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Short Communication

Validating a prediction tool to determine the risk of nosocomial multidrug-resistant Gram-negative bacilli infection in critically ill patients: A retrospective case–control study

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ABSTRACT

Background: The Singapore GSDCS score was developed to enable clinicians predict the risk of nosocomial multidrug-resistant Gram-negative bacilli (RGNB) infection in critically ill patients. We aimed to validate this score in a UK setting.
Method: A retrospective case–control study was conducted including patients who stayed for more than 24 h in intensive care units (ICUs) across two tertiary National Health Service hospitals in London, UK (April 2011–April 2016). Cases with RGNB and controls with sensitive Gram-negative bacilli (SGNB) infection were identified.
Results: The derived GSDCS score was calculated from when there was a step change in antimicrobial therapy in response to clinical suspicion of infection as follows: prior Gram-negative organism, Surgery, Dialysis with end-stage renal disease, prior Carbapenem use and intensive care Stay of more than 5 days. A total of 110 patients with RGNB infection (cases) were matched 1:1 to 110 geotemporally chosen patients with SGNB infection (controls). The discriminatory ability of the prediction tool by receiver operating characteristic curve analysis in our validation cohort was 0.75 (95% confidence interval 0.65–0.81), which is comparable with the area under the curve of the derivation cohort (0.77). The GSDCS score differentiated between low- (0–1.3), medium- (1.4–2.3) and high-risk (2.4–4.3) patients for RGNB infection ($P < 0.001$) in a UK setting.
Conclusion: A simple bedside clinical prediction tool may be used to identify and differentiate patients at low, medium and high risk of RGNB infection prior to initiation of prompt empirical antimicrobial therapy in the intensive care setting.

1. Background

Antimicrobial resistance (AMR) poses a profound global threat to economic security, human and animal health [1]. Rates of resistance and the risk associated with clinical failure may be higher in the intensive care unit (ICU) setting, leading to broader empirical antimicrobial therapy [2]. The World Health Organisation (WHO) highlighted multidrug-resistant (MDR) Gram-negative bacilli as 'Priority 1 Pathogens' and recommended innovative tools be developed to support clinical decision-making around the appropriate use of antimicrobial drugs [3]. Clinical prediction tools are used widely in the ICU to stratify patient risk for a variety of conditions [4,5] and may prove valuable to promptly assess the risk of MDR infection [6,7] prior to much anticipated rapid diagnostic

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tests (RDTs). A simple bedside score to facilitate prompt assessment of the risk of infection being caused by multidrug-resistant Gram-negative bacilli (RGNB) was developed and validated in Singapore [6]. We aimed to validate this score in a UK setting.

2. Method

The cohort of patients were from a 5-year retrospective study in ICUs across two large National Health Service tertiary referral teaching hospitals in London, UK, serving a population of almost 2 million. The ICUs at both Hospital A and B admit a heterogeneous cohort of patients with medical and surgical problems with an RGNB prevalence of 0.03%. All patients are screened on admission and weekly to assess carriage of methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenemase-producing Enterobacteriaceae (CPE), as per local policy with strict infection control policies being in place. All consecutive patients aged over 21 years admitted to the ICU in Hospital A or B, and who stayed for more than 24 h, from 5 April 2011 to 6 April 2016 were included. Those with GNB within 24 h prior to ICU admission and subsequent to ICU discharge were excluded. Microbiology data representing colonisation (rectal screening for CPE, those with no symptoms/signs of infection) were excluded. The four Gram-negative organisms mentioned in the original score were included for this study (*Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumannii*) [6]. RGNB was defined as acquired non-susceptibility to at least one drug in three or more antibiotic categories [8]. The three classes of antibiotics were cephalosporins (ceftazidime), fluoroquinolones (ciprofloxacin) and aminoglycosides (gentamicin). Sensitive Gram-negative bacilli (SGNB) were defined as the organisms that did not meet the criteria for RGNB.

Medical records were reviewed to identify those with RGNB for whom antimicrobial treatment had been initiated/changed based on clinical suspicion of infection within 24 h of the culture being taken (cases). A distinct group of patients with isolated SGNB (controls) from clinical specimens were identified geotemporally at random by an investigator who was not involved in data collection for the risk score and were matched 1:1 with the cases. Data were collected from electronic medical records (Acubase®), hospital pharmacy inpatient medication records and the Sunquest® laboratory information management system by investigators blinded to the results of the other components of the score and corroborated through detailed case note analysis. The risk score was calculated from the date of the step change in antimicrobial therapy, which preceded final culture and sensitivity results.

2.1. Statistical analysis

Baseline variables were represented as means/medians for continuous variables and proportions for categorical variables. Chi square (χ^2)/Fisher's exact tests were used to compare proportions, and Student *t*-tests/Wilcoxon rank-sum tests were used for continuous variables as appropriate. We calculated the GSDCS risk score based on the regression coefficients described by Vasudevan et al. [6]. One point was allocated for the presence of prior GNB in a clinical sample or prior administration of carbapenems within 6 months, with 0.6 points if the patient had undergone surgery before isolation of GNB, 0.7 points for prior dialysis with end-stage renal disease and 2 points for a stay of more than 5 days in the ICU prior to isolation of GNB. Points were summated to calculate the final score for each patient, and 1 point was subtracted for patients who had been admitted to the ICU for more than 5 days prior to isolation of GNB and with prior exposure to a carbapenem. The discriminatory ability was then assessed by a receiver operating characteristic (ROC) curve analysis and by measuring the area under the curve (AUC). The sensitivity, specificity and the likelihood ratios were then calculated for the different risk categories. Analyses were conducted using STATA 14.2 (STATA Corp, College Station, TX, USA). There is no widely acceptable approach to estimate sample size required for risk score validation studies, although limited evidence suggests a minimum of 100 events (RGNB) and 100 nonevents (SGNB) [9].

Table 1
Patient, infection characteristics and risk factors.

Variable	SGNB (*n* = 110) (controls)	RGNB (*n* = 110) (cases)	*P*-value
Median age (range)	62.5 (24–85)	65 (24–86)	0.49
Gender, *n* (%)			
Female	39 (35.5)	41 (37.3)	
Male	71 (64.6)	69 (62.7)	0.78
Median BMI (range)	24.5 (16.9–44.9)	23.4 (15.6–43.1)	0.85
Type of admission, *n* (%)			0.40
Planned	16 (14.8)	21 (19.1)	
Unplanned	92 (85.2)	89 (80.9)	
Site of infection			0.005
Blood (including intravascular catheter-related)	11 (10)	7 (6.4)	
Pneumonia	72 (65.5)	64 (58.2)	
Urine	11 (10)	14 (12.6)	
Complicated skin and soft tissue (including surgical site)	3 (2.7)	18 (16.4)	
Others (including intra-abdominal)	13 (11.8)	7 (6.4)	
Causative organism, *n* (%)			0.16
Acinetobacter baumannii	1 (0.9)	6 (5.5)	
Escherichia coli	38 (34.6)	40 (36.4)	
Klebsiella pneumoniae	31 (28.2)	22 (20)	
Pseudomonas aeruginosa	40 (36.3)	42 (38.1)	
Risk factors and GSDCS score categories			
Presence of any GNB within 6 months, *n* (%)	24 (21.8)	34 (30.9)	0.13
Surgery in this admission before RGNB, *n* (%)	57 (51.8)	92 (83.6)	<0.001
Dialysis with end-stage renal disease, *n* (%)	3 (2.7)	14 (12.7)	0.005
Carbapenems within 6 months, *n* (%)	29 (26.4)	76 (69.1)	<0.001
Stay in ICU > 5 days, *n* (%)	53 (48.2)	84 (76.4)	<0.001

BMI, body mass index; ICU, intensive care unit; RGNB, resistant Gram-negative bacilli; SGNB, sensitive Gram-negative bacilli.

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3. Results

A total of 4249 adult patients were admitted for more than 24 h to the ICUs of Hospital A and B during the study period. Medical records were reviewed for those with a positive RGNB culture that met inclusion criteria (n = 133), and 110 of them had antimicrobial treatment initiated/changed due to clinical suspicion of infection within 24 h of the RGNB culture being taken (cases). Medical records were reviewed for patients that met inclusion criteria with a positive culture yielding SGNB (n = 198). A total of 110 patients with RGNB infection (cases) were geotemporally matched 1:1 to 110 patients with SGNB infection (controls).

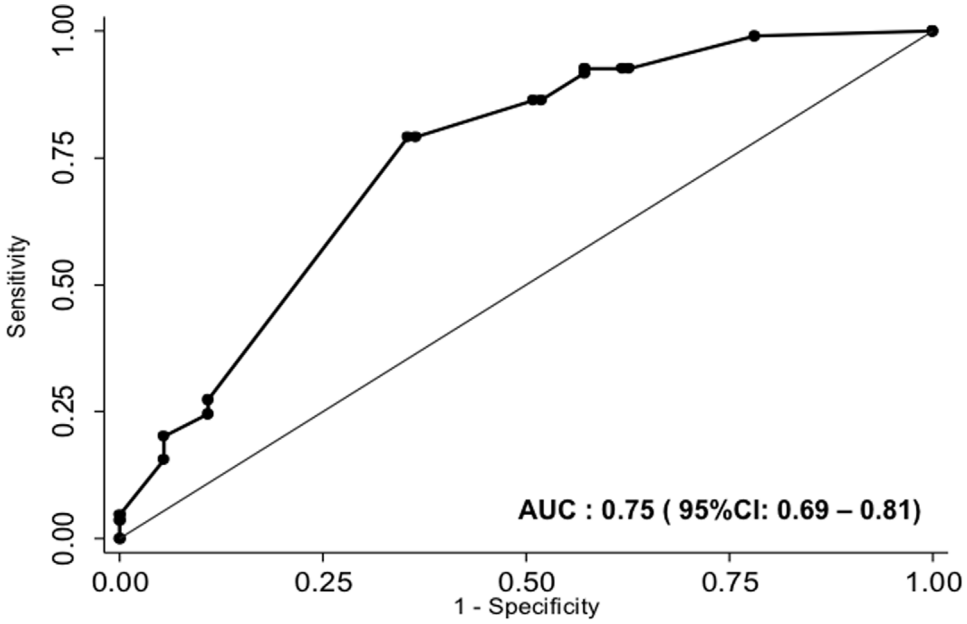
The characteristics of patients with RGNB and SGNB included in this validation study are presented in Table 1. RGNB infections were most frequently pneumonia (58.1%), followed by complicated skin and soft tissue infections (16.4%) and urinary tract infections (12.7%). SGNB infections were more frequently pneumonia (65.5%), followed by intra-abdominal infections (11.8%), blood (10%) and urinary tract infections (10%). Both groups had comparably low incidence of bacteraemia, and infections related to intravascular catheters (RGNB: 1, SGNB: 2). These were classified as blood for the final analyses.

By ROC curve analysis, the AUC for the GSDCS score was found to be 0.75 [95% confidence interval (CI) 0.65–0.81] (Fig. 1), when applied to predict RGNB infection in this cohort of ICU patients.

The proportion of RGNB patients in different GSDCS risk categories is shown in Fig. 2. The score reliably differentiated between patients at low, medium and high risk.

4. Discussion

The discriminatory ability (AUC) of the GSDCS score in our cohort was 0.75, which is comparable with the AUC from the cohort in the original risk score study (0.77). The GSCDS score, which was developed in Singapore, performed well for identifying risk of nosocomial infection caused by RGNB in our critically ill population in London. The score reliably differentiated between patients at low, medium and high risk. Furthermore, baseline characteristics and causative organisms among patients in each group were comparable.



Cutpoint	Sensitivity	Specificity	Correctly classified	LR+	LR-
(>= .6)	99.09%	21.82%	60.45%	1.2674	0.0417
(>= .7)	92.73%	37.27%	65.00%	1.4783	0.1951
(>= 1)	92.73%	38.18%	65.45%	1.5	0.1905
(>= 1.3)	92.73%	42.73%	67.73%	1.619	0.1702
(>= 1.6)	91.82%	42.73%	67.27%	1.6032	0.1915
(>= 1.7)	86.36%	48.18%	67.27%	1.6667	0.283
(>= 2)	86.36%	49.09%	67.73%	1.6964	0.2778
(>= 2.3)	79.09%	63.64%	71.36%	2.175	0.3286
(>= 2.6)	79.09%	64.55%	71.82%	2.2308	0.3239
(>= 2.7)	27.27%	89.09%	58.18%	2.5	0.8163
(>= 3)	24.55%	89.09%	56.82%	2.25	0.8469
(>= 3.3)	20.00%	94.55%	57.27%	3.6667	0.8462
(>= 3.6)	15.45%	94.55%	55.00%	2.8333	0.8942
(>= 3.7)	4.55%	100.00%	52.27%		0.9545
(>= 4.3)	3.64%	100.00%	51.82%		0.9636
(> 4.3)	0.00%	100.00%	50.00%		1

Fig. 1. Performance of GSDCS score for predicting RGNB infection in ICU patients aged over 21 years.

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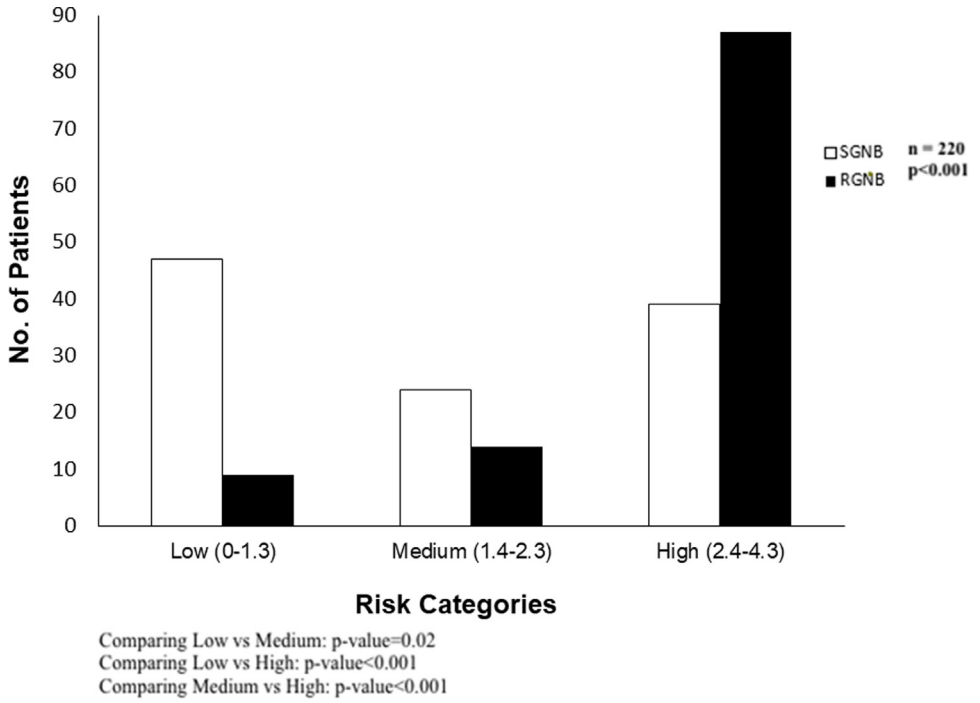

Fig. 2. Prevalence in different risk categories based on the GSDCS score.

Aggregation of component risk factors into predictive scoring systems for RGNB infection among critically ill patients has been developed for patients with blood stream infections [7], those on ventilator [10] and those with healthcare-associated pneumonia [11]. However, the applicability of these tools to other anatomical sites of nosocomial RGNB infections, within the ICU setting, remains restricted. The original derivation and validation of the GSDCS score included a variety of infections caused by four of the most common nosocomial Gram-negative organisms. A key advantage of this validation was inclusion of patients with different sites of infection which maintained predictive ability of the score to differentiate risk. The clinical utility is clear, as the site of infection may not be apparent when empirical prescribing decisions need to be made. Choosing appropriate empirical treatment will help improve outcomes in critically ill patients and help reduce any collateral damage related to ineffective therapy or antimicrobial drug resistance.

Previous studies designed to identify risk factors for RGNB infection in ICU have been limited by their specificity to specific patient populations or a single species of bacteria [12–16]. In these studies, disparities exist between definitions for MDR Gram-negative organisms, making comparisons between different predictive scores difficult. We adopted the international expert standard definition for acquired non-susceptibility to define MDR Gram-negative organisms [8], allowing for reliable comparison to the original study [6] in addition to setting a widely accepted standard for future risk scores. Earlier stratification of patients based on risk of RGNB can provide clinicians additional information to help inform appropriate empirical prescribing decisions. The date that the risk score was calculated preceded the final culture and sensitivity results. This is important as it reflects the predictive value and clinical utility for identifying patients who may benefit from broader-spectrum antimicrobial therapy before final culture and sensitivity results are confirmed, which can take up to 48 h from when the laboratory receives the culture.

5. Limitations

Data on illness severity scores, including APACHE and SOFA, were not included in this validation study as they do not reliably predict risk of infection caused by MDR bacteria in critically ill patients [17]. The original score and our validation excluded patients aged less than 21 years and hence requires further validation in younger adults and in paediatric populations, for whom different risk factors may exist. Notably, the GSDCS risk score is only validated for the four GNBs and should be used with caution in settings where the prevalence of resistance from another GNB is of concern. The score should not be used during outbreaks, as it has not been validated for this application. Variation in patient population may have implications on the predictive value of the score.

The limitations associated with this being a retrospective study should be considered. An observational validation study found limited applicability of the American Thoracic Society (ATS)/Infectious Diseases Society of America (ISDA) score when it was applied prospectively to predict MDR bacterial infection or colonisation in patients on admission to the ICU [18], and hence de-escalation of broad-spectrum agents remains a challenge in critical care settings [19]. The ATS/IDSA score did not differentiate between MDR infection and colonisation, whereas the GSDCS score is validated only in patients suspected of having an infection. This study included SGNB as control patients compared to the controls being with no infection in the study conducted by Vasudevan et al. However, we found that this tool effectively predicted patients with RGNB infection when compared with SGNB. The patients were classified into the distinct risk categories based on the cut-off presented in the original tool, and the prevalence in each setting needs to be considered when considering predictive values.

6. Conclusions

The GSDCS scoring system is a promising and effective tool for predicting risk of RGNB infection in ICU patients and may be

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usefully integrated into a clinical decision support system with machine-learning capabilities, allowing for refinement of predictive ability over time [20]. Targeting broad-spectrum antimicrobial therapy for patients at highest risk would spare others from 'collateral damage'. To our knowledge, this is the only externally validated scoring system to predict risk of infection caused by RGNB across a range of infection sites in a mixed population of critically ill patients.

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Competing interests

S.E.B. reports that outside of this work she receives research support from Roche Pharma. A.H.H. and L.S.P.M. have consulted for bioMérieux, and L.S.P.M. has also consulted for DNA electronics and Dairy Crest, and has received a research grant from Leo Pharma and educational grants from Eumedica, outside the scope of this work. M.G. reports that outside of this work he has consulted for MSD, Pfizer and Achaogen Pharmaceuticals. A.C.G. reports that outside of this work he has received speaker fees from Orion Corporation Orion Pharma and Amomed Pharma. He has consulted for Ferring Pharmaceuticals, Tenax Therapeutics, Baxter Healthcare and GSK, and received grant support from Orion Corporation Orion Pharma, Tenax Therapeutics and HCA International with funds paid to his institution. The other authors have no conflicts of interest to declare.

Ethical approval

Approval to conduct this study was obtained from the Joint Research Compliance Office (JRCO) of Imperial College Healthcare NHS Hospital and Imperial College London. Formal approval from the National Research Ethics Service was not required for this research as the JRCO identified the work as hospital service evaluation and audit.

Availability of data and materials

The data that support the findings of this study are not publicly available due to them containing information that would compromise participant privacy.

Authors' contributions

Concept and design: S.E.B., L.S.P.M., C.C., A.H.H.
Data acquisition: S.E.B., C..B., L.S.P.M., M.G.
Analysis and interpretation: S.E.B., A.V., L.S.P.M.
All authors were involved in drafting and approving the submitted version of the manuscript.

Disclaimer statement

The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the UK Department of Health.

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