A Novel Risk Predictive Scoring Model For Predicting Subsequent Infection After Carbapenem-Resistant Gram-Negative Bacteria Colonization In Hematological Malignancies Patients

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Keywords: Predictive model, Carbapenem-resistant Gram-negative bacteria, Hematologic malignancies, Colonization, Infection, Swabs cultures

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A novel risk predictive scoring model for predicting subsequent infection after Carbapenem-resistant Gram-negative bacteria colonization in hematological malignancies patients

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Abstract

Purpose

To investigate the high-risk factors associated with the increased vulnerability for subsequent clinical infection in Carbapenem-resistant Gram-negative bacteria (CR-GNB) colonized hematological malignancies (HMs) patients, and build a statistical model to predict subsequent infection.

Method

All adult HMs patients with positive anal swab culture for CR-GNB between January 2018 and June 2020 were prospectively followed to assess for any subsequent CR-GNB infections and to investigate the risk factors and clinical features of subsequent infection.

Results

A total of 392 HMs patients were enrolled. Of them, 46.7% developed a subsequent clinical infection, and 42 (10.7%) were confirmed infection and 141 (36%) were clinically diagnosed infection. Klebsiella pneumoniae was the dominant species. The overall mortality rate of patients colonized and infected with CR-GNB was 8.6% and 43.7%. A multivariate analysis showed that remission induction chemotherapy, the duration of agranulocytosis, mucositis, and hypoalbuminemia were significant predictors of subsequent infection after CR-GNB colonization. According to our novel risk predictive scoring model, the high-risk group were >3 times more likely to develop a subsequent infection in comparison with the low-risk group.

Conclusion

Our risk predictive scoring model can early and accurately predict subsequent infection in HMs patients with CR-GNB colonization. Early administration of CR-GNB-targeted empirical therapy in the high-risk group is strongly recommended to decrease their mortality.

Keywords: Predictive model; Carbapenem-resistant Gram-negative bacteria; Hematologic malignancies; Colonization; Infection; Swabs cultures

Introduction

Carbapenem-resistant Gram-negative bacteria (CR-GNB) are a major public
health threat posed by the Centers for Disease Control and the World Health Organization\textsuperscript{[12]}, including carbapenem-resistant Enterobacteriaceae (CRE), carbapenem-resistant Pseudomonas aeruginosa (CRPA), and carbapenem-resistant Acinetobacter baumannii (CRAB). In recent decades, their prevalence has increased year by year\textsuperscript{[3]}. The disease progresses rapidly in patients with CR-GNB infection, and very few anti-infectives are effective\textsuperscript{[4]}. The mortality rate of CR-GNB infection is significantly increased compared with carbapenem susceptible Gram-negative bacterium infection, which presents a tremendous challenge to clinicians\textsuperscript{[5]}. It is urgent to quantify the risk factors of CR-GNB infection to guide early clinical identification and rational treatment.

Immunodeficiency due to primary diseases, neutropenia, high-dose chemotherapy, hematopoietic stem cell transplantation (HSCT), and the abuse of broad-spectrum antibiotics all lead to an increased risk of CR-GNB infection in hematological malignancies (HMs) patients, and the mortality rate of infection is significantly higher than that in other patients\textsuperscript{[6]}. More than half of HMs patients are reported to die within one week after CR-GNB infection, and their 30-day mortality rate is as high as 70.3\textsuperscript{[7]}. Therefore, early diagnosis and appropriate treatment of CR-GNB infection in HMs patients have extremely important clinical significance.

Pathogenic microorganism culture is the gold standard for a definite diagnosis of CR-GNB infection, but a low positive rate of culture and long culture time directly delay the timing of medication and thus limit therapeutic effect\textsuperscript{[8]}. Previous studies have shown that CR-GNB infection is usually caused by colonized bacteria invading the body\textsuperscript{[910]} and colonization can early predict the existence of infection. At present, the common methods for detecting CR-GNB colonization include rectoanal swab culture, fecal culture, and pharyngeal wipe culture. Of them, the anal swab culture is most widely adopted because the specimen is easily obtained without contamination of miscellaneous bacteria and can accurately reflect the gastrointestinal bacterial status of the patient\textsuperscript{[11]}. Active surveillance of CR-GNB colonization has been demonstrated effective in the control of CR-GNB outbreaks. However, not all gut colonization patients will eventually develop into a clinical infection. The factors that influence
asymptomatic colonization to develop into subsequent infection remain unclear. An accurate and convenient prediction model for early recognizing high-risk CR-GNB infected patients after colonization may improve the empiric antibiotic prescription and decrease the mortality rate and healthcare costs.

In this study, we sought to develop a novel predictive model to determine who among newly identified CR-GNB colonization patients is prone to have a subsequent clinical infection, and thus it is helpful for early identification of high-risk infected patients and a reasonable selection of anti-infection regimen, so as to reduce the mortality rate and bacterial resistance rate.

**Subjects and Methods**

Study design and subjects

This study retrospectively reviewed the clinical and microbiological data of patients with HMs from January 2018 to June 2020 in Wuhan Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. The patients who were identified as CR-GNB carriers by anal swab screening tests were included. Exclusion criteria were age<18 years. They were followed up to assess for any subsequent infections caused by CR-GNB.

Demographic and clinical data, including gender, age, primary disease, length of hospitalization, HSCT, pneumonia, the duration of agranulocytosis, hypoalbuminemia, mucositis, exposure to antimicrobial agents or special drugs (chemotherapy, immunosuppressant, glucocorticoid, proton pump inhibitors (PPIs)) before infection, invasive procedure devices (central venous catheter (CVC), mechanical ventilation, sputum suction, catheterization) before infection, and survival status within 28 days after we acquired the first positive anal swab culture for CR-GNB. The culture results of blood, urine, sputum, and/or other sites of infection in all patients were recorded.

Bacterial identification and drug sensitivity test

Carbapenem resistance was defined as doripenem, meropenem, or imipenem
minimum inhibitory concentration (MIC) \( \geq 4 \mu g/mL \) or ertapenem MIC \( \geq 2 \mu g/Ml \)\(^{[12]}\).

Strain identification and drug sensitivity tests were performed using BDphoenix-100 automatic bacterial identification/drug sensitivity analysis system. Susceptibility results were interpreted according to Clinical and Laboratory Standards Institute (CLSI) 2020 criteria.

Grouping

Non-infection group: Patients had CR-GNB colonization based on at least 1 positive anal swab culture without fever and any clinical presentations of infection.

Infection group: Patients had at least 1 positive anal swab culture and subsequently developed fever (temperature \( >38^\circ C \) at three different times within a 12-hour period or as a temperature \( >38.5^\circ C \) in a single measurement) and/or clinical presentations of infection\(^{[13-14]}\). They were further divided into two groups based on CR-GNB microbiologically documented infections (MDIs):

1. Confirmed infections: Patients had the presence of documented CR-GNB MDIs (isolation of CR-GNB from one or more blood cultures or from a well-defined site of infection (urine, respiratory secretions obtained using sterile procedures, or fluid collection)\(^{[14]}\)).

2. Clinically diagnosed infection: Patients had the absence of CR-GNB MDIs who must meet the following criterias:

   (1) Positive cultures for other microorganisms were excluded;

   (2) Clinical and confirmed fungal infections were excluded\(^{[15]}\);

   (3) Conventional non-CR-GNB anti-infective treatments were ineffective.

Statistical analysis

Categorical data were analyzed utilizing Pearson’s chi-Square or Fisher’s exact test, and continuous data were analyzed utilizing the Mann–Whitney U test or Student’s t-test, as appropriate. Logistic regression (Backward LR) methods (univariate, multivariate) were used to determine the infection risk factors for HMs patients with CR-GNB colonization. Odds ratio (OR) and their corresponding 95% confidence
interval (CI) were calculated. The final model was constructed based on a forward stepwise method with the likelihood ratio test. Discrimination of the model was assessed by receiver-operator curve (ROC) characteristics and the area under the curve (AUC). An optimal breakpoint was assigned using Youden's J statistic. R 3.6.1 software was used for the analyses. Statistical significance was assigned to a P value of less than 0.05.

Study results

1. Microbiological characteristics

   A total of 392 hematological malignancy patients with positive CR-GNB colonization were included in this study, and the top three predominant pathogens of CR-GNB colonization were Klebsiella pneumoniae (32.1%), Escherichia coli (18.4%), and Mobility baumannii (15.8%). The other strains were Enterobacter cloacaee (12.8%), Klebsiella oxytoca (4.6%), Pseudomonas aeruginosa (3.6%), Klebsiella ozaenae (2.6%), Citrobacter freundii (2.3%), Enterobacter aerogenes (1.2%), Enterobacter polycluster (1.2%), Proteus (1.8%), and others(3.6%).( Figure 1)

2. Clinical characteristics

   As shown in table 1, among the 392 CR-GNB colonized patients, 183 (46.7%) subsequently developed CR-GNB infection including 42(10.7%) confirmed infections and 142(36.2%) clinically diagnosed infection. Non-infection group and infection group did not differ significantly in age and gender. In terms of disease distribution, acute myelocytic leukemia (AML )was the predominant primary disease (n=216, 55.1%), followed by acute lymphocytic leukemia ( ALL )(n=69, 17.6%), with no significant difference. Infected patients had longer length of hospitalization (27d VS 23d, p=0.028) and significantly higher mortality rate (43.7% VS 8.6%, P < 0.001).

3. Risk factors for subsequent infection after CR-GNB colonization

   A univariate analysis (Table 2) showed that risk factors for subsequent infection after CR-GNB colonization included HCST, mucositis, the duration of agranulocytosis,
hypoalbuminemia, pre-exposure to specific agents (carbapenems antibiotic, aminoglycosides antibiotic, remission induction chemotherapy, immunosuppressant, glucocorticoids, PPIs), and invasive procedures (CVC, sputum suction, catheterization) (p<0.05).

In order to avoid the interaction among the above risk factors and correct the bias, the factors with significant differences in univariate analysis were further included for multivariate logistic regression analysis. The results showed that remission induction chemotherapy (OR 1.921, 95%CI 1.217-3.054, p=0.005), the duration of agranulocytosis 1-14 days (OR 1.959, 95%CI 1.198-3.227, p=0.007), the duration of agranulocytosis ≥15 days (OR 2.651, 95%CI 1.509-4.717, p<0.001), mucositis (OR 3.248, 95%CI 2.089-5.114, p<0.001), and hypoalbuminemia (OR 1.837, 95% CI 1.170-2.904, p=0.009) were independent risk factors. The ROC curve showed that AUC=0.708>0.7 (p<0.005, 95%CI 0.697-0.794), indicating that multivariate analysis displayed acceptable goodness of fit. (Figure 2)

4. The establishment of a risk prediction score model for subsequent infection after CR-GNB colonization

In order to further quantify the proportion of independent risk factors, a scoring table was established. As shown in Table 3, the assignment of points based on the odds ratios for these four independent variables generated an individual risk score ranging from 0 to 6 (AUC=0.697, p<0.05, 95%CI: 0.647–0.747). The maximum value of the Youden index was taken as the optimal cutoff value for the scoring model. According to the coordinates of the ROC curve, the optimal cutoff value was determined to be 3.5. Colonized patients with a total score < 3.5 were defined as the Low-risk infection group and a total score ≥3.5 were defined as the High-risk infection group. All colonized patients were validated in this model. Among them, 209 cases were classified into the low-risk group, and 68 cases (32.54%) had a subsequent infection. The rest of 183 cases were classified in the high-risk group, including 113 cases (61.75%) with subsequent infection. There was a significant difference in subsequent infection rates between the
two groups (p<0.001). The OR was 3.347 (95% CI 2.218-5.094), suggesting that the risk of infection in the high-risk group was more than 3 times that in the low-risk group (Table 4). The sensitivity, specificity, positive predictive value, and negative predictive value were 62.4%, 67.1%, 0.6234, and 0.6682 respectively.

Discussion

In this retrospective case-control study, we found that 46.7% of HMs patients developed an infection after CR-GNB colonization, including confirmed infections (10.7%) and clinical infections (36.2%). Mucositis and the duration of agranulocytosis ≥15 days were the strongest predictors. According to our predictive scoring model, the total score ≥3.5 suggests that HMs patients with CR-GNB colonization may develop an infection.

The overall prevalence of CR-GNB colonization varies between 18.1% and 30.4% in different geographical regions and diseases\(^\text{[16[21]}\). In our study, the CR-GNB colonization rate in HMs patients was 35.7%, which was higher than that in the above study. HMs patients are prone to multiple drug-resistant bacterial infections, especially for febrile neutropenic patients\(^\text{[22][23]}\). It has been reported that the main CR-GNB strains include Klebsiella pneumoniae, Klebsiella acidogenes, Citrobacter freundii in Europe, and Klebsiella pneumoniae, Enterobacter cloacae, Escherichia coli in Asia\(^\text{[24][31]}\). In our study, the dominant strains were Klebsiella pneumoniae (32.1%), Escherichia coli (18.4%), and Mobility baumannii (15.8%), which was consistent with previous reports. These CR-GNB strains harboring hypervirulent and multidrug-resistant genes are also highly transmissible, strongly suggesting a necessity for effective strategies to prevent and control their spread.

Multiple risk factors were reported to be associated with the increased vulnerability for CR-GNB infection including immunocompromise, central venous catheter, chemotherapy or radiation therapy, neutropenia, carbapenems exposure, and prior colonization\(^\text{[32][35]}\). Similarly, in our univariate analysis, HCST, mucositis, the duration of agranulocytosis, hypoalbuminemia, pre-exposure to specific agents (carbapenems antibiotic, aminoglycosides antibiotic, remission induction chemotherapy, immunosuppressant, glucocorticoids, PPIs), and invasive procedures
(CVC, sputum suction, catheterization) may be risk factors for subsequent infection after CR-GNB colonization. However, in our multivariate logistic regression analysis, only remission induction chemotherapy, duration of agranulocytosis, mucositis, and hypoalbuminemia were independent risk factors.

During remission induction chemotherapy, extremely severe immunodeficiency is caused by both high tumor burden and potent high-dose chemotherapeutic drugs. Generally, the incidence of febrile granulocytopenia is highest during the first cycle of anticancer chemotherapy\textsuperscript{[36]}. A study showed that non-remission of primary disease after induction chemotherapy was an independent risk factor for infection and adversely affected the prognosis in patients with AML\textsuperscript{[37]}. However, transplantation patients have a higher colonization prevalence due to previous chemotherapy history compared with newly diagnosed HMs patients\textsuperscript{[38-39]}. However, stem cell transplantation and isolation in a laminar air-flow room have been also thought to be significant factors protecting against the occurrence of Gram-negative bacterial infections\textsuperscript{[40]}. These can explain that transplantation was no longer significant in the multivariate analysis either compared with univariate analysis in our study.

Compared with short-term agranulocytosis in patients with other malignant tumors, long duration of agranulocytosis is more common in HMs patients due to underlying disease and high-intensity chemotherapy, and leads to their significantly reduced ability to resist pathogenic microorganisms\textsuperscript{[41]}. Studies have shown that more than 80% of HMs patients will develop infections related to neutropenia after more than 1 course of chemotherapy, compared with 10%–50% of patients with solid tumors\textsuperscript{[42]}. In HMs patients, leukemia patients undergoing intensive induction chemotherapy have especially prolonged episodes of neutropenia. The presence of febrile neutropenia was independently associated with increased mortality in infections caused by Carbapenem-resistant Enterobacteriaceae in HMs patients in a Latin America study\textsuperscript{[43]}. In this cohort, we also found that the duration of agranulocytosis ($\geq 15$ days) independently increases the risk of subsequent infection due to CR-GNB colonization and thus negatively affects their clinical course.

Mucositis is a serious and debilitating side effect of cytotoxic chemotherapy and
persistent reduction of neutrophils\textsuperscript{44,45}. Oral and gut microbiome alterations are prevalent in HMs patients due to the administration of chemotherapeutic drugs and broad-spectrum antibiotics which favor the colonization or excessive growth of CR-GNB. Oral and gastrointestinal mucositis results in the damage of the mucous membrane barrier and promotes colonized CR-GNB to enter into the blood circulation\textsuperscript{46,47}. Therefore, for the CR-GNB colonized patients with mucositis, we must be highly suspicious of translocation with secondary invasive infection.

Hypoalbuminemia is a common complication in hematological malignancies due to inadequate nutrition intake and cachexia, which correlated with increased vascular permeability and interstitial volume. Besides, serum albumin has the effects of antioxidation and anti-apoptosis. Its reduction will cause low host immunity, delayed repair of microcirculatory mucosal injury, and increased infection\textsuperscript{48}. A retrospective chart review confirmed that hypoalbuminemia is a clinical predictor of early infection in HMs patients\textsuperscript{49}. In this study, multivariate logistic showed that hypoalbuminemia was an independent risk factor for subsequent infection after CR-GNB colonization and accounted for 1 point in our predictive scoring model.

It was seldomly reported on the prediction score model of infection for HMs patients with CR-GNB colonization. Recently, a risk prediction model for CRE bloodstream infection (BSI) in intestinal carriers in the hematology department and intensive care unit (ICU) was established in a retrospective study\textsuperscript{50}. Gastrointestinal injury, tigecycline exposure, and carbapenem resistance score were chosen as valuable markers for the risk prediction model of CRE BSI in intestinal carriers. However, the BSI rates are very low during HMs patients, those prediction score models may miss some clinically infected patients with negative blood culture. Therefore, we included both CR-GNB microbiologically documented infections and clinically CR-GNB infections in our cohort, and only 10.2\% of patients had positive blood cultures. We selected four independent variables including remission induction chemotherapy (score 1), the duration of neutropenia (score 1 for 1–14 days and score 2 for $\geq 15$ days), mucositis (score 2), and hypoalbuminemia (score 1) to establish our predicting model and divided all the colonized patients into a low-risk group (< 3.5points) and a high-
risk group (3.5 points). Our model has good sensitivity and specificity and is in high accordance with subsequent infection rates that high-risk group were \( \geq 3 \) times more likely to develop a subsequent infection in comparison with the low-risk group. Therefore, the early administration of CR-GNB-targeted empirical therapy in a high-risk group is strongly recommended to decrease their mortality.

**conclusion**

This study has several important limitations including its retrospective, observational design. An external validation cohort is needed to assess its discriminatory ability and goodness of fit. Additionally, the sample size of the transplantation group was still relatively small, limiting our ability to conduct a statistically significant comparison between the transplantation group and the nontransplant group. Finally, it needs to determine whether the established scoring model is reproducible through relevant prospective studies.

**Abbreviations**

- CR-GNB: Carbapenem-resistant Gram-negative bacteria
- CRE: Carbapenem-resistant Enterobacteriaceae
- CRPA: Carbapenem-resistant Pseudomonas aeruginosa
- CRAB: Carbapenem-resistant Acinetobacter baumannii
- HSCT: Hematopoietic stem cell transplantation
- HMs: Hematological malignancies
- PPIs: Proton pump inhibitors
- CVC: Central venous catheter
- MIC: Minimum inhibitory concentration
- CLSI: Clinical and Laboratory Standards Institute
- MDIs: Microbiologically documented infections
- OR: Odds ratio
- CI: Confidence interval
- ROC: Receiver-operator curve
- AUC: Area under the curve
BSI  Bloodstream infection
ICU  Intensive care unit

**Declarations**

**Ethics approval and consent to participate**
The study was approved by the Union Hospital ethics committee for research in health. Written informed consent was waived by the Union Hospital ethics committee for research in health due to the anonymized retrospective nature of the analysis.

**Consent for publication**

**Consent to publication**

**Availability of data and materials**
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests**
Not applicable.

**Funding**
Not applicable.

**Authors' contributions**
QW designed the study. CQ was responsible for the acquisition of data and analysis. YH, LF, WY, LW, XL and LM were responsible for helping in literature survey and reviewed the final draft of the manuscript. CQ and QW drafted and revised the manuscript. HM conceived the idea and interpreted the results. All authors read and approved the final manuscript.

**Competing interests**
The authors have no competing interests to declare.

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A total of 392 hematological malignancy patients with positive CR-GNB colonization were included in this study, and the top three predominant pathogens of CR-GNB colonization were Klebsiella pneumoniae (32.1%), Escherichia coli (18.4%), and Mobility baumannii (15.8%). The other strains were Enterobacter cloacae (12.8%), Klebsiella oxytoca (4.6%), Pseudomonas aeruginosa (3.6%), Klebsiella ozaenae (2.6%), Citrobacter freundii (2.3%), Enterobacter aerogenes (1.2%), Enterobacter polycluster (1.2%), Proteus (1.8%), and others (3.6%).
The ROC curve showed that AUC=0.708>0.7 (p<0.005, 95%CI 0.697-0.794), indicating that multivariate analysis displayed acceptable goodness of fit.