# Prediction of acute phase complications in patients with infectious endocarditis

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## Abstract

**Objective:** Embolic events are frequent and life-threatening complications of infective endocarditis (IE). Recently, an embolic risk assessment at admission, based on the Embolic Risk (ER) French Calculator, was designed to predict the development of symptomatic emboli associated with IE. This study aimed to validate the ER French Calculator for prediction of in-hospital events, including embolic events.

**Material and Methods:** We retrospectively analyzed clinical features of 52 consecutive patients with left-sided IE to identify possible predictors of in-hospital events within 30 days of admission.

**Results:** New embolic events were seen in 15 patients (29%), cardiac surgery was performed in 22 patients (42%), and one patient (2%) died within 30 days of admission. A composite endpoint of embolic complications, cardiac surgery, or death was observed in 28 patients (54%). The cumulative incidence of new embolic events was significantly higher in the high-risk group identified by the ER French Calculator, compared to the low-risk group (log-rank test; P=0.0004). The incidence of the composite endpoint was higher in the high-risk group (log-rank test; P<0.0001). A multivariate Cox proportional hazards model indicated that the high-risk designation on the ER French Calculator predicted embolic events (P=0.0410) and composite events (P=0.0371) independently of other candidate predictors.

**Conclusions:** The ER French Calculator may be a useful tool to predict new in-hospital embolic events and other unfavorable in-hospital events in patients with IE.

**Key words:** infective endocarditis, embolic event, embolic risk, French Calculator, cardiac surgery

# Introduction

Despite advances in diagnostic techniques, improved antibiotic therapy, and potentially curative surgery, infective endocarditis (IE) has a high morbidity and mortality, which have remained unchanged over the past two decades and may even be increasing (1-6). The most frequent and serious complications of IE are major embolic events, especially cerebral embolism, leading to adverse outcomes. Embolic events are believed to be caused by fragmentation of vegetations, but also depend on the prothrombogenic conditions associated with infection (7, 8).

The beneficial effects of early surgical treatment for patients with active IE have previously been emphasized. Although cardiac surgery can be life-saving, it also carries significant risk to the patient. For that reason, there is no consensus on the optimal timing of early surgery. In these situations, emergent or urgent surgical treatment is recommended if the patient has refractory heart failure, uncontrolled sepsis, or a high embolic risk. It has been stated in the US and European guidelines that a combination of previous embolic events and vegetations >10 mm in size is a criterion for cardiac surgery (9, 10). However, surgical treatment in the emergent or urgent setting should be avoided if possible.

Embolic events often occur during or after antibiotic therapy, and may be prevented by early valve surgery. Therefore, evaluation of embolic risk is important for prompt management, which can prevent catastrophic complications. Although numerous investigators have tried to identify predictive factors for embolic complications accompanied with IE, the results have been contradictory. The criterion

for cardiac surgery, i.e., previous embolic events and vegetation size >10 mm, was associated with a higher risk of new embolic events, as outlined in the international guidelines (9, 10). Nevertheless, accurate methods have not yet been established for predicting, at the time of admission, future embolic events. Recently, an embolic risk assessment based on the French Calculator was designed to predict symptomatic embolism associated with IE, and is expected to be a useful prediction model (11). However, current validation of the French Calculator has been insufficient.

In the present study, we retrospectively analyzed clinical features of 52 consecutive patients with left-sided IE to identify possible predictors of in-hospital events, such as new embolic events post-admission, incidence of emergent/urgent cardiac surgery, or death, to validate the French Calculator.

## Material and Methods

### Study design and subjects

This study was designed as a case series. Subjects included 52 consecutive patients with a definitive diagnosis of left-sided IE, based on the modified Duke diagnosis criteria, who were admitted to Dokkyo Medical University Hospital between January 2010 and May 2018. Patients with isolated right-sided IE and patients aged <18 yrs were excluded. In patients with recurrent episodes of IE, only the first episode was included in the analysis. The study protocol was approved by the ethics committee of Dokkyo Medical University.

**Data collection**

The following baseline characteristic data were collected from all patient clinical charts: age, gender, hypertension, diabetes mellitus, presence of chronic or paroxysmal atrial fibrillation, presence of previous embolic events, blood pressure, and blood test results. Hypertension was defined as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg, or receiving anti-hypertensive agents. Diabetes mellitus was defined as a fasting blood glucose level >140 mg/dl, based on the criterion of the Japanese Diabetes Society, or receiving anti-diabetic agents including oral hypoglycemic agents and insulin. We also collected IE-related data, including causative pathogen, vegetation location, and maximum vegetation length. Infection was assessed by patients' history, and causative pathogens were identified by blood culture, serological testing, valve culture, or polymerase chain reaction on a valve specimen, according to the international guideline (9). The presence of a vegetation and, if present, characteristics of the vegetation such as its location and length, were assessed using trans-thoracic and/or trans-esophageal echocardiography.

**Embolic risk assessment**

The risk of new, post-admission, embolic events was assessed using variables such as patients' characteristics, infection characteristics, causative pathogen, and vegetation characteristics. A combination of previous embolic events and maximum vegetation length >10 mm, recommended by the US and European guidelines as a criterion for cardiac surgery, was also assessed (Guideline recommendation). In addition, the risk of

new embolic events was also computed using the French Calculator (ER French Calculator), available online (11). Data included in the calculator include age, diabetes, atrial fibrillation, previous embolic events, vegetation length on echocardiography, and Staphylococcus aureus as a causative pathogen. After encoding these variables in the calculator, the day-by-day risk for new embolic events was automatically provided. Figure 1 indicates the embolic risk calculation of a 72-year-old female without diabetes mellitus but with atrial fibrillation who had experienced a previous embolic event, using the ER French Calculator. In this patient, the causative pathogen was not Staphylococcus aureus but maximum vegetation length was >10 mm. The cumulative embolic risk for this patient is 12% at day 28. In the present study, a high risk was defined as a probability on the 28th hospital day >8%, based on a previous report (12).

**In-hospital event assessment within 30 days of admission**

In-hospital new major embolic events within 30 days of admission, such as cerebral infarction or peripheral arterial emboli not attributable to any etiology other than endocarditis, were determined. These major embolic events were diagnosed based on symptoms and/or imaging modalities such as computed tomography and/or magnetic resonance imaging. Information regarding incidence of emergent or urgent cardiac surgery, and all cause death within 30 days of admission was also collected.

**Statistical analysis**

Values are expressed as mean ± standard deviation for continuous variables and as number and percentage for categorical variables. The incidence of clinical events within

30 days of admission, such as new embolic events, emergent or urgent cardiac surgery and death and the composite of these events was compared between high- and low-risk groups based on the ER French Calculator, using a chi-square test. The cumulative incidence of these events was estimated by Kaplan-Meier survival curve analysis and were compared between the high- and low-risk groups using the log-rank test. The Cox proportional hazards model, in which hazard ratios and 95% confidence intervals were calculated, was used to identify predictors of the cumulative incidence of clinical events in both univariate and multivariate fashions. First, we used univariate analysis to screen variables possibly associated with the adverse events. Then, multivariate analysis was performed using the candidates identified by the univariate analysis. A $p < 0.05$ was considered statistically significant.

## Results

### Baseline and IE characteristics

Baseline characteristics of all 52 patients are shown in Table 1. The average age was 61±16 years (range 25-89 years) and 31 patients (60%) were male. Diabetes mellitus and atrial fibrillation were present in 14 (27%) and 9 (17%) patients, respectively. Eight patients (15%) had previous embolic events, including cerebral embolism in 7 (13%) and splenic embolism in 1 (2%). Regarding blood test findings at admission, the average white blood cell count was 11.8±5.1 $\times 10^9$/l, C-reactive protein level 8.5±6.6 mg/dl, and brain natriuretic peptide (BNP) level 483±678 pg/ml. Pathogen and

vegetation characteristics are shown in Table 2. Oral infection was seen in 13 patients (25%) and in 28 patients (53%) the infection origin was unknown. Streptococci were the most frequent pathogens (14 patients; 27%), and Staphylococcus aureus was identified in 7 patients (13%). In 11 patients (21%), the causative pathogen was unknown. The vegetation was localized at the mitral valve in 32 patients (61%) and at the aortic valve in 13 patients (25%). In 2 patients (4%), both the mitral and aortic valves were involved (multivalvular IE). Prosthetic valve IE was seen in 2 patients (4%). In addition, maximum vegetation length >10 mm was identified in 20 patients (38%).

**Embolic risk assessment and in-hospital events**

Twenty-three patients (44%) met the Guideline recommendation for cardiac surgery (a combination of previous embolic events and maximum vegetation length >10 mm). Regarding the ER French Calculator, the probability for embolic events on the 28th hospital day was 8.1±6.9% among all 52 patients. The high-risk group (probability on the 28th day >8%) included 23 patients (44%) and the low-risk group (probability on the 28th day ≤8%) included 29 patients (56%) (Table 3).

New embolic events occurred in 15 patients (29%) within 30 days of admission: cerebral embolism in 12 (23%), renal embolism in 1 (2%), both cerebral and renal emboli in 1 (2%), and peripheral artery embolism in 1 (2%). In 22 patients (42%), emergent or urgent cardiac surgery was performed within 30 days of admission. Main surgical indication was prevention of embolic events in 13 (25%) (primary prevention in 3; 6% and secondary prevention in 10; 19%), uncontrolled infection in 7 (13%) and refractory heart failure due to valve destruction in 2 (4%). In addition, one patient (2%)

died from cardiogenic or septic shock on the day of admission. As a result, the composite endpoint of embolic events, cardiac surgery and death within 30 days of admission occurred in 28 patients (54%) (Table 3).

In 29 patients except for died one, who did not undergo cardiac surgery within 30 days of admission, 18 patients were judged to be low risk of embolic complications but in the remaining 11, cardiac surgery was deferred because they considered to have high operative risk.

**In-hospital events within 30 days of admission in low- and high-risk groups based on ER French Calculator**

The incidence of in-hospital events within 30 days of admission was compared between low- and high-risk group based on ER French Calculator (Table 4). The new embolic events showed higher incidence in the high-risk French Calculator group compared to the low-risk group (45% vs 12%, $P<0.05$). The incidence of cardiac surgery was more significantly higher in the high-risk group compared to low-risk group (74% vs 17%, $P=0.0001$). Even in the surgery based on the uncontrolled infection as a surgical indication, the incidence was higher in the high-risk group compared to the low-risk group (26% vs 3%, $P<0.05$). In addition, 2 patients whose surgical indication was refractory heart failure both belonged to the high-risk group. As a result, the incidence of composite of new embolic events, cardiac surgery and death was significantly higher in the high-risk group compared to the low-risk group (91% vs 24% $P<0.0001$).

**Cumulative incidence and prediction of in-hospital events within 30 days of**

**admission**

A Kaplan-Meier survival curve analysis was performed to assess the cumulative incidence of in-hospital events within 30 days of admission. The cumulative incidence of new embolic events was significantly higher in the high-risk ER French Calculator group compared to the low-risk group (log-rank test; P=0.0004). The cumulative incidence of the composite endpoint of new embolic events, cardiac surgery and death was more significantly higher in the high-risk group compared to the low-risk group (log-rank test; P<0.0001) (Fig. 2).

In addition to high-risk on the ER French Calculator, several factors were significantly associated with the cumulative incidence of new embolic events in the univariate Cox proportional hazards analysis showed that prevalence of hypertension (P=0.0186), multivalvular or prosthetic valve IE (P=0.0418), previous embolic events (P<0.0001), BNP level (P=0.0064), the Guideline recommendation (P=0.0120) and high-risk on the ER French Calculator (P=0.0031) predicted new embolic events in the univariate analysis. The multivariate analysis showed that hypertension (P=0.0139), multivalvular or prosthetic valve IE (P=0.0017), and previous embolic events (P=0.0012) as well as high-risk on the ER French Calculator (P=0.0410) independently predicted new embolic events. The most powerful independent predictor was previous embolic events (Table 5). Regarding the composite of new embolic events, cardiac surgery and death, maximum vegetation length>10 mm (P<0.0001), previous embolic events (P=0.0008), BNP level (P=0.0031), the Guideline recommendation (P<0.0001), and high-risk on the ER French Calculator (P<0.0001) were significantly associated with the composite endpoint in the univariate analysis. In multivariate analysis, the only

significant independent predictor of the composite endpoint was high-risk on the ER French Calculator (P=0.0371) (Table 6).

## Discussion

In the present study, we found that the cumulative incidence of in-hospital new embolic events within 30 days of admission was significantly higher in the high-risk ER French Calculator group compared to low-risk group. In addition, the composite of new embolic events, cardiac surgery and death within 30 days were more significantly higher in the high-risk group. The univariate Cox proportional hazards model indicated that the ER French Calculator could predict not only new embolic events but also the composite of embolic events, cardiac surgery and death. The multivariate Cox proportional hazards model showed that the ER French Calculator could predict the composite events as well as new embolic events, independent of other candidate predictors. Importantly, the ER French Calculator was the only independent predictor of the composite events.

Embolic events are frequent and life-threatening complications of IE. Embolic events occur in more than 50% of patients (2-6) and lead to poor prognoses. They often occur during and after antibiotic therapy, and can be prevented by valve surgery (13, 14). Thus, the evaluation of embolic risk at hospital admission is important for avoiding catastrophic events. Several factors are associated with embolic risk, including size and localization of vegetation, causative pathogen, and the presence of previous emboli (15,

16). Fabri et al. (17) demonstrated that embolic events occurred more frequently in Staphylococcus aureus IE and prosthetic valve IE. Vegetation size seems to be the most widely studied and most consistent echocardiographic predictor of embolic events. In particular, maximum vegetation length is a major determinant of embolic events. Early surgical treatment is recommended for patients with a maximum vegetation length >10 mm, and several reports have stated that this criterion for surgery might be associated with a risk for embolic events (14, 18-20). However, prediction of embolic events using a single variable has limitations. In the current international guidelines, a maximum vegetation length >10 mm and the presence of previous embolic events (the Guideline recommendation for cardiac surgery) are used to assess new embolic risk and are an indication for valve surgery (9, 10). However, this recommendation does not provide a precise quantification of new embolic risk and does not take into account other potentially important predictors. The ER French Calculator, in addition to vegetation length and previous embolism, takes into account other variables such as age, diabetes, atrial fibrillation and Staphylococcus aureus as a pathogen. This calculator focuses on prediction at admission, allowing for rapid therapeutic decision making to avoid new embolic events. Since the French Calculator was designed by Hubert et al. (11) to predict new embolic events in IE, several investigators have recently validated its accuracy and utility. Aherrera et al. (20) used the ER French Calculator to assess the risk for in-hospital new embolic events in IE patients, using the probability on the 28th hospital day, similar to our study. They found that a probability on the 28th hospital day >7% was closely associated with the in-hospital embolic risk. In contrast, Takahashi et al. (12) defined a probability on the 14th hospital day >8% as high-risk and

demonstrated that the incidence of new embolic events during a 12-week observation period was significantly higher in the high-risk group, compared to the low-risk group. Thus, the probability on the 14th hospital day may predict longer-term outcomes. In the present study, we first identified candidate predictors from several variables at admission that might be associated with embolic events using the univariate Cox proportional hazards model. Consequently, we found that possible predictors of new embolic events within 30 days of admission were hypertension, multivalvular or prosthetic valve IE, prevalence of previous embolic events, BNP level, and the Guideline recommendation, in addition to the high-risk designation on the ER French Calculator. Among these variables, independent predictors included hypertension, multivalvular or prosthetic valve IE, and previous embolic events as well as the high-risk designation on the ER French Calculator in the multivariate analysis results. While the association of multivalvular or prosthetic valve IE and previous embolic events with new embolic events has been previously reported (9, 10, 17), the predictive value of hypertension is a novel finding, although the mechanisms are uncertain. Moreover, in our results, maximum vegetation length >10 mm was not associated with new embolic events, being inconsistent with the previous reports (9, 10). Although the most powerful independent predictor was previous embolic events, our data could validate the use of the ER French Calculator to predict new embolic events.

Embolic events are related to mortality in IE, so the ER French Calculator might also be a predictor of death. Furthermore, embolic risk is a major indication for emergent or urgent surgical treatment in IE. Thus, the ER French Calculator might be associated with the incidence of cardiac surgery in IE. Since surgical management of IE

can optimize source control by removal of infected tissue, reduce morbidity from embolic events (14), and reduce mortality in the appropriate clinical context (21-24), embolic risk might be closely linked to the incidence of surgical treatment and death. We therefore assessed whether candidate predictors of new embolic events, including the ER French Calculator, could simultaneously predict the cumulative incidence of the composite of new embolic events, cardiac surgery and death. As a result, we found that maximum vegetation length >10 mm, BNP level, the Guideline recommendation, and the high-risk designation on the ER French Calculator were significantly associated with the incidence of cardiac surgery or death in the univariate Cox proportional hazards model. The association of vegetation size and the Guideline recommendation with the incidence of cardiac surgery has been previously reported (9, 10). The association of BNP level with the incidence of cardiac surgery is understandable because refractory heart failure is also an indication for emergent or urgent surgical treatment in IE. Regarding the composite of new embolic events, cardiac surgery and death, maximum vegetation length >10 mm, previous embolic events, BNP level, and the Guideline recommendation, as well as the high-risk designation on the ER French Calculator were significantly associated with the composite events in the univariate analysis. In addition, the only significant independent predictor of the composite events was the high-risk designation on the ER French Calculator in the multivariate analysis.

Although the major purpose of surgical treatment in IE was prevention of embolic events, uncontrolled infection and refractory heart failure are also important surgical indication. In the present study, patients with high-risk on ER French Calculator showed higher incidence of not only embolic events but also cardiac surgery, compared to

low-risk patients. It seems natural in patients undergoing cardiac surgery whose surgical indication was prevention of embolic events. Interestingly, however, higher incidence of cardiac surgery based on uncontrolled infection was also shown in high-risk patients on the ER French Calculator. In addition, 2 patients with refractory heart failure as the surgical indication both belonged to the high-risk group. The results suggest that the ER French Calculator may be a useful tool to predict not only embolic events but also other early adverse events in patients with IE.

**Study limitation/clinical implication**

The present study has several limitations. First, the sample size was too small to establish the validity of the ER French Calculator for predicting in-hospital outcomes including embolic events, so a larger validation study is needed. Second, we only evaluated the candidate predictors, including ER French Calculator, at admission, so we were unable to take into account modifications after the initial evaluation. Third, embolic events depend on prothrombogenic conditions associated with infection, in addition to fragmentation of vegetations. Atrial fibrillation and diabetes mellitus, both of which were assessed as candidate predictors of embolic events, could influence the prothrombotic state. Nevertheless, we did not assess prothrombic activity in the present study. Fourth, we used a probability >8% as the cut-off value for the high-risk group, according to a previous report (12). Alternatively, we could have independently determined the optimal cut-off value using the receiver operating characteristic curve analysis. Finally, in the present study, we assessed only in-hospital patients' outcomes within 30 days of admission as an endpoint, but we need to consider a prediction for

longer-term prognosis, which may be a future task. Despite these limitations, our data suggest that it is important and possible to predict in-hospital events using data collected at admission. Predictions can be used to make rapid therapeutic decisions and avoid adverse events. In the results of present study, the ER French Calculator predicted new embolic events and could more strongly predict composite of new embolic events, cardiac surgery and death. Moreover, indications of cardiac surgery included uncontrolled infection and refractory heart failure, in addition to prevention of embolic events, in the subjects of the present study. While the current guidelines (Guideline recommendation for cardiac surgery) consist of visitation size and the presence of previous embolic events, the ER French Calculator takes into account other variables such as age, diabetes, atrial fibrillation and Staphylococcus aureus as a pathogen. Our results suggest that diabetes, atrial fibrillation and Staphylococcus aureus would be also important factors relating to incidence of unfavorable in-hospital events. Toward this end, the ER French Calculator may be a sound predictor of in-hospital outcomes. The skillful use of ER French Calculator would be available for avoiding catastrophic events in the treatment of IE.

**Conclusion**

The French Calculator may be a useful tool to predict not only new in-hospital embolic events but also other unfavorable in-hospital events in patients with IE.

**The authors state that they have no Conflict of Interest (COI).**

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## Figure legends

**Figure 1** Embolic risk French Calculator. The embolic risk is calculated for a 72-year-old female without diabetes mellitus but with atrial fibrillation who had experienced a previous embolic event. In this patient, the causative pathogen was not Staphylococcus aureus but maximum vegetation length was >10 mm. The cumulative embolic risk for this patient is 12% at day 28. The figure shows an example of the embolic risk calculation for a 72-year-old female without diabetes mellitus but with atrial fibrillation who had experienced a previous embolic event. In this patient, the causative pathogen was not Staphylococcus aureus but maximum vegetation length was >10 mm. The cumulative embolic risk for this patient is 12% at day 28.

**Figure 2** Kaplan-Meier survival curve for the cumulative incidence of in-hospital events within 30 days of admission. The incidence of new embolic events was significantly higher in the high-risk group, based on the ER French Calculator, compared with the low-risk group (A). The incidence of the composite endpoint of new embolic events, cardiac surgery and death was also higher in the high-risk group, compared with the low-risk group (B).