Original article

Diagnostic accuracy of the Embolic Risk French Calculator for symptomatic embolism with infective endocarditis among Japanese population

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ABSTRACT

Background: Recently, the Embolic Risk French Calculator (ER-Calculator) was designed to predict symptomatic embolism (SE) associated with infective endocarditis (IE), but external validation has not been reported. This study aimed to determine predictors of SE and the diagnostic accuracy of the ER-Calculator in left-sided active IE among a Japanese population.
Methods: This retrospective cohort study included 166 consecutive patients with a definite diagnosis of left-sided IE from 1994 to 2015 in our institution. SE during the period after initiation of antibiotic therapy was defined as new SE and embolism during the period before initiation of antibiotic therapy was defined as previous embolism. The primary endpoint was new SE.
Results: The mean age of patients was 63 ± 17 years. New SE occurred in 23 (14%) patients at a median of 6 days (interquartile range: 2.5–12.5 days) after initiation of antibiotic therapy. The cumulative incidence of new SE at 12 weeks was 18.2%. The 2-week probability by the ER-Calculator as well as previously reported predictors, such as previous embolism, vegetation length (>10 mm), and their combination, were associated with a high risk of new SE. By receiver operating characteristic analysis, the area under the curve of the 2-week probability by the ER-Calculator for prediction of new SE was 0.75 and the optimal cut-off value was 8%. A 2-week probability $>8\%$ by the ER-Calculator was the most useful predictor of new SE (hazard ratio 3.63, 95% confidence interval 1.50–8.37; $p = 0.006$), which was more remarkable for fatal embolic events (hazard ratio 13.9, 95% confidence interval 3.19–95.4; $p = 0.004$).
Conclusions: The ER-Calculator is a useful predictor of new SE. Predictive ability is more remarkable for critical embolic events.

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Introduction

Despite advances in medical and surgical treatment, infective endocarditis (IE) remains associated with high mortality and morbidity [1–4]. Embolic events are common and critical complications of IE, and neurological complications lead to a poor prognosis [1,5–7,2,8].

Mortality benefit from early surgery for patients with active IE is now of increasing interest [9], but there has been no consensus on the optimal timing of early surgery. Emergency or urgent surgery for patients with left-sided active IE is recommended under the presence of refractory heart failure, uncontrolled sepsis, or a high embolic risk [3,4]. However, in the clinical setting, predicting embolic events is difficult. Embolic events often occur after initiation of antibiotic therapy, which may be prevented by

early surgery [10,11]. Therefore, an accurate prediction of embolic events on admission is important in managing IE to improve prognosis.

Several factors have been reported as predictors of embolic events associated with IE, but no definite predictors have been established. Recently, the Embolic Risk French Calculator (ER-Calculator) was designed to predict symptomatic embolism (SE) associated with IE, and is expected as a useful prediction model [12]. However, external validation of the ER-Calculator has not been reported and it is unclear whether the ER-Calculator can predict clinically-important critical embolic events accurately.

This study aimed to determine predictors of SE and the diagnostic accuracy of the ER-Calculator in left-sided active IE among a Japanese population.

Methods

Study patients

This was a retrospective single-center cohort study. We retrospectively investigated consecutive patients with the definite diagnosis of left-sided IE, according to the modified Duke criteria [13] from August 1994 to September 2015 in Tenri Hospital. Patients with isolated right-sided IE and pediatric patients (<18 years) were excluded. In patients with recurrent episodes of endocarditis, the first episode was included in the present study. Informed consent was obtained from all patients. The study protocol was approved by the institutional ethics committee at Tenri Hospital, judging it compliant with the principles outlined in the Helsinki Declaration.

ER-Calculator

The ER-Calculator was first described in the *Journal of the American College of Cardiology* October 2013 as an Online Appendix [12]. In univariate analysis, age, diabetes, atrial fibrillation, previous embolism, vegetation length, and *Staphylococcus aureus* were associated with embolic events. Using these variables, a multivariate embolic risk prediction model was developed. Fig. 1A shows the method for calculating a patient's embolic risk. Using an Excel file, a day-by-day risk calculation can be automatically performed once the individual variables have been entered.

Baseline data

We examined the following data on admission by checking previous clinical charts; age, sex, diabetes mellitus, hypertension, previous embolism, ischemic stroke, aspirin and/or anticoagulant therapy, immunosuppressant therapy, and causative pathogen which was determined by blood cultures, serology testing, valve culture, or polymerase chain reaction on a valve specimen according to international guidelines [3]. We also examined whether screening imaging tests, such as computed tomography and magnetic resonance imaging, were performed on admission. Additionally, a history of paroxysmal, persistent, or permanent atrial fibrillation on admission was examined. We evaluated the Euro Score and the Japan Score to assess the operative risk at the time of admission in emergent and urgent situations.

Diabetes mellitus was defined as hyperglycemia requiring medications or insulin. Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg and/or a diastolic pressure of ≥ 90 mmHg, or by the use of antihypertensive medications.

According to a previous study [12], previous embolism was defined as embolic events that occurred before initiation of antibiotic therapy and were associated with IE, which included symptomatic and asymptomatic embolic events (Fig. 1B). Ischemic stroke was defined as a focal neurologic deficit of an abrupt onset lasting >24 h with an evidence of new lesions on brain imaging, which occurred before admission and was not associated with IE.
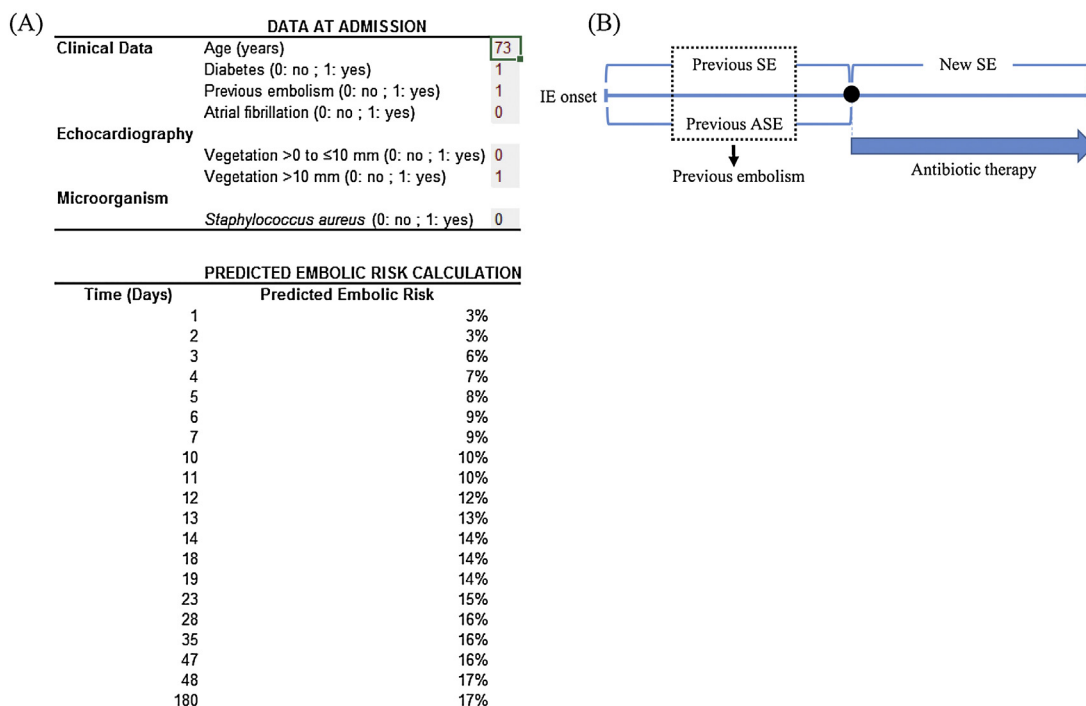

Fig. 1. Embolic Risk French Calculator (ER-Calculator) and the definition of embolism. (A) An example of embolic risk calculation for a 73-year-old man is shown. Day-by-day probability is calculated by entering each variable. In this case, the 2-week probability reached 14%. Reproduced, with permission, from Hubert et al. [12]. (B) Previous embolism was defined as embolic events that occurred before initiation of antibiotic therapy and were associated with IE, which included SE and ASE. Previous ASE was evaluated by screening imaging tests on admission. Total SE was defined as new SE and previous SE. IE, infective endocarditis; SE, symptomatic embolism; ASE, asymptomatic embolism.