A clinical decision rule to rule out bloodstream infection in the emergency department: retrospective multicentric observational cohort study

Jonathan Pehlivan,[1] Delphine Douillet ,[2,3] Riou Jérémie,[4,5] Clément Perraud,[2] Alexandre Niset,[6] Matthieu Eveillard,[7] Rachel Chenouard,[7] Rafael Mahieu [8,9]

Handling editor Kirsty Challen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/emermed-2022-212987).

For numbered affiliations see end of article.

Correspondence to
Dr Rafael Mahieu, Service de maladies infectieuses et tropicales, Centre hospitalier universitaire d'Angers, 4 rue Larrey, 49100 Angers, France, CHU Angers Maladies infectieuses et tropicales, Angers 49100, France;
rafael.mahieu@gmail.com

Received 19 November 2022
Accepted 27 October 2023

To cite: Pehlivan J, Douillet D, Jérémie R, *et al*. *Emerg Med J* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/emermed-2022-212987

ABSTRACT

Background We aimed to identify patients at low risk of bloodstream infection (BSI) in the ED.

Methods We derived and validated a prediction model to rule out BSI in the ED without the need for laboratory testing by determining variables associated with a positive blood culture (BC) and assigned points according to regression coefficients. This retrospective study included adult patients suspected of having BSI (defined by at least one BC collection) from two European ED between 1 January 2017 and 31 December 2019. The primary end point was the BSI rate in the validation cohort for patients with a negative Bacteremia Rule Out Criteria (BAROC) score. The effect of adding laboratory variables to the model was evaluated as a second step in a two-step diagnostic strategy.

Results We analysed 2580 patients with a mean age of 64 years±21, of whom 46.1% were women. The derived BAROC score comprises 12 categorical clinical variables. In the validation cohort, it safely ruled out BSI without BCs in 9% (58/648) of patients with a sensitivity of 100% (95% CI 95% to 100%), a specificity of 10% (95% CI 8% to 13%) and a negative predictive value of 100% (95% CI 94% to 100%). Adding laboratory variables (creatinine ≥177 µmol/L (2.0 mg/dL), platelet count ≤150 000/mm^3 and neutrophil count ≥12 000/mm^3) to the model, ruled out BSI in 10.2% (58/570) of remaining patients who had been positive on the BAROC score. The BAROC score with laboratory results had a sensitivity of 100% (95% CI 94% to 100%), specificity of 11% (95% CI 9% to 14%) and negative predictive value of 100% (95% CI 94 to 100%). In the validation cohort, there was no evidence of a difference in discrimination between the area under the receiver operating characteristic for BAROC score with versus without laboratory testing (p=0.6).

Conclusion The BAROC score safely identified patients at low risk of BSI and may reduce BC collection in the ED without the need for laboratory testing.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Less than 15% of patients with bblood culture (BC) collection have a bloodstream infection (BSI) and there are a high rate of false positive (1%–3% of BC and 30%–50% of positive BC).
⇒ No clinical rule readily identifies ED patients with a low risk of BSI for whom BC can be avoided.

WHAT THIS STUDY ADDS

⇒ Using data from two different EDs, we developed and validated a score that safely identifies ED patients at low risk of BSI without the need for laboratory testing.
⇒ The score might reduce the number of BCs drawn by clinicians.
⇒ We developed an internet app that eases the calculation of our score.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The use of this score could reduce unnecessary BC (approximately 10%) and their potential consequences.
⇒ Future research should incorporate an implementation study.

INTRODUCTION

Fever is one of the most frequent reasons for consultation in the ED, accounting for 5%–15% of visits.[1 2] Differentiating bacterial and other causes of fever may be challenging for the clinician, who faces numerous potential pitfalls.[1] Inflammatory markers like procalcitonin have failed in many situations to distinguish between infected patients who need antibiotic treatment in the ED and those that do not.[2]

Clinicians suspecting a bacterial infection may order blood cultures (BCs) to help identify the source of infection and to guide antibiotic therapy. BCs are thus collected in approximately 10% of patients admitted to the ED.[3] Except for those with suspected sepsis, the incidence of bloodstream infection (BSI) is low in this population, with positive BCs identifying a true pathogen in only 8.2%–11.0%.[4–7] Furthermore, a large proportion of positive BCs are not due to BSI but false positives due to the development of skin microorganisms in the BC (contaminants). These BC contaminants are responsible for unnecessary antibiotic prescriptions, more work for nurses, more discomfort for patients, longer hospital stays and, overall, additional costs.[8–11]

In 2006, using a prospective cohort of ED patients, Shapiro *et al* developed and validated a score to classify patients with a low, intermediate or high risk of BSI.[5] This score included clinical variables (suspected endocarditis, temperature >39.4°C, indwelling vascular catheter, age >65 years, chills, vomiting and systolic BP <90 mm Hg) as well as laboratory results (white blood cell count >18 000 mm^3, bands >5%, platelets

<150 000 mm^3 and creatinine >2 mg/dL). Using the rule by Shapiro *et al*, only 0.9% of low-risk patients had a BSI and the use of BCs could have been reduced by 27%.[5] However, the rule by Shapiro *et al* and other rules developed over the last 20 years require access to laboratory results to assess the risk of BSI. When venipuncture is performed for both BCs and other laboratory analyses, rules based on a two-step strategy (waiting for laboratory testing before ordering a BC) are hardly applicable and it seems that none of these models have been implemented in clinical practice.[12] Moreover, band counts (included in the rule by Shapiro *et al*) are not routinely performed in laboratories. Only one prediction model without laboratory testing has been proposed; however, the 2005 publication was only a derivation study, did not validate the model and included just 40 BSIs.[13] To date, none of these rules have been prospectively validated.

We aimed to derive and validate a score in a large retrospective cohort of patients admitted to the ED to identify patients at low risk of BSI for whom BCs could be avoided. The added value of laboratory results was also assessed in a second step.

METHOD

Study design and patients

This study was a two-centre two-country retrospective cohort of all adult patients presenting to the ED with a suspicion of BSI (defined by at least one BC collection) between 1 January 2017 and 31 December 2019. The decision to collect BCs was at the discretion of the clinician in charge of the patient. The sample size of the study is pragmatic and mainly determined by the feasibility of data collection. In order to account for seasonal variation, we used data collected over 3 years; however, for feasibility we restricted the sample to patients admitted during the first week of each month over this period. Angers University Hospital, France, is a 1374-bed academic hospital with 102 000 visits annually. The Cliniques Universitaires Saint-Luc, Belgium, is a 973-bed with 78 000 visits annually.

The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis and Standards for Reporting of Diagnostic Accuracy Studies checklists were followed.

Outcome measure

The outcome was the rate of false negative tests in the validation cohort. False negatives were defined as patients who had a BSI even though the prediction model was negative. A BSI meant a positive BC with a pathogen. Skin microorganisms, namely coagulase-negative staphylococci, viridans group streptococci, *Corynebacterium* spp, *Cutibacterium* spp (eg, *Propionibacterium* spp), *Bacillus* spp or *Micrococcus* spp, were considered BSIs if antimicrobial therapy was started and maintained after bacterial identification.[14] Without treatment, they were considered BC contaminants and as negative BCs in the model. The BC contamination rate was reported.

To validate the safety of ruling out a BSI in the ED, we considered that the proportion of missed BSIs should be <2.5% (arbitrarily defined as <3% in previous studies).[12 15 16] We arrived at this proportion using the observed rate of false positive BCs in the ED (ie, BC contaminants), assuming that for these patients the net clinical benefit of BC was questionable with an equivalent risk of inappropriate antibiotic prescription because of BC contaminants.[4 12] Our prediction score is a continuous score and provides an estimated risk of BSI for each patient. This cut-off was established to evaluate the performance of the score in a clinical decision rule of not collecting BCs. The accuracy of the final model was assessed using the cut-off by analysing the area under the receiver operating characteristic (AUROC) curve. We defined patients with an estimated risk of BSI below this cut-off as having a negative Bacteremia Rule Out Criteria (BAROC) score. The reduction in BCs if the BAROC score had been followed was evaluated in a two-step strategy. First, patients with a negative BAROC score (without laboratory testing) were identified. For the remaining patients (eg, those with a positive BAROC score), the BAROC score with laboratory results was applied.

Chart review process

Three clinicians (JP, CP, AN) collected data from the patients' records and one clinician reviewed the data collected (RM). A formal coding manual was defined before the collection of data started and 10 randomly selected records were used as a training test. For ambiguously recorded data, an adjudication committee with a least two of the mentioned clinicians was meeting. Missing data were left as missing. The outcome measure was blind for the data collector. The statistician in charge of the study did not participate in the data collection.

Study measurements

We assessed all variables known to be potentially associated with BSI. For the *suspicion of endocarditis*, we considered the variable as present when it was mentioned in the ED observation or when echocardiography was performed or ordered for suspicion of

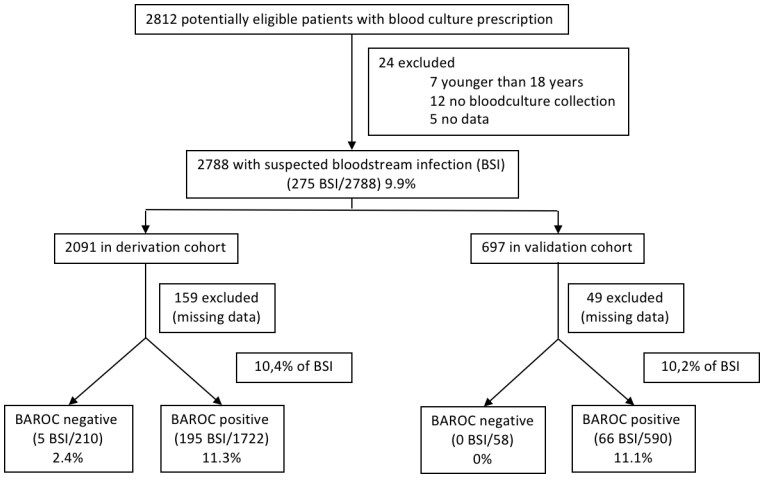

Figure 1 Enrolment and assignment of patients to derivation and validation cohorts. BAROC, Bacteremia Rule Out Criteria.

Table 1 Characteristics of the patients in both derivation and validation cohorts

Characteristics	Overall (n=2788)	Prediction cohort (n=2091)		Validation cohort (n=697)	
		Data available (n=1932)	Data missing (n=159)	Data available (n=648)	Data missing (n=49)
Age (year)—mean±SD	64±21	64±21.1	61.3±20.7	63.5±21.7	61.6±22.9
Female sex—no. (%)	1284 (46.1)	862 (44.6)	77 (48.4)	323 (49.8)	22 (49.9)
Pre-existing conditions—no. (%)					
Chronic heart failure	982 (35.2)	693 (35.9)	60 (37.7)	208 (32.1)	21 (42.9)
Chronic obstructive pulmonary disease	485 (17.4)	349 (18.1)	39 (24.5)	90 (13.9)	7 (14.3)
Chronic kidney disease	369 (13.2)	265 (13.7)	18 (11.3)	77 (11.9)	9 (18.4)
Liver cirrhosis	199 (7.1)	133 (6.9)	16 (10.1)	47 (7.3)	3 (6.1)
Cancer	457 (16.4)	328 (17)	20 (12.6)	104 (16)	5 (10.2)
Immune deficiency	336 (12.1)	225 (11.6)	10 (6.3)	96 (14.8)	5 (10.2)
Diabetes	547 (19.6)	391 (20.2)	35 (22)	109 (16.8)	12 (24.5)
Central venous catheter	200 (7.2)	145 (7.5)	5 (3.1)	48 (7.4)	2 (4.1)
Signs and symptoms—no. (%) or mean±SD					
Temperature (°C)	38±5.6	37.9±6.5	36.9±1	37,8±1.3	37.5±1
Systolic BP (mm Hg)	130±25	130±20	132.8±26	130±26	129±26
RR	25±8	25±8	27±12	26±9	22±8
GCS	15±1	15±1	15±1	15±1	14±3
Oxygen therapy (%)	436 (19)	297 (15.4)	31 (19.5)	101 (15.6)	7 (14.3)
Chills (%)	441 (15.8)	321 (16.6)	16 (10.1)	94 (14.5)	10 (20.4)
Mottling (%)	89 (3.2)	56 (2.9)	5 (3.1)	26 (4)	2 (4.1)
Vomiting (%)	336 (12.1)	232 (12)	12 (7.5)	89 (13.7)	3 (6.1)
Suspected endocarditis (%)	25 (0.9)	16 (0.8)	1 (0.6)	8 (1.2)	0
Biological covariates—mean±SD					
White blood count (G/L)	12±7.2	11.9±7	11.9±9	12.2±7.6	12.3±5.5
Neutrophils (G/L)	9.7±7.8	9.7±8.1	9.5±9.1	9.8±6.8	9.4±4.9
Platelets (G/L)	241±109	241±111	261±118	239±103	242±104
Creatinine (µmol/L)	101±99	102±104	113±110	95±70	140±144
Blood cultures (BC)					
Antibiotic therapy before BC (%)	436 (15.6%)	300 (15.5)	24 (16.4)	101 (15.6)	9 (18.4)
Bloodstream infection (%)	276 (9.9%)	200 (10.4)	7 (4.4)	66 (10.2)	3 (6.1)

G/L, giga/litter.

endocarditis. For the item *suspicion of bacterial infection* in ED, we have considered any mention of suspicion of bacterial infection in the ED or any AB started in the ED. Immunodeficiency was defined as any immunosuppressive therapy, HIV, congenital immunodeficiency and/or asplenia. We categorised continuous variables based on cut-off values according to their clinical relevance or if they were previously described for their association with BSI.[5 17–19] There were two categories for age (<65 years and ≥65 years), RR (<22/min or ≥22/min), GCS (<15 and 15), neutrophil count (<12 000/mm^3 and ≥12 000/mm^3), platelets (≤150 000/mm^3 and >150 000/mm^3) and creatinine (<2.0 mg/dL or 177 µmol/L, and ≥2.0 mg/dL). There were three categories for white blood cell count (<12 000/mm^3, ≥12 000/mm^3 and ≥18 000/mm^3) as well as four categories for systolic BP (≤90 mm Hg, ≤100 mm Hg, ≤110 mm Hg and >110 mm Hg) and temperature (≤36°C, ≥38.3°C, ≥38.5°C and ≥39.4°C).

Statistical analysis

Statistical analysis was performed with R software (V.3.5.1, www.*R*-project.org, Vienna, Austria). Subjects' characteristics were reported as number and percentage for categorical variables and as mean±SD or median (IQR), as appropriate, for continuous variables. For univariate analysis, data were compared using Fisher's exact test for categorical variables and Mann-Whitney U test or Kruskal-Wallis test for continuous variables.

To derive and validate the model, the database was randomly divided into two datasets with 75% for model derivation and 25% for model validation. First, univariate analysis of the derivation dataset was used to select predictor variables associated with BSI and then used Akaïke Information Criterion (AIC) to decide which to include in the final model. In order to choose the most parsimonious model, a selection of variables allowing the optimisation of the AIC was carried out in a manual backward selection process. All significant variables, as well as the non-significant variables that interact with the other items and provide the best AIC were retained.[20] The absence of collinearity between the predictor variables was also checked using the variance inflation factor. The shrink-package in R was used to shrink the model coefficients and reduce overfitting.[21] We assigned points for the score according to the regression coefficients (the point is the regression coefficient in its entirety and without simplification). Patients with missing data (at least one variable of the BAROC score) were excluded from the derivation and validation model. All remaining patients had all data points needed for both the BAROC score and the laboratory variables assessed.

The accuracy of the final model with and without laboratory items was assessed by analysing the AUROC curve and its CI using the pROC package in R.[22] The Brier score was reported to evaluate the accuracy of the probabilistic predictions. The lower the value, the better the prediction (between 0 and 1, where a perfectly calibrated model would give a score of 0).[23]

For patients with missing data, sensitivity analyses of best-case and worst-case scenarios were performed. The worst-case scenario considers a complete misclassification of the participants with missing data. The best-case scenario is the converse,

Table 2 Characteristics of the patients with and without bloodstream infection

Characteristics	Overall (n=1932)	Bloodstream infection (n=276)	No bloodstream infection (n=2512)	P value
Age—year	64±21	72±16	63±22	<0.001
Male sex—no. (%)	1069 (55%)	106 (54)	963 (56)	0.7
Pre-existing conditions—no. (%)				
Chronic heart failure	693 (36%)	94 (48)	599 (35)	<0.001
Chronic obstructive pulmonary disease	349 (18%)	29 (15)	320 (18)	0.2
Chronic kidney disease	265 (14%)	32 (16)	233 (13)	0.3
Liver cirrhosis	133 (6.9%)	31 (16)	102 (5.9)	<0.001
Cancer	328 (17%)	37 (19)	291 (17)	0.5
Immune deficiency	224 (12%)	28 (14)	196 (11)	0.2
Diabetes	391 (20%)	61 (31)	330 (19)	<0.001
Central venous catheter	145 (7.5%)	17 (8.6)	128 (7.4)	0.5
Signs and symptoms—no. (%) or mean±SD				
Temperature (°C)	37.9±6.5	38,3±1.4	37,8±6.8	0.03
Systolic BP (mm Hg)	130±25	123±27	131±25	<0.001
RR	25±8	25±7	± 8	0.6
GCS	15±1	15±1.3	15±1.1	0.02
Oxygen therapy (%)	296 (15%)	33 (17%)	263 (15%)	0.8
Chills (%)	321 (17%)	48 (24%)	273 (16%)	0.002
Mottling (%)	56 (2.9%)	14 (7.1%)	42 (2.4%)	<0.001
Vomiting (%)	232 (12%)	35 (18%)	197 (11%)	0.009
Suspected endocarditis (%)	16 (0.8%)	7 (3.6%)	9 (0.5%)	<0.001
Biological covariates—mean±SD				
White blood count (g/L)	11.9±7	13±7.4	11.7±7	0.03
Neutrophils (g/L)	9.7±8.1	11.5±6.8	9.5±8.2	<0.001
Platelets (g/L)	240±111	201±111	244±110	<0.001
Creatinine (µmol/L)	102±104	128±98	99±104	<0.001
Source of infection (n=1562)				<0.001
Abdomen	164 (8.5%)	37 (19%)	127 (7.3%)	
Cutaneous	116 (6%)	10 (5.1%)	106 (6.1%)	
Endocarditis	16 (0.8%)	14 (7.1%)	2 (0.1%)	
Lung	362 (19%)	22 (11%)	340 (20%)	
Meningitis	7 (0.4%)	3 (1.5%)	4 (0.2%)	
Oral and upper airway	40 (2.1%)	1 (0.5%)	39 (2.2%)	
Urinary tract	270 (14%)	70 (36%)	200 (12%)	
Septic arthritis	10 (0.5%)	2 (1%)	8 (0.5%)	
Other	91 (3.2%)	26 (9.4%)	65 (2.6%)	
Antibiotic therapy before BC (%)	300 (16%)	16 (8.1%)	284 (16%)	0.002
Suspicion of bacterial infection in ED (%)	1062 (55%)	160 (81%)	902 (52%)	<0.001
Definitive diagnosis of bacterial infection (%)	1120 (58%)	197 (100%)	923 (53%)	<0.001

BC, blood culture.

that is, all BSIs were BAROC positive and all non-BSIs were BAROC negative.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Overall, of 2788 patients 208 with missing data were excluded and 1932 patients were analysed in the derivation cohort and 648 in the validation cohort. The rate of BSI was 10.3% (266/2580) and the rate of BC contaminants was 2.6% (67/2580). The mean number of BCs collected was 1.32±0.52. The prevalence of BSI in the two cohorts is presented in figure 1. It was 10.4% (200/1932) in the derivation cohort and 10.2% (66/648) in the validation cohort (p=0.9). Characteristics of the study populations are presented in table 1. In the prediction cohort, there were more male patients (55.1 vs 50.5), more patients with chronic obstructive pulmonary disease (COPD) (18.6 vs 13.9), patients with less immune deficiency (11.2 vs 14.5) and patients with a lower RR (25±8 vs 26±9).

BAROC score

Derivation

The characteristics of the patients with and without BSI are presented in table 2. All patients taken together, the mean age was 64±21 years and 46.1% were women. Patients presenting with a BSI were significantly older (72±16 vs 63±22, p<0.001) and more likely to have chronic heart failure (48% vs 35%, p<0.001), liver cirrhosis (16% vs 5.9%, p<0.001) and diabetes (31% vs 19%, p<0.001). Although not significant, sex and immune deficiency were included in the multivariate logistic regression model because they were included in other prediction rules. The OR of each variable and 95% CI are provided in table 3. A suspicion of endocarditis was strongly associated with a BSI whereas the sex of the patient was of little predictive value, the ORs being 6.55 (2.41 to 17.24) and 1.15 (0.86 to 1.52), respectively. The final model included age 65 years

Table 3 Final model of the BAROC rule (no laboratory parameters)

Characteristics	OR	95% CI	Beta-coefficient	P value
Age ≥65 years	2.18	1.60 to 3.00	0.78	<0.001
Female sex	1.15	0.86 to 1.52	0.14	0.337
Chronic obstructive pulmonary disease	0.67	0.45 to 0.98	−0.40	0.049
Liver cirrhosis	2.69	1.74 to 4.09	0.99	<0.001
Immune deficiency	1.13	0.74 to 1.67	0.12	0.553
Diabetes	1.58	1.14 to 2.16	0.45	0.005
Chills	1.79	1.27 to 2.48	0.58	<0.001
Systolic BP ≤110 mm Hg	2.20	1.62 to 2.96	0.79	<0.001
Temperature ≤36°C	0.68	0.39 to 1.11	−0.39	0.140
Temperature >38.5°C	1.79	1.34 to 2.40	0.58	<0.001
Vomiting	1.46	0.99 to 2.12	0.38	0.049
Suspected endocarditis	6.55	2.41 to 17.24	1.88	<0.001

BAROC, Bacteremia Rule Out Criteria.

or older, female sex, COPD, liver cirrhosis, immunodeficiency, diabetes, chills, systolic BP ≤110 mm Hg, temperature ≤36°C or >38.5°C, vomiting and suspected endocarditis (table 3). Female sex, immune deficiency and COPD were added to the final model despite a p value >0.05 in the multivariate logistic regression model because they improved the AIC. In the derivation cohort, the area under the curve was 0.73 (0.69 to 0.77).

When using the predefined cut-off value of 2.5% as an acceptable rate of missed BSIs, the negative predictive value of the BAROC score was 98% (95% CI 95% to 99%) with a sensitivity of 97% (95% CI 94% to 99%) and a specificity of 12% (95% CI 10% to 13%) (table 4). The risk of BSI for each patient was easily estimated using a smartphone and computer application available at https://ceral-chu-angers-49.shinyapps.io/BAROC/.

Table 4 Performance of the BAROC rule in the derivation and validation cohort

Characteristics in the derivation cohort	Bloodstream infection	No bloodstream infection	Total
BAROC positive	195	1527	1722
BAROC negative	5	205	210
Total	200	1732	1932
Sensitivity	0.97 (0.94 to 0.99)		
Specificity	0.12 (0.10 to 0.13)		
Positive predictive value	0.11 (0.10 to 0.13)		
Negative predictive value	0.98 (0.95 to 0.99)		
Positive likelihood ratio	1.11 (1.08 to 1.14)		
Negative likelihood ratio	0.21 (0.09 to 0.51)		
Characteristics in the validation cohort	**Bloodstream infection**	**No bloodstream infection**	**Total**
BAROC positive	66	524	590
BAROC negative	0	58	58
Total	66	582	648
Sensitivity	1.00 (0.95 to 1.00)		
Specificity	0.10 (0.08 to 0.13)		
Positive predictive value	0.11 (0.09 to 0.14)		
Negative predictive value	1.00 (0.94 to 1.00)		
Positive likelihood ratio	1.11 (1.08 to 1.14)		
Negative likelihood ratio	0.00 (0.00 to 0.00)		

BAROC, Bacteremia Rule Out Criteria.

Validation

In the validation cohort, the area under the curve was 0.76 (95% CI 0.70 to 0.82) (figure 2). The Brier score was 0.081. When using the predefined cut-off value of 2.5%, the negative predictive value was 100% (95% CI 94% to 100%). Sensitivity was 100% (95% CI 95% to 100%) and specificity was 10% (95% CI 8% to 13%) (table 4).

Sensitivity analyses of best-case and worst-case scenarios for patients with missing data are presented in online supplemental tables S1 and S2. In the worst-case scenario, the negative predictive values of the BAROC score with and without laboratory values were 95% (95% CI 86% to 99%) and 88% (95% CI 78% to 95%), respectively.

Accuracy of the BAROC score after adding laboratory results

Derivation

When laboratory results were added to the model, three variables improved its performance: creatinine ≥177 µmol/L (2.0 mg/dL), platelet count ≤150 000/mm^3 and neutrophil count ≥12 000/mm^3 were predictive of BSI. Because of the influence of covariates, chronic heart failure was added to the model but immunodeficiency and vomiting were deleted. The OR of each variable and 95% CI are provided in table 5. The performance of the BAROC score in the derivation and validation cohorts after adding laboratory results are presented in online supplemental table S3. In the derivation cohort, the area under the curve was 0.83 (95% CI 0.78 to 0.88). The negative predictive value for BSI was 98% (95% CI 95% to 100%).

Validation

In the validation cohort, the area under the curve for the model with laboratory values was 0.81 (95% CI 0.75 to 0.86) (figure 2), the Brier score was 0.078 and the negative predictive value was 100% (95% CI 94% to 100%).

No difference was observed between the AUROC between the BAROC score with and without laboratory results, p=0.6.

Clinical value of the BAROC score

In the derivation and validation cohorts, 10.9% (210/1932) and 9% (58/648) of patients were classified as low risk by the BAROC score.

After laboratory tests were added for the remaining patients in the derivation and validation cohorts, 9.7% (161/1667) and 10.2% (58/570) were classified as low risk, with five BSIs in the derivation cohort and none in the validation cohort. For the 58 patients in the validation cohort with a negative BAROC score and no BSI, only 4 of them had a BC contaminants (6.9%).

DISCUSSION

Using a large two-country cohort, we were able to derive and validate a clinical predictive score that safely avoids BCs in patients at low risk of BSI. The BAROC score ruled out BSI in 9% of patients without laboratory testing, with a negative predictive value of 100% (95% CI 94% to 100%). The addition of laboratory testing did not significantly improve the performance of the BAROC score, its area under the curve being 0.76 and 0.81 before and after addition. However, for those not initially identified as low-risk patients, the addition of laboratory parameters prevented unnecessary BCs in 10.2% of the remaining patients.

The performance of our score is consistent with previous prediction models for BSI in the literature, where AUROC has varied between 0.6 and 0.83.[12] However, none of those scores seem to be routinely used, as illustrated by a survey by

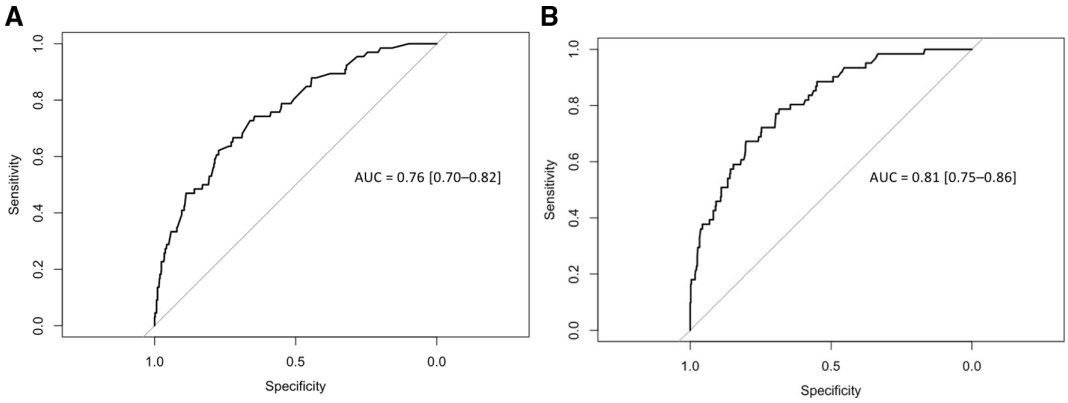

Figure 2 Receiver operating characteristic (ROC) curve for Bacteremia Rule Out Criteria (BAROC) score in the validation cohort. (A) ROC curve for the BAROC score (no laboratory tests available); (B) ROC curve for the BAROC score after adding laboratory tests. The difference between the area under the ROC of the BAROC score with and without laboratory tests is not different (p=0.6).

Eliakim-Raz *et al*. Fifteen authors who published articles about BSI prediction scores were contacted, of whom seven replied. When asked whether their score was being used in routine clinical practice, all stated that it was not.[12] The inclusion of laboratory parameters in those scores probably limits their use in EDs or hospital wards because BCs are often collected at the same time as samples for other laboratory tests. The two-step strategy of waiting for laboratory results before ordering BCs does not seem practical in the ED. Tokuda *et al* proposed a simple score with two scenarios: in the first, laboratory tests were not available; in the second, they were.[13] This model was promising as 68% of patients were classed as low risk, meaning that BCs could be avoided. That said, their study lacked power, with only 40 BSIs included and the score was not validated. We analysed 2580 patients and identified 276 BSIs. The advantage of the BAROC score is that it does not rely on laboratory testing before deciding whether BCs should be drawn.

The BAROC score was able to classify 10% of patients who would otherwise receive BC as low risk. While this may seem a small number, avoiding 10% of unnecessary BCs for a very frequent exam is far from negligible with associated direct and indirect cost savings. However, while the BAROC could reduce the number of BCs drawn for low-risk patients, it is possible that there would be patients who did not receive BCs in this study who would be classified high risk and would then have BCs drawn when they otherwise would not have. The score has 12 variables, which might seem complex but to facilitate its use in clinical practice, an application for smartphones and computers has been developed (https://ceral-chu-angers-49.shinyapps.io/BAROC/).

This study has several limitations. First, collecting data retrospectively can lead to classification bias, due to missing data in medical records at admission or because BC collection was not standardised either for the volume collected nor for the indication of BC. Second, the lack of guidelines on BC sampling in our centres may have led to an overprescription of BCs and underestimation of the incidence of BSI. However, the BSI rate was consistent with previous literature.[4 5] Another limitation is the absence of data on the treatment changes associated with BSI identification. Some BSIs may not have led to treatment changes, for example, when the bacterium had already been identified from pyelonephritis and urine culture. Additionally, some patients may have been misclassified as having or not having BSI because the recommended four to six bottles of BC (ie, 40–60 mL of blood) may not have been collected.[24] It is estimated that up to half of patients in the ED had only one BC set. This is known to reduce sensitivity for BSI detection.[25–29] A recent study in 10 US hospitals also reported that the filling volume of most BC bottles was insufficient, with a mean volume of 2.3 mL per bottle, and that none of the hospital collected the right volume of blood.[30] The distinction between contamination and BSI can sometimes be difficult and may also have contributed to a misclassification bias.[8] Nevertheless, we minimised this risk by reviewing all medical records.

A prospective study should be conducted to confirm these results and improve the performance of the score. A multifaceted training programme on the indications for BSI testing and use of a validated predictive score is probably the best way to limit inappropriate BC collections.

Table 5 Multivariate analysis of the BAROC rule when adding laboratory test

Characteristics	OR	95% CI	P value
Age ≥65 years	1.61	1.12 to 2.34	0.018
Female sex	1.41	1.03 to 1.95	0.032
Chronic obstructive pulmonary disease	0.58	0.37 to 0.89	0.017
Liver cirrhosis	2.81	1.75 to 4.41	<0.001
Chronic heart failure	1.50	1.08 to 2.10	0.016
Diabetes	1.47	1.04 to 2.06	0.028
Chills	1.77	1.24 to 2.52	0.002
Systolic BP ≤110 mm Hg	1.82	1.31 to 2.53	<0.001
Temperature ≤36°C	0.66	0.35 to 1.17	0.180
Temperature >38.5°C	1.61	1.17 to 2.22	0.003
Suspected endocarditis	6.52	2.25 to 18.9	<0.001
Bacterial infection suspected in the ED	2.79	1.95 to 4.09	<0.001
Neutrophils ≥12 g/L	1.91	1.38 to 2.64	<0.001
Creatinine ≥177 µmol/L (2.0 mg/dL)	1.99	1.25 to 3.09	0.003
Platelets ≤150 g/L	2.10	1.47 to 2.98	<0.001

BAROC, Bacteremia Rule Out Criteria.

CONCLUSION

The BAROC score safely identified patients at low risk of BSI and may reduce BC collection in the ED without the need for laboratory testing. The addition of laboratory variables only slightly improved its performance and is not a practical solution to this problem.

Author affiliations
[1]Service de maladies infectieuses et tropicales, Centre hospitalier universitaire d'Angers, Centre Hospitalier Universitaire d'Angers, Angers, France
[2]Emergency Department, Angers University Hospital, CHU Angers, Angers, France
[3]UMR MitoVasc CNRS 6015—INSERM 1083, University of Angers, Angers, France
[4]Micro et Nano médecines translationnelles, MINT, UMR INSERM 1066, UMR CNRS 6021, University of Angers, Angers, France
[5]Methodology and Biostatistics Department, Delegation to Clinical Research and Innovation, Angers University Hospital, CHU Angers, Angers, France
[6]Emergency Department, Cliniques Universitaires Saint-Luc, Université catholique de Louvain, Hopital à Bruxelles—Cliniques universitaires Saint-Luc, Bruxelles, Belgium
[7]Laboratoire de Bactériologie, Institut de Biologie en Santé—PBH, CHU Angers, Angers, France
[8]Service de maladies infectieuses et tropicales, Centre hospitalier universitaire d'Angers, CHU Angers Maladies infectieuses et tropicales, Angers, France
[9]Faculty of Medicine, Université de Nantes, Inserm, CRCINA, SFR ICAT, University of Angers, Angers, France

Contributors RM, JP, ME, RC and DD designed and supervised the study. JP, CP and AN supervised the study in their respective centres and included a large number of patients. RJ and RM performed statistical analysis. RM and JP drafted the manuscript and all authors contributed substantially to its revision. RM is responsible for all data and is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by Angers University Hospital (no. 2020/108) and Cliniques Universitaires Saint-Luc. The medical centre's institutional review board approved the study and granted a waiver of informed consent. The study was also approved by the French data protection authority, the Commission Nationale de l'Informatique et des Libertés (no. 202000128).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iDs
Delphine Douillet http://orcid.org/0000-0001-7986-7552
Rafael Mahieu http://orcid.org/0000-0002-9978-6714

REFERENCES

1 DeWitt S, Chavez SA, Perkins J, *et al*. Evaluation of fever in the emergency department. *Am J Emerg Med* 2017;35:1755–8.
2 van der Does Y, Limper M, Jie KE, *et al*. Procalcitonin-guided antibiotic therapy in patients with fever in a general emergency department population: a multicentre non-inferiority randomized clinical trial (HiTEMP study). *Clin Microbiol Infect* 2018;24:1282–9.
3 Rothe K, Spinner CD, Ott A, *et al*. Strategies for increasing diagnostic yield of community-onset Bacteraemia within the emergency department: a retrospective study. *PLoS ONE* 2019;14:e0222545.
4 Dargère S, Parienti J-J, Roupie E, *et al*. Unique blood culture for diagnosis of bloodstream infections in emergency departments: a prospective multicentre study. *Clin Microbiol Infect* 2014;20:920–7.
5 Shapiro NI, Wolfe RE, Wright SB, *et al*. Who needs a blood culture? A prospectively derived and validated prediction rule. *J Emerg Med* 2008;35:255–64.
6 Verboom DM, van de Groep K, Boel CHE, *et al*. The diagnostic yield of routine admission blood cultures in critically ill patients. *Crit Care Med* 2021;49:60–9.
7 Niven DJ, Stelfox HT, Shahpori R, *et al*. Fever in adult Icus: an interrupted time series analysis. *Crit Care Med* 2013;41:1863–9.
8 Dargère S, Cormier H, Verdon R. Contaminants in blood cultures: importance, implications, interpretation and prevention. *Clin Microbiol Infect* 2018;24:964–9.
9 Alahmadi YM, Aldeyab MA, McElnay JC, *et al*. Clinical and economic impact of contaminated blood cultures within the hospital setting. *J Hosp Infect* 2011;77:233–6.
10 Alahmadi YM, McElnay JC, Kearney MP, *et al*. Tackling the problem of blood culture contamination in the intensive care unit using an educational intervention. *Epidemiol Infect* 2015;143:1964–71.
11 Garcia RA, Spitzer ED, Beaudry J, *et al*. Multidisciplinary team review of best practices for collection and handling of blood cultures to determine effective interventions for increasing the yield of true-positive bacteremias, reducing contamination, and eliminating false-positive central line-associated bloodstream infections. *Am J Infect Control* 2015;43:1222–37.
12 Eliakim-Raz N, Bates DW, Leibovici L. Predicting bacteraemia in validated models--a systematic review. *Clin Microbiol Infect* 2015;21:295–301.
13 Tokuda Y, Miyasato H, Stein GH. A simple prediction algorithm for bacteraemia in patients with acute febrile illness. *QJM* 2005;98:813–20.
14 Rupp ME, Cavalieri RJ, Marolf C, *et al*. Reduction in blood culture contamination through use of initial specimen diversion device. *Clin Infect Dis* 2017;65:201–5.
15 Paul M, Andreassen S, Nielsen AD, *et al*. Prediction of bacteremia using TREAT, a computerized decision-support system. *Clin Infect Dis* 2006;42:1274–82.
16 Bates DW, Goldman L, Lee TH. Contaminant blood cultures and resource utilization: the true consequences of false-positive results. *JAMA* 1991;265:365–9.
17 Chase M, Klasco RS, Joyce NR, *et al*. Predictors of bacteremia in emergency department patients with suspected infection. *Am J Emerg Med* 2012;30:1691–7.
18 Coburn B, Morris AM, Tomlinson G, *et al*. Does this adult patient with suspected bacteremia require blood cultures *JAMA* 2012;308:502–11.
19 Leth RA, Forman BE, Kristensen B. Predicting bloodstream infection via systemic inflammatory response syndrome or biochemistry. *J Emerg Med* 2013;44:550–7.
20 Venables WN, Ripley BD. Random and mixed effects. In: Venables WN, Ripley BD, eds. *Modern applied statistics with S*. New York, NY: Springer, 2002: 271–300.
21 Dunkler D, Sauerbrei W, Heinze G. Parameterwise and joint shrinkage factor estimation. *J Stat Soft* 2016;69:1–19.
22 Robin X, Turck N, Hainard A, *et al*. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* 2011;12:77.
23 Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361–87.
24 Lamy B, Dargère S, Arendrup MC, *et al*. How to optimize the use of blood cultures for the diagnosis of bloodstream infections? A state-of-the art. *Front Microbiol* 2016;7:697.
25 Cockerill FR 3rd, Wilson JW, Vetter EA, *et al*. Optimal testing parameters for blood cultures. *Clin Infect Dis* 2004;38:1724–30.
26 Lee A, Mirrett S, Reller LB, *et al*. Detection of bloodstream infections in adults: how many blood cultures are needed? *J Clin Microbiol* 2007;45:3546–8.
27 Li J, Plorde JJ, Carlson LG. Effects of volume and periodicity on blood cultures. *J Clin Microbiol* 1994;32:2829–31.
28 Patel R, Vetter EA, Harmsen WS, *et al*. Optimized pathogen detection with 30- compared to 20-milliliter blood culture draws. *J Clin Microbiol* 2011;49:4047–51.
29 Choi J, Ensafi S, Chartier LB, *et al*. A quality improvement initiative to decrease the rate of solitary blood cultures in the emergency department. *Acad Emerg Med* 2017;24:1080–7.
30 Khare R, Kothari T, Castagnaro J, *et al*. Active monitoring and feedback to improve blood culture fill volumes and positivity across a large integrated health system. *Clin Infect Dis* 2020;70:262–8.

Table S1: Sensitivity analyses of best- and worst-case scenario of the BAROC rule in the derivation and validation cohort

Characteristics in the derivation cohort	Worst-case scenario			Best-case scenario		
	Bloodstream infection	No bloodstream infection	Total	Bloodstream infection	No bloodstream infection	Total
BAROC positive	195	1679	1874	202	1527	1729
BAROC negative	12	205	217	5	357	362
Total	207	1884	2091	207	1884	2091
Sensitivity	0.94 (0.90 – 0.97)			0.98 (0.94 – 0.99)		
Specificity	0.11 (0.10 – 0.12)			0.19 (0.17 – 0.21)		
Positive predictive value	0.10 (0.09 – 0.12)			0.12 (0.10 – 0.13)		
Negative predictive value	0.94 (0.91 – 0.97)			0.99 (0.97 – 1.00)		
Positive likelihood ratio	1.06 (1.02 – 1.10)			1.20 (1.17 – 1.24)		
Negative likelihood ratio	0.53 (0.30 – 0.94)			0.13 (0.05 – 0.30)		

Characteristics in the validation cohort	Worst-case scenario			Best-case scenario		
	Bloodstream infection	No bloodstream infection	Total	Bloodstream infection	No bloodstream infection	Total
BAROC positive	66	570	636	69	524	593
BAROC negative	3	58	61	0	104	104
Total	69	628	697	69	628	697
Sensitivity	0.96 (0.88 – 0.99)			1.00 (0.95 – 1.00)		
Specificity	0.09 (0.07 – 0.12)			0.17 (0.14 – 0.20)		
Positive predictive value	0.10 (0.08 – 0.13)			0.12 (0.09 – 0.14)		
Negative predictive value	0.95 (0.86 – 0.99)			1.00 (0.97 – 1.00)		
Positive likelihood ratio	1.05 (1.00 – 1.11)			1.20 (1.16 – 1.24)		
Negative likelihood ratio	0.47 (0.15 – 1.46)			0.00 (0.00 – NaN)		

Table S2: Sensitivity analyses of best- and worst-case scenario of the BAROC when adding biological parameters in the derivation and validation cohort

Characteristics in the derivation cohort	Worst-case scenario			Best-case scenario		
	Bloodstream infection	No bloodstream infection	Total	Bloodstream infection	No bloodstream infection	Total
BAROC + laboratory test positive	182	1726	1908	204	1324	1528
BAROC + laboratory test negative	25	158	183	3	560	563
Total	207	1884	2091	207	1884	2091
Sensitivity	0.88 (0.83 – 0.92)			0.99 (0.96 – 1.00)		
Specificity	0.08 (0.07 – 0.10)			0.30 (0.28 – 0.32)		
Positive predictive value	0.10 (0.08 – 0.11)			0.13 (0.12 – 0.15)		
Negative predictive value	0.86 (0.80 – 0.91)			0.99 (0.98 – 1.00)		
Positive likelihood ratio	0.96 (0.91 – 1.01)			1.40 (1.36 – 1.45)		
Negative likelihood ratio	1.44 (0.97 – 2.14)			0.05 (0.02 – 0.15)		

Characteristics in the validation cohort	Worst-case scenario			Best-case scenario		
	Bloodstream infection	No bloodstream infection	Total	Bloodstream infection	No bloodstream infection	Total
BAROC + laboratory test positive	61	570	631	69	451	520
BAROC + laboratory test negative	8	58	66	0	177	177
Total	69	628	697	69	628	697
Sensitivity	0.88 (0.78 – 0.95)			1.00 (0.95, 1.00)		
Specificity	0.09 (0.07 – 0.12)			0.28 (0.25, 0.32)		
Positive predictive value	0.10 (0.07 – 0.12)			0.13 (0.10, 0.16)		
Negative predictive value	0.88 (0.78 – 0.95)			1.00 (0.98, 1.00)		
Positive likelihood ratio	0.97 (0.89 – 1.06)			1.39 (1.33, 1.46)		
Negative likelihood ratio	1.26 (0.63 – 2.52)			0.00 (0.00, NaN)		

Table S3: Performance of the BAROC rule when adding biological test

Characteristics in the derivation cohort	**Bloodstream infection**	**No bloodstream infection**	**Total**
BAROC + laboratory test positive	182	1324	1506
BAROC + laboratory test negative	3	158	161
Total	185	1482	1667
Sensitivity	0.98 (0.95 – 1.00)		
Specificity	0.11 (0.09 – 0.12)		
Positive predictive value	0.12 (0.10 – 0.14)		
Negative predictive value	0.98 (0.95 – 1.00)		
Positive likelihood ratio	1.10 (1.07 – 1.13)		
Negative likelihood ratio	0.15 (0.05 – 0.47)		
Characteristics in the validation cohort	**Bloodstream infection**	**No bloodstream infection**	**Total**
BAROC + laboratory test positive	61	451	512
BAROC + laboratory test negative	0	58	58
Total	61	509	570
Sensitivity	1.00 (0.94 – 1.00)		
Specificity	0.11 (0.09 – 0.14)		
Positive predictive value	0.12 (0.09 – 0.15)		
Negative predictive value	1.00 (0.94 – 1.00)		
Positive likelihood ratio	1.13 (1.09 – 1.16)		
Negative likelihood ratio	0.00 (0.00 – 0.00)		