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Original article

The VIRSTA score, a prediction score to estimate risk of infective endocarditis and determine priority for echocardiography in patients with *Staphylococcus aureus* bacteremia

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Structured abstract (199 words)

Objectives. To develop and validate a prediction score, to quantify, within 48 hours of *Staphylococcus aureus* bacteremia (SAB) diagnosis, the risk of IE, and therefore determine priority for urgent echocardiography.

Methods. Consecutive adult patients with SAB in 8 French university hospitals between 2009 and 2011 were prospectively enrolled and followed-up 3 months. A predictive model was developed and internally validated using bootstrap procedures.

Results. Among the 2,008 patients enrolled, 221 (11.0%) had definite IE of whom 39 (17.6%) underwent valve surgery, 25% of them within 6 days of SAB diagnosis. Ten predictors independently associated with IE were used to build up the prediction score: intracardiac device or previous IE, native valve disease, intravenous drug use, community or non-nosocomial-acquisition, cerebral or extracerebral emboli, vertebral osteomyelitis, severe sepsis, meningitis, C-reactive protein above 190 mg/L, and H48-persistent bacteremia. Patients with a score ≤ 2 (n=792, 39.4%) were at low IE-risk (1.1%; negative predictive value: 98.8% (95% CI, 98.4-99.4)) compared to those ≥ 3 who were at higher risk (17.4%).

Conclusions. Physicians must be strongly encouraged to urgently perform echocardiography in SAB patients with a score ≥ 3 to establish IE diagnosis, to orient antimicrobial therapy and to help determine the need for valvular surgery.

Key words: *Staphylococcus aureus* Bacteremia; Infective endocarditis; prognostic score; echocardiography, VIRSTA score.

64 **Abbreviations list**

65 CI, confidence interval;

66 CRP, C-reactive protein;

67 ICD, implantable cardioverter defibrillator;

68 IE, infective endocarditis;

69 IQR, interquartile range;

70 SAB, *Staphylococcus aureus* bacteremia;71 *S aureus*, *Staphylococcus aureus*;

72 TEE , trans-esophageal echocardiography;

73 TTE, transthoracic echocardiography;

74

Introduction

Staphylococcus (S) aureus is among the most frequent causes of both healthcare-associated and community-acquired bloodstream infections worldwide, with incidence rates of between 20 and 50 cases / 100,000 population per year in industrialized countries [1,2]. One of the most severe complications of *S. aureus* bloodstream infection (SAB) is infective endocarditis (IE), reported to occur in 5-17% of cases [3].

Echocardiography plays a key role in IE diagnosis [4]. Recommendations on the systematic use of echocardiography in SAB patients are not consistent in the literature[4–10]. Even in situations for which most guidelines recommend echocardiography, it is not performed in a substantial number of SAB patients: in a recent pooled analysis of SAB prospective studies, echocardiography was performed in only 56% of patients despite being strongly recommended to investigators [11] . In this context, some authors have proposed criteria to guide the use of echocardiography. However, none of these studies were prospectively designed with a large number of patients who underwent echocardiography in all subset of community and health-care associated SAB patients.

In the present study, we developed and validated a simple score-based prediction rule to quantify the risk of IE within 48 hours after SAB diagnosis in patients with community- acquired or healthcare-associated SAB, using the largest prospective cohort of SAB patients reported to date [12–14]. This score could be used for the early identification of urgent echocardiography candidates, for rapid IE diagnosis, and early initiation of specific interventions for IE, including appropriate antimicrobial therapy, and multidisciplinary evaluation of indications for valvular surgery.

Methods

Setting and subjects

VIRSTA is an observational prospective cohort study previously described [15] conducted between April 2009 and January 2012 which included all consecutive adult patients having at least one blood culture positive for *S. aureus* in 8 tertiary-care university hospitals in France. Patients with catheter colonization without SAB, defined as positive blood cultures only through vascular access device specimen and those referred to the hospitals for the management of IE were excluded.

Trained research assistants prospectively collected clinical, biological (CRP measured at inclusion) and therapeutic data through a standardized case report form in each center. Clinical data included demographics, background characteristics (comorbidities, IE-predisposing conditions), healthcare contacts within the 90 days preceding hospitalization including invasive procedures, and setting of acquisition. Investigations for SAB complications present and/or occurring during the first 48 hours (including meningitis, vertebral osteomyelitis, cerebral emboli, and extracerebral emboli) as well as presence of severe sepsis or septic shock were recorded. Therapeutic data included antibiotics, catheter removal, surgery, and admission to intensive care unit.

Transthoracic echocardiography (TTE) and/or TEE were strongly encouraged. Patients, their relatives or physicians were contacted 12 weeks after the beginning of the SAB to check the patient's status.

Data acquisition and definitions

SAB was classified as healthcare-associated (nosocomial or non-nosocomial), or as community-acquired [16] (see in Appendix). Patients were considered as having a permanent intracardiac device in the presence of prosthetic heart valve, and/or pacemaker and/or implantable cardioverter defibrillator (ICD). Persistent bacteremia was defined as positive blood cultures more than 48 hours after the first positive blood culture result (Figure 1).

Infective endocarditis classification

The primary endpoint was the diagnosis of definite IE according to modified Duke classification [17] within 12 weeks established by a local adjudication committee made up of cardiologists, infectious diseases specialists and bacteriologists.

Statistical analysis

Predictive factors

First, a descriptive analysis of patients was performed. Potential IE predictors were then selected based on the literature [6,13,14,18–21], categorized as 1/ patient background characteristics, 2/ initial SAB presentation characteristics, and 3/ early extracardiac events (Table 1). Only SAB characteristics and extracardiac events present and/or occurring during the first 48 hours following the T0 blood sample collection were considered, as well as the result of the T48 hour blood sample collection.

Categorical variables were summarized using percentages and compared using Fisher exact test. Continuous variables were summarized using medians with interquartile ranges and compared using Wilcoxon test. All variables with a P value of < 0.20 in the bivariate analysis were entered into a multivariate logistic regression with a stepwise backward approach and a significance level at $P < 0.05$. All significant variables in the logistic model were used to build a predictive score of IE.

Model validation

To improve the final reduced model's stability, a validation was performed using a ".632 bootstrap procedure"[22]. One thousand bootstrap samples were drawn from the original sample, estimating the overfitting-corrected regression coefficients from the final model and the overfitting-corrected measures of the model performance on subjects not sampled. To quantify the model performance, we determined the discrimination computing the C statistic (area under the receiver operating characteristic curve) and its 95% confidence interval (CI) and the calibration using Hosmer-Lemeshow's test.

Scoring system

Median β coefficients from the bootstrap procedure were rounded to the nearest half, and then multiplied by 2 to build corresponding weights. For each patient, the score was then calculated by adding up the weights corresponding to each variable. Intrinsic (sensitivity, specificity) and extrinsic (positive and negative predictive value) qualities were then assessed using a classic bootstrap procedure for different values of the score. Finally, to ensure model performance consistency among subgroups, we applied the score separately according to 1/ setting of acquisition and 2/ the presence of predisposing cardiac conditions.). Analyses were performed with SAS software (version 9.3) and R software, version 2.13.0.

Sensitivity analyses

To assess the robustness of the model, two sensitivity analyses were performed. The first one was performed in the subpopulation of patients, who underwent echocardiography, or in whom echocardiography was not performed but for whom the addition of an echocardiographic major criterion would not have upgraded the modified Duke classification to a definite IE case (hereafter referred to as “echo sensitivity analysis”). In the second one, we excluded all definite IE in which definite classification was based on the presence of modified Duke Criteria which were included in the statistical model as potential predictors of IE to avoid the resulting tautology (hereafter referred to as “modified Duke criteria sensitivity analysis”).

A third sensitivity analysis was performed to evaluate the performance of the score among patients with highest diagnostic uncertainty. We excluded from our population patients with definite IE, based on duke criteria determined within the first 48 hours (patients with the microbiological major criteria AND ≥ 3 minor criteria).

166 **Ethics**

167 The VIRSTA study was approved by the French institutional review board for the protection of human
168 subjects (CPP Sud-Méditerranée IV) and registered in the European Clinical Trials Database (EUDRACT
169 2,008-A00680-55).

170

Results

Patient characteristics

During the 30-month study period, 2,091 consecutive patients with SAB were enrolled. Background characteristics, initial SAB features, and extracardiac events occurring in the first 48 hours in the 2,008 patients not referred for the management of IE are presented in Table 1.

Echocardiography was performed in 1,348 patients (67.1%), and 605 patients (30.1%) underwent TEE. According to setting of acquisition, echocardiography was performed in 678 patients with nosocomial SAB (63.1%), and in 641 patients with community-acquired or non-nosocomial healthcare-related SAB (73.3%). The extracardiac events which were present and/or occurred within the first 48 hours are listed in Table 1. The 30-day and the 12-week mortality rates were respectively 22.2% (445 patients) and 32.2% (646 patients).

Endocarditis classification

The adjudication committee categorized 221 (11.0%) (95% CI 9.6%-12.4%) patients as definite IE cases. Table 2 presents the distribution of the modified Duke criteria in the 2,008 patients. The rate of definite IE was 15.6% (n=211) in the 1,348 subjects in whom echocardiography was performed. Among them, echocardiography revealed one major criterion of IE in 80.6% (n=170), including vegetation in 139 patients (65.9%), abscess in 32 patients (15.1%), and new dehiscence of a prosthetic valve in 13 patients (6.2%). Valve surgery was performed in 39 of the 221 patients with definite IE (17.7%), with a median time interval of 12 days [IQR; 6-29] after T0 blood sample collection, and 6 days [IQR; 2-28] after echocardiography. In those patients, echocardiographic findings showed valvular regurgitations in 48.7%, vegetations at high risk of embolism in 56.4%, and cardiac abscesses in 30.8 %.

Predictive factors

Ten predictive factors were independently associated with definite IE (Table 3). The Hosmer-Lemeshow's test p-value for the final model was 0.60 and the median area under the curve after bootstrap procedure was equal to 0.85 (95% CI 0.84–0.86).

The “echo sensitivity analysis”, performed in 1,728 patients yielded a comparable final model with the same ten independent predictive factors. The “modified Duke criteria sensitivity analysis” performed in 1,950 patients also provided closely related results, with the exception of vertebral osteomyelitis, which was removed from the final model (see Table 1 in Appendix).

Scoring system

Score building is detailed in Table 4. After 1000 resampling iterations using a .632 bootstrap procedure, median β coefficients of the ten predictive factors were estimated. The weights varied from 1 to 5 points, leading to a theoretical score ranging from 0 to 30 for a given patient. In the VIRSTA cohort, the score ranged from 0 to 20. For instance a patient who presents vertebral osteomyelitis or a community acquired SAB without any other criteria or a patient with severe sepsis with or without CRP>190 mg/L have a score ≤ 2 . A patient with cerebral emboli (or with pre-existing native valve disease or with meningitis or with persistent bacteremia or with history of injection drug use) no needs to have more criteria to have a score ≥ 3 (Figure 2).

The rate of endocarditis increased significantly from 1.1% (9/792) when the score was ≤ 2 to 17.4% (212/1216) when the score was ≥ 3 and up to 70.8% (63/89) when the score was ≥ 10 (Figure 3).

TTE performance rate rose from 54.2% with a score ≤ 2 to 89.9% when the score was ≥ 10 . Score performance according to different cutoffs is presented in Table 4. For a score ≤ 2 , the negative predictive value was 98.8% (95% CI 98.4; 99.4) and the sensitivity was 95.8% (95% CI 94.3; 97.8).

217 After exclusion of (n=28) patients with definite IE as established within the first 48 hours (third sensitivity
218 analysis), the performance of the VIRSTA score was similar (95.3 % for sensitivity and 98.9% for negative
219 predictive value).”

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Discussion

In this large multicenter prospective cohort study on adult patients with SAB, we have developed and assessed the performance of an IE prediction model taking into account patients' background and initial SAB characteristics. The VIRSTA score provides an accurate estimation of IE probability in patients with SAB, whatever the setting of SAB acquisition and may be used by physicians to decide on the early use of echocardiography.

Our study is based on the largest prospective cohort of SAB patients reported to date. To enhance the generalizability of our results, we enrolled all patients in hospitals from different French regions with a large population pool and a representation of multiple medical specialties. Most SAB characteristics observed in our study are consistent with those reported in other SAB studies [11], including predominance of elderly individuals and men, the high proportion of nosocomial SAB, the rate of methicillin-resistant strains, and the 30-day and 12-week mortality rates. Although echocardiography use differs between studies, impacting IE diagnosis rate, the 15.6% or 11% endocarditis rates (according to restriction of analysis to patients with echocardiography), are also similar to those reported in the literature [11]. Our rate of 67.1 % echocardiography (1,348 of our 2,008 patients underwent echocardiography), is among the highest reported in the literature (43 to 79%) [6,10,12,23]. Furthermore, the establishment of IE diagnosis in each case by an adjudication committee using a validated classification (modified Duke) and follow-up data reinforces the study's validity.

Our goal was to quantify, as early as possible, the risk of IE among SAB patients and thus the indication for echocardiography for adjustment of antibacterial treatment, and early multidisciplinary evaluation of indication(s) for cardiac surgery. This is particularly critical for IE patients with, valvular or paravalvular complications, or high embolic risk [5,24]. Of note, 25% of VIRSTA patients who were operated on for IE underwent surgery before day 6 (after first blood sample collection), and 50% before day 12.

Our study shows several readily available predictors independently associated with IE such as patient background characteristics, including predisposing cardiac conditions. These findings agree with previous reports who proposed criteria to assess predictors of IE among SAB patients [6,13,18,21,25,26].

Other factors classified as initial SAB presentation – i.e IV drug use and community-acquired SAB - are IE predictors in our final model, as in previous studies [6,7,13,14]. Interestingly, CRP, another predictor of IE in our population, has been proposed to be an additional minor criteria of Duke modified classification by Lamas and colleagues [27] because it improved Duke classification sensitivity in patients with pathologically proven IE. To our knowledge, our VIRSTA study is the first who reported an independent association between CRP level and IE in patients with suspected IE in multivariable analysis. To our knowledge, this study is the first to report the CRP level as an independent predictor of IE. Some early extracardiac events such as embolic events, vertebral osteomyelitis, meningitis and severe sepsis or shock were associated with a higher frequency of IE. Persistent bacteremia was strongly associated with definite IE, and has been shown to be a predictor of complicated SAB [14,16,17,19,24].

The two sensitivity analyses, which found quite similar determinants of IE, argue for the robustness of the model. With the “echo sensitivity analysis”, we tested the risk that some IE cases may have been undetected in patients without echocardiography even with 12 weeks of follow-up data. Thanks to the “modified Duke criteria sensitivity analysis,” we ensured that ascertainment of candidate predictors was fully independent of ascertainment of criteria taken into account for the end-point; of note, to the best of our knowledge, such sensitivity analysis has never been performed before by authors developing prediction score in SAB patients. The excellent performance of the final predictive model also proved its reliability, which constitutes a strong argument for supporting its application in clinical practice.

The proportion of IE increases concomitantly with the score, from 1% for a score ≤ 2 to more than 70 % for a score ≥ 10 . For a score ≤ 2 , the negative predictive value was excellent (98.8%). The threshold of 2 is somewhat arbitrary but combines the assets of a high negative predictive value (>95%) and a small number of undiagnosed IE cases (1.1%). The score can be applied as soon as SAB is diagnosed and

echocardiography indicated if the score is above 2. Otherwise, occurrence of complications and/or of a positive T48h blood culture must lead to recalculation of the score and to indication for echocardiography in those with a score which has risen to above 2.

In patients with a score ≥ 3 , echocardiography should be performed urgently using the most sensitive method, *i.e.* TEE. According to the positive predictive value, more than one in 5 patients in this group would be classified as definite IE. Of note, patients with one of the characteristics weighted ≥ 3 (*i.e.* native valve disease or permanent intracardiac devices or previous IE or IVD use) exceed *per se* this cut-off.

In contrast, in patients with a score ≤ 2 , the probability of IE is very low and systematic urgent TEE appears less justified. The use of this score in our cohort would have permitted the avoidance of urgent TEE in 792 patients (39.4%). Of note, among the 9 patients with definite IE and a score ≤ 2 (false-negative), none would have had an increased IE prediction score ≥ 3 if SAB complications that occurred later than 48 hours had been considered (data not shown).

Limitations. We acknowledge several limitations to our study. First, as with other large observational prospective studies and despite recommendations to the contrary, a substantial proportion of our patients' cohort did not undergo echocardiography in our cohort. This underlines the reluctance of some physicians to perform echocardiography in all SAB patients, and supports the need for a scoring system. To maintain the external validity of this prospective cohort, we chose to perform the main analysis on the total population. However, we cannot exclude the possibility that cases of IE might have been missed. Nevertheless, the systematic 12-week follow-up limited this possibility, and the "echo sensitivity analysis" gives us confidence in the results. Second, patients were enrolled only in tertiary care centers. This probably led to the recruitment of more severe patients with a higher prevalence of comorbidities. However, we minimized the referral bias by excluding patients referred from other hospitals for the management of IE. Third, despite the large sample size (*i.e.* 2,008 SAB patients), and use of a bootstrap technique to validate our prediction model, it would have been of interest to add an external validity measurement using another data set in addition to the internal validity assessment. Third, confirmation of

these findings with patients originating from different countries and/or infected by different microbiological isolates is required.

In conclusion, our study is the largest multicenter prospective cohort of SAB patients reported to date, with a high rate of echocardiography and a systematic 12-week follow-up; it proposes a simple scoring system applicable in all subset of SAB patients within 48 hours and whatever the setting of acquisition (See Table S2 in Supplementary Appendix). The sensitivity analyses reinforce the robustness of the model and the validity of our results. We think that the early detection of IE in patients with SAB can be improved by the use of the VIRSTA score. The high predictive performance of this score makes possible a reliable assessment of the likelihood of IE. The routine use of this score may have important implications for clinical practice, in particular with regard to indications for echocardiography for a given patient. Early TEE should be performed urgently in patients with a score ≥ 3 , and repeated if initially negative, while in the large subgroup of patients with a score ≤ 2 , urgent TEE is not needed at an early stage, although the indications depend on the clinical context. The rationale behind early indications for echocardiography is of particular importance when local resources are limited. Finally, this score is useful to selectively draw the attention of clinicians to patients at high risk of IE, since recommendations for systematic echocardiography are not currently applied.

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Table 1. Demographic and clinical variables present at the time of *Staphylococcus aureus* bacteremia diagnosis in the 2,008 enrolled patients, VIRSTA Study

	N or med	IQR or %	Non IE N=1,787	IE N=221	p-value
Background characteristics					
Age (Yr)	67	(65 ; 78)	67(5;78)	67 (3 ;79)	0.9
Gender (male)	1295	(64.5)	1151 (64.4)	144 (65.2)	0.8
Chronic hemodialysis	211	(10.5)	185 (10.4)	26 (11.8)	0.5
Mac Cabe score					
Ultimately fatal disease	751	(37.4)	674 (37.8)	77 (34.8)	0.4
Rapidly fatal disease	368	(18.3)	332 (18.6)	36 (16.3)	
Predisposing cardiac conditions					
Permanent intracardiac device or previous IE*	341	(17.0)	255 (14.3)	86 (38.9)	<0.0001
Pre-existing native valve disease	264	(13.1)	221 (12.4)	43 (19.5)	
None	1403	(69.9)	1311 (73.4)	92 (41.6)	
Initial SAB presentation					
Intravenous drug use	63	(3.1)	39 (2.2)	24 (10.9)	<0.0001
Known source of infection†	1602	(79.8)	1441 (80.6)	161 (72.9)	0.01
Presumed setting of acquisition					
Nosocomial	1075	(53.5)	1006 (56.3)	69 (31.2)	<0.0001
Community or non-nosocomial Health care associated	875	(43.6)	726 (40.6)	146 (67.4)	
Unknown setting of acquisition	58	(2.9)	55 (3.1)	3 (1.4)	
C-reactive protein at inclusion > 190 mg/L ‡					
No	952	(47.4)	880 (49.2)	72 (32.6)	<0.0001
Yes	929	(46.3)	788 (44.1)	141 (63.8)	
Missing value	127	(6.3)	119 (6.7)	8 (3.6)	
Methicillin resistance					
No	1627	(81.0)	1436 (80.3)	191 (86.4)	0.02
Yes	381	(19.0)	351 (19.7)	30 (13.6)	
Early extracardiac events (0-48 hours)					
Severe sepsis or septic shock	495	(24.7)	400 (22.4)	95 (43.0)	<0.0001
Cerebral or peripheral emboli	90	(4.5)	38 (2.1)	52 (23.5)	<0.0001
Meningitis	22	(1.1)	9 (0.5)	13 (5.9)	<0.0001
Vertebral osteomyelitis	28	(1.4)	20 (1.1)	8 (3.6)	<0.008
Persistent bacteremia	344	(17.1)	259 (14.5)	85 (38.5)	<0.0001

IE, infective endocarditis ; IQR, Interquartile range

* Prosthetic valve in 140 patients (7.0 %), pacemaker or ICD in 217 (10.8%) and previous IE in 34 (1.7%)

† venous or arterial line in 527 patients (26.2%), skin in 384 (19.1%), surgical wound in 303 (15.0%), lung in 122 (6.1%), urinary tract in 103 (5.1%) and other presumed source in 163 (8.1%)

‡ categorized according to the median of the distribution

Table 2. Distribution of the modified Duke criteria in the 2,008 *Staphylococcus aureus* bacteremia enrolled patients, VIRSTA Study

Modified Duke Classification	n	%	n	%	Modified Duke criteria	Total number of patients	Number of patients without echocardiography
Definite	221	11.0	24	10.9	Histologically proven		
					Not concerned*	24	0
			197	89.1	2 major criteria	139	3
					1 major criteria + ≥ 3 minor criteria	56‡	7
Possible	965	48.1			≥ 5 minor criteria	2‡	0
					1 major criteria + 1 minor criteria	605	191†
					1 major criteria + 2 minor criteria	267	49†
					≥ 3 minor criteria	93	39†
Excluded	822	40.9			0 minor criteria	179	59
					1 minor criteria	261	115
					2 minor criteria	374	196
					3 minor criteria	8	1†

* Patients with histologically proven IE who don't need to fulfill the clinical modified Duke criteria

† Patients removed from the echo sensitivity analysis

‡ Patients removed from the modified Duke criteria sensitivity analysis

Table 3. Final predictive model of infective endocarditis and median β Coefficients estimated by Multivariate Logistic Regression Model and Bootstrapping Procedure in the 2008 enrolled *Staphylococcus aureus* bacteremia patients, VIRSTA Study

	Multivariate analysis				.632 Bootstrap procedure	
	Odds Ratio	(95% CI)	p-value	β	β'	Weight
Cerebral or peripheral emboli	10.4	(6.0 ; 17.9)	<0.0001	2.33	2.37	<u>5</u>
Meningitis	9.6	(3.2 ; 29.2)	<0.0001	2.27	2.31	<u>5</u>
Permanent intracardiac device or previous IE	7.3	(4.9 ; 10.9)	<0.0001	1.99	2.02	<u>4</u>
Pre-existing native valve disease	3.6	(2.3 ; 5.7)		1.29	1.29	<u>3</u>
Intravenous drug use	5.8	(2.8 ; 11.7)	<0.0001	1.75	1.77	<u>4</u>
Persistent bacteremia	3.9	(2.8 ; 5.7)	<0.0001	1.38	1.40	<u>3</u>
Vertebral osteomyelitis	3.2	(1.2 ; 8.9)	0.03	1.17	1.15	<u>2</u>
Community or Non nosocomial Health care associated acquisition	2.6	(1.8 ; 3.7)	<0.0001	0.96	0.96	<u>2</u>
Severe sepsis or shock	2.0	(1.4 ; 2.9)	0.0001	0.71	0.72	<u>1</u>
C-reactive protein > 190 mg/L	1.9	(1.3 ; 2.7)	0.0006	0.64	0.65	<u>1</u>

CI, Confidence Interval

Table 4. Performance score for IE in 2,008 patients with *Staphylococcus aureus* bacteremia, VIRSTA Study

VIRSTA Score	Sensitivity (CI 95%)	Specificity (CI 95%)	Positive predictive value (CI 95%)	Negative predictive value (CI 95%)
0 versus ≥ 1	99.3 (99.2 ; 99.3)	18.5 (17.3 ; 19.6)	13.1 (12.1 ; 14.2)	99.5 (99.5 ; 99.6)
≤ 1 versus ≥ 2	97.2 (96.1 ; 98.7)	32.2 (30.8 ; 33.5)	15.1 (13.9 ; 16.2)	98.9 (98.4 ; 99.5)
≤ 2 versus ≥ 3	95.8 (94.3 ; 97.8)	44.2 (42.6 ; 45.6)	17.6 (16.2 ; 18.9)	98.8 (98.4 ; 99.4)
≤ 3 versus ≥ 4	85.5 (82.4 ; 88.6)	61.9 (60.5 ; 63.3)	21.8 (20.0 ; 23.5)	97.2 (96.5 ; 97.8)
≤ 4 versus ≥ 5	78.3 (74.8 ; 81.9)	74.4 (73.1 ; 75.7)	27.5 (25.3 ; 29.7)	96.5 (95.9 ; 97.1)
≤ 5 versus ≥ 6	70.1 (66.0 ; 74.1)	83.2 (82.1 ; 84.3)	34.0 (31.3 ; 36.7)	95.8 (95.1 ; 96.4)
≤ 6 versus ≥ 7	57.9 (53.9 ; 62.1)	91.1 (90.2 ; 92.0)	44.6 (40.9 ; 48.4)	94.6 (93.9 ; 95.3)
≤ 7 versus ≥ 8	45.7 (41.5 ; 49.7)	95.1 (94.5 ; 95.8)	53.7 (49.1 ; 58.6)	93.4 (92.7 ; 94.1)
≤ 8 versus ≥ 9	38.5 (34.6 ; 42.4)	97.3 (96.8 ; 97.8)	63.9 (58.4 ; 69.1)	92.8 (92.0 ; 93.5)
≤ 9 versus ≥ 10	26.7 (23.2 ; 30.2)	98.7 (98.5 ; 99.0)	71.9 (65.4 ; 78.4)	91.6 (90.8 ; 92.4)
≤ 10 versus ≥ 11	20.4 (17.0 ; 23.8)	99.4 (99.2 ; 99.7)	81.8 (75.0 ; 88.2)	91.0 (90.1 ; 91.8)

CI, Confidence Interval

Figure titles and legends

Figure 1. Timeline for collection of infective endocarditis's predictive factors, VIRSTA Study

SAB: *Staphylococcus aureus* bacteremia

D1 (T0) is considered as the day during which the first *S. aureus* positive blood sample is drawn (T0 blood sample collection). The culture result of this blood sample, available at a mean time of 24 hours is the day of SAB diagnosis which corresponds to D2 (T 24h=T0 blood sample result). The T48h blood sample is therefore drawn at D3 (T48h blood sample collection) and its results available at D4 (T 72h=T48h blood sample result).

Figure 2. Proposed score for optimal use of TEE in patients with SAB, VIRSTA Study

SAB: *Staphylococcus aureus* bacteremia

TEE : trans-esophageal echocardiography;

Figure 3. Association between VIRSTA score and IE probability in 2,008 patients with *Staphylococcus aureus* bacteremia, VIRSTA Study

Infective endocarditis rate increased significantly from 1.1% (score≤2) to 701.8% (score≥10). Rate of echocardiography performed rose from 54.2% (score≤2) to 89.9% (score≥10).

Figure 1

Figure 2

Figure 3