ORIGINAL ARTICLE

The Novel "RISC" Score as a Risk-prediction Model of Carbapenem-resistant Hospital-acquired Infections in Adult Sepsis Patients – A Prospective Observational Study

Abhilash B Mareguddi[1], Souvik Chaudhuri[2], Sagar M Shanmukhappa[3], Vishwas Parampalli[4], Margiben T Bhatt[5], Roshan Fernandes[6], Shwethapriya Rao[7], Poornima S Birajdar[8]

Received on: 18 January 2025; *Accepted on:* 12 March 2025; *Published on:* 31 March 2025

Abstract

Aim and background: Antimicrobial sensitivity (AMS) reports are often available after 72 hours of identification of gram-negative (GN) hospital-acquired infection (HAI). Prediction of carbapenem-resistant infection (CRI) among GN strains is important even before AMS reports are available, for judicious use of empirical antibiotics. We aimed to study the predictors of CRI in patients with HAI.

Materials and methods: We conducted a single-center prospective observational study between April 2023 and September 2024 on patients of GN sepsis with HAI. The use of empirical carbapenem antibiotics, organ dysfunction scores, the modified nutritional risk in critically ill (mNUTRIC) score, blood-count-derived inflammation indices, type of HAI, AMS reports, and in-hospital mortality were noted.

Results: A total of 935 sepsis patients with HAI were screened, and there were 195 patients with GN infection. Among the 195 patients, 145 (74.4%) had CRI and 50 (25.6%) had non-CRI. Multivariable logistic regression revealed that the length of intensive care unit (ICU) stay before the day of HAI ($p = 0.009$, adjusted odds ratio (OR) 1.155, 95% confidence interval (CI) 1.037–1.286), presence of ventilator-associated pneumonia (VAP) (p-value < 0.001, adjusted OR 4.170, 95% CI: 1.858–9.361), empirical carbapenem antibiotics before the day of HAI (p-value = 0.004, adjusted OR 3.164, 95% CI: 1.439–6.957), and septic shock on the day of HAI (p-value 0.012, adjusted OR 4.162, 95% CI: 1.366–12.677) were the independent risk factors of CRI.

Conclusion: In GN sepsis patients with HAI, respiratory infection (VAP), length of ICU stay prior to HAI, septic shock, and empirical carbapenem antibiotic administration are risk factors of CRI.

Keywords: Carbapenem-resistant infection, Gram-negative sepsis, Hospital-acquired infection, Predictors.

Indian Journal of Critical Care Medicine (2025): 10.5005/jp-journals-10071-24953

Highlights

We devised the "RISC" score for the risk of carbapenem-resistant infection (CRI) among patients with hospital-acquired infection (HAI) with gram-negative (GN) sepsis, for judicious use of empirical carbapenem antibiotics when antimicrobial sensitivity (AMS) reports are awaited. Ventilator-associated pneumonia, intensive care unit stay ≥ 3 days before HAI, septic shock, and empirical carbapenems are predictors of CRI.

Introduction

Patients with HAI have a four-fold risk of mortality as compared with those without it.[1] The HAI is associated with high multidrug-resistant (MDR) infection rates.[2] The prevalence of HAI in the Indian intensive care units (ICUs) is about 25% and is a major cause of mortality.[3] Carbapenem-resistant infection (CRI) is one of the most important causes of MDR infections.[4,5] Since CRI is associated with higher mortality, an early prediction and optimal empirical antimicrobial therapy are quintessential.[6] A delay or inappropriate empirical antibiotics leads to an increase in mortality by up to three times.[7,8] Selecting the correct empirical antibiotic therapy for GN sepsis due to HAI, when AMS is unavailable is challenging. Even an hour of delayed incubation decreases the accurate detection of microorganisms in the culture.[9,10] Antimicrobial sensitivity reports are often available after 72 hours, and even in developed nations, only 20% of microbiological laboratories have the manpower to ensure round-the-clock operations.[11] Thus, even though clinicians are aware of microbiologically proven GN

[1–7]Department of Critical Care Medicine, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India

[8]Department of Anesthesiology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India

Corresponding Author: Shwethapriya Rao, Department of Critical Care Medicine, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India, Phone: +91 9964668404, e-mail: shwethapriya.rao@manipal.edu

How to cite this article: Mareguddi AB, Chaudhuri S, Shanmukhappa SM, Parampalli V, Bhatt MT, Fernandes R, *et al*. The Novel "RISC" Score as a Risk-prediction Model of Carbapenem-resistant Hospital-acquired Infections in Adult Sepsis Patients – A Prospective Observational Study. Indian J Crit Care Med 2025;29(4):352–362.

Source of support: Nil

Conflict of interest: None

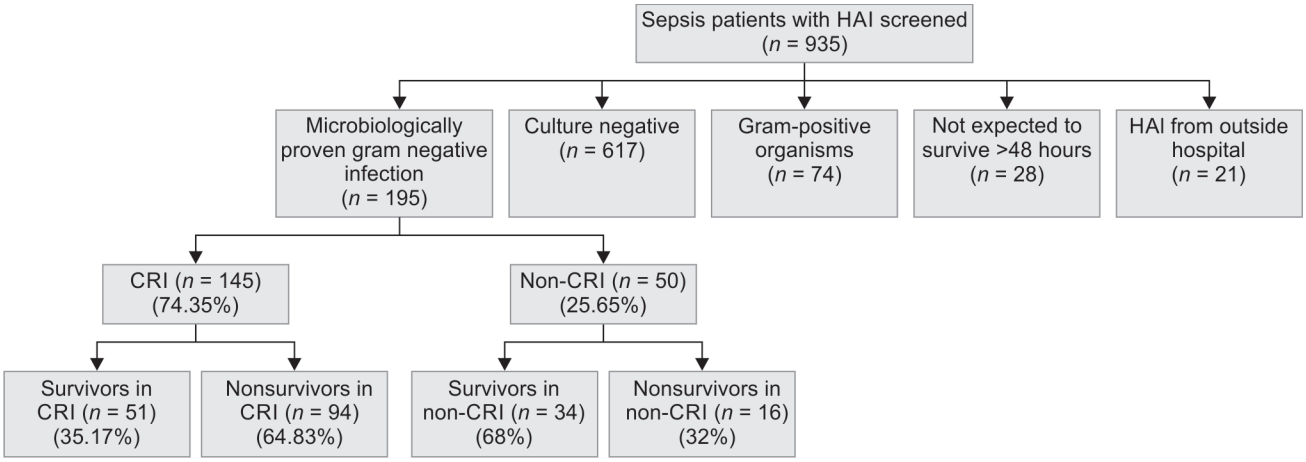

Fig. 1: Flowchart depicting the recruitment of HAI patients

sepsis, the AMS report is often unavailable initially. While awaiting AMS reports, appropriate empirical antimicrobial therapy must be initiated in patients with GN sepsis, with carbapenem use only when indicated. The CarbaSCORE was devised to predict the requirement of carbapenem therapy in bloodstream infections and pneumonia.[12] A score to predict CRI in sepsis has been reported; however, the study had predominantly nonfermenting GN bacteria (GNB), and may not be applicable in an Indian setting where the burden of fermenting GNB like *Klebsiella pneumoniae* is high.[13,14]

- **Aim** – To develop a model for predicting CRI among GN sepsis patients due to HAI before AMS reports are available.
- **Primary objective** – To determine the predictors of CRI in patients with HAI due to GNB.
- **Secondary objective** – To determine the predictors of mortality among patients with of HAI with CRI.
- **Primary outcome** – CRI among patients with HAI due to GNB.
- **Secondary outcome** – In-hospital mortality in CRI patients due to HAI.

Materials and Methods

Study Design and Setting

A single-center prospective observational study at a tertiary medical college hospital was conducted between April 2023 and September 2024.

Sample Size

The sample size was 195 based on the expected 75% sensitivity of the new prediction model to predict CRI, specificity of 70%, prevalence of CRI in our hospital of about 45%, precision of 10%, 95% confidence level, with a dropout rate of 15%. The sensitivity of 75% and specificity of 70% were based on a previous study where a risk prediction model to differentiate GN bacteremia from gram-positive bacteremia was investigated.[15]

Sample size $N = [Z\ (1 - \alpha/2)^2 \times \text{sensitivity} \times (1 - \text{sensitivity})]/d^2 \times \text{prevalence}$

Where, $Z = 1.96$ for 95% CI: and d = precision.

Study Population

Inclusion Criteria

All adult patients admitted to ICU with GNB sepsis due to HAI.

Exclusion Criteria

- Patients with Gram-positive bacterial or other nonbacterial infections.
- Pregnant patients.
- Patients are not expected to survive more than 48 hours.
- Patients with HAI from another hospital.

Operational Definitions

- **Hospital-acquired infection** – An infection developing > 48 hours after hospitalization.[1] HAI was classified as hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), central line-associated bloodstream infections (CLABSI), and catheter-associated urinary tract infections (CAUTI).[1]
- **Day of HAI** – The first day of sending the cultures in HAI patients to the microbiology laboratory for AMS.
- **MDR bacteria** – Resistance to at least one antimicrobial drug in three or more different categories of antimicrobial agents.[5]
- **Carbapenem-resistant infection** – Infection with bacteria resistant to one or more carbapenem antibiotics.[16]

Methodology

Patients were screened for sepsis due to HAI for the inclusion and exclusion criteria (Fig. 1). Written informed consent was obtained from the legally acceptable representatives of the patients before recruitment. The methodology is outlined in Figure 2. The HAI was classified as HAP, VAP, CLABSI, or CAUTI. Demographic details, comorbidities, reasons for ICU admission, acute physiology and chronic health evaluation (APACHE II), and sequential organ failure assessment (SOFA) scores were recorded on the day of ICU admission, along with the modified nutritional risk in critically ill (mNUTRIC) score.

The presence of chronic kidney disease on dialysis stage 5-D (CKD-5D), in-hospital cardiac arrest before the day of HAI, prior empirical antibiotic use and carbapenem use before the day of HAI, and immunocompromised status (history of organ transplant, chemotherapy, or radiotherapy for malignancy, prednisolone >10 mg/day or equivalent and 700 mg cumulative dose) were

noted.[17] Needs for invasive mechanical ventilation (IMV) before the day of HAI, corticosteroids administered before the day of HAI, septic shock and renal replacement therapy (RRT) on the day of HAI were also documented. The complete blood picture, serum electrolytes, renal function tests, liver function tests, arterial blood gas reports, C-reactive protein (CRP), procalcitonin, urea/albumin ratio, and CRP/albumin ratios were noted on the day of HAI. The microbiological reports of GNB and the AMS reports were recorded. The serum levels of albumin, CRP, arterial blood lactate, and CRP/albumin ratio on the third day of HAI were noted. The need for re-admission to the ICU within 72 hours of discharge, and hospital mortality outcomes were also followed up. As AMS takes up to 72 hours, we followed up the investigations that indicate inflammation up to 72 hours, to determine if they can indicate the presence of CRI when the AMS were unavailable to clinicians.[15]

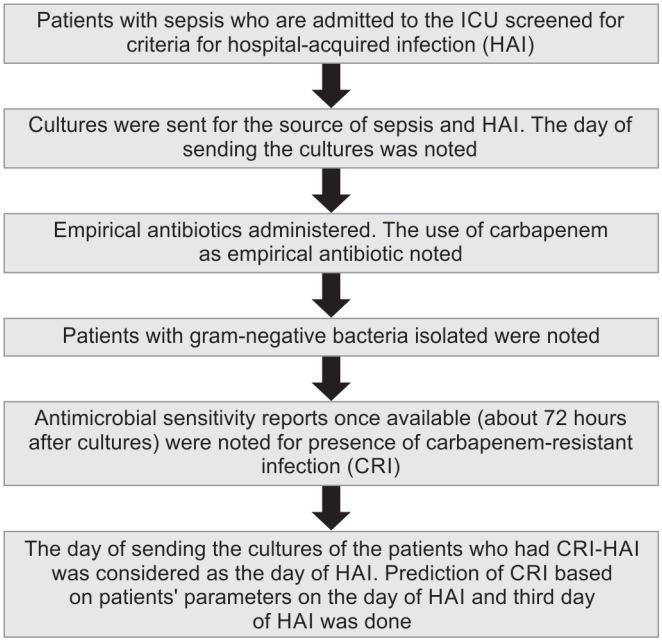

Fig. 2: The methodology followed to identify HAI due to CRI

Statistical Analysis

The statistical analysis was done using the software IBM Statistical Package for Social Sciences (SPSS), version 28.0.1.1(15) (IBM Corp., Armonk, NY). The categorical variables were expressed as percentages. For continuous variables, the normality of distribution was evaluated with the Shapiro–Wilk test or Kolmogorov–Smirnov test. Mean and standard deviation (SD) were used for variables with parametric distribution, whereas median and interquartile range were used for nonparametric distribution. Continuous variables with parametric distribution were compared using the independent Student *t*-test, and the Mann–Whitney *U*-test was used for nonparametrically distributed variables. Pearson's Chi-square test was used for the test of association.

The univariate analysis and multivariable logistic regression were done for the prediction of CRI with the significant categorical variables and continuous variables incorporating multicollinearity. A p-value < 0.05 was considered for all tests except for the univariate analysis, where a p-value < 0.2 was considered for incorporating variables in logistic regression. The adjusted odds ratio (OR) and 95% confidence interval (95% CI) were determined.

Based on the adjusted OR of the independent variables to predict the CRI, a scoring system was developed, and the points allocated to each of the independent predictors of CRI were the values of the adjusted OR in the multivariable logistic regression model. Bootstrap logistic regression was done with 1,000 samples using a bias-corrected accelerated method for internal validation.

For the independent continuous-variable predictors of CRI, the receiver operating characteristic (ROC) curve was plotted, and area under the curve (AUC), sensitivity and specificity, and p-value were determined.

Results

Out of 935 sepsis patients screened, there were 195 patients with GN infection (Fig. 1). Out of the 195 patients with GN infections, 145 (74.35%) patients had CRI and 50 (25.65%) had non-CRI (Fig. 1). The most common GN bacteria was *Acinetobacter baumannii* (AB) in 98 (50.3%) patients, followed by *Klebsiella pneumoniae* (Kp) in 64 (32.8%) and *Escherichia coli* (*E. coli*) in 18 (9.2%) patients (Table 1). The various parameters of the patients with GN HAI are shown in Table 2.

Table 1: Characteristics of patients with HAI and GNB isolated from cultures

Patient characteristics (N = 195)	*Frequency (%)*
Gender (male)	134 (68.7)
Predominant systemic complaints during ICU admission	Respiratory 88 (45.1)
	Neurological 46 (23.6)
	Cardiac 29 (14.9)
	Postoperative 25 (12.8)
	Abdominal 2 (1)
	Urological 1 (0.5)
	Others 4 (2)
Types of HAI	VAP 137 (70.3)
	CLABSI 47 (24.1)
	CAUTI 11 (5.6)
Patients with CKD 5D	13 (6.7)
Post cardiac-arrest survivors	13 (6.7)
Patients with history of hospitalization for more than 3 days in the last 6 months	67 (34.4)

(Contd...)

Table 1: *(Contd...)*

Patient characteristics (N = 195)	*Frequency (%)*
Patients with history of antibiotic use for more than 6 days in the last 6 months	57 (29.2)
Immunocompromised status	34 (17.4)
Patients with septic shock on the day of HAI	171 (87.7)
Patients on IMV before the day of HAI	180 (92.3)
Patients on RRT on the day of HAI	70 (35.9)
Empirical antibiotics administered before the day of HAI	Carbapenems 109 (55.9)
	Other beta lactams 63 (32.3)
	Tigecycline 10 (5.1)
	Ceftazidime–avibactum 7 (3.6)
	Others 4 (2.1)
	Colistin 2 (1)
Patients with central venous catheters before the day of HAI	175 (89.7)
Patients on corticosteroids before the day of HAI	37 (19)
Bacteria isolated among the patients	*Acinetobacter baumannii* 98 (50.3)
	Klebsiella pneumoniae 64 (32.8)
	Escherichia coli 18 (9.2)
	Pseudomonas aeruginosa 10 (5.1)
	Others 5 (2.6)
Patients with HAI due to GNB with microbiologically proven CRI	145 (74.4)
Patients with HAI due to GNB in-hospital mortality	110 (56.4)
Mortality among CRI patients	94/145 (64.8)
Mortality among non-CRI patients	16/50 (32)
Patients with HAI due to GNB with readmission to ICU within 72 hours	14 (7.2)

Table 2: The demographic characteristics, organ dysfunction scores, and laboratory parameters in the patient population with HAI and sepsis due to GNB (*N* = 195)

Variables	*Median (interquartile range)*
Patient characteristics	
Age (years)	60 (50–70)
CCI score on day of admission to ICU	4 (2–6)
SOFA score on day of admission to ICU	10 (8–12)
APACHE II score on day of admission to ICU	28 (22–32)
mNUTRIC score on day of admission to ICU	6 (5–7)
ICU days before HAI	6 (2–8)
Hospital days before HAI	8 (5–12)
Laboratory variables	
HbA1c	6 (5.5–7.2)
Hb (day of HAI) gm/dL	9.4 (8.2–11)
TLC (day of HAI) 10^3/µL	14.0 (8.9–20.7)
Platelet (day of HAI) 10^3/µL	192 (120–309)
Urea (day of HAI) mg/dL	61 (34–95)
Creatinine (day of HAI) mg/dL	1.26 (0.73–2.57)
Albumin (day of HAI) gm/dL	2.80 (2.45–3.40)
CRP (day of HAI) mg/L	144 (85–223)
Arterial lactate level (day of HAI) mg/dL	18 (12.46–28)
Procalcitonin (day of HAI) ng/mL	2.7 (0.75–12.80)
Albumin (third day of HAI) gm/dL	2.56 (2.2–3)
CRP (third day of HAI) mg/L	132 (84–211)
Arterial lactate level (third day of HAI) mg/dL	17.2 (12–26.4)
NLR (day of HAI)	10.6 (6.5–21.07)
PLR (day of HAI)	211 (112.18–440)
Urea/albumin ratio (day of HAI) (mg/gm)	26 (11.8–33.9)
CRP/albumin ratio (day of HAI) (mg/L/gm/dL)	58 (29.2–82.06)
CRP/albumin ratio (third day of HAI) (mg/L/gm/dL)	63 (30.9–87.5)

CCI, Charlson comorbidity index; HbA1c, glycated hemoglobin; Hb, hemoglobin; TLC, total leukocyte count; NLR; neutrophil–lymphocyte ratio; PLR; platelet-lymphocyte ratio

The comparison of the parameters between the patients with CRI and non-CRI is shown in Table 3. The days of ICU and hospital stay before HAI, SOFA score, APACHE II score, mNUTRIC score urea/albumin ratio, empirical carbapenem use, septic shock, IMV, RRT, and VAP incidence were significantly higher in CRI patients (Table 3).

Univariate analysis and multivariable logistic regression revealed that the length of ICU stay before the day of HAI ($p = 0.009$, adjusted OR 1.155, 95% CI: 1.037–1.286), presence of VAP (p-value < 0.001, adjusted OR 4.170, 95% CI: 1.858–9.361)], use of empirical carbapenem antibiotics before the HAI (p-value = 0.004, adjusted OR 3.164, 95% CI: 1.439 – 6.957), and septic shock on the day of HAI (p-value 0.012, adjusted OR 4.162, 95% CI: 1.366– 12.677) were the independent risk factors of CRI (Table 4). Using the adjusted OR of the independent variables to predict CRI in cases of GN sepsis with

Table 3: Comparison of the parameters among the patients of HAI with non-CRI vs CRI

Variable	*Patients with non-CRI infection (n = 50)*	*Patients with CR infection (n = 145)*	*p-value*
Age (years)	63 (44.75–71.00)	59 (51.50–69.00)	0.948
ICU days before HAI	3 (2–5.25)	5 (3–8)	**0.002***
Hospital days before HAI	7 (3–9)	8 (5–13)	**0.005***
CCI score	4 (1.75–6.00)	4 (2–6)	0.873
SOFA score	8.5 (6–11)	10 (8–12)	**0.002***
APACHE II score	24 (19.50–28.50)	28 (24–32)	**0.002***
mNUTRIC score	5.50 (4–7)	6 (5–8)	**0.015***
Laboratory variables			
HbA1c	6.10 (5.47–7.05)	6 (5.50–7.20)	0.985
Hb (day of HAI) (gm/dL)	10.35 (8.67–11.72)	9.1 (8.15–10.70)	**0.021***
TLC (day of HAI) (10^3/μL)	14.5 (10.82–21.37)	13.7 (8.65–20.65)	0.398
Platelet (day of HAI) (10^3/μL)	194 (123.0–311.25)	191 (114–312)	0.621
Urea (day of HAI) (mg/dL)	53 (32–86)	64 (35–106.50)	0.055
Creatinine (day of HAI) (mg/dL)	1.11 (0.68–1.89)	1.35 (0.74–2.84)	0.159
Albumin (day of HAI) (mg/dL)	3 (2.6–3.5)	2.80 (2.4–3.3)	0.137
CRP (day of HAI) (mg/L)	157 (100.75–248.65)	140 (80.99–213)	0.379
Arterial lactate level (day of HAI) (mg/dL)	20.50 (14.38–34.50)	16.90 (12.30–26.50)	0.063
Procalcitonin (day of HAI) (ng/mL)	2.97 (0.87–17.23)	2.70 (0.71–11.81)	0.553
Albumin (third day of HAI) (mg/dL)	2.75 (2.37–3.13)	2.5 (2.14–2.9)	**0.019***
CRP (third day of HAI) (mg/L)	132 (78.25–225.75)	132 (84–206.50)	0.850
Arterial lactate level (third day of HAI) (mg/dL)	16.45 (10.6–26.1)	17.20 (12–27.40)	0.872
NLR (day of HAI)	10.52 (6.82–19.04)	10.6 (6.42–21.47)	0.897
PLR (day of HAI)	204.61 (138.25–353.65)	216.04 (106.50–474.90)	0.998
Urea/albumin (day of HAI) mg/gm	18.9 (11.4–28.9)	23.6 (12.1–37.9)	**0.03***
CRP/albumin (day of HAI) (mg/L/gm/dL)	50.5 (33.8–93)	52.4 (27.8–82.03)	0.74
CRP/albumin (third day of HAI) (mg/L/gm/dL)	52.02 (32.4–88.9)	55.78 (30.4–88.4)	0.842
Variables regarding patient characteristics			
CKD-5D	3 (6%)	10 (6.89%)	0.827
Prior to in-hospital cardiac arrest	4 (8%)	9 (6.2%)	0.661
Prior hospitalization in 6 months	16 (32%)	51 (35.17%)	0.684
Prior antibiotic use before the day of HAI	17 (34%)	40 (27.6%)	0.390
Empirical carbapenem use before the day of HAI	19 (38%)	90 (62.06%)	**0.003****
Septic shock on the day of HAI	38 (76%)	133 (91.72%)	**0.004****
IMV before the day of HAI	42 (84%)	138 (95.18%)	**0.011****
RRT on the day of HAI	12 (24%)	58 (40%)	**0.042****
Corticosteroid use before day of HAI	8 (16%)	29 (20%)	0.534
Immunocompromised status	9 (18%)	25 (17.24%)	0.903
Respiratory tract infection (all VAP)	28 (56%)	109 (75.18%)	**0.011****

Values in bold indicate that *p*-values are significant; *Mann–Whitney *U*-test; **Pearson Chi-square test; CCI, Charlson comorbidity index; HbA1c, glycated hemoglobin; Hb, hemoglobin; NLR, neutrophil–lymphocyte ratio; PLR, platelet-lymphocyte ratio; TLC, total leukocyte count

HAI, the new "RISC" score was proposed. The points allocated were based on previous literature where a scoring system was developed to predict outcomes as:[18,19]

- If 1.0 < adjusted OR < 1.5, score = 1
- 1.5 < adjusted OR < 1.5, score = 2
- 2.5 < adjusted OR < 3.5, score = 3
- 3.5 < adjusted OR < 4.5, score = 4
- **R** – Respiratory infection (VAP) (4 points),
- **I** – ICU stay ≥3 days before the day of HAI (1 point) and
- **S** – Septic shock on the day of HAI (4 points)
- **C** – Carbapenem antibiotics used empirically before the day of HAI (3 points).

Out of the 145 patients who had CRI, 90 patients had received empirical carbapenem antibiotics before the day of HAI. The median duration of carbapenem antibiotics administration in those patients was 5 (3–6) days. Based on the ROC of the length of ICU stay before

Table 4: Univariate analysis and multivariable logistic regression to predict CRI among patients of HAI with GNB sepsis (n = 145)

	Univariate analysis			*Multivariate analysis*		
Variables	*p-value*	*Odds ratio*	*95% CI*	*p-value*	*Adjusted odds ratio*	*95% CI*
ICU days (before the day of HAI)	0.09	1.138	1.003–1.253	**0.009***	1.155	1.037–1.286
Respiratory infection (VAP) (on the day of HAI)	0.012	2.379	1.213–4.666	**<0.001***	4.170	1.858–9.361
Empirical carbapenem use (before the day of HAI)	0.004	2.670	1.377–5.177	**0.004***	3.164	1.439–6.957
RRT (on the day of HAI)	0.045	2.11	1.018–4.377	0.925	0.956	0.374–2.441
Septic shock (on the day of HAI)	0.005	3.500	1.455–8.418	**0.012***	4.162	1.366–12.677
mNUTRIC	0.027	1.206	1.021–1.424	0.400	1.100	0.882–1.372
Hb (day of HAI)	0.031	0.837	0.713–0.984	0.689	0.961	0.792–1.167
Albumin (third day of HAI)	0.019	0.496	0.276–0.892	0.154	0.580	0.274–1.228
Urea/albumin (day of HAI)	0.010	1.030	1.007–1.054	0.334	1.015	0.985–1.045

Values in bold indicate that the *p*-value is significant. The concept of multicollinearity was used for the variables to be entered in the regression model (SOFA score, APACHE II score, and mNUTRIC are related; ICU days before HAI and hospital days before HAI are related; need for IMV before the day of HAI and VAP are related). The overall percentage correct in the regression model is 82.1%, Hosmer and Lemeshow test 0.305, and Negelkerke *R* square 0.310

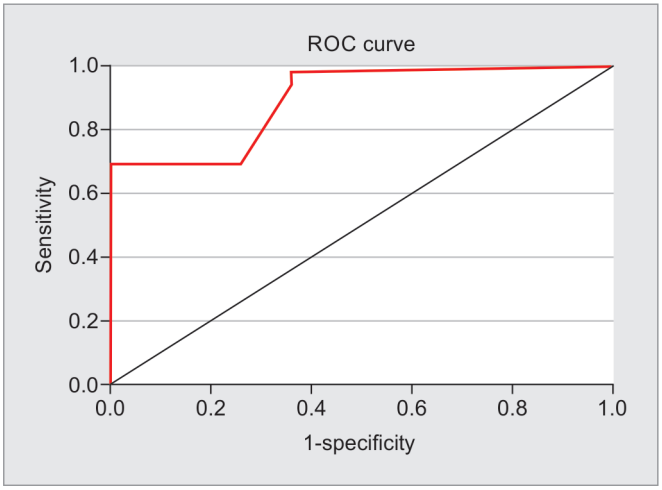

Fig. 3: The ROC curve depicting the AUC of the new "RISC" score to predict CRI among HAI patients with GN sepsis (diagonal segments are produced by ties). AUC 0.891, *p*-value < 0.001. 95% CI: (0.845–0.938), cut-off ≥8, sensitivity 93.1%, specificity 64%, diagnostic accuracy 85.64%, positive likelihood ratio 2.59, PPV 88.24%, and NPV 76.19%. AUC, area under curve; CI, confidence-interval; ICU, intensive-care unit; ROC, receiver operating characteristic; "RISC" score, Respiratory infection (VAP), length of stay in ICU ≥ 3 days before day of HAI, Septic shock, empirical carbapenem antibiotic use empirically

the day of HAI, the cut-off value of the number of ICU days before the day of HAI was ≥3 days (AUC 0.646, *p*-value < 0.002, 77% sensitivity, 48% specificity, 95% CI: 0.560–0.733) (Fig. 3).

The ROC of the RISC score to predict the CRI among patients of GN sepsis with HAI showed that AUC was 0.891, *p*-value < 0.001, 95% CI: 0.845–0.938 (Fig. 2), sensitivity 93.1%, specificity 64%, diagnostic accuracy 85.64%, positive likelihood ratio 2.59, PPV 88.24%, NPV 76.19%, and cut-off RISC score ≥ 8 (Fig. 2). The patients with a RISC score ≥8 were designated as having high RISC scores.

Bootstrap regression analysis showed that the factors in the "RISC" score were validated (Supplementary Table S1).

Among the 153 patients who had a high RISC score (≥8), 135 (88.2%) of the patients had CRI, whereas among the 42 patients with a low RISC score (<8), only 10 patients (23.8%) had CRI (p < 0.001, Pearson Chi-square test, Phi and Cramer's *V*-value = 0.607) (Table 5, Fig. 4).

Table 5: Association between high "RISC" score (≥8) and CRI

"RISC" score value	*CRI absent*	*CRI present*	*Total*	*p-value*
Low (≤/12)	32 (76.2%)	10 (23.8%)	42 (100%)	<0.001*
High (≥/12)	18 (11.8%)	135 (88.2%)	153 (100%)	
Total	50 (25.6%)	145 (74.4%)	195 (100%)	

"RISC" score, Respiratory infection (VAP), Length of stay in ICU ≥ 3 days before day of HAI, Septic shock, empirical Carbapenem antibiotic use; *Pearson Chi-square test, Phi, and Cramer's *V*-value = 0.607

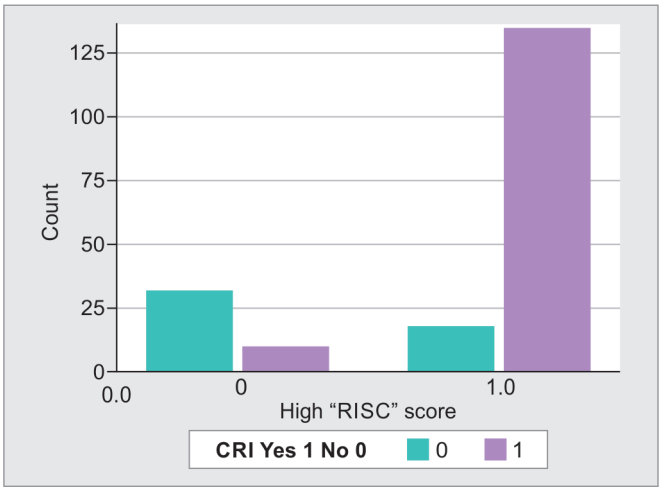

Fig. 4: Bar diagram depicting patients with high "RISC" score ≥8 and presence of CRI among the patients of HAI. Bar diagram depicting that among the 153 patients who had a high RISC score (≥8), 135 (88.2%) of the patients had CRI, whereas among the 42 patients with a low RISC score (<8), only 10 patients (23.8%) had CRI. The purple bar indicated CRI present and the green bar indicates CRI absent. "RISC" score, Respiratory infection (VAP), length of stay in ICU ≥ 3 days before day of HAI, Septic shock, empirical carbapenem antibiotic use empirically

The relationship map depicted that those patients with high RISC scores had a stronger strength of association with CRI, whereas those with low RISC scores had a stronger association with non-CRI (Fig. 5).

Among the patients with a high RISC score (≥8), 61.4% were nonsurvivors, whereas among the patients with a low RISC score (<8), there were 38.1% nonsurvivors (p-value = 0.007, Phi and Cramer's *V*-value = 0.607, Pearson Chi-square test).

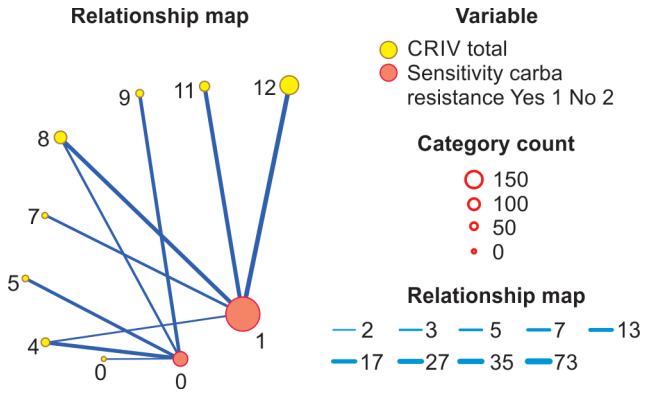

Fig. 5: The relationship map between the patients with CRI and "RISC" scores and non-CRI and RISC scores. The red circle labelled "1" indicates the presence of CRI and the red circle labelled "0" indicates the absence of CRI. The blue circles indicate the total RISC score values. The blue lines connecting the red circles with the blue circles indicate the strength of association between CRI and a high RISC score. This relationship map indicated that high RISC scores (8–12) are associated with CRI, whereas low RISC scores (0–7) are associated with an absence of CRI. "RISC" score, Respiratory infection (VAP), length of stay in ICU ≥3 days before day of HAI, Septic shock, empirical carbapenem antibiotic use empirically. The factors CRIV in the "RISC score" refers to empirical carbapenem use, respiratory infection, ICU stay >3 days and vasopressor use due to septic shock

In the patients with VAP (n = 137), CRI was present in 85.8% of patients with a high RISC score (≥8/12) and in none of the patients with a low RISC score (Pearson Chi-square test p-value < 0.001, Phi and Cramer's V = 0.554). Among the patients without VAP (n = 58), CRI was present in all the patients with a high RISC score (≥8/12) and in 31.3% of the patients with a low RISC score (Pearson Chi-square test p-value < 0.001, Phi and Cramer's V = 0.704). This was because all the non-VAP patients with CRI in our study had the presence of all three of the following – ICU stay ≥ 3 days before the day of HAI, septic shock on the day of HAI, and prior empirical carbapenem use. Univariate analysis of the RISC score to predict CRI among the non-VAP patients showed the following: p-value < 0.001, OR 5.811, 95% CI: 2.360–14.311, whereas among the VAP patients, the univariate analysis of the RISC score to predict CRI revealed a p-value < 0.001, OR 3.90, 95% CI: 2.376–6.401.

A comparison of the risk factors of mortality among patients with CRI is depicted in Table 6. Univariate and multivariable logistic regression to predict mortality in patients with Carbapenem-resistant infection showed that the presence of septic shock with vasopressor use on the day of HAI (p-value 0.019, adjusted OR 8.628, 95% CI: 1.423–52.323), the mNUTRIC score (p-value 0.009, adjusted OR 1.404, 95% CI: 1.008–1.813), procalcitonin level on the day of HAI (p-value 0.036, adjusted OR 1.031, 95% CI: 1.002–1.061), serum albumin on the third day of HAI (p-value 0.044, adjusted OR 0.339, 95% CI: 0.118–0.970), CRP on the third day of HAI (p-value 0.033, adjusted OR 1.007, 95% CI: 1.001–1.014), and arterial blood lactate

Table 6: Comparison of the variables between the survivors and nonsurvivors of patients with HAI patients having CRI (N = 145)

Variable	*Survivors in carbapenem-resistant group (n = 51)*	*Nonsurvivors in carbapenem-resistant group (n = 94)*	*p-value*
Age (years)	60 (50–69)	59 (52–69.25)	0.959
ICU days before HAI	4 (2–8)	6 (3–8)	0.210
Hospital days before HAI	7 (5–13)	9 (6–14)	0.222
CCI score	3 (1–6)	4 (2–6)	0.419
SOFA score	8 (6–10)	11 (10–13)	**<0.001***
APACHE II score	23 (17–28)	31 (28–35)	**<0.001***
mNUTRIC score	5 (4–6)	7 (6–8)	**<0.001***
Laboratory variables			
HbA1c	5.7 (5.1–6.6)	6.3 (5.6–7.95)	**0.002***
Hemoglobin (day of HAI) gm/dL	9.3 (8–10.8)	9 (8.2–10.32)	0.498
TLC (day of HAI) × 10^3/μL	12.7 (8.9–20.5)	16.15 (18.35–21.55)	0.406
Platelet (day of HAI) × 10^3/μL	182 (111–295)	194 (121–363)	0.533
Urea (day of HAI) (mg/dL)	56 (33–81)	72 (44.5–117)	**0.030***
Creatinine (day of HAI) (mg/dL)	1.18 (0.67–2.2)	1.51 (0.79–3.27)	0.138
Albumin (day of HAI) (gm/dL)	3 (2.57–3.4)	2.72 (2.34–3.22)	0.064
CRP (day of HAI) (mg/L)	144 (77–223)	139.4 (81.99–206)	0.716
Arterial lactate level (day of HAI) (mg/dL)	14.2 (11.7–26)	18.75 (12.56–27.10)	0.117
Procalcitonin (day of HAI) (ng/mL)	1.2 (0.5–6.7)	4.49 (1.15–19.68)	**0.001***
Albumin (third day of HAI) (mg/dL)	27 (2.4–3.03)	2.4 (2.1–2.8)	**0.001***
CRP (third day of HAI) (mg/L)	96 (59–156)	158 (99–236.25)	**<0.001***
Arterial lactate level (third day of HAI) (mg/dL)	12.8 (9.2–22)	19.3 (14.8–30.25)	**<0.001***
NLR (day of HAI)	10 (6.19–23.42)	10.7 (6.49–20.35)	0.885
PLR (day of HAI)	216 (103–407)	216.7 (106.87–488.72)	0.983
Urea/albumin (mg/gm) (day of HAI)	17.09 (10–31.2)	27.13 (14.75–43.41)	**0.008***
CRP/albumin (day of HAI) (mg/L/gm/dL)	49.36 (21.2–74.16)	55.07 (30.83–82.49)	0.250
CRP/albumin (day of HAI) (mg/L/gm/dL)	34.51 (19.09–65)	63.20 (35.99–109.26)	**<0.001***

(Contd...)

Table 6: *(Contd...)*

Variable	*Survivors in carbapenem-resistant group (n = 51)*	*Nonsurvivors in carbapenem-resistant group (n = 94)*	*p-value*
Variables regarding patient characteristics			
CKD-5D	5 (9.8%)	5 (5.3%)	0.309
Prior in-hospital cardiac arrest (before the day of HAI)	2 (3.9%)	7 (7.4%)	0.401
Prior hospitalization (before the day of HAI)	15 (29.4%)	36 (38.3%)	0.285
Prior antibiotic use (before the day of HAI)	12 (23.5%)	28 (29.8%)	0.421
Empirical carbapenem use (before the day of HAI)	34 (66.7%)	56 (59.6%)	0.401
Septic shock on the day of HAI	41 (80.4%)	92 (97.9%)	**<0.001****
Invasive mechanical ventilation (before the day of HAI)	47 (92.2%)	91 (96.8%)	0.212
RRT (on the day of HAI)	16 (31.4%)	42 (44.7%)	0.118
Corticosteroid use (before the day of HAI)	12 (23.5%)	17 (18.1%)	0.434
Immunocompromised status	9 (17.6%)	16 (17%)	0.924
Respiratory tract infection (VAP) (on the day of HAI)	42 (82.4%)	67 (71.3%)	0.140

The values in bold indicate that *p*-values are significant. *Mann–Whitney *U*-test; **Pearson Chi-square test. CCI, Charlson comorbidity index; HbA1c, glycated hemoglobin; Hb, hemoglobin; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; TLC, total leukocyte count;

Table 7: Univariate and multivariable logistic regression to predict mortality in patients with HAI with CRI (*n* = 94)

	Univariate analysis			*Multivariable analysis*		
Variables	*p-value*	*Odds ratio*	*95% CI*	*p-value*	*Adjusted odds ratio*	*95% CI*
Septic shock (on the day of HAI)	0.002	11.22	2.353–53.50	**0.019**	8.628	1.423–52.323
mNUTRIC	<0.001	1.629	1.306–2.033	**0.009**	1.404	1.088–1.813
HbA1c	0.004	1.483	1.138–1.931	0.058	1.389	0.989–1.949
Urea (the day of HAI)	0.063	1.007	1.000–1.015	0.880	0.998	0.967–1.029
Procalcitonin (the day of HAI)	0.059	1.028	0.999–1.058	**0.036**	1.031	1.002–1.061
Albumin (the third day of HAI)	0.002	0.345	0.174–0.684	**0.044**	0.339	0.118–0.970
CRP (the third day of HAI)	<0.001	1.008	1.004–1.013	**0.033**	1.007	1.001–1.014
Arterial lactate level (the third day of HAI)	0.008	1.047	1.012–1.084	**0.025***	1.048	1.006–1.092
Urea/albumin (the day of HAI)	0.046	1.020	1–1.040	0.935	1.003	0.929–1.084
CRP/albumin (the third day of HAI)	<0.001	1.022	1.011–1.033	0.129	0.988	0.973–1.003

The values in bold indicate that *p*-value is significant. HbA1c, glycated hemoglobin. Correct percentage for prediction using this model 80.7%, Hosmer and Lemeshow 0.656, and Nagelkerke *R* square 0.487

level on the third day after HAI (*p*-value 0.025, adjusted OR 1.048, 95% CI: 1.006–1.092) were the independent predictors of mortality in sepsis patients of HAI with CRI (Table 7).

The bootstrap analysis showed that vasopressors (*p*-value 0.007), mNUTRIC score (0.037), arterial blood lactate (third day after HAI, *p*-value 0.019), and albumin (third day after HAI, *p*-value 0.049) were found to be the independent predictors of mortality in CRI patients (Supplementary Table S2).

The ROC curve for the prediction of mortality in patients with CRI showed that the mNUTRIC score had the highest AUC (0.751), *p*-value < 0.001, cut-off ≥ 6, and 95% CI: 0.667–0.835, 82% sensitivity, and 60% specificity, 95% CI: 0.667-0.835 (Supplementary Fig. S1). The ROC curve of the arterial lactate level (third day of HAI) and serum albumin (third day of HAI) for the prediction of mortality in patients of HAI with CRI are depicted in Supplementary Figures S1 and S2.

Discussion

In this prospective study, we found that four variables were predictors of CRI among patients with GN sepsis having HAI – carbapenem use before the day of HAI (median of 5 days), respiratory infection (VAP), ≥3 days ICU stay before HAI, and the presence of septic shock on the day of HAI.

One of the main risk factors of CRI is the use of carbapenem antibiotics itself.[20,21] One of the mechanisms by which prior carbapenem use leads to CRI is due to selective antibiotic pressure, whereby the sensitive bacteria are killed and only the resistant bacteria remain and proliferate.[22] These bacteria may undergo genetic mutation and mobile genetic elements in them may be transferred to a sensitive bacteria, thus spreading resistance.[23–25] Due to the selective antibiotic pressure, GNB acquires the capability for incorporating new resistance mechanisms like the overexpression of multidrug efflux genes, beta-lactamases, and carbapenemases.[26] The prior use of carbapenem is a risk factor for resistant GN bacilli (RGNB).[27] Any receipt of carbapenem in the preceding 6 months was a risk factor for RGNB in a previous study.[27] In another study, the median days of carbapenem use was 8 days for developing MDR infection.[28] We found that the median days of empirical carbapenem administration were 5 days, and thus, a fewer number of days of carbapenem use does not reduce the risk of CRI.[28]

In literature, the length of ICU stay of 5 days was shown to be a risk factor for resistant GN infection.[27] This was similar to the findings in our study, where we found that ≥ 3 days of ICU stay was a risk factor for CRI. However, the results of our study differed from that of Sharma et al., where a median of 17 days of hospital

stay led to CRI.[29] Our results were also different from those of the findings in the study by Labaste et al., where although the authors found that the length of ICU stay was a risk factor for CRI, it was > 29 days, but the prevalence of CRI in the study was only 20.5%.[20] In our study, the prevalence of all types of CRI was significantly higher at 74.4% (145/195), though this data was among the patients with HAI. In a study from India, the prevalence of CRE causing only bacteremia was 45%.[30]

In a study in Brazil, however, it was shown that a stay in the emergency department for just >2 days leads to colonization with CR *Enterobacteriaceae*, and the odds of the risk of colonization was 5.85.[31] This was much higher than the odds of risk of CRI of 1.155 with ≥3 days of ICU stay in our study.

The highest risk of CRI in our study was the presence of VAP (OR 4.17) and the presence of septic shock (OR 4.16) in patients with HAI. The finding that respiratory infection is a risk factor for CRI was also found in a previous study, where intubation or mechanical ventilation was a risk factor (OR 1.59) for CRI.[32] *Acinetobacter baumannii* MDR infection due to VAP was the most common isolate (30.6%) in another Indian study, with 57% having early-onset VAP.[33]

The presence of septic shock as a risk factor for CRI was also found by Önal et al., and the association of septic shock with CRI has also been shown in another study.[34,35] The association between septic shock and CRI may be due to the exaggerated inflammatory response due to the CRI, impairment of host defense, and even immune paralysis.[36,37]

We found that AB constituted about half of the GN infections in our study, followed by Kp in 32.8%. Both AB and Kp constitute the leading cause of CRI among patients with HAI, depending on the specific hospital settings.[38–40] Literature also reveals that there is a very high prevalence of AB as a cause of CRI in the entire South-East Asian region.[40]

With respect to the cause of HAI in our study, we found that VAP was the predominant cause (70%). It was found to be the predominant cause of HAI in another Indian study also.[41] Among the HAI, VAP was 49%, followed by catheter-associated urinary tract infection (13%).[41] However, the incidence of VAP was much higher in our study, probably because we had 92% patients who were on invasive ventilation before the day of HAI in our study.

The RISC score performed well and was a reliable predictor of CRI in cases of GN HAI with VAP, as about 86% patients with the score ≥8 had CRI, whereas no patient with a RISC score <8 had CRI. However, in patients with nosocomial infections that are not due to VAP, though all the patients with RISC score ≥8 had CRI, nearly one-third of the patients who had the RISC score <8 also had CRI.

Thus, the RISC score is not sensitive enough to predict CRI in this group of nosocomial infections that are not due to VAP. The RISC score will not be reliable to make decisions regarding the empirical antibiotics cover for CRI in this group of non-VAP nosocomial infections.

Regarding the predictors of mortality in patients with CRI, it was shown that the presence of septic shock on the day of HAI, mNUTRIC score ≥6, arterial blood lactate level on the third day after HAI 13.3 mg/dL, and lower serum albumin level ≤ 2.2 gm/dL were the predictors. One of the significant findings in our study is that in patients with carbapenem-resistant HAI, the mNUTRIC score ≥6 is a reliable predictor of mortality, and had the highest AUC of 0.751 among the other predictors of mortality. The mNUTRIC has been shown in recent literature in a systematic review and meta-analysis (SRMA) in critically ill patients to be a predictor of mortality.[42] The SRMA had concluded that most studies had given a cut-off mNUTRIC score between 2 and 6 as a predictor of mortality among critically ill patients.[42] The factors of acute and chronic inflammation leading to immune dysfunction were conceptualized in the original NUTRIC score by Heyland et al., and this will be an important reason why we found that the mNUTRIC score is a suitable predictor in cases of CRI, where there is inflammation and possible impairment of host defenses.[36,37,43] The finding that low albumin level on the third day of HAI in patients with CRI is a risk factor for mortality may be explained by the fact that albumin has antioxidant properties, scavenges free radicals, and decreases platelet aggregation.[44] Hypoalbuminemia leads to an altered protein binding of antimicrobials, especially in sepsis patients, with an increased volume of distribution, causing suboptimal treatment.[45]

Strengths and Limitations

We determined the clinically relevant factors that can predict CRI before the AMS reports in HAI are available to clinicians. However, there were some limitations. The generalizability is questionable due to the single-center nature of the study. There are certain limitations of the RISC score. The RISC score was found to be reliable to predict CRI in nosocomial infections in patients with VAP; however, it was not sensitive to predict CRI in the patients with nosocomial infections that are not due to VAP. The study was not adequately powered to determine the factors predicting mortality in CRI patients. For the prediction of mortality in CRI patients, propensity score matching and therapeutic drug monitoring were not done.

Conclusion

In GN sepsis patients with HAI, the presence of VAP, ≥3 days of ICU stay before the day of HAI, septic shock, and empirical carbapenem use are predictors of CRI. Among patients with CRI, the mNUTRIC score, arterial blood lactate, serum albumin, and the presence of shock are predictors of mortality.

Ethics Approval

The study was approved by the Institutional Ethics Committee (IEC 524/2022), and Clinical Trials Registry of India registration was done CTRI/2023/03/051099 before recruitment for the study.

Author Contributions

Dr Abhilash Mareguddi – Conceptualization, methodology, investigation, data collection, Excel entry, and manuscript writing, review, and editing. Dr Souvik Chaudhuri – Conceptualization, methodology, Excel entry, analysis, and manuscript writing, review, and editing. Dr Sagar M Shanmukhappa, Dr P Vishwas, Dr Margiben T Bhatt, Dr Roshan Fernandes, and Dr Poornima Birajdar – Review and editing. Dr R Shwethapriya – Conceptualization, methodology, supervision, review and Editing.

Supplementary Materials

All the supplementary materials are available on the website www.ijccm.com

Orcid

Abhilash B Mareguddi https://orcid.org/0009-0000-9286-9050
Souvik Chaudhuri https://orcid.org/0000-0001-8392-2366
Sagar M Shanmukhappa https://orcid.org/0000-0003-0700-0532
Vishwas Parampalli https://orcid.org/0000-0002-6149-9509
Margiben T Bhatt https://orcid.org/0000-0002-8966-1096

Roshan Fernandes https://orcid.org/0009-0008-5836-3281
Shwethapriya Rao https://orcid.org/0000-0002-5635-5332
Poornima S Birajdar https://orcid.org/0009-0003-4391-1306

References

1. Nuckchady DC. Incidence, risk factors, and mortality from hospital-acquired infections at a hospital in Mauritius. Cureus 2021;13(11):e19962. DOI: 10.7759/cureus.19962.
2. Nuckchady DC, Boolaky SH. The prevalence of multi-drug resistant organisms and their outcomes in an ICU in Mauritius: An observational study. Asian J Med Health 2020;21:71–78. DOI: 10.9734/ajmah/2020/v18i1130270.
3. Nair V, Sahni AK, Sharma D, Grover N, Shankar S, Chakravarty A, et al. Point prevalence & risk factor assessment for hospital-acquired infections in a tertiary care hospital in Pune, India. Indian J Med Res 2017;145(6):824–832. DOI: 10.4103/ijmr.IJMR_1167_15.
4. Jean SS, Harnod D, Hsueh PR. Global threat of carbapenem-resistant gram-negative bacteria. Front Cell Infect Microbiol 2022;12:823684. DOI: 10.3389/fcimb.2022.823684.
5. Mancuso G, De Gaetano S, Midiri A, Zummo S, Biondo C. The challenge of overcoming antibiotic resistance in carbapenem-resistant gram-negative bacteria: "Attack on titan." Microorganisms 2023;11(8):1912. DOI: 10.3390/microorganisms11081912.
6. Yao H, Yang Y, Yao H, Bu S, Li L, Wang F, et al. Development of prediction models for carbapenem-resistant Klebsiella pneumoniae acquisition and prognosis in adult patients. Front Pharmacol 2024;15:1439116. DOI: 10.3389/fphar.2024.1439116.
7. Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillamet C, Kollef MH. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: A retrospective cohort study. Crit Care 2014;18(6):596. DOI: 10.1186/s13054-014-0596-8.
8. Lueangarun S, Leelarasamee A. Impact of inappropriate empiric antimicrobial therapy on mortality of septic patients with bacteremia: A retrospective study. Interdiscip Perspect Infect Dis 2012;2012:765205. DOI: 10.1155/2012/765205.
9. Roberts T, Chandna A, Watthanaworawit W, Thaiprakong A, Soeng S, Simmalavong M, et al. Impact of delayed processing of positive blood cultures on organism detection: A prospective multi-centre study. BMC Infect Dis 2022;22(1):517. DOI: 10.1186/s12879-022-07504-1.
10. Venturelli C, Righi E, Borsari L, Aggazzotti G, Busani S, Mussini C, et al. Impact of pre-analytical time on the recovery of pathogens from blood cultures: Results from a large retrospective survey. PLoS One 2017;12(1):e0169466. DOI: 10.1371/journal.pone.0169466.
11. Schwarzenbacher J, Kuhn SO, Vollmer M, Scheer C, Fuchs C, Rehberg S, et al. On-site blood culture incubation shortens the time to knowledge of positivity and microbiological results in septic patients. PLoS One 2019;14(12): e0225999. DOI: 10.1371/journal.pone.0225999.
12. Teysseyre L, Ferdynus C, Miltgen G, Lair T, Aujoulat T, Lugagne N, et al. Derivation and validation of a simple score to predict the presence of bacteria requiring carbapenem treatment in ICU-acquired bloodstream infection and pneumonia: CarbaSCORE. Antimicrob Resist Infect Control 2019;8:78. DOI: 10.1186/s13756-019-0529-z.
13. Gomes MZR, Braga DQ, Pinheiro DOBP, Verduc RCAS, Dos Reis LV, de Lima EM, et al. Nucleus of Hospital Research Study Collaborators. Predictive score for carbapenem-resistant gram-negative bacilli sepsis: Single-center prospective cohort study. Antibiotics (Basel) 2022;12(1):21. DOI: 10.3390/antibiotics12010021.
14. Veeraraghavan B, Shankar C, Karunasree S, Kumari S, Ravi R, Ralph R. Carbapenem resistant Klebsiella pneumoniae isolated from bloodstream infection: Indian experience. Pathog Glob Health 2017;111(5):240–246. DOI: 10.1080/20477724.2017.1340128.
15. Tabak YP, Vankeepuram L, Ye G, Jeffers K, Gupta V, Murray PR. Blood culture turnaround time in U.S. acute care hospitals and implications for laboratory process optimization. J Clin Microbiol 2018;56(12):e00500-18. DOI: 10.1128/JCM.00500-18.
16. Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA. Infectious Diseases Society of America 2024 guidance on the treatment of antimicrobial-resistant gram-negative infections. Clin Infect Dis 2024:ciae403. DOI: 10.1093/cid/ciae403.
17. Yıldızeli SO, Vezir D, Cimsit C, Kocakaya D, Mercanci Z, Balcan B, et al. Pre-existing immunocompromised status as a preventer of mortality in COVID-19 patients: Friend or foe? Cureus 2023;15(4):e37633. DOI: 10.7759/cureus.37633.
18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40(5):373–383. DOI: 10.1016/0021-9681(87)90171-8.
19. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011;173(6):676–682. DOI: 10.1093/aje/kwq433.
20. Labaste F, Grossac J, Bounes FV, Conil JM, Ruiz S, Seguin T, et al. Risk factors for acquisition of carbapenem-resistance during treatment with carbapenem in the intensive care unit: A prospective study. Eur J Clin Microbiol Infect Dis 2019;38(11):2077–2085. DOI: 10.1007/s10096-019-03644-6.
21. Harris AD, Johnson JK, Thom KA, Morgan DJ, McGregor JC, Ajao AO, et al. Risk factors for development of intestinal colonization with imipenem-resistant *Pseudomonas aeruginosa* in the intensive care unit setting. Infect Control Hosp Epidemiol 2011;32:719–722. DOI: 10.1086/660763.
22. Mmatli M, Mbelle NM, Maningi NE, Sekyere JO. Emerging transcriptional and genomic mechanisms mediating carbapenem and polymyxin resistance in *Enterobacteriaceae*: A systematic review of current reports. mSystems 2020;5(6):e00783-20. DOI: 10.1128/mSystems.00783-20.
23. Pérez-Varela M, Corral J, Aranda J, Barbé J. Roles of efflux pumps from different super-families in the surface-associated motility and virulence of *Acinetobacter baumannii* ATCC 17978. Antimicrob Agents Chemother 2019;63:e02190-18. DOI: 10.1128/AAC.02190-18.
24. Aurilio C, Sansone P, Barbarisi M, Pota V, Giaccari LG, Coppolino F, et al. Mechanisms of action of carbapenem resistance. Antibiotics (Basel) 2022;11(3):421. DOI: 10.3390/antibiotics11030421.
25. Xu C, Bilya S, Xu W. adeABC efflux gene in Acinetobacter baumannii. New Microbes New Infect 2019;30:100549. DOI: 10.1016/j.nmni.2019.100549.
26. Zou YM, Ma Y, Liu JH, Shi J, Fan T, Shan YY, et al. Trends and correlation of antibacterial usage and bacterial resistance: Time series analysis for antibacterial stewardship in a Chinese teaching hospital (2009–2013). Eur J Clin Microbiol Infect Dis 2015;34(4):795–803. DOI: 10.1007/s10096-014-2293-6.
27. Vasudevan A, Mukhopadhyay A, Li J, Yuen EG, Tambyah PA. A prediction tool for nosocomial multi-drug resistant gram-negative bacilli infections in critically ill patients – Prospective observational study. BMC Infect Dis 2014;14:615. DOI: 10.1186/s12879-014-0615-z.
28. Donaldson AD, Razak L, Liang LJ, Fisher DA, Tambyah PA. Carbapenems and subsequent multiresistant bloodstream infection: Does treatment duration matter? Int J Antimicrob Agents 2009;34(3):246–251. DOI: 10.1016/j.ijantimicag.2009.04.007.
29. Sharma K, Tak V, Nag VL, Bhatia PK, Kothari N. An observational study on carbapenem-resistant Enterobacterales (CRE) colonisation and subsequent risk of infection in an adult intensive care unit (ICU) at a tertiary care hospital in India. Infect Prev Pract 2023;5(4):100312. DOI: 10.1016/j.infpip.2023.100312.
30. Rajendran S, Gopalakrishnan R, Tarigopula A, Kumar DS, Nambi PS, Sethuraman N, et al. Xpert Carba-R assay on flagged blood culture samples: Clinical utility in intensive care unit patients with bacteremia caused by Enterobacteriaceae. Indian J Crit Care Med 2023;27(9):655–662. DOI: 10.5005/jp-journals-10071-24533.

31. Salomão MC, Freire MP, Boszczowski I, Raymundo SF, Guedes AR, Levin AS. Increased risk for carbapenem-resistant *Enterobacteriaceae* colonization in intensive care units after hospitalization in emergency department. Emerg Infect Dis 2020;26(6):1156–1163. DOI: 10.3201/eid2606.190965.
32. Kuloglu TO, Unuvar GK, Cevahir F, Kilic AU, Alp E. Risk factors and mortality rates of carbapenem-resistant gram-negative bacterial infections in intensive care units. J Intensive Med 2024;4(3):347–354. DOI: 10.1016/j.jointm.2023.11.007.
33. Gunalan A, Sastry AS, Ramanathan V, Sistla S. Early- vs late-onset ventilator-associated pneumonia in critically ill adults: Comparison of risk factors, outcome, and microbial profile. Indian J Crit Care Med 2023;27(6):411–415. DOI: 10.5005/jp-journals-10071-24465.
34. Önal U, Akyol D, Mert M, Başkol D, Memetali SC, Şanlıdağ G, e al. Carbapenem-resistant gram-negative pathogens associated with septic shock: A review of 120 cases. J Chemother 2022;34(7):436–445. DOI: 10.1080/1120009X.2022.2064703.
35. Liao Q, Feng Z, Lin H, Zhou Y, Lin J, Zhuo H, et al. Carbapenem-resistant gram-negative bacterial infection in intensive care unit patients: Antibiotic resistance analysis and predictive model development. Front Cell Infect Microbiol 2023;13:1109418. DOI: 10.3389/fcimb.2023.1109418.
36. Satlin MJ, Jenkins SG, Chen L, Helfgott D, Feldman EJ, Kreiswirth BN, et al. Septic shock caused by Klebsiella pneumoniae carbapenemase-producing Enterobacter gergoviae in a neutropenic patient with leukemia. J Clin Microbiol 2013;51(8):2794–2796. DOI: 10.1128/JCM.00004-13.
37. Pantelidou IM, Galani I, Georgitsi M, Daikos GL, Giamarellos-Bourboulis EJ. Interactions of Klebsiella pneumoniae with the innate immune system vary in relation to clone and resistance phenotype. Antimicrob Agents Chemother 2015;59(11):7036–7043. DOI: 10.1128/AAC.01405-15.
38. Banerjee T, Mishra A, Das A, Sharma S, Barman H, Yadav G. High prevalence and endemicity of multidrug resistant *Acinetobacter* spp. in intensive care unit of a tertiary care hospital, Varanasi, India. J Pathog 2018;2018:9129083. DOI: 10.1155/2018/9129083.
39. Vijay S, Bansal N, Rao BK, Veeraraghavan B, Rodrigues C, Wattal C, et al. Secondary infections in hospitalized COVID-19 patients: Indian experience. Infect Drug Resist 2021;14:1893–1903. DOI: 10.2147/IDR.S299774.
40. Hsu LY, Apisarnthanarak A, Khan E, Suwantarat N, Ghafur A, Tambyah PA. Carbapenem-resistant Acinetobacter baumannii and Enterobacteriaceae in South and Southeast Asia. Clin Microbiol Rev 2017;30(1):1–22. DOI: 10.1128/CMR.masthead.30-1.
41. Gunasekaran S, Mahadevaiah S. Healthcare-associated infection in intensive care units: Overall analysis of patient criticality by acute physiology and chronic health evaluation IV scoring and pathogenic characteristics. Indian J Crit Care Med 2020;24(4):252–257. DOI: 10.5005/jp-journals-10071-23384.
42. Prakash J, Verma S, Shrivastava P, Saran K, Kumari A, Raj K, et al. Modified NUTRIC score as a predictor of all-cause mortality in critically ill patients: A systematic review and meta-analysis. Indian J Crit Care Med 2024;28(5):495–503. DOI: 10.5005/jp-journals-10071-24706.
43. Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: The development and initial validation of a novel risk assessment tool. Crit Care 2011;15(6):R268. DOI: 10.1186/cc10546.
44. Vincent J-L, Russell JA, Jacob M, Martin G, Guidet B, Wernerman J, et al. Albumin administration in the acutely ill: What is new and where next? Crit Care 2014;18(4):231. DOI: 10.1186/cc13991.
45. Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet 2011;50(2):99–110. DOI: 10.2165/11539220-000000000-00000.