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ORIGINAL RESEARCH

Evaluation of the INCREMENT-CPE, Pitt Bacteremia and qPitt Scores in Patients with Carbapenem-Resistant Enterobacteriaceae Infections Treated with Ceftazidime–Avibactam

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ABSTRACT

Background: The aim of this study was to evaluate the predictive performance of the INCREMENT-CPE (ICS), Pitt bacteremia score (PBS) and qPitt for mortality among patients treated with ceftazidime–avibactam for carbapenem-resistant Enterobacteriaceae (CRE) infections.

Methods: Retrospective, multicenter, cohort study of patients with CRE infections treated with ceftazidime–avibactam between 2015 and 2019. The primary outcome was 30-day all-cause mortality. Predictive performance was determined by assessing discrimination, calibration and precision.

Results: In total, 109 patients were included. Thirty-day mortality occurred in 18 (16.5%) patients. There were no significant differences in discrimination of the three scores [area under the curve (AUC) ICS 0.7039, 95% CI 0.5848–0.8230, PBS 0.6893, 95% CI 0.5709–0.8076, and qPitt 0.6847, 95% CI 0.5671–0.8023; $P > 0.05$ all pairwise comparisons]. All scores showed adequate calibration and precision. When dichotomized at the

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optimal cut-points of 11, 3, and 2 for the ICS, PBS, and qPitt, respectively, all scores had NPV > 90% at the expense of low PPV. Patients in the high-risk groups had a relative risk for mortality of 3.184 (95% CI 1.35–8.930), 3.068 (95% CI 1.094–8.606), and 2.850 (95% CI 1.016–7.994) for the dichotomized ICS, PBS, and qPitt, scores respectively. Treatment-related variables (early active antibiotic therapy, combination antibiotics and renal ceftazidime–avibactam dose adjustment) were not associated with mortality after controlling for the risk scores.

Conclusions: In patients treated with ceftazidime–avibactam for CRE infections, mortality risk scores demonstrated variable performance. Modifications to scoring systems to more accurately predict outcomes in the era of novel antibiotics are warranted.

Keywords: Carbapenem-resistant Enterobacteriaceae; Ceftazidime–avibactam; INCREMENT-CPE; Pitt bacteremia

Key Summary Points

The INCREMENT CPE, Pitt Bacteremia and qPitt scores have recently been validated in patients with bacteremic and non-bacteremic carbapenem-resistant Enterobacteriaceae (CRE) infections.

However, these studies included no or few patients treated with newer anti-CRE antibiotics.

In patients treated with ceftazidime–avibactam for CRE infections, the mortality risk scores demonstrated variable performance.

Modifications to scoring systems to more accurately predict outcomes in the era of novel antibiotics is warranted.

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INTRODUCTION

Enterobacteriaceae are among the most frequent cause of bacterial infections in patients of all ages in both community and inpatient settings [1]. The remarkable ability of these organisms to acquire a growing array of mechanisms to evade the activity of broad-spectrum antibiotics therefore presents a growing challenge. In particular, the emergence and spread of carbapenem-hydrolyzing beta-lactamases (carbapenemases) limits our ability to treat many life-threatening infections [2]. Due to the well-rehearsed challenges of conducting randomized controlled trials (RCTs) in patients with carbapenem-resistant Enterobacteriaceae (CRE) infections, current management strategies are largely informed by observational data and expert opinion [3]. Observational studies can provide valuable insight into the real-world effectiveness of treatment alternatives in circumstances where execution of RCTs is not feasible. However, because treatment is not randomly assigned, confounding by indication may lead to a biased estimate of the treatment effect. Covariate adjustment is especially important in CRE studies due to the wide spectrum of disease severity and underlying health status of the patients who acquire these infections, which clearly influences both the management approach and outcomes. Risk scores are useful for covariate adjustment in these circumstances, and they can also facilitate comparisons of populations across different studies. Furthermore, some risk scores have been used clinically to define high-risk subgroups for whom more intensive management strategies may be targeted [4, 5]. A number of risk scores have recently been developed and/or validated specifically in patients with CRE infections [4, 6, 7]. The INCREMENT-CPE score (ICS) was developed to predict 14-day mortality in patients with carbapenemase-producing Enterobacteriaceae (CPE) bacteremia [4]. It was subsequently modified and validated for 30-day mortality in patients with bacteremic and non-bacteremic CPE infections [6]. The Pitt bacteremia score (PBS) and an abbreviated version of the PBS, the qPitt, were also recently validated in a large cohort of patients with bacteremic and non-bacteremic CRE infections [7]. Notably, these analyses included no [4, 6] or few [7] patients treated with newer antibiotics with activity against CRE. Their performance in the era of more effective and safer antibiotics [8, 9] is unclear. Therefore, the objective of this study was to evaluate the predictive performance of the ICS, PBS, and qPitt for mortality among patients with CRE infections treated with ceftazidime–avibactam.

METHODS

Study Design and Population

This was a secondary analysis of a multicenter, retrospective, observational, cohort study conducted at six geographically diverse academic and community medical centers in the U.S. between May 2015 and February 2019 [10]. Approval was obtained from each participating center's Institutional Review Board (IRB) with a waiver for informed consent (Supplementary Appendix 1). Wayne State University served as the master IRB. Pharmacy records were screened for all patients who received ceftazidime–avibactam between January 2015 and February 2019. Inclusion criteria were: (1) age ≥ 18 years, (2) receipt of ceftazidime–avibactam for ≥ 72 h, and (3) CRE infection [10].

Data Collection and Study Definitions

Relevant demographic, clinical, microbiological, and treatment data were extracted from the electronic medical record (EMR) by study investigators at each center and entered into a secure online data collection form [11]. Bacterial identification and antibiotic susceptibilities were performed by local laboratories according to standard procedures. CRE was defined by current US Centers for Disease Control and Prevention criteria [7]. Ceftazidime–avibactam susceptibility was determined using disk diffusion or gradient strips, where available. Hospital-acquired CRE infection was defined as the first CRE-positive culture collected ≥ 48 h after admission. Sources of infection were based on physician notes and available clinical, microbiological, and diagnostic data. Where available, resistance markers were identified by VERIGENE BC-GN (Luminex, Austin, TX, USA). Infection onset was defined as the day the index CRE culture was collected. Early active therapy was receipt of at least one in vitro active antibiotic within 48 h of infection onset. Early ceftazidime–avibactam therapy was defined as ceftazidime–avibactam initiated within 48 h of infection onset. Ceftazidime–avibactam combination therapy was the receipt of a concomitant antibiotic with Gram-negative activity for ≥ 48 h.

The primary outcome was 30-day all-cause mortality, measured from infection onset. Data were collected for up to 30 days after discharge (i.e., from health system outpatient clinics, rehabilitation centers, emergency departments, and hospital re-admissions, where available), and patients discharged before day 30 were assumed to have survived if death was not documented during this follow-up. The ICS, PBS, and qPitt were calculated for each patient using the worst physiological values recorded within 24 h of infection onset. The variables included in the ICS were severe sepsis/septic shock [12], PBS ≥ 6, Charlson comorbidity score ≥ 2, and non-biliary or non-urinary tract source of infection [6]. Scores range from 0 to 15 and patients with an ICS < 8 and ≥ 8 have been considered to be at low and high risk for mortality, respectively [4, 6]. The PBS is based on five variables: temperature, blood pressure, mechanical ventilation, cardiac arrest, and mental status [13]. The maximum PBS score is 14, with scores ≥ 4 generally considered to indicate increased risk of death [7, 13]. qPitt includes the same five variables as the PBS, but temperature and mental status are dichotomized rather than graded [14]. The qPitt ranges from 0 to 5, with scores ≥ 2 indicating increased mortality risk in previous studies [7, 14]. No patient in our cohort experienced cardiac arrest around infection onset, and therefore this variable was not included in the scores.

Statistical Analyses

Descriptive statistics were used to characterize the cohort. Continuous variables were reported as medians (interquartile ranges, IQR) whereas categorical variables were expressed as counts and percentages. Unadjusted comparisons were performed using Chi squared, Fisher's exact or Mann–Whitney *U* tests, as appropriate.

Scoring system performance was assessed by determining discrimination, calibration and precision. Discrimination in this setting refers to the ability to correctly classify those who died and those who survived. It was evaluated by calculating the area under to receiver operating characteristic curve (AUC). An AUC of 1.0 indicates perfect discrimination while a value 0.5 indicates no better than chance [15]. Although there are no universally agreed thresholds, values ≥ 0.90, ≥ 0.80 and ≥ 0.70 are generally considered to be excellent, good, and satisfactory, respectively [16, 17]. The non-parametric Delong–Delong test was used for pairwise AUC comparisons [18].

Calibration refers to agreement between observed and predicted mortality across deciles of risk, and was assessed using the Hosmer–Lemeshow goodness-of-fit test [19]. To account for the smaller sample size, and therefore reduced power to detect a lack of fit, a conservative P value < 0.10 was considered to indicate lack of fit [20].

Precision was measured by calculating the Brier score (mean squared difference between observed and predicted mortality). Brier scores can range from 0 for a perfect model to 0.25 for a non-informative model with an outcome incidence of 50% [16, 21].

The performance characteristics of each score as a binary classification tool were examined by calculating the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) at selected cut-points. The Youden Index J (J = sensitivity + specificity − 1 maximized) was chosen as the most appropriate summary measure. Modified Poisson regression analysis, using a robust error variance, was performed to estimate the relative risk (RR) and 95% confidence intervals for mortality at select cut-points.

The impact of early active antibiotic therapy, early ceftazidime–avibactam and combination therapy was evaluated by Poisson regression after adjustment for each score individually modeled as a continuous variable and as a categorical variable dichotomized at the score corresponding to the maximum J.

Analyses were performed using SAS 9.4 Statistical Software (SAS Institute, Cary, NC, USA) and SPSS, v.24 (IBM, Armonk, NY, USA). Unless otherwise stated, a two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

A total of 109 patients were included. The median age was 63 (53–74) years and 34.9% were admitted from a skilled nursing facility or long-term acute care hospital (Table 1). Over half (54.1%) of patients were in the intensive care unit (ICU) at infection onset and 16.5% were admitted during the remainder of their admission. The most common infection sources were respiratory (34.9%), intra-abdominal (21.1%) and urinary (20.2%). Nine (8.3%) patients had a positive CRE blood culture. A total of 113 CRE strains were isolated. *Klebsiella pneumoniae* was the most commonly identified pathogen, isolated in 71 (65.1%) patients followed by *Escherichia coli* in 16 (14.7%) and *Enterobacter* spp. in 12 (11.0%). Regarding antimicrobial susceptibility, among *K. pneumoniae* isolates tested for ceftazidime-avibactam susceptibility ($n = 48$), two were resistant, including one that carried New Delhi metallo-beta-lactamase and OXA enzymes.

Table 1 Baseline patient and infection characteristics stratified by 30-day mortality

Characteristic	Overall $N = 109$, n (%) or median (IQR)	Survivors $N = 91$, n (%) or median (IQR)	Non-survivors $N = 18$, n (%) or median (IQR)
Age (years)	63 (53–74)	65 (52–74)	63 (61–73)
Body mass index (kg/m^2)	28 (22–34)	27 (22–33)	30 (23–39)
Obese (BMI $\geq$ 30 kg/m^2)	38 (34.9)	29 (31.9)	18 (50.0)
Male	58 (53.2)	50 (54.9)	8 (44.4)
Race			
African American	52 (47.7)	40 (44.0)	12 (66.7)
Caucasian	37 (33.9)	31 (34.1)	6 (33.3)
Latino	6 (5.5)	6 (6.6)	0
Asian	2 (1.8)	2 (2.2)	0
Other	12 (11.0)	12 (13.2)	0
Admission from a skilled nursing facility/long-term acute care hospital	38 (34.9)	29 (31.9)	9 (50.0)
Comorbidities			
Heart failure	20 (18.3)	17 (18.7)	3 (16.7)
Diabetes mellitus	44 (40.4)	36 (39.6)	8 (44.4)
Chronic respiratory disease[a]	40 (36.7)	28 (30.8)	12 (66.7)**
End-stage renal disease on dialysis	15 (13.8)	12 (13.2)	3 (16.7)
Liver disease	14 (12.8)	12 (13.2)	2 (11.1)
Cancer	19 (17.4)	15 (16.5)	4 (22.2)
Charlson comorbidity index	4 (2–7)	4 (2–7)	6 (3–7)
Hospital-acquired infection	67 (61.5)	54 (59.3)	13 (72.2)
Intensive care unit at infection onset	59 (54.1)	44 (48.4)	15 (83.3)**
Mechanical ventilation at infection onset	35 (32.1)	25 (27.5)	10 (55.6)**
Severe sepsis/septic shock at infection onset	67 (61.5)	52 (57.1)	15 (83.3)**
Positive blood cultures	9 (8.3)	6 (6.6)	3 (16.7)
Infection source			
Respiratory tract	38 (34.9)	29 (31.9)	9 (50.0)
Intra-abdominal	23 (21.1)	21 (23.1)	2 (11.1)
Urinary tract	22 (20.2)	21 (23.1)	1 (5.6)
Skin and soft tissue	7 (6.4)	6 (6.6)	1 (5.6)
Osteoarticular	7 (6.4)	6 (6.6)	1 (5.6)
Primary bacteremia	7 (6.4)	4 (4.4)	3 (16.7)
Other	5 (4.6)	4 (4.4)	1 (5.6)

Table 1 continued

Characteristic	Overall $N = 109$, n (%) or median (IQR)	Survivors $N = 91$, n (%) or median (IQR)	Non-survivors $N = 18$, n (%) or median (IQR)
Microbiology			
Klebsiella pneumoniae	71 (65.1)	59 (64.8)	12 (66.7)
Escherichia coli	16 (14.7)	15 (16.7)	1 (5.6)
Enterobacter spp.	12 (11.0)	9 (9.9)	3 (16.7)
K. oxytoca	5 (4.6)	3 (3.3)	2 (11.1)
Citrobacter spp.	4 (3.7)	4 (4.4)	0
Serratia marcescens	4 (3.7)	4 (4.4)	0
Proteus mirabilis	1	0	1 (5.6)
Treatment			
Ceftazidime–avibactam renal adjusted dose	52 (47.7)	39 (42.9)	13 (72.2)**
Active antibiotic before ceftazidime–avibactam	25 (22.9)	22 (24.2)	3 (16.7)
Hours to active antibiotic[b]	72 (34–103)	74 (43–103)	55 (25–105)
Active antibiotic therapy within 48 hours[b]	32 (29.4)	25 (27.5)	7 (38.9)
Hours to ceftazidime–avibactam[b]	94 (54–145)	95 (55–145)	73 (33–154)
Ceftazidime–avibactam duration (days)	13 (6–17)	13 (7–18)	8 (4–15)
Ceftazidime–avibactam combination antibiotic therapy	44 (40.4)	36 (39.6)	8 (44.4)
Aminoglycoside	11 (10.1)	9 (9.9)	2 (11.1)
Polymyxin	10 (9.2)	7 (7.7)	3 (16.7)
Tigecycline	10 (9.2)	9 (9.9)	1 (5.6)
Risk scores			
ICS	8 (6–11)	8 (6–11)	11 (8–15)**
PBS	2 (0–5)	2 (0–4)	5 (2–6)**
qPitt	1 (0–2)	1 (0–2)	2 (1–3)**
APACHE II	21 (15–29)	19 (13–24)	30 (21–32)**
SOFA	5 (3–8)	4 (2–7)	10 (7–12)**

APACHE Acute Physiology and Chronic Health Evaluation, *ICS* INCREMENT-CPE score, *PBS* Pitt bacteremia score, *SOFA* Sequential Organ Failure Assessment

**$P < 0.05$ survivors vs. non-survivors

[a] Chronic obstructive pulmonary disease, asthma, chronic ventilator dependence

[b] From index culture collection

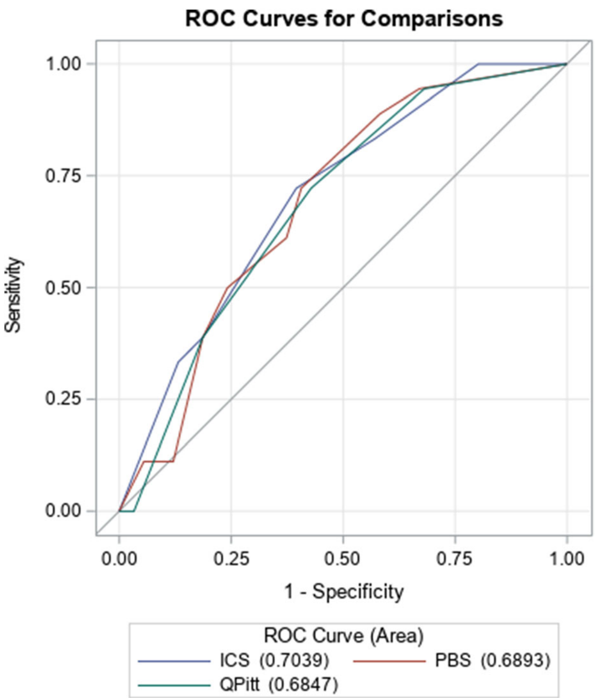

Fig. 1 Area under the curve (AUC) for 30-day mortality prediction

Overall, 30-day mortality was 16.5%, and was highest in patients with primary bacteremia (42.9%) or pneumonia (23.7%) and lowest in patients with urinary tract infection (4.5%). Chronic pulmonary disease was significantly more prevalent among patients who died compared to those who survived ($p = 0.004$). In addition, patients who died were significantly more likely to reside in the ICU, require mechanical ventilation, or have severe sepsis/septic shock at infection onset (Table 1). There were no associations between 30-day mortality and early active antibiotic therapy, early ceftazidime–avibactam, nor the use of combination therapy in univariate analyses. Patients who died were significantly more likely to have their ceftazidime–avibactam dose adjusted for decreased renal function (72.2% vs. 42.9% in non-survivors vs. survivors, respectively). The median ICS, PBS, and qPitt were significantly higher in patients who died compared to those who survived (Table 1).

Discrimination for 30-day mortality for the ICS, PBS, and qPitt was 0.704, 0.689, and 0.685, respectively (Fig. 1; Table 2). No significant differences in discrimination were found for all pairwise comparisons (Supplementary Appendix 2). All models showed adequate calibration for 30-day mortality according to the Hosmer–Lemeshow goodness-of-fit test (Table 2). Precision, as measured by the Brier score, ranged from 0.128 for the ICS score to 0.132 for the qPitt score for 30-day mortality.

The performance characteristics of the ICS, PBS, and qPitt as binary classification tools for 30-day mortality at selected cut-points are summarized in Table 3. Using an ICS cutoff ≥ 11 to indicate high mortality risk provided the best performance with a sensitivity, specificity, PPV, NPV, PLR, and NLR of 72.2%, 60.4%, 26.5%, 91.7%, 1.82, and 0.46, respectively. ICS ≥ 11 was significantly associated with 30-day mortality (RR 3.184, 95% CI 1.35–8.930). The post-test probability of mortality increases from 16.5% to 26.5% and decreases from 16.5% to 8.2% among patients with ICS ≥ 11 and < 11, respectively. The optimal cutoff scores to indicate high 30-day mortality risk for the PBS and qPitt were ≥ 3 and ≥ 2, respectively. The RR of mortality was 3.068 (95% CI 1.094–8.606) and 2.850 (95% CI 1.016–7.994) for patients with PBS ≥ 3 and qPitt ≥ 2, respectively. RRs and 95% CIs for the individual components of each score are shown in Supplementary Appendix 3. Although the

Table 2 Risk score discrimination, calibration, and precision for 30-day mortality

Score	Discrimination *C* statistic (95% CI)	Calibration Hosmer–Lemeshow *P* value	Precision Brier score
INCREMENT-CPE	0.7039 (0.5848–0.8230)	0.771	0.128
Pitt bacteremia	0.6893 (0.5709–0.8076)	0.238	0.131
QPitt score	0.6847 (0.5671–0.8023)	0.599	0.132

Table 3 Risk score performance characteristics for 30-day mortality at selected cut-points

	Patients, *n* (%)	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**PLR**	**NLR**	**AUC (95% CI)**
INCREMENT-CPE								
ICS ≥ 3	106 (97.2)	100.0	3.3	17.0	100.0	1.03	0	0.516 (0.373–0.660)
ICS ≥ 6	91 (83.5)	100.0	19.8	19.8	100.0	1.25	0	0.599 (0.472–0.726)
ICS ≥ 8	67 (61.5)	83.3	42.9	22.4	92.9	1.46	0.39	0.631 (0.501–0.761)
ICS ≥ 11[a]	49 (45.0)	72.2	60.4	26.5	91.7	1.82	0.46	0.663 (0.529–0.798)
ICS ≥ 12	24 (22.0)	38.8	81.3	29.2	87.1	2.07	0.75	0.601 (0.449–0.753)
ICS ≥ 15	18 (16.5)	33.3	86.8	33.3	86.8	2.52	0.77	0.601 (0.447–0.755)
Pitt bacteremia score								
PBS ≥ 1	78	94.4	33.0	21.8	96.8	1.41	0.17	0.637 (0.514–0.760)
PBS ≥ 2	69	88.8	41.8	23.2	95.0	1.53	0.27	0.653 (0.529–0.777)
PBS ≥ 3[a]	50	72.2	59.3	26.0	91.5	1.77	0.47	0.658 (0.523–0.793)
PBS ≥ 4	45	61.1	62.6	24.4	89.0	1.63	0.62	0.619 (0.476–0.762)
PBS ≥ 5	31	50.0	75.8	29.0	88.5	2.07	0.66	0.629 (0.481–0.777)
PBS ≥ 6	24	38.9	81.3	29.2	87.1	2.08	0.75	0.601 (0.449–0.753)
PBS ≥ 7	13	11.1	87.9	15.3	83.3	0.92	1.01	0.505 (0.359–0.651)
PBS ≥ 8	7	11.1	94.5	28.6	84.3	2.02	0.94	0.528 (0.377–0.679)
qPitt score								
qPitt ≥ 1	79 (72.5)	94.4	31.9	21.5	96.7	1.39	0.18	0.632 (0.508–0.755)
qPitt ≥ 2[a]	52 (47.7)	72.2	57.1	25.0	91.2	1.68	0.49	0.647 (0.511–0.782)
qPitt ≥ 3	24 (22.0)	38.9	81.3	29.2	87.1	2.08	0.75	0.601 (0.449–0.753)

AUC area under the receiver operator characteristic curve, *CI* confidence interval, *NLR* negative likelihood ratio, *NPV* negative predictive value, *PLR* positive likelihood ratio, *PPV* positive predictive value

[a] J (sensitivity + specificity − 1 is maximized)

confidence intervals were wide, all components of the ICS had RRs > 2. With regard to the components of the PBS and qPitt, altered mental status and respiratory failure/mechanical ventilation consistently had RRs > 2, while the association between temperature and mortality was variable. Survival curves for the dichotomized ICS, PBS, and qPitt are shown in Fig. 2a–c. Early and sustained separation between curves was seen for all scores, and the log rank tests were significant for ICS ≥ 11 and PBS ≥ 3 ($p = 0.0315$ and $p = 0.0242$, respectively) but not qPitt ≥ 2 ($p = 0.0521$).

No significant associations between 30-day mortality and early active, early ceftazidime–avibactam, combination ceftazidime–avibactam therapy nor ceftazidime–avibactam renal dose adjustment were found after controlling for each risk score (data not shown).

DISCUSSION

We conducted a retrospective, multicenter study evaluating the predictive performance of

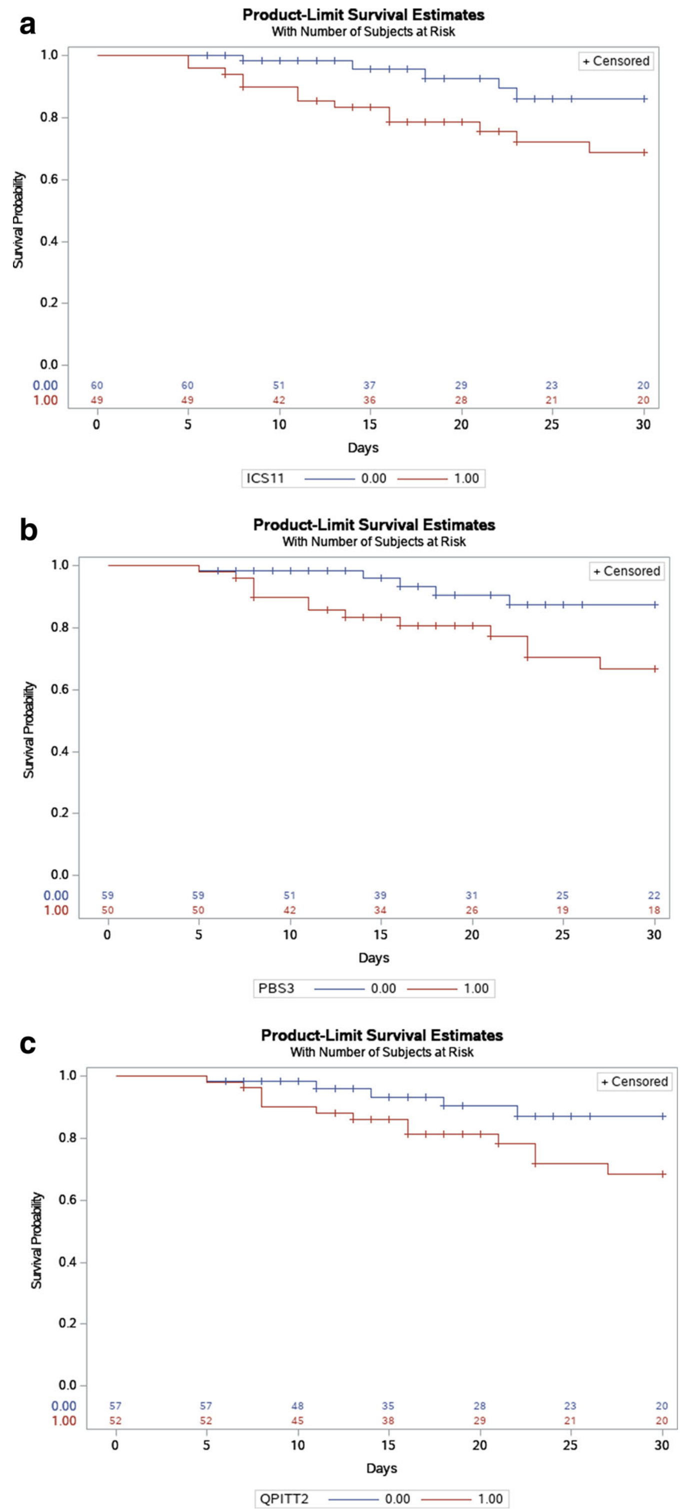

Fig. 2 Survival curves for **a** INCREMENT-CPE ≥ 11 vs. < 11, **b** Pitt Bacteremia score ≥ 3 vs < 3 and **c** qPitt ≥ 2 vs. < 2. ICS log-rank $p = 0.0315$. PBS log rank $p = 0.0242$. qPitt log rank $p = 0.0521$. *ICS* INCREMENT-CPE score, *PBS*: Pitt Bacteremia score

the ICS, PBS, and qPitt for mortality in patients with CRE infections treated with ceftazidime–avibactam. Overall, the scoring systems demonstrated adequate calibration and precision in our cohort. According to conventional thresholds to categorize score discrimination [16, 17], the ICS demonstrated satisfactory discrimination while the PBS and qPitt had poor discrimination. However, differences between scores were very small and not statistically significant.

RCTs to help guide treatment selection for patients with CRE infections are scarce. Most available clinical studies are observational and retrospective with important limitations, including selection bias and inadequate control for confounding. Risk scores are useful for confounding adjustment when analyzing observational data. However, they may perform less well in external cohorts, and, although a model may be successful at one point in time, antimicrobial resistance patterns, pathogen virulence, and standards of care change with time and therefore models must be updated. Our findings do not fully align with those of Henderson et al., who evaluated the performance of the PBS and qPitt for 14-day mortality in 475 patients with non-bacteremic and bacteremic CRE infections from the CRACKLE-1 database [7]. In their evaluation, the discriminatory ability of the PBS and qPitt was considerably higher than in our cohort (0.853 and 0.851, respectively). With regard to the ICS, which was recently validated in 42 patients with non-bacteremic and bacteremic *K. pneumoniae* carbapenemase-producing *K. pneumoniae* infections, 30-day mortality was substantially higher than in our cohort (57.1% vs. 16.5%), but discrimination was similar (AUC 0.78 vs. 0.70). The optimal cut-point to identify patients at high risk for 30-day mortality was 11 in our cohort versus 8 in the validation study by Cano et al. [6].

Several factors may account for these discrepancies. First, there are important differences between the cohorts with regard to infection source (less bacteremia and more respiratory in our cohort) and pathogen species (more diverse in this study vs. primarily *K. pneumoniae* in the other studies). It is notable, however, that Henderson et al. found the performance of the PBS and qPitt to be similar when analyses were restricted to the subgroup of patients with non-bacteremic CRE infections [7]. Furthermore, an important property of the most useful scoring systems is that they perform similarly across different target populations. Second, patients who died within 72 h of infection onset were excluded from our study (patients had to receive ≥ 72 h of ceftazidime–avibactam), and variables such as severe sepsis/septic shock may best predict very early versus later deaths. However, observational studies evaluating antibiotic alternatives typically have inclusion criteria based on receipt of ≥ 48–72 h of the antibiotics of interest [9, 22, 23]. Prediction scores that discriminate for later deaths may be more suited for adjustment in these studies. The ICS was developed and validated specifically in patients with CPE infections. We did not confirm carbapenemase production, and a proportion of patients were likely infected with non-carbapenemase-producing CRE which have been shown to confer a lower risk of poor outcomes compared to CPE [24]. However, as was the case in our study, these data are not always available for observational analyses.

As noted previously, the validation studies for the ICS, PBS, and qPitt were conducted largely in the era before the introduction of newer antibiotics with activity against CRE [6, 7]. Two recent observational studies found improved survival in patients with CRE infection treated with ceftazidime–avibactam compared to historical controls treated with colistin-, aminoglycoside-, and carbapenem-based regimens [8, 9]. It is plausible that the use of ceftazidime–avibactam in all patients in our cohort may have partly contributed to the observed differences in score performance. However, it is important to remember that other changes have occurred in recent years that may have influenced the relationship between baseline variables and outcomes. Rapid genomic and phenotypic methods are now available to accelerate the identification of CRE [25]. A great deal of progress has also been made with regard to our understanding of key aspects of the complex pharmacokinetics of polymyxins enabling the design of dosing regimens more likely to achieve therapeutic concentrations [26]. Ten percent of patients in this study received a polymyxin with ceftazidime–avibactam. Furthermore, at most institutions, the use of new antibiotics must be approved by the antimicrobial stewardship team or infectious diseases consult service. All patients in our study were managed by the infectious diseases consult service. The value of specialist involvement in the management of multidrug-resistant infections is well established [27–31].

The PBS and qPitt scores are based on the important severity of illness-related variables, while the ICS also adds comorbidities and site of infection. None of the scores incorporate key treatment-related factors that could influence outcomes. We observed that mortality was significantly higher in patients who had their ceftazidime–avibactam dose renally adjusted. The association was no longer significant after adjustment based on the scores, raising the possibility that need for dose adjustment may be a surrogate for other prognostic variables. Renal impairment and the need for renal replacement therapy have been identified by other investigators as risk factors for poor outcomes in patients treated with ceftazidime–avibactam [32–34] Antibiotic blood and tissue concentrations as well as minimum inhibitory concentrations may impact patient response, and inclusion in prognostic modeling could improve predictive performance at the expense of model simplicity. Conversely, it may be worthwhile to revisit and revise protocols pertaining to ceftazidime–avibactam renal dose adjustment criteria [35].

Our study has several important limitations. First, the study is subject to inherent bias with its retrospective, observational design. However, in-depth EMR reviews allowed us to obtain detailed patient level data that may not be available in validation studies that obtain data from large healthcare administrative databases. Second, although our data spanned 4 years and we enrolled patients from six medical centers, the number of patients included was relatively small owing to the infrequency of CRE infections and slow incorporation of new antibiotics into clinical practice. Our event rate was also low, which may partly explain the variable performance of the models. We calculated the scores using the worst physiological measurements within 24 h of culture collection as a proxy for infection onset. However, for patients with community-onset infections as well as those with chronic relapsing infections, the time-frame used may not have reflected the true infection onset. We included only patients treated with ceftazidime–avibactam. Evaluations of scoring system performance in patients treated with other novel agents would be valuable.

CONCLUSION

There is an ongoing trend in infectious diseases toward algorithmic approaches for risk stratification and treatment. With respect to clinical use, the ICS, PBS, and qPitt all have the advantages of being based on readily available variables and being simple to calculate compared to the more time-intensive APACHE II or SOFA scores. However, none performed well enough in our cohort to be used for clinical decision-making in individual patients. Updating the scores to more accurately predict outcomes in the era of novel antibiotics, rapid diagnostics, and infectious diseases specialist involvement would be worthwhile, not only to improve their utility as tools in observational research but also so that clinicians can use them as supplementary information when making appropriate decisions about the management of patients with CRE infections.

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