BMJ Open

Clinical prediction models for multidrug-resistant organism infection in critically ill patients: A systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-064566
Article Type:	Protocol
Date Submitted by the Author:	23-May-2022
Complete List of Authors:	Wang, Yi; Peking University First Hospital, Intensive Care Unit Xiao, Yanyan; Peking University First Hospital Yang, Qidi; Peking University First Hospital Wang, Fang; Peking University First Hospital Wang, Ying; Peking University First Hospital Yuan, Cui; Peking University First Hospital
Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Infection control < INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

Title: Clinical prediction models for multidrug-resistant organism infection in critically ill patients: A systematic review protocol

Yi Wang, MS, RN; Yanyan Xiao, MS, RN; Qidi Yang, BS, RN; Fang Wang, BS, RN; Ying Wang, BS, RN; Cui Yuan, MS, RN

Intensive Care Unit, Peking University First Hospital, Beijing, China

***Corresponding author details:** Cui Yuan, Department of Critical Care Medicine, Peking University First Hospital, No.8 Xishiku Street, Beijing, China. E-mail: yuancui2013@sina.com

Word Count: 3993 words

ABSTRACT

Introduction: Multidrug-resistant organisms (MDROs) are pathogenic bacteria that are the leading cause of hospital-acquired infection. MDRO infection is associated with high morbidity and mortality rates in intensive care units, increasing hospitalization duration and cost. Predicting the risk of MDRO infection for critically ill patients supports clinical decision-making. Several models predicting MDRO infection have been developed; however, the stability and applicability of these models vary widely across studies. The aim of this systematic review is to summarise and assess the models predicting MDRO infection in critically ill patients and to provide evidence-based recommendations for clinical practice and research.

Methods and analysis: We will perform a systematic search of PubMed, Cochrane Library, CINAHL, Embase, China National Knowledge Infrastructure, and WANFANG databases to identify all studies describing the development and/or external validation of models predicting MDRO infection in critically ill patients. Two reviewers will independently extract and review the data using the Data Extraction for Systematic Reviews of Prediction Modelling Studies checklist; they will also assess the risk of bias using the Prediction Model Risk of Bias Assessment Tool. Quantitative data on model predictive performance will be synthesised in meta-analyses, as applicable.

Ethics and dissemination: Ethical permissions will not be required because all data will be extracted from published studies. We intend to publish our results in peer-reviewed scientific journals and to present them at international conferences on critical care.

PROSPERO registration number CRD42022274175

Strengths and limitations of this study

- This systematic review will provide an overview of models predicting MDRO infection in critically ill patients, helping inform evidence-based recommendations.
- This systematic review will use the Prediction Model Risk of Bias Assessment Tool to evaluate the methodological quality of included studies.
- Meta-analysis and narrative summaries will be used for quantitative and qualitative evidence assessment, including pooled estimates, as suitable.
- The findings of this systematic review will provide a foundation for predicting and preventing MDRO using evidence-based methodology, helping reduce the rates of infection in critically ill patients.
- Potential limitations of this review include heterogenous data sources, e.g., studies with varied designs, populations, MDRO and ICU types, and timelines, which may require further research to standardise.

INTRODUCTION

Multidrug-resistant organisms (MDROs) increase the risk of poor outcomes worldwide.[1] MDROs, including methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Enterobacteriaceae* (CRE), vancomycin-resistant *Enterococcus* (VRE), and extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-EKP), among others, are the leading causes of hospital-acquired infections.[2] A recent study, based on data from patients treated across 890 hospitals in the United States from 2012 to 2017, reported 622,390 cases of infection; MRSA and ESBL infections accounted for most of these cases.[3] In China, the national report on bacterial resistance in 2020 found that the detection rates of erythromycin-resistant *Streptococcus pneumoniae*, methicillin-resistant coagulase-negative *Staphylococci*, and carbapenem-resistant *Acinetobacter baumanni* (CRAB) were highest at tertiary hospitals.[4] The intensive care unit (ICU) has the highest incidence of MDRO across all hospital departments. Even in developed countries, where infection control is well-organised, approximately 25% of ICU patients experience at least one hospital-acquired infection; the corresponding rate for developing countries is 50%.[5] Meanwhile, in China, the detection rates of ERSP, MRCNS, and CRAB in the ICU are estimated at 94.4%, 84.2%, and 78.2%, respectively.[4]

MDROs increase morbidity and mortality risks, and extend hospitalisation duration.[6] In 2015, there were 700,000 reported deaths due to MDRO infection globally; this number is expected to exceed 10 million by 2050.[7] In addition, cumulative economic losses related to bacterial antimicrobial resistance have been reported as $100 trillion. Giraldi et al. [8] estimated that infections extended general hospitalisations and ICU stays by an average of

18.8 days and 21.2 days, respectively. Wang et al.[9] reported that the length of ICU stay in patients with MDRO infection was 26.0 days longer than that of those without infection. Hence, infection control and prevention are important in the ICU setting. Antibiotic use helps manage infection risk and spread.[10] Nevertheless, it increases the risk of antimicrobial resistance, which is growing to pandemic proportions, hindering treatment progress.[11] According to the World Health Organization, most antimicrobials were discovered in the 20th century, and the development of new antibiotics has been limited since then.[12]

Guidelines for the prevention and control of MDRO outline some non-pharmaceutical interventions.[13-16] They require that risk factors for MDRO be ascertained to support accurate treatment choices. As no single risk factor can reliably predict MDRO infection due to disease heterogeneity and complexity, clinical prediction models are used for risk assessments.[17] Internally and externally validated prediction models may help identify critically ill patients at risk of MDRO, supporting suitable antibiotic prescriptions and infection control measures.

For example, Wang et al.[18] reported that male sex, higher C-reactive protein levels, and higher Pitt bacteraemia scores were independent predictors of MDRO colonisation or infection. In addition, Yoon et al.[19] showed that ICU readmission during hospitalisation, chronic obstructive lung disease, recent antibiotic treatment, and recent vancomycin use were independent risk factors for VRE carriage at ICU admission. Meanwhile, Ochotorena[20] found that the Acute Physiology and Chronic Health Evaluation score of more than 15 points and hospitalisation duration of more than 4 days increased the risk of MRSA colonisation/infection. Finally, Li et al.[21] proposed that carbapenem-resistant *Klebsiella*

pneumoniae colonisation or infection in the previous year, CD4/CD8 cell count ratio of less than 1, and parenteral nutrition duration of more than 48 h were independent risk factors for CRKP infection. This evidence notwithstanding, to the best of our knowledge, there is no globally endorsed prediction model for MDRO infection, and no risk-classification tools are used for the prediction of MDRO infection in critically ill patients in routine clinical practice. Therefore, a critical evaluation of studies proposing potentially relevant prediction models is warranted.

Review objectives

The aim of this systematic review is to evaluate the reporting and methodology of studies on models predicting MDRO infection in critically ill patients. We will apply the Prediction Model Risk of Bias Assessment Tool (PROBAST) to assess the risk of bias in studies on model development and validation. The specific objectives of this review are to:

1. Summarise models predicting MDRO infection in critically ill patients.

2. Critically assess the methodology of these models.

3. Qualitatively describe the relevant models.

4. Quantitatively compare model performance using meta-analytic methods, as suitable, across different types of MDRO.

METHODS AND ANALYSIS

This systematic review protocol has been registered on the International Prospective Register of Systematic Reviews on February 2, 2022 (CRD42022274175). This protocol is presented

according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines (Supplementary file 1).[22] This systematic review is scheduled to be performed from April to December 2022.

Literature search

PubMed, CINAHL, EMBASE, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang databases will be searched from inception until April 2022. Relevant unpublished studies and grey literature will be identified using Google, conference articles, shortlisted study reference lists, index-related articles on PubMed, and existing relevant reviews.

The following search strategy with related key words was developed: (extended-spectrum beta-lactamase OR multidrug-resistan* OR extensively drug-resistan* OR antimicrobial-resistan* OR antibiotic-resistan* OR antibacterial-resistan* OR pandrug-resistan* OR carbapenem-resistant* OR colistin-resistant* OR polymyxin-resistant* OR methicillin-resistant* OR vancomycin-resistant*) AND (Acinetobacter baumannii OR Pseudomonas aeruginosa OR Escherichia coli OR Klebsiella pneumoniae OR Enterobacteriaceae OR Staphylococc* OR Enterococc* OR microorganism* OR bacteria) AND ((prediction model* OR predicted model* OR predictive model* OR risk model* OR risk prediction OR predicted factor* OR predictive factor* OR prognostic model* prognosis model* OR prognostic factor* OR scoring model*) AND (critical care OR intensive care unit* OR critical illness OR ICU OR intensive care OR critically ill) in English and (耐药 OR 耐抗生素 OR 耐细菌 OR 耐甲氧西林 OR 耐碳青霉烯 OR 耐万古霉素 OR 超广谱 β 内酰

胺酶 OR 耐粘菌素 OR 耐多粘菌素) AND (细菌 OR 微生物 OR 肠杆菌 OR 肠球菌 OR 鲍曼不动杆菌 OR 铜绿假单胞菌 OR 肺炎克雷伯菌 OR 金黄色葡萄球菌 OR 结核分枝杆菌) AND (预测模型 OR 预警模型 OR 预判模型 OR 判别模型 OR 风险模型 OR 风险预测 OR 风险评估 OR 预测因素 OR 评分模型 OR 评分系统) AND (ICU OR 重症监护 OR 监护室) in Chinese. We will use medical subject headings and free-text to identify prediction model studies. Example search methods for PubMed and CNKI are included in Supplementary file 2.

Eligibility criteria

Studies may be included in this review if they are primary experimental or observational studies on the development and/or validation of a multi-variable prediction model for MDRO infection in critically ill patients and were published any time before April 2022. Population, intervention, comparator, outcomes, timing, and setting characteristics[23] are presented in Table 1. Additional eligibility criteria include the use of comparative study designs such as clinical trials, cohort, case-control, and cross-sectional studies; reporting of at least two predictors; and published in the English or Chinese language. Conference abstracts, editorials, clinical case reviews, letters, commentaries, book chapters, and surveys will be excluded.

Table 1 Eligibility criteria for the systematic review framed using the PICOTS system

Item	Definition
Population	Both male and female adult critically ill patients (aged ≥18 years) will be considered.The exclusion criteria were:(1) ICU duration less than 24 h; (2) MDOR were detected before the patient entered the ICU or within the first 48 h in the ICU.
Intervention	Any prediction model to predict the risk of MDRO colonization or infection in patients with critical illness, to distinguish critically ill patients with poor

	outcome (who will develop multidrug-resistant bacterial infection).
Comparator	Not applicable.
Outcomes	MDRO colonization or infection reported by prediction models.
Timing	Predictive variables measured at any time point during the course of the MDRO colonization or infection
Setting	intensive care unit

Study selection

We will remove record duplicates using the automatic replay function in NoteExpress software and by-hand assessments after each database search. Two researchers (WY, XYY), trained at the Joanna Briggs Institute, will independently screen the titles and abstracts to identify relevant studies using NoteExpress software. Full-text manuscripts will be retrieved and independently evaluated for inclusion. Disagreements will be resolved by consensus and third-researcher (YC or WF) arbitration. The selection process will be presented in a PRISMA flow diagram (Figure 1).

Data abstraction

At least two trained reviewers (WY, YQD) will independently extract data from included studies. A standardised data extraction form will be created based on the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies.[24] This data extraction form will be piloted on five papers and amended by at least three reviewers (WY,WF,XYY). Any revisions will be implemented based on group consensus. Data on the following study characteristics will be extracted: study design and characteristics, participants, predicted outcome, candidate predictors, missing data, model development,

model performance, model evaluation, results, and discussion/conclusions. If the data of interest are missing or unclear, we will refer to any cited papers and contact corresponding authors to obtain the desired information. Disagreements will be resolved by consensus between the two reviewers or by arbitration by a third (YC, WF) researcher. The lead investigator (YC) will upload the data and records on a shared secure platform accessible to all investigators (Baidu Netdisk, Baidu Netcom Technology Corporation, Beijing, Chnia).

Critical appraisal

Two reviewers (WY, XYY) will independently evaluate the risk of bias and applicability of each included prediction model using the PROBAST instrument.[25,26] PROBAST includes four steps (Table 2), which are described in detail to support assessment completion. The four domains are: participants, predictors, outcome, and analysis, and are divided into a total of 20 questions to support structured risk of bias assessments. Each domain is rated as at a "high", "low", or "unclear" risk of bias (Table 3). Any disagreement will be resolved by consensus and consultation with a third reviewer (YC/WY).

Table 2 Four steps in PROBAST

Step	Task	When to Complete
1	Specify your systematic review question(s)	Once per systematic review
2	Classify the type of prediction model evaluation	Once for each model of interest in each publication being assessed,for each relevant outcome
3	Assess risk of bias and applicability(per domain)	Once for each development and validation of each distinct prediction model in a publication
4	Overall judgment of risk of bias and applicability	Once for each development and validation of each distinct prediction model in a publication

PROBAST= Prediction model Risk Of Bias Assessment Tool.

Table 3 Details for the assessment rules to assess the risk of bias for four domains of participants, predictors, outcome and analysis

1.Participants	2.Predictors	3.Outcome	4.Analysis
Signaling questions			
1.1Were appropriate data sources used, for example, cohort,RCT or nested case-control study data?	2.1Were predictors defined and assessed in a similar way for all participants?	3.1 Was the outcome determined appropriately?	4.1 Were there a reasonable number of participants with the outcome?
1.2 Were all inclusions and exclusions of participants appropriate?	2.2 Were predictor assessments made without knowledge of outcome data?	3.2 Was a prespecified or standard outcome definition used?	4.2 Were continuous and categorical predictors handled appropriately?
—	2.3 Are all predictors available at the time the model is intended to be used?	3.3 Were predictors excluded from the outcome definition?	4.3 Were all enrolled participants included in the analysis?
—	—	3.4 Was the outcome defined and determined in a similar way for all participants?	4.4 Were participants with missing data handled appropriately?
—	—	3.5 Was the outcome determined without knowledge of predictor information?	4.5 Was selection of predictors based on univariable analysis avoided?*
—	—	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	4.6 Were complexities in the data (eg, censoring, competing risks and sampling of control participants) accounted for appropriately?
—	—	—	4.7 Were relevant model performance measures evaluated appropriately?
—	—	—	4.8 Were model overfitting and optimism in model performance accounted for?*
—	—	—	4.9 Do predictors and their assigned weights in the final model correspond to

			the results from the reported multivariable analysis?*
ROB			
Selection of participants	Predictors of their assessment	Outcome or its determination	Analysis
Applicability			
Included participants or setting does not match the review question	Definition, assessment, or timing of predictors does not match the review question	Its definition,timing or determination does not match the review question	

RCT= randomized controlled trial; ROB=risk of bias.

*Development studies only.

Statistical analysis

Descriptive and summary statistics will be provided and plotted. Counts and percentages will be used to describe categorical outcome data and risk of bias assessment findings. Continuous data, including sample size and predictor count, will be presented using means and standard deviations, and medians and interquartile ranges, for normally and non-normally distributed variables, respectively.

Meta-analytical methods will be used where data pooling is suitable. To pool prediction findings from models developed for different strains of drug-resistant bacteria, a random effects model will be used to obtain a summary estimate of model performance and calibration. As validation studies per model are likely to be few, they will be analysed using the C-statistic and 95% confidence intervals in a random-effect models based on the restricted maximum likelihood estimation method.[27] Finally, 95% prediction intervals, which account for heterogeneity, will be assessed to provide a predicted range of C-statistic values to be used for reference by future validation studies. Heterogeneity will be calculated with the chi-squared and I-squared tests.[28] A funnel plot will be generated to assess publication bias if more than 10 studies are included in a meta-analysis. All statistical analyses will be performed using R Statistical Software V.3.2.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) and Stata V.15.0 (Stata Corporation, College Station, TX, USA).

Patient and public involvement

No patient or member of the public will be involved in the design, conduct, or reporting of this systematic review.

ETHICS AND DISSEMINATION

Ethical approval will not be required because this systematic review will be based on data extracted from previous studies. We plan to publish our findings in peer-reviewed journals dedicated to critical care medicine or nursing research. We also plan to present our results at the International Council of Nurses and at other conferences relevant to critical care.

Amendments

This systematic review protocol will be amended during the peer-review process.

DISCUSSION

The rates of infections caused by multidrug-resistant organisms (e.g., MRSA, CRE, VRE, ESBL-EKP) are increasing. These infections lead to poor outcomes in critically ill patients.[29-32] Several models predicting MDRO infection have been developed,[18-21,33-34] potentially supporting infection control and prevention measures. To the best of our knowledge, one systematic review has evaluated the evidence on models predicting ESBL colonisation or infection.[17] This previous systematic review included studies published before April 2018 and focused on ESBL-EKP infection or colonisation. In contrast, the proposed systematic review has a broader scope, including all MDRO infections acquired in the ICU, and will interrogate five English- and three Chinese-language databases,

as well as grey literature to ensure comprehensive coverage. This review will contribute to the understanding of the risk of MDRO infection among critically ill patients. This review may also support evidence-based approaches to infection control and prevention that do not involve antibiotic use, helping improve outcomes.

Contributorship statement: The study concept and design were conceived by all authors. All authors drafted and revised the manuscript and agree to its content. WY, XYY, YQD, WF, WY will conduct article screening and data extraction. WY, XYY, WY will evaluate the risk of bias and applicability of each included prediction model. WYand YQD will perform data analysis. YC, the corresponding author, is the guarantor of the review.

Competing interests: None declared.

Funding: This study was supported by Peking University Seed Fund (2019SF65).

Provenance and peer review Not commissioned, externally peer reviewed.

References

1 Chedid K. Multidrug-resistant organisms: preventing acquisition and transmission. *Epidemiological Science*. University of Michigan 2021.

2 Wang J, Foxman B, Mody L, et al. Network of microbial and antibiotic interactions drive colonization and infection with multidrug-resistant organisms. *Proc Natl Acad Sci U S A* 2017;114:10467–72.

3 Jernigan JA, Hatfield KM, Wolford H, et al. Multidrug-resistant bacterial infections in us hospitalized patients, 2012–2017. *N Engl J Med* 2020;382:1309–19.

4 China antimicrobial resistance surveillance system. Surveillance report on Bacterial resistance in China in 2020. http://carss.cn/Report/Details?aId=808 (Accessed 17 Nov 2021).

5 Kollef MH, Bassetti M, Francois B, et al. The intensive care medicine research agenda on multidrug-resistant bacteria, antibiotics, and stewardship. *Intensive Care Med* 2017;43:1187–97.

6 Barrasa-Villar JI, Aibar-Remón C, Prieto-Andrés P, et al. Impact on morbidity, mortality, and length of stay of hospital-acquired infections by resistant microorganisms. *Clin Infect Dis* 2017;65:644–52.

7 Abat C, Rolain JM, Dubourg G, et al. Evaluating the clinical burden and mortality attributable to antibiotic resistance: the disparity of empirical data and simple model estimations. *Clin Infect Dis* 2017;65:S58–S63.

8 Giraldi G, Montesano M, Napoli C, et al. Healthcare-associated infections due to multidrug-resistant organisms: a surveillance study on extra hospital stay and direct costs. *Curr Pharm Biotechnol* 2019;20:643–52.

9 Wang D, Zhu D, Chen H, et al. Multidrug-resistant organism healthcare-associated infection and economic burden in general intensive care unite patients. *Chin J Infect Control* 2019;18:648–53.

10 Doernberg SB, Chambers HF. Antimicrobial stewardship approaches in the intensive care unit. *Infect Dis Clin North Am* 2017;31:513–34.

11 Laxminarayan R. The overlooked pandemic of antimicrobial resistance. *Lancet* 2022;399:606–7.

12 World Health Organization. Antimicrobial resistance: global report on surveillance.

Australas Med J 2014;7:237.

13 World Health Organization. *Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in health care facilities*. Geneva: World Health Organization 2017.

14 World Health Organization. *Guidelines on core components of infection prevention and control programmes at the national and acute health care facility level*. Geneva: World Health Organization 2016.

15 Ministry of Health PRC. Technical guidelines for the prevention and control of nosocomial infection with multidrug resistant bacteria (trial). *Chin Crit Care Med* 2011;13:108–9.

16 Huang X, Deng ZD, Ni YX, et al. Chinese experts' consensus on prevention and control of multidrug resistance organism healthcare-associated infection. *Chin J Infect Control* 2015;14:1–9.

17 Mohd Sazlly Lim S, Wong PL, Sulaiman H, et al. Clinical prediction models for esbl-enterobacteriaceae colonization or infection: a systematic review. *J Hosp Infect* 2019;102:8–16.

18 Wang L, Huang X, Zhou J, et al. Predicting the occurrence of multidrug-resistant organism colonization or infection in ICU patients: development and validation of a novel multivariate prediction model. *Antimicrob Resist Infect Control* 2020;9:66.

19 Yoon YK, Kim HJ, Lee WJ, et al. Clinical prediction rule for identifying patients with vancomycin-resistant enterococci (VRE) at the time of admission to the intensive care unit in a low VRE prevalence setting. *J Antimicrob Chemother* 2012;67:2963–69.

20 Ochotorena E, Hernández Morante JJ, Cañavate R et al. Methicillin-resistant Staphylococcus aureus and other multidrug-resistant colonizations/infections in an Intensive Care Unit: predictive factors. *Biol Res Nurs* 2019;21:190–7.

21 Li Y, Shen H, Zhu C et al. Carbapenem-resistant Klebsiella pneumoniae infections among ICU admission patients in central china: prevalence and prediction model. *BioMed Res Int* 2019;2019:9767313.

22 Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.

23 Debray TPA, Damen JAAG, Snell KIE, et al. A guide to systematic review and meta-analysis of prediction model performance. *BMJ* 2017;356:i6460.

24 Moons KGM, de Groot JAH, Bouwmeester W, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the charms checklist. *PLOS Med* 2014;11:e1001744.

25 Moons KGM, Wolff RF, Riley RD, et al. PROBAST: a tool to assess risk of bias and applicability of prediction model studies: explanation and elaboration. *Ann Intern Med* 2019;170:W1–W33.

26 Chen R, Wang SF, Zhou JC, et al. Introduction of the Prediction model Risk of Bias ASsessment Tool: a tool to assess risk of bias and applicability of prediction model studies. *Zhonghua Liu Xing Bing Xue Za Zhi* 2020;41:776–81.

27 Wang D, Zhang W, Luo JH, et al. Prediction models for acute kidney injury in critically ill patients: a protocol for systematic review and critical appraisal. *BMJ Open*

2021;11:e046274.

28 Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.

29 Karlowsky JA, Lob SH, DeRyke CA, et al. Prevalence of ESBL non-CRE Escherichia coli and Klebsiella pneumoniae among clinical isolates collected by the SMART global surveillance programme from 2015 to 2019. *Int J Antimicrob Agents* 2022;59:106535.

30 Li ZJ, Wang KW, Liu B, et al. The distribution and source of MRDOs infection: A retrospective study in 8 ICUs, 2013–2019. *Infect Drug Resist* 2021;14:4983–91.

31 Barnsteiner S, Baty F, Albrich WC, et al. Antimicrobial resistance and antibiotic consumption in intensive care units, Switzerland, 2009 to 2018. *Euro Surveill* 2021;26. 34794535.

32 Brinkwirth S, Ayobami O, Eckmanns T, et al. Hospital-acquired infections caused by enterococci: a systematic review and meta-analysis, WHO European Region, 1 January 2010 to 4 February 2020. *Euro Surveill* 2021;26. 34763754.

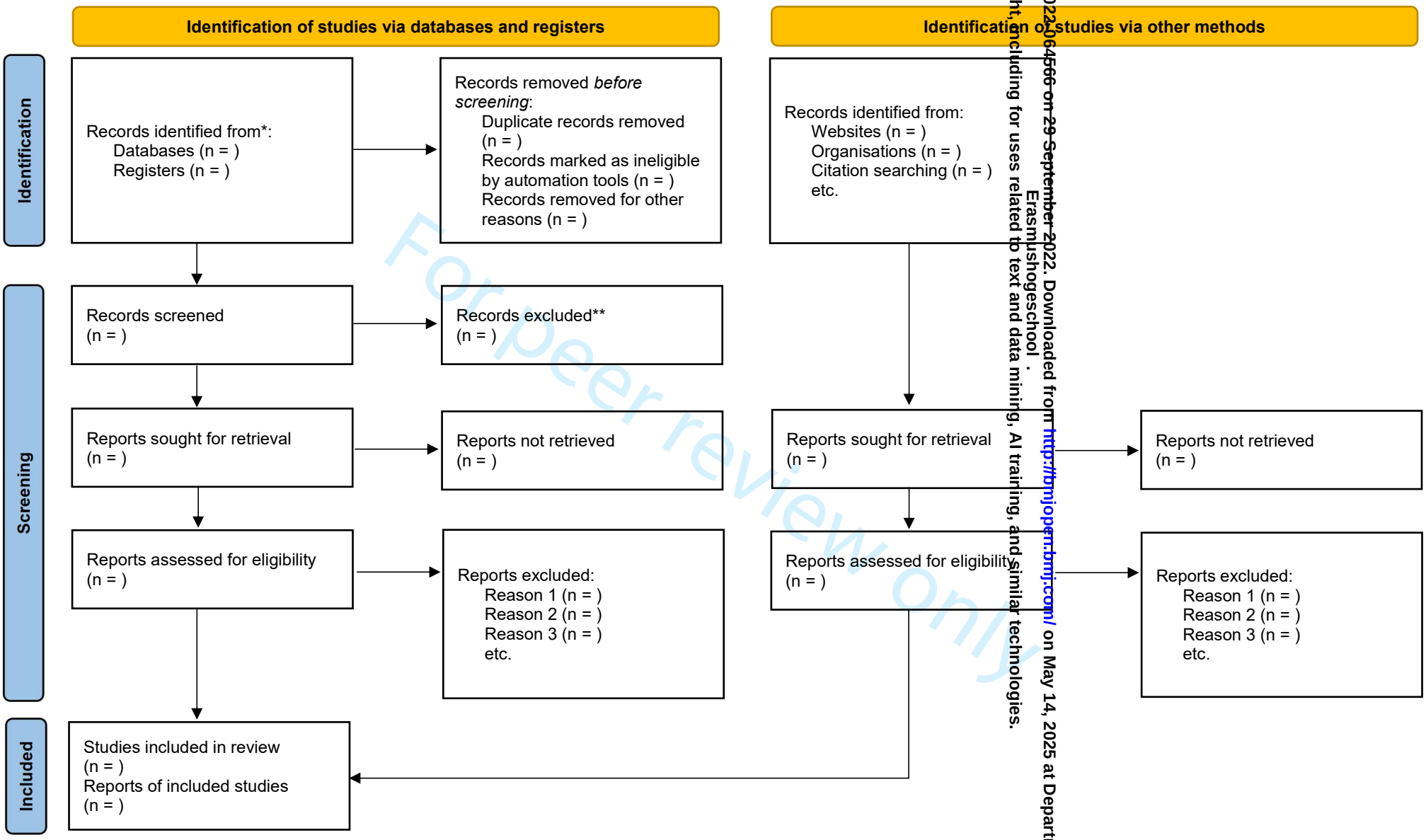
33 Kengkla K, Charoensuk N, Chaichana M et al. Clinical risk scoring system for predicting extended-spectrum β-lactamase-producing Escherichia coli infection in hospitalized patients. *J Hosp Infect* 2016;93:49–56.

34 Lee CH, Chu FY, Hsieh CC, et al. A simple scoring algorithm predicting extended-spectrum β-lactamase producers in adults with community-onset monomicrobial Enterobacteriaceae bacteremia: matters of frequent emergency department users. *Medicine (Baltimore)* 2017;96:e6648.

Figure Legend

Figure 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (2015 when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary file 2 Search Strings in Pubmed and CNKI

Search Strategy in Pubmed

#1:"extended spectrum beta lactamase"[Title/Abstract] OR "multidrug resistan*"[Title/Abstract] OR "extensively drug resistan*"[Title/Abstract] OR "antimicrobial resistan*"[Title/Abstract] OR "antibiotic resistan*"[Title/Abstract] OR "antibacterial resistan*"[Title/Abstract] OR "pandrug resistan*"[Title/Abstract] OR "carbapenem resistant*"[Title/Abstract] OR "colistin resistant*"[Title/Abstract] OR "polymyxin resistant*"[Title/Abstract] OR "methicillin resistant*"[Title/Abstract] OR "vancomycin resistant*"[Title/Abstract]

#2:"acinetobacter baumannii"[Title/Abstract] OR "pseudomonas aeruginosa"[Title/Abstract] OR "escherichia coli"[Title/Abstract] OR "klebsiella pneumoniae"[Title/Abstract] OR "Enterobacteriaceae"[Title/Abstract] OR "staphylococc*"[Title/Abstract] OR "enterococc*"[Title/Abstract] OR "microorganism*"[Title/Abstract] OR "bacteria"[Title/Abstract]

#3: "Acinetobacter baumannii"[MeSH Terms] OR "Pseudomonas aeruginosa"[MeSH Terms] OR "Escherichia coli"[MeSH Terms] OR "Klebsiella pneumoniae"[MeSH Terms] OR "Enterobacteriaceae"[MeSH Terms] OR "Staphylococcus"[MeSH Terms] OR "Enterococcus"[MeSH Terms] OR "Bacteria"[MeSH Terms]

#4:#1 AND (#2 OR #3)

#5: "Methicillin-Resistant Staphylococcus aureus"[MeSH Terms] OR "Carbapenem-Resistant Enterobacteriaceae"[MeSH Terms] OR "Vancomycin-Resistant Enterococci"[MeSH Terms] OR "Vancomycin-Resistant Staphylococcus aureus"[MeSH Terms] OR "drug resistance, microbial"[MeSH Terms] OR "drug resistance, multiple, bacterial"[MeSH Terms]

#6: #4 OR #5

#7: "prediction model*"[Title/Abstract] OR "predicted model*"[Title/Abstract] OR "predictive model*"[Title/Abstract] OR "risk model*"[Title/Abstract] OR "risk prediction"[Title/Abstract] OR "risk calculat*"[Title/Abstract] OR "risk assessment"[Title/Abstract] OR "predicted factor*"[Title/Abstract] OR "predictive factor*"[Title/Abstract] OR "prognostic model*"[Title/Abstract] OR "prognosis model*"[Title/Abstract] OR "prognostic factor*"[Title/Abstract] OR "scoring model*"[Title/Abstract] OR "scoring system"[Title/Abstract]

#8: "Risk Assessment"[MeSH Terms] OR "Survival Analysis"[MeSH Terms] OR "Predictive Value of Tests"[MeSH Terms]

#9: #7 OR #8

#10: "critical care"[Title/Abstract] OR "intensive care unit*"[Title/Abstract] OR "critical illness"[Title/Abstract] OR "ICU"[Title/Abstract] OR "intensive care"[Title/Abstract] OR "critically ill"[Title/Abstract]

#11:"Critical Care"[MeSH Terms] OR "Critical Illness"[MeSH Terms] OR "Intensive Care Units"[MeSH Terms]

#12: #10 OR #11

#13: #6 AND #9 AND #12

Filters applied: Chinese, English.

Search Strategy in CNKI

#1: (主题=耐药) OR (主题=耐抗生素) OR (主题=耐细菌) OR (主题=耐甲氧西林) OR (主题= 耐碳青霉烯) OR (主题=耐万古霉素) OR (主题=超广谱β内酰胺酶) OR (主题=耐粘菌素) OR (主题=耐多粘菌素)

#2: (主题=细菌) OR (主题=微生物) OR (主题=肠杆菌) OR (主题=肠球菌) OR (主题=鲍曼不动杆菌) OR (主题=铜绿假单胞菌) OR (主题=肺炎克雷伯菌) OR (主题=金黄色葡萄球菌) OR (主题=结核分枝杆菌)

#3: (主题=预测模型) OR (主题= 预警模型) OR (主题=预判模型) OR (主题=判别模型) OR (主题=风险模型) OR (主题=风险预测) OR (主题=风险评估) OR (主题=预测因素) OR (主题=评分模型) OR (主题=评分系统)

#4: (主题=重症监护) OR (主题=监护室) OR (主题=ICU)

#5: #1 AND #2 AND #3 AND #4

BMJ Open

Clinical prediction models for multidrug-resistant organism colonization or infection in critically ill patients: A systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-064566.R1
Article Type:	Protocol
Date Submitted by the Author:	27-Jul-2022
Complete List of Authors:	Wang, Yi; Peking University First Hospital, Intensive Care Unit Xiao, Yanyan; Peking University First Hospital Yang, Qidi; Peking University First Hospital Wang, Fang; Peking University First Hospital Wang, Ying; Peking University First Hospital Yuan, Cui; Peking University First Hospital
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Nursing, Infectious diseases
Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Infection control < INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

Title: Clinical prediction models for multidrug-resistant organism colonization or infection in critically ill patients: A systematic review protocol

Yi Wang, MS, RN; Yanyan Xiao, MS, RN; Qidi Yang, BS, RN; Fang Wang, BS, RN; Ying Wang, BS, RN; Cui Yuan, MS, RN

Intensive Care Unit, Peking University First Hospital, Beijing, China

***Corresponding author details:** Cui Yuan, Department of Critical Care Medicine, Peking University First Hospital, No.8 Xishiku Street, Beijing, China. E-mail: yuancui2013@sina.com

Word Count: 3542 words

ABSTRACT

Introduction: Multidrug-resistant organisms (MDROs) are pathogenic bacteria that are the leading cause of hospital-acquired infection which is associated with high morbidity and mortality rates in intensive care units, increasing hospitalization duration and cost. Predicting the risk of MDRO colonization or infection for critically ill patients supports clinical decision-making. Several models predicting MDRO colonization or infection have been developed; however, owing to different disease scenarios, bacterial species, and few externally validated cohorts in different prediction models; the stability and applicability of these models for MDRO colonization or infection in critically ill patients are controversial. In addition, there are currently no standardized risk scoring systems to predict MDRO colonization or infection in critically ill patients. The aim of this systematic review is to summarise and assess models predicting MDRO colonization or infection in critically ill patients and to compare their predictive performance.

Methods and analysis: We will perform a systematic search of PubMed, Cochrane Library, CINAHL, Embase, China National Knowledge Infrastructure, and Wanfang databases to identify all studies describing the development and/or external validation of models predicting MDRO colonization or infection in critically ill patients. Two reviewers will independently extract and review the data using the Data Extraction for Systematic Reviews of Prediction Modelling Studies checklist; they will also assess the risk of bias using the Prediction Model Risk of Bias Assessment Tool. Quantitative data on model predictive performance will be synthesised in meta-analyses, as applicable.

Ethics and dissemination: Ethical permissions will not be required because all data will be

extracted from published studies. We intend to publish our results in peer-reviewed scientific journals and to present them at international conferences on critical care.

PROSPERO registration number CRD42022274175

Strengths and limitations of this study

- This systematic review will provide an overview of models predicting MDRO colonization or infection in critically ill patients, helping inform evidence-based recommendations.
- This systematic review will use the Prediction Model Risk of Bias Assessment Tool to evaluate the methodological quality of included studies.
- Meta-analysis and narrative summaries will be used for quantitative and qualitative evidence assessment, including pooled estimates, as suitable.
- The findings of this systematic review will provide a foundation for predicting and preventing MDRO using evidence-based methodology, helping reduce the rates of infection in critically ill patients.
- Potential limitations of this review include heterogenous data sources, e.g., studies with varied designs, populations, MDRO and ICU types, and timelines, which may require further research to standardise.

INTRODUCTION

Multidrug-resistant organisms (MDROs) increase the risk of poor outcomes worldwide.[1] MDROs, including methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Enterobacteriaceae* (CRE), vancomycin-resistant *Enterococcus* (VRE), and extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-EKP), etc. among others, are the leading causes of hospital-acquired infections.[2] A recent study, based on data from patients treated across 890 hospitals in the United States from 2012 to 2017, reported 622,390 cases of infection; MRSA and ESBL infections accounted for most of these cases.[3] In China, the national report on bacterial resistance in 2020 found that the detection rates of erythromycin-resistant *Streptococcus pneumoniae* (ERSP), methicillin-resistant coagulase-negative *Staphylococci* (MRCNS), and carbapenem-resistant *Acinetobacter baumanni* (CRAB) were highest at tertiary hospitals.[4] The intensive care unit (ICU) has the highest incidence of MDROs across all hospital departments. Even in developed countries, where infection control is well-organised, approximately 25% of ICU patients experience at least one hospital-acquired infection; the corresponding rate for developing countries is 50%.[5] Meanwhile, in China, the detection rates of ERSP, MRCNS, and CRAB in the ICU are estimated at 94.4%, 84.2%, and 78.2%, respectively.[4]

MDROs increase morbidity and mortality risks, and extend hospitalisation duration.[6] In 2015, there were 700,000 reported deaths due to MDRO infections globally; this number is expected to exceed 10 million by 2050.[7] In addition, cumulative economic losses related to bacterial antimicrobial resistance have been reported as $100 trillion. Giraldi et al. [8] estimated that infections extended general hospitalisations and ICU stays by an average of 18.8 days

and 21.2 days, respectively. Wang et al.[9] reported that the length of ICU stay in patients with MDRO infection was 26.0 days longer than that of those without infection. Hence, infection control and prevention are important in the ICU setting. Antibiotic use helps manage infection risk and spread.[10] Nevertheless, it increases the risk of antimicrobial resistance, which is growing to pandemic proportions, hindering treatment progress.[11] According to the World Health Organization, most antimicrobials were discovered in the 20th century, and the development of new antibiotics has been limited since then.[12]

Guidelines for the prevention and control of MDRO outline some non-pharmaceutical interventions.[13-16] They require that risk factors for MDRO be ascertained to support accurate treatment choices. As no single risk factor can reliably predict MDRO infection due to disease heterogeneity and complexity, clinical prediction models are used for risk assessments.[17] Internally and externally validated prediction models may help identify critically ill patients at risk of MDRO, supporting suitable antibiotic prescriptions and infection control measures. For example, Wang et al.[18] reported that male sex, higher C-reactive protein levels, and higher Pitt bacteraemia scores were independent predictors of MDRO colonization or infection. In addition, Yoon et al.[19] showed that ICU readmission during hospitalisation, chronic obstructive lung disease, recent antibiotic treatment, and recent vancomycin use were independent risk factors for VRE carriage at ICU admission. Meanwhile, Ochotorena[20] found that an Acute Physiology and Chronic Health Evaluation score of more than 15 points and hospitalisation duration of more than 4 days increased the risk of MRSA colonisation/infection. Finally, Li et al.[21] proposed that carbapenem-resistant *Klebsiella pneumoniae* (CRKP) colonisation or infection in the previous year, CD4/CD8 cell count ratio

of less than 1, and parenteral nutrition duration of more than 48 h were independent risk factors for CRKP infection. These evidence notwithstanding, to the best of our knowledge, there is no globally endorsed prediction model for MDRO infection, and no risk-classification tools are used for the prediction of MDRO colonization or infection in critically ill patients in routine clinical practice. Therefore, a critical evaluation of studies proposing potentially relevant prediction models is warranted.

Review objectives

The aim of this systematic review is to evaluate the reporting and methodology of studies on models predicting MDRO colonization or infection in critically ill patients. We will apply the Prediction Model Risk of Bias Assessment Tool (PROBAST) to assess the risk of bias in studies on model development and validation. The specific objectives of this review are to:

1. Summarise models predicting MDRO colonization or infection in critically ill patients.

2. Critically assess the methodology of these models.

3. Qualitatively describe the relevant models.

4. Conduct meta-analyses, as suitable, to estimate the overall performance of each risk model for predicting MDRO colonization or infection.

METHODS AND ANALYSIS

This systematic review protocol has been registered on the International Prospective Register of Systematic Reviews on February 2, 2022 (CRD42022274175). This protocol is presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Protocols (PRISMA-P) guidelines (Supplementary file 1).[22] This systematic review is scheduled to be performed from April to December 2022.

Literature search

PubMed, CINAHL, Embase Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang databases will be searched from inception until April 2022. Relevant unpublished studies and grey literature will be identified using Google, conference articles, shortlisted study reference lists, index-related articles on PubMed, and existing relevant reviews.

The following search strategy with related key words was developed: (extended-spectrum beta-lactamase OR multidrug-resistan* OR extensively drug-resistan* OR antimicrobial-resistan* OR antibiotic-resistan* OR antibacterial-resistan* OR pandrug-resistan* OR carbapenem-resistant* OR colistin-resistant* OR polymyxin-resistant* OR methicillin-resistant* OR vancomycin-resistant*) AND (Acinetobacter baumannii OR Pseudomonas aeruginosa OR Escherichia coli OR Klebsiella pneumoniae OR Enterobacteriaceae OR Staphylococc* OR Enterococc* OR microorganism* OR bacteria) AND ((prediction model* OR predicted model* OR predictive model* OR risk model* OR risk prediction OR predicted factor* OR predictive factor* OR prognostic model* prognosis model* OR prognostic factor* OR scoring model*) AND (critical care OR intensive care unit* OR critical illness OR ICU OR intensive care OR critically ill) in English and (耐药 OR 耐抗生素 OR 耐细菌 OR 耐甲氧西林 OR 耐碳青霉烯 OR 耐万古霉素 OR 超广谱 β 内酰胺酶 OR 耐粘菌素 OR 耐多粘菌素) AND (细菌 OR 微生物 OR 肠杆菌 OR 肠球菌 OR 鲍

曼不动杆菌 OR 铜绿假单胞菌 OR 肺炎克雷伯菌 OR 金黄色葡萄球菌 OR 结核分枝杆菌) AND (预测模型 OR 预警模型 OR 预判模型 OR 判别模型 OR 风险模型 OR 风险预测 OR 风险评估 OR 预测因素 OR 评分模型 OR 评分系统) AND (ICU OR 重症监护 OR 监护室) in Chinese. We will use medical subject headings and free-text to identify prediction model studies. The search methods for databases are included in Supplementary file 2.

Eligibility criteria

Studies may be included in this review if they are primary experimental or observational studies on the development and/or validation of a multi-variable prediction model for MDRO colonization or infection in critically ill patients and were published any time before April 2022. Population, intervention, comparator, outcomes, timing, and setting characteristics[23] are presented in Table 1. Additional eligibility criteria include the use of comparative study designs such as clinical trials, cohort, case-control, and cross-sectional studies and published in the English or Chinese language.

We will exclude studies using the following criteria: (1) conference abstracts, editorials, clinical case reviews, letters, commentaries, book chapters, or systematic reviews; (2) studies involving other types of patients who are not critically ill; (3) studies on the associations between clinical variables and MDRO colonization or infection; (4) studies in which the study setting was in the community.

Table 1 Eligibility criteria for the systematic review framed using the PICOTS* system

Item	Definition
Population	Both male and female adult critically ill patients (aged ≥18 years) will be considered. The exclusion criteria are:(1) ICU duration less than 24 h; (2)

	MDROs detected before the patient entered the ICU or within the first 48 h in the ICU.
Intervention	Any prediction model which predicts the risk of MDRO colonization or infection in patients with critical illness, to distinguish critically ill patients with poor outcomes (who will develop multidrug-resistant bacterial infection), with reporting of at least two predictors. Any disease caused by MDRO will be included. All types of MDROs, including MRSA, CRE, VRE, ESBL-EKP, or others will be included.
Comparator	Not applicable.
Outcomes	The outcome (to be predicted) is MDRO cultured from any of the clinical specimens after 48 hours of admission to the ICU. MDRO infection is defined as the invasion of the body tissues by MDROs resulting in disease. Infectious diseases included but are not limited to bacteremia, pneumonia, and infections of the skin and soft issue, urinary tract, bloodstream, or abdomen. The legal communicable disease diagnostic criteria approved by countries or international organizations were applied to diagnose these infectious diseases. MDRO colonization is defined as any patient who had MDRO positive culture results and with no symptoms of clinical infection found.
Timing	Predictive variables measured at any time point during the course of the MDRO colonization or infection while patients were being treated in the ICU.
Setting	Any type of intensive care unit

PICOTS = population, intervention, comparator, outcomes, timing of prediction and of outcomes, and setting.

Study selection

We will remove record duplicates using the automatic replay function in NoteExpress software and by-hand assessments after each database search. Two researchers (WY, XYY), trained at the Joanna Briggs Institute, will independently screen the titles and abstracts to identify relevant studies using NoteExpress software. Full-text manuscripts will be retrieved and independently evaluated for inclusion. Disagreements will be resolved by consensus or a third-researcher (YC or WF) arbitration. The selection process will be presented in a PRISMA flow diagram (Figure 1).

Data abstraction

At least two trained reviewers (WY, YQD) will independently extract data from included studies. A standardised data extraction form will be created based on the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (the CHARMS checklist).[24] This data extraction form will be piloted on five papers and amended by at least three reviewers (WY, WF, XYY). Any revisions will be implemented based on group consensus. Data on the following study characteristics will be extracted: first author, year of publication, study design and characteristics, source of data, participant eligibility, recruitment, description and sample size, type of ICU, the number and/or incidence of predicted outcomes, the type of MDRO, infectious diseases, candidate predictors, missing data, modelling method and evaluation, risk ratios or odds ratios for the predictors (both overall and stratified), model performance and calibration (e.g., calibration plot and Hosmer-Lemeshow test), discriminating capacity (e.g., AUC and Concordance Index) and model evaluation (e.g., sensitivity, specificity, positive and negative predictive values), as well as the study discussion/conclusions. If the data of interest are missing or unclear, we will refer to any cited papers and contact corresponding authors to obtain the desired information. Disagreements will be resolved by consensus between the two reviewers or by arbitration by a third (YC or WF) researcher. The lead investigator (YC) will upload the data and records on a shared secure platform accessible to all investigators (Baidu Netdisk, Baidu Netcom Technology Corporation, Beijing, China).

Critical appraisal

Two reviewers (WY, XYY) will independently appraise each included prediction model using the PROBAST instrument, a tool for assessing the risk of bias and applicability of diagnostic and prognostic prediction model studies, which was published in 2019.[25 26] As well as serving clinical medical personnel who are considering using a prediction model, it is also used to help researchers develop a model or include models in a systematic review or meta-analysis.[27] In recent years, PROBAST has been used in systematic reviews of infection prediction models, like COVID-19 infection,[28] but unfortunately, it has not been fully applied in prediction models of MDRO colonization or infection. PROBAST is widely used for quality evaluation of prediction models, therefore, this study will use this tool for critical appraisal. PROBAST includes four steps, which are described in detail to support assessment completion. The four domains are: participants, predictors, outcome, and analysis, and are divided into a total of 20 questions to support structured risk of bias assessments. Each domain is rated as at a “high”, “low”, or “unclear” risk of bias. Any disagreement will be resolved by consensus and consultation with a third reviewer (YC/WY).

Statistical analysis

We will also produce a narrative summary of the included studies. A summary of the characteristics (e.g., study design, population size, national location, year, participants' characteristics, species of bacteria and statistical method) will be included. Counts and percentages will be used to describe categorical outcome data and risk of bias assessment findings. Continuous data, including sample size and predictor count, will be presented using means and standard deviations, and medians and interquartile ranges, for normally and non-normally distributed variables, respectively.

Meta-analytical methods will be used where data pooling is suitable. We will follow the recently published framework for the meta analysis of prediction models.[29,30] We will group study results according to the species of bacteria (e.g., MDRO, CRE, CRKP). To pool prediction findings from models developed for different strains of drug-resistant bacteria, a random effects model will be used to obtain a summary estimate of model performance and calibration. As validation studies per model are likely to be few, they will be analysed using the C-statistic and 95% confidence intervals in a random-effect models based on the restricted maximum likelihood estimation method.[31] Finally, 95% prediction intervals, which account for heterogeneity, will be assessed to provide a predicted range of C-statistic values to be used for reference by future validation studies. Heterogeneity will be calculated with the chi-squared and I-squared tests (<25%, low heterogeneity; 25%-50%, moderate heterogeneity; and >50%, strong heterogeneity).[32] A funnel plot will be generated to assess publication bias if more than 10 studies are included in a meta-analysis. All statistical analyses will be performed using R Statistical Software V.3.2.3 (R Core Team, R Foundation

for Statistical Computing, Vienna, Austria) and Stata V.15.0 (Stata Corporation, College Station, TX, USA). We will use the R package " metamisc " for the meta-analysis of prediction models, which is available from https://CRAN.R-project.org/package=metamisc.

Patient and public involvement

No patient or member of the public will be involved in the design, conduct, or reporting of this systematic review.

ETHICS AND DISSEMINATION

Ethical approval will not be required because this systematic review will be based on data extracted from previous studies. We plan to publish our findings in peer-reviewed journals dedicated to critical care medicine or nursing research. We also plan to present our results at the International Council of Nurses and at other conferences relevant to critical care.

Amendments

This systematic review protocol will be amended during the peer-review process.

DISCUSSION

The rates of infections caused by multidrug-resistant organisms (e.g., MRSA, CRE, VRE, ESBL-EKP) are increasing. These infections lead to poor outcomes in critically ill patients.[33-36] Several models predicting MDRO infection have been developed,[18-21,37-38] potentially supporting infection control and prevention measures. To the best of our

knowledge, one systematic review has evaluated the evidence on models predicting ESBL colonization or infection.[17] This previous systematic review included studies published before April 2018 and focused on ESBL-EKP infection or colonisation. In contrast, this proposed systematic review has a broader scope, including all MDRO colonization or infections acquired in the ICU, and will interrogate five English- and three Chinese-language databases, as well as grey literature to ensure comprehensive coverage. There is a strong research team and sufficient time to ensure literature screening, quality evaluation and data extraction. Owing to the complex and scattered influencing factors, we will package the similarity factors, and conduct a meta-analysis to draw valuable conclusions, which will be completed with the help of a statistician and an evidence-based expert. This review will contribute to the understanding of the risk of MDRO colonization or infection among critically ill patients. This review may also support evidence-based approaches to infection control and prevention that do not involve antibiotic use, helping improve outcomes.

Contributorship statement: The study concept and design were conceived by all authors. All authors drafted and revised the manuscript and agree to its content. WY, XYY, YQD, WF, WY will conduct article screening and data extraction. WY, XYY, WY will evaluate the risk of bias and applicability of each included prediction model. WY and YQD will perform data analysis. YC, the corresponding author, is the guarantor of the review.

Competing interests: None declared.

Funding: The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Provenance and peer review Not commissioned, externally peer reviewed.

References

1 Chedid K. Multidrug-resistant organisms: preventing acquisition and transmission. *Epidemiological Science*. University of Michigan 2021.

2 Wang J, Foxman B, Mody L, et al. Network of microbial and antibiotic interactions drive colonization and infection with multidrug-resistant organisms. *Proc Natl Acad Sci U S A* 2017;114:10467–72.

3 Jernigan JA, Hatfield KM, Wolford H, et al. Multidrug-resistant bacterial infections in us hospitalized patients, 2012–2017. *N Engl J Med* 2020;382:1309–19.

4 China antimicrobial resistance surveillance system. Surveillance report on Bacterial resistance in China in 2020. http://carss.cn/Report/Details?aId=808 (Accessed 17 Nov 2021).

5 Kollef MH, Bassetti M, Francois B, et al. The intensive care medicine research agenda on multidrug-resistant bacteria, antibiotics, and stewardship. *Intensive Care Med* 2017;43:1187–97.

6 Barrasa-Villar JI, Aibar-Remón C, Prieto-Andrés P, et al. Impact on morbidity, mortality, and length of stay of hospital-acquired infections by resistant microorganisms. *Clin Infect Dis* 2017;65:644–52.

7 Abat C, Rolain JM, Dubourg G, et al. Evaluating the clinical burden and mortality attributable to antibiotic resistance: the disparity of empirical data and simple model estimations. *Clin Infect Dis* 2017;65:S58–S63.

8 Giraldi G, Montesano M, Napoli C, et al. Healthcare-associated infections due to

multidrug-resistant organisms: a surveillance study on extra hospital stay and direct costs. *Curr Pharm Biotechnol* 2019;20:643–52.

9 Wang D, Zhu D, Chen H, et al. Multidrug-resistant organism healthcare-associated infection and economic burden in general intensive care unite patients. *Chin J Infect Control* 2019;18:648–53.

10 Doernberg SB, Chambers HF. Antimicrobial stewardship approaches in the intensive care unit. *Infect Dis Clin North Am* 2017;31:513–34.

11 Laxminarayan R. The overlooked pandemic of antimicrobial resistance. *Lancet* 2022;399:606–7.

12 World Health Organization. *Antimicrobial resistance: global report on surveillance*. Geneva: World Health Organization 2014.

13 World Health Organization. *Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in health care facilities*. Geneva: World Health Organization 2017.

14 World Health Organization. *Guidelines on core components of infection prevention and control programmes at the national and acute health care facility level*. Geneva: World Health Organization 2016.

15 Ministry of Health PRC. Technical guidelines for the prevention and control of nosocomial infection with multidrug resistant bacteria (trial). *Chin Crit Care Med* 2011;13:108–9.

16 Huang X, Deng ZD, Ni YX, et al. Chinese experts' consensus on prevention and control of multidrug resistance organism healthcare-associated infection. *Chin J Infect Control*

2015;14:1–9.

17 Mohd Sazlly Lim S, Wong PL, Sulaiman H, et al. Clinical prediction models for esbl-enterobacteriaceae colonization or infection: a systematic review. *J Hosp Infect* 2019;102:8–16.

18 Wang L, Huang X, Zhou J, et al. Predicting the occurrence of multidrug-resistant organism colonization or infection in ICU patients: development and validation of a novel multivariate prediction model. *Antimicrob Resist Infect Control* 2020;9:66.

19 Yoon YK, Kim HJ, Lee WJ, et al. Clinical prediction rule for identifying patients with vancomycin-resistant enterococci (VRE) at the time of admission to the intensive care unit in a low VRE prevalence setting. *J Antimicrob Chemother* 2012;67:2963–9.

20 Ochotorena E, Hernández Morante JJ, Cañavate R et al. Methicillin-resistant Staphylococcus aureus and other multidrug-resistant colonizations/infections in an Intensive Care Unit: predictive factors. *Biol Res Nurs* 2019;21:190–7.

21 Li Y, Shen H, Zhu C et al. Carbapenem-resistant Klebsiella pneumoniae infections among ICU admission patients in central china: prevalence and prediction model. *BioMed Res Int* 2019;2019:9767313.

22 Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.

23 Debray TPA, Damen JAAG, Snell KIE, et al. A guide to systematic review and meta-analysis of prediction model performance. *BMJ* 2017;356:i6460.

24 Moons KGM, de Groot JAH, Bouwmeester W, et al. Critical appraisal and data

extraction for systematic reviews of prediction modelling studies: the charms checklist. *PLOS Med* 2014;11:e1001744.

25 Moons KGM, Wolff RF, Riley RD, et al. PROBAST: a tool to assess risk of bias and applicability of prediction model studies: explanation and elaboration. *Ann Intern Med* 2019;170:W1–W33.

26 Wolff RF, Moons KGM, Riley RD, et al. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. *Ann Intern Med* 2019;170:51-8.

27 de Jong Y, Ramspek CL, Zoccali C, et al. Appraising prediction research: a guide and meta-review on bias and applicability assessment using the Prediction model Risk Of Bias ASsessment Tool (PROBAST). *Nephrology (Carlton)* 2021;26:939-47.

28 Wynants L, Van Calster B, Collins GS, et al. Update to living systematic review on prediction models for diagnosis and prognosis of covid-19. *BMJ* 2021;372:n236

29 Debray TP, Damen JA, Riley RD, et al. A framework for meta-analysis of prediction model studies with binary and time-to-event outcomes. *Statistical Methods Med Res* 2019;28:2768-86.

30 Debray TP, Damen JA, Snell KI, et al. A guide to systematic review and meta-analysis of prediction model performance. *BMJ* 2017; 356: i6460

31 Wang D, Zhang W, Luo JH, et al. Prediction models for acute kidney injury in critically ill patients: a protocol for systematic review and critical appraisal. *BMJ Open* 2021;11:e046274.

32 Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.

33 Karlowsky JA, Lob SH, DeRyke CA, et al. Prevalence of ESBL non-CRE Escherichia coli and Klebsiella pneumoniae among clinical isolates collected by the SMART global surveillance programme from 2015 to 2019. *Int J Antimicrob Agents* 2022;59:106535.

34 Li ZJ, Wang KW, Liu B, et al. The distribution and source of MRDOs infection: A retrospective study in 8 ICUs, 2013–2019. *Infect Drug Resist* 2021;14:4983–91.

35 Barnsteiner S, Baty F, Albrich WC, et al. Antimicrobial resistance and antibiotic consumption in intensive care units, Switzerland, 2009 to 2018. *Euro Surveill* 2021;26. 34794535.

36 Brinkwirth S, Ayobami O, Eckmanns T, et al. Hospital-acquired infections caused by enterococci: a systematic review and meta-analysis, WHO European Region, 1 January 2010 to 4 February 2020. *Euro Surveill* 2021;26: 2001628.

37 Kengkla K, Charoensuk N, Chaichana M et al. Clinical risk scoring system for predicting extended-spectrum β-lactamase-producing Escherichia coli infection in hospitalized patients. *J Hosp Infect* 2016;93:49–56.

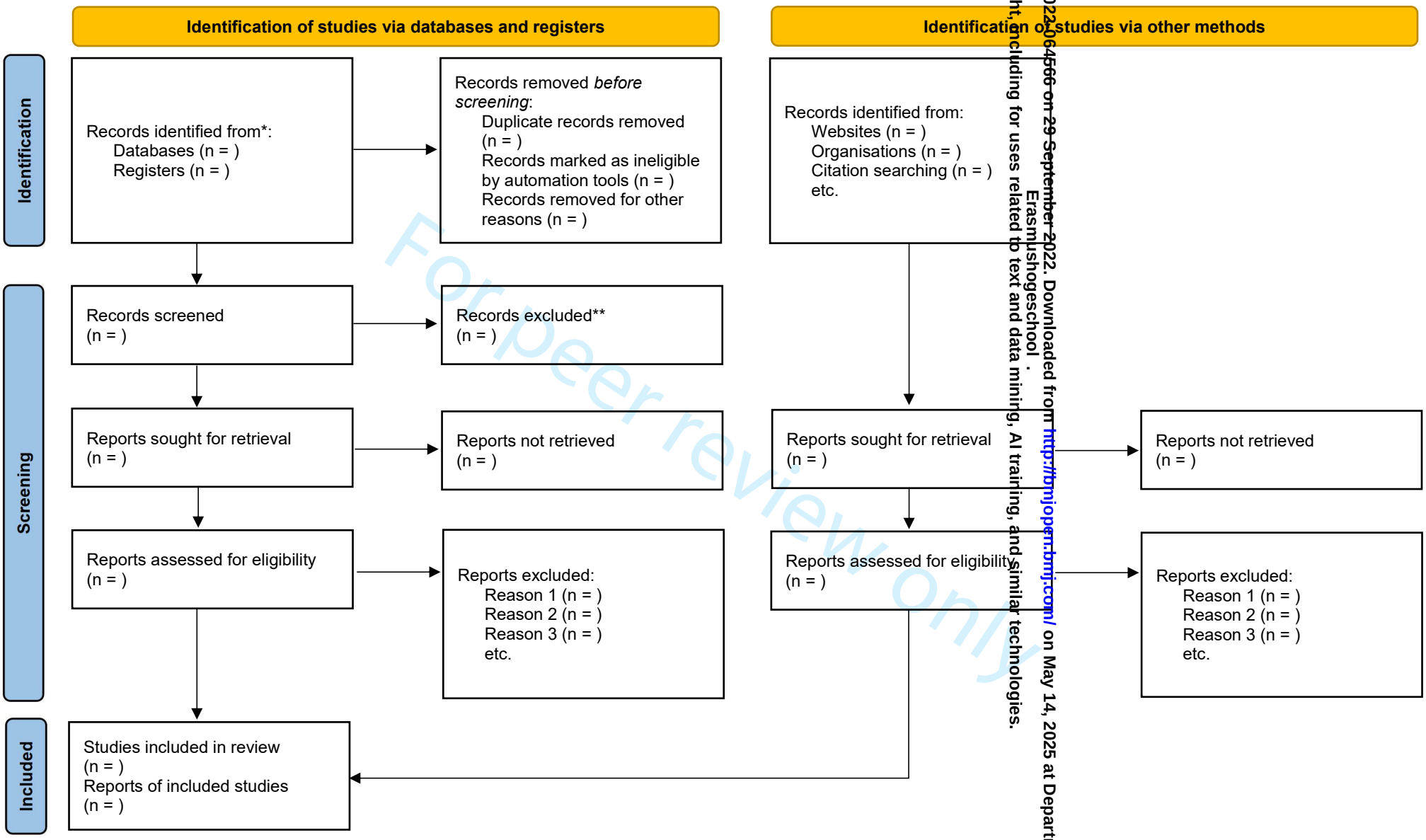
38 Lee CH, Chu FY, Hsieh CC, et al. A simple scoring algorithm predicting extended-spectrum β-lactamase producers in adults with community-onset monomicrobial Enterobacteriaceae bacteremia: matters of frequent emergency department users. *Medicine*

(Baltimore) 2017;96:e6648.

Figure Legend

Figure 1 PRISMA 2020 flow diagram for new systematic reviews which includes searches of databases, registers and other sources

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (2015 when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary file 2 Search Strings

Search Strategy in **Pubmed**

#1:"extended spectrum beta lactamase"[Title/Abstract] OR "multidrug resistan*"[Title/Abstract] OR "extensively drug resistan*"[Title/Abstract] OR "antimicrobial resistan*"[Title/Abstract] OR "antibiotic resistan*"[Title/Abstract] OR "antibacterial resistan*"[Title/Abstract] OR "pandrug resistan*"[Title/Abstract] OR "carbapenem resistant*"[Title/Abstract] OR "colistin resistant*"[Title/Abstract] OR "polymyxin resistant*"[Title/Abstract] OR "methicillin resistant*"[Title/Abstract] OR "vancomycin resistant*"[Title/Abstract]

#2:"acinetobacter baumannii"[Title/Abstract] OR "pseudomonas aeruginosa"[Title/Abstract] OR "escherichia coli"[Title/Abstract] OR "klebsiella pneumoniae"[Title/Abstract] OR "Enterobacteriaceae"[Title/Abstract] OR "staphylococc*"[Title/Abstract] OR "enterococc*"[Title/Abstract] OR "microorganism*"[Title/Abstract] OR "bacteria"[Title/Abstract]

#3: "Acinetobacter baumannii"[MeSH Terms] OR "Pseudomonas aeruginosa"[MeSH Terms] OR "Escherichia coli"[MeSH Terms] OR "Klebsiella pneumoniae"[MeSH Terms] OR "Enterobacteriaceae"[MeSH Terms] OR "Staphylococcus"[MeSH Terms] OR "Enterococcus"[MeSH Terms] OR "Bacteria"[MeSH Terms]

#4:#1 AND (#2 OR #3)

#5: "Methicillin-Resistant Staphylococcus aureus"[MeSH Terms] OR "Carbapenem-Resistant Enterobacteriaceae"[MeSH Terms] OR "Vancomycin-Resistant Enterococci"[MeSH Terms] OR "Vancomycin-Resistant Staphylococcus aureus"[MeSH Terms] OR "drug resistance, microbial"[MeSH Terms] OR "drug resistance, multiple, bacterial"[MeSH Terms]

#6: #4 OR #5

#7: "prediction model*"[Title/Abstract] OR "predicted model*"[Title/Abstract] OR "predictive model*"[Title/Abstract] OR "risk model*"[Title/Abstract] OR "risk prediction"[Title/Abstract] OR "risk calculat*"[Title/Abstract] OR "risk assessment"[Title/Abstract] OR "predicted factor*"[Title/Abstract] OR "predictive factor*"[Title/Abstract] OR "prognostic model*"[Title/Abstract] OR "prognosis model*"[Title/Abstract] OR "prognostic factor*"[Title/Abstract] OR "scoring model*"[Title/Abstract] OR "scoring system"[Title/Abstract]

#8: "Risk Assessment"[MeSH Terms] OR "Survival Analysis"[MeSH Terms] OR "Predictive Value of Tests"[MeSH Terms]

#9: #7 OR #8

#10: "critical care"[Title/Abstract] OR "intensive care unit*"[Title/Abstract] OR "critical illness"[Title/Abstract] OR "ICU"[Title/Abstract] OR "intensive care"[Title/Abstract] OR "critically ill"[Title/Abstract]

#11:"Critical Care"[MeSH Terms] OR "Critical Illness"[MeSH Terms] OR "Intensive Care Units"[MeSH Terms]

#12: #10 OR #11

#13: #6 AND #9 AND #12

Filters applied: Chinese, English.

Search Strategy in **Embase**

#1: 'extended spectrum beta lactamase':ti,ab,kw OR 'multidrug resistan*':ti,ab,kw OR 'extensively drug resistan*':ti,ab,kw OR 'antimicrobial resistan*':ti,ab,kw OR 'antibiotic resistan*':ti,ab,kw OR 'antibacterial resistan*':ti,ab,kw OR 'pandrug resistan*':ti,ab,kw OR 'carbapenem resistant*':ti,ab,kw OR 'colistin resistant*':ti,ab,kw OR 'polymyxin resistant*':ti,ab,kw OR 'methicillin resistant*':ti,ab,kw OR 'vancomycin resistant*':ti,ab,kw

#2: 'acinetobacter baumannii':ti,ab,kw OR 'pseudomonas aeruginosa':ti,ab,kw OR 'escherichia coli':ti,ab,kw OR 'klebsiella pneumoniae':ti,ab,kw OR enterobacteriaceae:ti,ab,kw OR staphylococc*:ti,ab,kw OR enterococc*:ti,ab,kw OR microorganism*:ti,ab,kw OR bacteria:ti,ab,kw

#3: 'acinetobacter baumannii'/exp OR 'pseudomonas aeruginosa'/exp OR 'escherichia coli'/exp OR 'klebsiella pneumoniae'/exp OR 'enterobacteriaceae'/exp OR 'staphylococcus'/exp OR 'enterococcus'/exp OR 'bacterium'/exp

#4:#1 AND (#2 OR #3)

#5: 'methicillin resistant staphylococcus aureus'/exp OR 'carbapenem-resistant enterobacteriaceae'/exp OR 'vancomycin resistant enterococcus'/exp OR 'vancomycin resistant staphylococcus aureus'/exp OR 'antibiotic resistance'/exp OR 'multidrug resistance'/exp

#6: #4 OR #5

#7: 'prediction model*':ti,ab,kw OR 'predicted model*':ti,ab,kw OR 'predictive model*':ti,ab,kw OR 'risk model*':ti,ab,kw OR 'risk prediction':ti,ab,kw OR 'risk calculat*':ti,ab,kw OR 'risk assessment':ti,ab,kw OR 'predicted factor*':ti,ab,kw OR 'predictive factor*':ti,ab,kw OR 'prognostic model*':ti,ab,kw OR 'prognosis model*':ti,ab,kw OR 'prognostic factor*':ti,ab,kw OR 'scoring model*':ti,ab,kw OR 'scoring system':ti,ab,kw

#8: 'risk assessment'/exp OR 'survival analysis'/exp OR 'predictive value'/exp OR 'predictive model'/exp OR 'risk model'/exp OR 'risk prediction'/exp OR 'risk prediction model'/exp OR 'risk calculator'/exp OR 'prognostic model'/exp OR 'prognostic factor'/exp OR 'scoring system'/exp

#9: #7 OR #8

#10:'critical care':ti,ab,kw OR 'intensive care unit*':ti,ab,kw OR 'critical illness':ti,ab,kw OR icu:ti,ab,kw OR 'intensive care':ti,ab,kw OR 'critically ill':ti,ab,kw

#11: 'critical illness'/exp OR 'intensive care unit'/exp OR 'critically ill patient'/exp OR 'intensive care'/exp

#12: #10 OR #11

#13: #6 AND #9 AND #12 AND ([chinese]/lim OR [english]/lim) NOT ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim)

Search Strategy in **CINAHL**

#1: SU "extended spectrum beta lactamase" OR SU "multidrug resistan*" OR SU "extensively drug resistan*" OR SU "antimicrobial resistan*" OR SU "antibiotic resistan*" OR SU "antibacterial resistan*" OR SU "pandrug resistan*" OR SU "carbapenem resistant*" OR SU "colistin resistant*" OR SU "polymyxin resistant*" OR SU "methicillin resistant*" OR SU "vancomycin resistant*"

#2: SU "acinetobacter baumannii" OR SU "pseudomonas aeruginosa" OR SU "escherichia coli" OR SU "klebsiella pneumoniae" OR SU Enterobacteriaceae OR SU staphylococc* OR SU enterococc* OR SU microorganism* OR SU bacteria

#3: (MH "Pseudomonas Infections") OR (MM "Acinetobacter Infections") OR (MH "Escherichia Coli") OR (MH "Escherichia Coli Infections") OR (MH "Enterobacteriaceae") OR (MH "Enterobacteriaceae Infections") OR (MH "Staphylococcus") OR (MH "Enterococcus") OR (MH "Bacteria")

#4:#1 AND (#2 OR #3)

#5: (MH "Methicillin-Resistant Staphylococcus Aureus") OR (MH "Carbapenem-Resistant Enterobacteriaceae") OR (MH "Vancomycin Resistant Enterococci") OR (MH "Vancomycin-Resistant Staphylococcus Aureus") OR (MH "Drug Resistance, Microbial") OR (MH "Drug Resistance, Microbial") OR (MH "Drug Resistance, Multiple") OR (MH "Drug Resistance, Neoplasm")

#6: #4 OR #5

#7: SU "prediction model*" OR SU "predicted model*" OR SU "predictive model*" OR SU "risk model*" OR SU "risk prediction" OR SU "risk calculat*" OR SU "risk assessment" OR SU "predicted factor*" OR SU "predictive factor*" OR SU "prognostic model*" OR SU "prognosis model*" OR SU "prognostic factor*" OR SU "scoring model*" OR SU "scoring system"

#8: (MH "Risk Assessment") OR (MH "Survival Analysis") OR (MH "Predictive Value of Tests") OR (MH "Prediction Models")

#9: #7 OR #8

#10: SU "critical care" OR SU "intensive care unit*" OR SU "critical illness" OR SU ICU OR SU "intensive care" OR SU "critically ill"

#11: (MH "Critical Care") OR (MH "Critical Illness") OR (MH "Intensive Care Units") OR (MH "Critically Ill Patients")

#12: #10 OR #11

#13: #6 AND #9 AND #12

Filters applied: Chinese, English.

Search Strategy in **Web of Science**

#1: extended spectrum beta lactamase (Topic) or multidrug resistan* (Topic) or extensively drug resistan* (Topic) or antimicrobial resistan* (Topic) or antibiotic resistan* (Topic) or antibacterial resistan* (Topic) or pandrug resistan* (Topic) or carbapenem resistant* (Topic) or colistin resistant* (Topic) or polymyxin resistant* (Topic) or methicillin resistant* (Topic) or vancomycin resistant* (Topic)

#2: acinetobacter baumannii (Topic) or pseudomonas aeruginosa (Topic) or escherichia coli (Topic) or klebsiella pneumoniae (Topic) or enterobacteriaceae (Topic) or staphylococc* (Topic) or enterococc* (Topic) or microorganism* (Topic) or bacteria (Topic)

#3: #1 and #2

#4: prediction model* (Topic) or predicted model* (Topic) or predictive model* (Topic) or risk model* (Topic) or risk prediction (Topic) or risk calculat* (Topic) or risk assessment (Topic) or predicted factor* (Topic) or 'predictive factor* (Topic) or prognostic model* (Topic) or prognosis model* (Topic) or prognostic factor* (Topic) or scoring model* (Topic) or scoring system (Topic)

#5: critical care (Topic) or intensive care unit* (Topic) or critical illness (Topic) or icu (Topic) or intensive care (Topic) or critically ill (Topic)

#6: #3 and #4 and #5

Filters applied: Chinese, English.

Search Strategy in **Cochrane Library**

#1: ("extended spectrum beta lactamase"):ti,ab,kw OR ("multidrug resistan*"):ti,ab,kw OR ("multidrug resistan*"):ti,ab,kw OR ("extensively drug resistan*"):ti,ab,kw OR ("antimicrobial resistan*"):ti,ab,kw OR ("antibiotic resistan*"):ti,ab,kw OR ("antibacterial resistan*"):ti,ab,kw OR ("pandrug resistan*"):ti,ab,kw OR ("carbapenem resistant*"):ti,ab,kw OR ("colistin resistant*"):ti,ab,kw OR ("polymyxin resistant*"):ti,ab,kw OR ("methicillin resistant*"):ti,ab,kw OR ("vancomycin resistant*"):ti,ab,kw

#2: ("acinetobacter baumannii"):ti,ab,kw OR ("pseudomonas aeruginosa"):ti,ab,kw OR ("escherichia coli"):ti,ab,kw OR ("klebsiella pneumoniae"):ti,ab,kw OR (Enterobacteriaceae):ti,ab,kw OR (staphylococc*):ti,ab,kw OR (enterococc*):ti,ab,kw OR (microorganism*):ti,ab,kw OR (bacteria):ti,ab,kw

#3: "Acinetobacter baumannii"[MeSH descriptor] OR "Pseudomonas aeruginosa"[MeSH descriptor] OR "Escherichia coli"[MeSH descriptor] OR "Klebsiella pneumoniae"[MeSH descriptor] OR "Enterobacteriaceae"[MeSH descriptor] OR "Staphylococcus"[MeSH descriptor] OR "Enterococcus"[MeSH descriptor] OR "Bacteria"[MeSH descriptor] explode all trees

#4:#1 AND (#2 OR #3)

#5: "Methicillin-Resistant Staphylococcus aureus"[MeSH descriptor] OR "Carbapenem-Resistant Enterobacteriaceae"[MeSH descriptor] OR "Vancomycin-Resistant Enterococci"[MeSH descriptor] OR "Vancomycin-Resistant Staphylococcus aureus"[MeSH descriptor] OR "drug resistance, microbial"[MeSH descriptor] OR "drug resistance, multiple, bacterial"[MeSH descriptor] explode all trees

#6: #4 OR #5

#7: ("prediction model*"):ti,ab,kw OR ("predicted model*"):ti,ab,kw OR ("predictive model*"):ti,ab,kw OR ("risk model*"):ti,ab,kw OR ("risk prediction"):ti,ab,kw OR ("risk calculat*"):ti,ab,kw OR ("risk assessment"):ti,ab,kw OR ("predicted factor*"):ti,ab,kw OR ("predictive factor*"):ti,ab,kw OR ("prognostic model*"):ti,ab,kw OR ("prognosis model*"):ti,ab,kw OR ("prognostic factor*"):ti,ab,kw OR ("scoring model*"):ti,ab,kw OR ("scoring system"):ti,ab,kw

#8: "Risk Assessment"[MeSH descriptor] OR "Survival Analysis"[MeSH descriptor] OR "Predictive Value of Tests"[MeSH descriptor] explode all trees #9: #7 OR #8 #10: ("critical care"):ti,ab,kw OR ("intensive care unit*"):ti,ab,kw OR ("critical illness"):ti,ab,kw OR (ICU):ti,ab,kw OR ("intensive care"):ti,ab,kw OR ("critically ill"):ti,ab,kw #11:"Critical Care"[MeSH descriptor] OR "Critical Illness"[MeSH descriptor] OR "Intensive Care Units"[MeSH descriptor]explode all trees #12: #10 OR #11 #13: #6 AND #9 AND #12 Filters applied: Chinese, English.
Search Strategy in **CNKI** #1: SU%=耐药+耐抗生素+耐细菌+耐甲氧西林+耐碳青霉烯+耐万古霉素+超广谱β内酰胺酶+耐粘菌素+耐多粘菌素 #2: SU%=细菌+微生物+肠杆菌+肠球菌+鲍曼不动杆菌+铜绿假单胞菌+肺炎克雷伯菌+金黄色葡萄球菌+结核分枝杆菌 #3: SU%=预测模型+预警模型+预判模型+判别模型+风险模型+风险预测+风险评估+预测因素+评分模型+评分系统 #4: SU%=重症监护+监护室+ICU #5: #1 and #2 and #3 and #4 Filters applied: academic journals, dissertations, Chinese
Search Strategy in **Wanfang** #1 主题:(耐药 or 耐抗生素 or 耐细菌 or 耐甲氧西林 or 耐碳青霉烯 or 耐万古霉素 or 超广谱β内酰胺酶 or 耐粘菌素 or 耐多粘菌素) #2:主题:(细菌 or 微生物 or 肠杆菌 or 肠球菌 or 鲍曼不动杆菌 or 铜绿假单胞菌 or 肺炎克雷伯菌 or 金黄色葡萄球菌 or 结核分枝杆菌) #3:主题:(预测模型 or 预警模型 or 预判模型 or 判别模型 or 风险模型 or 风险预测 or 风险评估 or 预测因素 or 评分模型 or 评分系统) #4:主题:(重症监护 or 监护室 or ICU) #5: #1 and #2 and #3 and #4 Filters applied: academic journals, dissertations, Chinese