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Original Article

Identifying risk factors for blood culture negative infective endocarditis: An international ID-IRI study

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ABSTRACT

Background: Blood culture-negative endocarditis (BCNE) is a diagnostic challenge, therefore our objective was to pinpoint high-risk cohorts for BCNE.
Methods: The study included adult patients with definite endocarditis. Data were collected via the Infectious Diseases International Research Initiative (ID-IRI). The study analysing one of the largest case series ever reported was conducted across 41 centers in 13 countries. We analysed the database to determine the predictors of BCNE using univariate and logistic regression analyses.
Results: Blood cultures were negative in 101 (11.65 %) of 867 patients. We disclosed that as patients age, the likelihood of a negative blood culture significantly decreases (OR 0.975, 95 % CI 0.963–0.987, $p < 0.001$). Additionally, factors such as rheumatic heart disease (OR 2.036, 95 % CI 0.970–4.276, $p = 0.049$), aortic stenosis (OR 3.066, 95 % CI 1.564–6.010, $p = 0.001$), mitral regurgitation (OR 1.693, 95 % CI 1.012–2.833, $p = 0.045$), and prosthetic valves (OR 2.539, 95 % CI 1.599–4.031, $p < 0.001$) are associated with higher likelihoods of negative blood cultures. Our model can predict whether a patient falls into the culture-negative or culture-positive groups with a threshold of 0.104 (AUC±SE = 0.707 ± 0.027). The final model demonstrates a sensitivity of 70.3 % and a specificity of 57.0 %.
Conclusion: Caution should be exercised when diagnosing endocarditis in patients with concurrent cardiac disorders, particularly in younger cases.

1. Introduction

Infective endocarditis (IE) poses a significant challenge to public health, claiming >66,000 lives globally in 2019 [1]. Despite advances in diagnosis and treatment, IE morbidity and mortality rates remain high [2,3]. The primary aim of the clinician managing endocarditis is to decrease complications and deaths by rapid diagnosis and administering appropriate treatment. Accordingly, early targeted therapy hinges on identifying the responsible microorganism through blood culture [4]. Nonetheless, blood culture negative endocarditis (BCNE) constitutes a notable portion of all cases (2.5–31 %) and presents diagnostic complexities, leading to higher long-term mortality rates compared to blood culture positive endocarditis (BCPE) [5,6].

Our understanding is constrained by the scarcity of randomized trials and meta-analyses on BCNE. To address this gap, we conducted an analysis to pinpoint risk groups for BCNE by contrasting the features of BCNE and BCPE utilizing the dataset from our previously published international study, recognized as one of the largest case series ever documented in literature [7].

2. Methods

2.1. Study design

The study was conducted between January 1, 2015, and October 1, 2018, involving 41 centers spanning 13 countries [7]. The primary data collection was facilitated by the Infectious Diseases International Research Initiative (ID-IRI). The data input was made through a web-based questionnaire. The questionnaire included demographic, clinical, laboratory, microbiologic, special tests, echocardiographic findings and outcome. We conducted a re-analysis of this database to determine the predictors of BCNE.

2.2. Case definition

The study comprised patients aged 18 and above, diagnosed with definite infective endocarditis according to the modified Duke criteria and the 2015 European Society of Cardiology (ESC) guideline [8]. The updated 2023 ESC guideline was very similar to the previous version and did not alter the diagnostic criteria for definitive endocarditis [9]. BCPE was defined as the presence of growth in blood culture and/or tissue culture obtained from the excised valve or vegetation, while BCNE was defined as the absence of growth in any of the blood cultures and/or tissue culture obtained from the excised valve or vegetation. Thus, comparisons were made between these two groups.

2.3. Statistical methods

The collected data were analysed with the software SPSS version 23 and the statistical package Stata/MP version 14.1 was used for the logistic regression analysis and the nomogram tables. Descriptive statistics were presented as frequency and percent or mean ± standard deviation

(SD) or median and range. Chi-square and Fisher's exact tests were used to compare categorical variables and Student's *t*-test and Mann-Whitney *U* test were used for comparisons of continuous variables. A logistic regression test was performed for multivariate analysis with the composite endpoint. In the univariate analysis, risk factors influencing the blood culture results at a significance level of $p < 0.05$ were incorporated into the multivariate binary logistic regression model. The "Backward Variable Elimination Method" was employed in this process, removing variables without statistical significance until only significant variables remained. A p value < 0.05 was considered significant.

3. Results

A total of 867 cases with a definite diagnosis of IE were included in the study. Among these, 292 (33.7 %) were female and the median age was 59.5 (16–96) years. A total of 711 cases had 2 major criteria and 136 cases had 1 major and ≥3 minor criteria.

Microbiological data: Blood cultures were negative in a total of 101 (11.65 %) patients. Among the remaining 766 patients (88.4 %) with identifiable microorganisms from blood cultures, the predominant pathogens were *Staphylococcus aureus* (n = 267, 33.6 %), *Streptococcus viridans* (n = 149, 18.7 %), enterococci (n = 128, 16.1 %), and coagulase-negative staphylococci (n = 92, 11.6 %) [7].

Univariate analyses: Demographic characteristics and concurrent cardiac disorders/conditions based on blood culture results were shown in Table 1, along with univariate comparisons. BCNE cases were younger than BCPE cases [median age 55 (18–86) versus 63 (16–96), $p < 0.001$].

Table 1
Demographic characteristics and coexistent cardiac disorders/conditions according to blood culture results.

		Culture Negative Endocarditis (n = 101, 11.65 %)	Total (N = 867)	*p* value
Age Median (Min – Max)		55 (18–86)	59,5 (16–96)	<0.001
Gender (n,%)	Female	27 (9.2 %)	292	0.116
	Male	74 (12.9 %)	575	
Ischemic Heart Disease (n,%)	Absent	92 (12.2 %)	756	0.213
	Present	9 (8.1 %)	111	
Congestive Heart Failure (n,%)	Absent	90 (11.7 %)	766	0.800
	Present	11 (10.9 %)	101	
Degenerative Cardiac Lesions (n,%)	Absent	94 (11.7 %)	802	0.818
	Present	7 (10.8 %)	65	
Cardiomyopathy (n,%)	Absent	96 (12 %)	800	0.266
	Present	5 (7.5 %)	67	
Rheumatic Heart Disease (n,%)	Absent	89 (10.9 %)	817	**0.005**
	Present	12 (24 %)	50	
Congenital Heart Disease (n,%)	Absent	94 (11.2 %)	838	**0.033**
	Present	7 (24.1 %)	29	
Cardiac Implants (Subtotal) (n,%)	Absent	59 (10.1 %)	584	**0.041**
	Present	42 (14.8 %)	283	
1. **Prosthetic valves** (n, %)	Absent	62 (9.8 %)	635	**0.004**
	Present	39 (16.8 %)	232	
2. **Pacemaker use** (n,%)	Absent	97 (12.4 %)	785	**0.045**
	Present	4 (4.9 %)	82	
Valvular Problems (Subtotal) (n,%)	Absent	61 (10.3 %)	592	0.070
	Present	40 (14.5 %)	275	
1. **Mitral regurgitation** (n,%)	Absent	75 (10.6 %)	708	**0.041**
	Present	26 (16.4 %)	159	
2. **Aortic regurgitation** (n,%)	Absent	88 (11.3 %)	782	0.270
	Present	13 (15.3 %)	85	
3. **Aortic stenosis** (n,%)	Absent	87 (10.8 %)	805	**0.005**
	Present	14 (22.6 %)	62	
4. **Tricuspid regurgitation** (n,%)	Absent	93 (11.5 %)	812	0.489
	Present	8 (14.5 %)	55	
5. **Mitral stenosis** (n,%)	Absent	92 (11.1 %)	829	**0.018**
	Present	9 (23.7 %)	38	
Antibiotic use prior to blood culture sampling (n = 377) (n, %)	Yes	53 (36.1 %)	147	**<0.001**
	No	31 (13.5 %)	230	

The percentage of BCNE was found to be statistically significantly higher in the presences of rheumatic heart disease, congenital heart disease, prosthetic valves, mitral regurgitation, aortic stenosis, mitral stenosis, and was lower in the absence of a pacemaker (Table 1).

Final model: The outcomes of our ultimate model indicate that the likelihood of a negative blood culture decreases significantly by 0.975 times (OR 0.975, 95 % CI 0.963–0.987, $p < 0.001$) with each year increase in age. Furthermore, it was noted to increase by 2.036 times (OR 2.036, 95 % CI 0.970–4.276, $p = 0.049$) in patients with rheumatic heart disease, 3.066 times (OR 3.066, 95 % CI 1.564–6.010, $p = 0.001$) in those with aortic stenosis, 1.693 times (OR 1.693, 95 % CI 1.012–2.833, $p = 0.045$) in individuals with mitral regurgitation, and 2.539 times (OR 2.539, 95 % CI 1.599–4.031, $p < 0.001$) in patients with prosthetic valves (Table 2).

The power of the model: The predictions of our model indicate the probabilities of patients belonging to culture-negative or culture-positive groups. When the cut-off value for these probabilities was calculated using the ROC analysis, the cut-off value corresponding to the best diagnostic success was found to be 0.104. The area under curve (AUC±SE) was calculated to be 0.707 ± 0.027 (Fig. 1). The classification of patients based on the cut-off value determined according to the model is shown in Table 3 ($p < 0.001$). With a cut-off value of 0.104, the sensitivity of the final model was 70.3 %, the specificity 57.0 %, the positive predictive value 93.6 % and the negative predictive value 17.8 %.

The nomogram, which facilitates the interpretation of the final model, is shown in Fig. 2. The value "Prob" at the bottom of the figure corresponds to the probability of a patient's blood culture result being negative. The higher this value is, the greater the probability of a negative blood culture.

4. Discussion

Identifying IE is easier in individuals with ongoing bacteremia [8, 10]. Yet, when BCNE emerges from uncommon or fastidious bacteria, or less virulent bacteria from normal flora, diagnosis becomes challenging. Due to their lower aggressiveness, detecting these bacteria through blood cultures is less likely [11,12]. In promptly formulating diagnostic approaches for BCNE cases, it is crucial to pinpoint specific patient cohorts warranting suspicion. Hence, in this study we demonstrated a significant reduction in the likelihood of a negative blood culture as age advances, while it rises in patients with underlying cardiac tissue damage like rheumatic heart disease or valvular problems such as aortic stenosis, mitral regurgitation, and implanted prosthetic valves.

Research conducted in developing nations identified rheumatic heart disease as the primary risk factor for IE, with nearly half of the patients

Table 2
Final model results.

	B	S.E.	OR	95 % C.I.for OR		
				Lower	Upper	p
Age	−0.025	0.006	0.975	0.963	0.987	<0.001
Rheumatic Heart Disease (Present *versus* Absent)	0.711	0.378	2.036	0.970	4.276	0.049
Aortic Stenosis (Present *versus* Absent)	1.120	0.343	3.066	1.564	6.010	0.001
Mitral Regurgitation (Present *versus* Absent)	0.527	0.263	1.693	1.012	2.833	0.045
Prosthetic Valves (Present *versus* Absent)	0.932	0.236	2.539	1.599	4.031	<0.001
Constant	−1.157	0.374	0.314			0.002

B: Regression coefficient, S.E.: Standard error, C.I.: Confidence interval, OR: Odds ratio.

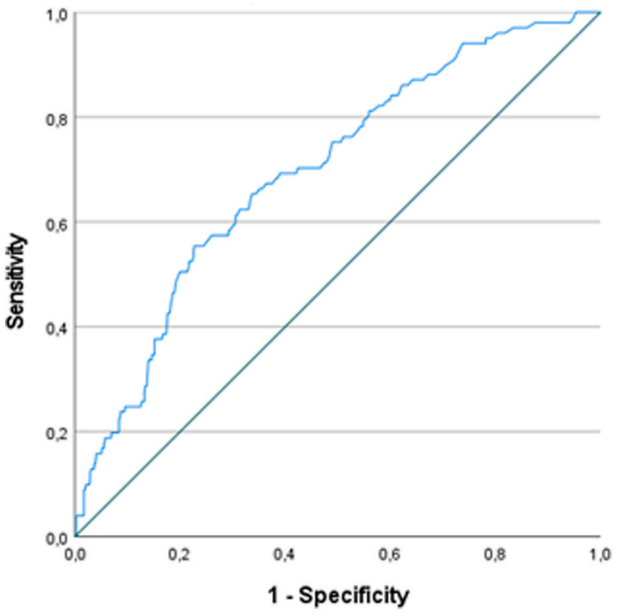

Fig. 1. Receiver operating characteristics (ROC) curve based on the probabilities of patients belonging to culture-negative or culture-positive groups. The final model cut-off value: 0.104, sensitivity 70.3 % and specificity 57.0 %.

experiencing BCNE [13,14]. However, detailed subgroup analysis of this data were lacking. Another paper analysing IE shows that BCNE is more common in the southern countries of this region, where rheumatic heart disease is prevalent, and points to the heterogeneity of the epidemiology [15]. Our study revealed a twofold increase in BCNE incidence among individuals with rheumatic heart disease. On the other hand, a younger demographic was more prevalent in BCNE cases compared to BCPE patients in our study, aligning with the existing literature [6,16,17]. This suggests that rheumatic heart disease may lead to the early onset of IE, particularly in BCNE format.

There are BCNE case reports in the literature related to patients with damaged heart tissues [18–21]. However, the data on this subject are limited and lack of a holistic perspective. In a review discussing BCNE risk factors, beyond well-known factors such as exposure to fastidious bacteria and pre-blood culture antibiotic usage, individuals with underlying valvular heart disease, right-sided endocarditis, the presence of intra-cardiac or vascular devices, and contact with foreign bodies in the bloodstream have also been recognized as risk factors [22]. Accordingly, in a 23-years descriptive analysis conducted at a tertiary center in Switzerland, the most common cardiac predisposing factor for BCNE was the implanted prosthetic valves (42 %) [23]. Similar findings were observed in other studies analysing BCNE characteristics, indicating that the most commonly noted cardiac predisposing factor was prosthetic valves [16,17]. Similarly, our study indicated a 2.5-fold increase in the probability of negative blood cultures when prosthetic valves were present.

The European Endocarditis (EURO-ENDO) international study represented one of the most extensive case series concerning BCNE (16.8 %), involving the evaluation of 3113 patients. Unlike our research, definite and possible cases of IE were collectively analysed in that study. Throughout the follow-up period, heart failure resulting from valve dysfunction was more commonly observed in BCNE patients compared to BCPE patients [6]. In addition, in a Spanish cohort study where 1001 patients with a definitive IE were evaluated, aortic problems in terms of valvular dysfunction were more commonly detected in BCNE patients (8.3 %) despite having fewer other comorbidities [24]. Thus, our study revealed a rise in the occurrence of BCNE in patients with heart valve dysfunction like aortic stenosis and mitral regurgitation, suggesting valvular damage as a potential surrogate marker for BCNE.

The strength of our study is that it included definite endocarditis cases and is one of the largest case series ever reported in the literature. Nevertheless, its primary limitation stems from its retrospective design. Moreover, the use of antibacterial medications at the time of taking blood cultures may have contributed to the negative culture results. This is because people with pre-existing cardiac problems might have been more likely to receive early antibiotic treatment, which could potentially confound the findings. In addition, updated studies with more recent data are required to reflect the current clinical and microbiological landscape. It is hypothesized that our model can be further validated by conducting new studies. While we agree that external validation is essential for a comprehensive evaluation of the model's performance, we believe that the high sensitivity of our model is a valuable asset in identifying patients with blood culture-negative endocarditis, which can be challenging to diagnose as one of the strengths of this study.

IE is a severe disease, and early diagnosis and treatment are crucial to improve the prognosis. However, our study illustrates that negative blood cultures are prevalent among patients with concurrent cardiac comorbidities, particularly within the non-elderly cohort, in cases with endocarditis. Therefore, caution is advised in the diagnosis and evidence-based treatment of IE in this subgroup of patients.

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Ethical approval

Yes, it is obtained from Fatih Sultan Mehmet Training and Research Hospital's Review Board.

Informed consent

Not applicable. The study has a retrospective design.

CRediT authorship contribution statement

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Table 3
The classification of patients based on the cut-off value determined according to the nomogram.

		Blood Culture Negative Endocarditis			Blood Culture Positive Endocarditis			Total (N, %)
		n	% within Model predictions	% within Blood Culture	n	% within Model predictions	% within Blood Culture	
Model Predictions	**Negative**	71	17.8 % (NPV)	70.3 % (Sensitivity)	329	–	43.0 % (FN)	400
	Positive	30	–	29.7 % (FP)	437	93.6 % (PPV)	57.0 % (Specificity)	467
Total (N, %)		101			766			867

NPV: Negative predictive value, PPV: Positive predictive value, FP: False positive, FN: False negative, —: The % in these cells were not written because they do not have any meaning.

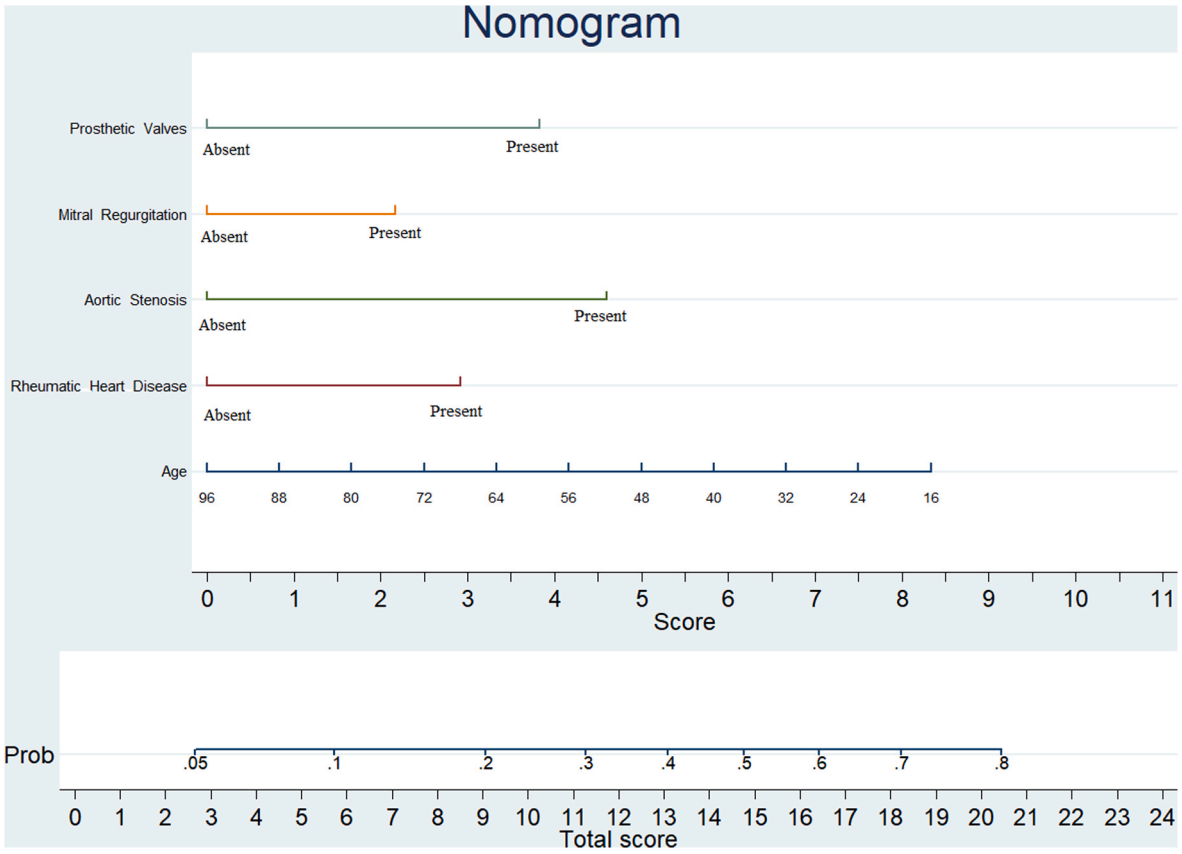

Figure-2. A nomogram of the final predictive model. The score is calculated separately for each line, based on the presence or absence of cardiac disorders and the patient's age. The 'Prob' value at the bottom of the figure corresponds to the calculated total score, and it indicates the probability that a patient's blood culture result will be negative. The higher the 'Prob' value, the greater the likelihood of a negative blood culture.

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Declaration of competing interest

None to declare.

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