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【 ORIGINAL ARTICLE 】

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 the prediction of in-hospital events, including embolic events.

Methods We retrospectively analyzed the 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 1 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 than in the low-risk group (log-rank test; p=0.0004). The incidence of the composite endpoint was higher in the high-risk group than in the low-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.

Conclusion The ER French Calculator may be a useful tool for predicting 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

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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 a 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 the 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, evaluating the embolic risk is important for prompt management, which can prevent catastrophic complications. Al-

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though numerous investigators have tried to identify predictive factors for embolic complications accompanied with IE, the results have been conflicting. The criterion for cardiac surgery, i.e., previous embolic events and vegetation size > 10 mm, was associated with an increased higher risk of new embolic events, as outlined in the international guidelines (9, 10). However, accurate methods for predicting future embolic events at the time of admission have not yet been established.

Recently, an embolic risk (ER) 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, the validation of the French Calculator is insufficient at present.

In the present study, we retrospectively analyzed the clinical features of 52 consecutive patients with left-sided IE in order to identify possible predictors of in-hospital events, such as new embolic events post-admission, incidence of emergent/urgent cardiac surgery, or death, and 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 those <18 years of age 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 its characteristics, 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 were the age, diabetes, atrial fibrillation, previous embolic events, vegetation length on echocardiography, and presence of *Staphylococcus aureus* as a causative pathogen. After encoding these variables in the calculator, the day-to-day risk for new embolic events was automatically obtained.

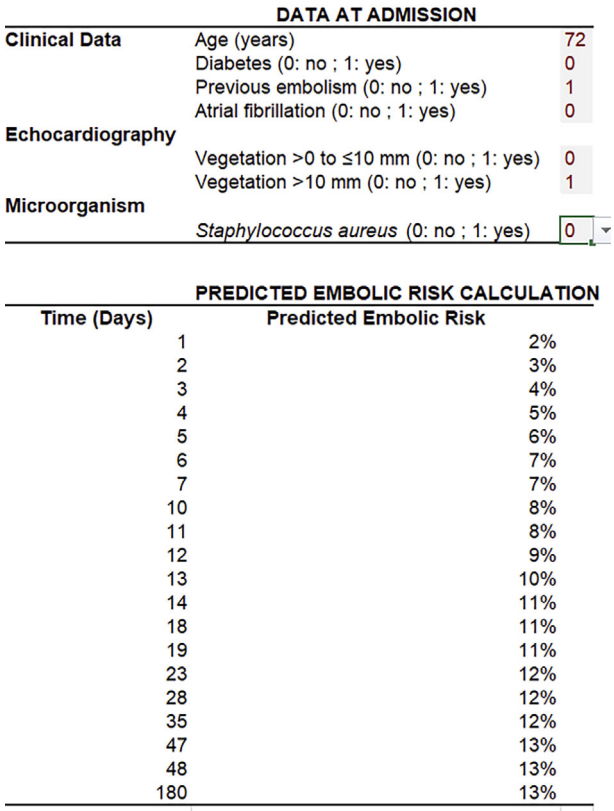
Fig. 1 indicates the embolic risk of a 72-year-old woman without diabetes mellitus but with atrial fibrillation who had experienced a previous embolic event, determined using the ER French Calculator. In this patient, the causative pathogen was not *Staphylococcus aureus*, but the maximum vegetation length was >10 mm. The cumulative embolic risk for this patient was 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).

The 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 the incidence of emergent or urgent cardiac surgery and all cause death within 30 days of admission was also collected.

Statistical analyses

Values are expressed as the 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 a 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 conducted a univariate analysis to screen variables



DATA AT ADMISSION

Clinical Data	Age (years)	72
	Diabetes (0: no ; 1: yes)	0
	Previous embolism (0: no ; 1: yes)	1
	Atrial fibrillation (0: no ; 1: yes)	0
Echocardiography		
	Vegetation >0 to ≤10 mm (0: no ; 1: yes)	0
	Vegetation >10 mm (0: no ; 1: yes)	1
Microorganism		
	Staphylococcus aureus (0: no ; 1: yes)	0

PREDICTED EMBOLIC RISK CALCULATION

Time (Days)	Predicted Embolic Risk
1	2%
2	3%
3	4%
4	5%
5	6%
6	7%
7	7%
10	8%
11	8%
12	9%
13	10%
14	11%
18	11%
19	11%
23	12%
28	12%
35	12%
47	13%
48	13%
180	13%

Figure 1. The embolic risk French Calculator. The embolic risk was calculated for a 72-year-old woman 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 the maximum vegetation length was >10 mm. The cumulative embolic risk for this patient was 12% at day 28.

Table 2. Infection Pathway, Pathogen and Vegetation Characteristics.

Infection pathway; n (%)	
Oral	13 (25)
Skin	4 (8)
Urinary tract	3 (6)
Others	4 (8)
Unknown	28 (53)
Causative pathogen; n (%)	
Staphylococcus aureus	7 (13)
Other staphylococci	6 (12)
Streptococci	14 (27)
Enterococcus faecalis	5 (10)
Others	9 (17)
Unknown	11 (21)
Vegetation localization; n (%)	
MV	32 (61)
AV	13 (25)
MV+AV	2 (4)
Prosthetic valve	2 (4)
None	3 (6)
Maximum vegetation length>10 mm; n (%)	20 (38)

MV: mitral valve, AV: aortic valve

Table 1. Baseline Characteristics in All Patients.

Patient number; n	52
Age; yr	61±16
Male gender; n (%)	31 (60)
Hypertension; n (%)	29 (56)
Diabetes mellitus; n (%)	14 (27)
Atrial fibrillation; n (%)	9 (17)
previous embolic events; n (%)	8 (15)
Systolic blood pressure; mmHg	128±21
Blood test	
White blood cell; $\times 10^9$/L	11.8±5.1
Hemoglobin; g/dL	10.9±2.0
Platelet count; $\times 10^9$/L	200±94
C-reactive protein; mg/dL	8.5±6.6
Albumin; g/dL	2.7±0.7
Creatinine; mg/dL	1.35±1.44
LDL-cholesterol; mg/dL	84±29
Fasting blood glucose; mg/dL	118±28
Hemoglobin A1c; %	5.7±0.7
Brain natriuretic peptide; pg/mL	483±678

LDL: low-density lipoprotein

possibly associated with the adverse events. A multivariate analysis was then performed using the candidates identified by the univariate analysis. A p value <0.05 was considered statistically significant.

Results

Baseline and IE characteristics

The 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 men. 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±5.1×10^9/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%), while the infection origin was unknown in 28 patients (53%). *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, a maximum vegetation length >10 mm was identified in 20 patients (38%).

Table 3. Embolic Risk Assessment and In-hospital Events within 30 Days Post-admission (n=52).

Guideline recommendation; n (%)	
(History of previous embolic events or maximum vegetation length>10 mmg)	23 (44)
ER French Calculator	
Probability on the 28th day: %	8.1±6.9
Low-risk (probability on the 28th day≤8%); n (%)	29 (56)
High-risk (probability on the 28th day>8%); n (%)	23 (44)
Embolic complications within 30 days	
Total; n (%)	15 (29)
Cerebral; n (%)	12 (23)
Renal; n (%)	1 (2)
Cerebro-renal; n (%)	1 (2)
Peripheral; n (%)	1 (2)
Surgical treatment within 30 days; n (%)	22 (42)
Prevention of embolic events; n (%)	13 (25)
Primary prevention; n (%)	3 (6)
Secondary prevention; n (%)	10 (19)
Uncontrolled infection; n (%)	7 (13)
Refractory heart failure; n (%)	2 (4)
Death within 30 days; n (%)	1 (2)
Composite of events within 30 days; n (%)	28 (54)

Composite of events: embolic complications, surgical treatment and death, ER: embolic risk

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. The main surgical indication was the 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, 1 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 four patients, the risk assessment differed between the guideline recommendation for cardiac surgery and the ER French Calculator. Two of these four patients were included in the high-risk group for ER French Calculator but did not meet the guideline recommendation for cardiac surgery, and one of them experienced a new embolic complication and underwent cardiac surgery while the other did not. The remaining two patients met the guideline recommendation for cardiac surgery but were included in the low-risk group for the ER French Calculator, and neither of them experienced new embolic complications or underwent cardiac surgery. Among the 29 patients (excluding 1 who died) who did not undergo cardiac surgery within 30 days of admission, 18 were judged to be at a low risk of embolic complications, while in the remaining 11, cardiac surgery was deferred because they were considered to have a high operative risk.

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

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

The 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 than in the low-risk group (log-rank test; $p=0.0004$). Furthermore, the cumulative incidence of the composite endpoint of new embolic events, cardiac surgery, and death was significantly higher in the high-risk group than in the low-risk group (log-rank test; $p<0.0001$) (Fig. 2).

In addition to a 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, which showed that the 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 a high risk on the ER French Calculator ($p=0.0031$) predicted new embolic events. 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 a high risk on the ER French

Table 4. Comparison of In-hospital Events within 30 Days Post-admission between Low- and High-risk Groups Based on ER French Calculator.

	Low-risk group (n=29)	High-risk group (n=23)	p
Embolic complications within 30 days			
Total; n (%)	5 (12)	10 (45)	0.0381
Cerebral; n (%)	4 (9)	8 (36)	0.0744
Renal; n (%)	0 (0)	1 (4.5)	0.2569
Cerebro-renal; n (%)	0 (0)	1 (4.5)	0.2569
Peripheral; n (%)	1 (3)	0 (0)	0.3685
Surgical treatment within 30 days; n (%)	5 (17)	17 (74)	0.0001
Prevention of embolic events; n (%)	4 (14)	9 (39)	0.0015
Primary prevention; n (%)	1 (3)	2 (9)	0.2439
Secondary prevention; n (%)	3 (10)	7 (30)	0.0679
Uncontrolled infection; n (%)	1 (3)	6 (26)	0.0175
Refractory heart failure; n (%)	0 (0)	2 (9)	0.1054
Death within 30 days; n (%)	0 (0)	1 (4.5)	0.2569
Composite of events within 30 days; n (%)	7 (24)	21 (91)	<0.0001

Low-risk group: probability on the 28th day≤8%, High-risk group: probability on the 28th day>8%

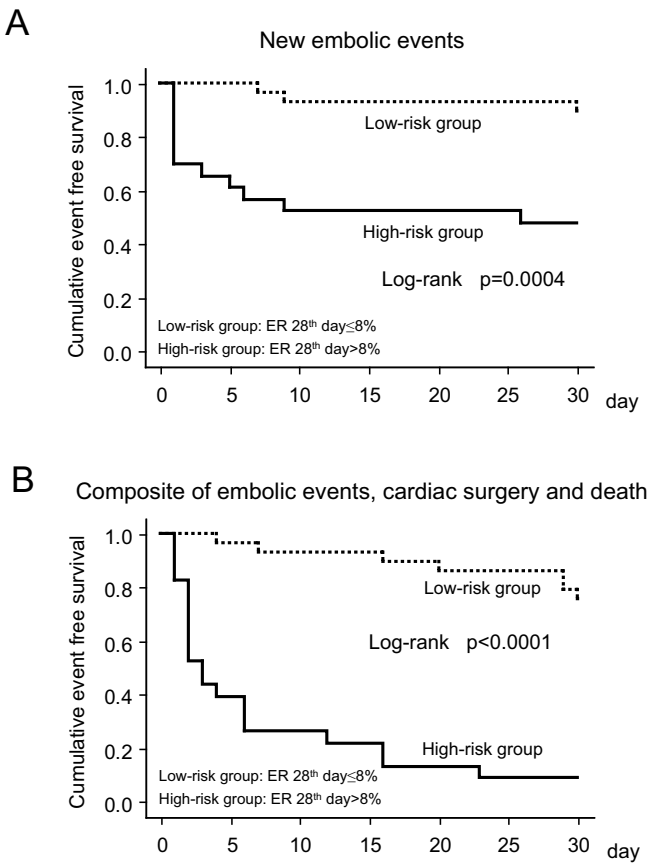


Figure 2. Kaplan-Meier survival curve for the cumulative incidence of in-hospital events within 30 days of admission. The incidence of new embolic events was significantly higher in the high-risk group, based on the ER French Calculator, than in the low-risk group (A). The incidence of the composite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

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, a maximum vegetation length >10 mm (p<0.0001), previous embolic events (p=0.0008), BNP level (p=0.0031), 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 the multivariate analysis, the only significant independent predictor of the composite endpoint was a 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 than in the low-risk group. In addition, the composite endpoint of new embolic events, cardiac surgery, and death within 30 days was significantly higher in the high-risk group than in the low-risk group. The univariate Cox proportional hazards model indicated that the ER French Calculator was able to 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 was able to 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 composite events.

Embolic events are frequent and life-threatening complications of IE that 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, evaluating the embolic risk at hospital

Table 5. Prediction of New Embolic Events within 30 Days Post-admission.

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age	1.029	0.994-1.066	0.1062			
Male gender	0.544	0.917-1.501	0.2396			
Hypertension	5.994	1.350-26.621	0.0186	9.424	1.577-56.319	0.0139
Diabetes mellitus	1.739	0.619-4.888	0.2940			
Atrial fibrillation	1.163	0.321-4.134	0.8725			
Unknown infection pathway	0.742	0.269-2.046	0.5462			
Staphylococcus aureus	0.428	0.056-3.258	0.4126			
Multivalvular or prosthetic valve	3.741	1.050-13.334	0.0418	15.643	2.189-86.813	0.0017
Maximum vegetation length>10 mm	2.048	0.741-5.658	0.1666			
Previous embolic events	11.373	3.746-34.534	<0.0001	16.978	3.062-94.144	0.0012
White blood cell count	1.072	0.975-1.178	0.1506			
C-reactive protein	0.969	0.888-1.058	0.4808			
Brain natriuretic peptide	1.001	1.000-1.001	0.0064	1.000	1.000-1.002	0.0577
Hemoglobin A1c	1.242	0.587-2.623	0.5719			
Guideline recommendation	4.367	1.383-13.787	0.0120	0.931	0.104-8.383	0.9487
High-risk on ER French Calculator	6.806	1.097-1.501	0.0031	10.188	1.100-94.366	0.0410

HR: hazard ratio, CI: confidence interval, ER: embolic risk

Table 6. Prediction of Composite Events within 30 Days Post-admission (New Embolic Events, Cardiac Surgery and Death).

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age	1.013	0.990-1.037	0.2558			
Male gender	0.817	0.386-1.727	0.5959			
Hypertension	0.855	0.407-1.797	0.6802			
Diabetes mellitus	1.669	0.769-3.621	0.1949			
Atrial fibrillation	1.021	0.386-2.698	0.9667			
Unknown infection pathway	0.921	0.438-1.935	0.8770			
Staphylococcus aureus	1.153	0.339-3.328	0.7926			
Multivalvular or prosthetic valve	2.451	0.846-7.926	0.0986			
Maximum vegetation length>10 mm	4.846	2.202-10.663	<0.0001	0.697	0.128-3.790	0.6765
Previous embolic events	4.497	1.859-10.873	0.0008	1.817	0.445-7.425	0.4056
White blood cell count	1.057	0.977-1.144	0.1698			
C-reactive protein	1.007	0.956-1.061	0.7906			
Brain natriuretic peptide	1.001	1.000-1.001	0.0031	1.000	1.000-1.001	0.4428
Hemoglobin A1c	1.343	0.793-2.272	0.2724			
Guideline recommendation	7.546	3.209-17.742	<0.0001	2.271	0.154-33.383	0.5948
High-risk on ER French Calculator	10.368	4.194-25.630	<0.0001	5.119	0.981-29.402	0.0371

admission is important for avoiding catastrophic events. Several factors have been shown to be associated with embolic risk, including the size and localization of the vegetation, causative pathogen, and a history of emboli (15, 16). Fabri et al. (17) showed that embolic events occurred frequently in cases of *Staphylococcus aureus* IE and prosthetic valve IE. Vegetation size seems to be the most widely studied and consistent echocardiographic predictor of embolic events. In particular, the 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 suggested that this criterion for surgery might be associated with a risk for embolic events (14, 18-20). However, predicting embolic events using a single variable has limitations. Under 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

the patient age, presence of diabetes, atrial fibrillation, and presence of *Staphylococcus aureus* as a pathogen. This calculator focuses on prediction at admission, allowing for rapid therapeutic decision-making in order 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 indicative of a 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 than in 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 according to the multivariate analysis. 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. Furthermore, in our results, a maximum vegetation length >10 mm was not associated with new embolic events, a finding that was inconsistent with those of previous reports (9, 10). Although the most powerful independent predictor was previous embolic events, our data validated the utility of the ER French Calculator for predicting 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 removing infected tissue, thereby reducing morbidity from embolic events (14) and mortality in the appropriate clinical context (21-24), the embolic risk might be closely linked to the incidence of surgical treatment and death. We therefore assessed whether or not 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. We found that a 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 the vegetation size and the Guideline recommendation with the incidence of cardiac surgery has been previously reported (9, 10). The association of the 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, a 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 to prevent embolic events, uncontrolled infection and refractory heart failure are also important surgical indications. In the present study, patients with high-risk on the ER French Calculator showed a higher incidence of not only embolic events but also cardiac surgery than low-risk patients. The ER French Calculator is therefore considered to be able to predict the incidence of cardiac surgery and thereby prevent the occurrence of embolic events. Interestingly, however, a higher incidence of cardiac surgery due to uncontrolled infection was also shown in high-risk patients according to the ER French Calculator. In addition, two patients with refractory heart failure as the surgical indication were both classified into the high-risk group. These results suggest that the ER French Calculator may be a useful tool for predicting 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, can influence the prothrombotic state. Nevertheless, we did not assess the 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 a 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, and predicting the longer-term prognosis should be explored in the future.

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 present study, the ER French Calculator predicted new embolic events and was able to predict the composite endpoint of new embolic events, cardiac surgery, and death. Furthermore, indications of cardiac surgery included uncontrolled infection and refractory heart failure, in addition to the prevention of embolic events, in the subjects of the present study. While the current guidelines (Guideline recommendation for cardiac surgery) include vegetation size and the presence of previous embolic events, the ER French Calculator takes into account other variables, such as age, diabetes, atrial fibrillation and the presence of *Staphylococcus aureus* as a pathogen. Our results suggest that diabetes, atrial fibrillation, and *Staphylococcus aureus* presence are also important factors relating to the incidence of unfavorable in-hospital events. Therefore, the ER French Calculator may be a sound predictor of in-hospital outcomes. The skillful use of the ER French Calculator can be used to help prevent catastrophic events in the treatment of IE.

Conclusion

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

Author's disclosure of potential Conflicts of Interest (COI).
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