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ORIGINAL PAPER

A risk factor analysis for in-hospital mortality after surgery for infective endocarditis and a proposal of a new predictive scoring system

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Abstract
Purpose Risk stratification is of utmost importance for patients with infective endocarditis (IE) who need surgery. However, for these critically ill patients, aspecific scoring systems are used to predict the risk of death after surgery. The aim of this study was both to analyze the risk factors for in-hospital death, which complicates surgery for IE and to create a mortality risk score based on the results of this analysis.
Methods Outcomes of 138 consecutive patients (mean age 60.6 ± 8.5 years) who had undergone surgery for IE in an Italian cardiac surgery center between 1999 and 2015 were reviewed retrospectively and a risk factor analysis (multivariable logistic regression) for in-hospital death was performed. The discriminatory power of a new predictive scoring system was assessed with the receiver-operating characteristic (ROC) curve analysis.
Results Twenty-eight (20.3%) patients died in hospital following surgery. Anemia [odds ratio (OR) 11.0, $p = 0.035$), New York Heart Association class IV (OR 2.61, $p = 0.09$), critical state (OR 4.97, $p = 0.016$), large intracardiac destruction (OR 6.45, $p = 0.0014$), and surgery of the thoracic aorta (OR 7.51, $p = 0.041$) were independent predictors of hospital death. A new scoring system was devised to predict in-hospital death after surgery for IE (area under ROC curve, 0.828, 95% confidence interval, 0.754–0.887). The score outperformed six of seven scoring systems, for early death after cardiac surgery, that were considered.
Conclusions A simple scoring system based on risk factors for in-hospital death was specifically created to predict mortality risk after surgery for IE. Prospective studies are needed for the score validation.

Keywords Cardiac surgery · Infective endocarditis · In-hospital mortality · Risk factor analysis · Quality of results improvement

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Introduction

Despite improvements in medical therapies and surgical techniques, infective endocarditis (IE) is still characterized by high levels of in-hospital mortality, which accounts up to 30%. Staphylococci and enterococci are the most common species isolated and their prevalence has been associated with the increased patient's age, chronic diseases, surgical procedures, and health care-associated infections. Logistical barriers and an absence of randomized trials hinder clinical management, and longstanding controversies such as use of antibiotic prophylaxis remain unresolved [1].

In 25–30% of cases, medical treatment alone is inadequate and must be combined with surgery, which aims to control infection by debridement and removal of necrotic tissue and to restore cardiac morphology by surgical repair and/or valve replacement. Cardiac operations in some of these critically ill patients may be challenging and give poor, early and late results even when carefully performed. Mortality rates have been reported to range between 10%, for elective patients, and up to 30%

in urgent surgery. Prolonged invasive ventilation, low cardiac output, acute kidney injury, sepsis, and bleeding are frequent postoperative complications [1–3]. Consequently, for patients with IE, risk stratification is important not only for the surgeon's decision-making, but also for counseling the patients and their family (ensuring a true informed consent) and a comparative assessment of quality of care. Currently, the estimation of risk of death after surgery is made using predictive scoring systems that have been derived from patient databases where most of patients had undergone cardiac operations other than those for endocarditis [4–8]. Because of this inherent limitation, some investigators are questioning as to the utility of these aspecific predictive systems for patients with IE [9–12]. Actually, specific predictive systems for in-hospital death after surgery in patients with IE have been devised as well [13–15]. Yet, no external validation has been performed and it is not clear about their impact into the clinical practice.

The authors of the present study have reviewed, retrospectively, the results of surgery for IE in their patients. The aims of the study were both to analyze the risk factors for in-hospital death and create a risk score based on the results of this analysis.

Materials and methods

Between 1999 and 2015, 138 consecutive patients (mean age 60.6 ± 8.5 years; females 19.6%) with definite IE according to the modified Duke criteria [16] underwent surgery at the Cardiovascular Department of the University Hospital of Trieste, Italy. Baseline characteristics of patients, surgical data, and endocarditis-related features were prospectively recorded for every patient in a computerized data registry (FileMaker Pro 12.0; FileMaker, Inc., Santa Clara, CA, USA).

Unless otherwise stated, the definitions and cut-off values of the preoperative variables were those employed for the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) [5]. In particular, anemia was defined as haemoglobin <12 g/dl for women and <13 g/dl for men; severe renal impairment was defined as estimated glomerular filtration rate <50 ml/min; large intracardiac destruction was defined as extensive valve destruction, perivalvular complications or multivalvular involvement. Definitions of postoperative complications were in accordance with the internationally agreed definitions of complications after cardiac surgery [17, 18].

Approval to conduct the study was acquired from the hospital ethics committee based on retrospective data retrieval; the need for patients to provide individual written consent was waived.

Statistical methods

Continuous variables with normal distribution were expressed as mean and standard deviation and those without normal distribution as median and the range between the first and the third quartile. Discrete variables were expressed as frequencies and percentages. Statistical comparison of baseline characteristics was performed using the Chi-squared or the Fisher's exact test for categorical variables, and the Student's *t* test or the Mann–Whitney *U* test for continuous variables, when appropriate. Backward, stepwise, multivariable, logistic regression analysis was used to identify independent predictors of in-hospital mortality after surgery. All the variables with a *p* value <0.1 by univariable analysis were included in a multivariable analysis model. For each significant variable, an odds ratio (OR) with the corresponding 95% confidence interval (95% CI) was calculated. Each of the risk indices had the variable weighted according to its regression coefficient. The goodness-of-fit of the model was evaluated with the Hosmer–Lemeshow test for logistic regression. The discriminatory power of the model was assessed with the receiver-operating characteristic curve and the calculation of the area under the curve (AUC). The new predictive scoring system was compared (using the method of DeLong) with four existing scoring systems for in-hospital mortality after cardiac surgery, EuroSCORE II [5], the additive EuroSCORE [19], the logistic EuroSCORE [6] and the Ontario Province Risk (OPR) score [7], as well as with three existing scoring systems specifically created to predict early mortality after surgery for IE, the prosthetic valve, age ≥70, large intracardiac destruction, *Staphylococcus* spp, urgent surgery, sex (female), EuroSCORE ≥10 (acronym: PALSUSE) score [13], the De Feo score (for native-valve IE) [14] and the Society of Thoracic Surgeons (STS) risk score for IE [15]. An internal validation procedure based on the 0.632 bootstrap was obtained. Statistical analysis was performed by the SPSS program for Windows, version 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics of patients, surgical data, and endocarditis-related features

Anemia (81.9%) and severe renal impairment (36.2%) were unusually frequent comorbidities. New York Heart Association (NYHA) class III–IV and critical state were present in 62.4 and 19.6% of patients, respectively. In 13% of cases, there was a concomitant, significant coronary artery disease. Embolism (34.8%) was the most frequent indication for surgery. The target organs were the skeleton (14 patients), the brain (13 patients), the spleen (12 patients), the kidneys (6 patients), and the heart (3 patients). Among the patients who experienced a cerebral embolism, three had a stroke, which was ischemic in two cases and haemorrhagic in one. Surgical priority was emergency or salvage in 15.9% of cases. A native valve was affected in 74.6% of patients and a prosthetic valve in 19.6%. The most common locations were the aortic valve (62.3%) and the mitral valve (43.5%). Surgery on thoracic aorta was performed in 6.5% of patients. A large intracardiac destruction occurred in 41.3% of cases. The infective organism was identified in only 71.7% of cases. The most common causal agents were Streptococcus species (32.6%) and *Staphylococcus aureus* (16.7%). The median period from hospital admission to surgery was of 6 days (Tables 1, 2, 3, 4).

Immediate outcomes

Twenty-eight (20.3%) patients died in hospital after surgery (Table 5). Surgery-related complications were common. Prolonged invasive ventilation, pneumonia, low cardiac output, acute kidney injury, renal replacement therapy, sepsis, multiple blood transfusion, and mediastinal re-exploration were the most frequent complications (Table 6).

Risk factors for in-hospital death and multivariable analysis models

Baseline characteristics and operative data of dead patients and the corresponding endocarditis-related features were compared with those of alive patients after surgery. Anemia, estimated glomerular filtration rate <50 ml/min, NYHA class IV, Canadian Cardiovascular Society class 4, left ventricular ejection fraction <50%, critical state, platelets $<231 \times 10^3/\mu l$, urgent surgical priority, large intracardiac destruction, two procedures, surgery on thoracic aorta, aortic cross-clamping time >150 min, and fungal etiology were risk factors for in-hospital death after surgery for IE according to the univariable analysis (Tables 1, 2, 3, 4). Using these risk factors for in-hospital death, two multivariable analysis models, preoperative and combined, were created. Anemia, NYHA class IV, critical state, large intracardiac destruction, and surgery on thoracic aorta (acronym: ANCLA) were the independent predictors of postoperative in-hospital death common to both models. The combined model includes aortic cross-clamping time >150 min as well (Table 7).

The ANCLA score

According to the multivariable analysis, a new scoring system, the ANCLA score, was created to predict in-hospital mortality after surgery for IE (Table 7). The ANCLA score performance is summarized in Table 8. No difference was found between the preoperative and the combined model of the score ($p = 0.86$, Fig. 1). In the study population, the ANCLA score was superior, in discrimination power, to every specific and aspecific score that was considered for comparison in the present study. Actually, AUC difference with EuroSCORE II was not quite significant ($p = 0.072$) (Table 8; Fig. 2). A positive internal validation procedure based on bootstrap was performed (Tables 9, 10).

Discussion

Between 1999 and 2015, a total of 138 patients with IE were operated on at the Cardiovascular Department of the University Hospital of Trieste, Italy. A weighted scoring system to predict in-hospital mortality after surgery for IE, the ANCLA score, was devised on the basis of the analysis of the perioperative data of these patients. The score was derived from a backward, stepwise, logistic regression model that was created to find the independent predictors of in-hospital mortality in this series of patients. The variables of the model were chosen from a pool of baseline characteristics of patients, surgical data, and endocarditis-related features. The ANCLA score variables refer to the patient's preoperative state (anemia, NYHA class IV, and critical state) and to surgical features and operative data (large intracardiac destruction, surgery on thoracic aorta, and aortic cross-clamping time). Consequently, preoperative correction of anemia, surgery performed before that severe congestive heart failure, critical state, or large cardiac involvement develops, and a fast surgical treatment could reduce the mortality risk, significantly, in these patients. This was also the practical aspect of the present analysis.

Table 1 Baseline characteristics of patients[a]

Variable	Total ($n = 138$)	Dead ($n = 28$)	Alive ($n = 110$)	p value
Age (years)	60.6 ± 8.5	61.6 ± 16	60.4 ± 14.8	0.69
<60	56 (40.6)	9 (32.1)	47 (42.7)	
60–70	38 (27.5)	8 (28.6)	30 (27.3)	
>70	44 (31.9)	11 (39.3)	33 (30)	
Female gender	27 (19.6)	7 (25)	20 (18.2)	0.42
Hypertension	21 (15.2)	4 (14.3)	17 (15.5)	1
Current smoker	11 (8)	2 (7.1)	9 (8.2)	1
Body mass index (kg/m^2)	25.5 ± 4.1	26 ± 4.1	25.3 ± 4.1	0.43
>30	18 (13)	5 (17.9)	13 (11.8)	0.53
Diabetes	22 (15.9)	5 (17.9)	17 (15.5)	0.77
Diabetes on insulin	9 (6.5)	3 (10.7)	6 (5.5)	0.39
Anemia[b]	113 (81.9)	27 (96.4)	86 (78.2)	0.025
Poor mobility[c]	2 (1.4)	1 (3.6)	1 (0.9)	0.37
Chronic lung disease[c]	13 (9.4)	4 (14.3)	9 (8.2)	0.47
eGFR (ml/min)[e]	67.7 ± 37.3	53.9 ± 30.9	71.3 ± 38.1	0.028
>85[c]	35 (25.4)	4 (14.3)	31 (28.2)	
50–85[c]	53 (38.4)	8 (28.6)	45 (40.9)	
<50[c]	50 (36.2)	16 (57.1)	34 (30.9)	
Dialysis	13 (9.4)	4 (14.3)	9 (8.2)	0.47
Extracardiac arteriopathy[c]	22 (15.9)	6 (21.4)	18 (16.4)	0.58
NYHA class				0.012
I	25 (18.1)	3 (10.7)	22 (20)	
II	27 (19.6)	1 (3.6)	26 (23.6)	
III	31 (22.5)	6 (21.4)	25 (22.7)	
IV	55 (39.9)	18 (64.3)	37 (33.6)	
CCS class 4	20 (14.5)	8 (28.6)	12 (10.9)	0.031
Left ventricular ejection fraction (%)	56.6 ± 3.5	54.6 ± 12.1	57.2 ± 10.3	0.29
>50[c]	106 (76.8)	18 (64.3)	88 (80)	
30–50[c]	28 (20.3)	9 (32.1)	19 (17.3)	
20–30[c]	3 (2.2)	1 (3.6)	2 (1.8)	
<20[c]	1 (0.7)	0	1 (0.9)	
Pulmonary artery pressure, systolic (mmHg)				0.12
<35	127 (92)	24 (85.7)	103 (93.6)	
35–55[c]	8 (5.8)	2 (7.1)	6 (5.5)	
>55[c]	3 (2.2)	2 (7.1)	1 (0.9)	
Coronary artery disease	18 (13)	5 (17.9)	13 (11.8)	0.53
Previous cardiac surgery	37 (26.8)	10 (35.7)	27 (24.5)	0.23
Critical state[d]	27 (19.6)	10 (35.7)	17 (15.5)	0.016
Length of the preoperative hospital stay (days)	6 (2–19)[f]	6 (3–19)[f]	6 (1–26)[f]	0.72

CCS Canadian Cardiovascular Society, *EuroSCORE* European System for Cardiac Operative Risk Evaluation, *eGFR* estimated glomerular filtration rate, *NYHA* New York Heart Association, *ROC* receiver-operating characteristic curve

[a] Unless otherwise stated, the values are the mean ± standard deviation, or the number of patients with the percentage in brackets

[b] Defined as haemoglobin <12 g/dl for women and <13 g/dl for men

[c] The definitions and the cut-off values are those employed for the EuroSCORE II [5]

[d] Defined as the presence of ventricular tachycardia/ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anaesthetic room, preoperative inotropes or intra-aortic balloon pump, preoperative acute renal failure (anuria or oliguria <10 ml/h)

[e] The creatinine clearance rate, calculated according to the Cockcroft–Gault formula, was used for approximating the GFR [5]

[f] The values are the median with the range between the first and the third quartile in brackets

Table 2 Baseline laboratory data[a]

Variable	Total ($n = 138$)	Dead ($n = 28$)	Alive ($n = 110$)	p value
White blood cell (10^3/μl)	12 ± 5.9	12 ± 6.3	12 ± 5.9	0.92
Platelets (10^3/μl)	221 ± 107	184 ± 80	229 ± 111	0.073
<231[b]	82 (59.4)	21 (75)	61 (55.5)	0.06
C-reactive protein (mg/dl)[c]	203.8 ± 91.8	181.6 ± 90.5	209.4 ± 91.6	0.15
Procalcitonin (ng/ml)[d]	12.6 ± 1.8	12.2 ± 1.7	12.7 ± 1.5	0.13
Pro-BNP (pmol/l)[e]	1286.2 ± 529.4	1181.7 ± 205.8	1313 ± 479.7	0.16

BNP brain natriuretic peptide, *ROC* receiver-operating characteristic curve

[a] The values are the mean ± standard deviation, or the number of patients with the percentage in brackets

[b] The best discriminative value for in-hospital mortality by ROC analysis

[c] Disposable only for 124 patients

[d] Disposable only for 109 patients

[e] Disposable only for 93 patients

Table 3 Surgical features and operative data[a]

Variable	Total ($n = 138$)	Dead ($n = 28$)	Alive ($n = 110$)	p value
Reason for surgery				
Refractory heart failure due to valvular dysfunction	32 (23.2)	9 (32.1)	23 (20.9)	0.21
Persistent infection	8 (5.8)	1 (3.6)	7 (6.4)	0.69
Embolism/Cerebral embolism/Stroke[b]	48 (34.8)/13 (9.4)/3 (2.2)	10 (35.7)/3 (10.7)/1 (3.6)	38 (34.5)/10 (9.1)/2 (1.8)	0.92/0.92/0.87
Recurrent	4 (2.9)	1 (3.6)	3 (2.7)	1
Perivalvular complications[c]	30 (21.7)	9 (32.1)	21 (19.1)	0.14
Surgical priority[d]				0.31
Elective	26 (18.8)	2 (7.1)	24 (21.8)	
Urgent	90 (65.2)	22 (78.6)	68 (61.8)	
Emergency	16 (11.6)	3 (10.7)	13 (11.8)	
Salvage	6 (4.3)	1 (3.6)	5 (4.5)	
Large intracardiac destruction[e]	57 (41.3)	17 (60.7)	40 (36.4)	0.019
Weight of the intervention[c]				
Combined CABG	25 (18.1)	7 (25)	18 (16.4)	0.29
Single non-CABG	89 (64.5)	13 (46.4)	76 (69.1)	0.025
Two procedures	46 (33.3)	14 (50)	32 (29.1)	0.036
Three procedures	3 (2.2)	1 (3.6)	2 (1.8)	0.5
Surgery on thoracic aorta	9 (6.5)	4 (14.3)	5 (4.5)	0.083
Surgical technique				0.82
Off-pump	3 (2.2)	1 (3.6)	2 (1.8)	
Beating heart on-pump	4 (2.9)	1 (3.6)	3 (2.7)	
On-pump	131 (94.9)	26 (92.9)	105 (95.5)	
Cardiopulmonary bypass time (min)	167.8 ± 78.5	218.5 ± 103.2	154.5 ± 65	<0.0001
Aortic cross-clamping time (min)	122.9 ± 50.9	152.7 ± 65.1	115.2 ± 43.6	0.0005
>150[f]	33 (23.9)	14 (50)	19 (17.3)	<0.0003
Duration of surgery (min)	300.1 ± 124.2	381.5 ± 175.5	280.5 ± 98.5	<0.0001

CABG coronary artery bypass grafting, *EuroSCORE* European System for Cardiac Operative Risk Evaluation, *ROC* receiver-operating characteristic curve

[a] The values are the mean ± standard deviation, or the number of patients with the percentage in brackets

[b] Neurological dysfunction lasting more than 24 h

[c] Perivalvular leak, annular or aortic abscess, sinus of Valsalva aneurysm, aortic fistula and prosthetic valve detachment

[d] The definitions are those employed for the EuroSCORE II [5]

[e] Defined as extensive valve destruction, perivalvular complications or multivalvular involvement

[f] The best discriminative value for in-hospital mortality by ROC analysis

Table 4 Endocarditis-related features[a]

Variable	Total (*n* = 138)	Dead (*n* = 28)	Alive (*n* = 110)	*p* value
Endocarditis				0.31
Active[b]	72 (52.2)	17 (60.7)	55 (50)	
Treated[b]	66 (47.8)	11 (39.3)	55 (50)	
Type of endocarditis				
Native valve	103 (74.6)	18 (64.3)	85 (77.3)	0.16
Prosthetic valve	27 (19.6)	8 (28.6)	19 (17.3)	0.18
Intracardiac device or other side	12 (8.7)	0	12 (10.9)	0.13
Involved structures				
Aortic valve	86 (62.3)	20 (71.4)	66 (60)	0.27
Mitral valve	60 (43.5)	13 (46.4)	47 (42.7)	0.73
Tricuspid valve	7 (5.1)	1 (3.6)	6 (5.5)	1
Multivalvular	23 (16.7)	7 (25)	17 (15.5)	0.27
Causal agents				0.041
Streptococcus species	45 (32.6)	9 (32.1)	36 (32.7)	
Staphylococcus aureus	23 (16.7)	2 (7.1)	21 (19.1)	
Coagulase-negative Staphylococci	10 (7.2)	4 (14.3)	6 (5.5)	
Enterococcus species	13 (9.4)	2 (7.1)	11 (10)	
Gram-negative bacteria	6 (4.3)	2 (7.1)	4 (3.6)	
Fungi	2 (1.4)	2 (7.1)	0	
Not identified	39 (28.3)	7 (25)	32 (29.1)	

EuroSCORE European System for Cardiac Operative Risk Evaluation

[a] The values are the number of patients with the percentage in brackets

[b] The definitions are those employed for the EuroSCORE II [5]

Critical state and large intracardiac destruction were defined incidentally according to the EuroSCORE [5, 6, 19] and the PALSUSE definition [13], respectively (actually, there are some little differences between the PALSUSE and the ANCLA definition). Also, NYHA class IV variable is common both to the De Feo score [14] and EuroSCORE II [5], and surgery on thoracic aorta variable is common to all the three EuroSCORE models [5, 6, 19]. Consequently, there is some degree of overlapping between the ANCLA score and the considered predictive systems, especially with EuroSCORE II.

There are two models of the ANCLA score: the preoperative model is composed of five variables; the combined model includes aortic cross-clamping time >150 min in addition to the variables of the preoperative model. There are two composite variables: critical state and large intracardiac destruction. The first is a well-defined composite variable of events indicating the critical preoperative state of the patient: ventricular tachycardia or ventricular fibrillation or aborted sudden death, cardiac massage, ventilation before anaesthetic room, inotropes or intra-aortic balloon pumping, and acute renal failure (defined as diuresis <10 ml/h) [5]. The further one was defined arbitrarily by the present authors as extensive valve destruction, perivalvular complications, or multivalvular involvement. Both variables take into account the fact that the results of cardiac operations in critically ill patients and of the treatment of complex intracardiac lesions are heavily dependent on the experience and the expertise of the surgeon. Unlike from other predictive systems [13], no causal agent (e.g. *Staphylococcus aureus*) was related to an increased in-hospital mortality after surgery. Actually, fungal etiology was a risk factor for in-hospital death after surgery according to the univariable analysis but it was not confirmed by the multivariable analysis. However, this might be due to the relatively small number of patients in the study.

Both preoperative and combined model of the scoring system showed good calibration and discrimination power. All the ANCLA score variables remained significant at the bootstrap internal validation. In the study population, the

Table 5 Comparison between specific predictive scoring systems for in-hospital mortality after surgery for IE

Characteristics	STS risk score for IE[a]	De Feo score (for native-valve IE)[b]	PALSUSE score[c]	ANCLA score[d]
Publication date	2011	2012	2014	2017
Study period	2002–2008 (7 years)	1980–2009 (30 years)	2008–2010 (3 years)	1999–2015 (17 years)
Source	STS database	University Hospital of Naples, Italy	GAMES registry (26 Spanish hospitals)	University Hospital of Trieste, Italy
No. of patients (mean age)	19,543 (55.1 years)	440 (49 ± 16 years)	437 (61.4 ± 15.5 years)	138 (60.6 ± 8.5, years)
Female	33.2%	28.2%	24.7%	19.6%
Diabetes	23.5%	11.6%	24.3%	15.9%
Chronic lung disease	22.8%	–	16.9%	9.4%
Severe renal impairment	23.3%	13.6%	–	36.2%
NYHA III–IV	–	15.9%	52.3%	62.4%
Previous cardiac surgery	32.9%	8.6%	–	26.8%
Embolism/Cerebral embolism	–/3.9% (stroke)	32.3%/13.4%	7.3%/4.8% (stroke)	34.8%/9.4% (stroke, 2.2%)
Perivalvular complications	–	15.9%	14.4%	21.7%
Emergency + Salvage	7.1%	12.5%	–	15.9%
Active IE	51.5%	83%	100%	52.2%
Prosthetic valve IE	20.6%	0	27.9%	19.6%
Multivalvular involvement	19.9%	19.5%	–	16.7%
30-Day/In-hospital mortality	8.2%/7.7%	9.1%/9.1%	–/24.3%	17.4%/20.3%

ANCLA anemia, *NYHA class IV* critical state, large intracardiac destruction, surgery on thoracic aorta; *EuroSCORE* European System for Cardiac Operative Risk Evaluation, *GAMES* Grupo de Apoyo al Manejo de la Endocarditis infecciosa en España, *IE* infective endocarditis, *NYHA* New York Heart Association, *PALSUSE* prosthetic valve, Age ≥70, large intracardiac destruction, *Staphylococcus* spp, urgent surgery, sex [female], EuroSCORE II ≥10%, *STS* The Society of Thoracic Surgery

[a] [15]

[b] [14]

[c] [13]

[d] Table 6

ANCLA score outperformed the three specific scoring systems for in-hospital (or 30-day) mortality after surgery for IE that were considered [13–15] and was superior to three of the four scoring systems for in-hospital (or 30-day) mortality after any cardiac operation that were used for comparison [6, 7, 19]. Actually, the ANCLA score showed a higher discrimination power even when compared to EuroSCORE II [5] but difference was not quite significant. However, EuroSCORE II consists of 18 variables and has been modeled from a contemporary surgical cohort of 22,381 patients, including 497 (2.2%) with active IE [5]. The performance of EuroSCORE II in estimating the perioperative risk of patients undergoing surgery for IE has been evaluated by other investigators. Some authors believe that EuroSCORE II underestimates post-cardiac-surgery mortality in these patients [10]; others have demonstrated poor calibration and comparatively poor discrimination of the system for emergency cardiac surgery [12]; others authors, finally, trust that EuroSCORE II may be a useful and appropriate tool for estimating perioperative risk even for IE patients and that specific endocarditis features will increase the model complexity without an unequivocal improvement in predictive ability [9, 11]. Consequently, there is no agreement on this issue.

Overall, the in-hospital mortality (20.3%) of the present series of patients was high. It was higher than that reported by the STS risk score (7.7%) and the De Feo score (9.1%). In the present authors' opinion, the more advanced age (5–10 years) of patients, as well as the higher rates of preoperative severe renal impairment, congestive heart failure, perivalvular complications, and emergency/salvage surgical priority of the present series, could give reason for this

Table 6 Perioperative complications and hospital course of patients[a]

Variable	$n = 138$
Stroke[b]	6 (4.3)
Ischemic	5 (3.6)
Bleeding	1 (0.7)
Delayed awakening	1 (0.7)
Prolonged (>48 h) invasive ventilation	48 (34.8)
Pneumonia	23 (16.7)
Atrial fibrillation, new onset	34/134[c] (25.4)
Myocardial infarction[d]	2 (1.4)
Immediate reoperation for acute prosthetic failure	2 (1.4)
Low cardiac output[e]	18 (13)
Intra- and postoperative use of IABP	8 (5.8)
Use of ECMO	5 (3.6)
Acute kidney injury[f]	21 (15.2)
Renal replacement therapy	17 (12.3)
Bleeding peptic disease	3 (2.2)
Mesenteric ischemia	3 (2.2)
Acute pancreatitis	1 (0.7)
Multiorgan failure	5 (3.6)
Sepsis	13 (9.4)
48-h Chest tube output/BSA (ml/m^2)	467.7 (264.3–1121.4)
Blood transfusion	90 (65.2)
Multiple blood transfusion (>2 RBCs)	65 (47.1)
Mediastinal re-exploration for bleeding or tamponade[g]	28 (20.3)
Length of the postoperative hospital stay (days)	18.5 (9–35)[h]
Length of intensive care unit stay (days)	5 (2–13)[h]

BSA body surface area, *ECMO* extracorporeal membrane oxygenator, *IABP* intra-aortic balloon pumping, *KDIGO* kidney disease: improving global outcomes, *RBCs* red blood cells

[a] Unless otherwise stated, the values are the number of patients with the percentage in brackets

[b] Neurological dysfunction lasting more than 24 h

[c] Patients with preoperative stable sinus rhythm or paroxysmal atrial fibrillation

[d] Defined according to the definition criteria for type V myocardial infarction by Moussa et al. [17]

[e] Defined as three consecutive cardiac index measurements <2.0 l/min/m^2 despite adequate preload, afterload and inotropic support, or IABP

[f] Defined according to the KDIGO criteria [18]

[g] Through re-sternotomy or subxiphoid window

[h] The values are the median with the range between the first and the third quartile in brackets

poor result. Besides, the De Feo score has been devised for native-valve IE, and consequently, there were no cases of prosthetic valve endocarditis among the patients from whom the score has been derived. When compared with

Table 7 The risk factors for in-hospital death (by multivariable analysis[a]) and the scoring

Variable	Preoperative model						Combined model					
	Regression coefficient	SE	*p* value	OR	95% CI	Points	Regression coefficient	SE	*p* value	OR	95% CI	Points
Anemia[b]	2.40	1.14	0.035	11.0	1.18–102.9	2.5	2.33	1.18	0.048	10.3	1.02–104.2	2.8
NYHA class IV	0.96	0.57	0.09	2.61	0.86–7.92	1	0.84	0.58	0.15	2.31	0.74–7.24	1
Critical state[c]	1.60	0.67	0.016	4.97	1.34–18.4	1.7	1.68	0.68	0.014	5.37	1.40–20.5	2
Large intracardiac destruction[d]	1.86	0.58	0.0014	6.45	2.05–20.3	1.9	1.63	0.60	0.0067	5.11	1.57–16.6	1.9
Surgery on thoracic aorta	2.02	0.99	0.041	7.51	1.09–51.8	2.1	1.80	1.01	0.076	6.05	0.83–44.1	2.1
Aortic cross-clamping time > 150 min[e]	–	–	–	–	–	–	1.03	0.53	0.051	2.81	1.00–7.91	1.2

95% CI 95% confidence interval, *EuroSCORE* European System for Cardiac Operative Risk Evaluation, *NYHA* New York Heart Association, *OR* odds ratio, *ROC* receiver-operating characteristic curve, *SE* standard error

[a] According to backward stepwise method, all the variables with a p-value <0.1 were included into the model; next, all the variables with a *p* value >0.2 were removed from the model

[b] Defined as haemoglobin <12 g/dl for women and <13 g/dl for men

[c] The definition is that employed for the EuroSCORE II [5]

[d] Defined as extensive valve destruction, perivalvular complications or multivalvular involvement

[e] The best discriminative value for in-hospital mortality by ROC analysis

Table 8 Performance of the ANCLA score and of other specific/aspecific predictive scoring systems for in-hospital mortality after surgery for IE

System	Goodness-of-fit[a]			Discrimination power[b]	
	Chi-squared	*df*	*p* value	AUC	95% CI
Specific					
ANCLA score, the preoperative model	4.66	6	0.588	0.828	0.754–0.887
ANCLA score, the combined model	1.31	7	0.988	0.823	0.749–0.883
PALSUSE score[c]	3.36	7	0.850	0.694	0.610–0.770
De Feo score (for native-valve IE)[d]	5.32	8	0.722	0.695	0.611–0.771
STS score for IE[e]	3.26	8	0.917	0.540	0.453–0.625
Aspecific					
Additive EuroSCORE[f]	15.5	8	0.050	0.733	0.651–0.805
Logistic EuroSCORE[g]	15.5	8	0.050	0.658	0.572–0.736
EuroSCORE II[h]	4.19	8	0.839	0.763	0.683–0.831
OPR score[i]	13.8	8	0.087	0.637	0.551–0.717

ANCLA anemia, *NYHA class IV* critical state, large intracardiac destruction, surgery on thoracic aorta, *AUC* area under the receiver-operating characteristic curve, *95% CI* 95% confidence interval, *DF* degrees of freedom, *EuroSCORE* European System for Cardiac Operative Risk Evaluation, *IE* infective endocarditis, *NYHA* New York Heart Association, *OPR* Ontario Province Risk, *PALSUSE* prosthetic valve, age ≥70, large intracardiac destruction, *Staphylococcus* spp, urgent surgery, sex (female), EuroSCORE ≥10, *STS* The Society of Thoracic Surgeons

[a] By the Hosmer–Lemeshow test for logistic regression

[b] By ROC analysis

[c] [13]

[d] [14]

[e] [15]

[f] [19]

[g] [6]

[h] [5]

[i] [7]

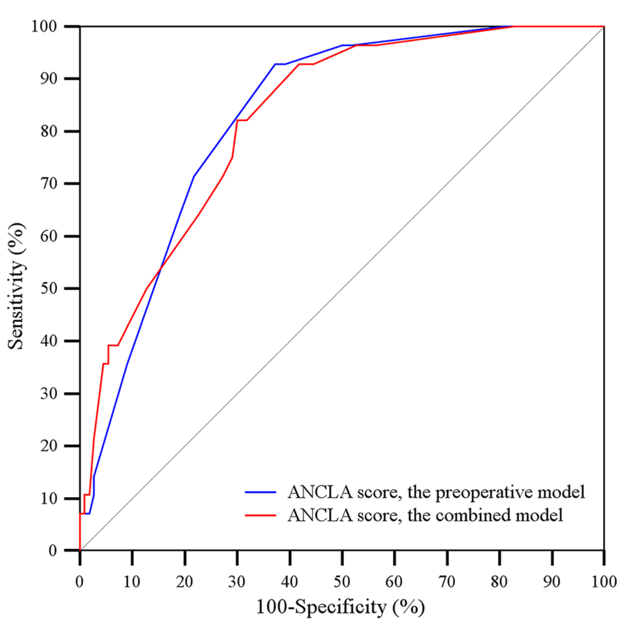
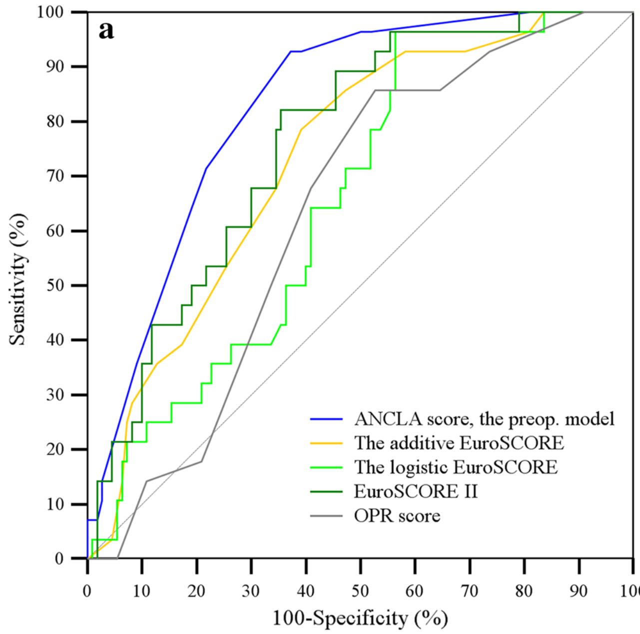


Fig. 1 The ANCLA score, the preoperative versus the combined model ($p = 0.86$). *ANCLA* anemia, *NYHA class IV* critical state, large intracardiac destruction, surgery on thoracic aorta

other similar series of patients in the literature, the rate of acute kidney injury (15.2%) of the present series was found to be elevated. This could be due to the unusually high rates of preoperative severe renal impairment (36.2%) and documented renal embolism (4.3%), as well as to routine use of high doses of norepinephrine in these patients with very low peripheral vascular resistance.

The primary limitation of the present study is the retrospective nature of the analysis performed on a relatively small number of patients. Also, the long period of data collection in a single center does certainly limit the value of the new score derived from the analysis. The ANCLA score has not been validated using other more numerous datasets. Of course, this validation will be performed with further data collected prospectively. However, a positive internal validation procedure based on bootstrap was performed. Because the causative microbial agents were not identified in about 28% of cases, there is a possibility that such unrecognized organisms might be associated to an increased mortality rate after surgery. This study did not evaluate the contribution to mortality risk of potentially important factors such as antibiotic treatment and preoperative patient preparation. The impact of different



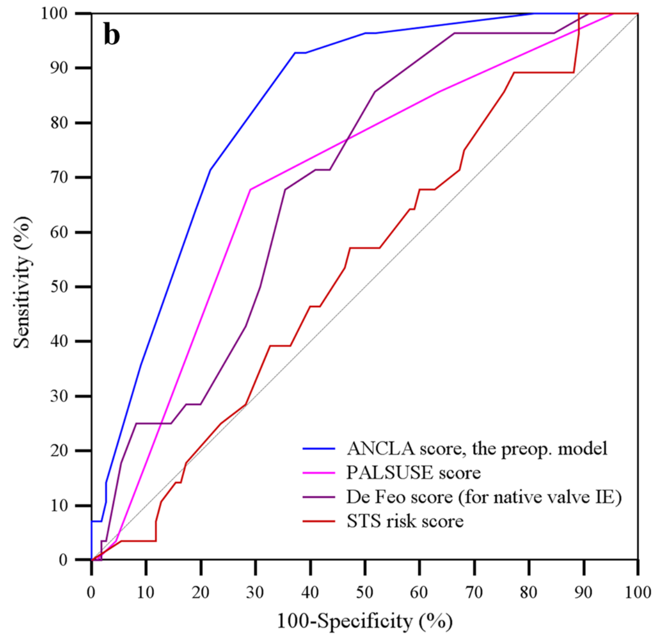


Fig. 2 The ANCLA score versus: **a** four predictive scoring systems for in-hospital death after cardiac surgery: the additive EuroSCORE ($p = 0.022$), the logistic EuroSCORE ($p = 0.0003$), EuroSCORE II ($p = 0.072$) and OPR score ($p = 0.0009$); **b** three specific predictive scoring systems for in-hospital death after surgery for IE: PALSUSE score ($p = 0.011$), the De Feo score (for native valve IE; $p = 0.0022$) and STS score for IE ($p < 0.0001$). *ANCLA* anemia, *NYHA class IV* critical state, large intracardiac destruction, surgery on thoracic aorta, *EuroSCORE* European System for Cardiac Operative Risk Evaluation, *IE* infective endocarditis, *OPR* Ontario Province Risk, *PALSUSE* prosthetic valve, age ≥70, large intracardiac destruction, *Staphylococcus* spp, urgent surgery, sex (female), EuroSCORE ≥10; *STS* The Society of Thoracic Surgeons

Table 9 The ANCLA score (the preoperative model): internal validation

Estimated specificity at fixed sensitivity				Estimated sensitivity at fixed specificity			
Sensitivity (%)	Specificity (%)	95% CI[a] (%)	Criterion (points)	Specificity (%)	Sensitivity (%)	95% CI[a] (%)	Criterion (points)
80	70.3	57.1–81.7	>6.2	80	65.4	43–84.6	>6.5
90	61.6	41.1–72.6	>5.4	90	38.2	17.9–60.7	>7
95	54.4	30.2–68.5	>4.4	95	21.9	4.1–44.2	>7.3
97.5	41.3	23.2–65.9	>3.8	97.5	10.4	0–25.8	>8.6

ANCLA anemia, *NYHA class IV* critical state, large intracardiac destruction, surgery on thoracic aorta, *95% CI* 95% confidence interval

[a] The bias-corrected and accelerated bootstrap interval (1000 iterations)

Table 10 The ANCLA score (the combined model): internal validation

Estimated specificity at fixed sensitivity				Estimated sensitivity at fixed specificity			
Sensitivity (%)	Specificity (%)	95% CI[a] (%)	Criterion (points)	Specificity (%)	Sensitivity (%)	95% CI[a] (%)	Criterion (points)
80	70.3	56.2–83.6	>4.8	80	65.3	43.7–84.2	>5.7
90	60.8	38.2–74.9	>4.2	90	50	31.6–70.9	>5.8
95	50.5	24.5–67.2	>3.5	95	42.9	21.4–63.8	>6
97.5	35.7	19.4–63.9	>2.6	97.5	30.4	3.6–54.1	>6.9

ANCLA anemia, *NYHA class IV* critical state, large intracardiac destruction, surgery on thoracic aorta, *95% CI* 95% confidence interval

[a] The bias-corrected and accelerated bootstrap interval (1000 iterations)

strategies of myocardial protection and of techniques such as intraoperative ultrafiltration on the risk of death was not taken into account. Another limitation is that the ANCLA score performance was measured in the patients from whom it had been derived; consequently, it was expected that the score would perform better than the other scoring systems considered in predicting in-hospital death after surgery for IE. Yet, no external validation of the score was performed.

Conclusions

For patients with IE undergoing surgery, preoperative risk stratification is of utmost importance. However, to predict in-hospital mortality after cardiac surgery in these critically ill patients, aspecific and relatively complex scoring systems derived from large populations of patients are being used. Specific and simpler predictive systems such as the ANCLA score could aid a rapid and reliable framing of the patient with IE. Of course, further large validation studies are necessary before introducing the ANCLA score into the clinical practice.

Compliance with ethical standards

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Conflict of interest None declared.

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