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An external validation study of a clinical prediction rule for medical patients with suspected bacteraemia

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ABSTRACT

Objective The objective of this study was to externally validate a clinical prediction rule (CPR)—the 'Shapiro criteria'—to predict bacteraemia in an acute medical unit (AMU).

Methods Prospectively collected data, retrospectively evaluated over 11 months in an AMU in the UK. From 4810 admissions, 635 patients (13%) had blood cultures (BCs) performed. The 100 cases of true bacteraemia were compared with a randomly selected sample of 100 control cases where BCs were sterile.

Results To predict bacteraemia (at a cut-off score of two points), the Shapiro criteria had a sensitivity of 97% (95% CIs 91% to 99%), specificity 37% (28% to 47%), positive likelihood ratio 1.54 (1.3 to 1.8) and a negative likelihood ratio of 0.08 (0.03 to 0.25). The area under the receiver operating curve was 0.80 (0.74 to 0.86), and the Hosmer–Lemeshow p value was 0.45.

Conclusions A score ≥2 on the Shapiro criteria had high sensitivity in a study of acute general medical admissions. Application of the rule in patients being considered for a BC could identify those at low risk of bacteraemia. Though the model demonstrated good discrimination, the lengthy number of variables (13) and difficulty automating the CPR may limit its use.

Key messages

What is already known on this subject?

- Bacteraemia is clinically relevant, but often difficult to predict, while indiscriminate drawing of blood cultures (BC) can negatively impact on the management of patients.
- A Clinical prediction rule (the Shapiro criteria) has been proposed to help guide when to perform a BC, in particular by identifying those patients with a suspected infection, but who are at very low risk of bacteraemia.
- Our study looked to externally validate the Shapiro criteria in a UK general medical cohort of patients.

What might this study add?

- The Shapiro criteria has good discrimination to predict bacteraemia when applied to a general medical cohort in the UK.
- Its low specificity and use of a large number of (sometimes subjective) variables may limit its clinical application and more parsimonious models should be investigated.

INTRODUCTION

Early detection of bacteraemia is of indisputable clinical importance, indicating disseminated infection, which is associated with a worse prognosis than that for patients with local infection.[1] The systemic inflammatory response syndrome (SIRS) criteria[2] are of limited use in differentiating a patient with and without infection.[3–5] A fever commonly prompts a blood culture (BC), yet ,13%–24% of patients with significant bacteraemia are normothermic,[5–7] and in one study, over half the patients admitted to an intensive care unit (ICU) with sepsis were normothermic.[8] BC results take at least 24 h to be known, and false-positive or false-negative results are common. This has implications for antimicrobial stewardship, and patients may undergo unnecessary treatment and investigations.[9–13] Positive yields are remarkably low (4%–8%), reflecting the lack of well-defined indications to take a BC.[3 14–16]

Prompt initiation of appropriate antimicrobial therapy improves outcomes in patients with severe sepsis, yet is commonly absent, suggesting diagnosis in some patients is challenging.[17–20] Senior clinicians may be more accurate at predicting risk of death compared with available clinical scoring systems.[21] However, it is junior clinicians who often make the decision to draw a BC and initiate antibiotics, and there is evidence that this group both overestimate and underestimate the probability of bacteraemia.[22 23] Challenges in diagnosis, investigation and management of patients with significant infections have led to the development of a number of clinical prediction rules (CPRs) to help predict bacteraemia.[24] Few have been externally validated, and where this has occurred, performance has been inferior.[25] None have undergone an impact analysis—unfortunately true of most CPRs in the medical literature.[26] One CPR with major and minor criteria[27]—the 'Shapiro criteria' (see table 1)—has been shown to be a sensitive but not specific predictor, and was recently validated in an emergency department (ED) setting.[28] The objective of this study was to provide further external validation of the Shapiro criteria in an acute medical unit (AMU) population. The TRIPOD checklist[29] for the study can be seen in online supplementary appendix 1.

METHODS

Design

Single-centre nested case–control study with prospectively collected data, retrospectively analysed.

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Table 1 Shapiro *et al*'s clinical prediction rule—a blood culture is indicated if at least one major criterion or two minor criteria are present, that is, ≥2 pts

Major criteria*	Minor criteria (1 point each)
Suspected endocarditis (3)	Temperature 38.3°C–39.4°C
Temperature >39.4°C (3)	Age >65
Indwelling vascular catheter (2)	Chills
	Vomiting
	Hypotension—SBP <90 mm Hg
	White blood cell >18×10^9/L
	Platelets <150×10^9/L
	Neutrophil ratio >80%
	Creatinine >2.0 mg/dL (>177 µmol/L)

Bands >5% (immature white blood cells) were not included as part of the present analysis as bandaemia is not routinely reported at the study site.
*() indicates the points score.
SBP, systolic BP.

The study proposal was internally peer reviewed, and a favourable ethical opinion was given from the NHS NRES Committee London South-East (REC reference 13/LO/0884). The Research and Governance Department of the Trust approved and provided research governance for the study. The consent of participants was deemed unnecessary due to the study design; anonymised data analysis without clinical intervention.

Setting

The AMU on one site of an 870-bed hospital in the UK. Across the two sites, the combined annual ED attendance is >75 000, with 35–40 acute medical admissions per 24 h period. There is a separate admissions unit for frail elderly patients. Patients are admitted through the ED or directly from the local primary care physicians or outpatients.

Subjects

Consecutive patients over an 11-month period (March 2012–end January 2013), age ≥18 years who stayed at least one night in hospital on the AMU were included in the provisional data collection and followed up until discharge from hospital. No patient was included on more than one occasion. Exclusion criteria included patients <18 years, staying less than one night in hospital or admitted to non-medical wards. All patients had physiological observations measured and entered as part of standard clinical practice via handheld systems into the hospitals clinical data software system (Patientrack) by nursing staff with no input from the research team. Baseline characteristics, demographic data and blood results were obtained at the time of enrolment. During the 11-month study period from 4810 patient episodes, 635 BCs were drawn (13%) within 24 h of admission. One hundred and four (17%) were judged to represent true bacteraemia, having excluded 50 (7.9%) cultures deemed to be contaminants (37 of which were coagulase-negative *Staphylococcus* species) using published criteria,[30 31] and the opinion of the clinical team and consultant microbiologist (independent of the study team). Four patients were excluded as the relevant patient data were unavailable, leaving 100 patients with bacteraemia in the analysis to be compared with 100 patients, randomly selected (using Excel) from the sterile-BC cohort (of 531 patients). The research team had no influence on the care delivered to the patients who received routine standard medical care.

Outcome measures

Patients with cultures were identified from the microbiology department database. A positive BC result (reported by a consultant microbiologist according to the result at 5 days) was defined as growth of bacteria with recognised pathogenic capacity in ≥1 BC or a growth of a common skin pathogen in ≥2 BCs in the presence of SIRS and/or clinical evidence or microbiological findings suggesting a primary focus of infection—a decision made jointly by the microbiology consultant and clinical team looking after the patient with no influence from the research team.[30 31]

Data included the relevant variables and independent predictors of bacteraemia as noted by Shapiro *et al*[27] apart from the 'bands >5%' variable, as this is not a routine test performed at the Trust (see table 1). Band cells are immature white blood cells (WBCs) and if their number is proportionately increased, can suggest infection. In the original SIRS definition, Bone and colleagues[2] proposed that elevated levels of band cells be defined as >10% of WBCs.

Blood tests for the relevant variables were taken from the result closest to admission and additional results included C reactive protein (CRP) and lymphocyte count. Suspicion of endocarditis, presence of an indwelling vascular catheter and the presence of chills or vomiting were obtained from review of the ED and AMU admission notes independently by two of the researchers. If there was disagreement, the decision of the senior researcher was the one taken. As the research team reviewed the medical notes to ascertain risk factors, it was not always possible to blind the result of the BC; however, the team aimed to limit their notes review to the admission clerking to minimise the introduction of bias. Blood result variables for the CPR were collected automatically in a blinded fashion; however, again by reviewing the medical notes, blinding of the results to the researchers was not always possible.

Statistics

Predictive performance was assessed by discrimination (using receiver operating characteristic (ROC) curve analysis) and calibration (using the Hosmer–Lemeshow (HL) test). An area under the ROC curve (AUC) of 0.5 indicates no discrimination, whereas an AUC of 1.0 indicates perfect discrimination.[29] A significant HL test statistic (p value <0.05) implies that the model does not calibrate perfectly, and is, therefore, suspect, though this does have limitations.[32]

There is no consensus on how to determine what counts as an adequate sample size in such studies;[29] however, a minimum of 100 events is generally accepted as adequate sample size when validating a CPR.[33] Due to resource constraints, it was not possible to review the notes of all negative BCs, and hence, a random sample of 100 was taken—a nested case–control design, which has been shown to have advantages in prediction research.[34] Four of the bacteraemic patients notes were unavailable for analysis, and were excluded. The remaining 100 patients in each group underwent a complete case analysis. The only potential missing data were in the history elicited on the medical clerking—for example, some patients may not have volunteered or been asked specifically about vomiting.

Following collection, the data were anonymised on Excel, and analysis performed on SPSS V.22 (Chicago, Illinois, USA).

RESULTS

From a total of 635 BCs, 104 (17%) were judged to represent true bacteraemia, compared with 8.3% in the original derivation study.[27] Table 2 summarises the patient characteristics (n=100 bacteraemic, n=100 sterile BC) included in the full analysis.

Figure 1 depicts the frequency of organisms cultured, with *Escherichia coli*, *Staphylococcus* and *Streptococcus* species

Table 2 Patient characteristics

	Bacteraemia (n=100)	Blood culture sterile (n=100)	p Value	Original Shapiro derivation cohort
Demographics				
Age (mean (SD))	68.4 (15.4)	62.8 (17.2)	0.01*	59.9 (20.2)
Male sex (%)	58	58	0.58	45
Characteristics				
In-hospital mortality (%)	11	6.0	0.15	
Length of stay (mean (SD)) (days)	13.4 (16.7)	9.9 (13.8)	0.66	
ICU admissions (%)	7	4	0.27	
Shapiro criteria				
Suspected endocarditis (%)	6	0	0.01*	2
Indwelling vascular catheter (%)	4	3	0.5	
Temperature >39.4°C (%)	17	5	<0.01*	
Temperature 38.3°C–39.4°C (%)	31	24	0.17	
Hypotension (SBP <90 mm Hg) (%)	13	3	<0.01*	
Age >65 (%)	64	49	0.023*	
Chills (%)	40	9	<0.01*	
Vomiting (%)	37	25	0.05*	
White blood cell count >18×10^9/L (%)	27	14	0.02*	
Platelets <150×10^9/L (%)	20	15	0.23	
Creatinine >2.0 mg/dL (>177 μmol/L) (%)	14	6	0.05*	
Shapiro score				
0	1	15		
1	2	22		
2	15	24		
3	26	25		
4	19	6		
≥5	37	8		
Other results				
Lactate (mean (SD))	2.58 (2.7)	2.0 (1.6)	0.27	
SIRS ≥2 (%)	51	37	0.03*	
Comorbidities				
On steroids (%)	17	10	0.10	
Immunosuppressed	31	17	0.02*	
Cancer	28	22	0.21	19
Diabetes	24	12	0.02*	22
CKD	28	21	0.16	
Recent chemotherapy	11	9	0.41	

Student's t test or χ^2 test.
*p Value <0.05.
CKD, chronic kidney disease; ICU, intensive care unit; SBP, systolic BP; SIRS, systemic inflammatory response syndrome.

accounting for over half the cultures. Males accounted for 58% of both groups (compared with 45% of patients in the Shapiro derivation cohort[27]) with a mean age of 68 (SD 15) in the bacteraemic and 63 (17) in the sterile-BC group, respectively (p=0.01). Mean age in the Shapiro study was 60 (20). Length of stay averaged 13 (17) days in the bacteraemic cohort, and 10 (14) days in the sterile-BC group (p=0.66). In-hospital mortality rate was 11% in the bacteraemic group and 6% in the sterile-BC group (p=0.15). SIRS criteria (≥2) was met in 51% of the bacteraemic group and 37% of the sterile-BC group (p=0.03).

To predict bacteraemia, the Shapiro criteria,[27] at a cut-off of two points, had 97% (95% CIs 91% to 99%) sensitivity, 37% specificity (28% to 47%), positive predictive value 61% (53% to 68%), negative predictive value (NPV) 93% (80% to 98%), positive likelihood ratio 1.54 (1.3 to 1.8) and a negative likelihood ratio of 0.08 (0.03 to 0.25). AUC was 0.80 (0.74 to 0.86) (see figure 2)—similar to that found in Shapiro's derivation (0.80) and validation (0.75) groups and the recently published external validation study (0.83).[28] The Hosmer–Lemeshow p value was 0.45.

DISCUSSION

This study provides further external validation of the CPR proposed by Shapiro *et al*[27] uniquely in an acute medical UK cohort, with similar results to the original study and other external validation study.[28] The initial CPR was proposed to reduce routine (potentially inappropriate) ordering of BCs and also highlighted a group at high risk of bacteraemia. Using plausible clinical history, observations and blood tests, the CPR estimates the probability of bacteraemia at the point at which a clinician has decided to draw a BC, identifying a group at low risk of bacteraemia (score <2 points).

Limitations

The limited sample size in a single unit should be considered when drawing comparisons with the Shapiro study (3901 subjects).[27] Patients were on average older than the original study,

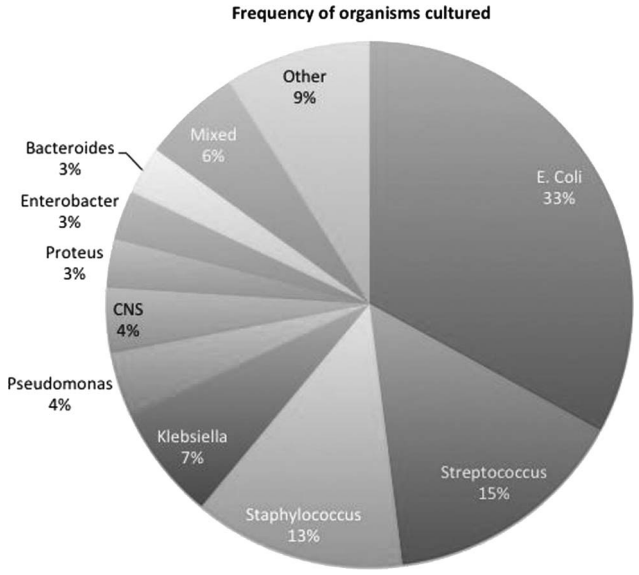

Figure 1 Organisms cultured in the cohort (n=100). CNS, coagulase-negative *Staphylococcus* species; *E. coli, Escherichia coli*.

but representative of a typical general medical hospital setting in the UK. The external validation study in an ED in Denmark had a similar age demographic (mean age 71 in the bacteraemia and 63 in the non-bacteraemia groups) and produced statistically similar results (see table 3).

Though the data were prospectively gathered by clinical teams as part of routine practice, the retrospective nature of the analysis is a limitation, whereby bias could be introduced, for example, by omission of relevant history within the medical clerking. Local guidelines for taking BCs are available; however, clinical staff may not have adhered to them. Due to resource limitations (for the retrospective notes review), only a sample (100) of the (531) sterile BC episodes were compared with the bacteraemia episodes, and four of the bacteraemia patients were excluded from analysis due to unavailable notes. However, the sample of sterile BCs was comparable with the full dataset of sterile BCs in the parameters available, with no statistically significant differences between the sampled group and those not sampled (see online supplementary appendix 2 and table S4). Second, although case–control studies have been shown to be associated with a risk of bias,[35] by randomly selecting from a known number of negative BC cases, the design is a nested case–control. In a nested case–control, cases emerge from a well-defined source population, and the controls are sampled from that same population. Biesheuvel and colleagues have previously discussed some of the potential advantages of such a design in prediction research.[34] The nested case–control was an efficient use of limited resources, but we acknowledge that it does introduce the potential risk of bias. Jessen and colleagues also used a similar study design in their validation study.[28]

Bandaemia was not included in the study as this is not routinely reported in our Trust. One study previously reported the presence of bandaemia in 80% of bacteraemia cases; however, the already high sensitivity would be unlikely to be altered, and potentially, specificity may have reduced further by the inclusion of this variable.[36]

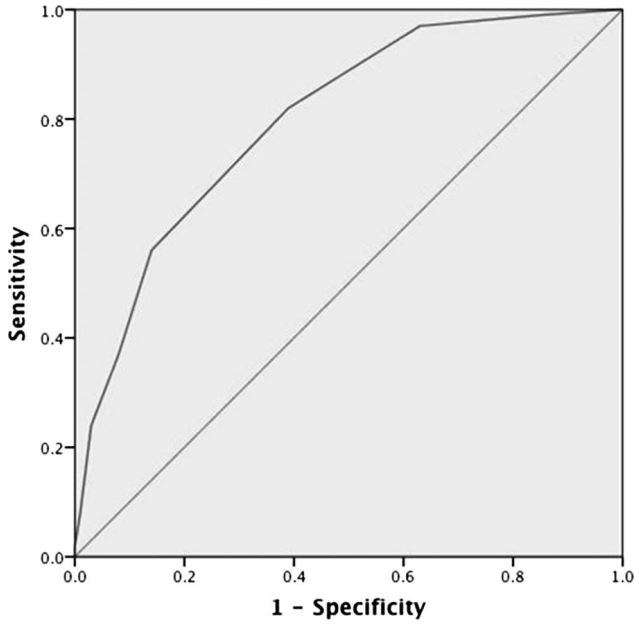

Figure 2 Area under the receiver operator curve for the Shapiro criteria to predict bacteraemia—0.80 (95% CI 0.74 to 0.86).

Implications for future research and practice

A systematic review evaluating decision support systems found independent predictors of improved clinical practice, including automatic provision as part of clinician workflow, support at the time and location of decision making and computer-based decision support.[37] This highlights one potential drawback of the current CPR: the relatively subjective criteria (suspicion of endocarditis and chills) limits the ability to automate into an electronic patient record. Second, the use of 13 predictors may limit widespread uptake as a decision aid.[38 39] Bandaemia is not routinely reported in most hospitals, making its inclusion questionable. Using white cell count (WCC), bandaemia and neutrophil ratio >80% could be considered problematic as they are not independent.[40] In the presented study, 17% of BCs were judged to be cases of true bacteraemia, compared with only 8% in the original derivation study and 6.9% in the Danish validation study. This may reflect different practice in the threshold to take a BC between the UK and the USA or the temporal differences between the studies. Despite the higher prevalence of bacteraemia, an AUC of 0.80 still suggests it is possible to discriminate those at lower risk of bacteraemia using the CPR, and calibration was not found to be inadequate using the HL test.

In the studied cohort, on the basis of likelihood ratios (see online supplementary appendix 3) and attempting to reduce overlapping, removing 7 of the 12 studied variables and introducing two other variables (lymphopenia and elevated CRP) did not lead to a significant deterioration in sensitivity or NPV while increasing specificity and the AUC (see table 3 and online supplementary appendix 3, tables S5, S6 and figure S3). Although age >65 was significantly different, and temperature 38.3°C–39.4°C was not, the former was not included to minimise variables, and excluding the elevated temperature would have resulted in an increase in false negatives, scoring <2. The literature has consistently demonstrated absolute WCC, as a discriminator, is inferior to lymphocyte count (or neutrophil: lymphocyte ratio) and CRP.[41–46] This more parsimonious model with seven variables (compared with the Shapiro derivation/validation studies in table 3) could be further explored and validated in the future.

An impact analysis study after implementing such a model as the Shapiro criteria[27] should be considered to see whether its

Table 3 Comparison of the Shapiro derivation study (1),[27] internal validation (2),[27] external validation (3)[28] and presented Worthing data (4)

	Sensitivity	Specificity	PLR	NLR	AUC
(1) Shapiro derivation	98% (96%–100%)	29% (27%–31%)	1.38 (1.34–1.43)	0.07 (0.03–0.18)	0.75
(2) Shapiro validation	97 (95–100)	9 (26–31)	1.36 (1.30–1.43)	0.10 (0.03–0.32)	0.80
(3) Shapiro–Denmark	94 (87–98)	48 (42–53)	1.79 (1.59–2.01)	0.13 (0.06–0.29)	0.83
(4) Shapiro–Worthing	97 (91–99)	37 (28–47)	1.54 (1.32–1.80)	0.08 (0.03–0.25)	0.80 (0.74–0.86)
(5) Modified Worthing–Shapiro	97 (95–100)	53 (43–63)	2.06 (1.67–2.55)	0.06 (0.02–0.18)	0.83 (0.77–0.88)

Row (5) shows the results of a modified Worthing–Shapiro score (see online supplementary appendix 3, tables S5 and S6).
AUC, area under the receiver operating curve; NLR, negative likelihood ratio; PLR, positive likelihood ratio.

employment provides clinical benefit. The Shapiro criteria has relatively low specificity for predicting bacteraemia; however, this may not be unacceptable clinically as it is well known that a proportion of patients with severe infection, including those with septic shock, are never proven to be bacteraemic, particularly if antibiotics have already been given, culture sample size is inadequate or the organism is fastidious. Knowing who is at very low risk of bacteraemia could be beneficial by reducing unnecessary BCs. However, another equally important challenge for clinicians wishing to develop a prediction model in this field would be to accurately risk stratify patients admitted with 'suspected infection' into high-risk or lower-risk groups (such as risk of mortality or requirement for ICU) that could ensure optimal early treatment and appropriately intensive monitoring.

This study presents further external validation of a prediction rule identifying with high sensitivity the patients who will be bacteraemic from a cohort of patients whose clinical team felt BCs were indicated to investigate for possible bacteraemia. Perhaps, the major implication of the Shapiro criteria rule is that with a low score (<2), a patient is at low risk of bacteraemia, and this could safely allow a significant reduction in the number of cultures performed with the subsequent advantage of reducing contaminant results. The large number of variables and difficulty in automating the model are the shortcomings that could be addressed by exploring the modified Worthing–Shapiro model.

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