

# The Clinical Impacts of Apparent Embolic Event and the Predictors of In-Hospital Mortality in Patients with Infective Endocarditis

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Embolic event is a common and important complication of infective endocarditis (IE). The objective of this study was to investigate the clinical impacts of embolic event in patients with IE and the predictors of in-hospital mortality. Data was collected in Pusan National University Hospital and Pusan National University Yangsan Hospital between January 2009 and December 2010. One hundred ten patients were included. Embolic events occur in 39 of 110 patients (35.5%). Brain ( $n = 18$ , 38.5%) was the main site of embolic infarction. Patients with embolism showed higher in-hospital mortality (46.2% vs. 8.5%, respectively,  $P = 0.03$ ), more frequent ICU admission (53.8% vs. 35.2%, respectively,  $P = 0.045$ ) and more accompanying other cardiac complication (43.6% vs. 21.1%, respectively,  $P = 0.017$ ). The in-hospital mortality rate was 18.2%. On the logistic regression analysis of the predictors for in-hospital mortality, age (RR, 1.079; 95% CI, 1.036-1.123,  $P = 0.001$ ), embolic event (RR, 3.510; 95% CI, 1.271-9.69,  $P = 0.015$ ) and staphylococcal infection (RR, 5.098; 95% CI, 1.308-18.508,  $P = 0.023$ ) were independently associated with in-hospital mortality. Embolic events in IE are associated with poor in-hospital outcome; and these data about embolic events and the predictors of in-hospital mortality may improve the management of this disease in hospitals.

**Keywords:** Endocarditis; Embolism; Mortality; Staphylococcus

## INTRODUCTION

Despite the great advances in the diagnosis and treatment of infective endocarditis (IE), it remains a disease with high in-hospital mortality (16%-25%) and a high incidence of complications (1-5). In contrast to decreasing some of the other complications such as renal failure and uncontrolled intra-cardiac or metastatic infection with using antibiotics, embolic event is still a distressingly common complication of IE and this can occur even during administering appropriate therapy (6, 7). The incidence of clinically recognized embolism is known to 13% to 44% (6, 7). Adam et al. reported that cerebral infarction is a presenting sign of IE in 4% to 14% of all infective endocarditis (8).

All the patients who present with signs and symptoms of systemic arterial embolization should have IE considered as a possible cause (6, 7). Several studies have attempted to evaluate the predictors of embolic events and mortality. The reports have had conflicting results, vegetation > 10 cm in size, left-side valve infection and *Staphylococcus aureus* infection were suggested as the risk factors of embolic infarction (2, 9-13). Diabetes mellitus, *Staphylococcus aureus* infection and embolic events are known to be predictors of in-hospital mortality (3-5, 12). But there are few studies that have focused on the clinical influence

of embolic event in IE and the predictors of in-hospital mortality in an Asian population.

The objective of this study was to investigate the clinical impacts of embolic event on IE and the predictors of in-hospital mortality. Determining the clinical effects of embolic event on IE and the predictors of in-hospital mortality may improve the management of this disease in hospitals.

## MATERIALS AND METHODS

### Patients and population

This retrospective study was performed at two teaching hospitals: Pusan National University Hospital, which is a 1,000-bed teaching hospital, between January 2003 and December 2010 and Pusan National University Yangsan hospital, which is a 700-bed teaching hospital, between January 2009 and December 2010. All the medical records were reviewed for the patients with infective endocarditis and who were over 18 yr of age. All the patients with infective endocarditis met the modified Duke's criteria (14) for definite IE or possible IE. The demographic data, the baseline characteristics and the outcomes were collected. The following data was recorded for each patient: age, gender, the underlying disease, the involved valves, a native valve ver-

sus a prosthetic valve, a community origin versus a nosocomial origin, the cardiac and extracardiac complications, the treatment given during hospitalization, the surgical requirements, the need for ICU admission, the echocardiographic findings, the total admission days and the in-hospital mortality.

Nosocomial IE was defined as an infection occurring more than 72 hr after admission to the hospital or the IE acquired in patients discharged from the hospital within 6 months before the onset of symptoms (15). Cardiac complication was defined as cardiac structural complication such as new onset of valvular functional abnormality, valvular abscess, valvular perforation and intracardiac abscess. Four to six blood cultures were obtained for all the patients.

### Embolitic event

We evaluated the radiologic/clinical evidence of embolism. The CT scans, MRI and chest radiographic findings were collected for the patients with signs or symptoms suggestive of an embolic event such as abdominal pain, chest discomfort, abrupt dyspnea and sudden neurologic or visual dysfunction. Renal and splenic embolisms were included if they were confirmed by radiographic imaging.

### Statistical analyses

Statistical analyses were done using SPSS version 12.0 (SPSS Corp, Chicago, IL, USA). The descriptive analysis consisted of the median, mean and range of the various parameters. The differences between the embolic and nonembolic patients were compared using the chi-square test for the categorical variables, and the *t*-test or the rank-sum test was used for the numerical variables. Logistic regression analysis was performed to determine the predictors that were independently associated with in-hospital mortality. *P* values < 0.05 were considered to be statistically significant.

### Ethics statement

This study protocol was approved by the institutional review board (IRB) of Pusan National University Yangsan Hospital (IRB No. 05-2014-017). Informed consent was waived by the boards.

## RESULTS

### Demographic features and the clinical outcomes

One hundred and ten patients who met the modified Duke's criteria for definite IE or possible IE (14) were analyzed. The median age was 52 yr (16-85 yr). Sixty seven patients (60.9%) were men and forty three patients (39.1%) were women. Most patients had native valve IE (*n* = 100, 90.9%) and a community origin of IE (*n* = 101, 91.8%). The mitral valve was the predominant infected valve (*n* = 43, 39.1%) followed by the aortic valve (*n* = 39, 35.5%). Eight patients with right-sided valve IE (7.3%)

and five patients with multi-valve IE (4.5%) were observed. The most frequent causative organisms were *Streptococci* in 38 patients (34.6%), followed by *Staphylococci* in 27 patients (24.5%) and other organisms in 8 patients (7.3%), and these included 2 patients with *Pseudomonas aeruginosa*, 2 patients with *Candida*, 2 patients with *Enterococcus*, 1 patient with *E. coli* and 1 patient with *gram-negative rods* (not identified). Thirty-seven patients (33.6%) had culture negative endocarditis. Fifty-seven patients (51.8%) had underlying disease. Previous heart disease (*n* = 37, 33.6%; 17 patients with valvular heart disease, 14 patients with congenital heart disease, 3 patients with heart failure, 1 patient with a prosthetic valve and 2 patients with coronary heart disease) was the most common underlying disease. The mean of total admission days was 36.1 days (range, 3-125 days) and 46 patients were admitted to the ICU. Surgery was performed on 41 patients (37.3%). Heart failure was main cause of surgical intervention (*n* = 18, 43.9%) and median day of surgery was 4 admission days (range, 1-7). Failure of medical treatment is secondary cause of surgical intervention (*n* = 12, 39.3%). In group of medical failure, 7 persistent bacteremia (> 7 days) and 5 increasing vegetation and re-embolism during treatment were observed and median operation day was 12 admission days (range, 7-18). Large vegetation and high mobile vegetation were third cause of surgical intervention for prevention of embolism (*n* = 6, 14.6%) and median surgery day was 5 admission days (range, 2-9). Three ventricular septum defect repairs (7.3%) and 2 permanent pacemaker insertion (4.9%) were undertaken.

The demographic, clinical and microbiological characteristics of the patients with and without embolism combined with IE are shown Tables 1 and 2.

### Embolitic events

Embolitic events occur in 39 of 110 patients (35.5%). The brain (*n* = 18, 38.5%) was main site of embolic infarction. Other sites included the spleen (*n* = 12, 30.8%), the lung (*n* = 11, 28.2%), the kidney (*n* = 9, 23.1%), the liver (*n* = 1, 2.6%) and main vessels (*n* = 1, 2.6%). Multi-site embolic infarctions were observed in 19 patients (48.7%). Embolic events were recognized at the time of hospital admission in 30 of 39 patients with embolic events (76.9%) and other 9 patients (23%) were recognized during hospital management due to new clinical symptom. There were no significant differences in the demographic characteristics (age, gender, underlying disease, the involved valve site, causative organism, the type of infected valve and the positivity of blood culture) between the patients with and without embolism. But nosocomial IE was observed only in the patients without embolism (0% vs. 12.7%, respectively, *P* = 0.016).

For the clinical outcome, the group of patients with embolism showed higher in-hospital mortality (46.2% vs. 8.5%, respectively, *P* = 0.03), more frequent ICU admission (53.8% vs. 35.2%, respectively, *P* = 0.045) and more accompanying other

**Table 1.** The demographic, clinical and microbiological characteristics of the patients with and without embolism and who had infective endocarditis (IE)

Parameters	All patients (n = 110)	Embolitic patients (n = 39)	Nonembolic patients (n = 71)	P value
Age (yr) [median (range)]	52 [16-85]	51.5 [20-85]	52 [16-82]	0.875
Gender (male/female)	67/43	20/19	47/24	0.125
Type of valve (%)				0.284
Native valve	100 (90.9)	37 (95)	63 (88.7)	
Prosthetic valve	10 (9.1)	2 (5)	8 (11.3)	
Site of the valve (%)				0.619
Aortic valve	39 (35.5)	13 (33.3)	26 (36.6)	
Mitral valve	43 (39.1)	15 (38.5)	28 (39.4)	
Aortic + Mitral valve	15 (13.6)	4 (10.3)	11 (15.5)	
Right sided valve	8 (7.3)	4 (10.3)	4 (5.7)	
Multi-valve	5 (4.5)	3 (7.6)	2 (2.8)	
Blood culture (%)				0.527
Positive	73 (66.4)	24 (61.5)	49 (69.1)	
Negative	37 (33.6)	15 (38.5)	22 (30.9)	
Pathogen (%)				0.613
<i>S. aureus</i>	27 (24.5)	7 (17.9)	20 (28.2)	
<i>Streptococcus</i>	38 (34.6)	13 (33.3)	25 (35.2)	
Others	8 (7.3)	4 (10.3)	4 (5.7)	
Culture negative	37 (33.6)	15 (38.5)	22 (30.9)	
Underlying disease (%)				0.294
Previous heart disease	37 (33.6)	11 (28.2)	26 (36.6)	
Diabetes	6 (5.5)	1 (2.6)	5 (7.0)	
Liver cirrhosis	3 (2.7)	1 (2.6)	2 (2.8)	
Brain lesion	8 (7.3)	3 (7.6)	5 (7.0)	
Others	9 (8.2)	3 (7.6)	6 (8.5)	
No underlying disease	53 (48.2)	20 (51.4)	33 (46.5)	
Origin of IE (%)				0.016
Nosocomial	9 (8.2)	0 (0)	9 (12.7)	
Community	101 (91.8)	39 (100)	62 (87.3)	

**Table 2.** Clinical influence of embolic infarction in the patients with infective endocarditis

Variables	All patients (n = 110) No. (%)	Embolitic patients (n = 39) No. (%)	Nonembolic patients (n = 71) No. (%)	P value
Admission days (days) [mean (range)]	36.1 (3-125)	34 (3-125)	37.3 (5-90)	0.488
In hospital mortality	24 (18.2)	18 (46.2)	6 (8.5)	0.030
Surgery	41 (37.3)	17 (43.6)	24 (33.8)	0.410
ICU admission	46 (41.8)	21 (53.8)	25 (35.2)	0.045
Accompanied with other cardiac complications	32 (29.1)	17 (43.6)	15 (21.1)	0.017

ICU, intensive care unit.

cardiac complication (43.6% vs. 21.1%, respectively,  $P = 0.017$ ). Table 2 shows clinical influence of embolic infarction in the patients with infective endocarditis.

### In-hospital mortality

The in-hospital mortality rate was 18.2%. The leading causes of death were sepsis ( $n = 8$ , 33.3%) and heart failure ( $n = 5$ , 20.8%) and these were followed by brain complications ( $n = 4$ , 16.7%), multi-organ failure ( $n = 3$ , 12.5%), sudden death ( $n = 3$ , 12.5%) and hospital acquired pneumonia ( $n = 1$ , 4.2%). The causes of death in group of patients with embolism were surgery related

**Table 3.** Simple logistic regression analysis of the potential independent risk factors for in hospital mortality

Variables	RR	95% CI	P value
Age	1.061	1.027-1.097	0.004
Total embolic events	3.000	1.086-8.287	0.034
CNS embolism	7.000	1.694-28.917	0.072
Multiple embolism	1.450	0.456-4.614	0.529
Surgery	0.366	0.125-1.070	0.066
<i>S. aureus</i>	4.068	2.205-22.508	0.005
Community origin	1.026	0.199-5.295	0.975
Cardiac complications	3.211	0.672-7.221	0.241

RR, relative risk; CI, confidence interval; CNS, central nervous system.

**Table 4.** Multiple logistic regression analysis of the potential independent risk factors for in hospital mortality

Variables	RR	95% CI	P value
Age	1.079	1.036-1.123	0.001
Total embolic events	3.510	1.271-9.690	0.015
<i>S. aureus</i>	5.098	1.308-18.508	0.023
Community origin	0.663	0.101-4.353	0.650
Cardiac complications	2.199	0.589-6.213	0.241

RR, relative risk; CI, confidence interval.

infection and sepsis ( $n = 6$ , 33.3%) and heart failure ( $n = 4$ , 22.2%) and followed by brain complications ( $n = 3$ , 16.7%: 2 brain hemorrhage: 1 massive brain infarction), multi-organ failure ( $n = 2$ , 11.1%), sudden death ( $n = 2$ , 11.1%) and hospital acquired pneumonia ( $n = 1$ , 7.6%). In embolic group, there were no significant differences in in-hospital mortality between the patients with embolic event during management and the patients with embolism at the time of admission (55.5% vs. 43.4%, respectively,  $P = 0.23$ ). On the multiple logistic regression analysis of the predictors of in hospital mortality, age (RR, 1.079; 95% CI, 1.036-1.123,  $P = 0.001$ ), embolic event (RR, 3.510; 95% CI, 1.271-9.69,  $P = 0.015$ ) and *staphylococcal* infection (RR, 5.098; 95% CI, 1.308-18.508,  $P = 0.023$ ) were independently associated with in-hospital mortality (Tables 3, 4).

## DISCUSSION

In this study, embolic events occurred in 35.5% of the patients with IE, and this was similar to that of the previous studies (30%-44%) (6, 7, 15-17). Contrary to several other studies (2, 9-13), there was no significant difference of the demographic characteristics (age, gender, underlying disease, the involved valve site, the causative organism, the type of infected valve and positivity of blood culture) between the embolic and non-embolic groups in this study.

*Staphylococcus* infection shows no difference between the embolic and non-embolic groups, but there was an independent association of *Staphylococcus* infection with in-hospital mortality in our study. In some earlier studies, *Staphylococcus* infection has been associated with both higher rates of compli-

cations and mortality in patients with IE (4, 11, 18), whereas other reports did not find any association between embolism and the causative microorganism (7, 21). The high rate of culture negative cases (33.6%) in this study could have affected interpreting the results about the causative organism. Previously receiving antibiotics is known to be the main cause of culture negative endocarditis (19, 20). In this study, out of 37 culture negative patients, 22 patients (59.5%) were referred from other hospitals under antibiotic treatment.

We evaluated the clinical impacts of embolism. The group of patients with embolism showed higher in-hospital mortality (46.2% vs. 8.5% respectively,  $P = 0.03$ ), more frequent ICU admission (53.8% vs. 35.2%, respectively,  $P = 0.045$ ) and a higher tendency to be accompanied with other cardiac complications (43.6% vs. 21.1%, respectively,  $P = 0.017$ ) as compared to the patients without embolism. Chu et al. (4) reported embolic events were closely related with surgery and mortality. Even though statistically significant differences were not observed, more patients of the embolic group received surgery (43.6% vs. 33.8%, respectively,  $P = 0.410$ ) in this study.

The in-hospital mortality rate was 18.2%, which was similar to those of other studies (3-5, 9, 18). Age, embolic events and *Staphylococcus* infection showed independent associations with in-hospital mortality in this study (Table 4). As for the predictors of mortality, several clinical variables have been investigated in previous studies, including age (22), *Staphylococcus* infection (4, 11, 18), prosthetic valve IE (2) and embolic events (2, 4, 9, 12, 13). Other studies have shown different results: Chu et al. (4) reported male gender, diabetes mellitus and the APACHE II score were independent predictors of mortality, and Hasbun et al. (5) reported comorbidity, an abnormal mental status, moderate to severe congestive heart failure and medical therapy without an operation were also independent predictors of mortality. Thuny et al. (9) showed a vegetation length > 15 mm as a predictor of mortality. We could not find any correlation between the underlying diseases, including heart failure, diabetes or surgery, and the in-hospital mortality. Higher in-hospital mortality in the patients with a cardiac complications were observed, but there was no statistically significance. In the Asian population, Nomura et al. (23) reported "at least one complication" was a risk factor of mid-term mortality in 62 patients of a single center retrospective cohort. However there have been few studies on the predictors of mortality and the impact of embolism. Recognition of these predictors of in-hospital mortality and the impact of embolism can be expected to improve the risk stratification and allow for more intensive treatment of patient with IE.

This study has several limitations. First, the study was performed in two referral, large teaching hospitals. This is might have caused a selection bias, including a high culture negative rate and relatively faster operations, and it could have affected the evaluation of the predictors of in-hospital mortality. Second,

the data on the vegetation size was not prospectively collected, so we could not evaluate the correlation between the vegetation size and the in-hospital mortality or embolism. Third, the study evaluated embolism on the basis of radiologic and clinical evidence. So clinically silent embolism may be not included in this study. Finally, this study may be affected by all of the limitations of the study's retrospective design. Therefore, further prospective large multi-centered studies are required to provide more accurate results in Asian populations.

## DISCLOSURES

The authors disclose no conflicts of interest.

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## REFERENCES

- Durack DT, Lukes AS, Bright DK. *New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med* 1994; 96: 200-9.
- Bayer AS, Bolger AF, Taubert KA, Wilson W, Steckelberg J, Karchmer AW, Levison M, Chambers HF, Dajani AS, Gewitz MH, et al. *Diagnosis and management of infective endocarditis and its complications. Circulation* 1998; 98: 2936-48.
- Wallace SM, Walton BL, Kharbanda RK, Hardy R, Wilson AP, Swanton RH. *Mortality from infective endocarditis: clinical predictors of outcome. Heart* 2002; 88: 53-60.
- Chu VH, Cabell CH, Benjamin DK Jr, Kuniholm EF, Fowler VG Jr, Engemann J, Sexton DJ, Corey GR, Wang A. *Early predictors of in-hospital death in infective endocarditis. Circulation* 2004; 109: 1745-9.
- Hasbun R, Vikram HR, Barakat LA, Buenconsejo J, Quagliarello VJ. *Complicated left-sided native valve endocarditis in adults: risk classification for mortality. JAMA* 2003; 289: 1933-40.
- Steckelberg JM, Murphy JG, Ballard D, Bailey K, Tajik AJ, Taliencio CP, Giuliani ER, Wilson WR. *Emboli in infective endocarditis: the prognostic value of echocardiography. Ann Intern Med* 1991; 114: 635-40.
- De Castro S, Magni G, Beni S, Cartoni D, Fiorelli M, Venditti M, Schwartz SL, Fedele F, Pandian NG. *Role of transthoracic and transesophageal echocardiography in predicting embolic events in patients with active infective endocarditis involving native cardiac valves. Am J Cardiol* 1997; 80: 1030-4.
- Adam O, Kramm T, Klein HH, Schäfers HJ. *Intraaortic vegetations as a manifestation of infective endocarditis. N Engl J Med* 2007; 356: 874-5.
- Thuny F, Di Salvo G, Belliard O, Avierinos JF, Pergola V, Rosenberg V, Casalta JP, Gouvenet J, Derumeaux G, Iarussi D, et al. *Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. Circulation* 2005; 112: 69-75.

10. Rohmann S, Erbel R, Görge G, Makowski T, Mohr-Kahaly S, Nixdorff U, Drexler M, Meyer J. *Clinical relevance of vegetation localization by transoesophageal echocardiography in infective endocarditis. Eur Heart J* 1992; 13: 446-52.
11. Fowler VG Jr, Sanders LL, Kong LK, McClelland RS, Gottlieb GS, Li J, Ryan T, Sexton DJ, Roussakis G, Harrell LJ, et al. *Infective endocarditis due to Staphylococcus aureus: 59 prospectively identified cases with follow-up. Clin Infect Dis* 1999; 28: 106-14.
12. Sanfilippo AJ, Picard MH, Newell JB, Rosas E, Davidoff R, Thomas JD, Weyman AE. *Echocardiographic assessment of patients with infectious endocarditis: prediction of risk for complications. J Am Coll Cardiol* 1991; 18: 1191-9.
13. Kupferwasser LI, Hafner G, Mohr-Kahaly S, Erbel R, Meyer J, Darius H. *The presence of infection-related antiphospholipid antibodies in infective endocarditis determines a major risk factor for embolic events. J Am Coll Cardiol* 1999; 33: 1365-71.
14. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, Bashore T, Corey GR. *Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis* 2000; 30: 633-8.
15. Ben-Ami R, Giladi M, Carmeli Y, Orni-Wasserlauf R, Siegman-Igra Y. *Hospital-acquired infective endocarditis: should the definition be broadened? Clin Infect Dis* 2004; 38: 843-50.
16. Schünemann S, Werner GS, Schulz R, Bitsch A, Prange HW, Kreuzer H. *[Emboloc complications in bacterial endocarditis]. Z Kardiol* 1997; 86: 1017-25.
17. Sandre RM, Shafran SD. *Infective endocarditis: review of 135 cases over 9 years. Clin Infect Dis* 1996; 22: 276-86.
18. Hill EE, Herijgers P, Claus P, Vanderschueren S, Peetermans WE, Herregods MC. *Clinical and echocardiographic risk factors for embolism and mortality in infective endocarditis. Eur J Clin Microbiol Infect Dis* 2008; 27: 1159-64.
19. Hoen B, Selton-Suty C, Lacassin F, Etienne J, Briançon S, Leport C, Canton P. *Infective endocarditis in patients with negative blood cultures: analysis of 88 cases from a one-year nationwide survey in France. Clin Infect Dis* 1995; 20: 501-6.
20. Werner M, Andersson R, Olaison L, Hogevik H. *A clinical study of culture-negative endocarditis. Medicine (Baltimore)* 2003; 82: 263-73.
21. Deprèle C, Berthelot P, Lemetayer F, Comtet C, Fresard A, Cazorla C, Fascia P, Cathébras P, Chaumentin G, Convert G, et al. *Risk factors for systemic emboli in infective endocarditis. Clin Microbiol Infect* 2004; 10: 46-53.
22. Di Salvo G, Thuny F, Rosenberg V, Pergola V, Belliard O, Derumeaux G, Cohen A, Iarussi D, Giorgi R, Casalta JP, et al. *Endocarditis in the elderly: clinical, echocardiographic, and prognostic features. Eur Heart J* 2003; 24: 1576-83.
23. Nomura A, Omata F, Furukawa K. *Risk factors of mid-term mortality of patients with infective endocarditis. Eur J Clin Microbiol Infect Dis* 2010; 29: 1355-60.