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Original Article

Validation of Euroscore II Cut-off at 12% for Active Infective Endocarditis

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Abstract

Objective: Patients with infective endocarditis (IE) have a high risk of perioperative death. An accurate and reliable predictive score is crucial for decision making. The aim of this study is to externally validate Euroscore II, at a cut-off of 12%, in the prediction of hospital mortality.

Patients and Methods: Data were collected from medical records of patients who were diagnosed with active IE between June 1st 2017 and June 1st 2020. Preoperative Euroscore II was calculated. Patients were categorized into 2 groups according to Euroscore II: those with scores < 12 and ≥ 12. The discriminatory ability using the cut-off value was determined from observed perioperative mortality.

Results: There were 43 patients diagnosed with active IE. None had prosthetic IE. Most were male (56%). The mean age was 47.7 years. Large vegetation was found in 89%. Only one patient had ejection fraction < 40%. The most common clinical manifestation was heart failure (81%). Around four-fifths had single valvular involvement (82%). The most affected site was the aortic valve (44%). Median time from diagnosis to surgery was 7.5 days. Median duration of aortic cross-clamp time and cardiopulmonary bypass time were 83 mins and 99 mins respectively. The mean Euroscore II was 8.6%. There was 7% mortality (3/43). All deaths occurred in patients with Euroscore II ≥ 12 (30% actual mortality in this group). By using cut-off value of Euroscore II at 12%, the area under the receiver operating characteristic curve was 91.3% (95% CI 85.3 – 97.2%).

Conclusion: This study confirmed the validity of using Euroscore II ≥ 12% to help discriminate high-risk active IE patients. It might be accurate enough external to help decision making for surgery in high-risk active IE patients in centers with similar circumstances.

Keywords: Active infective endocarditis, Euroscore II, External validity

Introduction

From our previous study, active infective endocarditis (IE) patients with values of Euroscore II at least 12% had significantly higher mortality when compared to patients with Euroscore II less than 12%.[1] In the present study, we aimed to externally validate this cut-off value in an independent group of patients with active IE. The management of IE is focused on early surgery, but patients who undergo early surgery have a 50% chance of active IE. Active IE might increase hospital mortality by up to 20 %.[2,3] The ability to accurately predict hospital mortality is therefore of paramount importance in surgical decision making.

The original Euroscore is one of the most useful

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scores for predicting in-hospital mortality and long-term survival in patients undergoing coronary artery bypass grafting (CABG)[4,5] as well as valvular surgery[6]. A limitation of this score is that it overestimates mortality in patients with Euroscore ≤ 6 undergoing valvular surgery, and underestimates mortality in patients with Euroscore > 13.[7,8] Although Euroscore II has better predictive ability than the original Euroscore especially for isolated CABG, CABG with aortic valve replacement (AVR), and isolated valve surgery,[9-11] it still underestimates actual mortality in high-risk patients.[12,13]

Based on these studies, to increase the usefulness and reliability of the Euroscore II, we focused only a subset of diseases in a specific population. We chose patients with active IE, as these patients have relatively poor outcomes after cardiac surgery. The scoring system used for counselling patients and their family must be very accurate in this situation.

Patients and Methods

The present study was approved by the Maharat Nakhon Ratchasima Hospital institutional review board (IRB) on June 18th, 2020. Data were retrospectively collected from patients 18 years or older who were diagnosed as having infective endocarditis according to modified Duke's criteria, between June 1st, 2017 to June 1st, 2020. Patients with intraoperative findings of obvious active endocarditis, and those who had antibiotics treatment less than 4 to 6 weeks were considered to have active IE.[14] Data collected included demographic data; echocardiographic data; type of endocarditis categorized as definite, possible, native, and prosthetic valve endocarditis; and lastly in-hospital mortality. The Euroscore II was calculated using an online application.

All patients were managed by an IE multidisciplinary team. Preoperative evaluation included transthoracic echocardiography (TTE) and coronary angiography (CAG) in patients who were 40 years or older. Surgery was performed via full sternotomy with standard cardiopulmonary bypass under mild to moderate hypothermia (body temperature of 32 to 34 ˚C). Cold-blood cardioplegia was used for myocardial protection. The aortic valve was exposed via oblique aortotomy and the mitral valve was exposed via Waterston groove or biatrial-transseptal approach. Infected valves would be radically excised. Prosthetic valves were selected according to patients' preferences or the surgeon's decision. Valve repair was performed if there was a high likelihood of a successful and durable repair of remaining normal valvular leaflet, as determined by direct visualization and intraoperative transesophageal echocardiography (TEE). All patients were transferred to the ICU for postoperative care, then to a step-down unit. Antibiotics was continued until completion of the planned course.

Numerical data were analyzed and presented in frequencies, percentages, means and standard deviations. P-values less than 0.05 were considered statistically significant. The discriminatory ability of the Euroscore II cut-off at 12% was assessed using estimated area under the receiver operating characteristic curve (AUROC), and its 95% confidence interval (95% CI).

Results

There were 43 patients who had native-valve active endocarditis. There was no patient with prosthetic-valve endocarditis during the study period. Most patients were men (56%). The mean age was 47.7 ± 14.7 years. Comorbidities included renal insufficiency (serum creatinine of at least 2 mg/dL), coronary artery disease, diabetes mellitus, rheumatic heart disease, congenital heart disease, hypertension and stroke (see Table 1). Hypoalbuminemia was seen in 32 patients (74%). Around one-third of patients (37%) had anemia. The presence of vegetation that was larger than 10 mm was found in 32 cases (89%). Only 1 patient (2%) had an ejection fraction (EF) less than 40%. Clinical manifestations included congestive heart failure (81%), new murmur (70%), embolic events (28%) and sepsis (19%).

Around four-fifths of cases had single valvular involvement (82%). There were 8 patients (19%) who had combined aortic and mitral endocarditis. The most affected site was the aortic valve (19 patients, 44%). The second most common site was the mitral valve (15 patients, 35%). Isolated tricuspid endocarditis was found in only 1 patient (2%).

All patients underwent urgent surgery. Median interval from the day of diagnosis to surgery was 7.5 days with an interquartile range (IQR) of 5 to 15 days. The median aortic cross-clamp time was 83 minutes (IQR, 66 to 108 mins) and the median cardiopulmonary-bypass (CPB) time was 99 minutes (IQR, 79 to 134 mins). The median length of stay in cardiac-care unit (CCU) was 5 days (IQR, 3 to 10 days). The median length of postoperative stay was 15 days (IQR, 10 to 23 days). The median length of overall-hospital stay was 30 days (IQR, 20 to 43 days) (see Table 1).

Table 1 Baseline, disease and operative characteristics of patients

		Euroscore		
Characteristics	**All patients (n=43)**	**< 12 (n = 33)**	**≥ 12 (n = 10)**	***p*-value**
Age(years): mean (SD)	47.7 (14.7)	57.7 (10.2)	44.6 (14.7)	**0.012**
Male gender: num (%)	24 (56)	18 (55)	6 (60)	0.999
Comorbid disease: num (%)				
DM	3 (7)	1 (3)	2 (20)	0.130
HT	8 (19)	5 (15)	3 (30)	0.362
Renal insufficiency (Creatinine > 2.0)	1 (2)	1 (3)	0	0.999
Coronary artery disease	2 (5)	1 (3)	1 (10)	0.415
Stroke	2 (5)	2 (6)	0	0.999
Rheumatic	4 (9)	4 (12)	0	0.558
Congenital heart disease	4 (9)	2 (6)	2 (20)	0.226
Laboratory finding: num (%)				
Albumin < 3 gm/dL	32 (74.4)	23 (69.7)	9 (90)	0.409
Hct < 30%	16 (37.2)	13 (39.4)	3 (30)	0.719
EF < 40%: num (%)	1 (2)	1 (3)	0	0.999
Vegetation size: num (%)				0.591
< 10 mm.	4 (11)	4 (14)	0	
10 to 15 mm.	18 (50)	15 (52)	3 (30)	
> 15 mm.	14 (39)	10 (34)	4 (40)	
Clinical presentation: num (%)				
New heart murmur	30 (70)	23 (70)	7 (70)	0.999
Embolic events	12 (28)	10 (30)	2 (20)	0.698
Sepsis	8 (19)	6 (18)	2 (20)	0.999
Congestive heart failure	35 (81)	27 (82)	8 (80)	0.999
Involved structures: num (%)				**< 0.001**
AV	19 (44)	16 (49)	3 (30)	
MV	15 (35)	15 (45)	0	
TV	1 (2)	0	1 (10)	
AV+MV	8 (19)	2 (6)	6 (60)	
Time to surgery (day): (median IQR)	7.5 (5, 15)	7.5 (4, 15)	7.5 (6, 15)	0.744
Clamp time (minutes): (median IQR)	83 (66, 108)	78 (62, 92)	114 (83, 156)	**0.033**
Bypass time(minutes): (median IQR)	99 (79, 134)	94 (77, 106)	143 (102, 183)	**0.030**
CCU stay (day): (median IQR)	5 (3, 10)	5 (3, 7)	7 (2, 13)	0.688
Post op. stay (day): (median IQR)	15 (10, 23)	15 (9, 21)	15.5 (13, 34)	0.335
Hospital stay (day): (median IQR)	30 (20, 43)	25 (18.5, 43.5)	35 (30, 42)	0.165

SD: standard deviation; DM: diabetes mellitus; HT: hypertension; wbc: white blood cell count; HCT: hematocrit; AV: aortic valve; MV: mitral valve; TV: tricuspid valve; CCU: critical care unit; IQR: interquartile range

Using the Euroscore II cut-off value of 12%, we compare patients with Euroscore II < 12% to those with Euroscore II ≥ 12 %. In the group with Euroscore II < 12%, with 33 patients, the mean age was significantly higher (*p*-value = 0.012). The group with Euroscore II ≥ 12%, with 10 patients, had tricuspid valve involvement in only 1 patient (10%), and combined aortic and mitral endocarditis in 6 patients (60%). The median operative times were significantly longer in the group with Euroscore II ≥ 12% (see Table 1).

The mean Euroscore II of all patients was 8.6% (range, 0.8% to 33.9%). There were 3 in-hospital deaths (7%). The mean Euroscore II in the group with Euroscore II < 12% and ≥ 12%, was 4.8% (range, 0.8% to 11%) and 21.4% (range, 13.5% to 33.9%) respectively. All patients who died postoperatively had Euroscore II ≥ 12 %. By using cut-off value of Euroscore II at 12%, the discriminatory ability of the Euroscore II to predict operative deaths as measured using the AUROC was 91.3% (95% CI 85.3- 97.2%) (see Figure 1).

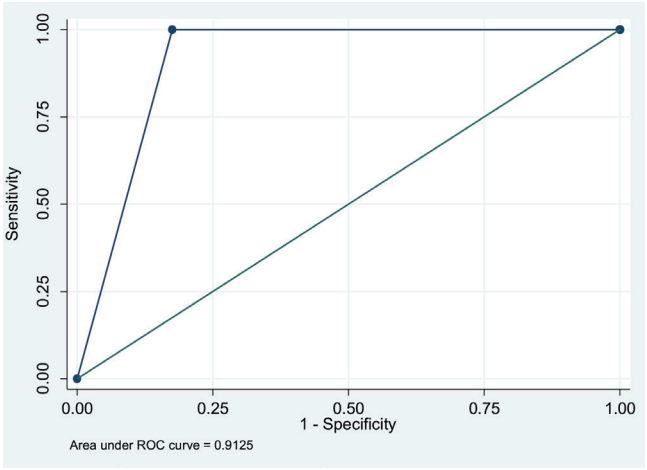

Figure 1 ROC curve for the Euroscore II cut-off at 12%

The majority of the patients had creatinine clearance of at least 50 mL/min (79%), good LV function (86%), no pulmonary hypertension (88%), and isolated single-valve endocarditis (72%). Almost half of the patients had functional class (NYHA) IV and were presented in a critical state (47%). In patients with Euroscore II ≥ 12%, 80% of patients had creatinine clearance < 50 mL/min, 90% had NYHA class IV and almost all were in a critical state. These risk factors were all significantly more frequent in patients with Euroscore II ≥ 12% than in those with Euroscore II < 12%. At least two interventions were needed in 70% of these patients (see Table 2).

Table 2 Euroscore factors

		Euroscore		
Factors	**All patients (n = 43)**	**< 12 (n = 33)**	**≥ 12 (n = 10)**	***p*-value**
Age: mean (SD)	47.7 (14.7)	57.7 (10.2)	44.6 (14.7)	0.012
Female gender: num (%)	19 (44)	15 (46)	4 (40)	0.999
Renal impairment: num (%)				< 0.001
Creatinine clearance > 85 ml/min	19 (44)	19 (58)	0	
Creatinine clearance 50 - 85 ml/min	15 (35)	13 (39)	2 (20)	
Creatinine clearance < 50 ml/min	9 (21)	1 (3)	8 (80)	
Extracardiac arteriopathy: num (%)	2 (5)	1 (3)	1 (10)	0.415
Poor mobility: num (%)	3 (7)	3 (9)	0	0.999
Previous cardiac surgery: num (%)	1 (2)	1 (3)	0	0.999
Chronic lung disease: num (%)	0	0	0	NA
Critical preoperative state: num (%)	20 (47)	11 (33)	9 (90)	0.003
Diabetes on insulin: num (%)	0	0	0	NA
NYHA: num (%)				0.004
II	10 (23)	9 (27)	1 (10)	
III	13 (30)	13 (40)	0	
IV	20 (47)	11 (33)	9 (90)	
LV function: num (%)				0.999
Good (> 50%)	37 (86)	28 (85)	9 (90)	
Moderate (31-50%)	6 (14)	5 (15)	1 (10)	
Poor (21-30%)	0	0	0	
Pulmonary hypertension: num (%)				0.059
no	38 (88)	30 (91)	8 (80)	
31 - 55 mmHg	3 (7)	3 (9)	0	
> 55 mmHg	2 (5)	0	2 (20)	
Urgency: num (%)				
Urgency	43 (100)	33 (100)	10 (100)	NA
Emergency	0	0	0	
Weight of the intervention				0.001
non - CABG	31 (72)	28 (85)	3 (30)	
2 procedures	10 (23)	5 (15)	5 (50)	
3 procedures	2 (5)	0	2 (20)	

Discussion

The results of the present study seemed to confirm that a Euroscore II ≥ 12% was correlated with significantly increased in-hospital mortality in patients with active IE. The cut-off value of 12% was obtained from a previous study which enrolled 121 patients who had active IE. This cut-off value provided a sensitivity of 40.9%, specificity of 92.2%, positive predictive value (PPV) of 75% and negative predictive value (NPV) of 73.2%.[1] In the present validation study, this cut-off value was used to predict in-hospital mortality in patients with active IE at the same Medical Center as that of the previous study. Patients thus had similar demographics, were looked after by the same care team, and treated under the same management protocols. The time frame of the present study was a continuation of the previous study. The present in-hospital mortality was 7% which was lower than that of the previous study. However, all deaths occurred in the group with Euroscore II ≥ 12%. The mean Euroscore II in this group was similar to the mean Euroscore II from the previous study in patients who died.[1] The AUROC in the present study was 91.3% (95% CI: 85.3% to 97.2%).

Koshy et al. studied the validity of Euroscore II in patients with active IE. They found that Euroscore II > 12% accurately predicted early and mid-term mor-tality with a sensitivity of 73%, specificity of 88%, PPV of 44% and AUROC of 80%.[15] These results seem to suggest that the cut-off value of 12% can be applied to other centers with similar settings. The patients' characteristics were similar to those of our study, although there might be some differences in the comorbidities which we found underlying rheumatic valvular heart disease in 9% whereas in their study they found 84%.

IE is considered one of the most severe valvular heart diseases. In-hospital mortality is approximately 9.6% to 45%.[16-18] This can increase to 25% to 36% if urgent surgery is needed.[19] Currently the treatment for IE is focused on early surgery, which may increase the chances of encountering active IE, so the in-hospital mortality is around 5% to 26%, which is relatively high.[20-26] Therefore, it is useful to have an accurate scoring system such as Euroscore II in the counseling and decision making in surgery.

Siregar et al. studied the performance of the original Euroscore. They found that this score was not sufficiently accurate in predicting operative mortality due to overestimation.[27] Although Euroscore II was developed for improved accuracy, to substitute for the original Euroscore, by increasing the number of patients in the development set from 19,000 to 22,381 from 154 centers in 43 countries, these patients were of diverse demographic, geographic, socioeconomic, and cultural background. Stavridis et al. found that the Euroscore II in patients who underwent cardiac surgery had an AUROC of 85% (95% CI: 75% to 94%).[28] Kartal et al. studied a subgroup of patient undergoing isolated coronary artery bypass and isolated mitral valve replacement surgery. They found that Euroscore II had good accuracy in predicting postoperative mortality.[29]

There are many reports confirming good accuracy of Euroscore II. When the details of the development of both versions of the Euroscore were examined, active IE was considered an important factor in the prediction of mortality. However, the number of patients with active IE was only 202 (1.1%) and 497 (2.2%) in the original Euroscore and Euroscore II development sets, respectively.[30] There were a few studies on Euroscore II in active IE, which underestimated the actual mortality but showed better accuracy than the original Euroscore, which overestimated actual mortality.[31-32] It is difficult to define the appropriate cut-off value of Euroscore II that is accurate and reliable enough for use in difficult treatment decisions.

There are several limitations in the present study. The present study is a retrospective observational study. It cannot adjust or control for all confounding factors. Conclusions from a study of patients at one Medical Center may not be applicable to other patients in other institutions. IE is not a common disease. There were too few patients in the present study (43) and too few outcomes (3) for the conclusions to be reliable. Further collection of data will require a prolonged period of study, during which time patient characteristics and treatment practices may change. Therefore, the cut-off value may change with time as well. The first important thing in applying the cut-off value of 12% is that the clinical circumstances must be similar.

Conclusion

The present study seemed to confirm the external validity of the cut-off value of Euroscore II at 12% in patients with active IE. Scores higher than the cut-off

were associated with significantly higher mortality. It might be useful for surgical decision making in high-risk active IE patients at medical institutions with similar circumstances.

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บทคัดย่อ **ความเที่ยงตรงของ Euroscore II ในการพยากรณ์โอกาสการเสียชีวิตของผู้ป่วยลิ้นหัวใจติดเชื้อในระยะรุนแรง**

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นิสิต พูลธนะนันท์, พบ.

กลุ่มงานศัลยกรรม โรงพยาบาลมหาราชนครราชสีมา จังหวัดนครราชสีมา

ความเป็นมา: ผู้ป่วยที่มีภาวะลิ้นหัวใจอักเสบติดเชื้อในระยะเฉียบพลันมีความเสี่ยงสูงต่อการเสียชีวิตภายหลังการผ่าตัด ตัวเลขพยากรณ์ความเสี่ยงก่อนการผ่าตัดที่เชื่อถือได้เป็นข้อมูลที่มีความสำคัญอย่างยิ่งในการตัดสินใจรักษา การศึกษานี้จึงมีขึ้นเพื่อจุดประสงค์ในการพิสูจน์ความตรงภายนอกของค่า Euroscore II ที่ ≥ 12 ในการทำนายโอกาสในการเสียชีวิตจริง

วิธีการศึกษา: การวิจัยนี้เป็นการศึกษาย้อนหลังซึ่งรวบรวมข้อมูลของผู้ป่วยที่ได้รับการวินิจฉัยมีการติดเชื้อในระยะเฉียบพลันของลิ้นหัวใจตั้งแต่ 1 มิ.ย. 2560 ถึง 1 มิ.ย. 2563 ผู้ป่วยถูกแบ่งเป็น 2 กลุ่มตามค่า Euroscore II (< 12 และ ≥ 12) ค่าพยากรณ์โอกาสเสียชีวิตจะถูกนำมาเปรียบเทียบกับอัตราการเสียชีวิตที่เกิดขึ้นจริง

ผลการศึกษา: มีผู้ป่วยทั้งหมด 43 รายที่ได้รับการวินิจฉัยการติดเชื้อในระยะเฉียบพลันของลิ้นหัวใจ ไม่มีผู้ป่วยรายใดที่มีการติดเชื้อของลิ้นหัวใจเทียม ส่วนมากเป็นผู้ป่วยชาย (56%) อายุเฉลี่ย 47.7 ปี พบว่ามีก้อนเชื้อโรคขนาดใหญ่ (Large vegetation) 89% มีผู้ป่วยเพียง 1 รายเท่านั้นที่มีการบีบตัวของหัวใจน้อยกว่า (Ejection fraction) 40% ส่วนมากผู้ป่วยมาด้วยภาวะหัวใจล้มเหลว (81%) ผู้ป่วยมักมีลิ้นหัวใจอักเสบติดเชื้อเพียงลิ้นเดียว (82%) ส่วนมากมักเป็นที่ลิ้นหัวใจเอออร์ติก (44%) ระยะเวลาเฉลี่ยหลังจากได้รับการวินิจฉัยจนถึงการผ่าตัดคือ 7.5 วัน ระยะเวลาเฉลี่ยของการหยุดหัวใจ และการใช้หัวใจและปอดเทียมอยู่ที่ 83 และ 99 นาที ตามลำดับ ค่าเฉลี่ย Euroscore II อยู่ที่ 9% ผู้ป่วยเสียชีวิตทั้งหมดอยู่ในกลุ่ม Euroscore II ≥ 12 (อัตราการเสียชีวิตที่เกิดขึ้นจริงในกลุ่มนี้คือ 30%) เมื่อใช้ค่า Euroscore II ที่ 12% เป็นเกณฑ์พิจารณาในการหาค่าความแม่นยำต่อการทำนายการเสียชีวิต พบว่าค่าพื้นที่ใต้กราฟ (Area under receiver operating characteristic curve) คือ 91.3% ค่าความเชื่อมั่น 95% (95% confidence interval) 85.3-97.2

สรุปผลการศึกษา: การศึกษานี้ยืนยันถึงความเที่ยงตรงของค่า Euroscore II ≥ 12% ซึ่งมีความสัมพันธ์กับอัตราการเสียชีวิตที่เกิดขึ้นจริงสูงขึ้นกว่าที่คำนวณได้ในผู้ป่วยที่ได้รับการวินิจฉัยมีการติดเชื้อในระยะเฉียบพลันของลิ้นหัวใจ มีความน่าเชื่อถือเพียงพอในการนำไปใช้เพื่อช่วยตัดสินใจก่อนผ่าตัดในผู้ป่วยความเสี่ยงสูงที่ได้รับการวินิจฉัยมีการติดเชื้อในระยะเฉียบพลันของลิ้นหัวใจในสถานพยาบาลที่มีสภาพแวดล้อมคล้ายคลึงกัน