Predicting mortality in intensive care unit patients infected with **Klebsiella pneumoniae** : a retrospective cohort study

Predicting mortality in intensive care unit patients infected with *Klebsiella pneumoniae*: a retrospective cohort study

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Authorship statement

All authors meet the ICMJE authorship criteria. Study concept and design: TNT, SC, HAN, DHV, GBN. Project administration: TNT, DHV. Supervision: SC, HAN, GBN. Acquisition of data: TTN, NMT, TAT, THGD, HNP. Statistical analysis: TNT, SA, RB, DHV. Interpretation of data: all authors. Drafting the manuscript: TNT. Critical revision of the manuscript and approval of the final version: all authors.

Abstract

Introduction

Although several models to predict intensive care unit (ICU) mortality are available, their performance decreases in certain subpopulations because specific factors are not included. Moreover, these models often involve complex techniques and are not applicable in low-resource settings. We developed a prediction model and simplified risk score to predict 14-day mortality in ICU patients infected with *Klebsiella pneumoniae.*

Methodology

A retrospective cohort study was conducted using data of ICU patients infected with *Klebsiella pneumoniae* at the largest tertiary hospital in Northern Vietnam during 2016-2018. Logistic regression was used to develop our prediction model. Model performance was assessed by calibration (area under the receiver operating characteristic curve-AUC) and discrimination (Hosmer-Lemeshow goodness-of-fit test). A simplified risk score was also constructed.

Results

Two hundred forty-nine patients were included, with an overall 14-day mortality of 28.9%. The final prediction model comprised six predictors: age, referral route, SOFA score, central venous catheter, intracerebral haemorrhage surgery and absence of adjunctive therapy. The model showed high predictive accuracy (AUC=0.83; p-value Hosmer-Lemeshow test=0.92). The risk score has a range of 0-12 corresponding to mortality risk 0-100%, which produced similar predictive performance as the original model.

Conclusions

The developed prediction model and risk score provide an objective quantitative estimation of individual 14-day mortality in ICU patients infected with *Klebsiella pneumoniae*. The tool is highly applicable in practice to help facilitate patient stratification and management, evaluation

of further interventions and allocation of resources and care, especially in low-resource settings where electronic systems to support complex models are missing.

Key words

Klebsiella pneumoniae; intensive care unit; mortality; prediction; prognosis

Introduction

In 2017, carbapenem-resistant *Enterobacteriaceae* were listed among antibiotic-resistant "critical priority pathogens" by the World Health Organization [1]. In the *Enterobacteriaceae* family, *Klebsiella pneumoniae* (*K. pneumoniae*) is one of the most commonly isolated pathogens in nosocomial infections. Carbapenem-resistant *K. pneumoniae* has been reported in many serious and life-threatening infections. A meta-analysis of studies published between 2005 and 2017 reported a 41% overall mortality rate related to carbapenem-resistant *K. pneumoniae* [2]. A recent review (2020) also presented *K. pneumoniae* as an increasing threat to public health in many Asian countries [3]. During 2012-2016, in the Bach Mai Hospital, the largest tertiary hospital in the North of Vietnam, the number of *K. pneumoniae* isolates doubled (from 551 to 1029). Alarmingly, the susceptibility rate of *K. pneumoniae* to carbapenems at the intensive care unit (ICU) of this hospital declined by three times (from 88% to 27%) [4].

The ICU is one of the most high-priced units of any hospital, which requires expert personnel, high-end facilities and services. To assist ICU clinicians, researchers have developed models and risk scores to increase the accuracy in predicting ICU mortality [5, 6]. These models enable clinicians to calculate a patient's mortality risk according to the patient's risk profile (combination of various risk predictors). However, these models often involve complex techniques and demand proper computational systems, which are not applicable in low-resource settings.

Furthermore, these models are developed for the general ICU population [5, 6], so their performance might decrease when applied in a specific subpopulation of ICU patients. When considering ICU patients infected with *K. pneumoniae*, the models for general ICU patients do not include infection-related factors, so their predictive ability in this subpopulation may

decrease. To our knowledge, there has been only one study to develop a risk score to predict 28-day mortality in patients with *K. pneumoniae* bloodstream infections [7]. However, this study did not report performance parameters of the score (discrimination and calibration), which does not allow for further evaluation and comparison and restricts the generalizability of the risk score.

In the current study, we developed a prediction model to predict 14-day mortality in ICU patients infected with *K. pneumoniae*. Based on the original model, we also constructed a simplified risk score to enhance the applicability of the prediction rule in practice. All the steps of model development, assessment and validation, and risk score construction are presented to facilitate the comparison, reproducibility, and generalizability of the prediction model and risk score.

Methodology

Study design and study population

A retrospective cohort study was conducted at the ICU of the Bach Mai Hospital, the largest tertiary hospital in Northern Vietnam. Data were retrieved from medical records of adult patients (age ≥ 18) admitted to the ICU between 1 January 2016 and 31 December 2018, who had at least a microbiological isolation of *K. pneumoniae*. Patients were excluded if they stayed in the ICU for less than 48 hours or were only colonized with *K. pneumoniae* without any sign of infection based on their diagnoses, results of physical examination and laboratory tests. The classification of *K. pneumoniae* infection/colonization was performed by a senior ICU physician. In the case of multiple *K. pneumoniae* infection episodes in a patient, only the first episode was included. Infection onset was defined as the date of the first positive *K. pneumoniae* culture [7-13].

Outcome

The study outcome was 14-day all-cause mortality, defined as "died at hospital" or "discharged with a prognosis of imminent death" (made by the treating physician) within 14 days of infection onset. The latter is a typical situation in Vietnam where nearly 70% of critically ill patients with a prognosis of death within hours or days choose to die at home rather than at hospital [14]. Fourteen-day mortality was chosen as the primary outcome for this study since this outcome has widely been used in a number of previous studies on predictors of mortality in ICU [15, 16] and other patients [9, 11, 12, 17-19] with carbapenem-resistant *K. pneumoniae* infections. This outcome is particularly suitable for the context of Vietnam and other developing countries with a high burden of multidrug-resistant infections and lack of resources in the ICU setting. The patients' stay in the ICU is often short due to the requirement for a high patient turnover. Additionally, since most Vietnamese families of critically ill patients with a prognosis of death within hours or days normally ask for early discharge so that the patient can die at home, a prediction rule for predicting 14-day mortality is useful for ICU clinicians in the study context.

Predictors

Eighteen variables (Fig.1) were selected based on three criteria: 1) Reported in the literature as predictive of *K. pneumoniae*/ICU-related mortality; 2) Readily available in ICU medical records; 3) Considered relevant by ICU and infection control experts. Although intracerebral haemorrhage surgery has not been reported in previous research as a risk factor of *K. pneumoniae*/ICU-related mortality, this was among the most commonly performed procedures at the ICU of the study hospital and therefore was included.

Variable explanation: The Acute Physiology And Chronic Health Evaluation (APACHE) II score was measured within the first 24 hours of ICU admission [11, 13]. The Sequential Organ Failure Assessment (SOFA) score [11, 20] and the Charlson Comorbidity index [20, 21] were measured at infection onset. Septic shock, measured at infection onset, was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [7, 11, 22]. Carbapenem resistance was defined as resistance to one of the three carbapenems (imipenem, meropenem, ertapenem) [13, 23]. In the study setting, the result of susceptibility test normally came one day after culture result. Invasive procedures (central venous catheter [13, 24], urinary catheter [24], endotracheal tube [24, 25], dialysis [24] and intracerebral haemorrhage surgery) were captured within 72 hours before infection onset. Antibiotic therapy was classified as empirical or definitive if administered before or after the availability of susceptibility results, respectively. Antibiotic therapy was considered adequate if including at least one active antibiotic (according to the susceptibility test) that was administered for at least 48 hours [11, 26, 27]. Adjunctive therapy was defined as any adjunctive measure to remove sources of infection or control and manage infection, implemented for example by drainage, debridement, tube/catheter removal or phlegm suction, within three days before and including the date of infection onset [11, 28]. Referral route was classified as intra-hospital or outside-hospital if the patients had already been staying at the ICU/were admitted from another department of the same hospital or were admitted from outside of the hospital (primary/secondary care or community), respectively [11]. Co-infection was defined as any other bacterial pathogen concomitantly isolated with *K. pneumoniae*. Other variables are self-explanatory.

Statistical analysis

Two antibiotic susceptibility results were lost without a specific reason and were considered missing completely at random (MCAR). Therefore, a complete case analysis was applied. To explore the assumption of MCAR, we performed Little's MCAR test based on all continuous quantitative variables. The p-value of 0.607 indicated that there is no evidence against the MCAR assumption. However, the test result should be interpreted with caution given that Little's test could have insufficient power to reject the null hypothesis when data are missing at random or missing not at random (MAR or MNAR, respectively) [29, 30].

Because we aimed to construct a simplified risk score, continuous variables were categorized using clinically relevant thresholds previously described and validated: age (<65, ≥65), APACHE II (0-14, 15-19, ≥20) [16], SOFA (0-3, 4-11, ≥12) [31, 32] and Charlson index (0, 1, ≥2) [21].

Logistic regression was used to assess the associations between predictors and mortality. The development of our prediction model and risk score followed four steps [33, 34]:

- *Model development:* Variables with p-value<0.15 from univariable analyses were included in the multivariable model. Multicollinearity was checked using generalized variance-inflation factors (GVIFs). Backward selection was performed using the likelihood ratio test with p-value threshold of 0.1.
- *Model performance:* Predictive accuracy of the final model was assessed by calibration and discrimination parameters: Discrimination was estimated by the area under the receiver operating characteristic curve (AUC) (0.5 indicates no discrimination - 1.0 indicates perfect discrimination); Calibration was assessed visually with a calibration plot and formally using the Hosmer-Lemeshow goodness-of-fit test (p>0.05 indicates good fit).

- *Internal validation:* The model was internally validated using a nonparametric bootstrap approach (1,000 samples). The model's over-optimism (when applied to new patients in a similar population) was measured by the AUC difference between the bootstrap samples (average AUC) and the original full sample.

- *Risk score construction:* A simplified risk score was constructed based on the hierarchy of the regression coefficients in the final model (each coefficient was divided by the smallest coefficient and rounded to the nearest integer). The score's predictive performance (AUC) was assessed and compared with that of the original model. Mortality risk corresponding to each score was calculated. We also grouped mortality risk into four categories: "low" (<5%), "moderate" (5%-25%), "high" (25%-75%) and "very high" (>75%).

All analyses were performed with R (version 3.4.4) [35].

Ethics

The study was approved by the Scientific and Ethics Committee of the Bach Mai Hospital (reference number 126/QD-BM). No consent was obtained as the data were analysed anonymously. Our reporting adhered to the TRIPOD checklist for prediction model development and validation [36] (Supplementary Table 2).

Results

Patient characteristics

In total, 249 patients were included in data analysis (Fig. 2). The patients' characteristics are presented in Table 1. Most of the patients were intra-hospital referred (69%), had SOFA score ≥4 (74%), Charlson index ≥1 (67%) and APACHE II score ≥15 (51%). Endotracheal

tube (68%) and central venous catheter (57%) were the two most frequently performed invasive procedures. More than 70% of the *K. pneumoniae* isolates were carbapenem-resistant. Up to 90% of the patients had adjunctive therapy. The overall 14-day all-cause mortality was 28.9%.

Prediction model to predict 14-day mortality in ICU patients infected with K. pneumoniae

Multicollinearity among variables in the multivariable model was low (GVIFs 1.13-1.62). The final prediction model contained six predictors: age, referral route, SOFA score, central venous catheter, intracerebral haemorrhage surgery and absence of adjunctive therapy (Table 2). The two strongest predictors of 14-day mortality in the study population were absence of adjunctive therapy (OR 19.52, 95%CI: 6.46-68.66) and SOFA score (score 4-11: OR 3.68, 95%CI: 1.47-10.70; score ≥12: OR 9.93, 95%CI: 2.85-38.74).

Based on the regression coefficients and intercept, we obtained the prediction model to predict 14-day mortality of ICU patients infected with *K. pneumoniae* as follows (events are coded as "1" if present and "0" if absent):

Probability of 14-day mortality = 1/[1+exp-(-4.68 + 0.88 × Age ≥65 + 1.11 × Intra-hospital referral + 1.30 × SOFA score 4-11 + 2.29 × SOFA score ≥12 + 1.52 × Central venous catheter + 1.73 × Intracerebral haemorrhage surgery + 2.97 × Absence of adjunctive therapy)]

Model performance

The model demonstrated a good ability to separate individuals with and without 14-day mortality (good discrimination), with AUC=0.83 (95% CI: 0.77-0.88) (Fig. 3-A). The predicted probabilities were closed to observed probabilities, indicating a good calibration (Fig. 3-B, Hosmer-Lemeshow test p-value=0.92).

Internal validation

According to the results of internal validation, the model showed low level of optimism when applied in new patients: AUC-optimism 0.021 (95% CI: 0.019-0.023). The calibration plot after bootstrapping also showed similar predicted and observed mortality probabilities (Fig. 4).

Simplified risk score

Based on the hierarchy of the corresponding regression coefficients in the original prediction model, we constructed a simplified risk score as follows (events are coded as "1" if present and "0" if absent):

Total score = (1 × Age ≥65) + (1 × Intra-hospital referral) + (1 × SOFA score 4-11) + (3 × SOFA score ≥12) + (2 × Central venous catheter) + (2 × Intracerebral haemorrhage surgery) + (3 × Absence of adjunctive therapy).

The score has a range of 0-12, corresponding to mortality risk 0-100%. Compared with the original model, the simplified score yielded a similar predictive performance (AUC 0.82, 95% CI 0.76-0.88). Mortality risk was also categorized into 4 groups: low risk ~ 3.2% (score 0-1), moderate risk ~ 9.9% (score 2-3), high risk ~ 42.1% (score 4-6) and very high risk ~ 85.0% (score 7-12) (Fig. 5 and Supplementary Table 1).

Discussion

In this study, we developed a prediction model to predict 14-day mortality in ICU patients infected with *K. pneumoniae*. The model comprised six predictors: age, referral route, SOFA score, central venous catheter, intracerebral haemorrhage surgery and absence of adjunctive

therapy. A simplified 12-point risk score was also constructed to enhance the applicability of the prediction rule in practice.

Several models to predict ICU mortality have been developed [5, 6]. However, they involve complex techniques and require considerable computational efforts, and therefore are not applicable in low-resource settings. In the context of tremendous pressure and time constraints faced by ICU clinicians, a simple-to-calculate, easy-to-interpret and actionable risk score is needed. With our simplified risk score, individual score of 14-day mortality can be calculated based on the presence/absence of six predictors, which are routinely collected and readily available from ICU medical records. Each risk score corresponds to a probability of 14-day mortality and a risk category. For example, scores 0-1 indicate low mortality risk (3.2%) while scores above 7 indicate very high risk (85%). To enhance the applicability of the risk score in practice, we also provide a visualization of the relationship between each risk score and the corresponding mortality risk (Fig. 5).

The performance of previous models to predict mortality in general ICU patients may decrease when applied in ICU patients infected with *K. pneumoniae* since infection-related factors are not included in these models [5, 6]. There has been only one risk score developed by Chang *et al* (2020) to predict mortality in patients with *K. pneumoniae* bloodstream infections, but no performance parameters of the score were reported [7], which restricts further evaluation and comparison. We also did not agree with the use of ORs in Chang's study to construct the risk score for the following reasons: While a predictor may have a risk or protective effect, OR can only be positive. Weight is still assigned to a predictor when OR=1 while actually, the predictor has no effect (corresponding regression coefficient = 0). From an algebraical point of view, ORs are supposed to be multiplied, not added [37]. We addressed these issues by using regression coefficients, instead of ORs, to assign weights in our risk score. Moreover, we presented all the steps of model development, assessment and

validation, and risk score construction to facilitate the comparison, reproducibility and generalizability of the prediction model.

Our final model exhibited high predictive accuracy both before and after internal validation. Our study agreed with previous studies that predictive accuracy improves when the conventional ICU scores (APACHE, SOFA) are combined with additional determinants [5, 7, 38]. In our study, the SOFA score alone exhibited only a modest predictive ability (AUC 0.66) while in the final model where SOFA score was combined with other predictors, the prognostic performance increased substantially (AUC 0.83). A review evaluating SOFA-based models in predicting ICU mortality showed that the Max SOFA score (highest SOFA score in a pre-specified time interval) produced AUCs of 0.79-0.92 [38], higher than the AUC of SOFA score in our study. The predictive performance of SOFA may vary across populations and settings [28, 39]. Our study focused on a specific ICU subpopulation infected with *K. pneumoniae*. Additionally, we used SOFA score at infection onset, instead of the Max SOFA, because the data is more readily available.

Our final model comprised five predictors related to patients' conditions (age, referral route, SOFA score, central venous catheter and intracerebral haemorrhage surgery) and one related to infection (absence of adjunctive therapy). Although being the only infection-related predictor remained, absence of adjunctive therapy proved to be the strongest predictor (largest regression coefficient, 2.97). The importance of adjunctive measures to remove foci of infection or control and manage infection has been well documented [11, 28]. In ICU patients with infections, regardless of the pathogen, along with the management of patients' underlying conditions, infection source identification and elimination are key to improve prognosis.

The predictive value of carbapenem resistance in predicting mortality risk may vary across

settings. While this predictor remained in the final risk score of Chang *et al* [7], it was not included in our final prediction model and risk score. A Korean study also reported no association between carbapenemase production and 14-day mortality in carbapenem-resistant *Enterobacteriaceae* bacteraemia [11]. The authors hypothesized that carbapenem resistance, rather than carbapenemase production, would affect mortality probability. However, this hypothesis was not supported by our study in a context where the rate of carbapenem resistance was high (73%).

In practice, clinicians often estimate a patient's prognosis based on their mechanistic and pathophysiologic knowledge, in combination with their clinical experiences. Although useful, such knowledge and experiences rarely enable them to differentiate between patients with a high risk from patients with a low risk of developing a certain outcome, especially when the prognostication requires a combination of different factors [33]. Prediction models and risk scores provide an objective, quantitative estimation of a patient's risk based on the different combinations of predictors (risk profiles), and therefore can help assist clinicians in patients' risk stratification, patient management and evaluation of further interventions.

Fast and precise patient prognosis also plays a significant part in the allocation of resources and care, especially in the ICU setting where expert personnel, high-end facilities and services are required. ICU is also one of the most high-priced parts of every hospital. An efficient prediction rule can help improve the outcomes of ICU patients and reduce costs since high-risk patients are provided with greater access and resources, and patients can be discharged as soon as possible [40, 41]. An ICU mortality prediction rule can also be helpful in clinical trials to ensure baseline risk similarities between groups being compared [39]. Such a tool is also used to assess the performance of various medical facilities and services [42].

Several limitations of the study need to be acknowledged. First, our sample size was small. However, internal validation showed no problem of model overfitting: small AUC-optimism 0.021 (95% CI: 0.019-0.023). Second, despite an internal validation, our model was not validated externally. Third, time to initiation and number of active antibiotics against *K. pneumoniae* were not included. The dosage of antibiotics was not assessed and was assumed to be appropriate. Nevertheless, our final model and simplified risk score exhibit good prediction accuracy (AUC 0.82-0.83). Fourth, in patients where other bacterial pathogens were concomitantly isolated with *K. pneumoniae*, it was not possible to judge whether the infection was caused by *K. pneumoniae* or the concomitant pathogen(s), or both. Fifth, we could not control for lead-time bias [39]. The patients might have received resuscitative therapy before ICU admission and patient evaluation at the ICU might suggest a less severe condition than the actual one. Finally, since our data was from a single centre where the rate of carbapenem-resistant *K. pneumoniae* was high and intracerebral haemorrhage surgery was among the most commonly performed procedures at the ICU, the generalizability of the developed prediction model and risk score might be limited. External validation in other areas of Vietnam and other countries is required in the future.

Conclusion

We developed a prediction model and a simplified 12-point risk score to predict 14-day mortality in ICU patients infected with *K. pneumoniae*. This prediction rule can assist ICU clinicians in their daily practice by providing an objective, quantitative estimation of patients' mortality risk based on individual risk profiles. The tool can help facilitate patient stratification and management, evaluation of further interventions and allocation of resources and care. With the inclusion of readily available variables from ICU medical records in a simple formula, our risk score can be highly applicable in low-resource settings. To increase

the generalizability of the prediction model and risk score, multicentre research with model external validation is needed.

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Authorship statement

All authors meet the ICMJE authorship criteria. Study concept and design: TNT, SC, HAN, DHV, GBN. Project administration: TNT, DHV. Supervision: SC, HAN, GBN. Acquisition of data: TTN, NMT, TAT, THGD, HNP. Statistical analysis: TNT, SA, RB, DHV. Interpretation of data: all authors. Drafting the manuscript: TNT. Critical revision of the manuscript and approval of the final version: all authors.

Conflict of interest

None.

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Figures

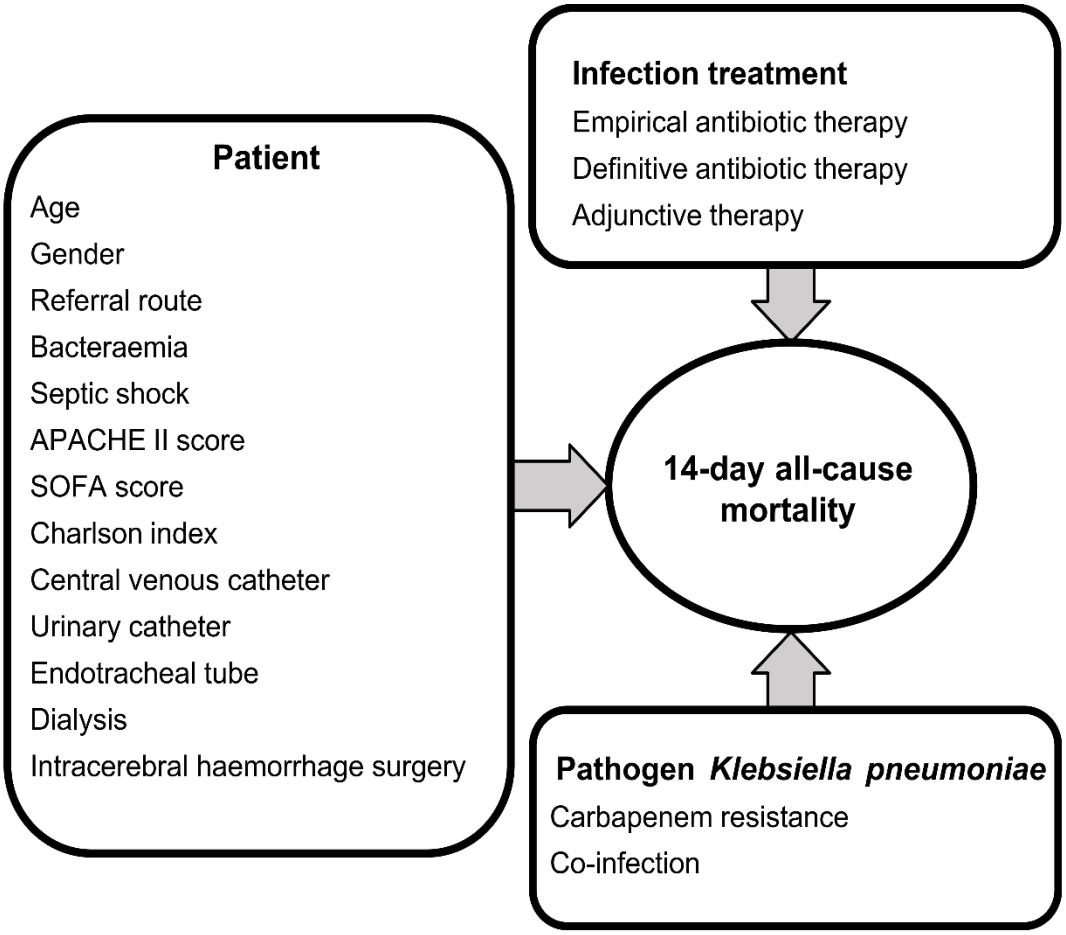

Fig. 1. Diagram of the candidate predictors of 14-day all-cause mortality in ICU patients infected with *Klebsiella pneumoniae*. Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment.

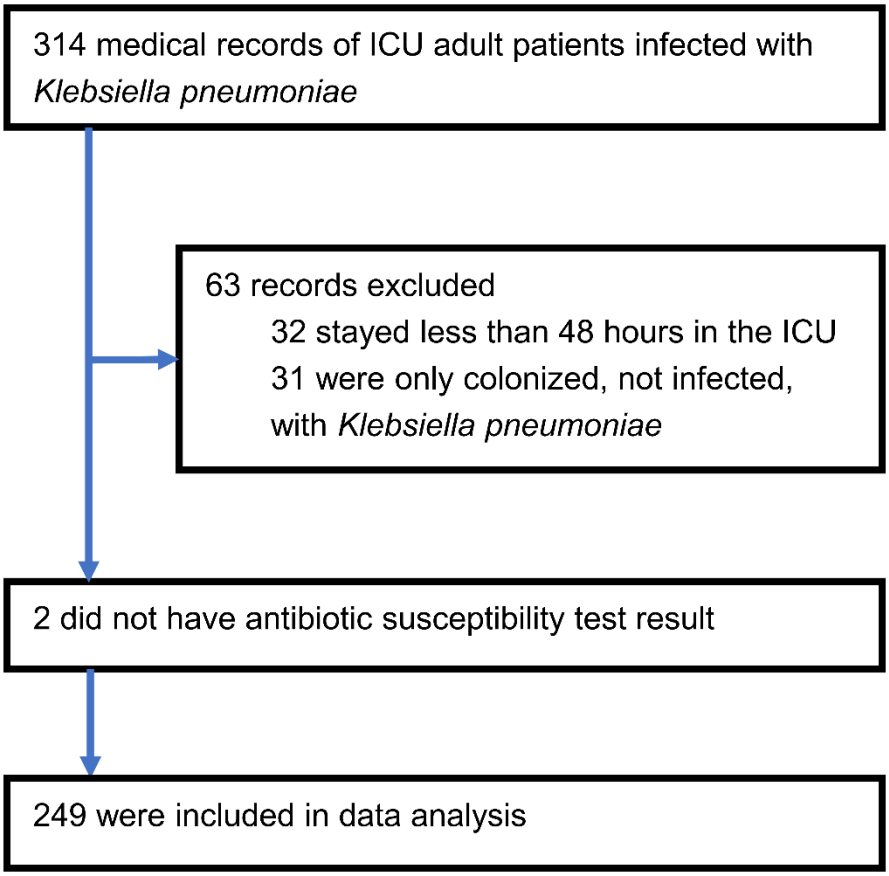

Fig. 2. Flow chart of medical records inclusion process.

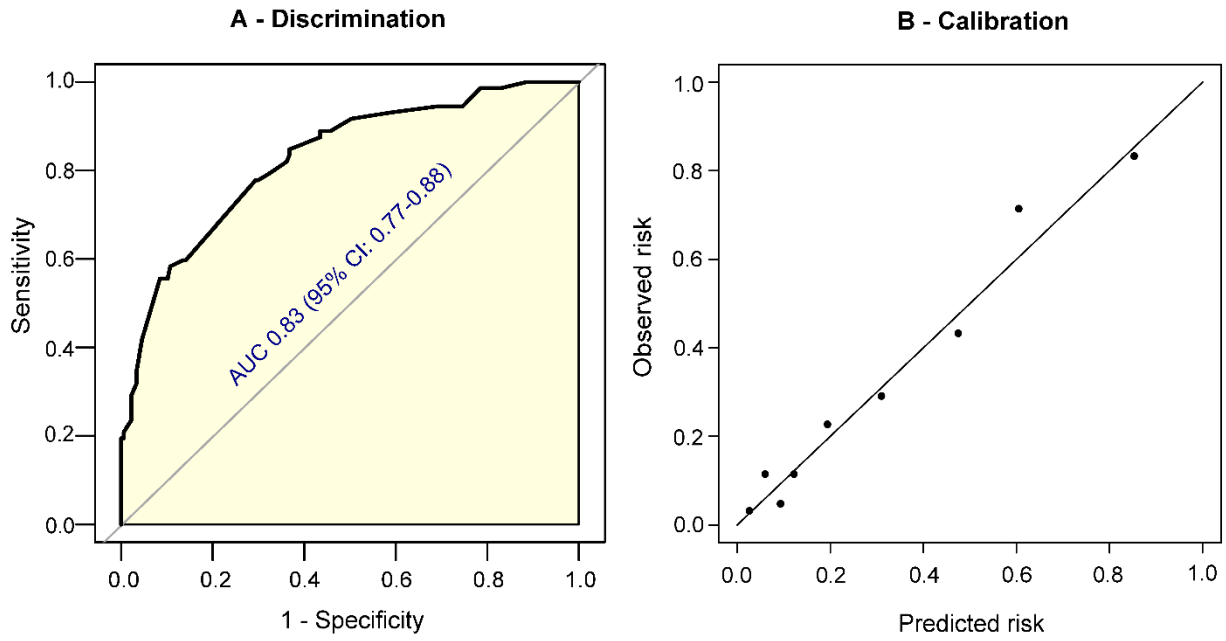

Fig. 3. Performance of the 14-day mortality prediction model in ICU patients infected with *Klebsiella pneumoniae*. (A) Receiver operating characteristic (ROC) curve to assess discrimination of the prediction model. (B) Calibration plot to assess calibration of the prediction model.

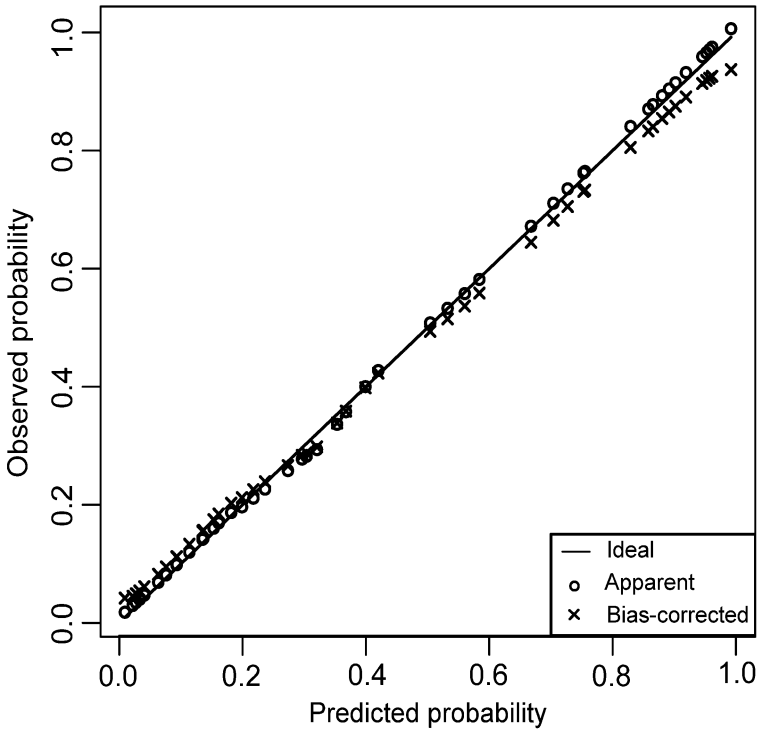

Fig. 4. Calibration plot to illustrate calibration of the original prediction model (Apparent) and the model after bootstrapping (Bias-corrected) in predicting 14-day mortality in ICU patients infected with *Klebsiella pneumoniae*. The "ideal" line denotes perfect calibration.

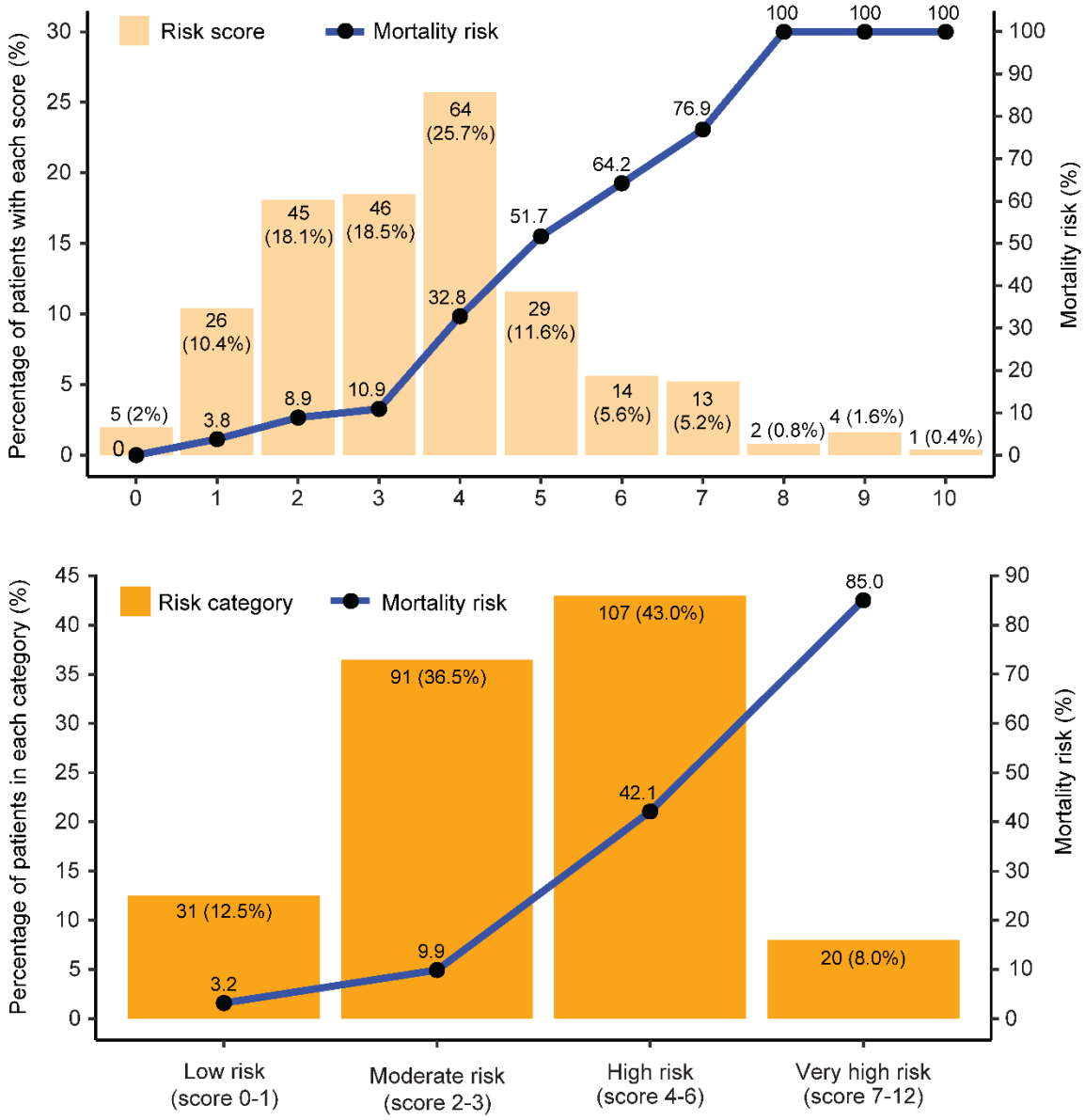

Fig. 5. Distribution of risk scores, risk categories and the corresponding 14-day mortality risk of 249 ICU patients infected with *Klebsiella pneumoniae*.

Risk score formula: Total score = (1 × Age ≥65) + (1 × Intra-hospital referral) + (1 × SOFA score 4-11) + (3 × SOFA score ≥12) + (2 × Central venous catheter) + (2 × Intracerebral haemorrhage surgery) + (3 × Absence of adjunctive therapy). Note: The theoretical range of the risk score is 0-12. No patients in the study population scored 11-12.

Tables

Table 1

Characteristics of a cohort of ICU patients infected with *Klebsiella pneumoniae* in a tertiary hospital.

Characteristics	**Number (percentage)** N=249
Predictors	
Age	
≥65	85 (34.1)
Gender	
Male	185 (74.3)
Referral route	
Intra-hospital	171 (68.7)
Site of infection	
Respiratory tract infections	190 (76.3)
Bacteraemia	48 (19.3)
Intra-abdominal infections	32 (12.9)
Urinary tract infections	6 (2.4)
Skin and soft tissue infections	5 (2.0)
Surgical site infections	2 (0.8)
Septic shock	41 (16.5)
APACHE II	
0-14	122 (49.0)
15-19	57 (22.9)
≥20	70 (28.1)
SOFA	
0-3	66 (26.5)
4-11	156 (62.6)
≥12	27 (10.8)
Charlson index	
0	83 (33.3)
1	45 (18.1)
≥2	121 (48.6)
Central venous catheter	141 (56.6)
Urinary catheter	32 (12.9)
Endotracheal tube	169 (67.9)
Dialysis	70 (28.1)
Intracerebral haemorrhage surgery	18 (7.2)
Carbapenem resistance	181 (72.7)
Co-infection	122 (49.0)
Acinetobacter baumannii	79 (31.7)
Pseudomonas aeruginosa	21 (8.4)
Escherichia coli	13 (5.2)
Staphylococcus aureus	9 (3.6)
Inadequate empirical antibiotic therapy	86 (34.5)
Inadequate definitive antibiotic therapy	35 (14.1)
Absence of adjunctive therapy	27 (10.8)
Outcome	
14-day mortality	72 (28.9)

APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment

Table 2
Associations between predictor variables and 14-day all-cause mortality among 249 ICU patients infected with *Klebsiella pneumoniae*.

Characteristics		Univariable analysis				Final model		Simplified risk score
		Died (N = 72) n (%)	**Survived (N = 177) n (%)**	**OR (95 % CI)**	**p-value**	**aOR (95% CI)**	**Regression coefficient**	**Weight**
Patient factors								
Age	<65 years	42 (58.3)	122 (68.9)	Ref.		Ref.		
	≥65 years	30 (41.7)	55 (31.1)	1.58 (0.90–2.79)	*0.113**	2.41 (1.97–4.96)	0.88	1
Sex	Female	15 (20.8)	49 (27.7)	Ref.				
	Male	57 (79.2)	128 (72.3)	1.45 (0.77–2.88)	*0.255*			
Referral route	Outside-hospital	15 (20.8)	63 (35.6)	Ref.		Ref.		
	Intra-hospital	57 (79.2)	114 (64.4)	2.10 (1.12–4.12)	*0.020**	3.02 (1.38–7.12)	1.11	1
Bacteraemia	No	55 (76.4)	146 (82.5)	Ref.				
	Yes	17 (23.6)	31 (17.5)	1.46 (0.74–2.81)	*0.276*			
Septic shock	No	55 (76.4)	153 (86.4)	Ref.				
	Yes	17 (23.6)	24 (13.6)	1.97 (0.97–3.93)	*0.059**			
APACHE II	0-14	25 (34.7)	97 (54.8)	Ref.	*0.0079**			
	15-19	18 (25.0)	39 (22.0)	1.79 (0.87–3.64)				
	≥20	29 (40.3)	41 (23.2)	2.74 (1.44–5.28)				
SOFA	0-3	7 (9.7)	59 (33.3)	Ref.	*<0.0001**	Ref.		
	4-11	49 (68.1)	107 (60.5)	3.86 (1.73–9.82)		3.68 (1.47–10.70)	1.30	1
	≥12	16 (22.2)	11 (6.2)	12.26 (4.27–38.99)		9.93 (2.85–38.74)	2.29	3
Charlson index	0	13 (18.1)	70 (39.5)	Ref.	*0.0031**			
	1	15 (20.8)	30 (16.9)	2.69 (1.15–6.43)				
	≥2	44 (61.1)	77 (43.5)	3.08 (1.57–6.39)				
Central venous catheter	No	18 (25.0)	90 (50.8)	Ref.		Ref.		
	Yes	54 (75.0)	87 (49.2)	3.10 (1.71–5.83)	*0.0001**	4.58 (2.11–10.85)	1.52	2
Urinary catheter	No	60 (83.3)	157 (88.7)	Ref.				
	Yes	12 (16.7)	20 (11.3)	1.57 (0.71–3.37)	*0.261*			
Endotracheal tube	No	18 (25.0)	62 (35.0)	Ref.				
	Yes	54 (75.0)	115 (65.0)	1.62 (0.89–3.06)	*0.119**			
Dialysis	No	46 (63.9)	133 (75.1)	Ref.				
	Yes	26 (36.1)	44 (24.9)	1.71 (0.94–3.07)	*0.077**			
	No	62 (86.1)	169 (95.5)	Ref.		Ref.		

Intracerebral haemorrhage surgery	Yes	10 (13.9)	8 (4.5)	3.41 (1.29–9.30)	*0.014**	5.65 (1.68–20.00)	1.73	2
Pathogen factors								
Carbapenem resistance	No	17 (23.6)	51 (22.8)	Ref.				
	Yes	55 (76.4)	126 (71.2)	1.31 (0.70–2.52)	*0.399*			
Co-infection	No	34 (47.2)	93 (52.5)	Ref.				
	Yes	38 (52.8)	84 (47.5)	1.24 (0.72–2.15)	*0.446*			
Treatment factors								
Inadequate empirical antibiotic therapy	No	47 (65.3)	116 (65.5)	Ref.				
	Yes	25 (34.7)	61 (34.5)	1.01 (0.56–1.79)	*0.969*			
Inadequate definitive antibiotic therapy	No	61 (84.7)	153 (86.4)	Ref.				
	Yes	11 (15.3)	24 (13.6)	1.15 (0.51–2.44)	*0.725*			
Absence of adjunctive therapy	No	53 (73.6)	169 (95.5)	Ref.		Ref.		
	Yes	19 (26.4)	8 (4.5)	7.57 (3.24–19.29)	*<0.0001**	19.52 (6.46–68.66)	2.97	3

APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment
*Statistically significant

Supplementary tables

Supplementary Table 1 Distribution of risk scores, risk categories and the corresponding 14-day mortality risk of 249 ICU patients infected with *Klebsiella pneumoniae*.

Supplementary Table 2 The TRIPOD checklist for prediction model development and validation applied in this study.