Infection (2019) 47:571–578
https://doi.org/10.1007/s15010-019-01277-7

ORIGINAL PAPER

Derivation of a quick Pitt bacteremia score to predict mortality in patients with Gram-negative bloodstream infection

Sarah E. Battle[1] · Matthew R. Augustine[2] · Christopher M. Watson[3] · P. Brandon Bookstaver[4,5] · Joseph Kohn[5] · William B. Owens[1,2] · Larry M. Baddour[6] · Majdi N. Al-Hasan[1,2]

Received: 2 October 2018 / Accepted: 4 February 2019 / Published online: 8 February 2019

Abstract

Purpose This retrospective cohort study derived a "quick" version of the Pitt bacteremia score (qPitt) using binary variables in patients with Gram-negative bloodstream infections (BSI). The qPitt discrimination was then compared to quick sepsis-related organ failure assessment (qSOFA) and systemic inflammatory response syndrome (SIRS).

Methods Hospitalized adults with Gram-negative BSI at Palmetto Health hospitals in Columbia, SC, USA from 2010 to 2013 were identified. Multivariate Cox proportional hazards regression was used to determine variables associated with 14-day mortality.

Results Among 832 patients with Gram-negative BSI, median age was 65 years and 449 (54%) were women. After adjustments for age and Charleston comorbidity score, all five components of qPitt were independently associated with mortality: temperature < 36 °C [hazard ratio (HR) 3.02, 95% confidence interval (CI) 1.95–4.62], systolic blood pressure < 90 mmHg or vasopressor use (HR 2.40, 95% CI 1.37–4.13), respiratory rate ≥ 25/min or mechanical ventilation (HR 3.01, 95% CI 1.81–5.14), cardiac arrest (HR 5.35, 95% CI 2.81–9.43), and altered mental status (HR 3.99, 95% CI 2.44–6.80). The qPitt had higher discrimination to predict mortality [area under receiver operating characteristic curve (AUROC) 0.85] than both qSOFA (AUROC 0.77, $p < 0.001$) and SIRS (AUROC 0.63, $p < 0.001$). There was a significant difference in mortality between appropriate and inappropriate empirical antimicrobial therapy in patients with qPitt ≥ 2 (24% vs. 49%, $p < 0.001$), but not in those with qPitt < 2 (3% vs. 5%, $p = 0.36$).

Conclusions The qPitt had good discrimination in predicting mortality following Gram-negative BSI and identifying opportunities for improved survival with appropriate empirical antimicrobial therapy.

Keywords Bacteremia · Sepsis · Antibiotics · Outcomes · Survival

Introduction

Bloodstream infection (BSI) is among the leading causes of death in North America and Europe with nearly one-half of BSI caused by Gram-negative bacilli [1, 2]. High acute severity of illness, major chronic comorbidities, and inappropriate empirical antimicrobial therapy have been

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s15010-019-01277-7) contains supplementary material, which is available to authorized users.

✉ Majdi N. Al-Hasan
majdi.alhasan@uscmed.sc.edu

[1] Department of Medicine, Palmetto Health University of South Carolina Medical Group, Columbia, SC, USA

[2] University of South Carolina School of Medicine, 2 Medical Park, Suite 502, Columbia, SC 29203, USA

[3] Department of Acute Care Surgery, Prisma Health Richland Hospital, Columbia, SC, USA

[4] Department of Clinical Pharmacy and Outcomes Sciences, University of South Carolina College of Pharmacy, Columbia, SC, USA

[5] Department of Pharmacy, Prisma Health Richland Hospital, Columbia, SC, USA

[6] Department of Medicine, Division of Infectious Diseases, Mayo Clinic, Rochester, MN, USA

associated with increased mortality in patients with Gram-negative BSI [3–7].

The Pitt bacteremia score (PBS) has been used for decades as an objective measure of acute severity of illness in patients with serious infections such as BSI and sepsis [8–10]. Higher PBS has been consistently associated with increased mortality, with only a fraction of patients with BSI categorized as critically ill based on a PBS ≥ 4 [4, 5, 8, 9].

More recently, simpler binary scores for acute severity of illness have gained popularity since the recommendation to use quick sepsis-related organ failure assessment (qSOFA) as a screening tool for sepsis [11, 12]. In addition, recent literature has demonstrated that high fever, which is a component in the PBS, is not associated with increased mortality [13]. Moreover, in an era where early identification of patients with life-threatening infections is highly desired, some clinicians may be concerned that mechanical ventilation, another component of the PBS, may not detect respiratory failure at an early stage.

The primary aim of this retrospective cohort study is to derive a simplified quick form of the PBS (qPitt) using binary variables for acute severity of illness that are independently associated with 14-day mortality in patients with Gram-negative BSI. Secondary aims are to compare the discriminative ability of qPitt, qSOFA and systematic inflammatory response syndrome (SIRS) in predicting mortality following Gram-negative BSI and to determine the impact of inappropriate empirical antimicrobial therapy on mortality in patients with low and high qPitt.

Methods

Setting

The study was conducted at Palmetto Health Richland and Baptist Hospitals in Columbia, SC, USA. Combined, the two hospitals have > 1000 licensed beds to provide medical and surgical subspecialty care to both local residents of Richland County along with regional referrals. Palmetto Health Richland is a community-teaching hospital and a level 1 trauma center; Palmetto Health Baptist is a community hospital. The Institutional Review Board at Palmetto Health approved the study and waived informed consent.

Definitions

Gram-negative BSI was defined as the isolation of any aerobic Gram-negative bacillus in a blood culture. Monomicrobial BSI was defined as the recovery of a single species of bacteria in a blood culture and polymicrobial BSI as the recovery of more than one bacterial species in a blood culture [14]. Centers for Disease Control and Prevention criteria were used to define the primary source of BSI [15]. Previously defined criteria were used to classify the site of infection acquisition into community acquired, healthcare associated or hospital acquired [16]. Inappropriate empirical antimicrobial therapy was based on dosing, route of administration and in vitro antimicrobial susceptibility testing results as previously defined [6, 7]. The original PBS variables are summarized in Table 1 [9]. qSOFA includes systolic blood pressure ≤ 100 mmHg, respiratory rate ≥ 22 breaths/min, and change in mental status [11]. SIRS includes temperature > 38° or < 36 °C, heart rate > 90 beats/min, respiratory rate > 20 breaths/min, and peripheral white blood cell count > 12,000/mm^3, < 4000/mm^3, or > 10% immature bands [17]. Acute severity of illness variables were collected within 24 h prior to and 24 h following collection of index blood culture in concordance with the original PBS.

Case ascertainment

In this retrospective cohort study, microbiology laboratory databases at Palmetto Health were used to identify all patients with BSI due to aerobic Gram-negative bacilli from January 1, 2010 to December 31, 2013. Inclusion criteria included hospitalized adults with initial episode of monomicrobial BSI due to Gram-negative bacilli ($n = 832$). Polymicrobial BSI ($n = 121$), recurrent episodes of BSI ($n = 34$), patients who were treated in outpatient settings ($n = 29$), and children < 18 years old ($n = 98$) were excluded.

Table 1 The Pitt bacteremia score. Modified with kind permission of the publisher from Paterson DL, et al. [9]

Variable	Point allocation
Temperature	
36.1–38.9 °C	0
35.1–36.0 °C or 39.0–39.9 °C	1
≤ 35 °C or ≥ 40 °C	2
Hypotension (systolic blood pressure < 90 mmHg or vasopressor use)	2
Mechanical ventilation	2
Cardiac arrest	4
Mental status	
Alert	0
Disoriented	1
Stuporous	2
Comatose	4

All variables are recorded within 24 h leading to and 24 h following collection of index blood culture. The worst readings are recorded during that time period

Statistical analysis

Cox proportional hazards regression was used to identify clinical variables independently associated with 14-day all-cause mortality. Patients were followed for 14 days from time of collection of index blood culture or until death. This allowed for censoring of patients who were lost to follow-up between hospital discharge and the end of 14-day follow-up period on the day of last healthcare visit. Demographics, Charlson comorbidity index, site of infection acquisition, source of BSI, appropriateness of empirical antimicrobial therapy, respiratory rate, and individual components of the PBS were evaluated as potential risk factors for mortality in univariate analysis. Temperature was examined as a categorical variable (36°–39°, < 36° or > 39 °C) as well as mental status (alert, disoriented, stuporous or comatose). To allow early detection of respiratory failure, respiratory rate was first examined as a continuous variable and then converted into a binary variable using the best cutoff point from the receiver operating characteristic (ROC) curve. Clinical variables associated with mortality with a p value < 0.05 in the univariate analysis were included in the multivariate model to allow adjustment for potential confounders. Hazard ratios (HR) with 95% confidence intervals (CI) were reported to indicate the strength of association between each variable and mortality.

A quick form of the PBS (qPitt) was derived from clinical variables that were independently associated with mortality after adjustments for other predictors of mortality (demographics, comorbidities, etc.), as applicable. Individual components of the BPS that were not associated with mortality were excluded from qPitt. In addition, categorical variables in the PBS that were associated with mortality were simplified into binary variables.

The qPitt model was internally validated by bootstrap resampling and examination of model calibration. Variables that were retained in ≥ 95% of 200 bootstrap samples were included in qPitt. Model calibration was examined by plotting the deciles of predicted 14-day mortality from the qPitt model by the actual fraction of patients who died within 14 days of BSI to visually access calibration.

Area under ROC curve (AUROC) was then used to examine qPitt model discrimination and compare it to qSOFA and SIRS in patients who had completed 14 days of follow-up in the study. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were reported for the best cutoff point in each score. Comparison of AUROC between various scores was performed using the Hanley and McNeil method [18].

Secondary analyses were performed to compare qPitt discrimination in predicting 14-day mortality to the original PBS and to evaluate qPitt discrimination in predicting in-hospital, 28-day, and 90-day mortality following Gram-negative BSI.

Finally, Kaplan–Meier analysis and multivariate Cox model were used to determine the impact of inappropriate empirical antimicrobial therapy on 14-day mortality in patients with low and high qPitt. Log-rank p value was reported to determine statistical significance of the difference in mortality between patients who received appropriate and inappropriate empirical therapy within each qPitt stratum. Number needed to treat (NNT) to save one life with appropriate empirical antimicrobial therapy was calculated from the absolute difference in mortality between inappropriate and appropriate therapy.

JMP Pro (version 12.0, SAS Institute Inc, Cary, NC, USA) was used for statistical analysis. The level of significance for statistical testing was defined as $p < 0.05$ (two-sided) unless otherwise specified.

Results

Demographics and clinical characteristics

During the 4-year study period, 832 unique patients with Gram-negative BSI were included. The median age was 65 years and 449 (54%) were women. The study population was ethnically diverse. There was also diversity in the source of infection with the urinary tract being the most common source. *Escherichia coli* was the most common bloodstream isolate (Table 2). Overall, 98 patients (12%) died within 14 days of BSI, 99 (12%) were lost to follow up within 14 days, and the remaining 635 (76%) survived.

Derivation and internal validation of qPitt

Age, male sex, Charlson comorbidity score, source of infection, site of BSI acquisition, and inappropriate empirical antimicrobial therapy were associated with mortality in univariate analysis (Table 3). All individual components of PBS were associated with 14-day mortality except temperature > 39 °C (HR 0.84, 95% CI 0.50–1.41; $p = 0.52$). In addition, higher respiratory rate was associated with increased mortality; a respiratory rate ≥ 25 breaths/min was determined the best breakpoint in ROC curve.

The qPitt was derived from clinical variables that were associated with mortality. Hypothermia (temperature < 36 °C) was included in qPitt, but high fever (temperature > 39 °C) was excluded since it did not predict mortality. Respiratory rate ≥ 25 breaths/min was combined with mechanical ventilation as one binary variable to allow early detection of respiratory failure. All mental status categories that were associated with mortality were combined into one binary variable of altered mental status for simplification.

Table 2 Demographics and clinical characteristics of patients with bloodstream infections

Variable	($n=832$)
Age in years, median (IQR)	65 (54–78)
Male sex, *n* (%)	383 (46)
Ethnicity, *n* (%)	
White	402 (48)
African American	401 (48)
Other	29 (3)
Diabetes mellitus, *n* (%)	316 (38)
End-stage renal disease, *n* (%)	78 (9)
Liver cirrhosis, *n* (%)	30 (4)
Cancer, *n* (%)	152 (18)
Immune-compromised host, *n* (%)	106 (13)
Charleston comorbidity score, median (IQR)	2 (1–3)
Site of acquisition, *n* (%)	
Community acquired	345 (41)
Healthcare associated	317 (38)
Hospital acquired	170 (20)
Source of infection, *n* (%)	
Urinary tract	444 (53)
Gastrointestinal tract	65 (8)
Central venous catheter infection	61 (7)
Respiratory tract	49 (6)
Biliary tract	41 (5)
Skin and soft tissue infection	34 (4)
Other	15 (2)
Unknown	123 (15)
Temperature	
36.1–38.9 °C	393 (47)
35.1–36.0 °C or 39.0–39.9 °C	362 (44)
≤ 35 °C or ≥ 40 °C	77 (9)
Hypotension	337 (41)
Mechanical ventilation	122 (15)
Cardiac arrest	22 (3)
Mental status	
Alert	523 (63)
Disoriented	120 (14)
Stuporous	136 (16)
Comatose	53 (6)
Microbiology, *n* (%)	
Escherichia coli	444 (53)
Klebseilla spp.	155 (19)
Proteus mirabilis	58 (7)
Pseudomonas aeruginosa	50 (6)
Enterobacter spp.	50 (6)
Serratia spp.	23 (3)
Other	52 (6)
Inappropriate empirical therapy, *n* (%)	72 (9)

IQR interquartile range

The remaining two components of the PBS, hypotension and cardiac arrest, were also included in qPitt since they were both associated with mortality.

After adjustments in multivariate model, all five components of qPitt were independently associated with mortality: temperature < 36 °C, systolic blood pressure < 90 mmHg or vasopressor use, respiratory rate ≥ 25 breaths/min or requirement for mechanical ventilation, cardiac arrest, and altered mental status (Table 3).

Bootstrap resampling was performed to assess the internal validation of qPitt model. All five individual components of qPitt were retained in ≥ 95% of 200 bootstrap samples (Table 4). Model calibration was satisfactory since the observed outcomes were fairly close to the predictions (Supplemental Fig. 1). AUROC for qPitt model was 0.85 using score ≥ 2 to identify patients at high risk of mortality (Supplemental Fig. 2). The 14-day mortality was 3% and 26% in patients with qPitt < 2 and ≥ 2, respectively (log-rank $p < 0.001$).

Comparison between different scores

Among this cohort, 324 (39%), 450 (54%), and 771 (93%) patients had qPitt ≥ 2, qSOFA ≥ 2, and SIRS ≥ 2, respectively. The qPitt had higher discrimination to predict mortality (AUROC 0.85) than both qSOFA (AUROC 0.77, $p < 0.001$) and SIRS (AUROC 0.63, $p < 0.001$) among patients who were followed for 14 days after BSI ($n = 733$). The performance characteristics of each score are summarized in Table 5. Since 93% of patients with Gram-negative BSI had SIRS ≥ 2, the score had very low specificity and positive predictive value for 14-day mortality. Both qPitt and qSOFA had very high negative predictive values and comparable sensitivity. However, qPitt had higher specificity and positive predictive value than qSOFA.

In a secondary analysis, qPitt had comparable discrimination to predict 14-day mortality to the original PBS (AUROC 0.85 vs. 0.83, respectively). The qPitt also had good discrimination in predicting in-hospital, 28-day, and 90-day mortality following Gram-negative BSI (AUROC 0.85, 0.85, and 0.81, respectively).

Impact of inappropriate empirical therapy on mortality

Overall, inappropriate empirical antimicrobial therapy was associated with increased mortality in patients with Gram-negative BSI after adjustments for other variables in multivariate Cox model (Table 3). In the stratified analysis by acute severity of illness using qPitt, inappropriate therapy was associated with increased mortality in critically ill patients with qPitt ≥ 2 (HR 2.91, 95% CI 1.62–4.92; $p < 0.001$), but not in patients with qPitt < 2 (HR 2.18, 95%

Table 3 Risk factors for mortality following bloodstream infection in univariate and multivariate analyses

Variable	Univariate model		Multivariate model	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (per decade)	1.15 (1.02–1.31)	0.02	1.21 (1.05–1.40)	0.009
Male sex	1.62 (1.09–2.42)	0.02	0.92 (0.60–1.41)	0.70
African American	0.69 (0.44–1.02)	0.07	–	–
Charleston score (per point)	1.22 (1.14–1.31)	< 0.001	1.17 (1.08–1.27)	< 0.001
Non-urinary source	2.73 (1.80–4.26)	< 0.001	1.80 (1.13–2.91)	0.01
Site of acquisition				
Community acquired	1 (referent)		1 (referent)	
Healthcare associated	2.08 (1.28–3.48)	0.003	1.20 (0.71–2.06)	0.50
Hospital acquired	2.51 (1.46–4.35)	0.001	1.78 (0.97–3.28)	0.06
Inappropriate empirical therapy	2.62 (1.52–4.26)	< 0.001	2.04 (1.14–3.47)	0.02
Respiratory rate ≥ 25 breaths/min	3.36 (2.25–5.10)	< 0.001	3.01 (1.81–5.14)[a]	< 0.001
Mechanical ventilation	9.72 (6.52–14.56)	< 0.001		
Temperature				
36–39 °C	1 (referent)		1 (referent)	
< 36 °C	3.60 (2.27–5.37)	< 0.001	3.02 (1.95–4.62)	< 0.001
> 39 °C	0.84 (0.50–1.41)	0.52	–	–
SBP < 90 mmHg or vasopressor use	6.35 (3.97–10.66)	< 0.001	2.40 (1.37–4.13)	0.002
Cardiac arrest	22.97 (13.22–37.80)	< 0.001	5.35 (2.81–9.43)	< 0.001
Mental status				
Alert	1 (referent)		1 (referent)	
Disoriented	4.32 (2.36–7.89)	< 0.001	3.99 (2.44–6.80)[b]	< 0.001
Stuporous	4.44 (2.49–7.97)	< 0.001		
Comatose	23.20 (13.48–40.63)	< 0.001		

HR hazard ratio, *CI* confidence intervals, *SBP* systolic blood pressure

[a]Hazard ratio for respiratory rate ≥ 25 breaths/min or requirement for mechanical ventilation

[b]Hazard ratio for altered mental status

Table 4 Quick Pitt bacteremia score (qPitt)

Variable
Hypothermia (temperature < 36 °C)
Hypotension (systolic blood pressure < 90 mmHg or vasopressor use)
Respiratory failure (respiratory rate ≥ 25 breaths/min or need for mechanical ventilation)
Cardiac arrest
Altered mental status

The worst (highest or lowest) variable is collected in the 24 h leading to and 24 h following collection of index blood culture

CI 0.34–8.15; $p = 0.35$) after adjustments for age, Charlson comorbidity score and source of infection. In patients with qPitt ≥ 2, mortality increased from 24% with appropriate empirical antimicrobial therapy to 49% with inappropriate therapy ($p < 0.001$; Fig. 1). The absolute risk reduction with appropriate empirical therapy was 0.25, corresponding to NNT of 4. There was no significant difference in mortality between inappropriate and appropriate therapy in patents with qPitt < 2 (5% vs. 3%; $p = 0.36$; Supplemental Fig. 3). The absolute risk reduction and NNT with appropriate

Table 5 Performance characteristics of various scores to predict mortality in bloodstream infections

Score	AUROC	Score ≥ 2, *n* (%)	Sensitivity[a]	Specificity[a]	PPV[a]	NPV[a]
qPitt	0.85	324 (39)	87	69	30	97
qSOFA	0.77	450 (54)	89	50	22	97
SIRS	0.63	771 (93)	97	8	14	95

AUROC area under receiver operating characteristic curve, *PPV* positive predictive value, *NPV* negative predictive value, *qPitt* quick Pitt bacteremia score, *qSOFA* quick sepsis-related organ failure assessment, *SIRS* systemic inflammatory response syndrome

[a]Values for score ≥ 2

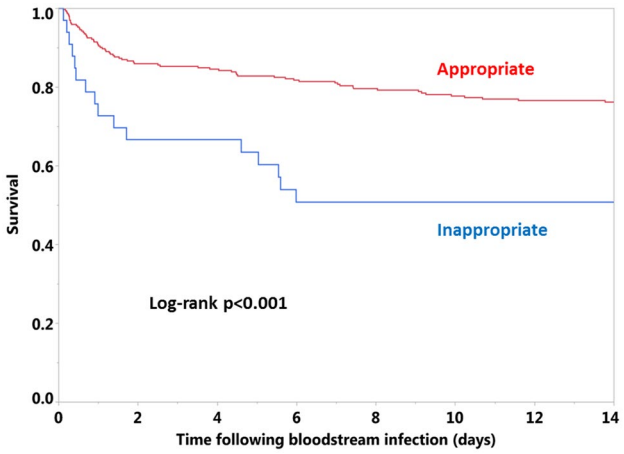

Fig. 1 Kaplan–Meier survival curves of critically ill patients with bloodstream infection (qPitt ≥ 2) based on empirical antimicrobial therapy

therapy in this group were 0.026 and 38, respectively, if any at all given lack of statistical significance.

Discussion

The qPitt simplified the PBS into five binary variables by excluding fever and converting mental status categories into one binary variable. It also broadened the definition of acute respiratory failure to allow early detection in patients with respiratory rate ≥ 25, not yet requiring mechanical ventilation. The qPitt had good discrimination (AUROC 0.85) and performed better than qSOFA and SIRS in predicting 14-day mortality following Gram-negative BSI. In addition, it identified critically ill patients (qPitt ≥ 2) in whom appropriate empirical antimicrobial therapy was associated with improved survival.

Since the adoption of the new sepsis-3 criteria, the debate regarding the optimal score to identify patients with life-threatening infections continues [11, 12, 19, 20]. The qSOFA has attracted many healthcare providers recently, because it can be calculated at the bedside without the need for further laboratory studies. The same holds true for qPitt, but not SIRS, giving qSOFA and qPitt a significant time advantage in clinical evaluation of patients with suspected infections [12, 17]. The current study suggests that SIRS remains a valuable tool in identifying patients with systemic infections, since 93% of patients with BSI had SIRS ≥ 2. This supports the clinical practice of obtaining two sets of blood cultures in patients with SIRS ≥ 2 prior to starting antimicrobial therapy to better substantiate a diagnosis of BSI. However, the specificity of SIRS in identifying BSI could not be determined since all patients in the current study had BSI. Moreover, the performance of SIRS was nondiscriminatory in identification of patients with life-threatening infections given AUROC of 0.63 for mortality.

There is a considerable overlap between clinical variables included in qPitt and qSOFA. Altered mental status is a common variable between the two scores. The differences in hypotension and respiratory failure definitions between the two scores may appear subtle. However, the slightly higher thresholds for both systolic blood pressure and respiratory rate in qPitt compared to qSOFA likely improved specificity and PPV of qPitt. This has not been achieved at the expense of sensitivity and NPV, which remain comparable between the two scores. The discrimination of qSOFA improved (AUROC 0.77–0.80) when systolic blood pressure < 90 mmHg and respiratory rate ≥ 25 breaths/min were used in an exploratory analysis. Adding hypothermia, an independent predictor of mortality, to qPitt likely contributed to further increase in discrimination over qSOFA. It is notable that the discrimination of qSOFA to predict mortality in patients with Gram-negative BSI in this study was comparable to its discrimination in other patient populations in different healthcare and geographical settings [11, 20–22]. However, the sensitivity of qSOFA in patients with Gram-negative BSI in the current study was notably higher than that previously reported in patients with suspected infections [23, 24]. This potential difference in sensitivity across cohorts of patients with proven and suspected infections emphasizes the need for external validation of qPitt in patients' suspected infections to support its clinical value in this population.

The survival benefit of antimicrobial therapy supports initiation of appropriate empirical therapy as quickly as possible in critically ill patients with qPitt ≥ 2. In contrast, lack of difference in mortality between appropriate and inappropriate empirical therapy argues that there may be a higher margin of error in patients with qPitt < 2. This allows starting targeted antimicrobial therapy according to established source of infection based on the screening results of clinical, laboratory and radiographic evaluations, as indicated. It also encourages the selection of empirical antimicrobial therapy based on predicted probability of BSI due to *P. aeruginosa* or extended-spectrum beta-lactamase-producing *Enterobacteriaceae* as estimated by clinical risk assessment tools rather than the conservative and popular "one size fits all" approach [25–27]. Nevertheless, appropriate empirical antimicrobial therapy has been associated with shorter hospital length of stay in patients with BSI, including those with low predicted mortality at initial presentation [28].

Inclusion of patients with Gram-negative BSI allowed derivation of qPitt in a cohort of patients with indisputable evidence of infection. This provided an advantage over cohorts of patients with Gram-positive BSI or other infections where positive cultures may be occasionally regarded as skin contamination or colonization of the urinary or

respiratory tracts, etc. The current derivation cohort seemed also preferable to patients with suspected infections such as those meeting the SIRS criteria in whom a large proportion might not have clinical or microbiological evidence of infections. However, external validation of qPitt in patients with suspected infections at initial presentation improves generalizability of the model and increases its utility in clinical practice. The study shares common limitations of retrospective cohorts. However, all variables in the study, including markers for acute severity of illness, were clearly predefined prior to data collection. Second, the two hospitals included in the study are located in the same geographical area within one healthcare system. Multicenter studies add variety to the study population and prescription practices. Third, since the qPitt was derived in patients with Gram-negative BSI, its performance may vary in those with more diverse sources of infection, especially given the small percentage of patients with a respiratory source of infection in the current study as compared to other sepsis cohorts. Evaluation and external validation of qPitt in patients with suspected sepsis based on sequential organ failure assessment should be pursued in future studies. Finally, the study used 14-day mortality as primary outcome to minimize potential impact of late mortality due to major comorbidities such as cancer and liver cirrhosis [4, 5]. However, qPitt performed well in predicting in-hospital, 28-day, and 90-day mortality.

Conclusions

The qPitt had good discrimination and performed better than other acute severity of illness scores in predicting mortality following Gram-negative BSI. In addition, it stratified patients based on the life-saving potential with antimicrobial therapy. Appropriate empirical therapy was associated with improved survival in critically ill patients with a qPitt ≥ 2, but not in those with a qPitt < 2.

Acknowledgements The authors thank Prisma Health Antimicrobial Stewardship and Support Team in South Carolina, USA for their help in facilitating the conduct of this study. SEB, MRA and MNA have full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the analysis. The preliminary results of this study were presented in part at IDWeek annual meeting on October 7, 2017 in San Diego, CA, USA.

Funding The study received internal funding from the Grant-in-Aid, Palmetto Health Richland Research and Education Foundation, Columbia, SC, USA. There were no other sources of funding for this study.

Compliance with ethical standards

Conflict of interest MNA: Continuing medical education steering committee, Rockpointe Corporation. PBB: Advisory board member, CutisPharma; Speaker's Bureau, Melinta Therapeutics; speaker and continuing medical education steering committee, Rockpointe Corporation. SEB, MRA, CMW, WO, JK, LMB: no conflicts.

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