Construction of a risk prediction model for subsequent bloodstream infection in intestinal carriers of carbapenem-resistant Enterobacteriaceae: a retrospective study in hematology department and intensive care unit

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Research

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Abstract

Background

To establish a risk prediction model for carbapenem-resistant Enterobacteriaceae (CRE) bloodstream infection (BSI) in intestinal carriers.

Methods

CRE screenings were performed every two weeks in hematology department and intensive care unit (ICU). Patients with positive CRE rectal swab screening were identified using electronic healthcare records from 15 May 2018 to 31 December 2019. All CRE strains were collected and identified. Carriers who developed CRE BSI were compared with those who did not develop CRE infection. The control group 1:1 stratified randomly matched the case group. Univariate logistic analysis, multivariate logistic analysis and stepwise regression analysis were carried out.

Results

A total of 42 cases were included. Multivariate analysis showed that gastrointestinal injury (OR 86.82, 95%CI 2.58-2916.59, P = 0.013), tigecycline exposure (OR 14.99, 95%CI 1.82-123.74 P = 0.012) and carbapenem resistance score (OR 11.24, 95% CI 1.81–69.70, P = 0.009) were independent risk factors for CRE BSI in intestinal carriers (P < 0.05). They were included in the Logistic regression model to predict BSI. According to receiver operating characteristic (ROC) curve analysis, the cut-off value of the model was 0.72, and the sensitivity, specificity and area under the curve (AUC) were 90.5%, 85.7% and 0.92, respectively.

Conclusions

The risk prediction model based on gastrointestinal injury, tigecycline exposure and carbapenem resistance score of colonizing strain can effectively predict CRE BSI in patients with CRE colonization. Early CRE screening and detection for inpatients in key departments may early warning and reduce the risk of nosocomial infection of CRE.

Background

Carbapenem-resistant Enterobacteriaceae (CRE) has attracted widespread attention due to its rapid growth, treatment difficulty, high mortality and high economic burden [1–3]. The course of CRE bloodstream infection (BSI) in immunocompromised patients is usually abrupt and fatal [4]. A cohort study of the impact of CRE infections on mortality of patients presenting with sepsis showed that

patients with CRE infections had significantly higher 30-day mortality: 63.8% versus 33.4% ($P < 0.01$) [5]. Therefore, the study of CRE BSI has important clinical significance.

Studies have shown that CRE colonization is an independent risk factor for CRE infection [6]. Could we effectively prevent CRE infection by CRE de-colonization? It may take a lot of effort for little return. In fact, the majority of CRE carriers would not suffer from CRE infection. A retrospective study showed that only 16.5% (299/1806) of 1806 patients with CRE colonization subsequently developed CRE infection [7]. Excessive de-colonization will only lead to the waste of medical resources and the abuse of antibiotics.

WHO recommend surveillance cultures for asymptomatic CRE colonization should be performed, guided by local epidemiology and risk assessment [8]. Populations to be considered for such surveillance include patients with previous CRE colonization, patient contacts of CRE colonized or infected patients and patients with a history of recent hospitalization in endemic CRE settings [8]. Since 15th May 2018, our institute has carried out regular CRE screening for all inpatients in intensive care unit (ICU) and hematology department, two high-risk departments of CRE infection. It provided a very suitable observation population for this study. Standardized screening and isolation made the research results more valuable for clinical reference.

In previous studies, we found that the majority of CRE strains isolated from infection patients showed high-level carbapenems resistance. The minimum inhibitory concentrations (MICs) were > 32 μg/ml. The inhibition zone diameters of these strains were usually 6 mm. In contrast, the MIC value distribution of CRE strains isolated from rectal swabs were significantly different. Thus, we proposed the hypothesis that strains isolated from rectal swabs with high resistance to carbapenems might be associated with CRE infection. It is well known that the occurrence of infection depends on the interaction between pathogen and host. We aimed to establish a risk prediction model for CRE BSI subsequent CRE colonization simultaneously based on the pathogenic characteristics of colonized CRE strains and host risk factors, in order to early identify high-risk inpatients and prevent of CRE BSI infection.

Methods

Study design and setting

CRE infection control project has been carried out in hematology department and ICU since 15 May 2018 in a 6000 beds general teaching hospital in Wuhan, China. At the beginning of the project, all inpatients were screened and grouped. All the newly admitted patients were assessed according to the guidance from the European Centre for Disease Prevention and Control [9]. The patients who met the requirements were screened for CRE and reexamined regularly (**Fig.1**). We collected data from 15 May 2018 to 31 December 2019. Rectal swab CRE screening positive cases in hematology department and ICU were enrolled. CRE BSI was defined as isolation of CRE strains from one or more blood cultures and has clinical infection symptoms. Hospital admission was >48h from hospital admission to sepsis diagnosis. Patients with CRE BSI already, patients with spontaneous or drug-induced de-implantation, and patients with inconsistent positive results were excluded. The uninfected patients should be reexamined for CRE

screening at least once before discharge. Cases without reexamination should be excluded. Patients with CRE BSI subsequent to CRE intestinal colonization were included in the case group. Patients without secondary CRE infection were included in the control group. CRE intestinal colonization is defined as a positive result of CRE rectal swab screening without invasive infection.

Microbiology

The rectal swabs were inoculated directly to a chromogenic agar plate containing carbapenem as selective agent (CHROMagar, France) for CRE screening. All the isolated bacteria were identified by MALDI-TOF mass spectrometer (Bruker Daltonics, USA). The sensitivity of meropenem and imipenem were detected by Kirby-Bauer method. The results were interpreted according to Clinical and Laboratory Standards Institute (CLSI) M100-S29 breakpoints.

Variables and definitions

The data were collected through case review and laboratory record. Variables possibly related to BSI were collected: General information (gender, age, department), underlying conditions (hypertension, diabetes, tumor, impaired immune function, gastrointestinal injury), invasive procedures and devices (solid organ transplantation, hematopoietic stem cell transplantation, surgery, mechanical ventilation, central venous catheter, urinary catheter, gastric tube, drainage tube), antibiotic exposure, length of stay from CRE screening to outcome (occurrence of CRE BSI or discharge), colonizing bacteria and carbapenem resistance score, etc.

Impaired immune function included receiving radiotherapy and chemotherapy, agranulocytosis, long-term or massive hormone therapy, and HIV infection. Gastrointestinal injury included gastrointestinal bleeding or perforation, ostomy or excision of stomach and intestine, gastroenteritis, cholecystitis and pancreatitis. Antibiotic exposure and duration were considered from CRE screening to CRE BSI onset for the case group, or to hospital discharge for the control group.

The inhibition zone diameters of meropenem and imipenem were discontinuous numerical variables, so we used carbapenem resistance score as a categorical variable to represent the resistance of carbapenems. When the inhibition zone diameters of meropenem and imipenem were both >6mm, it was recorded as "1"; when either the inhibition zone diameter of meropenem or the inhibition zone diameter of imipenem was equal to 6mm, it was recorded as "2"; when the diameter of meropenem and imipenem were both equal to 6mm, it was recorded as "3".

Statistical analysis

Carriers who developed CRE BSI were compared with those who did not develop CRE infection. Pearson chi-square test was used for binary data. Nonparametric Mann-Whitney rank sum test was used for ordered categorical data. T-test was used for measurement data. The variables with $P<0.05$ in univariate analysis were included in multivariate analysis. Then stepwise regression analysis was carried out to determine the parameters in the risk prediction model and establish the logistic regression model. The OR

value and 95% confidence interval of each factor were calculated. The receiver operating characteristic (ROC) curve was used to evaluate the predictive ability of the model.

Results

Patient cohort

During the study period, 12754 rectal swabs (7456 inpatients) were screened. 860 patients being admitted to hematology department and ICU with positive CRE rectal swab screening were identified. After exclusion criteria were applied, a total of 73 patients met the standard. 21 patients developed CRE BSI were included in the case group, matched with 21 patients who did not have CRE infection with 1:1 matching ratio (**Fig.1**).

Strains and carbapenem resistance score

Among 42 colonized bacteria, 31 (73.8%) were Klebsiella pneumoniae, 9 (21.4%) were Escherichia coli, 2 (4.8%) were Citrobacter spp.. There were 18 cases of Klebsiella pneumoniae in the case group, accounting for 85.7%, while there were 13 cases of Klebsiella pneumoniae in the control group, accounting for 61.9%. There was no statistical difference between the two groups (P=0.079).

In total, Carbapenem resistance score was “3” in 23 cases (54.8%), “2” in 5 cases (11.9%), “1” in 14 cases (33.3%). In the case group, the score was “3” in 17 cases (81.0%), “1” in 3 cases (14.3%); In the control group, the score was “3” in 6 cases (28.6%), “1” in 11 cases (52.4%). There was a significant difference between the two groups (P<0.05).

Fig.2 showed distribution of carbapenem resistance score and colonizing bacteria in case group and control group.

Independent risk factors of CRE BSI in intestinal carriers

Univariate and multivariate logistic regression analysis was used to analyze the variables. The results are shown in Table 1. Gastrointestinal injury, tigecycline exposure and carbapenem resistance score were independent risk factors for CRE BSI in intestinal carriers (P<0.05).

The time for patients to develop CRE BSI

The median time from positive screening to CRE BSI was 13 days (range from 1 to 202) (**Table 1**).

Development of CRE BSI risk prediction model

Stepwise logistic regression analysis showed that gastrointestinal injury (OR 86.82, 95%CI 2.58-2916.59, P = 0.013), tigecycline exposure (OR 14.99, 95%CI 1.82-123.74 P=0.012) and carbapenem resistance score (OR 11.24, 95% CI 1.81-69.70, P=0.009) were valuable for risk prediction model of CRE BSI (**Table 2**). The logistic regression model was established as follows:

PV = 1 / (1+e^-(-8.488+4.464×gastrointestinal injury+2.707×tegacyclin exposure 2.419×carbapenem resistance score))

Abbreviation: PV, predictive value; e, natural logarithm

Variable: carbapenem resistance score, it was given 1, 2 or 3 according to the inhibition zone diameter; gastrointestinal jury, “Yes” and “No” were given 1 and 0, respectively.

Validation of the risk prediction model

By ROC curve analysis (Fig.3), area under the curve (AUC) was 0.92. The cut off value of the model was 0.72. The sensitivity and specificity of the model were 90.5% and 85.7% respectively.

Discussion

Of the 7456 patients screened for CRE, 860 found CRE colonization, with the colonization rate of 11.5%. Among all CRE colonizers, only 2.4% (21/860) had subsequent CRE BSI, of which 57.1% (12/21) had adverse outcomes. Whether and when CRE colonizers need to be de-colonization is a clinical unsolved puzzle. Due to the critical consequences of CRE bloodstream infection, our study focused on the identification of high-risk patients with CRE bacteremia to provide a theoretical basis for de-colonization.

Patients with hematologic malignancies and hematopoietic stem cell transplant recipients are at high risk of developing invasive infections due to enteric bacteria because of chemotherapy-induced neutropenia and gastrointestinal mucositis [10]. In fact, gastrointestinal mucositis is a complex inflammatory reaction of the mucous membranes, a side effect of both chemotherapy and radiotherapy [11]. Its severity is difficult to assess. Interestingly, we found that gastrointestinal injury with definite diagnosis including gastrointestinal bleeding or perforation, ostomy or excision of stomach and intestine, gastroenteritis, cholecystitis and pancreatitis was an independent risk factor and could be included in the model for risk assessment of CRE BSI in CRE carriers.

Tigecycline has a large volume of distribution and high concentration in gallbladder, colon and pulmonary tissue. In contrast, the serum concentrations of tigecycline are relatively low [12]. After a single 100 mg dose of tigecycline, serum concentrations of tigecycline rapidly declined from a mean value of 1.94 mg/L to 0.31 mg/L between 3 min and 1 h after the end of the infusion. The subsequent concentrations in serum slowly declined to mean values of 0.22 ng/mL and 0.07 mg/L at 4 and 24 h after the start of the tigecycline infusion [12]. Tigecycline is not approved for the treatment of BSI because its serum concentrations are generally deemed not adequate. Therefore, conventional dose of tigecycline (100 mg initially, followed by 50 mg q12h) cannot prevent CRE BSI. In addition, tigecycline has a wide antibacterial spectrum, which is active against a wide range of Gram-positive and -negative aerobic and anaerobic bacteria [13]. In most large-scale monitoring studies, the sensitivity of tigecycline in Enterobacteriaceae is kept at a high level of > 90% [14–16]. CRE isolates also showed high susceptibility to tigecycline (89.7%) [17]. It should be noted that tigecycline resistance rate of Klebsiella

pneumoniae in hematopoietic stem cell transplant patients can reach 16% [18]. Taken together, we inferred that tigecycline exposure increased the risk of CRE BSI might due to intestinal flora disorder.

There were few studies on the correlation between bacterial characteristics of colonized CRE and the subsequent occurrence of infection currently. Giannella M et al established a prediction model of carbapenem-resistant Klebsiella pneumoniae (CR-KP) BSI following CRKP colonization, based on whether there was ICU admission, radiotherapy and chemotherapy, abdominal invasive operation and multi-site CR-KP colonization [19]. The sensitivity and specificity were 93% and 42% respectively. In our study, what makes sense is that three significant variables which included carbapenem resistance score of colonizing CRE were screened out to establish the risk prediction model for subsequent BSI in intestinal carriers of CRE. The sensitivity and specificity of the model were 90.5% and 85.7% respectively. It suggested that the drug resistance of colonizing bacteria is closely related to the occurrence of infection.

Carbapenem resistance score was given according to the inhibition zone diameter instead of MIC. The advantage is that it can be evaluated at the same time as the CRE screening. Rectal swabs could be directly inoculated into MacConkey agar medium, then the paper disks of meropenem and imipenem could be pasted in the original area. It greatly simplifies the detection and evaluation process, and is helpful for the promotion and use of the model. However, it should be noted that the number of cases is small and the model is currently only suitable for hematology department and ICU. Further studies are still needed.

Conclusions

To summarize, gastrointestinal injury, tigecycline exposure and carbapenem resistance score of colonizing bacteria can effectively predict the risk of subsequent BSI in CRE carriers. Our findings suggested that carbapenem susceptibility test of colonized bacteria in critical patients can identify patients at high risk of CRE infection and prevent them from CRE infection as early as possible. The application of this risk prediction model may reduce the incidence and mortality of CRE infection. It may also avoid unnecessary use of antibiotics in low-risk groups to reduce the selective pressure of antibiotics, and further reduce the production of CRE.

Abbreviations

CRE carbapenem-resistant Enterobacteriaceae

BSI bloodstream infection

ICU intensive care unit

ROC receiver operating characteristic

AUC area under the curve

MICs minimum inhibitory concentrations

PV predictive value

CR-KP carbapenem-resistant Klebsiella pneumoniae

Declarations

Ethics approval and consent to participate

The study was approved by the ethical committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. The data are anonymous, and the requirement for informed consent was therefore waived.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

We declare no competing interests.

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Authors' contributions

Ziyong Sun contributed to the conception of the study. Qun Lin performed the experiment. Zhongju Chen collected data. Hongyan Hou and Feng Wang contributed significantly to analysis and manuscript preparation. Yue Wang performed the data analyses and wrote the manuscript. Na Shen helped perform the analysis with constructive discussions.

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Tables

Table 1 Univariate and multivariate analysis of risk factors for subsequent BSI in CRE intestinal carriers

Variable		Infection group N=21 （%）	Non-infection group N=21（%）	Univariable *P* value[ab]	Multivariable *P* value[b]
Patient factors	**General information**				
	Male	12 （57.1）	12（57.1）	1.000	
	Age, median	45（17-62）	51（17-91）	0.161	
	ICU	12 （57.1）	12（57.1）	1.000	
	Underlying conditions				
	Hypertension	8（38.1）	5（23.8）	0.317	
	Diabetes	4（19.0）	6（28.6）	0.469	
	Tumor[c]	8（40.0）	9（45.0）	0.749	
	Impaired immune function	9（42.9）	9（42.9）	1.000	
	Gastrointestinal injury[d]	9（42.9）	2（9.5）	0.014	0.013
	Invasive procedures and devices				
	Solid organ transplantation	1（4.8）	2（9.5）	0.549	
	Hematopoietic stem cell transplantation	3（14.3）	3（14.3）	1.000	
	Surgery	8（38.1）	10（47.6）	0.533	
	Mechanical ventilation	12 （57.1）	9（42.9）	0.355	
	Central venous catheter	19 （90.5）	17（81.0）	0.378	
	Urinary catheter	12 （57.1）	12（57.1）	1.000	
	Gastric tube	11 （52.4）	11（52.4）	1.000	
	Drainage tube	15 （71.4）	9（42.9）	0.061	
	Antibiotic exposure[e]				
	Exposure	21 （100.0）	21 （100.0）		

Drug combination		21 (100.0)	20 (95.2)	0.311	
Antibiotic classes					
Cephalosporins	Exposure	4 (19.0)	5 (23.8)	0.707	
	Days of exposure, median	0 (0-16)	0 (0-8)	0.921	
β-lactam/β-lactamase inhibitors	Exposure	15 (71.4)	15 (71.4)	1.000	
	Days of exposure, median	8 (0-116)	9 (0-43)	0.780	
Aminoglycosides	Exposure	1 (4.8)	2 (9.5)	0.549	
	Days of exposure, median	0 (0-2)	0 (0-24)	0.244	
Fluoroquinolones	Exposure	12 (57.1)	13 (61.9)	0.753	
	Days of exposure, median	4 (0-95)	5 (0-35)	0.947	
Carbapenems	Exposure	17 (81.0)	13 (61.9)	0.172	
	Days of exposure, median	4 (0-26)	4 (0-19)	0.718	
Tegacyclin	Exposure[d]	17 (81.0)	9 (42.9)	0.011	0.012
	Days of exposure, median	5 (0-15)	0 (0-26)	0.730	
Polymyxin B	Exposure	1 (4.8)	2 (9.5)	0.549	
	Days of exposure, median	0 (0-10)	0 (0-9)	0.941	
TMP/SMX[f]	Exposure	1 (4.8)	3 (14.3)	0.293	
	Days of exposure, median	0 (0-6)	0 (0-35)	0.229	
Glycopeptides	Exposure	4 (19.0)	6 (28.6)	0.469	

		Days of exposure, median	0（0-13）	0（0-18）	0.207	
Strain factors	**Colonizing bacteria**				0.101	
	Klebsiella pneumoniae		18（85.7）	13（61.9）	0.079	
	Escherichia coli		2（9.5）	7（33.3）	0.060	
	Other Enterobacteriaceae		1（4.8）	1（4.8）	1.000	
	Carbapenem resistance score[d]				0.001	0.009
	1		3（14.3）	11（52.4）	0.009	
	2		1（4.8）	4（19.0）	0.153	
	3		17（81.0）	6（28.6）	0.001	
Outcome	**Days from screening to outcome (infection / discharge), median**		13（1-202）	18（4-60）	0.784	

1. According to the type of data, the appropriate analysis method was selected. Pearson chi-square test was used for binary data. Nonparametric Mann-Whitney rank sum test was used for ordered categorical data. T-test was used for measurement data.
2. $P < 0.05$ was considered statistically significant.
3. Including solid organ tumors and hematogenous malignancies.
4. These variables were $P < 0.05$ in univariate analysis, and then were included in the multivariate analysis.
5. These variables were considered from CRE screening to CRE BSI onset for cases, or to hospital discharge for controls
6. TMP/SMX, sulfamethoxazole and trimethoprim

Table 2 Risk fators of subsequent BSI in CRE intestinal carriers using binary logistic regression analysis

Independent variables	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI for EXP(B)	
							Lower	Upper
Gastrointestinal mucosa damage	4.464	1.793	6.198	1	0.013	86.819	2.584	2916.592
Tegacyclin exposure	2.707	1.077	6.321	1	0.012	14.991	1.816	123.737
Carbapenem resistance score	2.419	0.931	6.749	1	0.009	11.236	1.811	69.700
Constant	-8.488	2.971	8.164	1	0.004	0.000		

Note: Nagelkerke R^2=0.700.

Figures

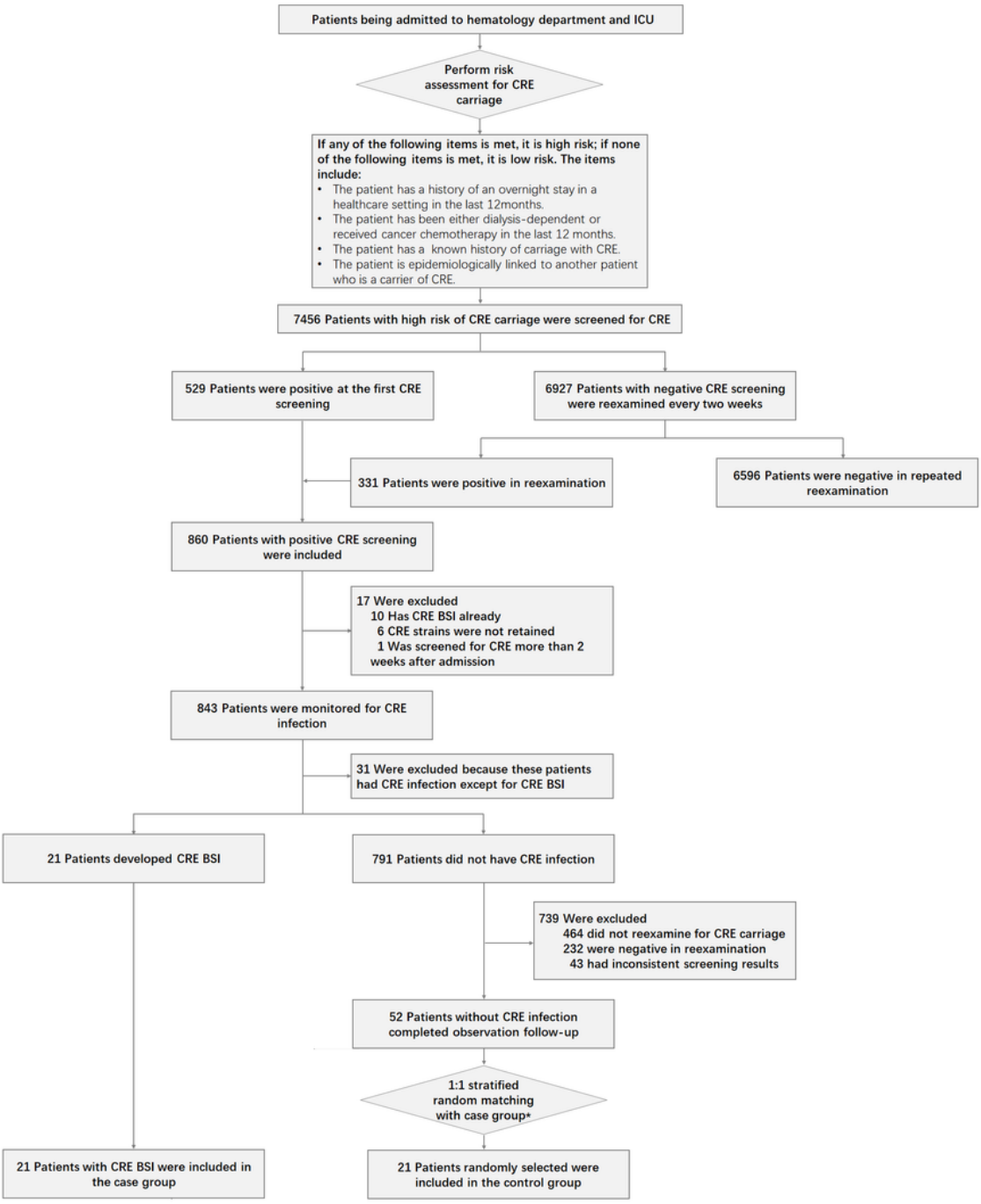

Figure 1

CRE screening, enrollment and follow-up *Patients in the control group were selected using stratified random sampling according to the departments to ensure that all the departments were represented.

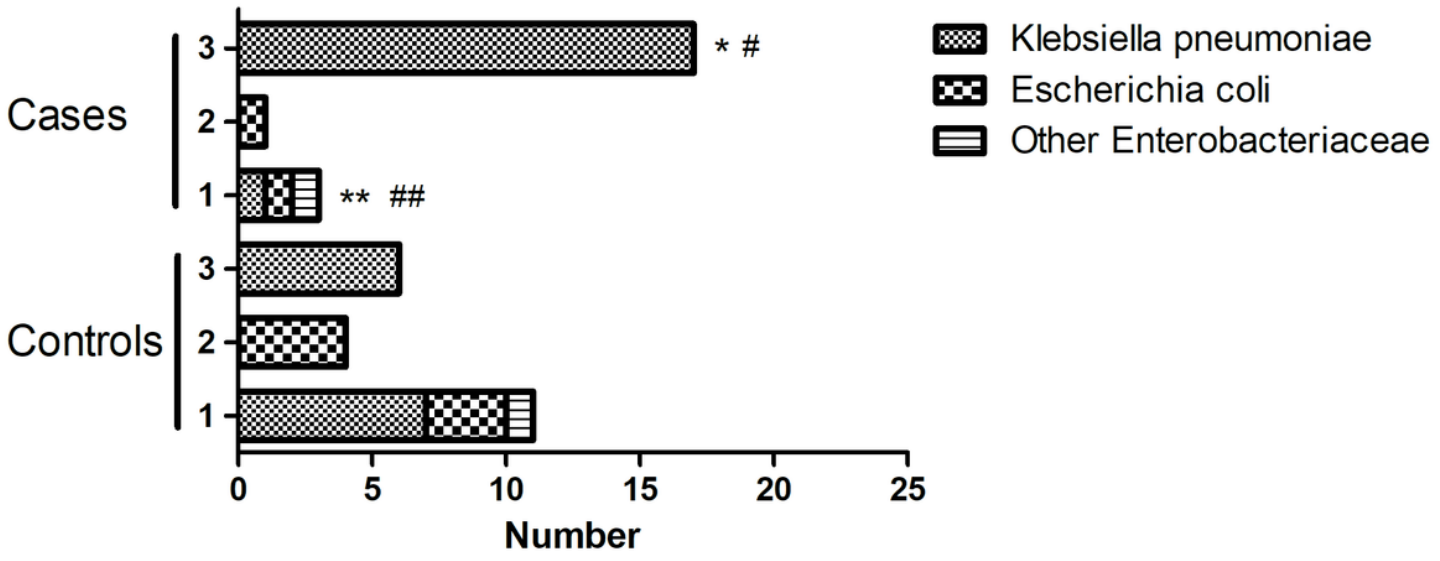

Figure 2

Distribution of carbapenem resistance score and colonizing bacteria in case group and control group X axis is number of strains, Y axis is the score of carbapenem resistance. * Klebsiella pneumoniae with carbapenem resistance score 3 accounted for 94.4% (17/18) of all Klebsiella pneumoniae in the case group and 46.2% (6/13) in the control group. There was a significant difference between the two groups (P = 0.002). **Klebsiella pneumoniae with carbapenem resistance score 1 accounted for 5.6% (1/18) of all Klebsiella pneumoniae in the case group and 53.8% (7/13) in the control group. There was a significant difference between the two groups (P = 0.002). # Klebsiella pneumoniae accounted for 100% (17/17) of all strains with carbapenem resistant score 3 in the case group and 100% (6/6) in the control group. There was no statistical difference between the two groups. ##Klebsiella pneumoniae accounted for 33.3% (1/3) of all strains with carbapenem resistant score 1 in the case group and 63.6% (7/11) in the control group. There was no statistical difference between the two groups (P = 0.347).

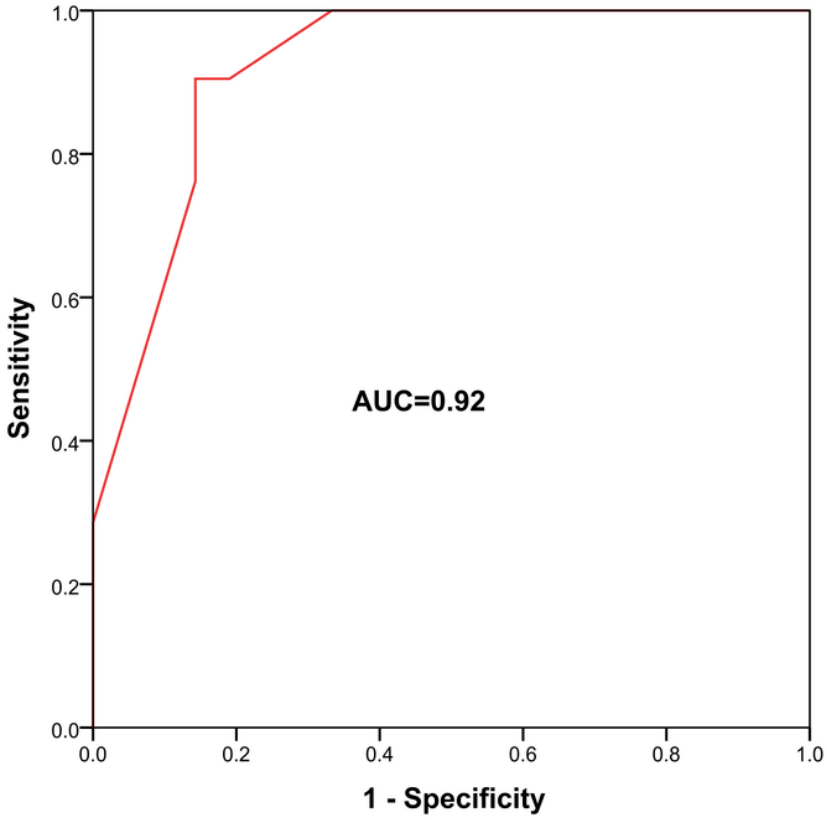

Figure 3

ROC curve analysis was performed to evaluate the predictive ability of risk prediction model AUC=0.92, cut-off value = 0.72, sensitivity = 90.5%, specificity = 85.7%.

Supplementary Files

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- Additionalfile1.xls