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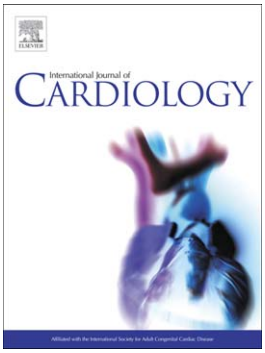

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A Predictive Model for Early Mortality after Surgical Treatment of Heart Valve or Prosthesis Infective Endocarditis. The EndoSCORE

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Structured Abstract

Background. The aim of this large retrospective study was to provide a logistic risk model along an additive score to predict early mortality after surgical treatment of patients with heart valve or prosthesis infective endocarditis (IE).

Methods. From 2000 to 2015, 2715 patients with native valve endocarditis (NVE) or prosthesis valve endocarditis (PVE) were operated on in 26 Italian Cardiac Surgery Centers. The relationship between early mortality and covariates was evaluated with logistic mixed effect models. Fixed effects are parameters associated with the entire population or with certain repeatable levels of experimental factors, while random effects are associated with individual experimental units (centers).

Results. Early mortality was 11.0% (298/2715); At mixed effect logistic regression the following variables were found associated with early mortality: age class, female gender, LVEF, preoperative shock, COPD, creatinine value above 2mg/dl, presence of abscess, number of treated valve/prosthesis (with respect to one treated valve/prosthesis) and the isolation of Staphylococcus Aureus, Fungus spp, Pseudomonas Aeruginosa and other micro-organisms, while Streptococcus spp, Enterococcus spp and other Staphylococci did not affect early mortality, as well as no micro-organisms isolation. LVEF was found linearly associated with outcomes while non-linear association between mortality and age was tested and the best model was found with a categorization into four classes (AUC = 0.851).

Conclusions. The following study provides a logistic risk model to predict early mortality in patients with heart valve or prosthesis infective endocarditis undergoing surgical treatment, called "*The EndoSCORE*".

Abstract word count: 240

Keywords

Infective endocarditis, risk score, valve surgery.

Introduction

Surgical treatment of heart valve and prosthesis infective endocarditis (IE) is account for 25-50% of cases in active IE and 20-40% in treated IE[1-4]. The mortality rate is very heterogeneous, ranging from 6 to 36%[5-14].

The European System for Cardiac Operative Risk Evaluation (Euroscore), either I or II[15,16], have been developed for risk assessment in general population undergoing cardiac surgery. Recently, these models were demonstrated to underestimate mortality in patients within lower risk strata and to overestimate mortality among patients at higher risk[17-19]. In a recent study[19], the Euroscore II was applied in a cohort of 149 cases with IE undergoing surgery, demonstrating as Euroscore II underestimates mortality by 5–10% when predicted mortality was higher than 10%.

Some studies have already addressed the issue to provide a specific risk score for early outcome according to pre- and operative data[20-23.]. De Feo et al[20] compared Euroscore with their specific score in a subset of 252 patients undergoing surgery for IE; Area under curve of their score was significantly higher than Euroscore for the more specific model (0.91 versus 0.84). However, the role of Euroscore in this specific field remains still debated, since other studies showed good discrimination[24,25].

Given the recent callout to report logistic models for the assessment of risk for surgery in case of valve or prosthesis IE[26], we reviewed the experience of 26 Italian Cardiac Surgery Centers to provide a logistic risk model for predicting early mortality of patients with heart valve and prosthesis IE undergoing surgery.

Methods

Study population

From 2000 to 2015, 2715 patients with native valve endocarditis (NVE) or prosthesis valve endocarditis (PVE) were operated on in 26 Italian Cardiac Surgery Centers (Appendix A) with a mean prevalence of 2.0% (1.4%-2.5%) of overall surgical population in the same Centers across the same period. Pre- and Operative characteristics are listed in the table 1.

Definition of terms and end-points

All the variables collected in the dataset were defined according to EuroscoreII[15]. The primary end-point was early mortality, defined as death by 30 days after surgery due to any cause.

Statistics.

Normal distribution of continuous variables was assessed by Kolmogorov-Smirnov test. Normally distributed variables are reported as mean and standard deviation; conversely non-normally distributed variables are reported as median and quartiles. Pairwise comparison was performed with T-test or Mann-Whitney U-test in case of continuous variables and chi-square with Fisher exact test in case of categorical variables. Variables with p-value <0.2 at univariate were initially entered into the multivariable model (Table 1). The relationship between early mortality and covariates was evaluated with logistic mixed effect models that incorporated both fixed and random effects and within-center correlation was taken into account as random effect. Fixed effects are parameters associated with the entire population or with certain repeatable levels of experimental factors, while random effects are associated with individual experimental units (centers). Linear association between outcome and continuous covariates was tested and potential non-linear effect was modeled with restricted cubic spline function or categorization, as described by Harrell[27,28].

The final reduced model was validated by parametric bootstrap (1000 runs) adjusted by the degree of optimism in bootstrap estimates and bootstrapping model performance tests of the score (1000 runs) was tested. Summarizing, the discrimination was evaluated by constructing receiver operating characteristic curve and calculating the area under the curve (AUC) with 95% confidence intervals. The accuracy of the models was also tested calculating the Brier score (quadratic difference between predicted probability and observed outcome for each patient), an overall performance measure that is 0 when the prediction is perfect. The calibration performance was evaluated comparing the comparison of actual slope and intercept with the ideal value of 1 and 0 was performed with the U statistic and tested against a χ^2 distribution with 2 degrees of freedom[27,28]

Two-sided statistics were performed with a significance level of 0.05. Statistical analyses were performed with R 3.3.1(R Development Core Team (2016), R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/).

Results

Early mortality was 11.0% (298/2715). The following variables were found to be related to higher early mortality at univariate analysis (Table 1): age classes; female gender; lower left ventricular ejection fraction (LVEF); site of IE; aortic regurgitation; prosthesis involvement, preoperative shock or heart failure, severe pulmonary hypertension, diabetes, chronic obstructive pulmonary disease (COPD), creatinine value equal or higher 2mg/dl, reoperation, presence of abscess, number of treated valves or prostheses, either mitral valve or prosthesis replacement, adding CABG procedure, some pathogens at blood or specimen cultures. Early mortality was found significant different among centers; hence, in order to quantify between-centers variability, we employed mixed effect models, with centers as random effect. No time-dependency of the outcome was shown.

At mixed effect logistic regression the following variables were found associated with early mortality: age class, female gender, LVEF, preoperative shock, COPD, creatinine value above 2mg/dl, presence of abscess, number of treated valve/prosthesis (with respect to one treated valve/prosthesis) and the isolation of Staphylococcus Aureus, Fungus, Pseudomonas Aeruginosa and other micro-organisms, while Streptococcus spp, Enterococcus spp and Staphylococci other than aureus did not affect early mortality, as well as negative cultures. Left ventricular ejection fraction was found to be linearly associated with outcomes while non-linear association between mortality and age was tested and the best model was found with a categorization into four classes (Table 2). A random effect was found only on intercept and intercept variation among centers accounted for most of the model's variance (standard deviation of the random effect 0.74, standard deviation of the residual variance0.86).The final model was reported in the table 1. Validation of the model by bootstrapping with 1000 repetitions did not show significant overfitting. Area under curve of the final model was 0.836 (95%CI: 0.813 – 0.860) in original dataset (Fig. 1) Bootstrapping corrected AUC was 0.851 (95%CI 0.845 – 0.858). The accuracy of the model by the Brier score was good (0.078) and bootstrapping corrected Brier score was 0.065 (95%CI 0.057 –

0.072). Also calibration performance was good (U statistic p-value 0.64) and bootstrapping corrected U statistic p-value was 0.065 (95%CI 0.057 – 0.072). The beta-coefficient was reported in the appendix B.

Discussion

The possible reason for discrepancy between Euroscore and more specific scores is very likely due to the low prevalence of IE among cohorts used to develop both versions of Euroscore (1.1% in Euroscore I and 2.2% in Euroscore II). Hence, the contribution of IE related features might have been diluted in the final models. In fact, Euroscore does not sufficiently take into account surgical difficulties due to extent of locally infected tissue (i.e. abscess), sepsis-related disorders (i.e. haemodynamic alterations and immunological paralysis), infection-related impairment in the process of valvular replacement and the type of pathogen[19,23].

In a recent review[14], results of studies from 1997 to 2009 are summarized. The age of patients seems to be the most common predictor for higher early mortality, followed by heart failure and the presence of staphylococcus aureus. Revilla[12] reported also renal failure as risk factor. However, all the cohorts were small, ranging from 104 to 559 patients and no risk model was provided. De Feo and coworkers[20] built a specific risk score from a cohort of 440 patients with native valve IE. The model showed high discriminative power (AUC 0.88), but it was not validated, neither internally nor externally. The largest cohort used for a specific model included more than 19000 patients from STS database[23], with following risk variables: urgency/emergency, cardiogenic shock, preoperative inotropes or intra-aortic balloon pump, prior surgery (either CABG or valve), multiple valve procedure, diabetes, chronic lung disease, active endocarditis, renal failure, hypertension and arrhythmia. Although the very large cohort enrolled, it was just additive score without including pathogens, its discriminative power was not so high (c-statistic 0.76) and the final model was not validated. A risk model for predicting 6-month mortality has been recently built starting from a large cohort of 4049 patients and validated externally in 1197 patients[29]. The final model included age classes, dialysis, IE factors, IE complications and surgery and it is somehow similar to our model, sharing most of the variables. However, again, it was an additive model and so just able to provide ordinal risk score rather than expected mortality rate; moreover, discriminative power was low both in original cohort (0.71) and in validation cohort (0.68).

In a very recent "callout for a logistic score", Wang et al[26] highlighted the lack of a logistic score for mortality after surgery for IE, since all the reported models were addictive without reporting beta coefficients and intercept useful to obtain a predictive mortality.

The present study is the first to provide logistic risk scores specific for early mortality after surgery for either native valve or prosthesis endocarditis, with high discriminative power and internal validation. The final model presents some variables previously reported in Euroscore[15,16] as age, LVEF, COPD, preoperative shock and renal failure and multiple valve procedures; the reasons of their prognostic weight are already clearly explained

Beside them, the presence of a perivalvular lesion, already described by others as large intracardiac destruction[21] or perivalvular involvement[20,29], mirrors a more aggressive infection status with destroyed tissue to repair that makes surgery more technical demanding with higher likelihood of failure. Beyond already described staphylococcus aureus[20,21,29], some other pathogens have been found to be associated with higher early mortality rate: Fungus spp, Pseudomonas Aeruginosa and other micro-organisms; in particular under the label of "other microorganisms" are all those less common microorganisms, often more difficult to eradicate with antibiotic therapy both before and after surgery and that could cause sepsis or major damage at the level of cardiac structures, resulting in a poor outcome.

The assessment of the surgical risk helps to measure the healthcare service quality, and risk profile is essential to differentiate patients by severity of health status. Likewise, knowing the risk of the patient can allow implementing individualized strategies to prevent complications. Hence, the main clinical implications of this risk score are providing prognosis prediction on an individual basis, establishing a benchmark for adjusting results from different experiences in order to evaluate and compare the outcome, improving decision-making process, adopting multidisciplinary approach for management of IE that involves cardiologists, infectious disease specialists and cardiac surgeons, that has been found to be crucial for survival[31]

Limitations

The main limitation of this study is the retrospective nature so that we were unable to investigate the prognostic role of some variables as the interval time from IE onset and surgery, recurrent embolization, persistent positive cultures. Concerning the timing of surgery, no significant difference was found for active versus treated endocarditis at univariate; however, we are unable to define the exact timing of surgery for any patient.

In conclusion, although these limitations, GIROC provides a logistic risk model to predict early mortality in patients with heart valve or prosthesis IE undergoing surgery, called "*The Endoscore*".

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Figure legends

Figure 1. Receiver operating characteristic (ROC) curves for the final model. The diagonal line represents no discriminatory power (AUC 0.50).

Tables

Table 1. Preoperative and operative characteristics of entire population and dead patients.

	Population	Dead	p-value
	N=2715	N=298	
Age (years)	59.6±15.1	66.0±13.7	
Age class			<0.001
<60	1196 (44.1%)	80 (6.7%)	
60-69	684 (25.2%)	69 (10.1%)	
70-79	708 (26.1%)	113 (16.0%)	
≥80	127 (4.7%)	36 (28.3%)	
Females	730 (26.9%)	112 (15.3%)	<0.001
Males	1985 (73.1%)	186 (9.4%)	
LVEF (%)	53.4±10.2	49.2±11.9	
LVEF class			<0.001
>50	1740 (64.1%)	145 (8.3%)	
31-50	862 (31.7%)	123 (14.3%)	
≤30	113 (4.2%)	30 (26.5%)	
Site of IE			<0.001
NVE	2160 (79.6%)	203 (9.4%)	
PVE	494 (18.2%)	82 (16.6%)	
NVE and PVE	61 (2.2%)	13 (21.3%)	
Isolated NVE*			0.015
Isolated AR	673 (24.8)	53 (7.9%)	
Isolated AS or ASR	154 (5.7%)	16 (10.4%)	
Isolated MR	690 (25.4%)	59 (8.6%)	
Isolated MS or MSR	62 (2.3%)	5 (8.1%)	
Isolated TR	95 (3.5%)	4 (4.2%)	
Isolated TS or TSR	4 (.01%)	0	
Isolated PR	4 (0.1%)	0	
Multi NVE	478 (17.6.%)	66 (13.8%)	
Isolated PVE			<0.001
Isolated APE	327 (12.0%)	47 (14.4%)	
Isolated MPE	143 (5.3%)	30 (21.0%)	
Isolated TPE	7 (0.3%)	3 (42.9%)	
Isolated PPE	5 (0.2%)	0	
Multi PVE	12 (0.4%)	2 (16.7%)	
Status of endocarditis			0.215
Active	1901 (70.1%)	219 (11.5%)	
Treated	814 (29.9%)	79 (9.7%)	

Preoperative Shock			<0.001
YES	296 (10.9%)	93 (31.4%)	
NO	2419 (89.1%)	205 (8.5%)	
Heart failure**			0.806
YES	285 (8.6%)	35 (12.3%)	
NO	2063 (91.4%)	243 (11.8%)	
Comorbidities			
Creatinine ≥ 2.0mg/dl			<0.001
YES	233 (8.6%)	55 (23.6%)	
NO	2482 (91.4%)	243 (9.8%)	
COPD			<0.001
YES	156 (5.7%)	36 (23.1%)	
NO	2559 (94.3%)	262 (10.2%)	
Previous neurological embolization			0.532
YES	296 (10.9%)	34 (11.4%)	
NO	2419 (89.1%)	265 (10.9%)	
Pathogens			
Staphylococcus aureus			<0.001
YES	483 (17.8%)	103 (21.3%)	
NO	2232 (82.2%)	195 (8.7%)	
Staph. non- aureus			0.268
YES	281 (10.3%)	25 (8.9%)	
NO	2464 (89.7%)	273 (11.2%)	
Streptococcus			<0.001
YES	941 (34.7%)	60(6.4%)	
NO	1774 (65.3%)	238 (13.4%)	
Pseudomonas			0.059
YES	21 (0.8%)	5 (23.8%)	
NO	2694 (99.2%)	293 (10.9%)	
Enterococcus			0.255
YES	289 (10.6%)	26 (9.0%)	
NO	2426 (89.4%)	272 (11.2%)	
Fungal IE			0.045
YES	38 (1.4%)	8 (22.1%)	
NO	2677 (98.6%)	290 (10.8%)	
Other germs			0.346
YES	142 (5.2%)	19 (13.4%)	
NO	2573 (94.8%)	279 (10.8%)	
Negative culture/specimen			0.553
YES	480 (17.7%)	49 (10.2%)	

NO	2235 (74.8%)	249 (11.2%)	
Surgery			
Redo			<0.001
YES	684 (25.2%)	110 (16.1%)	
NO	2031 (74.8%)	188 (9.3%)	
Abscess			<0.001
YES	397 (14.6%)	90 (22.7%)	
NO	2318 (85.4%)	208 (9.0%)	
Number of treated valves/prostheses			<0.001
One	2162 (79.6%)	213 (9.9%)	
Two	504 (18.6%)	72 (14.3%)	
Three	49 (1.8%)	13 (26.5%)	
AV/AP replacement			0.241
YES	1646 (60.6%)	190 (11.5%)	
NO	1069 (39.4%)	108 (10.1%)	
Type of implanted prosthesis			0.091
Bioprosthesis	950 (23.4%)	121 (12.7%)	
Mechanical	636 (35.0%)	60 (9.4%)	
Homograft	60 (2.2%)	9 (15.0%)	
AV repair			0.389
YES	6 (0.2%)	0	
NO	2709 (99.8%)	298 (11%)	
MV procedure			<0.001
MV/MP replacement	986 (36.3%)	141 (14.3%)	
MV repair/MP re-suture	408 (15.0%)	29 (7.1%)	
Type of implanted MV prosthesis			0.016
Bioprosthesis	477 (%)	84 (17.6%)	
Mechanical	486 (%)	54 (11.1%)	
Unknown	23 (%)	3 (13.0%)	
TV surgery			0.042
TV/TP replacement	76 (2.8%)	6 (7.9%)	
TV repair	162 (6.0%)	29 (17.9%)	
PV surgery			0.482
YES	4 (0.1%)	0	
NO	2711 (99.9%)	298 (11.0%)	
Aortic surgery			0.515
YES	67 (2.5%)	9 (13.4%)	
NO	2648 (97.5%)	289 (10.9%)	
CABG			0.223

YES	150 (5.5%)	21 (14%)	
NO	2565 (94.5%)	277 (10.8%)	
CPB time (min)	72 (16-98)	63 (16-111)	
Ischemic time (min)	61 (35-85)	57 (21-92)	

* requiring surgical treatment

** excluding patients on shock

Legend. LVEF = left ventricular ejection fraction, NVE = native valve endocarditis, PVE = prosthetic valve endocarditis, AR = aortic regurgitation, AS = aortic stenosis, ASR = aortic steno-regurgitation, MR = mitral regurgitation, MS = mitral stenosis, MSR = mitral steno-regurgitation, TR = tricuspid regurgitation, TS = tricuspid stenosis, TSR = tricuspid steno-regurgitation, PR = pulmonary regurgitation, APE = aortic prosthesis endocarditis; MPE = mitral prosthesis endocarditis; TPE = tricuspid prosthesis endocarditis; PPE = pulmonary prosthesis endocarditis; COPD =chronic obstructive pulmonary disease, AV = aortic valve, AP = aortic prosthesis, MV = mitral valve, MP = mitral prosthesis, TV = tricuspid valve, TP = tricuspid prosthesis, PV =pulmonary valve, CABG = coronary artery bypass grafting, CPB =cardiopulmonary bypass.

Table 2. Odds ratios of the fixed effects of the adjusted Logistic mixed effect model for predicting early mortality

Variable	Odds Ratio	95%CI	P value
Age			
<60 (reference)			
60-70 years	1.59	1.09 - 2.31	0.014
70-80 years	2.41	1.71 – 3.40	<0.001
> 80 years	4.65	2.80 – 7.73	<0.001
Female gender	1.67	1.26 – 2.23	<0.001
Left Ventricular Ejection Fraction (%)	0.97	0.96 – 0.98	<0.001
Creatinine >= 2 mg/dL	1.66	1.08 – 2.53	0.02
Chronic obstructive pulmonary disease	1.98	1.23 – 3.18	<0.001
Preoperative Shock	4.31	3.00 -6.21	<0.001
Number of Treated valves/prostheses			
1 (reference)			
2	1.65	1.19 – 2.28	<0.001
3	4.49	2.02 – 9.99	0.003
Presence of abscess	2.97	2.04 – 4.31	<0.001
Pathogen isolated on blood or specimen culture			
Negative colture; Streptococcus spp; Enterococcus spp; Staphylococcus non-Aureus (Reference)			
Pseudomonas Aeruginosa	*4.33*	*1.35 – 13.93*	0.014
Staphylococcus Aureus	*3.45*	*2.52 – 4.73*	<0.001
Fungal disease	*5.26*	*2.15 – 12.90*	<0.001
Other	*1.83*	*1.02 – 3.27*	0.039

Appendix A. Involved Italian Centers of Cardiac Surgery

University Hospital - "Aldo Moro" University – Bari

AO Papa Giovanni XIII – Bergamo

S. Orsola-Malpighi University Hospital – Bologna

Spedali Civili Hospital – Brescia

Poliambulanza Hospital – Brescia

S. Anna e S. Sebastiano Hospital – Caserta

Magna Grecia University Hospital – Catanzaro

S. Anna Hospital – Catanzaro

SS. Annunziata Hospital – "G. D'Annunzio" University – Chieti

S. Croce Hospital - Cuneo

S. Martino IRCCS Hospital – University of Genova - Genova

Vito Fazi Hospital – Lecce

Niguarda Hospital – Milan

Sacco Hospital – University of Milan - Milan

San Raffaele IRCCS Hospital – Milan

Monaldi University Hospital – University of Napoli - Napoli

University Hospital – University of Padua - Padua

Maggiore University Hospital – University of Parma - Parma

AO Pisana University Hospital – University of Pisa - Pisa

San Camillo-Forlanini Hospital - Rome

San Donato IRCCS Hospital – San Donato Milanese, Milan

Mauriziano Hospital – Turin

Molinette Città della Scienza Hospital – University of Turin -Turin

University Hospital –University of Varese - Varese

University Hospital –University of Verona - Verona

S. Maria Misericordia Hospital – University of Udine - Udine

Appendix B. Beta coefficient and Standard error

Variable	Beta – coefficent	Standard error
Age		
60-70 years	0.46	0,19
70-80 years	0.88	0.17
> 80 years	1.53	0.25
Female gender	0.51	0.15
Left Ventricular Ejection Fraction (%)	-0.03	0.006
Creatinine >= 2 mg/dL	0.50	0.21
Chronic obstructive pulmonary disease	0.68	0.24
Preoperative Shock	1.46	0.19
Number of Treated valves/prostheses		
2	0.50	0.17
3	1.50	0.40
Presence of abscess	1.09	0.19
Pathogen isolated on blood or specimen culture		
Pseudomonas Aeruginosa	*1.46*	*0.60*
Staphylococcus Aureus	*1.24*	*0.16*
Fungal disease	*1.66*	*0.45*
Other	*0.60*	*0.30*
Intercept	*-2.60*	*0.42*

Fig. 1