Editorial Commentary

Should we include microorganisms in scores to predict outcome in candidates for cardiac surgery during the acute phase of endocarditis?

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Infective endocarditis (IE) is a complex disease, at the crossroad of a large number of medical specialties, including cardiology, infectious diseases, internal medicine, neurology, intensive care, microbiology, and radiology (1,2). In addition, cardiac surgeons have been increasingly involved, as 60–70% of patients with IE present theoretical indication(s) for cardiac surgery (3). The selection of patients in whom cardiac surgery must be performed during the acute phase of IE is among the most difficult medical decisions in contemporary medicine, as both the benefits and the risks are high. Indeed, the strategy that will be finally selected, in agreement with other colleagues, the patient, and/or his relatives, may be a major determinant of whether the patient will die, or survive, with or without impairment of their quality of life.

To assist these tricky medical decisions, most clinicians use two complementary tools: (I) international guidelines from Europe (1), and/or America (3); (II) scores that have been developed from large cohorts, to predict outcome in patients candidates for cardiac surgery (4-23). The guidelines performed a complex process of weighing the pros, and the cons, for cardiac surgery, in a broad range of clinical situations commonly encountered in patients with IE. As could be expected, major indications for cardiac surgery are very similar in Europe and America guidelines, because the authors based their recommendations on the same tools, i.e., a comprehensive review of literature data, complemented by their opinions, as experts in the field. In brief, major indications for cardiac surgery are categorized in three groups in these guidelines: (I) heart failure, (II) uncontrolled infection, and (III) prevention of embolism (1,2). However, the selection of patients who will benefit from cardiac surgery is much more complex than merely screening whether they present, or not, one of these indications: as for any major decision in medicine, the benefits of the intervention must be weighed against the risk(s). The specific situation of cardiac surgery during the acute phase of IE is even more complex, as the timing of cardiac surgery also plays an important role in the risk/benefit balance. As an example, guidelines state that early surgery should be considered in IE patients with large vegetation(s), for the prevention of embolism (1,2). But they also outline literature data clearly demonstrating that the risk of embolism dramatically decreases following the start of appropriate antibiotics in patients with IE. As a consequence, the benefit of cardiac surgery for the prevention of embolism sharply decreases once an active anti-infective treatment is initiated, while the risk associated with cardiac surgery will remain grossly similar during the first days. Hence, a careful consideration of the risk/benefit balance for this specific indication advocates for cardiac surgery to reduce embolism risk only if performed very early after appropriate anti-infective treatment has been started (1,2). As stated by the European guidelines, 'the decision to operate early to prevent embolism is always difficult'. Then, they insist that, for this indication, 'surgery must be performed very early, during the first few days following initiation of antimicrobial treatment' (1). The situation is quite different when cardiac surgery is considered in patients with IE because of heart failure, or because of uncontrolled infection, as the situation will often get worse, with time, in patients who are not operated. In patients with life-threatening conditions (e.g., sepsis, or shock), early cardiac surgery is often a condition sine qua non for survival. For others, the decision may be postponed for a few days, when the indication, whether it is 'heart failure', or 'uncontrolled infection', is considered as 'borderline'. A proportion of them will finally be operated, as the potential benefit of cardiac surgery becomes more obvious, because for such indications, a few days of appropriate anti-infective treatment will not dramatically change the indication.

Only one randomized trial has been published, to better inform the decision to perform cardiac surgery during the acute phase of IE. However, patients enrolled in this unique trial were much younger than contemporary cohorts of patients with IE, they had less comorbidities, and inclusion criteria included a combination of two potential indications for cardiac surgery, i.e., severe valvular regurgitation, and vegetation >10 mm (24). In this situation, early cardiac surgery has proven beneficial, but this only applies to a limited subgroup of patients, in whom the decision to operate is quite straightforward. A large number of observational studies, retrospective or prospective, aimed at better defining benefit/risk ratio of cardiac surgery during the acute phase of IE, but they present all the same major limitation: among patients with theoretical indications for cardiac surgery, those who are finally operated are not the same as those who are denied cardiac surgery (3,25). Even high-level statistical methods, such as propensity-matched analysis cannot eliminate these potential biases.

All patients diagnosed with endocarditis should be screened to detect whether they present any indication for cardiac surgery. This screening is mandatory at diagnosis, and should be repeated in case of complications (e.g., heart failure, persistent bacteremia, progression of regurgitation or development of perivalvular abscess on echocardiography). The guidelines are particularly helpful for this process, although the decision to perform cardiac surgery in a patient with endocarditis cannot be based solely on guidelines: indeed, the second step in the decision-making process is the difficult evaluation of the risk/benefit ratio in an individual patient. At this stage, different scores that have been developed to predict outcome in patients candidates for cardiac surgery are used (4-23), although they all present limitations (*Table 1*): (I) those derived from cohorts of patients with heterogenous cardiac diseases may not be accurate for patients with IE (21); (II) early scores that were built by the time techniques for cardiac surgery, and intensive care were much different than current practices, probably overestimate major complications, including mortality (4,5,8,14,17,21); (III) scores that have been validated in a specific cohort, with no validation in another group of patients, may not be generalizable.

To improve the performance of the scores currently available to predict outcome in IE patients candidates for cardiac surgery, Williams and colleagues performed a retrospective study of a large prospective cohort of patients who underwent cardiac surgery for IE during years 2011–2016 in North America, and were enrolled in the Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS ACSD) (26). Their primary hypothesis was that the microorganisms responsible for IE have an impact on the prognosis of cardiac surgery, although to date no score took into account this parameter, readily available in >90% of patients in most contemporary cohort studies. They developed univariable and risk-adjusted models with odds ratio (OR) for mortality for each organism type, taking 'streptococci' as the reference. To focus on adverse events most likely related to the surgical procedure, they used as primary endpoints: (I) operative mortality, using the STS ACSD standard definition: 'the greater of in-hospital, or 30-day mortality'; (II) STS major morbidity composite (stroke, deep sternal infection, prolonged ventilation, new onset renal failure, and/or reoperation); (III) hospital length of stay (26).

They could analyze 23,086 records for IE surgery, originating from 1,049 medical centers. Patients characteristics are in line with current epidemiology of IE patients who require cardiac surgery: median age was 56 years, 69% were males, with a large predominance of left-sided IE (93%, n=21,388), mostly due to streptococci (32%), staphylococci (30%), and enterococci (15%). They found that two microorganisms are independently associated with operative mortality, and 30-day major morbidity, in left-sided IE: (I) fungal IE, with adjusted OR of, respectively, 2.89 [95% confidence interval (CI), 1.996–4.190], and 1.87 (95% CI, 1.43–2.45), and (II) *Staphylococcus aureus* (*S. aureus*) IE, with OR of 1.41 (95%

Table 1 Risk scores for in-hospital mortality after surgery for IE

Score	Derivation cohort size	External validation	Variables	Discrimination power (AUC)
RISK-E score (18)	n=424 (multicentre, left-sided IE only)	Yes	Age, prosthetic valve IE, periannular complications, *Staphylococcus aureus* or fungi IE, acute renal failure, septic shock, cardiogenic shock, thrombocytopenia	0.82 (95% CI, 0.75–0.88)
ANCLA score (23)	n=138 (single-centre)	No	Anemia, NYHA class IV, critical state, large intracardiac destruction, surgery on thoracic aorta	0.828 (95% CI, 0.754–0.887)
AEPEI score I (11)	n=361 (multicentre)	Yes	BMI >27 kg/m^2, Egfr <50 mL/mn, NYHA class IV, sPAP >55 mmHg, critical state	0.780 (95% CI, 0.734–0.822)
AEPEI score II (11)	Idem	Idem	eGFR <50 mL/mn, NYHA class IV, critical state	0.774 (95% CI, 0.727–0.816)
PALSUSE score (16)	n=437 (multicentre)	No	Prosthetic valve IE, age ≥70 years, large intracardiac destruction, *Staphylococcus spp* IE, urgent surgery, sex (female), EuroSCORE ≥10	0.84 (95% CI, 0.79–0.88)
STS-EI score (6)	n=19,730 (multicentre)	Yes	Emergency, salvage status, cardiogenic shock, preoperative hemodialysis, renal failure or creatinine <2.0 mg/dL, preoperative inotropic or balloon pump support, active (*vs.* treated) IE, multiple valve IE, insulin-dependent diabetes, hypertension, chronic lung disease	0.7578
De Feo score (22)	n=440 (single-centre, prosthetic valve IE excluded)	No	Age, renal failure, NYHA class IV, ventilatory support, positivity of latest preoperative blood culture, perivalvular involvement	0.88

AUC, area under curve; IE, infective endocarditis; CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate; EuroScore, European system for cardiac operative risk evaluation; NYHA, New York heart association; sPAP, systolic pulmonary artery pressure; STS, Society of Thoracic Surgeons.

CI, 1.21–1.65) for operative mortality, and 1.42 (95% CI, 1.30–1.56) for 30-day major comorbidity. Culture-negative IE were associated with operative mortality [OR, 1.35 (95% CI, 1.10–1.66)], but not with major morbidity. They also found that operative mortality was higher for prosthetic valve left-sided IE, than for native valve left-sided IE (12% *vs.* 8%, P<0.0001). For right-sided IE, overall mortality was much lower (4%), and ranking of mortality among main microorganisms tended to be similar (i.e., operative mortality of 6%, 4%, and 2%, for, respectively, fungal, *S. aureus*, and streptococci right-sided IE), but it didn't reach significance, so that the impact of microorganisms on post-operative adverse events could not be demonstrated.

The strength of this study includes the impressive number of observations available for analysis in the large STS ACSD database (n=23,086 cases), with standardized definitions, regular training of data coordinators, quality control including annual on-site data audits, and adequate fulfilment of ethical and regulatory requirements. Rates of missing data appear to be very low (e.g., 0% for mortality), and causative organisms were reported for 94% of cases. These assets ensure that data are reliable, and results may be applied to most sites with similar epidemiology and practices. This study also has limitations. Firstly, by essence, only patients who were operated could be included in this database: hence, it provides no information on patients who had indications for cardiac surgery, but were not operated, whatever the reasons (major comorbidities, patients or relatives refusal, or death before surgery could be performed) (3). This is well illustrated by the rather low post-operative mortality (12% for prosthetic valve left-sided IE, 8% for native valve left-sided IE), which suggest that patients who were operated were indeed the most likely to survive, due to exclusion of patients with major comorbidities, or too severely ill due to IE, what is usually referred to as 'survival bias' (27). Secondly, information on microorganisms are sometimes not available by the times cardiac surgery must be decided, notably when microbiological diagnosis will be obtained through analysis of valve tissues (28). In that situation, not uncommon, data on microorganisms involved cannot be used as an early tool to predict post-operative complications. Thirdly, as the database was not primarily focused on microorganisms, important microbiological information are missing, including susceptibility (e.g., no information about methicillin-resistance for staphylococci), although this has a documented impact on patients outcome. However, the strengths of this study largely surpass the limitations, and the authors should be commended for this impressive amount of work, and the quality of original data presented.

Maybe the major criticism of this article would be the following: the authors merely confirmed, in the population of patients who are operated at the acute phase of IE, what has been known for decades in the overall population of patients with IE: *S. aureus*, and fungal IE (29), are associated with bad prognosis, whether they are operated or not. This also applies for the comparison of outcome for prosthetic valve IE versus native valve IE, or for left-sided IE versus right-sided IE. For the latter, even in the pre-antibiotic era, it has been documented that mortality was lower in right-sided IE (75%, with a median survival of 27 days after diagnosis), than in left-sided IE [100% mortality, median survival 12 days, reviewed in (30)]. Hence, although the data provided by Wiliams *et al.* are indeed original, they only confirm in a sub-group of patients previous findings in the overall population of patients with IE. The extrapolation of these findings in routine practice may not be dramatic: thanks to Williams *et al.* study, we now have robust data to support the higher risk of severe post-operative complications in patients with *S. aureus*, or fungal IE, who are candidates for cardiac surgery. However, these patients also have higher risk of bad outcome if they are not operated. Hence, the risk-benefit ratio may not be impacted by microbiological documentation, as microorganisms at higher risk of post-operative complications are also at risk of worse outcome in the absence of surgery.

In conclusions, despite the limitations detailed above, this study provides original data in the field, and suggests that additional variables may be incorporated in this complex decision-making process. Time will tell whether microorganisms will be integrated in future scores to predict post-operative complications in candidates for cardiac surgery during the acute phase of IE, and whether they will improve the performance of these scores, to assist clinicians in this difficult decision-making process

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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