

# What is the Advantage of using Risk Score in Infective Endocarditis: An Opinion

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**Abstract:** Infectious endocarditis (IE) is a very heterogeneous condition, which often requires surgical treatment. Even with surgical treatment, 30-day mortality rate can be high. A risk stratification is needed for the individual prognosis of the patient, but also for quality of care. Existing scores such as EuroSCORE II and STS scores do not include specific IE related parameters and give a poor assessment of the prognosis.

A literature search was made in Web of Science for existing risk scores. The use of secondary references from comparative series proved to be necessary.

Eight useful manuscripts could be identified in which a model was constructed. Two more comparative manuscripts are also found. Regression coefficients were mostly used to achieve this aim. However, there is considerable variation in study design, inclusion of patients and of risk factors. Definitions of risk factors and length of inclusion also vary. Five factors are of major importance: hemodynamic status, renal dysfunction, age, prosthetic valve infection and periannular involvement. In only one report medically treated patients are included which allows inclusion surgery itself as a factor.

Hemodynamic status (including heart failure and need for mechanical support), renal dysfunction and age prove in most instances to be the dominant factors, but more specific IE related factors such as microbial data, Periannular involvement and cardiac damage should not be neglected. Because of the lengthy inclusion time, improvement of operative and postoperative care should be taken into consideration. These models have a potential value, but continuous recalibration, based on future international prospective data collection (such as in ICE-PCS) is necessary.

**Keywords:** Infective endocarditis, Mortality, Risk score, Hemodynamic status, Renal dysfunction, Age.

## INTRODUCTION

Infective endocarditis (IE) is a serious and heterogeneous condition [1-4] varying in clinical presentation and microbial agents. It can present as native (NVE) and prosthetic (PVE) valve IE, with or without cardiac and extra-cardiac complications. Its incidence has not diminished in the past 30 years [2]. This condition is the result of a complex interaction between the microorganism, its virulence and patient related factors, which include demographics and potential preexisting comorbidity. IE is becoming more prevalent in elderly patients with degenerative valve disease. A particular aggressive microorganism, *Staphylococcus aureus*, is also on the rise [2]. Surgery is often required to treat IE [2, 4-6]. Debridement of all necrotic and infected tissue and repair of cardiac damage often makes this a difficult and hazardous procedure. The indications are heart failure or hemodynamic instability, uncontrolled infection and risk for embolism [7]. In experienced centers, 30-day mortality could exceed 20% [2]. In urgent cases, this could even be 30% [5, 8]. This rate is higher than for any other surgical procedure on heart valves.

Moreover, the number of patients for any given center is small, leading to long inclusion times and slow learning curves, which adds to this problem. Rapid surgical decision-making concerning complex and potentially hazardous procedure with incomplete adequate clinical information is the most difficult aspect in dealing with patients with IE. Although the indication for surgery is becoming increasingly clear [1, 5], in some cases, microbial information is absent because cultures remain negative and some preexisting comorbid conditions might still be in the asymptomatic phase and therefore be undetected. An adequate scoring system leading to optimal patient selection, indication, timing and technique of surgery can be helpful herein [4]. Classic score systems such as EuroSCORE and STS systems are considered by most authors as neither specific nor accurate for IE [2-6]. These score systems lack the discrimination and calibration capacity for emergency cardiac surgery [3, 8]. Predictive risk models should be accurate and easy to use by physicians. The research questions are: what are the available risk score systems for IE, how do they compare and what is their quality?

## METHODS

A literature search was performed in PubMed and Web of Science, with the search terms "endocarditis

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AND risk score". Use of secondary references proved to be necessary. Absence of a multivariate analysis is an exclusion criterion. The Duke criteria are universally applied. Right-sided IE is excluded in most papers. The manuscripts are evaluated for their inclusion criteria of patients, design, statistical technique and construct of the model with validation and calibration techniques. This review focuses only on hospital or 30-day mortality, with one exception [9].

## RESULTS

Using secondary references, eight papers could be selected. Seven of them investigate the 30-day mortality [1-6, 8]. One paper is focused on mortality at six months, and includes also medically treated patients. This allows the inclusion of surgery itself as a factor in the analysis as well as in the score model [9]. Two additional manuscripts make a comparison between some of these scores [7, 10]. Only the series based on the STS-IE score includes a large number of patients and is derived from the STS Adult Cardiac Surgery Database [2]. Another smaller series is derived from an ongoing multipurpose database and analyzes surgical patients with active IE for the RISK-E score [4]. One manuscript is derived from a prospective population-based observational study in 8 European centers, as members of the AEPEI association [8]. One older Brazilian small study includes a rather young population, in which rheumatic heart valve disease is more common and whose patients suffer from active IE

[1]. For sake of homogeneity, another series includes only patients with NVE. Surgery has been considered urgent or emergent in over 90% of these patients [3]. One manuscript is based on 26 centers, but the sample is still rather small [5].

Table 1 shows the size of the populations, the number of involved centers, the mean or median age, the hospital mortality, the percentage of NVE and active IE as well as the inclusion era. It is immediately obvious that there is a wide variation in these parameters, which makes comparison between the different scoring systems difficult. Specific risk factors could have an entirely different meaning in series with a low hospital mortality compared with those with a high mortality. Some findings are rather unexpected. One older Brazilian series with a relatively high mortality of 26.3% has a mean patient age of 33.9 years [1] while in three other series with much older patients [55, 59 resp. 60 year] show a lower mortality, between 8.2 and 15.5% [2, 6, 8]. Table 2 shows the models, together with the area under the curve (AUC) which is helpful to estimate the discriminative power of the model. For the sake of simplicity, some parameters have to be grouped as stated previously [11]. It is also immediately clear that different series usually study different factors. Left ventricular factors including the hemodynamic status (such as emergent or urgent status), congestive heart failure (CHF), New York Heart Association functional class IV, need for intra-aortic balloon pump and need for mechanical ventilation because of pulmonary edema, but also renal dysfunction

**Table 1: Characteristics of the Series**

Author (Ref N°)	Score Name	N	Centers	Hosp.mort (%)	Age (y)	NVE (%)	Act IE (%)	Era
Gaca 2011 [2]	STS-IE	13,617	824	8.2	55 (45-66)	not stated	51.5	2002-2008
Olmos 2017 [4]	RISK-E	424 (D) 247 (V)	3	29.2	61+/- 14	60	100	1996-2014
Gatti 2017 [8]		361	8	15.5	59+/-15	80.7	12.8	2000-2015
Martinez 2014 [5]		437	26	24.3	61+/-15	61.1	100	2008-2010
Da Costa 2007 [1]	Da Costa	186	1	26.3	33.9	69.9	64.0	1988-1998
De Feo 2012 [3]	De Feo	440	1	9.1	49+/-16	100	83.0	1980-2009
Di Mauro 2017 [6]	Endoscore	2715	26	11.0	60+/-15	79.6	70.1	2000-2015
Park 2016* [9]		4049	ICE-PCS	24.0	59 (45-72)	76.1	9.3	2000-2006
		1197	ICE-PCS+	28.6				2008-2012
Varela 2017* [10]		18	1	26.8**	63+/-1	62.8	100	2002-2016

D: development sample; hosp. mort: hospital mortality (or 30-day mortality); IE: infective endocarditis; N: number of patients; NS: not stated; NVE: native valve endocarditis; surg: surgery; V: validation sample.

\*The series of Park and Varela compare some of the score models and are not designed for the development of such model.

\*\*The series of Park 2016 shows mortality at 6 months and not at 30 days.

**Table 2: Score for the Grouped Preoperative Factors**

Author	Gaca 2011	Olmos 2017	Gatti 2017	Martinez 2014	DaCosta 2007	De Feo 2012	Di Mauro 2017	Park 2016
Reference N°	[2]	[4]	[8]	[5]	[1]	[3]	[6]	[9]
<i>Cardiac factors</i>								
Card shock	17	15	1.1		5**	11***		
IABP	10							
Urgent surgery			1	1				
CHF/NYHA IV			1		5**	9		3
Multiple valves	9				8			
Arrhythmia	8							
Prior CABG	7							
Prior valve surg.	7							
PVE		6		1	5**			1
peri-ann		5		1	5**	5		2
CD					5			
Veget > 10mm					4			1
<i>Non-cardiac complications of IE</i>								
Renal dysf.	12	5	1.8			5		3
Stroke								2
TC-penia		7						
<i>Demographics and chronic disease</i>								
Age		0/9/13/14*		1	4	5/7/9/11/13		0/2/3/4
Female gender				1				
Diabetes	8/9							
COPD	5							
Hypertension	5							
ES>10				1				
<i>Microbial related factors</i>								
Sepsis		7			6			
Active IE	10							
Staphyloc				1				1
virulent m-o		9						
Nosocomial								2
Str. vir								-2
Pos cult					5			2
Diagn delay								-1
Surgery								-2
<b>AUC</b>	<b>0.758</b>	<b>0.82</b>	<b>0.715</b>	<b>0.84</b>	<b>0.872</b>	<b>0.88</b>	<b>0.851</b>	<b>0.715</b>

\* according age classes; \*\* CHF or shock; PVE or periannular abscess; \*\*\* mechanical ventilation for pulmonary edema or poor hemodynamic status  
 Card: cardiogenic shock; CD: conduction defect; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; diagn delay: diagnostic delay (symptoms <1month before admission) dysf: dysfunction; ES: EuroSCORE; IABP: intra-aortic balloon pump; IE: infective endocarditis; m-o: microorganism; NYHA: New York Heart Association functional class; peri-ann: periannular complication (includes cardiac damage); pos cult.: positive culture; Staphyloc: staphylococcus; Str. vir: streptococcus viridans; surg: surgery; TC-penia: thrombocytopenia; veget: vegetation;  
 NOTE: the original model of Gatti et al included also BMI >27 and systolic pulmonary artery pressure >55 mmHg as factors.  
 NOTE: in the series of Park et al, about half of the patients underwent surgery, therefore surgical treatment could be included within the score and received a value of -2 and is protective.

(with all possible definitions based on plasma creatinine or need for dialysis) and age, with all different age categories, are analyzed in most papers.

Other IE-related parameters which are often scrutinized are PVE and periannular involvement (abscesses, fistulae and dehiscence of an infected valve

prosthesis). More common chronic comorbidity as well as gender are rarely included. Especially the hemodynamic factors, and particularly cardiogenic shock and need for mechanical support or for emergency surgery show high scores.

Definitions of the variables under scrutiny are supplied by most authors [2-6, 8]. Sometimes, these definitions are based on those used in the EuroSCORE [6]. Then, the analysis leading to the model is usually performed in steps. First, a univariate analysis identifies the factors which have an effect on the outcome [1-4, 6, 8]. Second, the significant data are entered in a multivariate logistic regression analysis [1-6, 8]. In the PALSUSE study, seven prognostic factors have a similar odds ratio, between 1.7 and 2.3. Each of these seven scores is assigned a value of "1" [5]. In one series, the odds ratios are used to calculate the items within the risk model [1]. Third, from the regression coefficients [2-4, 8], the scores themselves are derived mostly as integers. By adding these scores, the individual patients risk score can be calculated [1, 2, 4, 5]. Most factors are binary, except age, which is sometimes categorized [3, 4]. Age is not always included in the analysis [2, 8]. Fourth, C-statistics is performed by plotting a Receiver-operating-characteristic (ROC) curve and by determining the area under the curve (AUC) which serves as discriminatory power of the risk model [1-6, 8]. Sometimes, additional steps are taken. The internal (bootstrapping) and external validation [4, 6, 8] as well as calibration is performed by a second cohort of patients [9], or by comparing expected with observed mortality [2, 4]. An internal validation is absent in some series [1, 3, 5]. In one series, the 5-variable AEPEI model is compared with the 3-variable model by removing BMI and systolic pulmonary artery pressure as parameters. The latter parameter requires more complex measurement techniques, while BMI is not a part of the EuroSCORE II model [8]. In another series, the correlation with the EuroSCORE is determined by the Kendall's tau test [3]. Goodness-of-fit is also tested in several series [3-5, 8]. Patients of the De Feo analysis are divided according the risk in four classes and predicted mortality is plotted against the score, using a one way analysis of variance and Bonferroni's correction [3]. The possible effect of long inclusion times is taken into account by dividing the whole period in two episodes, thereby determining the specificity and sensitivity of the risk model [4]. A score system is not offered in one manuscript, although all statistical steps have been taken. Moreover, it is the only logistic model [6], while all other models are additive.

Comparison with other recently developed IE-specific and older scores has been performed, either by authors who developed their own score [4, 5, 8] or by others, who did not develop a model and can be considered as more "neutral" [7, 10]. Authors who developed their own risk model show superior results compared to the classic score such as the logistic EuroSCORE and EuroSCORE II [4]. A comparison between two of these scores [2, 3] with the more conventional EuroSCOREs is also made by these more "neutral" authors using their own series of IE patients. These series are also relatively small. The same analytical steps have been followed [7]. For hospital mortality, the model developed by De Feo [3] is the only one with an AUC above the level of 0.70. In contrast to models derived from the EuroSCORE and the STS database, the De Feo score relies heavily of IE-specific parameters. This could explain its success. However, with 3 predictors for 10/146 fatal events, the logistic regression in this comparative analysis seems over-fitted [7]. Nevertheless, need for inotrope medication or use of intra-aortic balloon pump and dialysis are well recognized predictors. The De Feo score has the additional advantage of its simplicity, but its applicability in PVE needs further investigation. Moreover, this score performs poorly in another very recently published comparative analysis [10]. This comparison includes also the STS-IE, PALSUSE, and Da Costa models. The sample of 180 patients is also relatively small, but it confirms the prognostic importance of age, hemodynamic status and renal dysfunction as well as of septic shock, but not of *S. aureus*. The steps taken in this analysis are aimed at determining the AUC for each model. The hospital mortality of 26.8%, however is much higher compared to analysis by Wang *et al.* [7]. The STS-IE and PALSUSE model show a relatively high AUC of 0.76 (0.68-0.82) and 0.73 (0.66-0.79), and are comparable to that of EuroSCORE I and II, both with 0.74 (0.66-82), and STS score with 0.73 (0.63-0.84). However, the De Feo and Da Costa do significantly worse with AUC 0.68 (0.58-0.76) and 0.65 (0.57-0.72) compared to the classic scores. Calibration with the Hosmer-Lemeshow test is only inaccurate for the Euroscore II, although the obsolete EuroSCORE I overestimates mortality considerably in the sample with an already high mortality of 26.8%. Involvement of multiple valve IE in one third of the sample could affect this result [10]. Both more comparative series differ in hospital mortality and in included scores, which makes drawing conclusions difficult, but for the moment, it seems that the models cannot be generalized. Moreover, the only

logistic and very recently developed Endoscore [6] is not involved.

Remarkably, only two papers give explicitly causes of death, namely cardiogenic shock [1], low output syndrome, intractable arrhythmia, pulmonary embolism, multi-organ failure, persistent sepsis and pneumonia [3]. In two other papers, the postoperative complications are described extensively, which offer a clue for the causes of mortality [2, 5]. Other papers mention no causes [4, 6, 8]. Anyway, the score models are based on preoperative risk factors and not on the postoperative cause of mortality. Therefore, this information has no added value within this context.

## DISCUSSION

The aim of the included papers is to provide an easy bed-side decision model for prognostic reasons [3, 6], for counseling of patients, decision making and comparative assessment for quality of care with benchmarking [2, 6, 8]. These models differ from the classic score models by inclusion of IE-specific parameters. The reason for the differences between the traditional and IE models might be the low incidence (1 to 2%) of IE in the series from which the EuroSCORE models were developed [6]. Even among patients with the highest scores, mortality does not exceed 30% in one model [2], hence potentially lifesaving surgery should not be denied in patients with high scores, especially since medical treatment alone carries a worse prognosis [5]. In one series, no patient was refused for surgery for the sake of risk [1]. The relative importance of each factor or component should be weighed within each model before an attempt of comparing the models can be made. The most important recognized risk factors are age, hemodynamic status (including signs of heart failure and dependence on mechanical support), renal dysfunction as well as cardiac damage or periannular involvement. Other factors such as gender, size of vegetation and microbial data are included in a considerably less degree.

Age is considered as a universal predictor for a poor prognosis [5]. In some studies, age is dichotomized with a cut off at 40 [1], 60 years [2] or 70 years [5, 8]. Sometimes, age is given as categories [3, 4, 9]. In one series, age has not been identified as predictor [2]. In series with older patients, this factor receives high ranking [3, 4, 9]. These difference in approach makes comparison difficult between the models. Use of a threshold of 55 or 60 year as proposed in EuroSCORE

and STS score systems seems also a reasonable option for IE specific models. The preoperative hemodynamic status in its broadest sense is not only an indication for surgery but also a powerful predictor for the 30-day mortality in IE and is almost universally recognized [1-5, 8]. Often, need for urgent or emergent surgery is already represented by critical conditions such as heart failure, need for mechanical circulatory support or shock. A comparable observation has also been made for more conventional cardiac procedures such as aortic valve replacement [12]. Nevertheless, surgery should not be withheld from patients with high risk, since satisfactory results still can be obtained. Renal dysfunction is another major predictor [2-4, 8, 9], and in some series the second most powerful predictor for 30-day mortality [2]. In one series, however, it could not be identified as predictor [1]. In another model, this predictor is indirectly included in the PALSUSE model, through the EuroSCORE [5]. This way of inclusion carries the risk of multiple collinearity. Moreover, acute renal dysfunction could be the marker a hemodynamic compromised status because of a decreased renal perfusion. The same remark can be made for need of mechanical ventilation, as result of pulmonary edema. Introduction of this factor in the model abolished the effect of "emergency" as predictor since all patients with mechanical ventilation were operated on emergency basis [3]. Arrhythmia as risk factor [1, 2] might also serve as marker for of impaired myocardial perfusion. It must be said, however that renal dysfunction [2-4, 8] and arrhythmia [1, 2] are included together with hemodynamic and left ventricular factors. This indicates that there is some independent effect, especially of renal function, on the outcome.

PVE, periannular complications and cardiac damage are not always identified as a risk factor [6, 8]. Older series found an effect of PVE, and of conduction defects – as sign of cardiac damage – and echocardiographic complicated IE [1]. It could also be a marker of more virulent disease, more complex surgery, longer bypass and cross-clamp times, and hence higher mortality [3-5]. There is also an interaction with the expertise of the individual surgeon which is not easy to measure. The successful use of reparative techniques – if applicable – might serve as parameter, but this does not appear in any model. In any case, the change in incidence of aggressive microorganisms as cause for IE, as well as the change in approach and expertise make continuous recalibration of any model necessary. Septic shock has been labeled less powerful compared to cardiogenic shock in at least one series [4], but this is not a

universal observation. This finding should be treated with caution, since the degree of “sickness” can vary between population and the type of microorganisms has been included in only a few series [4-6]. Moreover, sepsis, or uncontrollable infection can be expected in complicated IE, with periannular extension of the infection. Thrombocytopenia has also been connected to uncontrolled infection and could have an impact on short-term outcome. However, “active IE” has not been identified as a risk [3]. The use of cardiac implants, and with it, the incidence of Staphylococcal IE are on the rise [2]. Microbial data are not provided by the STS database, but are important because of the aggressiveness of some microorganisms. Under representation of virulent microorganisms might lead to non-inclusion in score systems [1-3, 6, 8]. Positivity of the latest blood test sometimes replaces *S. aureus* as risk factor [3]. This might be related to need for early surgery but also to an unresolved IE. Furthermore, vegetation over 10mm has been identified as a risk factor for mortality, but only in two series [1, 9]. It carries the risk for embolization, but this risk decreases rapidly once an adequate antibiotic treatment has started. Recent preoperative stroke and preoperative cerebrovascular disease does not seem to be a contraindication for surgery [2, 4] and is identified as risk factor only at six months [9]. The practice of postponing surgery for IE in patients with stroke should be reexamined, especially since stroke and the risk for stroke is one of the indications for cardiac surgery. Nevertheless, in some series [4], surgery is less performed in patients with stroke.

The limitations in the included papers are usually identified by the authors themselves. These have been highlighted extensively earlier [11]. Most studies are of observational and of retrospective nature. This makes the estimation of treatment policy before referral to a tertiary cardiac center, the referral policy itself, possible delay of diagnosis and consequently and timing of surgery difficult. All these issues can introduce a serious bias. Definitions differ between series, which complicates any comparison further. Small patient samples with consequently low number of variables within the model provide insufficient power for rather complex, heterogeneous and relatively infrequent diseases such as IE [3, 5, 8]. The smaller sample size and single center design make models less applicable in general. In some series PVE is excluded, the number of patients with healed IE is low and the urgency/emergency rate is high [3] which makes the series less representative for general application. In one paper, surgery was performed in 27% of the cases

within the first 24 hours after diagnosis, which should be labeled as “emergent” [5]. In another series, urgent and emergent surgery was needed in over 90% of the patients [3]. This makes comparison between these series extremely difficult! Large databases are usually less detailed and are based on voluntary participation. Furthermore, the STS database does not make distinction between NVE and PVE and does not provide microbial data or data concerning periannular complications [2]. Not all scores are validated [3, 5]. It remains doubtful if external validation samples that are derived from expert tertiary cardiac centers will solve the problem. The composition of the patient sample determines which risk factors can be included within the model. Surgical treatment of active as well as healed IE allows the inclusion of active IE as a factor in the risk model. The same remark could be made for inclusion of right sided IE [3]. A major limitation is the patient group with surgical indication, but in which surgery is deemed too risky. In one paper, this is a considerable part of the population [4]. The exclusion of high risk patients could distort the whole model. In series, in which virulent microorganisms are underrepresented, this could lead to non-inclusion of this parameter in the risk score model [1-3, 8]. Last but not least, there are some statistical issues. Most scores models are additive, while there is a callout for logistic score [7], with the request to include regression coefficients and intercept. Only one paper provides such logistic model [6]. With c-statistics being performed, one should wonder if a discriminative power between 0.70 and 0.80 is high enough. Lastly, some factors are not so easy to disentangle: one example is: aggressive microorganism – PVE – cardiac damage – more hemodynamic instability and sepsis – more complex surgery with longer bypass time.

## CONCLUSIONS

The risk scores for patients with IE should have a good discriminatory power and be user friendly. Besides the classic clinical risk factors, they should contain also IE-specific predictors of mortality such as virulence, inflammatory parameters, and IE related complications such paravalvular involvement, compromised hemodynamic status, renal dysfunction and chronic comorbid conditions such as diabetes. The risk score models should be useful in clinical decision making and comparison of the quality of healthcare facilities but should not be used to deny a possible beneficial treatment in more difficult patients. Even with high surgical risk, medical treatment alone would have a worse prognosis. These score, systems do not offer

exact selection criteria. This is all the more important since these scores are, although useful, imperfect and should be recalibrated continuously with the changing clinical presentation of IE. The development of a score system based on international prospective collection with uniform and clear definition of preoperative baseline parameters is highly desirable. This will allow inclusion of a large number of patients in a reasonably short time and allows construction of a model based on contemporary standards in pre, peri and postoperative care. With a large sample, under-representation of uncommon risk factors could be avoided. As temporary solution, comparisons should be made for all seven available score models, using contemporary multicenter series which are large and diverse enough.

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