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CLINICAL RESEARCH — Coronary Artery Disease

Prognostic Stratification of Patients With Vasospastic Angina

A Comprehensive Clinical Risk Score Developed by the Japanese Coronary Spasm Association

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Objectives The present study aimed to develop a comprehensive clinical risk score for vasospastic angina (VSA) patients.

Background Previous studies demonstrated various prognostic factors of future adverse events in VSA patients. However, to apply these prognostic factors in clinical practice, the assessment of their accumulation in individual patients is important.

Methods The patient database of the multicenter registry study by the Japanese Coronary Spasm Association (JCSA) (n = 1,429; median 66 years; median follow-up 32 months) was utilized for score derivation.

Results Multivariable Cox proportional hazard model selected 7 predictors of major adverse cardiac events (MACE). The integer score was assigned to each predictors proportional to their respective adjusted hazard ratio; history of out-of-hospital cardiac arrest (4 points), smoking, angina at rest alone, organic coronary stenosis, multivessel spasm (2 points each), ST-segment elevation during angina, and beta-blocker use (1 point each). According to the total score in individual patients, 3 risk strata were defined; low (score 0 to 2, n = 598), intermediate (score 3 to 5, n = 639) and high (score 6 or more, n = 192). The incidences of MACE in the low-, intermediate-, and high-risk patients were 2.5%, 7.0%, and 13.0%, respectively ($p < 0.001$). The Cox model for MACE between the 3 risk strata also showed prognostic utility of the scoring system in various clinical subgroups. The average prediction rate of the scoring system in the internal training and validation sets were 86.6% and 86.5%, respectively.

Conclusions We developed a novel scoring system, the JCSA risk score, which may provide the comprehensive risk assessment and prognostic stratification for VSA patients. (J Am Coll Cardiol 2013;62:1144–53) © 2013 by the American College of Cardiology Foundation

Vasospastic angina (VSA) is one of the important functional cardiac disorders characterized by transient myocardial ischemia due to epicardial coronary artery spasm (1–3). The terms for VSA are basically synonymous with the terms *Prinzmetal's angina* and *variant angina*, and is known to be associated with a wide variety of cardiac conditions, including stable angina, acute coronary syndrome, and life-threatening arrhythmic events (4,5).

A number of studies have elucidated patient characteristics, outcomes, and prognostic factors of VSA (6–12), which led to a better understanding and management for this disorder. We have also recently reported the prognostic importance of the history of out-of-hospital cardiac arrest (OHCA) (13) and specific angiographic findings during diagnostic testing (14) in VSA patients from the multicenter registry study with more than 1,400 patients. However, because the patient characteristics and the number of prognostic factors present in individual patients may vary and the potential interaction between each prognostic factor may exist, it is difficult to accurately evaluate risk stratification of VSA patients in the current clinical practice. Thus, the comprehensive assessment tool

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that provides a valid risk prediction in individual patients needs to be developed. As one of the useful means to assess the comprehensive risk, simple scoring models, in which the prognostic factors identified by multivariable analysis are combined, have been developed for several disorders (15), although there is currently no tool available for VSA patients.

In the present study, we thus aimed to develop a comprehensive clinical risk scoring system that provides the prediction of future adverse cardiac events and the prognostic stratification for VSA patients in the nationwide multicenter registry study conducted by the Japanese Coronary Spasm Association (JCSA).

Abbreviations and Acronyms

AIC = Akaike Information Criterion
ECG = electrocardiography
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
IQR = interquartile range
JCSA = Japanese Coronary Spasm Association
MACE = major adverse cardiac event
OHCA = out-of-hospital cardiac arrest
SD = standard deviation
VSA = vasospastic angina

Methods

The JCSA was founded in 2006 and currently consists of 81 institutes in Japan. The present study was conducted as an investigator initiated observational clinical research. The study was approved by the institutional review boards or ethics committees of all participating institutes.

Study patients. The VSA patients diagnosed between April 1, 2003, and December 31, 2008 were enrolled. The registration was made between September 1, 2007, and December 31, 2008. The data collection was conducted in a retrospective fashion for patients seen before September 2007 and in a prospective manner for those seen after that date. The diagnosis of VSA was made based on the spasm provocation tests and/or spontaneous angina attack defined by the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina of the Japanese Circulation Society (16). The positive diagnosis of the provocation tests was defined as a total or subtotal (>90%) coronary artery narrowing induced by pharmacological (e.g., acetylcholine and ergonovine) or nonpharmacological (e.g., hyperventilation) challenge during coronary angiography, accompanied by chest pain and/or ischemic electrocardiography (ECG) changes. The definition of spontaneous attack was angina at rest and/or effort, accompanied by a transient ST-segment elevation or depression of more than 0.1 mV, or a new appearance of negative U-wave on ECG (16). The criterion of spontaneous attack was applied when the patients did not have significant organic coronary stenosis that can explain their angina attacks.

Data collection. The demographic and clinical data were submitted to a central database system, including age, sex, coronary risk factors, types of angina episodes, ST-segment changes and arrhythmias during spontaneous angina attack, angiographic findings of the spasm provocation tests, medications, and device therapy such as implantable cardioverter defibrillator (ICD). The clinical outcomes during the follow-up period were also collected. Follow-up data were obtained from each participating or cooperating hospital records and patients' regular visits to physicians in the outpatient clinic. The outcomes of the retrospective population were evaluated retrospectively. The prospective cohort was followed up until December 31, 2008.

Hypertension, dyslipidemia, and diabetes mellitus were diagnosed based on the guidelines of the Japanese Society of Hypertension, Japan Atherosclerosis Society, and Japan Diabetes Society, respectively (17–19). The OHCA was defined as the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation that occurred outside of the hospital setting (20). Organic coronary stenosis was assessed as either nonsignificant (25% to 50% luminal narrowing) or significant (more than 50% luminal narrowing) by coronary angiography.

Endpoints. The primary endpoint was defined as major adverse cardiac events (MACE), including cardiac death, nonfatal myocardial infarction, hospitalization due to unstable angina pectoris, heart failure, and the appropriate ICD shocks during the follow-up period that began at the date of the diagnosis of VSA. In particular, cardiac death, nonfatal myocardial infarction and ICD shocks were categorized as hard MACE. The secondary endpoint was all-cause mortality. The definition of these events was previously described (13).

Statistical analysis. Continuous variables are presented as medians and interquartile ranges (IQR) or means and standard deviations (SD) and categorical variables as numerals and percentages. Group comparisons were performed with the Kruskal-Wallis test for continuous variables, the chi-square test for categorical variables, and the log-rank test for survival curves. Survival free from MACE and death were analyzed by the Kaplan-Meier method. A value of $p < 0.05$ was considered to be statistically significant.

The clinical variables included in our JCSA risk score and respective scoring points were determined based on their prognostic contribution for VSA patients. Univariable and multivariable Cox proportional hazard model were applied to select the demographic and angiographic characteristics and treatments that correlated with MACE. The variables showing statistical significance or a trend ($p < 0.1$) in univariable Cox model were subjected to multivariable analysis with a forced-entry method. The Akaike Information Criterion (AIC) was used to select appropriate explanatory variables (21). Missing data were handled using a multiple imputation procedure with 20 resampling replications. The proportional hazards assumption for the Cox model was examined with the log minus log plot. Significant variables selected from multivariable Cox model were assigned integer score proportional to their adjusted hazard ratio (HR) for MACE. The variables with