The BETA-GBS score: A prediction tool for infective endocarditis in beta-haemolytic streptococcal bacteraemia

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Research Article

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Abstract

Background: Although beta-haemolytic streptococci (BHS) is a less common causative pathogen of infective endocarditis (IE) than *Staphylococcus aureus* or viridans group streptococci, IE is a serious condition, and it is important to predict IE in BHS bacteraemia (BHS-IE). The purpose of this study was to develop a predictive score for BHS-IE.

Methods: We conducted a retrospective study comparing the clinical features of BHS-IE and BHS-non-IE in adult patients with BHS bacteraemia at a 520-bed tertiary hospital in Tokyo, Japan, from 2004 to 2020. IE was diagnosed according to modified Duke's criteria, and both 'Definite' and 'Possible' were included. Univariate and multivariable analyses were conducted using logistic regression.

Results: Among 250 patients with BHS bacteraemia, 47 (19%) were diagnosed with BHS IE. The median (Interquartile rate) patient age was 71 (59, 84) years, and 121 (68%) were male. The proportions of group A streptococci, group B streptococci (GBS), group C/G streptococci were 14%, 38.4%, and 47.6%, respectively. Five predictors, either independently associated with BHS IE or clinically relevant, were used to develop the BETA-GBS prediction score: Blood pressure drop (systolic blood pressure < 90 mmHg or on vasopressor) (1 point); Elevated C-reactive protein (CRP ≥ 10 mg/dl) (2 points); Thrombocytopenia (Platelet count < 150 /μl) (1 point); Auscultation of heart murmur (1 point); GBS (1 point). In a receiver operating characteristic analysis, the area under the curve was 0.74 (95% confidence interval [CI]: 0.66 - 0.82). The cut-point was 2. A score < 2 had a sensitivity of 87% (95%CI: 0.743 - 0.952), a specificity of 37% (95%CI: 0.308 - 0.445), and a negative predictive value of 93%, respectively.

Conclusions: We developed the score to help clinicians rule out IE in BHS bacteraemia. Further research is warranted for validation.

Background

Beta-haemolytic streptococci (BHS) are gram-positive cocci mainly found in the skin, gastrointestinal, and genital tracts, and cause various infections ranging from soft tissue infections and pharyngitis to severe invasive infections such as infective endocarditis (IE). BHS are less common IE pathogens than *Staphylococcus aureus* (*S. aureus*), viridians group streptococci, and enterococci [1–4] BHS IE is associated with a high mortality rate [5, 6]. In addition, because of the low rate of persistent BHS bacteraemia [7], it is challenging to predict IE. Previous studies have reported the clinical characteristics and outcomes of BHS IE [1, 6]. However, to the best of our knowledge, only a few studies have provided score predictors.

Therefore, in this study, we aimed to identify factors associated with BHS IE based on the clinical characteristics of patients with BHS bacteraemia and create a prediction tool.

Methods

Study Design and Setting

This single-centre retrospective study was conducted at St. Luke's International Hospital, a 520-bed tertiary teaching hospital in Tokyo, from April 2004 to July 2020.

Inclusion and Exclusion Criteria

Hospitalized patients aged ≥ 18 years who presented with beta-haemolytic bacteraemia were included. Patients who declared non-participation, duplicates, outpatients, transfers, mixed infections, and group F streptococci were excluded.

Data Collection

Patient data were extracted from the inpatient electronic medical records. The variables included patient demographics, history of immunodeficiencies, use of immunosuppressive agents and chemotherapies, comorbidities, vital signs, results of laboratory tests conducted within 24 h after admission, microbiological test results, and complications including IE.

Variable Definitions

We used the following definitions: ‘follow-up blood cultures’ were collected 2–7 days after the reference date [7]; ‘persistent bacteraemia’ was defined as the growth of the same strain in follow-up blood cultures [7]; blood cultures collected within 48 h of the start date of appropriate antimicrobials were considered equivalent to the first [7]; ‘cleared bacteraemia’ was defined as a negative follow-up blood culture [7]; ‘recurrence’ was defined as the growth of the same organism after two weeks of effective antimicrobial therapy following negative blood culture; ‘nosocomial bacteraemia’ was defined as blood cultures obtained more than 48 h after admission [7]; IE was defined as definite or possible based on Duke's criteria [8]; Pitt bacteraemia score was used to predict mortality risk, with a score of ≥ 4 indicating severe disease and increased mortality risk [9]; ‘malignancy’ was defined as a disease registered between April 2004 and the date of discharge or having received chemotherapies in the previous 90 days; ‘immunocompromised state’ was defined as human immunodeficiency virus infection or the use of immunosuppressants; immunosuppressants included systemic corticosteroids, calcineurin inhibitors, antiproliferative drugs such as mycophenolate, mTOR inhibitors, interleukin-2 receptor antibodies, interleukin-6 receptor antibodies, and monoclonal antibodies; ‘implanted prostheses’ include artificial objects in the body; extravascular devices were defined as prosthetic joints, whereas intravascular devices were defined as prosthetic valves and prosthetic vascular grafts; and ‘hypotension’ was defined as systolic blood pressure of less than 90 mmHg, including the use of vasopressors.

Statistical Analyses

Bivariate associations were assessed using the chi-square test or Fisher's exact test for categorical variables, and the Mann-Whitney U test for continuous variables. The association between individual predictors and the risk of BHS IE was assessed using a multivariate logistic regression model including variables that were significantly associated with BHS IE in univariate analyses. The final variables in the

model were selected by using a stepwise forward approach. Multivariate logistic regression analysis was performed to calculate a specific cut-off point for BHS IE as the dependent variable, and a receiver operating characteristic (ROC) curve was plotted using this model. To evaluate the performance of the proposed model, we estimated the area under the curve (AUC) and 95% confidence interval (CI) on the ROC plot. A conservative cut-off for the predictive score was based on the maximization of sensitivity, as recommended for disease rejection. All analyses were performed using the EZR statistical software [10].

Patient Consent Statement

This study was approved by the Institutional Review Board of St. Luke's International Hospital in Tokyo, Japan (number: 20-R111). The requirement for patient consent was waived based on our retrospective analysis of routinely collected data.

Results

Study Participants

A total of 328 patients aged ≥ 18 years with BHS bacteraemia were hospitalized at St. Luke's International Hospital from 2004 to 2020. A total of 78 patients who met the exclusion criteria were excluded, and 250 patients who met the study criteria were included. A total of 47 patients were diagnosed with IE (7 patients with definite IE and 40 patients with suspected IE). Patient characteristics are shown in Table 1. In the IE group, five patients (10.6%) had group A streptococci (GAS), 24 patients (51.1%) had group B streptococci (GBS), and 18 patients (38.3%) had group C/G streptococci (GCGS) infections. In the non-IE group, GAS was detected in 30 patients (14.8%), GBS in 72 (35.5%), and GCGS in 101 (49.8%). The median ages were 71 and 75 years in the IE and non-IE groups, respectively. Male patients constituted 53.2% and 47.3% of the total patients in the IE and the non-IE groups, respectively. Hypertension (48.9% and 53.2%, respectively) was the most common comorbidity, followed by diabetes mellitus (44.7% and 34.5%, respectively) and heart failure (23.4% and 23.4%, respectively). Follow-up blood cultures were collected in 74.5% and 52.7% of the cases in the IE and the non-IE groups, respectively; however, only one patient in the non-IE group had persistent bacteraemia. Single regression analysis showed that a history of surgery within one year, hypotension (including demand for vasopressors), increased respiratory rate, elevated white blood cell count, low platelet count, elevated total bilirubin, elevated transaminases, and elevated C-reactive protein (CRP) were significantly more common in the IE group.

Table 1
Patient characteristics of IE and non-IE groups

	IE (N = 47)	Non-IE (n = 203)	p-value
Group of Streptococcus (%)			
GAS	5 (10.6)	30 (14.8)	0.152
GBS	24 (51.1)	72 (35.5)	
GCGS	18 (38.3)	101 (49.8)	
Age, median [IQR]	71 [59, 84]	75 [59, 85]	0.348
Sex (male), n (%)	25 (53.2)	96 (47.3)	0.519
Body mass index, median [IQR]	22.9 [21.09, 26.34]	22.7 [19.68, 25.83]	0.283
Hypertension, n (%)	23 (48.9)	108 (53.2)	0.629
Diabetes mellites, n (%)	21 (44.7)	70 (34.5)	0.239
Heart failure, n (%)	11 (23.4)	38 (18.7)	0.541
Cerebrovascular disease, n (%)	4 (8.5)	18 (8.9)	1
Cirrhosis, n (%)	4 (8.5)	17 (8.4)	1
Chronic kidney disease, n (%)	5 (10.6)	22 (10.8)	1
Haemodialysis, n (%)	4 (8.5)	9 (4.4)	0.274
Community acquired, n (%)	46 (97.9)	190 (93.6)	0.479
Operation within 1 year, n (%)	12 (25.5)	25 (12.3)	0.037
Implanted prostheses, n (%)	11 (23.4)	33 (17.0)	0.3
Extravascular devices, n (%)	7 (14.9)	16 (8.2)	0.17
Intravascular devices, n (%)	4 (8.5)	19 (9.6)	1
Pitt bacteraemia score, median [IQR]	1 [1, 3]	1 [1, 2]	0.386
qSOFA score ≥ 2, n (%)	28 (59.6)	99 (48.8)	0.198
Hypotension (Vital sign), n (%)	20 (42.6)	55 (27.1)	0.051
Body temperature (ºC), median [IQR]	38.7 [37.7, 39.2]	38.8 [37.9, 39.5]	0.145
Respiratory rate (/minute), median [IQR]	25 [21, 28]	22 [18, 28]	0.015

Abbreviations: IE, infective endocarditis; GAS, group A Streptococci; GBS, group B Streptococci; GCGS, group C and group G Streptococci; IQR, interquartile range; qSOFA, quick sequential organ failure assessment; WBC, white blood cell count

	IE (N = 47)	Non-IE (n = 203)	p-value
Pulse rate (/minute), median [IQR]	88 [79, 104]	94 [82, 108]	0.454
Auscultation of heart murmur, n (%)	16/40 (40.0)	40/155 (25.8)	0.082
WBC (x10^3/μL), median [IQR]	9.1 [8.0, 16.3]	8.6 [7.0, 9.7]	0.035
Haemoglobin (g/dL), median [IQR]	12.4 [9.7, 13.5]	11.8 [9.7, 13.6]	0.743
Platelet count (x10^3/μL), median [IQR]	114 [82, 199]	186 [105, 248]	0.001
Total bilirubin (mg/dL), median [IQR]	1.2 [0.8, 1.9]	0.8 [0.5, 1.2]	0.001
Creatinine (mg/dL), median [IQR]	1.10 [0.80, 1.71]	0.95 [0.72, 1.46]	0.133
C-reactive protein (mg/dL), median [IQR]	19.7 [9.3, 28.9]	9.2 [6.7, 21.8]	0.001
Follow up blood culture, n (%)	35/47 (74.5)	107/203 (52.7)	0.009
Persistent bacteraemia, n (%)	0/35 (0)	1/107 (0.9)	1
Recurrence bacteraemia, n (%)	1/47 (2.1)	2/203 (1.0)	0.466

Abbreviations: IE, infective endocarditis; GAS, group A Streptococci; GBS, group B Streptococci; GCGS, group C and group G Streptococci; IQR, interquartile range; qSOFA, quick sequential organ failure assessment; WBC, white blood cell count

Logistic regression analysis using the stepwise method showed that heart murmur and CRP level were independent risk factors for IE. GBS infection, low platelet count, and hypotension were added to the model, which were clinically meaningful. Using these models, the risk of IE in BHS bacteraemia was scored using beta coefficients in the range of 0–6.

We developed the BETA-GBS using the variables selected in the multivariate model. These included blood pressure drop (1 point), elevated CRP (CRP ≧ 10 mg/dl) (2 points), thrombocytopenia (platelet count < 150 /μl) (1 point), auscultation of heart murmur (1 point), and GBS infection (1 point). The results of the multivariate model used to determine the scores are shown in Table 2. Figure 1 shows the ROC curve of the tool for predicting IE and non-IE in patients with BHS bacteraemia. The AUC was 0.737 (95% CI 0.657–0.817), and the cut-off was less than two points, which reduced the possibility of IE. Sensitivity, specificity, positive predictive value, and negative predictive value were 87.2%, 37.4%, 24.4%, and 92.7%, respectively.

Table 2
Results of the multivariate logistic regression analysis used to determine the BETA-GBS predictive score

	Adjusted OR	Beta-coefficient	p value	Points
Blood pressure drop	2.0	0.68	0.099	1
Elevated CRP	4.2	1.43	< 0.001	2
Thrombocytopenia	2.2	0.79	0.044	1
Auscultation of heart murmur	2.2	0.76	0.066	1
GBS	2.1	0.72	0.067	1
Abbreviations: OR, odds ratio; CRP, C-reactive protein; GBS, group B streptococci.				

The BETA-GBS predictive score was based on the five items shown in the left column. One to two points were assigned to each item (shown in the right column), based on the rounding of the beta coefficient value, for a maximum possible score of 6.

Discussion

Our scoring system is the first tool to predict IE in patients with BHS bacteraemia. Heart murmur and elevated C-reactive protein levels are independent predictors of IE, and by adding GBS infection, low platelet count, and low blood pressure to the prediction model, the likelihood of IE occurrence can be estimated.

Several studies have scored the risk of IE in gram-positive cocci bacteraemia, such as the PREDICT study [2] and VIRSTA study [11] for *S. aureus* bacteraemia, HANDOC score for non-BHS bacteraemia [3], and DENOVA scores for *Enterococcus faecalis* [4]. However, to the best of our knowledge, there is no scoring system for BHS IE. The mortality rate of BHS IE is high, ranging from 18.4–29.3% [1, 12, 13], and is comparable to that of IE caused by *S. aureus* [13, 14]. Therefore, early therapeutic intervention after hospitalization is necessary.

This scoring tool used vital signs, physical examination results, and blood test results to determine the risk of IE at a relatively early clinical stage. As hypotension was reported to be associated with a higher rate of septic shock in an article comparing BHS IE with other streptococci and enterococci [13], it was appropriate to include it in this score. Platelet count, which is also included in the SOFA score [15], is considered a valid indicator of IE. As shown by the NOVA [16] and DENOVA scores [4], which evaluate the necessity of transoesophageal echocardiography (TEE) in enterococcal bacteraemia, a heart murmur is an essential physical finding in IE. CRP is an inflammatory protein often used for scoring, such as in the LRINEC score [17]. Although CRP levels have no correlation with the likelihood of IE occurrence as per previous studies [18], our study found that they could be a potential marker of IE, especially in BHS bacteraemia. In addition, CRP can be used to determine the response to treatment and prognosis by

measuring its levels over time; therefore, CRP can be measured at the beginning of treatment [19–21]. The ability of bacteria to bind fibrinogen is thought to be a factor that causes IE [22]. Seo [22] have shown the ability of GBS to bind to fibrinogen via the glycoprotein Srrl, which explains that GBS is more likely to cause IE among BHS [1].

In our study, 74.5% of the follow-up blood cultures were collected from the IE group, but none showed persistent bacteraemia. This result was the same as that reported in previous studies [7]. Some physicians may recommend TEE since IE cannot be completely ruled out even if the BETA-GBS score is less than two in BHS bacteraemia; however, the low rate of persistent bacteraemia makes it challenging to determine the indication for invasive testing such as TEE in BHS bacteraemia. Therefore, our scoring is based on minimally invasive testing, utilizing physical examination and laboratory findings, and we believe that the combination of these findings reduces the probability of IE to a very low level. Some papers [7, 23] have indicated that unnecessary follow-up blood cultures increase the cost of medical care, and there is a need for more appropriate testing. The scoring system that was developed in this study was highly sensitive and can help rule out IE in BHS bacteraemia, and has potential reduce the unnecessary burden on patients and medical staff.

Our study had some limitations. First, this was a relatively small, single-centre, observational study. External validation for the implementation of this score by comparison with patients with BHS in other countries or facilities and prospective validation of the results of this study are warranted. Second, the prevalence of IE may be overestimated because the definition of IE included ‘Possible IE’ in Duke’s criteria. However, since our purpose was to create a scoring system that can exclude IE, it may be helpful as a screening tool with high sensitivity. Third, in this retrospective study, it is possible that some information regarding the physical examination and medical history was missing. In addition, echocardiography was not performed in all patients in the BHS-non-IE group; therefore, IE evaluation may not have been sufficient. Finally, because follow-up blood cultures were not collected from all patients, persistent bacteraemia in BHS IE may have been underestimated. However, because persistent bacteraemia tended not to occur in a previous study [7], follow-up blood cultures may not be necessary.

In summary, our BETA-GBS score is a tool for clinicians and may enable them to assess reduced likelihood of IE with a score of less than two in BHS bacteraemia.

Conclusion

Our BETA-GBS score is a simple tool for predicting the likelihood of IE in BHS bacteraemia. This score can help make decisions early in treatment by using only vital signs and laboratory and culture results. This tool may reduce the burden on patients by avoiding unnecessary tests.

Abbreviations

BHS, beta-haemolytic streptococci

IE, infective endocarditis

BHS-IE, IE in BHS bacteraemia

CRP, C-reactive protein

ROC, receiver operating characteristic

AUC, area under the curve

CI, confidence interval

GAS, group A streptococci

GBS, group B streptococci

GCGS, group C/G streptococci

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of St. Luke's International Hospital in Tokyo, Japan (number: 20-R111). All methods were carried out in accordance with relevant guidelines and regulations. Informed consent is waived by St Luke's International Hospital Clinical Ethics Committee.

Consent for publication

Not applicable

Competing interests

No conflict of interest

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None

Author contributions

The manuscript has been reviewed and approved by all authors and is not under consideration for publication elsewhere. All authors contributed to the work of this report. RH collected clinical data and wrote the initial draft of the manuscript. TM and NM assisted in study conception and design. RH and OT analysed the data. TM and NM assisted with the interpretation of the results and writing of the manuscript.

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None

Data availability

The datasets generated and/or analysed during the current study are not publicly available due to the possibility of personal identification but are available from the corresponding author on reasonable request.

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Figures

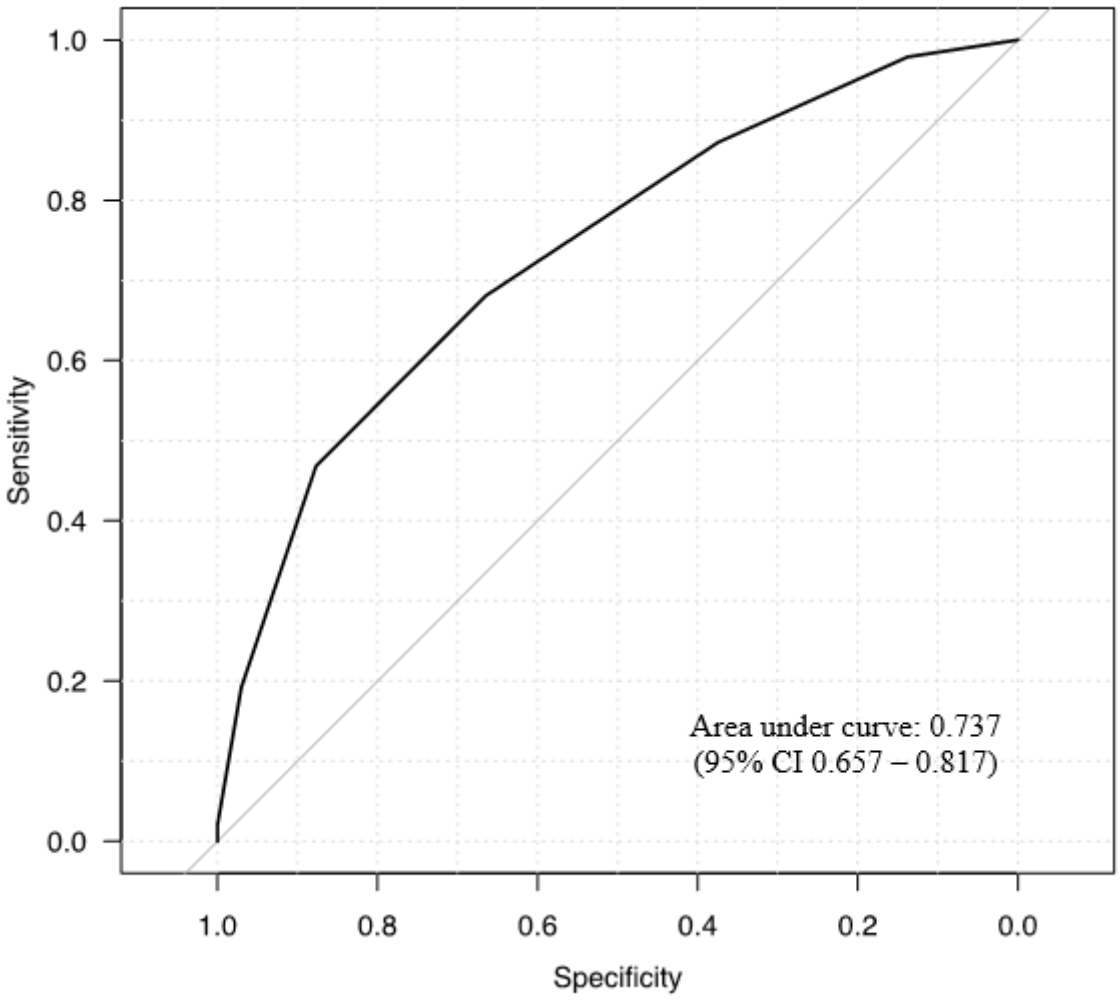

Figure 1

The receiver operating characteristic curve of the BHS-IE predictive score