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Serum transaminase determined in the emergency room predicts outcomes in patients with acute ST-segment elevation myocardial infarction who undergo primary percutaneous coronary intervention

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ABSTRACT

Background: Elevated serum aspartate and alanine aminotransferase (AST and ALT) are often observed in patients with acute ST-segment elevation myocardial infarction (STEMI) and the condition is ascribed to liver hypoperfusion. We evaluated the prevalence and prognostic implication of hypoxic liver injury (HLI) in STEMI.
Methods: Patients with STEMI and no preexisting liver disease who underwent primary percutaneous coronary intervention (PCI) were enrolled. A blood test was performed at the time of presentation and transthoracic echocardiography was performed after the index PCI. We reviewed medical records and contacted families of the patients by telephone to assess outcomes.
Results: Of 456 patients (age 60 ± 13 years, 370 males), 31 patients (7%) died during follow-up (duration: 754 ± 540 days). Those patients were older (72 ± 10 vs. 59 ± 13 years), had higher AST (179 ± 224 vs. 64 ± 103 U/L), ALT (56 ± 79 vs. 35 ± 33 U/L), blood urea nitrogen (25 ± 15 vs. 17 ± 7 mg/dL), uric acid (6.9 ± 2.9 vs. 5.8 ± 1.6 mg/dL), creatine kinase-myocardial band isoenzyme (76 ± 104 vs. 41 ± 79 ng/mL), troponin I (19.9 ± 23.0 vs. 10.8 ± 19.1 ng/mL), and lower albumin (4.0 ± 0.5 vs. 4.2 ± 0.4 g/dL) at the time of presentation ($p < 0.05$ for all). Particularly, AST independently predicted all-cause mortality (per 10 U/L increase, hazard ratio: 1.06, 95% confidence interval: 1.02–1.10, $p = 0.007$), whereas cardiac markers did not. HLI (>2-fold elevation of AST or ALT upper normal limits) showed close correlation with reduced left ventricular ejection fraction ($\beta = -0.12$, $p = 0.03$) and patients with the condition ($n = 100$ [20%]) had poorer survival than the others (Log-Rank, $p = 0.005$).
Conclusion: The presence of HLI predicts mortality in patients with STEMI who undergo successful primary PCIs.

1. Background

Despite recent advances in techniques and improved outcomes of percutaneous coronary intervention (PCI) [1,2], patients with acute ST-segment elevation myocardial infarction (STEMI) are still at increased risk for major adverse cardiovascular events (MACE), including mortality [3], even after a timely revascularization [4,5]. Therefore, early risk stratification at the time of presentation is of clinical importance.

Owing to the dual blood supply from the portal vein and the hepatic artery, the liver is relatively resistant to minor circulatory disturbances [6]. Nevertheless, the liver, which receives approximately one quarter of total cardiac output, is an organ of high vascularity and metabolic activity; thus, it is very sensitive to hemodynamic changes [7]. In fact, in patients with acute myocardial infarction, abnormal results on liver function test are often observed [8] on the very first blood test performed in the emergency room (ER), and if there is no other identifiable cause of liver damage, these results might be ascribed to hypoxic liver injury (HLI) due to circulatory failure. However, not much is known about the clinical meaning of HLI in STEMI patients. We hypothesized that HLI diagnosed in the ER can serve as an early prognostic marker for grave outcomes in patients with STEMI. To prove our hypothesis, we sought to evaluate the prevalence, prognostic implication, and potential mechanism of abnormal liver functional test in patients with STEMI who underwent primary PCI.

2. Method

2.1. Study population

This retrospective study was approved by the institutional ethics committee of the Gil Medical Center and complies with the Declaration of Helsinki (6th revision). We used a single center registry data of STEMI; patients who were diagnosed with STEMI in the ER of our institution, underwent primary PCI and attained complete revascularization between 2007 and 2013 were enrolled. Patients with prior history of coronary artery

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disease, cardiomyopathy, more than mild valvular heart disease, and congenital heart disease or pericardial disease were excluded. In addition, patients who had taken any potentially hepatotoxic medication, including herb, during the previous three months before presentation, who had known liver disease or who had positive results for serologic marker for hepatitis A, B or C were excluded from this study. All 496 consecutive STEMI patients were enrolled in this study. Of them, 34 patients were not met inclusion criteria and 6 patients were lost to follow-up. Consequently, 456 patients remained for statistical analysis (Fig. 1). The diagnosis of STEMI was made with typical symptoms, 12-lead electrocardiography, and blood test; after that, the decision regarding primary PCI was made by two attending cardiologists with consensus in the ER.

2.2. Blood test in the ER

All blood tests were obtained and recorded as part of the routine care for patients who visited the ER for chest pain and in whom acute coronary syndrome was suspected. In this study, HLI was defined as serum transaminase level >2 times of normal range (i.e. aspartate aminotransferase [AST] > 80 U/L or alanine aminotransferase [ALT] > 80 U/L) and hypoxic hepatitis as serum transaminase level >10 times of normal range (i.e. AST > 400 U/L or ALT > 400 U/L).

2.3. Primary PCI

Patients were pre-medicated with aspirin (at least 100 mg, orally) and unfractionated heparin (10,000 IU, intravenous injection). A loading dose of 300 mg of clopidogrel was administered orally before the index PCI. Intravenous glycoprotein IIb/IIIa receptor blocker was administered at the discretion of the operator. Coronary angiography was performed through the femoral or radial artery using standard techniques. Thrombectomy devices, intravascular ultrasound and an intra-aortic balloon pump were used at the operators' discretion. Direct implantation of a stent without previous balloon angioplasty was allowed if the culprit lesion was adequately visualized during the initial contrast injection or after guidewire placement. In cases of insufficient stent expansion, the stent was dilated after placement with another angioplasty balloon that was shorter than the total length of the stent. If more than one stent was implanted, the same type of stent was recommended. Intervention in non-infarct-related arteries during the initial procedure was discouraged. Heparin was administered throughout the procedure in order to maintain an activated clotting time of 250 s or longer. Final angiography was performed in order to obtain views similar to those obtained before the procedure. Procedural success was defined as no laboratory deaths, no emergency bypass surgery, and TIMI 3 flow in the distal part of the infarct-related artery with a residual stenosis of less than 30%.

2.4. Echocardiography

Standard 2-dimensional transthoracic echocardiography was performed within 12 h after the index primary PCI. Left ventricular (LV) end-diastolic dimension (LVEDD) was measured, and the LV ejection fraction (EF) was obtained using the modified Simpson's method. Left atrial (LA) volume was determined from two imaging planes using the biplane area-length method and was indexed to the body surface area (LAVI). From the apical window, a 1–2 mm pulsed Doppler sample volume was placed at the mitral valve tip and mitral flow velocities from 5 to 10 cardiac cycles were recorded. The mitral inflow velocities were traced and peak velocity of early diastolic filling (E) was determined. Early diastolic mitral annulus velocity (E′) was measured by Doppler tissue imaging at the septal corner of the mitral annulus. For estimation of LV filling pressures, the ratio of E/E′ was calculated. The analysis of echocardiographic data was performed by two experienced echocardiographers who were unaware of patients' clinical data.

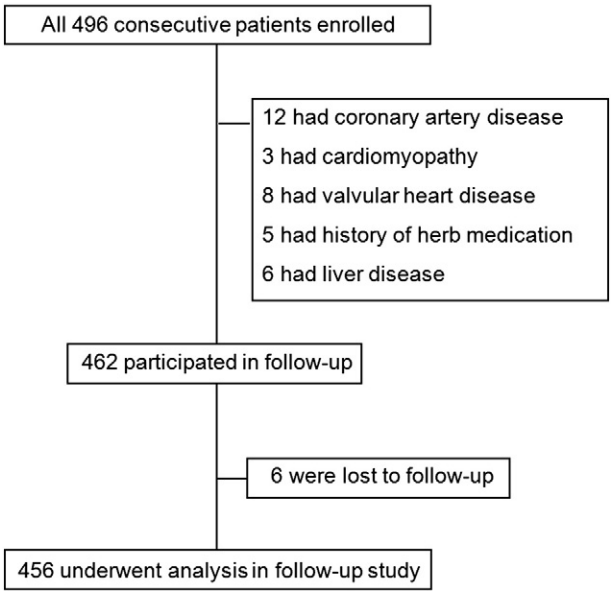

Fig. 1. Diagram for detailed enrollment of patients.

2.5. Follow-up

After the index PCI, all patients were monitored in the coronary care unit or the intensive care unit for at least 24 h. Standard medical management was provided by responsible physicians. After discharge, the clinical courses of the patients were monitored by cardiologists within one month and with three-month intervals after that. The primary outcome of the current research was all-cause mortality. Mortality (+) group included patients who died during follow-up and the others were allocated to Mortality (−) group. MACE was designated as the secondary outcome and defined as death by any cause, recurrent myocardial infarction, and occurrence of heart failure requiring unplanned hospitalization. To assess the outcomes, we reviewed all medical records and in cases of loss to follow-up, we contacted families of the patients by telephone.

2.6. Statistical analysis

Continuous data are expressed as a mean ± standard deviation and normality tests were performed in each variable for determination of whether a data set is well-modeled by a normal distribution or not. The baseline characteristics of the two groups were compared using the two-sample *t*-test for continuous variables, and chi-square test and Fisher's exact test for categorical variables. A paired *t*-test was used for comparison of repeated-measure values. Because the pro brain-type natriuretic peptide (proBNP) distribution was positively skewed, we used log-transformed proBNP values in statistical analysis. Cox multiple regression analysis was performed for quantification of the relationships between time to death and each potential risk factor, while simultaneously accounting for the effects of patients' other characteristics. Receiver operating characteristic curve was used to determine the accuracy of AST/ALT in predicting mortality and area under curve (AUC) was calculated. Additionally, binary logistic regression analysis was performed to evaluate the power of HLI in predicting in-hospital/1-month mortality. Multiple linear regression analysis was performed in order to test the association of LV EF and other parameters that were previously well known prognosticators in STEMI and/or statistically significant. Analysis of longitudinal data for the MACE was performed using Kaplan–Meier estimates with the log-rank test. A p-value of <0.05 was considered significant. Statistical analysis was performed using SPSS software (Chicago, IL, USA), version 11.

3. Results

3.1. Baseline characteristics and intergroup comparison

Overall monitoring period was 754 ± 540 days (median: 720 days, range: 0–2124 days). In Mortality (+) group, time to death was 199 ± 397 days (median: 12 days, range: 0–1439 days). In addition, 53 patients experienced MACE (time to MACE: 239 ± 402 days [median: 41 days, range: 0–1531 days]). Table 1 shows the baseline characteristics determined in the ER and intergroup comparison between Mortality (+) and Mortality (−) groups. Age of our cohort was 60 ± 13 years and study patients were predominantly male. Patients who died were significantly older and had lower systolic and diastolic blood pressure at the time of presentation, although the prevalence of hypertension was similar between the two groups. Regarding the laboratory findings, the Mortality (+) group showed significantly lower serum sodium and higher potassium levels. In terms of liver panel, patients who died showed significantly higher AST/ALT and lower albumin, whereas total bilirubin, alkaline phosphatase, and γ-glutamyltransferase were not different. The number of patients with HLI was 100 (22%). Fig. 2 shows changes in serum AST and ALT levels from baseline (values measured in ER) to follow-up (values measured 12 h after the primary PCI) in patients with HLI. Significantly elevated levels of both enzymes in such a short time period are suggestive of an acute hepatic injury process (i.e. HLI) rather than chronic liver disease. In particular, HLI was more prevalent in the Mortality (+) group than in the Mortality (−) group. The number of patients with hypoxic hepatitis was 14 (3%), and the prevalence was higher in the Mortality (+) group than in the Mortality (−) group. Patients in the Mortality (+) group had higher serum blood urea nitrogen, uric acid, and lactate dehydrogenase levels. In addition, creatine kinase-myocardial band isoenzyme (CK-MB) and troponin I were also higher in the Mortality (+) group than in the Mortality (−) group.