Original Article

CAD

Activin A Predicts Left Ventricular Remodeling and Mortality in Patients with ST-Elevation Myocardial Infarction

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Background: Activin A levels increase in a variety of heart diseases including ST-elevation myocardial infarction (STEMI). The aim of this study is to investigate whether the level of activin A can be beneficial in predicting left ventricular remodeling, heart failure, and death in patients with ST-elevation myocardial infarction (STEMI).
Methods: We enrolled 278 patients with STEMI who had their activin A levels measured on day 2 of hospitalization. Echocardiographic studies were performed at baseline and were repeated 6 months later. Thereafter, the clinical events of these patients were followed for a maximum of 3 years, including all-cause death and readmission for heart failure.
Results: During hospitalization, higher activin A level was associated with higher triglyceride level, lower left ventricular ejection fraction (LVEF), and lower left ventricular end diastolic ventricular volume index (LVEDVI) in multivariable linear regression model. During follow-up, patients with activin A levels > 129 pg/ml had significantly lower LVEF, and higher LVEDVI at 6 months. Kaplan-Meier survival curves showed that activin A level > 129 pg/ml was a predictor of all-cause death (p = 0.022), but not a predictor of heart failure (p = 0.767).
Conclusions: Activin A level > 129 pg/ml predicts worse left ventricular remodeling and all-cause death in STEMI.

Key Words: Activin A • Acute myocardial infarction • Left ventricular remodeling

INTRODUCTION

After a patient has undergone ST-elevation myocardial infarction (STEMI), a series of histopathological and structural changes occurs in the left ventricular (LV) myocardium and leads to LV remodeling.[1] LV remodeling is characterized by progressive LV dilatation and systolic dysfunction that lead to an increased risk of congestive heart failure and mortality.[2,3] Most of the interventions that limit or reverse LV remodeling after STEMI are later associated with improved clinical outcome.[4] Therefore, the predictors and mechanisms of LV remodeling after STEMI require further investigation. Additionally, biomarkers for LV remodeling appear to be useful in risk stratification and may be potential therapeutic targets in patients with STEMI.[5-8]

Activin A, a member of the transforming factor-β cytokine superfamily, has been recognized to be increased in several inflammatory diseases, such as inflammatory arthropathies,[9] septicemia,[10] and atherosclerotic lesion.[11] Activin A level is elevated in patients with heart failure, whereas inhibition of activin A improves cardiac function in mice with dilated cardiomyopathy.[12,13] Moreover, activin A level has been shown

to increase in patients with STEMI and may counteract the effects of inflammatory cytokines and protect myocardium from oxidative stress.[14,15] However, the effects of activin A on LV remodeling and clinical events in patients with STEMI have not been clearly elucidated.

The aim of this study is to investigate whether plasma Activin A will be of benefit in predicting the prognosis after STEMI, particularly for LV remodeling, heart failure, and all-cause death.

MATERIALS AND METHODS

Study population

The study population was enrolled at Taipei Tzu Chi Hospital in Taiwan between December 7, 2007, and April 21, 2013. With institutional ethics committee approval and written informed consent, we enrolled patients who presented to the emergency department with STEMI and received primary percutaneous coronary intervention (PCI) within 12 hours of symptom onset. Patients were excluded if there was a scheduled coronary bypass graft operation, previous myocardial infarction (MI), cardiac disease states other than ischemic heart disease, a history of active malignancy in the past 3 years, significant renal or hepatic dysfunction (baseline serum creatinine > 2.0 mg/dL; aspartate aminotransferase or alanine aminotransferase > 80 mg/dL before MI), chronic bedridden status, or concomitant inflammatory diseases such as infections or autoimmune disorders.

Laboratory analysis

Approximately 10 ml of blood from a peripheral vein was collected into a tube containing potassium ethylenediamine tetra-acetic acid (1 mg/ml) at post-MI day 2. The samples were centrifuged at 4 °C within 20 minutes. The plasma was separated and subsequently frozen at -80 °C until further analysis without undergoing any additional freeze-thaw cycles. Activin A levels were determined by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, St. Paul, MN, USA). The intra- and interassay coefficients of variation were 7.8% and 2.1%, respectively.

Echocardiographic analysis

Comprehensive 2D Doppler echocardiographic stu-dies were performed on the patients in the partial left lateral decubitus at baseline (mostly post-MI day 2), and were repeated 6 months later. The equipment used was a Philip SONOS 7500 (Agilent Technologies, Andover, MA, USA) system. All measurements were performed and repeated by the same experienced echocardiologist and all images were stored on magneto-optical discs for further analysis.[16,17] The LV end-diastolic volume index (LVEDVI) was measured from an M-mode recording according to the recommendations of the American Society of Echocardiography.[18] With the use of apical 4- and 2-chamber views, LV ejection fraction (LVEF) was estimated by the modified Simpson's method. The degree of ventricular dilatation was evaluated by the change in LVEDVI between baseline and 6-month follow-up. Significant LV dilatation was defined as a > 20 ml/m^2 increase in LVEDVI at 6 months, compared with baseline.[19] The analysis remained unlinked to Activin A levels until the study was completed.

Clinical endpoints

The clinical events, including all-cause death and readmission to hospital for heart failure, were recorded by reviewing electric medical record or contacting patients by telephone. Patients were followed for a maximum of 3 years.

Statistical analysis

The optimum cut-off value of activin A level for predicting mortality or heart failure was identified by receiver-operating characteristic (ROC) curve. Patients were divided into two groups based on the above cut-off value. Categorical variables were expressed as a number (percentage) and compared with chi-square test. All continuous variables were tested for normal distribution by using the Kolmogorov-Smirnov test. Depending on normality, continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) and compared using Student's t test or Mann-Whitney U test, respectively. Univariable linear regression was applied to identify the predictors of log-transformed activin A level and the predictors of increase in LVEDVI. Univariable logistic regression was applied to identify the predictors of significant increase (> 20 ml/m^2) in LVEDVI. Stepwise multivariable regression was then performed using variables

with p values < 0.10 in univariable model. The timing of clinical events was plotted according to the Kaplan-Meier method and compared using the log-rank test. We also used a stepwise multivariate Cox regression model (entry threshold, p < 0.05; removal threshold, p > 0.10) to assess whether log-transformed activin level was an independent predictor of clinical events. These statistics were computed using SPSS statistical software (SPSS Inc., Chicago, Illinois, USA). A value of p < 0.05 was considered significant.

RESULTS

During the study period, 43 patients were excluded arising from underlying disease. Another 31 patients were excluded for lack of informed consent (12 patients refused to participate; the other 19 patients were in cardiogenic shock and could not provide informed consent before the time of blood sampling). We finally enrolled 278 patients who were followed for a maximum of 3 years. The average period of follow-up was 865 days and the last patient had follow-up for a period of 365 days.

Activin A levels and patient characteristics

Activin A levels on day 2 of hospitalization ranged from 9.3 to 4668.7 pg/ml, with a median of 111.8 (IQR 60.9-312.7). An activin A level of 129 pg/ml was the best prognostic cut-off value for predicting death or heart failure (area under ROC curve: 0.699, sensitivity 80%, specificity 57%). Baseline clinical and demographic characteristics are listed in Table 1. Patients with high activin A levels tended to have anterior wall MI,

Table 1. Clinical and demographic characteristics

	Activin A < 129 (N = 153)	Activin A > 129 (N = 125)	p value
Age	59.8 ± 11.6	58.3 ± 12.1	.322
Male gender	135 (88.2%)	103 (82.4%)	.174
History			
Current smoker	87 (56.9%)	72 (57.6%)	1.000
Diabetes mellitus	36 (23.5%)	37 (29.6%)	.275
Hypertension	82 (53.6%)	78 (62.4%)	.146
Hypercholesterolemia	68 (44.4%)	59 (47.2%)	.717
Coronary heart disease	21 (13.7%)	11 (8.8%)	.257
Stroke	5 (3.3%)	12 (9.6%)	.042
Presentation			
Symptom-to-door time, min	87 (47-211)	103 (36-225)	.999
Door-to-balloon time, min	74 (60-104)	78 (63-117)	.259
Killip class > I	34 (22.2%)	32 (25.6%)	.571
Heart rate	75 ± 19	79 ± 19	.100
SBP, mmHg	133 ± 29	131 ± 27	.632
Multivessel disease	78 (51.0%)	67 (53.6%)	.718
Anterior MI	66 (43.1%)	74 (59.2%)	.008
Body mass index	25.3 (23.0-27.5)	25.9 (24.2-28.0)	.079
Peak CK, IU/L	2061 (1060-3409)	2478 (1323-4387)	.092
Hemoglobin, g/dL	14.9 (13.5-15.8)	15.5 (14.4-16.4)	.005
Creatinine, mg/dL	1.01 (0.87-1.21)	1.00 (0.90-1.20)	.594
Potassium, mmol/L	3.60 (3.30-3.90)	3.60 (3.40-3.90)	.889
LDL cholesterol, mg/dL	119 (97-152)	119 (104-139)	.737
Triglyceride, mg/dL	110 (62-162)	138 (90-209)	.001
NT-proBNP, pg/ml	592 (305-1234)	754 (286-1568)	.629
LVEF, %	51.3 ± 12.4	47.5 ± 10.6	.009
Mitral E/E' ratio	11.9 ± 3.8	12.4 ± 3.5	.477
LVMI, g/m^2	127.4 ± 34.0	121.1 ± 31.0	.112
LVEDVI, ml/m^2	70.1 ± 19.4	65.4 ± 19.0	.044
LVMV ratio, g/ml	1.87 ± 0.43	1.97 ± 0.52	.175

Values are expressed as the number of patients (%), mean ± SD, or median (25th-75th percentile).
CK, creatine kinase; LDL, low-density lipoprotein; LVEDVI, left ventricular end-diastolic volume index; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; LVMV ratio, left ventricular mass/volume ratio; MI, myocardial infarction; Mitral E/E' ratio, early transmitral flow velocity (E) to early diastolic mitral annular velocity (E') ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.

history of stroke, higher hemoglobin level, higher triglyceride level, and lower baseline LVEDVI. In multivariable linear regression analysis adjusted for significant variables in univariable regression model, higher log-transformed activin A level was independently associated with lower baseline LVEF [standardized coefficient (B) = -0.183, p = 0.005], lower baseline LVEDVI (B = -0.137, p = 0.033), and higher triglyceride level (B = 0.123, p = 0.042).

Echocardiographic analysis

Compared with the low activin A group, patients with high activin A levels had lower LVEF at baseline (47.5 ± 10.6% vs. 51.3 ± 12.4%, p = 0.009) and lower LVEF at 6 months (54.6 ± 13.9% vs. 58.9 ± 14.2%, p = 0.016) (Figure 1A). The absolute increase in LVEF was similar in both groups (7.3 ± 10.3% vs. 7.1 ± 12.2%, p = 0.873).

Compared with the low activin A group, patients with high activin A levels had lower LVEDVI at baseline (65.4 ± 19.0 vs. 70.1 ± 19.5, p = 0.044) and higher LVEDVI at 6 months (76.9 ± 26.9 vs. 68.5 ± 17.5, p = 0.005). The absolute change in LVEDVI at 6 months was greater in the high activin A group (11.2 ± 23.5 vs. 0.6 ± 16.4, p < 0.001) (Figure 1B).

In univariable linear regression model, log-transformed activin A level was a predictor of increase in LVEDVI (B = 0.267, p < 0.001). In multivariable linear regression analysis, the independent predictors of increase in LVEDVI at 6 months were log activin A (B = 0.199, p < 0.001), log peak creatine kinase (CK) (B = 0.222, p < 0.001), baseline LVEF (B = -0.220, p = 0.001), and baseline LVEDVI (B = -0.409, p < 0.001).

In the univariable logistic regression model, log-transformed activin-A level was a predictor of a significant increase (> 20 ml/m^2) in LVEDVI at 6 months (B = 3.129, p < 0.001). In multivariable logistic regression analysis, the independent predictors of a significant increase in LVEDVI were log activin A (B = 2.648, p = 0.008), log peak CK (B = 8.968, p < 0.001), and baseline LVEDVI (B = 0.973, p = 0.023) (Table 2).

Clinical endpoints

In patients with activin A levels > 129 pg/ml, 8 patients (6.4%) died and 7 patients (5.6%) were readmitted to the hospital for heart failure. In patients with

activin A values < 129 pg/ml, 2 patients (1.3%) died and 10 patients (6.5%) were readmitted for heart failure. Kaplan-Meier survival curves showed that activin A level > 129 pg/ml was a predictor of all-cause death (p = 0.022) but not a predictor of heart failure (p = 0.767) (Figure 2). The rate of cardiovascular death (5 patients vs. 2 patients, p = 0.151) and non-cardiovascular death (3 patients vs. 0 patients, p = 0.049) both tended to be higher in patients with activin A levels > 129 pg/ml.

In multivariable Cox regression analysis using significant variables in the univariable model, the independent predictors of all-cause death were diabetes mellitus [hazard ratio (HR) 7.68, 95% confidence interval (CI) 1.53-38.58, p = 0.013], symptom-to-door time (HR 1.004, 95% CI 1.001-1.007, p = 0.010), and log activin A (HR 3.56, 95% CI 0.995-12.73, p = 0.051). Log activin A remained an independent predictor (p < 0.10) in the final predictive model but was not statistically significant.
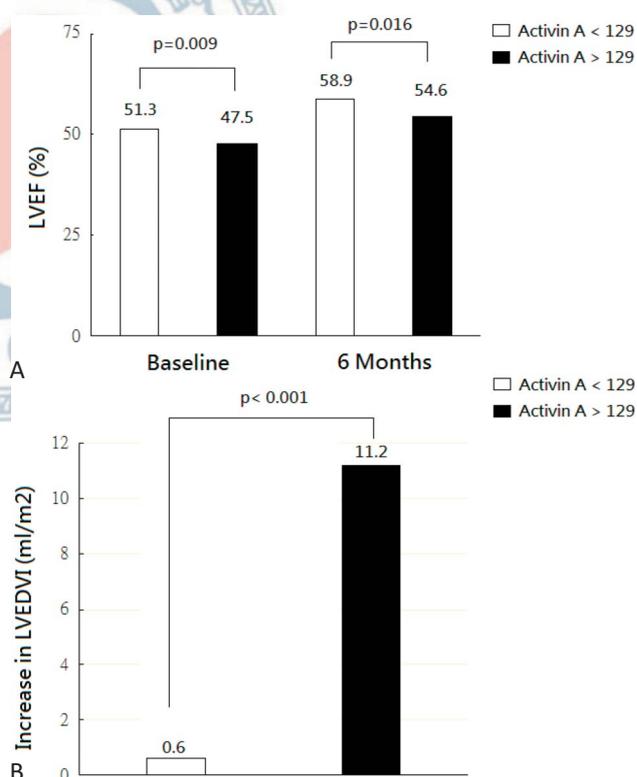

Figure 1. (A) Left ventricular ejection fraction (LVEF) at baseline and at 6 months. (B) Increase in left ventricular end-diastolic volume index (LVEDVI) from baseline to 6 months stratified according to plasma activin A level above or below 129 pg/ml.

Table 2. Predictors of a significant increase in LVEDVI (> 20 ml/m^2) in logistic regression analysis

	Univariable		Multivariable	
	Standardized coefficient	p value	Standardized coefficient	p value
Log activin A	3.129	< 0.001	2.648	0.008
Heart rate	1.018	0.035		
Log peak CK	11.458	< 0.001	8.968	< 0.001
Log NT-proBNP	2.270	0.020		
WBC	1.106	0.032		
Hemoglobin	1.268	0.021		
Diabetes mellitus	2.165	0.023		
Hypercholesterolemia	2.171	0.019		
LVEF at baseline	0.953	0.001		
LVEDVI at baseline	0.975	0.017	0.973	0.023
LVMI	0.988	0.039		
Killip class > I	2.037	0.041		

Activin A, CK, and NT-proBNP are analyzed as log transformed variables.
CK, creatine kinase; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; WBC, white blood cells.

DISCUSSION

Our investigation indicates that, during hospitalization for STEMI, elevated log-transformed activin A level is independently related to higher triglyceride level, reduced baseline LVEF, and lower baseline LVEDVI. Higher activin A level is associated with lower LVEF and higher LVEDVI at 6 months. Activin A level > 129 pg/ml is a predictor of all-cause death in 3 years.

To the best of our knowledge, there were only two previous studies evaluating the levels of activin A in patients with STEMI.[14,15] However, our study is the first study to evaluate the effects of activin A on the long-term outcomes of patients with STEMI. Other studies evaluated activin A levels in a variety of heart diseases, such as stable and unstable angina,[20] heart failure,[12] severe aortic stenosis,[21] and LV remodeling in uncomplicated diabetes mellitus (DM).[22] Although the clinical situations are somewhat different, we will compare our results with the findings of the above studies.

One main purpose of our study was to evaluate the process of LV remodeling after STEMI. All of the echocardiographic measurements during hospitalization and 6 months later were done by the same experienced echocardiologist.[16,17] Accordingly, the values of LVEF and LVEDVI were relatively reliable. LVEF had been proven to be a powerful independent predictor of clinical events after MI and can be used as an indicator of prognosis in clinical practice.[5] One previous study showed that activin A levels increased in STEMI and correlated with higher peak CK levels and lower LVEF.[14] These findings agree well with our results, which revealed that activin A levels were associated with higher peak CK levels and lower LVEF in univariable linear regression analysis. In a previous non-ischemic heart failure mice model, upregulated activin A inhibited cardioprotective growth hormone secretion from myeloid cells. Inhibition of activin A with anti-activin A antibody increased serum growth hormone levels and improved LV fractional shortening, a parameter similar to LVEF.[13] These findings indicate that activin A may have detrimental effects on the systolic function of left ventricle in non-ischemic heart failure. However, further investigation is necessary to evaluate whether activin A and its growth hormone suppression effect play a similar role in patients with STEMI.

Baseline LVEDVI and percentage change during follow-up were powerful predictors of cardiovascular mortality and adverse cardiovascular events in patients with heart failure or MI.[3,23] There is a paucity of information in previous studies on the associations between activin A levels and LVEDVI or relative parameters in patients with STEMI.[14,15] In our investigation, log-transformed activin A level is an independent predictor of increase in LVEDVI at 6 months in multivariable linear regression analysis and is also an independent predictor of a significant increase in LVEDVI (> 20 ml/m2) at 6 months in
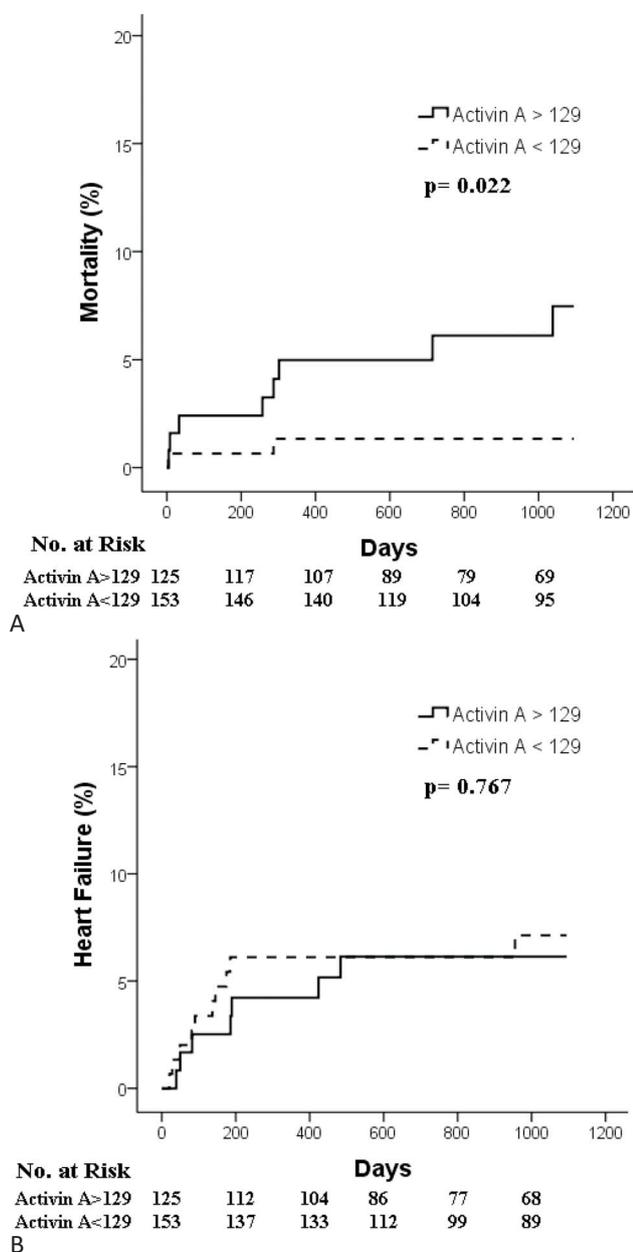
Figure 2. *Kaplan-Meier curves of the cumulative incidence of (A) all-cause death (B) readmission for heart failure stratified according to plasma activin A level above or below 129 pg/ml.*

multivariable logistic regression analysis. By comparison, in uncomplicated type 2 DM, activin A levels were positively associated with left ventricular mass/volume ratio,[22] an index of concentric hypertrophy.[24] In rat cardiomyocyte, activin A treatment significantly increased gene expression of mediators involved in myocardial remodeling (e.g. brain natriuretic peptide, matrix metalloproteinase-9, and tissue inhibitor of metalloproteinase-

1).[12,25] Elevated activin A may thus contribute to worse myocardial remodeling, increasing LVEDVI, and ultimately heart failure.

Although the abovementioned studies showed that activin A may play detrimental roles in myocardial remodeling,[12,13,22] other investigations revealed the cardioprotective effects of activin A. Recombinant activin A protein treatment protected cultured cardiomyocyte against hypoxia/reoxygenation-induced apoptosis and adenovirus-mediated overexpression of activin A protected hearts from ischemia/reperfusion injury in mice.[26] Activin A dose-dependently decreased the release of the inflammatory cytokines interleukin (IL)-6, IL-8, and macrophage inflammatory protein-1-alpha from mononuclear cells in angina patients and thus may have anti-inflammatory potential.[20] Activin A treatment attenuated the release of IL-8 and increased the mRNA levels of the antioxidant metallothionein in cultured endothelial cells.[15] Activin A had also been demonstrated to reduce cytokine-medicated increase in cardiomyocyte length, perimeter, and sarcomeric organization.[27] Taken together, activin A may be a double-edged sword for patients with STEMI. It may have cardioprotective effects and is induced to counteract the process of LV remodeling after STEMI. On the one hand, persistently elevated activin A may induce the secretion of other mediators, worsen LV remodeling, and increase LVEDVI.[12]

One interesting and unexplained finding is that patients with higher activin A levels have significantly lower LVEDVI at baseline. In one previous study, gene expression of activin A subunit (activin beta$_A$) was upregulated in mononuclear cells from a patient with stable angina but was unchanged in a patient with unstable angina.[20] Thus, the gene expression of activin A may be variable in different heart diseases. In our study, 15 patients have severe LV dilatation (LVEDVI > 97 ml/m^2) at baseline.[28] These 15 patients have significantly lower median activin A level compared with other patients (78.9 vs. 116.9 pg/ml, p = 0.031). Furthermore, 8 patients in the baseline LV dilatation group have a history of coronary artery disease, (53% vs. 9%, p < 0.001 compared with non-dilatation group). It is possible that the lower activin A levels after STEMI in patients with baseline LV dilatation is due to insufficient activin A gene expression caused by previous coronary artery disease or other unrecognized heart diseases.

In previous studies, elevated activin A levels were significantly related to death and higher cardiovascular events in type 2 DM,[29] higher cardiopulmonary death in patients with pulmonary hypertension,[30] and higher mortality during endotoxemia in mice.[31] In our study, activin A level > 129 pg/ml was also a predictor of all-cause death in patients with STEMI. The incidence of non-cardiovascular death was not a predefined end point, however, and was only borderline higher (p = 0.049) in patients with activin A level > 129 pg/ml. The exact role of high activin A level in non-cardiovascular death in patients with STEMI needs further studies.

The present study had some limitations. First, although we tried to include patients in Killip class IV in our study, the majority of patients with cardiogenic shock (19 of 27 patients) were excluded because it is difficult to get informed consent. This may partly explain why Killip class > 1 is not an independent predictor of death in our Cox regression analysis. Our survival data should be interpreted with caution and should not be applied to patients with severe cardiogenic shock. Second, this is a single-center study enrolling patients exclusively reperfused by PCI, which may limit the generalizability of our findings. Third, the study is neither designed nor powered for analysis of the effects of activin A on LV remodeling, and thus the findings should be regarded as hypothesis-generating only.

CONCLUSIONS

In conclusion, activin A level > 129 pg/ml predicts worse LV remodeling and all-cause death in patients with STEMI.

ACKNOWLEDGMENT

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