within 2-3 hrs from the onset of symptoms (p<0.001). IMA- ischemia modified albumin (0.83), CK: Creatine kinase (0.77), CK-MB: Creatine kinase MB (0.74), NTproBNP: N terminal pro brain natriuretic peptide (0.82), high sensitive cardiac troponin I (0.81), myoglobin (0.86), heart type fatty acid binding protein (0.89), CI: confidence interval**

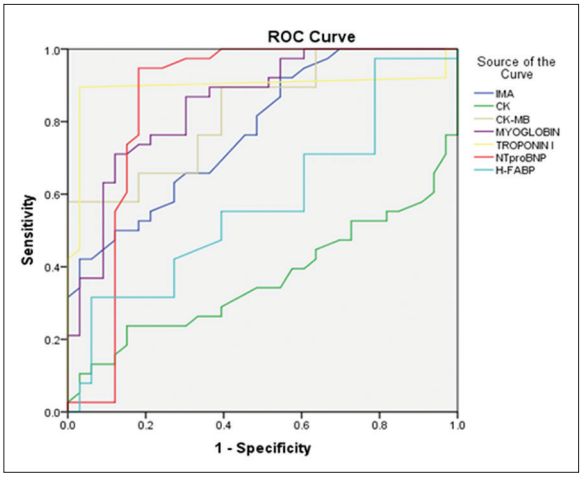

Fig. 2: Receiver operating characteristic curves (ROC) of markers in acute myocardial infarction cases at 6th hr from the onset of symptoms, shown are ROC at 95% CI, for parameters at 6th hr the onset of symptoms (p<0.001). IMA: ischemia modified albumin (0.84), CK: Creatine kinase (0.89), CK-MB: Creatine kinase MB (0.92), NTproBNP: N terminal pro brain natriuretic peptide (0.93), high sensitive cardiac troponin I (0.94), myoglobin (0.90), heart type fatty acid binding protein (0.90), CI: Confidence interval**

a compromised metabolic state which leads to rise of catecholamines and reduced insulin sensitivity [19]. Blood urea in AMI cases showing no significant difference against control group and increased creatinine levels may be found in worsening renal function associated with AMI and have no diagnostic role [20]. Dyslipidemia is one of the major risk factor for atherosclerosis and in the current study, total cholesterol, TAG, LDL and VLDL showed marked raise whereas slight low levels of HDL was observed. LDL is the main culprit, increases the risk of CAD and the oxidized LDL has got sticky nature and infiltrates into intimal region of arterial wall and taken up by macrophages to cause foam cell formation followed by atherosclerosis [21]. After post-AMI, the elevated levels of TAG in serum are due to increased cellular uptake of cholesterol for hormonal synthesis and tissue repair [22]. Our findings are similar to the study of Ferdous *et al.*, that total cholesterol, TAG and LDL cholesterol significantly increased [23]. Total bilirubin did not show any significant alteration from those of control and our study do not concur with the results of Okuhara *et al*. that elevated levels of total bilirubin seen in AMI because of activation of heme oxygenase [24]. The serum levels of AST, ALT showing significant elevation and ALP showing no statistically significant change in AMI cases in comparison to control. Studies reported AST and ALT elevations due to leakage from myocardium damage, and there is a positive correlation between elevated transaminases and atherosclerosis [25]. Lazzeri *et al.* found in their study, ALT and AST showed a significant rise in AMI cases with other cardiac parameters like NT-pro-BNP, cTnI in the overall population and in non-diabetic AMI patient [26].

In comparison with control, the cardiac parameters of AMI cases at different time periods (i.e. during admission, 6th hr, 12th hr, 24th hr, and at 48th hr) showed a significant difference in our study. This elevated level of cardiac biomarkers in AMI indicates the leakage from damaged tissue myocardium. Myocardial damage cause transient and permanent increases in wall tension and myocardial stretch followed by release of natriuretic peptides from ventricles of myocardium [27]. Studies report that elevated CK activity appears due to tissue necrosis within 6 hrs of onset of symptoms and shows maximum peak at 20-24 hrs, returns to normal after 3-4 days [28]. The elevation of CK-MB can be raised initially at 6 hrs after onset of infarction and reaches the peak levels at 32 hrs, whereas troponins have got wide window period from 4 hrs to 7 days and our study confirmed these findings [29]. Myoglobin released from damaged myocardium within 2-3 hrs and return to the normal value after 7 hrs and there are significant changes with IMA at different time periods after AMI [30]. H-FABP is elevated within 1-3 hrs after onset of infarction and peaks at 8 hrs and return to normal at 16-24 hrs with a sufficient diagnostic window period in the early stages [31] and our study corroborate with these findings.

The diagnostic accuracy of the markers was calculated by constructing the ROC. Our results found that the AUC for IMA demonstrates better diagnostic performance in the early stages. As per the study of Bhakthavatsala Reddy *et al.* and Pan *et al.* in the early stages of AMI the AUC for IMA at 0.96 (95% CI) and reported as a good marker for diagnosis, however the test is a poor discrimination between ischemic patients with and without MI [32,33]. The measurement of IMA yields diagnostic information on identifying patients with acute MI. H-FABP can be considered as promising marker within 6 hrs from the onset of symptoms, showing more AUC than any other markers in the early diagnosis of AMI. Studies demonstrated that the area under the ROC curve 0.729 (95% CI: 0.63-0.83) which is significantly better than cardiac troponin I and CK-MB in the early stages and during this period myoglobin is also elevated because of similar kinetics [34]. In our study, H-FABP demonstrated the AUC 0.89 and our results goes in accordance with the results of Elmadbouh *et al*., which was reported an increased AUC for H-FABP (0.945) than myoglobin (0.892) in patients admitted after 3-6 hrs after symptom onset. Our results corroborate with previous claims, that H-FABP showing highest area at admission period possessing superior diagnostic ability in the early stages [35]. Our results showed that the hscTnI showed excellent AUC with large window period in the entire episode of AMI. It was observed in our results, that NTproBNP can be considered as one of the potential diagnostic marker of AMI. Christenson and Christenson found that, NTproBNP use in combination with cTn increases the diagnostic capability and assists the clinicians in differentiating between MI, unstable angina, and non-cardiac causes of chest pain [36]. One study shown, in low-risk patients, combining cTn and NT-proBNP rule-out the disease and avoid the patient to undergo the current expensive standard health care procedures including stress test. Heeschen *et al.* demonstrated, NT-proBNP is independent from other serum biochemical markers in myocardial necrosis, inflammation and is a powerful and independent determinant of acute coronary syndrome [37]. The diagnostic accuracy

of myoglobin concentration as indicated by the AUC ROC increased significantly from 3 hrs to 5 hrs after onset of symptoms and can be considered as an early and efficient marker within 5 hrs from the onset of infarction and in agreement with the findings of other studies [31]. Earlier works showed CK-MB surpass Myoglobin for early detection of AMI (0.97 vs. 0.81; 95% CI for difference between areas 0.09-0.24) [38]. One previous study shown that there is equivalent performance in diagnosis of AMI, exerted by myoglobin (AUC=0.71), cTnI (AUC=0.71) and CK-MB (AUC=0.70) [39].

To summarize, according to the data which is evident in the tables in the current study, eventually, H-FABP is showing the best diagnostic efficiency in the early diagnosis of AMI followed by myoglobin and IMA. These three markers can be considered early markers but showing no much diagnostic significance after initial hours, i.e. up to 6 hrs, which were surpassed by other markers. Early detection is more crucial rather than later stages of AMI in saving the patient's life by accurate diagnosis by the clinicians. It is found that in entire episode of AMI hscTnI is considered as a promising marker in the diagnosis. NTproBNP and CK-MB follow closely at the heels of hscTnI in serving as a reliable marker.

CONCLUSION

H-FABP in the early stages of AMI and NTproBNP, hscTnI and CK-MB in the later stages of AMI showed potential diagnostic role. Laboratories where facility for H-FABP is not available can utilize the assessment of myoglobin and IMA for the early diagnosis of AMI. However, hscTnI is considered as a most reliable marker in the entire episode of AMI. In respect of multi-marker strategy, hscTnI, NTproBNP and CK-MB provides the more information than a single marker that will be useful for the risk stratification of AMI patients.

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REFERENCES

1. Mendis S, Thygesen K, Kuulasmaa K, Giampaoli S, Mähönen M, Ngu Blackett K, *et al.* World Health Organization definition of myocardial infarction: 2008-09 revision. Int J Epidemiol 2011;40(1):139-46.
2. Troughton RW, Richards AM. B-type natriuretic peptides and echocardiographic measures of cardiac structure and function. JACC Cardiovasc Imaging 2009;2(2):216-25.
3. Horwich TB, Hamilton MA, Fonarow GC. B-type natriuretic peptide levels in obese patients with advanced heart failure. J Am Coll Cardiol 2006;47(1):85-90.
4. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. Eur J Heart Fail 2004;6(3):257-60.
5. Trinder P. Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor. Ann Clin Biochem 1969;6:24-7.
6. Talke H, Schubert GE. Enzymatic urea determination in the blood and serum in the Warburg optical test. Klin Wochschr 1965;19(43):174.
7. Bowers LD. Kinetic serum creatinine Assays I. The role of various factors in determining specificity. Clin Chem 1980;26(5):551-4.
8. Pearlman FC, Lee RT. Detection and measurement of total bilirubin in serum, with use of surfactants as solubilizing agents. Clin Chem 1974;20(4):447-53.
9. Thefeld W, Hoffmeister H, Busch EW, Koller PU, Vollmar J. Reference values for the determination of GOT, GPT, and alkaline phosphatase in serum with optimal standard methods (author's transl). Dtsch Med Wochenschr 1974;99(8):343-4.
10. IFCC methods for the measurement of catalytic concentrations of enzymes. Part 3, IFCC. Method for alanine aminotransferase (l-alanine 2 - oxoglutarate aminotransferase, ec 2.6.1.2). Clin Chim Acta 1980;105(1):145F-72.
11. Szasz G, Rautenburg HW. Normal values of diagnostically important enzymes in the serum of children. Z Kinderheilkd 1971;111(3):233-9.
12. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem 1974;20(4):470-5.
13. McGowan MW, Artiss JD, Strandbergh DR, Zak B. A peroxidase-coupled method for the colorimetric determination of serum triglycerides. Clin Chem 1983;29(3):538-42.
14. Burstein M, Scholnick HR, Morfin R. Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions. J Lipid Res 1970;11(6):583-95.
15. Tietz N, editor. Fundamentals of Clinical Chemistry. Philadelphia, PA: W.B. Saunders Co.; 1976.
16. Bremmer FW. Cardiac disease and hypertension. In: Kalpan L, Pesce A, editors. Clinical Chemistry Theory, Analysis and Correlation. St. Louis, USA: C.V. Mosby Company; 1987.
17. Apple FS, Christenson RH, Valdes R Jr, Andriak AJ, Berg A, Duh SH, *et al.* Simultaneous rapid measurement of whole blood myoglobin, creatine kinase MB, and cardiac troponin I by the triage cardiac panel for detection of myocardial infarction. Clin Chem 1999;45(2):199-205.
18. Behera S, Mangaraj M, Mohapatro PC. Diagnostic efficacy of ischemia modified albumin and its correlation with lipid profile, oxidative stress in acute myocardial infarction patients on admission. Asian Pac J Trop Dis 2012;2(1):62-5.
19. Koracevic G, Petrovic S, Tomasevic M, Apostolovic S, Damjanovic M. Stress hyperglycemia in acute myocardial infarction. Facta J Univ Ser Med Biol 2006;13(3):152-7.
20. Jose P, Skali H, Anavekar N, Tomson C, Krumholz HM, Rouleau JL, *et al*. Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. J Am Soc Nephrol 2006;17:2886-91.
21. Varbo A, Benn M, Nordestgaard BG. Remnant cholesterol as a cause of ischemic heart disease: Evidence, definition, measurement, atherogenicity, high risk patients and present and future treatment. Pharm Ther 2014;141:358-67.
22. Gaziano JM, Hennekens CH, Satterfield S, Roy C, Sesso HD, Breslow JL, *et al.* Clinical utility of lipid and lipoprotein levels during hospitalization for acute myocardial infarction. Vasc Med 1999;4(4):227-31.
23. Ferdous BA, Sultana N, Ahmed S, Khan EH, Sultana S, Parvin T. Serum lipid profile in ischemic heart disease: A cross sectional analytical study. Bangladesh J Med Biochem 2014;7(1):14-6.
24. Okuhara K, Kisaka T, Ozono R, Kurisu S, Inoue I, Soga J, *et al.* Change in bilirubin level following acute myocardial infarction is an index for heme oxygenase activation. South Med J 2010;103(9):876-81.
25. Lofthus DM, Stevens SR, Armstrong PW, Granger CB, Mahaffey KW. Pattern of liver enzyme elevations in acute ST-elevation myocardial infarction. Coron Artery Dis 2012;23(1):22-30.
26. Lazzeri C, Valente S, Tarquini R, Chiostri M, Picariello C, Gensini GF. Prognostic values of admission transaminases in ST-elevation myocardial infarction submitted to primary angioplasty. Med Sci Monit 2010;16(12):CR567-74.
27. Lindahl B, Lindback J, Jemberg T, Johnston N, Stridsberg M, Venge P, *et al*. Serial analyses of N-terminal pro B type natriuretic peptide in patients with non-ST-segment elevation acute coronary syndromes: A fragmin and fast revascularisation during instability in coronary artery disease (FRISC)-II sub study. J Am Coll Cardiol 2005;45(4):533-41.
28. ALGani FA. Significance of total creatine kinase and creatine kinase-MB levels in patients with acute myocardial infarction. Int J Biol Med Res 2011;2(3):762-5.
29. Shah H, Haridas N. A serial follow up study of cardiac marker enzymes during the week after acute myocardial infarction. Indian J Clin Biochem 2007;22(1):33-6.
30. de Winter RJ, Lijmer JG, Koster RW, Hoek FJ, Sanders GT. Diagnostic accuracy of myoglobin concentration for the early diagnosis of acute myocardial infarction. Ann Emerg Med 2000;35(2):113-20.
31. Alhadi HA, Fox KA. Heart-type fatty acid-binding protein in the early diagnosis of acute myocardial infarction: The potential for influencing patient management. Sultan Qaboos Univ Med J 2010;10(1):41-9.
32. Bhakthavatsala Reddy C, Cyriac C, Desle HB. Role of "ischemia modified albumin" (IMA) in acute coronary syndromes. Indian Heart J 2014;66(6):656-62.
33. Pan SM, Tong CY, Lin Q, Yao CL, Zhao J, Deng Z. Ischemia-modified albumin measured with ultra-filtration assay in early diagnosis of acute coronary syndrome. World J Emerg Med 2010;1(1):37-40.
34. Garcia-Valdecasas S, Ruiz-Alvarez MJ, Garcia De Tena J, De Pablo R, Huerta I, Barrionuevo M, *et al.* Diagnostic and prognostic value of heart-type fatty acid-binding protein in the early hours of acute myocardial infarction. Acta Cardiol 2011;66(3):315-21.
35. Elmadbouh I, Mahfouz R, Bayomy N, Faried W, Ghanayem N. The

value of human heart-type fatty acid binding protein in diagnosis of patients with acute chest pain. Egypt Heart J 2012;64:179-84.

36. Christenson E, Christenson RH. The role of cardiac biomarkers in the diagnosis and management of patients presenting with suspected acute coronary syndrome. Ann Lab Med 2013;33(5):309-18.
37. Heeschen C, Hamm CW, Mitrovic V, Lantelme NH, White HD; Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Investigators. N-terminal pro-B-type natriuretic peptide levels for dynamic risk stratification of patients with acute coronary syndromes. Circulation 2004;110(20):3206-12.
38. Fesmire FM, Christenson RH, Fody EP, Feintuch TA. Delta creatine kinase-MB outperforms myoglobin at two hours during the emergency department identification and exclusion of troponin positive non-ST-segment elevation acute coronary syndromes. Ann Emerg Med 2004;44(1):12-9.
39. Tanasijevic MJ, Cannon CP, Antman EM, Wybenga DR, Fischer GA, Gruzien C, *et al*. Myoglobin, creatine-kinase-MB and cardiac troponin-I 60-minute ratios predict infarct-related artery patency after thrombolysis for acute myocardial infarction results from the thrombolysis in myocardial infarction study. J Am Coll Cardiol 1999;34(3):739-47.