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TITLE***Enterococcus faecalis* endocarditis risk assessment in patients with bacteremia: external validation of the DENOVA score.**

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Running title:

External validation of the DENOVA score

INTRODUCTION

We read with great interest the article by Vignau *et al.*, which compares the performances of the various existing scores used to guide echocardiography indication in patients with *Staphylococcus aureus* bacteremia (SaB), and proposes an algorithm for their use [1]. Endocarditis complicates an estimated 5-20% of cases of SaB. Such scores could then be useful in clinical practice because, despite international guidelines, performing an echocardiography for all patients with SaB can be difficult for organizational and financial reasons.

This issue also concerns other species responsible for endocarditis, particularly enterococci. Enterococcal endocarditis represents 13 to 18% of all endocarditis cases with an increasing incidence and an estimated 1-year mortality of 29-31% [2,3]. *Enterococcus faecalis* is the predominant species responsible for enterococcal endocarditis, accounting for about 90% of cases. Among patients with *E. faecalis* bacteremia (EfB), endocarditis is diagnosed in 8-26% of cases [4-6]. This proportion is higher than for other species [5]. NOVA and DENOVA scores have been developed to help physicians target patients requiring echocardiography in EfB cases [4,7].

The NOVA score was originally proposed by Bouza *et al.*, then validated and updated by Dahl *et al.* [7,8]. The score includes 4 criteria: Number of positive blood cultures ≥ 2 (5 points), Origin of infection unknown (4 points), Valve disease (2 points), and Auscultation of heart murmur (1 point). More recently, Berge *et al.* proposed the DENOVA score adding two new criteria to the forementioned four (Duration of symptoms ≥ 7 days and Embolization) wherein each criterion only counts for 1 point [4]. Berge *et al.* observe that the DENOVA score shows a better performance (Sensitivity 100% and Specificity 85% for a threshold ≥ 3) than the NOVA score (Sensitivity 97% and Specificity 23% for a threshold ≥ 4). However, no external validation has been performed so far.

We performed a retrospective study to compare the performance of the NOVA and DENOVA scores.

METHODS

In cohort A, we retrospectively included all cases of EfB diagnosed in two French hospitals (around 2,500 beds in total) between January 2015 and December 2019. We also included additional cases of *E. faecalis* endocarditis from the EFEMER cohort (retrospective multicenter cohort of *E. faecalis* infective endocarditis in Western France), which constituted cohort B [9]. Only endocarditis cases classified as “definite” according to the modified Duke criteria were included. If the patient had multiple episodes of EfB, only the last one was considered. Patients with age <18 years, missing data precluding the calculation of the scores, and endocarditis without initial bacteremia were excluded.

Definitions used in the study are detailed in Supplementary Materials

Sensitivity and specificity were compared using the McNemar Chi²-test and areas under the curve (AUC) of receiving operator curves (ROC) using the DeLong test. All tests were two-tailed, and significance was set at $p < 0.05$. Statistical analyses were performed using R software version 4.0.3.

The study was approved by an institutional review board, the Ethical Committee of Research in Tropical and Infectious Diseases (CER-MIT 2022-0106).

RESULTS

During the study period, 503 patients were diagnosed with EfB in the two participating hospitals. Ninety-one were excluded, leaving 412 patients included in cohort A, of which 56 (13.6%) were diagnosed with definite endocarditis and 44 with possible endocarditis (10.7%); 163 (39.6%) had an echocardiography of which 62 (15.0%) had a transoesophageal echocardiography (TOE). Cohort B comprised 223 cases of *E. faecalis* endocarditis from 12 other hospitals. The flow chart is presented in Supplementary Figure 1. The clinical characteristics of the 635 patients of the study, including 279 definite endocarditis, are presented in Table 1.

All criteria of the DENOVA score were significantly associated with the risk of endocarditis, as well as male sex, and monobacterial bacteremia.

In cohort A (n=412), DENOVA score was positive (≥ 3) for 109 patients (26.4%), missing 3 endocarditis; and NOVA for 214 (51.9%), missing 1 endocarditis. According to scores, the number of echocardiography needed to be performed to find one case of endocarditis was 2.1 for DENOVA and 3.9 for NOVA. Negative Predictive Value (NPV) was >99% for both scores (Table 2). If only patients who had an echocardiography were considered (n=163), NPV was 96% for DENOVA and 97% for NOVA.

In cohort A+B, for a threshold ≥ 3 , the DENOVA score showed a sensitivity (Se) of 95.3% (95% confidence interval [CI], 92.2%-97.5%) and a specificity (Sp) of 84.3% (95% CI, 80.1%-87.9%). For a

threshold ≥ 4 , the NOVA score showed a greater Se at 98.9% (95% CI, 96.9%-99.8%, $p=0.003$) and a lower Sp at 56.0% (95% CI, 50.6%-61.2%, $p<0.001$) than the DENOVA score. The positive and negative likelihood ratios were respectively 6 and 0.06 for DENOVA; 2 and 0.03 for NOVA. The DENOVA score had a greater AUC than the NOVA score ($p=0.001$) in predicting the risk of endocarditis in a patient with EfB (Supplementary Figure 2).

DISCUSSION

Our results are consistent with the performances of both scores shown in previous studies [4,7,8]. Compared to the study conducted by Berge *et al.*, the difference between the two scores was slightly attenuated, with a lower sensitivity for DENOVA and a higher specificity for NOVA [4].

We confirmed that both scores had an excellent negative predictive value and a strong negative likelihood ratio enabling to rule out echocardiography in patients with EfB. The advantage of the DENOVA score therefore lies in its greater specificity. In theory, it could reduce the number of echocardiographies required by half.

Despite the retrospective nature of our study, the addition of many cases of endocarditis improved score specificity estimates and allowed a more detailed assessment of endocarditis predictive factors.

The predictive factors for endocarditis in EfB are currently clearly defined [4,6–8]. Community acquisition and monomicrobial infection can also be added to the DENOVA criteria. More studies are needed to better define the interest of the endocarditis scores in real life, and their performance versus clinical judgment guided by risk factors.

In conclusion, when assessing the risk of endocarditis in patients with EfB, the DENOVA score may guide physicians, especially in identifying patients who do not require TEE.

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Table 1. Characteristics of 635 cases of EfB with and without endocarditis.

Variable	Endocarditis (n=279)	No Endocarditis (n=356)	Crude Odds Ratio (95% CI)
Age (years)	74 [66-83]	74 [63-83]	-
Sex (male)	222 (79.6)	252 (70.8)	1.61 (1.11-2.33)
D: duration of symptoms ≥ 7 days	186 (66.7)	45 (12.6)	13.82 (9.27-20.61)
E: embolization	132 (47.3)	20 (5.6)	15.09 (9.07-25.09)
Embolization sites ≥ 2	34 (12.2)	1 (0.3)	49.27 (6.60-362.3)
Embolization sites ≥ 3	12 (4.3)	0 (0.0)	-
N: positive blood culture ≥ 2	248 (88.9)	88 (24.7)	24.36 (15.62-37.99)
Positive blood culture ≥ 3	170 (60.9)	40 (11.2)	12.32 (8.10-18.52)
Number of positive blood culture	3 [2-4]	1 [1-1]	-
Blood culture interval (days)*	2.0 [0.5-5.0]	0.0 [0.0-0.0]	-
Blood culture interval ≥ 12 h	194/261 (74.3)	52 (14.6)	18.84 (12.47-28.47)

	166/261		
Blood culture interval ≥ 24 h	(63.6)	31 (8.7)	19.72 (12.57-30.92)
Blood culture interval ≥ 72 h	96/261 (36.8)	18 (5.1)	11.38 (6.64-19.48)
O: unknown origin of infection	227 (81.4)	106 (29.8)	10.3 (7.06-15.02)
Urinary tract origin	26 (9.3)	122 (34.3)	0.10 (0.12-0.31)
Gastrointestinal and biliary origin	24 (8.6)	88 (24.7)	0.29 (0.18-0.46)
Intravenous catheter origin	1 (0.4)	22 (6.2)	0.05 (0.01-0.41)
Wound origin	0 (0.0)	10 (2.8)	-
Other origin	1 (0.4)	8 (2.2)	0.16 (0.02-1.26)
V: endocarditis predisposing heart condition	183 (65.6)	67 (18.8)	8.22 (5.72-11.82)
Previous endocarditis	24 (8.6)	11 (3.1)	2.95 (1.42-6.14)
Prosthetic valve	115 (41.2)	24 (6.7)	9.70 (6.01-15.64)
Native valve disease	69 (24.7)	37 (10.4)	2.83 (1.83-4.38)
A: murmur auscultation	180 (64.5)	67 (18.8)	7.84 (5.46-11.26)
Monobacterial bacteremia	258 (92.5)	189/307 (61.6)	7.67 (4.65-12.66)
Echocardiography	278 (99.6)	108 (30.3)	638.37 (88.45-4607.3)
Transthoracic (TTE)	278 (99.6)	108 (30.3)	638.37 (88.45-4607.3)
Transoesophageal (TOE)	210 (75.3)	25 (7.0)	40.3 (24.71-65.72)
DENOVA score	4 [3-5]	1 [0-2]	-
Positive DENOVA score	266 (95.3)	56 (15.7)	109.61 (58.64-204.9)
NOVA score	10 [8-12]	2 [0-5]	-
Positive NOVA score	276 (98.9)	159 (44.7)	113.98 (35.85-362.43)

Quantitative variables are expressed as medians [IQR], qualitative variables are expressed as numbers (%). Percentages were calculated with all patients in the column as the denominator, except for variables with missing data, for which the number of patients with available data is mentioned.

*Data available for 617 patients, if the patient had only one positive blood culture the duration considered was 0 days.

Table 2. Performance of NOVA and DENOVA scores

Score	Cohort	Se%	Sp%	PPV%	NPV%	LR+	LR-
DENOVA	Cohort A (n=412)	94.64	84.27	48.62	99.01	6.02	0.06
	Cohort A+B (n=635)	95.34	84.27	-	-	6.06	0.06

	Cohort A+B with echocardiography (n=386)	95.32	59.26	-	-	2.34	0.08
NOVA	Cohort A (n=412)	98.21	55.34	25.70	99.49	2.20	0.03
	Cohort A+B (n=635)	98.92	55.34	-	-	2.21	0.02
	Cohort A+B with echocardiography (n=386)	98.92	28.70	-	-	1.39	0.04

Se: Sensitivity. Sp: Specificity. PPV: Predictive Positive Value. NPV: Negative Predictive Value. LR: Likelihood Ratio.

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